

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

Elsie C. Jimenez

Department of Physical Sciences, College of Science, University of the Philippines Baguio, Baguio City 2600, Philippines

## 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 ( $\omega$ -MVIIA) from *Conus magus*, serves as an analgesic that is stronger than morphine but does not cause opioid-like dependence (Rubiu et al. 2024).

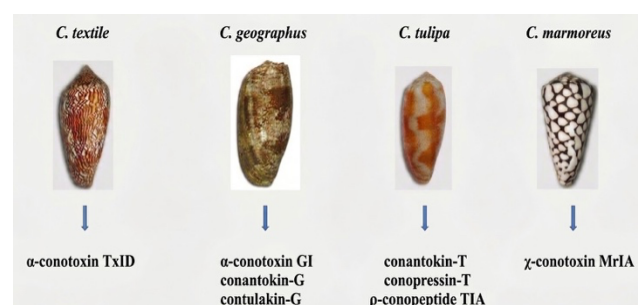


**Figure 1:** Shells of *Conus* species from which peptides described in this review were characterized.

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),

\*Corresponding author

Email Address: [ecjimenez@up.edu.ph](mailto: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  $\alpha$  subunits or heteropentamers of two  $\alpha$  and three  $\beta$  subunits (Figure 2). Muscle nAChRs contain two  $\alpha 1$ , one  $\beta 1$ , one  $\delta$ , and either a  $\gamma$  subunit (fetal) or an  $\epsilon$  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).

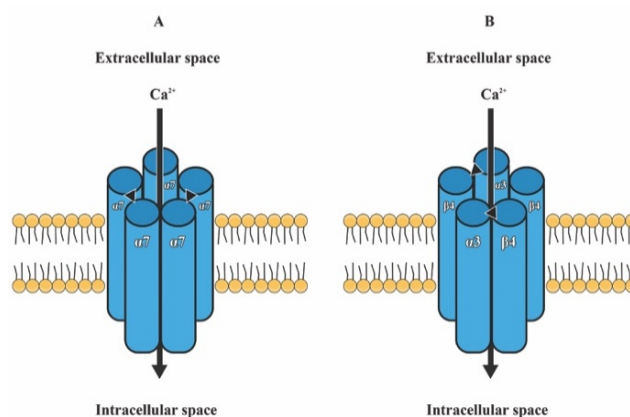


**Figure 2:** (A) Homopentameric ( $\alpha 7$ )<sub>5</sub> and (B) heteropentameric ( $\alpha 3$ )<sub>2</sub>( $\beta 4$ )<sub>3</sub> neuronal nAChRs. The symbol  $\Delta$  marks acetylcholine-binding sites. Binding of two acetylcholine molecules at subunit interfaces opens the pore; the homomeric  $\alpha 7$  receptor has high  $\text{Ca}^{2+}$  permeability, whereas heteromeric receptors have lower  $\text{Ca}^{2+}$  permeability.

Adrenoceptor has seven transmembrane domains. The  $\alpha$ -adrenoceptors comprise  $\alpha 1A$ ,  $\alpha 1B$ ,  $\alpha 1D$ ,  $\alpha 2A$ ,  $\alpha 2B$ , and  $\alpha 2C$ , and the  $\beta$ -adrenoceptors comprise  $\beta 1$ ,  $\beta 2$ , and  $\beta 3$ . 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  $\alpha\beta_2$  heterotetramer (a dimer of  $\alpha\beta$  half-receptors): the two extracellular  $\alpha$  subunits bind insulin, and the two transmembrane  $\beta$  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  $\alpha$ -,  $\alpha B$ -,  $\alpha C$ -,  $\alpha D$ -,  $\alpha M$ -,  $\alpha O$ -, and  $\alpha S$ -conotoxins.

### Alpha-conotoxins

$\alpha$ -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  $\alpha$ -GI,  $\alpha$ -ImI,  $\alpha$ -PnIA,  $\alpha$ -AuIB,  $\alpha$ -Vc1.1,  $\alpha$ -RgIA,  $\alpha$ -TxID,  $\alpha$ -LsIA,  $\alpha$ -AusIA,  $\alpha$ -MilIA,  $\alpha$ -VnIB,  $\alpha$ -Bt1.8,  $\alpha$ -Vt1.27,  $\alpha$ -AtIA,  $\alpha$ -NcIA,  $\alpha$ -NcIA[E15U],  $\alpha$ -NcIB, and  $\alpha$ -NcIB[E13U] (Table 1).

**Table 1: Sequences, molecular targets and potencies of  $\alpha$ -conotoxins**

| Peptide              | Sequence            | nAChR subunits                                                                         | IC50                    | References                                  |
|----------------------|---------------------|----------------------------------------------------------------------------------------|-------------------------|---------------------------------------------|
| $\alpha$ -GI         | ECCNPACGRH YSC*     | XO m $\alpha$ 1 $\beta$ 1 $\delta\epsilon$                                             | 5.86 nM                 | Gray et al. 1981; Ning et al. 2018          |
| $\alpha$ -ImI        | GCCSDPRCAW RC*      | h $\alpha$ 7                                                                           | 440 nM                  | McIntosh et al. 1994, Wan et al. 2015       |
| $\alpha$ -PnIA       | GCCSLPPCAA NNPDYC*  | XO r $\alpha$ 7, XO r $\alpha$ 3 $\beta$ 2, XO h $\alpha$ 7, XO h $\alpha$ 3 $\beta$ 2 | No data                 | Fainzilber et al. 1994, Hopping et al. 2014 |
| $\alpha$ -AuIB       | GCCSYPPCFA TNPDC*   | XO r $\alpha$ 3 $\beta$ 4                                                              | 0.75 $\mu$ M            | Luo et al. 1998, Wu et al. 2018             |
| $\alpha$ -Vc1.1      | GCCSDPRCNY DHPEIC*  | r $\alpha$ 9 $\alpha$ 10, h $\alpha$ 9 $\alpha$ 10                                     | No data                 | Sandall et al. 2003, Yu et al. 2013         |
| $\alpha$ -RgIA       | GCCSDPRCRY RCR      | r $\alpha$ 9 $\alpha$ 10                                                               | No data                 | Ellison et al. 2006, Li et al. 2019         |
| $\alpha$ -TxID       | GCCSHPVCSA MSPIC*   | r $\alpha$ 3 $\beta$ 4                                                                 | 12.5 nM                 | Luo et al. 2013a, Dong et al. 2023          |
| $\alpha$ -LsIA       | SGCCSNPACR VNNPNIC* | h $\alpha$ 3 $\beta$ 2, h $\alpha$ 7                                                   | 10 nM                   | Inserra et al. 2013, Abraham et al. 2017    |
| $\alpha$ -AusIA      | SCCARNPACR HHNPVCV* | h $\alpha$ 7, SH-SY5Y $\alpha$ 7                                                       | 47.0 $\pm$ 6.70 $\mu$ M | Lebbe et al. 2014, Ho et al. 2021           |
| $\alpha$ -MilIA      | DMCCHPACMN HFNC*    | XO $\alpha$ 1 $\beta$ 1 $\gamma\delta$                                                 | 13130 $\pm$ 1125 nM     | Peigneur et al. 2019                        |
| $\alpha$ -VnIB       | GGCCSHPVCY TKNPNCG* | r $\alpha$ 6 $\beta$ 4, r $\alpha$ 6/ $\alpha$ 3 $\beta$ 4                             | 12 nM, 18 nM            | van Hout et al. 2019                        |
| $\alpha$ -Bt1.8      | GCCSNPACIL NNPNQC*  | r $\alpha$ 6/ $\alpha$ 3 $\beta$ 2 $\beta$ 3, r $\alpha$ 3 $\beta$ 2                   | 2.1 nM, 9.4 nM          | Ning et al. 2021                            |
| $\alpha$ -Vt1.27     | NCCMFHTCPI DYSRFNC* | HEK r $\alpha$ 3 $\beta$ 2                                                             | 1160 nM                 | Wang et al. 2022a                           |
| $\alpha$ -AtIA       | ZGCCSHPACS VNHPELCW | XO m $\alpha$ 7                                                                        | 0.16 $\mu$ M            | Neves et al. 2024                           |
| $\alpha$ -NcIA       | GGCCSNPPCI ANHPEIC* | No data                                                                                | No data                 | Ramones et al. 2025                         |
| $\alpha$ -NcIA[E15U] | GGCCSNPPCI ANHPUIC* | No data                                                                                | No data                 | Ramones et al. 2025                         |
| $\alpha$ -NcIB       | CCSNOOCIAN HPEIC*   | $\alpha$ 7                                                                             | 102.7 nM                | Ramones et al. 2025                         |
| $\alpha$ -NcIB[E13U] | CCSNOOCIAN HPUIC*   | $\alpha$ 7                                                                             | 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.

$\alpha$ -GI is a 13-mer peptide isolated from *C. geographus* venom (Gray et al. 1981); it binds the mouse  $\alpha$ 1 $\beta$ 1 $\delta\epsilon$  nAChR. Alanine replacement showed that Pro5, Gly8, Arg9, and Tyr11 are crucial for inhibition of the  $\alpha$ 1 $\beta$ 1 $\delta\epsilon$  nAChR, since each substitution caused a marked loss of potency. The  $\alpha$ -GI[E1A] was 3-fold more potent at the mouse receptor. Molecular dynamics (MD) simulations indicated that loop 2 of  $\alpha$ -GI contributes substantially to the interaction with the  $\alpha$ 1 $\beta$ 1 $\delta\epsilon$  nAChR, with Tyr11 interacting with Leu93, Tyr95, and Leu103 of the  $\delta$  subunit (Ning et al. 2018). In voltage-clamp recordings, both the globular and ribbon isomers of  $\alpha$ -GI selectively inhibited human  $\alpha$ 1 $\beta$ 1 $\delta\epsilon$  nAChRs expressed in *Xenopus* oocytes (Tae et al. 2021). Fatty-acid modification substantially improved the stability and albumin-binding ability of  $\alpha$ -GI, in proportion to the length of the fatty acid, while the modified peptide retained its nAChR antagonist activity (Qi et al. 2023).

$\alpha$ -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  $\alpha$ -ImI dendrimers ( $\alpha$ -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  $\alpha$ 7 nAChRs (IC50 = 4 nM) than  $\alpha$ -ImI (IC50 = 440 nM) (Wan et al. 2015).

