International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 3, Suppl 2, 2011

Review Article

CONOTOXINS: A POTENTIAL NATURAL THERAPEUTIC FOR PAIN RELIEF

BABY JOSEPH*, SHEEJA S RAJAN, JEEVITHA.M.V, AJISHA.S.U, JINI.D,

Interdiscipilinary Research Center, Malankara Catholic College, Mariagiri, Kaliakkavilai-629 153, Tamil Nadu India

Received: 13 Sep 2010, Revised and Accepted: 16 Oct 2010

ABSTRACT

The venom of the Conus species is composed of conotoxins, which are neurotoxins of low molecular weight. Their action is extremely fast, which is compatible with the slowness of the snail in its environment and the consequent difficulty involved in capturing the poisoned prey. Conotoxins produced by cone snail contain a tremendously diverse natural pharmacology. Conotoxins contains hundreds of different compounds, and its exact composition varies widely from one species of cone snail to another. Some cone snail venoms also contain a pain-reducing toxin, which the snail uses to pacify the victim before immobilising and then killing it. Conotoxins produced by certain species of cone snails shows much promise for providing a non-addictive pain reliever 1000 times as powerful as, and possibly a replacement for, morphine. Many peptides such as AVC1 isolated from Australian species *Conus victoriae* has proved very effective in treating post surgical and neuropathic pain, even accelerating recovery from nerve injury. The pain killer "Ziconotide" derived from conotoxins was approved by the U.S. Food and Drug Administration in December 2004 under the name "Prialt". Other drugs are in clinical and preclinical trials, such as compounds of the toxin that may be used in the treatment of Alzheimer's disease, Parkinson's disease and epilepsy.

Keywords: Conotoxin, Ziconotide, Pharmacology, Conus, Neurotoxins

INTRODUCTION

Cones are a type of sea snails that belong to Conus, which is a large genus of small to large, predatory sea snails and marine gastropod molluscs. Cone snails are mostly tropical in distribution. There are over 500 different species of cone snails. They are all venomous to one degree or another. These unique marine organisms deliver their complex venom through a specialized radular tooth that serves as both a harpoon and disposable hypodermic needle. The venom is an extremely complex concoction of 20-200 components composed mostly of modified peptides (conopeptides) [1]. Conopeptides elicit a wide range of strong neurophysiological responses. The larger species hunt fish using harpoon-like teeth and a poison gland. Venom produced by cone snails is called as conotoxins[2].Conus species have shells that are shaped like geometric cones. Many species have colorful patterning on the shell surface. Live cone snails are handled with care or not handled at all, as they are capable of "stinging" humans with unpleasant results. The sting of small cones is no worse than a bee sting, but the sting of a few of the larger species of tropical cone snails can be serious, and has even occasionally been fatal to human beings[3].

Most commercial drugs in the developed world are based on natural products, reflecting the complex arsenals of pharmacologically active compounds that organisms use to interact with each other. Research into the venoms of the predatory marine cone snails validates the great degree of pharmaceutical interest that rests on natural products[3]. Cone venom shows great promise as a source of new, medically important substances. The venom of some cone snails, such as the Magician cone, *Conus magus*, shows much promise for providing a non-addictive pain reliever 1000 times as powerful as, and possibly a replacement for, morphine[4]. The small, disulfide-rich peptides that enrich *Conus* venoms (i.e., conotoxins, or conopeptides) have been shown to have considerable therapeutic potential and biomedical research utility, such as AVC1, isolated from the Australian species, the Queen Victoria cone, *Conus victoriae*[5]. This has proved very effective in treating post-surgical and neuropathic pain, even accelerating recovery from nerve injury. The first painkiller Ziconotide derived from cone snail toxins was approved by the U.S. Food and Drug Administration in December 2004 under the name "Prialt". Other drugs are in clinical and preclinical trials, such as compounds of the toxin that may be used in the treatment of Alzheimer's disease, Parkinson's disease, and epilepsy[6]. The concerted analysis of ligands and targets that has defined *Conus* research over the years provides a systematic way to face this pharmacological challenge[7]. The sets of peptides in *Conus* venoms (e.g., the ω-conotoxin family) have been arrayed over evolutionary time to selectively target certain isoforms of receptors and channels e.g., a specific voltage-gated Ca^{2+} channel subtype)[8]. The continuing discovery work on *Conus* venom peptides, now spanning three decades, has resulted in an increasingly sophisticated interdisciplinary discovery platform that should be generally applicable to other biodiverse animal lineages. This platform allows investigators to coordinate the development of a great number of ligands, each with its own selectivity for members of large ion channel or receptor families and similar targets.