$\alpha$ -PnIA, a 16-residue peptide isolated from *C. pennaceus* venom blocks neuronal nChRs of cultured *Aplysia* neurons (Fainzilber et al. 1994). The analog  $\alpha$ -PnIA[A10L] potently and selectively

inhibited rat and human  $\alpha$ 7 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  $\alpha$ 7 and  $\alpha$ 3 $\beta$ 2, whereas charged or polar residues decreased  $\alpha$ 7 binding. Substituting norleucine gave the largest increase in affinity for  $\alpha$ 7, yet the analog remained selective for  $\alpha$ 3 $\beta$ 2. Docking showed that the hydrophobic interactions with  $\alpha$ 7 and  $\alpha$ 3 $\beta$ 2 residues occur through a hydrophobic funnel (Hopping et al. 2014).

$\alpha$ -AuIB is a 15-mer peptide isolated from *C. aulicus* venom; it potently inhibits the  $\alpha$ 3 $\beta$ 4 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  $\alpha$ 3 $\beta$ 4 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  $\alpha$ -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  $\gamma$ -carboxyglutamate-14 (Gla14), was deduced to be the native post-translationally modified form (Jakubowski et al. 2004).  $\alpha$ -Vc1.1 is a potent antagonist of the  $\alpha$ 9 $\alpha$ 10 nAChR (Vincler et al. 2006). Its interactions with the  $\alpha$ 9 $\alpha$ 10 and  $\alpha$ 10 $\alpha$ 9 interfaces were consistent with computational models predicting preferential binding to the  $\alpha$ 10 $\alpha$ 9 interface. A hydrogen bond between  $\alpha$ -Vc1.1

and position 59 of the  $\alpha 10\alpha 9$  pocket conferred specificity for rat over human  $\alpha 9\alpha 10$  nAChR (Yu et al. 2013). The hydroxyl group of Tyr10 formed a hydrogen bond with the carbonyl of  $\alpha 9$  Asn107. Ser4 of  $\alpha$ -Vc1.1 lies next to  $\alpha 9$  Asp166 and Asp169, and substituting a positively charged residue enhanced binding affinity. The carboxyl group of Asp11 formed hydrogen bonds with  $\alpha 9$  Asn154 and Arg81, and adding a second carboxyl group at this position markedly reduced potency (Chu et al. 2019).  $\alpha$ -Vc1.1 selectively inhibited human  $\alpha 9\alpha 10$  and  $\alpha 3\beta 2$  nAChRs. At the  $\alpha 9\alpha 10$ [N179A] mutant its potency decreased 20-fold relative to wild-type  $\alpha 9\alpha 10$ , due to loss of a hydrogen bond with the peptide. At  $\alpha 3\beta 2$ [D86A]  $\alpha$ -Vc1.1 was four-fold more potent than at wild-type  $\alpha 3\beta 2$ , possibly because of the neighboring residue  $\beta 2$  Lys104. The potency of  $\alpha$ -Vc1.1 doubled at  $\alpha 9\alpha 10$ [N213K], while it was unchanged at  $\alpha 9\alpha 10$ [N213R]. MD simulations indicated that altered interactions between the mutated  $\alpha 9$  side chains (N179A, N213K, N213R) and Asp5 of  $\alpha$ -Vc1.1 may partly explain the differences in potency (Tae et al. 2025). Cyclization of  $\alpha$ -Vc1.1 improved serum stability and oral bioavailability. Polyethylene glycol (PEG) linkers preserved the stability of cyclic  $\alpha$ -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  $\alpha$ -RgIA identified by cDNA cloning from *C. regius* specifically blocks the  $\alpha 9\alpha 10$  nAChR (Ellison et al. 2006). NMR was used to determine the solution structures of  $\alpha$ -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  $\alpha 9\alpha 10$  and  $\alpha 7$  nAChRs. The loop-2 analog [Y10W] had a structure and activity like  $\alpha$ -RgIA, with high potency at  $\alpha 9\alpha 10$  and low potency at  $\alpha 7$ . Arg9 in loop 2 is vital for specific binding to  $\alpha 9\alpha 10$  (Ellison et al. 2008). Globular  $\alpha$ -RgIA bound Ac-AChBP more efficiently than the ribbon isomer (Kryukova et al. 2018). Docking and MD simulations indicated that  $\alpha 9$  Asp168 and  $\alpha 10$  Glu197 and Asp205 contributed to the interaction between  $\alpha$ -RgIA and the rat  $\alpha 9\alpha 10$  nAChR (Li et al. 2019). The Arg7 side chain length and charge were found to be important for  $\alpha$ -RgIA activity at  $\alpha 9\alpha 10$  nAChR (Huynh et al. 2020).

$\alpha$ -TxID, a 15-mer peptide identified in *C. textile* by cDNA cloning potently inhibits rat  $\alpha 3\beta 4$  nAChRs (Luo et al. 2013a).  $\alpha$ -TxID[S9A] was 46-fold more potent at  $\alpha 3\beta 4$  than at  $\alpha 6/\alpha 3\beta 4$ . Ser9 of  $\alpha$ -TxID was involved in weak hydrogen bond with  $\beta 4$  Lys81 in the  $\alpha 6\beta 4$  binding site but not in the  $\alpha 3\beta 4$  binding site, and replacement by Ala caused disruption of the hydrogen bond (Wu et al. 2017a). The best selectivity for  $\alpha 3\beta 4$  was achieved with  $\alpha$ -TxID [S9K], which inhibited  $\alpha 3\beta 4$  but had little effect on  $\alpha 6/\alpha 3\beta 4$  (Yu et al. 2018a). Native  $\alpha$ -TxID blocked both rat  $\alpha 3\beta 4$  and  $\alpha 6/\alpha 3\beta 4$ . Alanine-insertion mutants ([+9A], [+10A], [+14A]) and loop-2 truncation mutants showed reduced inhibition of both receptors (Dong et al. 2023).

The 17-residue  $\alpha$ -LsIA isolated from *C. limpusi* venom potently inhibits  $\alpha 3\beta 2$  and  $\alpha 7$  nAChRs. N-terminally truncated analogs were 9-fold less potent at  $\alpha 3\beta 2$  and  $\alpha 7$  nAChRs. C-terminal carboxylation increased potency 3-fold at  $\alpha 3\beta 2$  but reduced it at  $\alpha 7$  (Insera et al. 2013). Interactions of  $\alpha$ -LsIA[R10F] with  $\beta 4$  Lys57, and of the conserved -NN- motif with  $\beta 4$  Ile77 and Ile109, caused its activity at human  $\alpha 3\beta 4$  nAChRs (Abraham et al. 2017).

$\alpha$ -AusIA is a 16-mer peptide isolated from *C. australis* venom. Electrophysiology showed that the globular and ribbon isomers blocked the  $\alpha 7$  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).

$\alpha$ -MilIA (14-residue peptide) was purified from *C. milneedwardsi* venom. It is a highly selective antagonist of muscle  $\alpha 1\beta 1\gamma\delta$

nAChRs. The M9G and N10K substitutions produced strong discrimination between  $\alpha 1\beta 1\gamma\delta$  and  $\alpha 1\beta 1\epsilon\delta$  receptors.  $\alpha$ -MilIA[M9G, N10K] potently inhibited the acetylcholine-evoked current at  $\alpha 1\beta 1\gamma\delta$ . The analog [ $\Delta 1$ , M2R, M9G, N10K, H11K] was significantly more potent than  $\alpha$ -MilIA and preferred the  $\alpha 9\alpha 10$  nAChR (Peigneur et al. 2019).

The 17-residue  $\alpha$ -VnIB was characterized from *C. ventricosus* genomic DNA. It is selective for  $\alpha 6\beta 4$  nAChRs over  $\alpha 3\beta 4$  and  $\alpha 6\beta 2\beta 3$  receptors. The  $\alpha$ -VnIB potently inhibited acetylcholine-elicited currents at rat  $\alpha 6\beta 4$  and  $\alpha 6/\alpha 3\beta 4$  nAChRs. Greater selectivity was also shown for human  $\alpha 6/\alpha 3\beta 4$ . The peptide exhibited greater selectivity for human  $\alpha 6/\alpha 3\beta 4$  and quick binding kinetics at rat  $\alpha 6/\alpha 3\beta 4$  (van Hout et al. 2019).

$\alpha$ -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  $\alpha 6/\alpha 3\beta 2\beta 3$  and  $\alpha 3\beta 2$  nAChRs. It had higher binding affinity with a slower dissociation rate for the rat  $\alpha 6/\alpha 3\beta 2\beta 3$  compared with  $\alpha 3\beta 2$ . The three-dimensional structure of  $\alpha$ -Bt1.8 revealed a larger hydrophobic region that may account for its potent inhibition of  $\alpha 6/\alpha 3\beta 2\beta 3$ . Ala scan showed that Ile9, Leu10, Asn11, Asn12 and Asn14 were essential for the  $\alpha 6/\alpha 3\beta 2\beta 3$  and  $\alpha 3\beta 2$  inhibition (Ning et al. 2021).

$\alpha$ -Vt1.27 with 17 amino acid residues was identified by cDNA cloning from *C. vitulinus*. It blocked rat  $\alpha 3\beta 2$  nAChRs in sensory neurons and high voltage-activated Cav2.2 channels expressed in HEK293T cells. Ala scan revealed that Phe5, Pro9, Ile10, and Ser13 significantly contributed to the activity. The  $\alpha$ -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).

$\alpha$ -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  $\alpha 7$  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  $\alpha$ -AtIA potently inhibited mouse  $\alpha 7$  nAChR ( $IC_{50}=0.16 \mu M$ ), but inhibited  $\alpha 6/\alpha 3\beta 4$  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  $\alpha$ -NcIA,  $\alpha$ -NcIA[E15U],  $\alpha$ -NcIB and  $\alpha$ -NcIB[E13U]. The  $\alpha$ -NcIA and  $\alpha$ -NcIA[E15U] consist of 17 residues, while  $\alpha$ -NcIB and  $\alpha$ -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  $\alpha$ -NcIA inhibited nicotine-evoked responses by more than 70%,  $\alpha$ -NcIA[E15U] did not.  $\alpha$ -NcIB[E13U] showed ~60% inhibitory effect, but not  $\alpha$ -NcIB.  $\alpha$ -NcIA[E15U],  $\alpha$ -NcIB and  $\alpha$ -NcIB[E13U] were almost fully inhibitory against choline-evoked responses, while NcIA was weakly inhibitory. The  $\alpha$ -NcIB and  $\alpha$ -NcIB[E13U] showed specificities for the  $\alpha 7$  nAChR (Ramones et al. 2025).

#### AlphaB-conotoxin

$\alpha B$ -Conotoxins contain two disulfide bonds with the framework C-CC-C. The only identified member is  $\alpha B$ -VxXXIVA (Table 2), a 40-residue peptide characterized by cDNA cloning from *C. vexillum*. It is an  $\alpha 9\alpha 10$  nAChR antagonist (Luo et al. 2013b).

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

immunosorbent assay (ELISA) could be utilized with  $\alpha$ B-VxXXIVA in drug analysis (Tang et al. 2022).

**Table 2: Sequences, targets, and potencies of  $\alpha$ B-,  $\alpha$ C-,  $\alpha$ D-,  $\alpha$ M-,  $\alpha$ O-, and  $\alpha$ S-conotoxins**

| Peptide            | Sequence                                                    | nAChR subunits                                                                                             | IC50                                                       | References                                |
|--------------------|-------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------|
| $\alpha$ B-VxXXIVA | VRCLEKSGAQ PNKLFRRPCC<br>QKGPSFARHS RCVYYTQSRE              | ra9 $\alpha$ 10                                                                                            | 1.2 $\mu$ M                                                | Luo et al. 2013b;<br>Tang et al. 2022     |
| $\alpha$ C-PrXA    | TYGIYDAKPO FSCAGLRGGC<br>VLPONLROKF KE*                     | ma1 $\beta$ 1 $\epsilon\delta$ ,<br>ma1 $\beta$ 1 $\gamma\delta$                                           | 1.8 nM,<br>3.0 nM                                          | Jimenez et al. 2007;<br>Taiwe et al. 2019 |
| $\alpha$ D-VxXXB   | DDUSUCIINT RDSPWGRCCR<br>TRMCGSMCCP RNGCTCVYHW<br>RRGHGSCPG | XO ra7                                                                                                     | No data                                                    | Loughnan et al. 2006;<br>Ho et al. 2022   |
| $\alpha$ D-GeXXA   | DVHRPCQSVR PGRVWGKCL<br>TRLCTMCCA RADCTCVYHT<br>WRGHGSCVM   | ra9 $\alpha$ 10<br>ha9 $\alpha$ 10                                                                         | 1.2 nM<br>28 nM                                            | Xu et al. 2015;<br>Yang et al. 2017       |
| $\alpha$ D-PiXXA   | AVKKTClRST OGSNWGRCC<br>TKMCHTLCCA RSDCTCVYRS<br>GKGHGCSCTS | XO ha7                                                                                                     | 6.2 $\mu$ M                                                | Hernández-Sámano et al. 2019              |
| $\alpha$ D-FrXXA   | EARITCQPRG RSKWGRCCLT<br>QMCGRNYCCYK HGCRCVYHSW<br>RGHGSC   | ha7,<br>ha3 $\beta$ 2,<br>ma1 $\beta$ 1 $\epsilon\delta$ ,<br>ma1 $\beta$ 1 $\gamma\delta$                 | 125 nM,<br>282 nM,<br>351 nM,<br>447 nM                    | Rodriguez-Ruiz et al. 2022                |
| $\alpha$ M-MIIIJ   | ZKCCSGGSCP LYFRDRLICP CC                                    | ma $\beta$ 8 $\epsilon$ ,<br>ma $\beta$ 8 $\gamma$ ,<br>ha $\beta$ 8 $\epsilon$ ,<br>ha $\beta$ 8 $\gamma$ | 3.6 $\mu$ M<br>44.4 $\mu$ M<br>4.1 $\mu$ M<br>19.6 $\mu$ M | Rybin et al. 2020                         |
| $\alpha$ M-SIIID   | CCGEGSSCPK YFKNNFICGC C                                     | HEK ha7                                                                                                    | 880.71 $\pm$ 271.91 nM                                     | Wang et al. 2022b                         |
| $\alpha$ O-It14a   | MCPPLCKPSC TNC*                                             | rneuronal                                                                                                  | No data                                                    | Peng et al. 2006;<br>Ren et al. 2015b     |
| $\alpha$ O-GeXIVA  | TCRSSGRYCR SPYDRRRRYC<br>RRITDACV*                          | ra9 $\alpha$ 10,<br>ha9 $\alpha$ 10                                                                        | 4.6 nM                                                     | Luo et al. 2015;<br>Wang et al. 2024b     |
| $\alpha$ S-GVIIIB  | SGSTCTCFTS TNCQGSCECL<br>SPPGCYCSNN GIRQRGCST<br>CPGT*      | XO<br>$\alpha$ 9 $\alpha$ 10                                                                               | 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**

$\alpha$ C-Conotoxins have one disulfide bond with Cys pattern C–C. The characterized family member is  $\alpha$ C-conotoxin PrXA (Table 2).  $\alpha$ C-PrXA, a 32-residue peptide, was isolated from *C. parius* venom. It acted as a potent competitive antagonist of mouse  $\alpha$ 1 $\beta$ 1 $\gamma\delta$  and  $\alpha$ 1 $\beta$ 1 $\epsilon\delta$  nAChRs (Jimenez et al. 2007).

**AlphaD-conotoxins**

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

$\alpha$ D-VxXXB, a dimer of a 50-residue peptide, was isolated from *C. vexillum* venom. It potently inhibited the  $\alpha$ 7 nAChR (Loughnan et al. 2006). The C-terminal domain blocked  $\alpha$ 7 and bound allosterically to *Lymanaea stagnalis* AChBP (Ls-AChBP), whereas the anti-parallel dimeric N-terminal domain inhibited  $\alpha$ 7 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  $\alpha$ D-VxXXB suggested that the N-terminal domain had little contribution to the potency but may affect the positioning of the two C-terminal domains for maximal potency (Ho et al. 2022).

$\alpha$ D-GeXXA, a homodimer of a 50-residue peptide, was characterized from *C. generalis* venom. The C-terminal domain of monomeric peptide retained the  $\alpha$ 9 $\alpha$ 10 nAChR inhibitory activity.

The rat  $\alpha$ 10 nAChR His7 defined the species preference of  $\alpha$ D-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  $\beta$  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).

$\alpha$ D-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  $\alpha$ 7 nAChR expressed in *Xenopus* oocytes (Hernández-Sámano et al. 2019).

$\alpha$ D-FrXXA (a homodimer of a 47-residue peptide) was characterized from *C. fergusonii* by Edman degradation and transcriptomics. The conotoxin blocked the acetylcholine-induced response on human nAChRs  $\alpha$ 7,  $\alpha$ 3 $\beta$ 2, and  $\alpha$ 4 $\beta$ 2; mouse  $\alpha$ 1 $\beta$ 1 $\epsilon\delta$  and  $\alpha$ 1 $\beta$ 1 $\gamma\delta$  nAChRs. In  $\alpha$ 7 and  $\alpha$ 3 $\beta$ 2 nAChRs the inhibition was irreversible because the current amplitude did not increase in spite of time elapsed and washout of the peptide. In  $\alpha$ 1 $\beta$ 1 $\epsilon\delta$  and  $\alpha$ 1 $\beta$ 1 $\gamma\delta$  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  $\alpha$ 4 $\beta$ 2 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

$\alpha$ M-Conotoxins contain three disulfide bonds with the framework CC–C–C–CC. The characterized family members are  $\alpha$ M-MIIII and  $\alpha$ M-SIIID (Table 2).

$\alpha$ M-MIIII 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  $\alpha 1\beta 1\epsilon\delta$  and  $\alpha 1\beta 1\gamma\delta$  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).

$\alpha$ M-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  $\alpha 7$  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

$\alpha$ O-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  $\alpha$ O-Ilt14a and  $\alpha$ O-GeXIVA (Table 2).

$\alpha$ O-Ilt14a 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).  $\alpha$ O-Ilt14a 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).

$\alpha$ O-GeXIVA (28-mer peptide) was identified by cDNA cloning from *C. generalis*. Its bead and ribbon isomers blocked the  $\alpha 9\alpha 10$  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  $\alpha 9\alpha 10$  (Wu et al. 2017b). Several disulfide-deficient analogs of the bead isomer retained potent inhibition of  $\alpha 9\alpha 10$ , 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  $\alpha 9\alpha 10$ , and the  $\alpha$ O-GeXIVA[I23A] ribbon isomer was 10-fold more active at rat and human  $\alpha 9\alpha 10$  receptors (Xu et al. 2023).

AlphaS-conotoxin

$\alpha$ S-Conotoxins have five disulfide bonds with framework C–C–C–C–C–C–C–C. The only characterized member is  $\alpha$ S-GVIIIIB (Table 2), a 44-residue peptide isolated from *C. geographus* venom and confirmed by cDNA cloning. Physiological studies revealed that  $\alpha$ S-GVIIIIB had great selectivity for the  $\alpha 9\alpha 10$  nAChR. Inhibition by  $\alpha$ S-GVIIIIB was reversed much more slowly than inhibition by  $\alpha$ -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  $\alpha$ -RgIA prevented the slow reversible block by  $\alpha$ S-GVIIIIB (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  $\gamma$ -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, p-conopeptide, consomatin,  $\chi$ -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 $\mu$ M                          | Teichert et al. 2007                                         |
| Conantokin-P    | GEUUHskyQU CLRUIRVNkV QQUC* | XO rGluN2B                          | IC50=0.3 $\mu$ M                          | Gowd et al. 2008                                             |
| Conantokin Bk-B | GEUUYsUAI*                  | XO GluN2D                           | IC50=1.91 $\mu$ M                         | Platt et al. 2014                                            |
| Contulakin-G    | ZSEEGGSNAT KkPYIL           | HEK rNTSR1, HEK hNTSR1, HEK rNTSR2  | EC50=524 nM<br>EC50=960 nM<br>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                                        |
| $\rho$ -TIA     | FNWRCCLIpA CRRNHKKFC*       | zfAR $\alpha$ 1                     | No data                                   | Sharpe et al. 2001; Lim et al. 2025                          |
| Consomatin Ro1  | UGYKCVwKTC MOA              | hSST1<br>hSST4                      | EC50=2.9 $\mu$ M<br>EC50=5.3 $\mu$ M      | Ramiro et al. 2022                                           |
| $\chi$ -MrIA    | NGVCCGYKLC HOC              | rNET                                | No data                                   | McIntosh et al. 2000; Hu et al. 2024                         |
| $\chi$ -AoIA    | RCCGYKMCHO C                | HEK hNET                            | IC50=1.06 $\pm$ 0.48 $\mu$ M              | Gupta et al. 2010; Belleza et al. 2026                       |

| Peptide      | Sequence                                                                                  | Molecular Targets | IC50/EC50       | References                                                                |
|--------------|-------------------------------------------------------------------------------------------|-------------------|-----------------|---------------------------------------------------------------------------|
| $\chi$ -PnID | STCCGYRMCV PC*                                                                            | rNET              | IC50=10 $\mu$ M | Espiritu et al. 2023                                                      |
| Con-Ins G1   | A chain<br>GVVUHCCHRP CSNAEFKKYC*<br>B chain<br>TFDTOKHRCG SUITNSYMDL CYR                 | hIR               | EC50=16.3 nM    | Menting et al. 2016;<br>Ahorukomeye et al. 2019;<br>Gorai & Vashisth 2022 |
| Con-Ins T1A  | A chain<br>GVVUHCCHRP CSNAEFKKFC*<br>B chain<br>NSTDOKYRCG SUIPNSYIDL CF                  | hIR               | EC50=12 nM      | Ahorukomeye et al. 2019;<br>Gorai & Vashisth 2022                         |
| Con-Ins K1   | A chain<br>GIVUDCCYND CTDEKLKEYC<br>HTLQ*<br>B chain<br>SDSGTTLVRR RLCGSULVTY<br>LGELCLGN | hIR               | EC50=30.5 nM    | Ahorukomeye et al. 2019;<br>Gorai & Vashisth 2022                         |
| Conkazal-M1  | QFFCPDSEND PLNCVETMAT<br>TATCMQSNKD KSYSYACGYC<br>GKKKESCFNG NKVPVRDYN<br>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<sub>50</sub> 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  $\beta$ -D-Galp-(1 $\rightarrow$ 3)- $\alpha$ -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