Conotoxins

A conotoxin is one of a group of neurotoxic peptides isolated from the venom of the marine cone snail, genus *Conus*. Conotoxins, which are peptides consisting of 10 to 30 amino acid residues, typically have one or more disulfide bonds. Conotoxins have a variety of mechanisms of actions, most of which have not been determined. However it appears that many of these peptides modulate the activity of ion channel[9]. The action of the conotoxins occurs by blockage of muscular and neural receptors. There are two different toxin effects in the venom. The first, the "lightning-strike" effect, causes immediate immobilization of the injected prey through peptides that inhibit voltage-gated sodium channel inactivation, as well as peptides that block potassium channels. Together, this combination results in a massive depolarization of any axons in the immediate vicinity of the venom injection site, causing an effect similar to electrocuting the prey. The second effect is achieved more slowly and involves total inhibition of neuromuscular transmission through conopeptides, which act at sites

remote from the venom injection site, such as neuromuscular junctions[10]. The toxins from the fish hunting cone snails are also more bioactive upon the human system than the mollusk hunting cone snails, with deaths having occurred.

Types of Conotoxins

The chart below indicates the known neurotoxic peptides in the venom, and their actions. It is designed to be delivered directly into the cerebrospinal fluid by means of a small pump.

The number of conotoxins whose activities have been determined so far is five, and they are called α (alpha)-, δ (delta)-, κ (kappa)-, μ (mu)-, and ω (omega) - types.

Alpha-Conotoxins

Sequences of several alpha-conotoxins have been determined with a high degree of homology evident. They contain two cysteine bonds and thirteen to fifteen residues, with the majority coming from fish eating species. Diversity of spacing between toxins from fish eating and non-fish-eating species is evident although the cysteine framework is conserved except for conotoxin-SII.

The alpha conotoxins cause postsynaptic inhibition at the synaptic junction which results in paralysis and death. Alpha-conotoxins of particular interest are SI and SII from *Conus striatus*[11]. SI differs from other acetylcholine receptor ligands by binding differentially to a variety of vertebrate nicotinic acetylcholine receptors, an activity that may be explained by the presence of a proline in place of a positively charged amino acid at residue 9. Alpha-conotoxin SII, meanwhile, is structurally quite distinct in having three disulfide bonds, rather than the usual two, with no net positive charge and a free C-terminus. Not all of the alpha-conotoxins target the neuromuscular junction, neuronal-specific peptides selectively target the alpha7, alpha3beta2 and alpha3beta4 neuronal nicotinic receptor subtypes[12]. In addition to MII, four other neuronal alpha-conotoxins (AuIB, EpI, ImI and PnIB) have been isolated. **Delta-Conotoxins**

Class	Action
α-conotoxins	Competitively block muscle and vertebrate neuronal nicotinic ACh receptors
γ-conotoxins	Activate pacemaker cationic channels
δ-conotoxins	Activate predominantly mollusc sodium channels
κ -conotoxins	Block potassium channels
μ-conotoxins	Block vertebrate muscle/nerve sodium channels
σ-conotoxins	Inhibit 5HT3 channel
ψ-conotoxins	Non-competitively block muscle ACh receptors
ω-conotoxins	Block N-type or P/Q type vertebrate calcium channels
conopressin	Vasopressin agonist
conantokin	Inhibit vertebrate NMDA-glutamate channels

Despite a lack of toxicity towards vertebrates, the delta-conotoxins such as conotoxin SVIA from *Conus striatus* bind with high affinity to voltage-independent sodium channels. In contrast, the venom of the fish hunting species *C. purpurascens* contains a delta-conotoxin (PVIA) termed the 'lock-jaw' peptide, a vertebrate specific delta-conotoxin targeting the voltage-sensitive sodium channels[13]. This sort of toxin is termed an excitotoxin due to its distinct production of rigid, rather than the typical flaccid, paralysis in fish. These results suggest that these toxins may be quite useful due to their ability to bind to the same site on receptors from different phyla yet produce different results[11]. These sorts of results make possible further understanding of the structural criterion determining gating variations in sodium channels.