$\rho$ -Conopeptides have two disulfide bonds (framework CC-C-C).  $\rho$ -T1A with 19 amino acid residues (Table 3) was isolated from *C. tulipa* venom; it inhibits the  $\alpha$ 1-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).  $\rho$ -T1A interacts with the  $\alpha$ 1B-adrenoceptor through (1) a salt bridge between Arg4 and Asp327 and a cation- $\pi$  interaction between Arg4 and Phe330; (2) a T-stacking  $\pi$  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).  $\rho$ -T1A markedly reduced the escape response of zebrafish larvae and blocked the zebrafish  $\alpha$ 1-

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

$\chi$ -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  $\chi$ -conotoxins normally adopt ribbon configuration. The characterized family members are  $\chi$ -MrIA,  $\chi$ -AoIA and  $\chi$ -PnID (Table 3).

$\chi$ -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  $\chi$ -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).

$\chi$ -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– $\chi$ -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  $\chi$ -AoIA complement the S1 microenvironment, accounting for its high affinity.  $\chi$ -AoIA was more potent than its globular isomer.  $\chi$ -AoIA caused potent antinociception in mice with inflammatory pain, without sedation or motor dysfunction after subcutaneous injection (Belleza et al. 2026).

The 12-mer  $\chi$ -PnID was purified from *C. pennaceus* venom. It selectively blocked norepinephrine uptake at the rat NET. The globular  $\chi$ -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). Konkazal-M1, from *C. magus*, was the first characterized member of the MKAVA superfamily (Table 3). Konkazal-M1 was shown to assume a fold typical of the Kazal-type protease inhibitor family, with a Glu residue positioned at the inhibitory P1. Konkazal-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),  $\alpha$ -Vc1.1 (ACV1), Xen2174 (a  $\chi$ -MrIA analog),  $\alpha$ -RglA,  $\alpha$ -TxID,  $\alpha$ -ImI,  $\alpha$ -PnIA,  $\alpha$ -AulB,  $\alpha$ -LsIA,  $\alpha$ -C-PrXA,  $\alpha$ -O-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  $\alpha 9\alpha 10$  nAChR compared with the rat receptor (Safavi-Hemami et al. 2018). Further studies undertaken to develop  $\alpha$ -Vc1.1 as a therapeutic lead confirmed that the peptide inhibited the  $\alpha 9$ -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  $\chi$ -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  $\chi$ -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  $\chi$ -MrIA dendrimers retained the  $\chi$ -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  $\chi$ -MrIA analogs had human NET-inhibitory activity comparable to  $\chi$ -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  $\chi$ -MrIA or its analogs.

$\alpha$ -RgIA is less potent at human than at rat nAChRs. The analog RgIA4 is highly potent at both human and rat  $\alpha 9\alpha 10$  receptors and more selective for  $\alpha 9\alpha 10$  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  $\alpha 9$ -containing nAChRs (Romero et al. 2017). Hot-plate, cold-allodynia, grip-strength, and von Frey tests showed that  $\alpha$ -RgIA alleviated long-term oxaliplatin-induced peripheral neuropathy in mice. Histology of dorsal root ganglion neurons showed improved nuclear morphology (Dyachenko et al. 2022).

$\alpha$ -TxID was tested on human cervical cancer cell lines. The  $\alpha 3$  and  $\beta 4$  nAChR subunits were overexpressed in SiHa cells compared with normal ectocervical Ect1/E6E7 cells.  $\alpha$ -TxID markedly inhibited SiHa cell proliferation, providing a basis for potential cervical cancer therapy (Liu et al. 2019).  $\alpha 3$  and  $\beta 4$  subunits were upregulated in the lung cancer cell lines A549 and NCI-H1299, and co-treatment with  $\alpha$ -TxID enhanced the inhibitory effect of adriamycin (doxorubicin) on cell growth (Qian et al. 2019).

$\alpha$ -ImI-modified PEG-DSPE micelles ( $\alpha$ -ImI-PMs) improved delivery of paclitaxel to MCF-7 human breast cancer cells that overexpress  $\alpha 7$  nAChRs, through binding of  $\alpha$ -ImI to the receptor. Paclitaxel delivered with  $\alpha$ -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,  $\alpha$ -ImI upregulated the pro-inflammatory cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) while the anti-inflammatory cytokine TGF- $\beta$  was almost unaffected.  $\alpha$ -ImI may therefore serve as a molecular probe of  $\alpha 7$  nAChR function in these cells (Padilla et al. 2017). Docetaxel loaded in  $\alpha$ -ImI-PMs had a stronger antiproliferative effect on non-small cell lung cancer cells (Mei et al. 2018). Simulations of the  $2\times\alpha$ -ImI dendrimer with the  $\alpha 7$  nAChR indicated greater potency than the  $\alpha$ -ImI monomer, due to a stable hydrogen-bond network formed by the linker (Xu et al. 2019).  $\alpha$ -ImI was fused to alpha-fetoprotein domain 3 (AFP3),

a prototype anticancer agent. The fusion protein  $\alpha$ -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  $\alpha$ -PnIA (an  $\alpha 3\beta 2$  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).

$\alpha$ -AuIB reduced the viability of small cell lung carcinoma cells, whereas nicotine promoted it. Variants in the nAChR genes *CHRNA3*, *CHRNA5*, and *CHRNA4* 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,  $\alpha$ -AuIB abolished nicotine-evoked currents. *Chrna3* hypomorphic mice, which express low levels of the  $\alpha 3$  subunit, consumed more nicotine than wild-type mice, and knocking down the gene transcript in rats markedly increased nicotine consumption.  $\alpha 3\beta 4$  nAChRs thus control the stimulatory effect of nicotine on the medial habenula–interpeduncular nucleus circuit and nicotine-avoidance behavior (Elayouby et al. 2021).

An  $\alpha$ -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  $\alpha 7$  and rat  $\alpha 3\beta 2$  nAChRs. The stapled peptide-drug conjugates also retained cytotoxic activity against human A549 cancer cells (Sun et al. 2024).

$\alpha$ -Conotoxin  $\alpha$ C-PrXA was used to select peptide-binding DNA aptamers, which effectively neutralized the toxin-induced displacement of radiolabeled  $\alpha$ -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  $\alpha$ C-PrXA on acetylcholine-evoked responses. Two DNA aptamers reduced the affinity of  $\alpha$ C-PrXA for the receptor, probably by interfering with its pharmacophore. When co-administered, the aptamers also reduced  $\alpha$ C-PrXA-induced spasmodic muscle contraction and lethality in mice, consistent with formation of a stable toxin–aptamer complex (Taiwe et al. 2019).

$\alpha$ O-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,  $\alpha$ O-GeXIVA bead isomer decreased mechanical hyperalgesia without effect on motor activity. The isomers differed ~5-fold in potency at human versus rat  $\alpha 9\alpha 10$  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).  $\alpha$ O-GeXIVA also blocked proliferation and induced apoptosis in MDA-MB-157 breast cancer cells, apparently by downregulating  $\alpha$ 9 nAChR expression, and suppressed their migration. The growth of an  $\alpha$ 9 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 Glu 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).  $\alpha$ -Vc1.1,  $\alpha$ -Rg1A,  $\alpha$ -Vt1.27,  $\alpha$ O-It14a, and  $\alpha$ O-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  $\alpha$ -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  $\alpha$ -ImI and  $\alpha$ -LsIA (Mei et al. 2018; Sun et al. 2024), and may find application in targeted drug delivery. The binding of  $\alpha$ -ImI dendrimers to  $\alpha$ 7 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  $\alpha$ -GI while preserving its nAChR antagonism (Qi et al. 2023), deserves further investigation. Peptide engineering by insertion, deletion, truncation, and cyclization, as with  $\alpha$ -TxID,  $\alpha$ -AusIA, and  $\alpha$ O-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  $\alpha$ -ImI,  $\alpha$ -PnIA[A10L],  $\alpha$ -AusIA,  $\alpha$ -AtIA,  $\alpha$ D-VxXXB,  $\alpha$ D-PiXXA,  $\alpha$ D-FrXXA, and  $\alpha$ M-SIIID, act on the neuronal  $\alpha$ 7 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  $\alpha$ 7 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 as  $\alpha$ -MilIA,  $\alpha$ C-PrXA,  $\alpha$ D-FrXXA and  $\alpha$ M-MIIJ (Peigneur et al. 2019, Taiwe et al. 2019, Rodriguez-Ruiz et al. 2022, Rybin et al. 2020) could be undertaken alongside  $\alpha$ -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  $\alpha$ -TxID and  $\alpha$ O-GeXIVA (Liu et al. 2019; Sun et al. 2020). The use of  $\alpha$ -AuIB to probe nicotine addiction, and possibly to develop treatments for it, is worth pursuing. The use of  $\alpha$ C-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 conantokin-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 conantokinins 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 p-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),  $\alpha$ -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  $\omega$ -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  $\omega$ -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  $\omega$ -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.