Kappa-Conotoxins

Kappa-Conotoxin inhibits the potassium channel. Kappa families of conotoxins have a knotting or inhibitor cysteine knot scaffold[14]. The knotting scaffold is a very special disulfide-through-disulfide knot, in which the III-VI disulfide bond crosses the macro cycle formed by two other disulfide bonds (I-IV and II-V) and the interconnecting backbone segments, where I-VI indicates the six cysteine residues starting from the N-terminus. The cysteine arrangements are the same for omega, delta and kappa families[11].

Mu-Conotoxins

The tissue specific sodium channel blocking mu-conotoxins act primarily upon voltage-sensitive sodium channels in muscle, with only minimal binding to neuronal sodium channel[15]. This is unlike tetrodotoxin and saxitoxin which bind to both muscle and nerve sodium channels with equal affinity and independent of voltage. Mu-conotoxins are typified by conotoxin GIII isoforms from *C. geographus* venom[11]. These toxins are similar to tetrodotoxin in the selective blocking of skeletal muscle sodium channels, as well as competitively inhibiting saxitoxin binding to receptor site 1 of voltage-sensitive sodium channels. The 22 amino acid GIII isoforms also inhibit muscle sodium channel activation through tetrodotoxin and saxitoxin-like voltage dependent interaction[16].

Omega-Conotoxins

The omega-conotoxins are all 24-30 amino acids in length with three disulfide bonds. However, these toxins are no less subtle in activity or diverse in sequence than the other classes of conotoxins. The divergent bioactivities make the omega conotoxins quite useful in furthering the understanding of calcium channels of the presynaptic terminal[17]. Because N-type voltage-dependent calcium channels are related to algesia (sensitivity to pain) in the nervous system, ω-conotoxin has an analgesic effect: the effect of ω-conotoxin M VII A is 100 to 1000 times that of morphine[18]. Therefore a synthetic version of ω-conotoxin M VII A has found application as an analgesic drug ziconotide (Prialt). By way of example, omega-conotoxin SVIB from *C. striatus* is bioactively distinct from other omega-conotoxins. It is the only one that is lethal through intracerebral injections of mice, utilizing a high-affinity binding site different from the high-affinity binding sites of other conotoxins such as GVIA from *C. geographus* or MVIIA from *C. magus*. Omega-conotoxin GVIA is also unique in binding to a site distinct from omega-conotoxin MVIIA as well as most omega-agatoxins from the spider *Agelenopsis aperta*[19].

O-superfamily of Conotoxins

This superfamily consists of presynaptic channel blocking peptides: sodium channel blocking mu-O-conotoxins; sodium channel blocking delta-conotoxins; and calcium channel blocking omega-conotoxins[15].

Despite very limited sequence homology with the mu-conotoxins, the sodium channel inhibitor conotoxin GS was reported to be similar to the mu-conotoxins in also acting upon tetrodotoxin and saxitoxin sensitive sites but this data remains to be confirmed. A more recently isolated toxin, mu-PIIIA from *Conus purpurascens*, reversibly blocks a sodium channel in the rat brain which is tetrodotoxin-sensitive but not blocked by mu-conotoxin-GIIIA[11].

'King-Kong' Peptides

The so-called 'king-kong peptides' from the mollusk hunting *C. textile* (*Textile* cone; Cloth-of-Gold cone) are mollusk specific paralytic neurotoxins of high affinity receptors and ion channels. These conotoxins have a disulfide linked molecule similar to that of the omega-conotoxins yet differ in features such as an unusual net negative charge and a high content of hydrophobic residues. Further, one of the toxins (TxIIA) is especially unique with its uneven number of cysteine residues. The king-kong toxins induce membrane depolarization and spontaneous repetitive firing in addition to inducing a marked prolongation of the sodium dependent action potential duration. TxVIA mediates sodium channel inactivation through selective action upon mollusk sodium channels at a binding site distinct from that acted upon by other conotoxins[9].

Currently, conotoxins are a valuable tool of scientific research, due to the intense pharmacological activity presented by the peptides. One of the drugs in clinical tests is ziconotide, which is a peptide that blocks the neuronal calcium canals with excellent effect in the treatment of chronic and severe painful processes[20].The conotoxins

may ultimately prove to be some of the most interesting and useful peptidic toxins. Subtle variations in the sequences of these natural wonders demonstrate the profound potential for dramatic differences in specificity and potency that can occur. The small size, multiple disulfide bonding and ingenious variations make conotoxins a tremendous natural pharmacological library.