## REFERENCES

- Abraham N, Healy M, Ragnarsson L, Brust A, Alewood PF, Lewis RJ. Structural mechanisms for  $\alpha$ -conotoxin activity at the human  $\alpha 3 \beta 4$  nicotinic acetylcholine receptor. *Sci Rep* 2017; 7:45466.
- Ahorukomeye P, Disotuar MM, Gajewiak J, Karanth S, Watkins M, Robinson SD, Flórez Salcedo P, Smith NA, Smith BJ, Schlegel A, Forbes BE, Olivera B, Hung-Chieh Chou D, Safavi-Hemami H. Fish-hunting cone snail venoms are a rich source of minimized ligands of the vertebrate insulin receptor. *Elife* 2019; 8:e41574.
- Balsara R, Dang A, Donahue DL, Snow T, Castellino FJ. Conantokin-G attenuates detrimental effects of NMDAR hyperactivity in an ischemic rat model of stroke. *PLoS One* 2015; 10:e0122840.
- Belleza OJV, Zhang H, Schmidhammer H, Gonzalez TI, Ciotu CI, Tomašević N, Ocampo CMM, Fernando JC, Koehbach J, Schwarz P, Al Makhlof M, Tajti G, Hasinger S, Kastner N, Avsar O, Retzl B, Jäntsche K, Jiang Y, Hellinger R, Fischer MJM, Rosengren KJ, Gruber CW, Villaraza AJL, Stockner T, Spetea M, Xu HE, Sitte HH. Structural and functional basis of antinociceptive action of  $\chi$ -conotoxin AoIA at the noradrenaline transporter. *Nat Struct Mol Biol* 2026; 33:1311-1323.
- Bjørn-Yoshimoto WE, Ramiro IBL, Yandell M, McIntosh JM, Olivera BM, Ellgaard L, Safavi-Hemami H. Curses or cures: A review of the numerous benefits versus the biosecurity concerns of conotoxin research. *Biomedicines* 2020; 8:235.
- Bönisch H, Brüss M. The norepinephrine transporter in physiology and disease. *Handb Exp Pharmacol* 2006; 175:485–524.
- Brust A, Palant E, Croker DE, Colless B, Drinkwater R, Patterson B, Schroeder CI, Wilson D, Nielsen CK, Smith MT, Alewood D, Alewood PF, Lewis RJ.  $\chi$ -Conopeptide pharmacophore development: toward a novel class of norepinephrine transporter inhibitor (Xen2174) for pain. *J Med Chem* 2009; 52:6991–7002.
- Carmi I, Zoabi S, Bittan AM, Kellner S, Oz S, Heinrich R, Berlin S. A genetically encoded secreted toxin potentiates synaptic NMDA receptors in hippocampal neurons and confers neuroprotection. *PNAS Nexus* 2025; 4:pgaf041.
- Carstens BB, Clark RJ, Daly NL, Harvey PJ, Kaas Q, Craik DJ. Engineering conotoxins for the treatment of pain. *Curr Pharm Des* 2011; 17:4242–4253.
- Chen X, Zou Z, Li W, Dong X, Chen Y, Lu Y, Zhu M, Li M, Lin B.  $\alpha$ -Conotoxin recombinant protein ImI-AFP3 efficiently inhibits the growth and migration of lung cancer cells. *Protein Expr Purif* 2024; 215:106405.
- Choi E, Bai XC. Activation mechanism of the insulin receptor: a structural perspective. *Annu Rev Biochem* 2023; 92:247-272.
- Christensen SB, Bandyopadhyay PK, Olivera BM, McIntosh JM.  $\alpha$ S-conotoxin GVIIIB potently and selectively blocks  $\alpha 9 \alpha 10$  nicotinic acetylcholine receptors. *Biochem Pharmacol* 2015; 96:349–356.
- Chu X, Tae HS, Xu Q, Jiang T, Adams DJ, Yu R.  $\alpha$ -Conotoxin Vc1.1 structure-activity relationship at the human  $\alpha 9 \alpha 10$  nicotinic acetylcholine receptor investigated by minimal side chain replacement. *ACS Chem Neurosci* 2019; 10:4328–4336.
- Clark RJ, Akcan M, Kaas Q, Daly NL, Craik DJ. Cyclization of conotoxins to improve their biopharmaceutical properties. *Toxicon* 2012; 59:446–455.
- Craig AG, Norberg T, Griffin D, Hoeger C, Akhtar M, Schmidt K, Low W, Dykert J, Richelson E, Navarro V, Mazella J, Watkins M, Hillyard D, Imperial J, Cruz LJ, Olivera BM. Conulakin-G, an O-glycosylated invertebrate neurotensin. *J Biol Chem* 1999; 274:13752–13759.
- Dekan Z, Wang CI, Andrews RK, Lewis RJ, Alewood PF. Conotoxin engineering: dual pharmacophoric noradrenaline transport inhibitor/integrin binding peptide with improved stability. *Org Biomol Chem* 2012; 10:5791–5794.
- Dong J, Zhang P, Xie J, Xie T, Zhu X, Zhangsun D, Yu J, Luo S. Loop2 size modification reveals significant impacts on the potency of  $\alpha$ -conotoxin TXID. *Mar Drugs* 2023; 21: 286.
- Dutertre S, Croker D, Daly NL, Andersson A, Muttenthaler M, Lumsden NG, Craik DJ, Alewood PF, Guillon G, Lewis RJ. Conopressin-T from *Conus tulipa* reveals an antagonist switch in vasopressin-like peptides. *J Biol Chem* 2008; 283:7100–7108.
- Dutt M, Giacomotto J, Ragnarsson L, Andersson A, Brust A, Dekan Z, Alewood PF, Lewis RJ. The  $\alpha 1$ -adrenoceptor inhibitor p-TIA facilitates net hunting in piscivorous *Conus tulipa*. *Sci Rep* 2019; 9:17841.
- Dyachenko IA, Palikova YA, Palikov VA, Korolyova YV, Kazakov VA, Egorova NS, Garifulina AI, Utkin YN, Tsetlin VI, Kryukova EV.  $\alpha$ -Conotoxin RgIA and oligoarginine R8 in the mice model alleviate long-term oxaliplatin induced neuropathy. *Biochimie* 2022; 194:127–136.
- Elayouby KS, Ishikawa M, Dukes AJ, Smith ACW, Lu Q, Fowler CD, Kenny PJ.  $\alpha 3^*$  Nicotinic acetylcholine receptors in the habenula-interpeduncular nucleus circuit regulate nicotine intake. *J Neurosci* 2021; 41:1779–1787.
- El-Aziz TMA, Ravelet C, Molgo J, Fiore E, Pale S, Amar M, Al-khoury S, Dejeu J, Fadl M, Ronjat M, Taiwe GS, Servent D, Peyrin E, De Waard M. Efficient functional neutralization of lethal peptide toxins in vivo by oligonucleotides. *Sci Rep* 2017; 7:7202.
- Ellison M, Haberlandt C, Gomez-Casati ME, Watkins M, Elgoyhen AB, McIntosh JM, Olivera BM. Alpha-RgIA: a novel conotoxin that potently and specifically blocks the  $\alpha 9 \alpha 10$  nAChR. *Biochemistry* 2006; 45:1515–1517.
- Ellison M, Feng ZP, Park AJ, Zhang X, Olivera BM, McIntosh JM, Norton RS. Alpha-RgIA, a novel conotoxin that blocks the  $\alpha 9 \alpha 10$  nAChR: structure and identification of key receptor-binding residues. *J Mol Biol* 2008; 377:1216–1227.
- Espirito MJ, Taylor JK, Sugai CK, Thapa P, Loening NM, Gusman E, Baoanan ZG, Baumann MH, Bingham JP. Characterization of the native disulfide isomers of the novel  $\chi$ -conotoxin PnID: Implications for further increasing conotoxin diversity. *Mar Drugs* 2023; 21:61.
- Fainzilber M, Hasson A, Oren R, Burlingame AL, Gordon D, Spira ME, Zlotkin E. New mollusc-specific alpha-conotoxins block *Aplysia* neuronal acetylcholine receptors. *Biochemistry* 1994; 33:9523–9529.
- Gilles N. Natural peptide toxins as an option for renewed treatment of type 2 vasopressin receptor-related diseases. *Biology* 2023; 12:544.
- Giribaldi J, Ragnarsson L, Pujante T, Enjalbal C, Wilson D, Daly NL, Lewis RJ, Dutertre S. Synthesis, pharmacological and