Conopeptides

Marine snails have the prettiest shells on their backs and the deadliest poison in their sting. The potent armamentarium of the *Conus* snails includes conotoxins, a fascinating series of peptides. These peptides, known as conopeptides, have been optimized through evolution to target specific ion channels and receptors with very high affinities and selectivities[21]. The peptides possess pharmacological properties that make them valuable tools for pain therapy and certain disorders of the central nervous system. Thousands of different conopeptides have evolved in these predatory snails so that their venom very rapidly inactivates the nerves of their prey. The potential utility of conopeptides in pain (one is already in clinical use) stems from their high potency to very specifically block individual types of excitability molecules on nerve cells, some of which give rise to pain states.

Structure of Conopeptides

The peptides are merely 10–40 residues and therefore smaller than most known protein toxins. These linear peptides tend to be girded by several disulphide bonds making them structurally rigid. They also have a large number of post-translational modifications, some of which are unusual. This has given rise to about 50,000 sequences in the estimated 500 species[9]. This cocktail of peptides targets a diverse range of voltage-sensitive sodium, calcium, and potassium channels and *N*-methyl-d-aspartate, glutamate, vasopressin, serotonin, and acetylcholine receptors, which leads to an immediate and efficient immobilisation of the prey. The conotoxins present in the venom have been divided into a number of major classes based on their pharmacological activity and cysteine frameworks (Table 1). Their high potency and specificity, and convenient chemical synthesis, also make the conotoxins attractive leads in drug design programs. In addition to the conotoxins being among the smallest bioactive peptides, they are unusual in containing a high density of cysteine residues and posttranslation modifications, including hydroxylation, carboxylation, amidation, sulphation, and bromination. These features often complicate their chemical characterisation and occasionally their chemical synthesis. All major classes of conotoxins have been identified through initial in vitro or in vivo functional assays[22].

Table 1: Six Major Classes of conopeptides and Their Disulfide Connectivity

γ-conopeptides (2 loop framework peptides that inhibit nicotinic acetylcholine receptors)		
GI	E C C N – P A C G R H Y S - - C*`	
GIA	E C C N – P A C G R H Y S - - C G K*`	
GII	E C C H – P A C G K H F S - - C*	
MI	G R C C H – P A C G K N Y S - - C*	C C..C...C
SI	I C C N – P A C G P K Y S - - C*	
SIA	Y C C H – P A C G K N F D - - C*	
SII	G C C C N O A C G P B Y G- - C G T S C S	
PnIA	G C C S L P P C A A N N P D Y C*	
PnIB	G C C S L P P C A L S N P D Y C*	
ImI	G C C S D P R C A W R - - - -C*	
EI	R D O C C Y H P T C N M S N P Q I C*	
MII	G C C S N P V C H L E H S N L C*	
EpI	G C C S D P R C N M N N P D Y (SO_4) C*	
AuIB	G C C S Y P P C F A T N P D – C *	
μ-conopeptides (3 loop framework that block sodium channels)		
GIIIA	R D C C T O O K K C K D R Q C K O Q R C C A*	
GIIIB	R D C C T O O R K C K D R R C K O M K C C A*	C C.C...C.C C
GIIIC	R D C C T O O K K C K D R R C K O L K C C A*	
PIIIA	R L C C G F O K S C R S R Q C K O H R C C*	
ω-conopeptides (4 loop framework peptides that block sodium channels)		
GVIA	C K S O G S S C S O T S Y N C C – R S C N O Y T K R C Y	
GVIB	C K S O G S S C S O T S Y N C C – R S C N O Y T K R C Y G*	
GVIC	C K S O G S S C S O T S Y N C C – R S C N O Y T K R C*	
SVIA	C R S S G S O C G V T S I – C C G R – C – – Y R G K C T*	
SVIB	C K L K G Q S C R K T S Y D C C S G S C G R S – G K C*	
GVIIA	C K S O G T O C S R G M R D C C – – S C L L Y S N K C R R Y*	
GVIIB	C K S O G T O C S R G M R D C C T – S C L S Y S N K C R R Y*	