- structural characterization of novel conopressins from *Conus milaris*. *Mar Drugs* 2020; 18:150.
- Gorai B, Vashisth H. Structures and interactions of insulin-like peptides from cone snail venom. *Proteins* 2022; 90:680-690.
- Gowd KH, Twede V, Watkins M, Krishnan KS, Teichert RW, Bulaj G, Olivera BM. Conantokin-P, an unusual conantokin with a long disulfide loop. *Toxicon* 2008; 52:203–213.
- Grand T, Abi Gerges S, David M, Diana MA, Paoletti P. Unmasking GluN1/GluN3A excitatory glycine NMDA receptors. *Nat Commun* 2018; 9:4769.
- Gray WR, Luque A, Olivera BM, Barrett J, Cruz LJ. Peptide toxins from *Conus geographus* venom. *J Biol Chem* 1981; 256:4734–4740.
- Günther T, Tulipano G, Dournaud P, Bousquet C, Csaba Z, Kreienkamp HJ, Lupp A, Korbonits M, Castaño JP, Wester HJ, Culler M, Melmed S, Schulz S. International Union of Basic and Clinical Pharmacology. CV. Somatostatin receptors: structure, function, ligands, and new nomenclature. *Pharmacol Rev* 2018; 70:763-835.
- Gupta K, Kumar M, Balaran P. Disulfide bond assignments by mass spectrometry of native natural peptides: cysteine pairing in disulfide bonded conotoxins. *Anal Chem* 2010; 82:8313–8319.
- Haack JA, Rivier J, Parks TN, Mena EE, Cruz LJ, Olivera BM. Conantokin-T. A gamma-carboxyglutamate containing peptide with N-methyl-D-aspartate antagonist activity. *J Biol Chem* 1990; 265:6025–6029.
- Hackney CM, Koch TL, Ryding NL, Rogalski A, Chase K, Giglio ML, Espino SS, Acyatan ZG, Watkins M, Olivera BM, Safavi-Hemami H, Teilum K, Ellgaard L. Conkazol-M1 from the MKAVA family of conotoxins: A dual-function protease inhibitor and neuroactive peptide. *Protein Sci* 2026; 35:e70580.
- Hernández-Sámamo AC, Falcón A, Zamudio F, Batista CVF, Michel-Morfin JE, Landa-Jaime V, López-Vera E, Jeziorski MC, Aguilar MB.  $\alpha$ D-Conotoxins in species of the eastern pacific: The case of *Conus princeps* from Mexico. *Toxins (Basel)* 2019; 11:405.
- Ho TNT, Abraham N, Lewis RJ. Rigidity of loop 1 contributes to equipotency of globular and ribbon isomers of  $\alpha$ -conotoxin AusIA. *Sci Rep* 2021; 11:21928.
- Ho TNT, Abraham N, Lewis RJ. Synthesis of full-length homodimer  $\alpha$ D-VxXXB that targets human  $\alpha 7$  nicotinic acetylcholine receptors. *RSC Med Chem* 2022; 13:1410–1419.
- Hone AJ, McIntosh JM. Nicotinic acetylcholine receptors: therapeutic targets for novel ligands to treat pain and inflammation. *Pharmacol Res* 2023; 190:106715.
- Hopping G, Wang CI, Hogg RC, Nevin ST, Lewis RJ, Adams DJ, Alewood PF. Hydrophobic residues at position 10 of  $\alpha$ -conotoxin PnIA influence subtype selectivity between  $\alpha 7$  and  $\alpha 3\beta 2$  neuronal nicotinic acetylcholine receptors. *Biochem Pharmacol* 2014; 91:534–542.
- Hu T, Yu Z, Zhao J, Meng Y, Salomon K, Bai Q, Wei Y, Zhang J, Xu S, Dai Q, Yu R, Yang B, Loland CJ, Zhao Y. Transport and inhibition mechanisms of the human noradrenaline transporter. *Nature* 2024; 632:930–937.
- Huynh PN, Harvey PJ, Gajewiak J, Craik DJ, McIntosh JM. Critical residue properties for potency and selectivity of  $\alpha$ -conotoxin RgIA towards  $\alpha 9\alpha 10$  nicotinic acetylcholine receptors. *Biochem Pharmacol* 2020; 181:114124.
- Improgo MR, Soll LG, Tapper AR, Gardner PD. Nicotinic acetylcholine receptors mediate lung cancer growth. *Front Physiol* 2013; 4:251.
- Inserra MC, Kompella SN, Vetter I, Brust A, Daly NL, Cuny H, Craik DJ, Alewood PF, Adams DJ, Lewis RJ. Isolation and characterization of  $\alpha$ -conotoxin LsIA with potent activity at nicotinic acetylcholine receptors. *Biochem Pharmacol* 2013; 86:791–799.
- Jakubowski JA, Keays DA, Kelley WP, Sandall DW, Bingham JP, Livett BG, Gayler KR, Sweedler JV. Determining sequences and post-translational modifications of novel conotoxins in *Conus victoriae* using cDNA sequencing and mass spectrometry. *J Mass Spectrom* 2004; 39:548–557.
- Jimenez EC, Olivera BM, Teichert RW. AlphaC-conotoxin PrXA: a new family of nicotinic acetylcholine receptor antagonists. *Biochemistry* 2007; 46:8717–8724.
- Jimenez EC. Peptide antagonists of NMDA receptors: Structure-activity relationships for potential therapeutics. *Peptides* 2022; 153:170796.
- Jimenez EC. Pharmacological classes of *Conus* peptides targeted to calcium, sodium, and potassium channels. *Protein Pept Lett* 2023; 30:913–929.
- Jin AH, Muttenthaler M, Dutertre S, Himaya SWA, Kaas Q, Craik DJ, Lewis RJ, Alewood PF. Conotoxins: chemistry and biology. *Chem Rev* 2019; 119:11510–11549.
- Kryukova EV, Ivanov IA, Lebedev DS, Spirova EN, Egorova NS, Zouridakis M, Kasheverov IE, Tzartos SJ, Tsetlin VI. Orthosteric and/or allosteric binding of  $\alpha$ -conotoxins to nicotinic acetylcholine receptors and their models. *Mar Drugs* 2018; 16:460.
- Kunda S, Cheriyan J, Hur M, Balsara RD, Castellino FJ. Antagonist properties of *Conus parvus* peptides on N-methyl-D-aspartate receptors and their effects on CREB signaling. *PLoS One* 2013; 8:e81405.
- Lanoie A, Ferková S, Caron-Duval É, Dallagnol JCC, Diarra S, Murza A, Tremblay A, Thérault L, Breault É, Ranjbaran A, Landry L, Côté J, Longpré JM, Boudreault PL, Chatenet D, Sarret P. Structure-activity relationships of conulakin-G: Design, synthesis, and characterization of Thr<sup>10</sup> analogs for pain modulation. *Biomed Pharmacother* 2025; 192:118664.
- Lebbe EKM, Peigneur S, Maiti M, Mille BG, Devi P, Ravichandran S, Lescrinier E, Waelkens E, D'souza L, Herdewijn P, Tytgat J. Discovery of a new subclass of  $\alpha$ -conotoxins in the venom of *Conus australis*. *Toxicon* 2014; 91:145–154.
- Lewis R. Discovery and development of the  $\chi$ -conopeptide class of analgesic peptides. *Toxicon* 2012; 59:524–528.
- Li X, Hu Y, Wu Y, Huang Y, Yu S, Ding Q, Zhangsun D, Luo S. Anti-hypersensitive effect of intramuscular administration of  $\alpha$ O-conotoxin GeXIVA[1,2] and GeXIVA[1,4] in rats of neuropathic pain. *Prog Neuropsychopharmacol. Biol Psychiatry* 2016; 66:112–119.
- Li R, Li X, Jiang J, Tian Y, Liu D, Zhangsun D, Fu Y, Wu Y, Luo S. Interaction of rat  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor with  $\alpha$ -conotoxin RgIA and Vc1.1: Insights from docking, molecular

- dynamics and binding free energy contributions. *Mol Graph Model* 2019; 92:55–64.
- Li Z, Han X, Hong X, Li X, Gao J, Zhang H, Zheng A. Lyophilization serves as an effective strategy for drug development of the  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor antagonist  $\alpha$ -conotoxin GeXIVA[1,2]. *Mar Drugs* 2021; 19:121.
- Lim S, Woo J, Pak S, Paik J, Hong GS, Wi JH, Lee S, Fenollar-Ferrer C, Han K, Shin YK, Oh U. Molecular basis for a pore block of Tentonin 3 expressed in HEK293 cells by a conopeptide, NMB-1. *Br J Pharmacol* 2026;183:1845–1859.
- Lin J, Chen S, Butt UD, Yan M, Wu B. A comprehensive review on ziconotide. *Heliyon* 2024; 10:e31105.
- Liu Y, Qian J, Sun Z, Zhangsun D, Luo S. Cervical cancer correlates with the differential expression of nicotinic acetylcholine receptors and reveals therapeutic targets. *Mar Drugs* 2019; 17:256.
- Liu Z, Yu Z, Yu S, Zhu C, Dong M, Mao W, Hu J, Prorok M, Su R, Dai Q. A conantokin peptide con-T[M8Q] inhibits morphine dependence with high potency and low side effects. *Mar Drugs* 2021; 19:44.
- Loughnan M, Nicke A, Jones A, Schroeder CI, Nevin ST, Adams DJ, Alewood PF, Lewis RJ. Identification of a novel class of nicotinic receptor antagonists: dimeric conotoxins VxXIIA, VxXIIB, and VxXIIC from *Conus vexillum*. *J Biol Chem* 2006; 281:24745–24755.
- Luo S, Kulak JM, Cartier GE, Jacobsen RB, Yoshikami D, Olivera BM, McIntosh JM.  $\alpha$ -conotoxin AuIB selectively blocks  $\alpha 3\beta 4$  nicotinic acetylcholine receptors and nicotine-evoked norepinephrine release. *J Neurosci* 1998; 18:8571–8579.
- Luo S, Zhangsun D, Zhu X, Wu Y, Hu Y, Christensen S, Harvey PJ, Akcan M, Craik DJ, McIntosh JM. Characterization of a novel  $\alpha$ -conotoxin TxID from *Conus textile* that potently blocks rat  $\alpha 3\beta 4$  nicotinic acetylcholine receptors. *J Med Chem* 2013a; 56:9655–9663.
- Luo S, Christensen S, Zhangsun D, Wu Y, Hu Y, Zhu X, Chhabra S, Norton RS, McIntosh JM. A novel inhibitor of  $\alpha 9\alpha 10$  nicotinic acetylcholine receptors from *Conus vexillum* delineates a new conotoxin superfamily. *PLoS One* 2013b; 8:e54648.
- Luo S, Zhangsun D, Harvey PJ, Kaas Q, Wu Y, Zhu X, Hu Y, Li X, Tsetlin VI, Christensen S, Romero HK, McIntyre M, Dowell C, Baxter JC, Elmslie KS, Craik DJ, McIntosh JM. Cloning, synthesis, and characterization of  $\alpha$ O-conotoxin GeXIVA, a potent  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor antagonist. *Proc Natl Acad Sci U. S. A.* 2015; 112:E4026–35.
- Manda P, Kushwaha AS, Kundu S, Shivakumar HN, Jo SB, Murthy SN. Delivery of ziconotide to cerebrospinal fluid via intranasal pathway for the treatment of chronic pain. *J Control Release* 2016; 224: 69–76.
- Martin L, Ibrahim M, Gomez K, Yu J, Cai S, Chew IA, Bellampalli SS, Moutal A, Largent-Milnes T, Porreca F, Khanna R, Olivera BM, Patwardhan A. Conotoxin contulakin-G engages a neurotensin receptor 2/R-type calcium channel (Cav2.3) pathway to mediate spinal antinociception. *Pain* 2022; 163:1751–1762.
- Martin LF, Almuslim M, Ismail KA, Ibrahim MM, Moutal A, Heng K, Stratton HJ, Price TJ, Vanderah TW, Olivera BM, Khanna R, Patwardhan A. The conotoxin Contulakin-G reverses hypersensitivity observed in rodent models of cancer-induced bone pain without inducing tolerance or motor disturbance. *Pain* 2025; 166:376–387.
- Matta JA, Gu S, Davini WB, Bredt DS. Nicotinic acetylcholine receptor redux: Discovery of accessories opens therapeutic vistas. *Science* 2021; 373:eabg6539.
- McIntosh JM, Olivera BM, Cruz LJ, Gray WR. Gamma-carboxyglutamate in a neuroactive toxin. *J Biol Chem* 1984; 259:14343–14346.
- McIntosh JM, Yoshikami D, Mahe E, Nielsen DB, Rivier JE, Gray WR, Olivera BM. A nicotinic acetylcholine receptor ligand of unique specificity,  $\alpha$ -conotoxin ImI. *J Biol Chem* 1994; 269:16733–16739.
- McIntosh JM, Corpuz GO, Layer RT, Garrett JE, Wagstaff JD, Bulaj G, Vyazovkina A, Yoshikami D, Cruz LJ, Olivera BM. Isolation and characterization of a novel *Conus* peptide with apparent antinociceptive activity. *J Biol Chem* 2000; 275:32391–32397.
- Mei D, Lin Z, Fu J, He B, Gao W, Ma I, Dai W, Zhang H, Wang X, Wang J, Zhang X, Lu W, Zhou D, Zhang Q. The use of  $\alpha$ -conotoxin ImI to actualize the targeted delivery of paclitaxel micelles to  $\alpha 7$  nAChR-overexpressing breast cancer. *Biomaterials* 2015; 42:52–65.
- Mei D, Zhao L, Chen B, Zhang X, Wang X, Yu Z, Ni X, Zhang Q.  $\alpha$ -Conotoxin ImI-modified polymeric micelles as potential nanocarriers for targeted docetaxel delivery to  $\alpha 7$ -nAChR overexpressed non-small cell lung cancer. *Drug Deliv* 2018; 25:493–503.
- Menting JG, Gajewiak J, MacRaid CA, Chou DH, Disotuar MM, Smith NA, Miller C, Erchevgy J, Rivier JE, Olivera BM, Forbes BE, Smith BJ, Norton RS, Safavi-Hemami H, Lawrence MC. A minimized human insulin-receptor-binding motif revealed in a *Conus geographus* venom insulin. *Nat Struct Mol Biol* 2016; 23:916–920.
- Millar NS, Gotti C. Diversity of vertebrate nicotinic acetylcholine receptors. *Neuropharmacology* 2009; 56:237–246.
- Mucchiello V, Crespi A, Fasoli F, Clementi F, Gotti C. Neuronal acetylcholine nicotinic receptors as new targets for lung cancer treatment. *Curr Pharm Des* 2016; 22:2160–2169.
- Neves JLB, Urcino C, Chase K, Dowell C, Hone AJ, Morgenstern D, Chua VM, Ramiro IBL, Imperial JS, Leavitt LS, Phan J, Fisher FA, Watkins M, Raghuraman S, Tun JO, Ueberheide BM, McIntosh JM, Vasconcelos V, Olivera BM, Gajewiak J. Using constellation pharmacology to characterize a novel  $\alpha$ -conotoxin from *Conus ateralbus*. *Mar Drugs* 2024; 22:118.
- Ning J, Li R, Ren J, Zhangsun D, Zhu X, Wu Y, Luo S. Alanine-scanning mutagenesis of  $\alpha$ -conotoxin GI reveals the residues crucial for activity at the muscle acetylcholine receptor. *Mar Drugs* 2018; 16:507.
- Ning H, Huang B, Tae HS, Liu Z, Yu S, Li L, Zhang L, Adams DJ, Guo C, Dai Q.  $\alpha$ -Conotoxin Bt1.8 from *Conus betulinus* selectively inhibits  $\alpha 6/\alpha 3\beta 2\beta 3$  and  $\alpha 3\beta 2$  nicotinic acetylcholine receptor subtypes. *J Neurochem* 2021; 159: 90–100.
- Okkerse P, Hay JL, Sitsen E, Dahan A, Klaassen E, Houghton W, Groeneveld GJ. Pharmacokinetics and pharmacodynamics of intrathecally administered Xen2174, a synthetic conopeptide with norepinephrine reuptake inhibitor and analgesic properties. *Br J Clin Pharmacol* 2017; 83:751–763.

- Olivera BM, Cruz LJ, de Santos V, LeCheminant GW, Griffin D, Zeikus R, McIntosh JM, Galyean R, Varga J, Gray WR, et al. Neuronal calcium channel antagonists. Discrimination between calcium channel subtypes using omega-conotoxin from *Conus magus* venom. *Biochemistry* 1987; 26:2086–2090.
- Olivera BM, Corneli PS, Watkins M, Fedosov A. Biodiversity of cone snails and other venomous marine gastropods: evolutionary success through neuropharmacology. *Annu Rev Anim Biosci* 2014; 2:487–513.
- Olivera BM, Seger J, Horvath MP, Fedosov AE. Prey-capture strategies of fish-hunting cone snails: Behavior, neurobiology and evolution. *Brain Behav Evol* 2015; 86:58–74.
- Osipov AV, Terpinskaya TI, Yanchanka T, Balashevich T, Zhmak MN, Tsetlin VI, Utkin YN.  $\alpha$ -Conotoxins enhance both the in vivo suppression of Ehrlich carcinoma growth and in vitro reduction in cell viability elicited by cyclooxygenase and lipoxigenase inhibitors. *Mar Drugs* 2020; 18:193.
- Ouyang Q, Zhou J, Yang W, Cui H, Xu M, Yi L. Oncogenic role of neurotensin and neurotensin receptors in various cancers. *Clin Exp Pharmacol Physiol* 2017; 44:841–846.
- Padilla A, Keating P, Hartmann JX, Mari F. Effects of  $\alpha$ -conotoxin ImI on TNF- $\alpha$ , IL-8 and TGF- $\beta$  expression by human macrophage-like cells derived from THP-1 pre-monocytic leukemic cells. *Sci Rep* 2017; 7:12742.
- Peigneur S, Devi P, Seldeslachts A, Ravichandran S, Quinton L, Tytgat J. Structure-function elucidation of a new  $\alpha$ -conotoxin, Milla, from *Conus milneedwardsi*. *Mar Drugs* 2019; 17:535.
- Peng C, Tang S, Pi C, Liu J, Wang F, Wang L, Zhou W, Xu A. Discovery of a novel class of conotoxin from *Conus litteratus*, It14a, with a unique cysteine pattern. *Peptides* 2006; 27:2174–2181.
- Peraire M, Gimeno-Vergara R, Pick-Martin J, Boscá M, Echeverria I. Ziconotide and psychosis: from a case report to a scoping review. *Front Mol Neurosci* 2024; 17:1412855.
- Platt RJ, Curtice KJ, Twede VD, Watkins M, Gruszczynski P, Bulaj G, Horvath MP, Olivera BM. From molecular phylogeny towards differentiating pharmacology for NMDA receptor subtypes. *Toxicon* 2014; 81:67–79.
- Qi P, He Q, Zhang J, Lian Y, Xie T, Dong J, Zhangsun D, Wu Y, Luo S. Enhancing stability and albumin binding efficiency of  $\alpha$ -conotoxin GI through fatty acid modification. *Biochemistry* 2023; 62:3373–3382.
- Qian J, Liu YQ, Sun ZH, Zhangsun DT, Luo SL. Identification of nicotinic acetylcholine receptor subunits in different lung cancer cell lines and the inhibitory effect of alpha-conotoxin TxID on lung cancer cell growth. *Eur J Pharmacol* 2019; 865:172674.
- Ragnarsson L, Wang CI, Andersson A, Fajarningsih D, Monks T, Brust A, Rosengren KJ, Lewis RJ. Conopeptide p-TIA defines a new allosteric site on the extracellular surface of the  $\alpha$ 1B-adrenoceptor. *J Biol Chem* 2013; 288:1814–1827.
- Ramiro IBL, Bjørn-Yoshimoto WE, Imperial JS, Gajewiak J, Salcedo PF, Watkins M, Taylor D, Resager W, Ueberheide B, Bräuner-Osborne H, Whitby FG, Hill CP, Martin LF, Patwardhan A, Concepcion GP, Olivera BM, Safavi-Hemami H. Somatostatin venom analogs evolved by fish-hunting cone snails: From prey capture behavior to identifying drug leads. *Sci Adv* 2022; 8:eabk1410.
- Ramones CMV, Taguchi RS, Gamba EME, Johann E Isagan AE, Watkins M, Chicote MO, Velarde MC, Villaraza AJL, Yu ET, Olivera BM, Concepcion GP, Lluisma AO. Variable peptide processing of a *Conus* (Asprella) *neocostatus*  $\alpha$ -conotoxin generates bioactive toxiforms that are potent against distinct nicotinic acetylcholine receptor subtypes. *Biochem Pharmacol* 2025; 233:116781.
- Ren Z, Wang L, Qin M, You Y, Pan W, Zhou L, Sun D, Xu A. Pharmacological characterization of conotoxin It14a as a potent non-addictive analgesic. *Toxicon* 2015a; 96:57–67.
- Ren B, Zhou Z, Liu Z, Li B, Ou J, Dai Q. Con-T[M8Q] potently attenuates the expression and development of morphine tolerance in mice. *Neurosci Lett* 2015b; 597:38–42.
- Rodriguez-Ruiz XC, Aguilar MB, Ortiz-Arellano MA, Safavi-Hemami H, López-Vera E. A novel dimeric conotoxin, FrXXXA, from the vermivorous cone snail *Conus fergusonii*, of the Eastern Pacific, inhibits nicotinic acetylcholine receptors, *Toxins* (Basel) 2022; 14:510.
- Romero HK, Christensen SB, Di Cesare Mannelli L, Gajewiak J, Ramachandra R, Elmslie KS, Vetter DE, Ghelardini C, Iadonato SP, Mercado JL, Olivera BM, McIntosh JM. Inhibition of  $\alpha$ 9 $\alpha$ 10 nicotinic acetylcholine receptors prevents chemotherapy-induced neuropathic pain. *Proc Natl Acad Sci U S A* 2017; 114:E1825–e1832.
- Rubiu E, Restelli F, Nazzi V, Mazzapicchi E, Bonomo G, Veiceschi P, Alfiero T, Agresta G, Locatelli D, Dario A. A benefit/risk assessment of intrathecal ziconotide in chronic pain: A narrative review *J Clin Med* 2024; 13:1644.
- Rybin MJ, O'Brien H, Ramiro IBL, Azam L, McIntosh JM, Olivera BM, Safavi-Hemami H, Yoshikami D.  $\alpha$ M-Conotoxin MIIII blocks nicotinic acetylcholine receptors at neuromuscular junctions of frog and fish, *Toxins* (Basel) 2020; 12:197.
- Safavi-Hemami H, Brogan SE, Olivera BM. Pain therapeutics from cone snail venoms: from ziconotide to novel non-opioid pathways. *J Proteomics* 2018; 190:12–20.
- Sandall DW, Satkunanathan N, Keays DA, Polidano MA, Liping X, Pham V, Down JG, Khalil Z, Livett BG, Gayler KR. A novel alpha-conotoxin identified by gene sequencing is active in suppressing the vascular response to selective stimulation of sensory nerves in vivo. *Biochemistry* 2003; 42:6904–6911.
- Sang CN, Barnabe KJ, Kern SE. Phase IA Clinical trial evaluating the tolerability, pharmacokinetics, and analgesic efficacy of an intrathecally administered neurotensin A analogue in central neuropathic pain following spinal cord injury. *Clin Pharmacol Drug Dev* 2016; 5:250–258.
- Sharpe IA, Gehrmann J, Loughnan ML, Thomas L, Adams DA, Atkins A, Palant E, Craik DJ, Adams DJ, Alewood PF, Lewis RJ. Two new classes of conopeptides inhibit the  $\alpha$ 1-adrenoceptor and noradrenaline transporter. *Nat Neurosci* 2001; 4:902–907.
- Sheng Z, Liang Z, Geiger JH, Prorok M, Castellano FJ. The selectivity of conantokin-G for ion channel inhibition of NR2B subunit-containing NMDA receptors is regulated by amino acid residues in the S2 region of NR2B, *Neuropharmacology* 2009; 57:127–136.
- Sun Z, Bao J, Zhangsun M, Dong S, Zhangsun D, Luo S.  $\alpha$ O-Conotoxin GeXIVA inhibits the growth of breast cancer cells via interaction with  $\alpha$ 9 nicotine acetylcholine receptors. *Mar Drugs* 2020; 18:195.

- Sun X, Hu J, Ren M, Chang H, Zhangsun D, Zhang B, Dong S. Stapling cysteine[2,4] disulfide bond of  $\alpha$ -conotoxin LsIA and its potential in target delivery. *Mar Drugs* 2024; 22:314.
- Tae H, Gao B, Jin A, Alewood PF, Adams DJ. Globular and ribbon isomers of *Conus geographus*  $\alpha$ -conotoxins antagonize human nicotinic acetylcholine receptors. *Biochem Pharmacol* 2021; 190:114638.
- Tae HS, Adams DJ. Nicotinic acetylcholine receptor subtype expression, function, and pharmacology: therapeutic potential of  $\alpha$ -conotoxins. *Pharmacol Res* 2023; 191:106747.
- Tae HS, Hung A, Clark RJ, Adams DJ. Molecular determinants of the selectivity and potency of  $\alpha$ -conotoxin Vc1.1 for human nicotinic acetylcholine receptors. *J Biol Chem* 2025; 301:108017.
- Taiwe GS, Montnach J, Nicolas S, De Waard S, Fiore E, Peyrin E, El-aziz TMA, Amar M, Molgó J, Ronjat M, Servent D, Ravelet C, De Waard M. Aptamer efficacies for in vitro and in vivo modulation of  $\alpha$ C-conotoxin PrXA pharmacology. *Molecules* 2019; 24:229.
- Tang H, Liu H, Gao Y, Chen R, Dong M, Ling S, Wang R, Wang S. Detection of  $\alpha$ B-conotoxin VxXXXIVA ( $\alpha$ B-CTX) by ic-ELISA based on an epitope-specific monoclonal antibody. *Toxins (Basel)* 2022; 14:166.
- Tao Y, Sun Y, Jiang X, Tao J, Zhang Y. The role of alpha-7 nicotinic acetylcholine receptors in pain: Potential therapeutic implications. *Curr Neuroparmacol* 2025; 23:129–144.
- Teichert RW, Jimenez EC, Twede V, Watkins M, Hollmann M, Bulaj G, Olivera BM. Novel conantokins from *Conus parvus* venom are specific antagonists of N-methyl-D-aspartate receptors. *J Biol Chem* 2007; 282:36905–36913.
- van Hout M, Valdes A, Christensen SB, Tran PT, Watkins M, Gajewiak J, Jensen AA, Olivera BM, McIntosh JM.  $\alpha$ -Conotoxin VnIB from *Conus ventricosus* is a potent and selective antagonist of  $\alpha 6\beta 4^*$  nicotinic acetylcholine receptors. *Neuropharmacology* 2019; 157:107691.
- Vinclair M, Wittenauer S, Parker R, Ellison M, Olivera BM, McIntosh JM. Molecular mechanism for analgesia involving specific antagonism of  $\alpha 9\alpha 10$  nicotinic acetylcholine receptors. *Proc Natl Acad Sci U S A*. 2006; 103:17880–17884.
- Wan J, Huang JX, Vetter I, Mobli M, Lawson J, Tae HS, Abraham N, Paul B, Cooper MA, Adams DJ, Lewis RJ, Alewood PF.  $\alpha$ -Conotoxin dendrimers have enhanced potency and selectivity for homomeric nicotinic acetylcholine receptors. *J Am Chem Soc* 2015; 137:3209–3212.
- Wan J, Brust A, Bhola RF, Jha P, Mobli M, Lewis RJ, Christie MJ, Alewood PF. Inhibition of the norepinephrine transporter by  $\chi$ -conotoxin dendrimers. *J Pept Sci* 2016; 22:280–289.
- Wang H, Li X, Zhangsun D, Yu G, Su R, Luo S. The  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor antagonist  $\alpha$ O-conotoxin GeXIVA[1,2] alleviates and reverses chemotherapy-induced neuropathic pain. *Mar Drugs* 2019; 17:265.
- Wang S, Bartels P, Zhao C, Yousuf A, Liu Z, Yu S, Bony AR, Ma X, Dai Q, Sun T, Liu N, Yang M, Yu R, Du W, Adams DJ, Dai Q. A 4/8 subtype  $\alpha$ -conotoxin vt1.27 inhibits n-type calcium channels with potent anti-allodynic effect. *Front Pharmacol* 2022a; 13:881732.
- Wang H, Li Y, Yang M, Zhou M. Synthesis and characterization of  $\alpha$ M-conotoxin SIID, a reversible human  $\alpha 7$  nicotinic acetylcholine receptor antagonist. *Toxicon* 2022b; 210:141–147.
- Wang H, Li X, Qiao Y, Wang M, Wang W, McIntosh JM, Zhangsun D, Luo S.  $\alpha$ O-Conotoxin GeXIVA[1,2] reduced neuropathic pain and changed gene expression in chronic oxaliplatin-induced neuropathy mice model. *Mar Drugs* 2024; 22:49.
- Wu Y, Zhangsun D, Zhu X, Kaas Q, Zhangsun M, Harvey PJ, Craik DJ, McIntosh JM, Luo S.  $\alpha$ -Conotoxin [S9A]TxID potently discriminates between  $\alpha 3\beta 4$  and  $\alpha 6/\alpha 3\beta 4$  nicotinic acetylcholine receptors. *J Med Chem* 2017a; 60:5826–5833.
- Wu X, Huang YH, Kaas Q, Harvey PJ, Wang CK, Tae HS, Adams DJ, Craik DJ. Backbone cyclization of analgesic conotoxin GeXIVA facilitates direct folding of the ribbon isomer. *J Biol Chem* 2017b; 292:17101–17112.
- Wu X, Tae HS, Huang YH, Adams DJ, Craik DJ, Kaas Q. Stoichiometry dependent inhibition of rat  $\alpha 3\beta 4$  nicotinic acetylcholine receptor by the ribbon isomer of  $\alpha$ -conotoxin AuIB. *Biochem Pharmacol* 2018; 155:288–297.
- Wu Y, Qiang Y, Zhang G, Zhou M. Acute toxicity and micronucleus test of conotoxin It14a in mice. *Basic Clin Pharmacol Toxicol* 2021; 129:52–60.
- Wu X, Hone AJ, Huang YH, Clark RJ, McIntosh JM, Kaas Q, Craik DJ. Computational design of  $\alpha$ -conotoxins to target specific nicotinic acetylcholine receptor subtypes. *Chemistry* 2024; 30:e202302909.
- Xanthopoulos A, Daskalopoulou I, Frountzi S, Papadimitriou E. A systematic review on the role of adrenergic receptors in angiogenesis regulation in health and disease. *Int J Transl Med* 2021; 1:353–365.
- Xiong X, Menting JG, Disotuar MM, Smith NA, Delaine CA, Ghabash G, Agrawal R, Wang X, He X, Fisher SJ, MacRaid CA, Norton RS, Gajewiak J, Forbes BE, Smith BJ, Safavi-Hemami H, Olivera B, Lawrence MC, Chou DH. A structurally minimized yet fully active insulin based on cone snail venom insulin principles. *Nat Struct Mol Biol* 2020; 27:615–624.
- Xu S, Zhang T, Kompella SN, Yan M, Lu A, Wang Y, Shao X, Chi CX, Adams DJ, Ding J, Wang C. Conotoxin  $\alpha$ D-GeXXA utilizes a novel strategy to antagonize nicotinic acetylcholine receptors. *Sci Rep* 2015; 5:14261.
- Xu X, Liang J, Zhang Z, Jiang T, Yu RM. Blockade of human  $\alpha 7$  nicotinic acetylcholine receptor by  $\alpha$ -conotoxin Iml dendrimer: Insight from computational simulations. *Mar Drugs* 2019; 17:303.
- Xu P, Kaas Q, Wu Y, Zhu X, Li X, Harvey PJ, Zhangsun D, Craik DJ, Luo S. Structure and activity studies of disulfide-deficient analogues of  $\alpha$ O-conotoxin GeXIVA. *J Med Chem* 2020; 63:1564–1575.
- Xu P, Zhang P, Zhu X, Wu Y, Harvey PJ, Kaas Q, Zhangsun D, Craik DJ, Luo S. Structure-activity relationships of alanine scan mutants  $\alpha$ O-conotoxins GeXIVA[1,2] and GeXIVA[1,4]. *J Med Chem* 2023; 66:10092–10107.
- Yamamoto H, Hagino Y, Kasai S, Ikeda K. Specific roles of NMDA receptor subunits in mental disorder. *Curr Mol Med* 2015; 15:193–205.
- Yang L, Tae HS, Fan Z, Shao X, Xu S, Zhao S, Adams DJ, Wang C. A novel lid-covering peptide inhibitor of nicotinic

acetylcholine receptors derived from  $\alpha$ D-conotoxin GeXXA. *Mar Drugs* 2017; 15:164.

Yu R, Kompella SN, Adams DJ, Craik DJ, Kaas Q. Determination of the  $\alpha$ -conotoxin Vc1.1 binding site on the  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor. *J Med Chem* 2013; 56:3557–3567.

Yu J, Zhu X, Harvey PJ, Kaas Q, Zhangsun D, Craik DJ, Luo S. Single amino acid substitution in  $\alpha$ -conotoxin Tx1D reveals a specific  $\alpha 3\beta 4$  nicotinic acetylcholine receptor antagonist. *J Med Chem* 2018a; 61:9256–9265.

Yu S, Wu Y, Xu P, Wang S, Zhangsun D, Luo S. Effects of serum, enzyme, thiol, and forced degradation on the stabilities of  $\alpha$ O-Conotoxin GeXIVA[1,2] and GeXIVA [1,4]. *Chem Biol Drug Des* 2018b; 91:1030–1041.

Zhang Y, Tae HS, Adams DJ, Durek T, Craik DJ. Cyclization of the analgesic  $\alpha$ -conotoxin Vc1.1 with a non-natural linker: Effects on structure, stability, and bioactivity. *J Pept Sci* 2025; 31:e70017.

Zhangsun D, Zhu X, Kaas Q, Wu Y, Craik DJ, McIntosh JM, Luo S.  $\alpha$ O-Conotoxin GeXIVA disulfide bond isomers exhibit differential sensitivity for various nicotinic acetylcholine receptors but retain potency and selectivity for the human  $\alpha 9\alpha 10$  subtype. *Neuropharmacology* 2017; 127:243–252.

Ziegman R, Brust A, Jha P, Cardoso FC, Lewis RJ, Alewood PF. 'Messy' processing of  $\chi$ -conotoxin MrIA generates homologues with reduced hNET potency. *Mar Drugs* 2019; 17:165.