MVIIA	C K G K G A K C S R L M Y D C C T G S C R S – – G K C*	C . . . C . . C C . C . . C
MVIIB	C K G K G A S C H R T S Y D C C T G S C N R – – G K C*	
MVIIC	C K G K G A P C R K T M Y D C C S G S C G R R – G K C*	
MVIID	C Q G R G A S C R K T M Y N C C S G S C N R – – G R C*	
TVIA	C L S O G S S C S O T S Y N C C – R S C N O Y S R K C Y*	
δ-conopeptides		
TxVIA	W C K Q S G E M C N L L D Q N C C D G Y – C I V L V C T	
TxVIB	W C K Q S G E M C N L L D Q N C C D G Y – C I V F V C T	C . . . C . . C C . C . . C
GmVIA	V K P C R K E G Q L C D P I F Q N C C R G W N C – C F S L F C IS F E	
NgVIA	S K C F S O G T F C G I K O G L C C S V R – C F S L F C I S F E	
PVIA	E A C Y A P G T F C G I K O G L C C S E F – C L P G V C F G*	
κ -conopeptides		
PVIIA	C R I O N Q K C F Q H L D D C C S R K C N R F N K C V	C . . . C . . C C . C . . C
conantokins		
Con-G	G E Z Z L Q Z N Q Z L I R Z K S N	
Con-T	G E Z Z Y Q K M L Z N L R Z A E V K K N A	

Amino acid sequences shown with cysteines aligned within such structural frame work.

*Processed carboxyl terminal; O- hydroxyproline residue, Z- carboxyglutamic acid RESIDUE. Letter prefixes indicate conpeptides from the fish hunters C.magus (M), C.geographus (G), C.striatus (S), C.purpurascens (P) and C.ermineus (E); the mollusc hunters, C.textile (Tx), C.episcopatus (Ep), C.gloriamaris (Gm), C.nigropunctatus (Ng), and C.aulicus (Au); and the worm hunter C.imperialis (Im).

Purification of Conopeptides

Conotoxins are multiple disulfide-bonded peptides isolated from marine cone snail venom. These toxins have been classified into several families based on their disulfide pattern and biological properties. The venom of cone snails can be extracted from their venom glands. The peptides from conotoxins can be separated and eluted by reverse phase HPLC. The molecular masses of the peptides can be determined by electrospray ionization mass spectrometry[23]. Further purification and synthesis of peptides can be done by solid phase peptide synthesis method and amino acid analysis can be done by amino acid analyzer followed perhaps by NMR-based structure determination.

Conopeptide and drug production

Synthesis of prialt

Based on their modes of action, it might be expected that conotoxins would be effective analgesics or useful in the treatment of epilepsy, Parkinson's disease, schizophrenia, etc.

In vivo targets of purified conopeptides are identified by behavioural studies as well as binding or other assays. By way of ratification, the putative peptide may be synthesized in the laboratory and its behaviour by HPLC and mass spectrometry compared with that of the isolated peptide. The special features of conotoxins add to the chemist's task in terms of having to (a) identify residues with post-translational modifications and (b) decipher the disulphide connectivity[24].

Prialt is the drug designed from conopeptides. Prialt is a solution for infusion that contains the active substance ziconotide.The active substance in Prialt, ziconotide, is a copy of a natural substance called omega conopeptide, which is found in the venom of a type of sea snail.

Function:

Ziconotide acts by blocking special pores called calcium channels on the surface of the nerve cells that transmit the pain signals. By blocking the flow of calcium into the nerve cells, ziconotide interferes with the transmission of pain signals within the spine. This helps to bring relief from pain .Ziconotide is a synthetic analogue of a 25-amino acid ω-conopeptide, MVIIA, found in the venom of the *Conus magus* marine snail. It is an N-type calcium channel blocker (NCCB). Voltage-sensitive calcium channel (VSCC) conduction plays a major role in the transmission of pain. Ziconitide has been developed for use as an intrathecal analgesic for the treatment of chronic pain in patients requiring IT analgesia. The product is formulated as a solution for infusion (100 μg/ml) and must be administered as a continuous infusion via an intrathecal catheter, using an external or internally implemented mechanical infusion pump.

CONCLUSION

From this review it is clear that the conotoxin play an important role in medical field. Conotoxins is one of the attributes that make them diagnostic tools in the characterization of neural pathway, as therapeutic agents in medicine, and potentially as biodegradable toxic agents in agroveterinary applications. Conotoxin is widely used in the pain relief Since cancer is a multi-factorial condition, treatment has to be go beyond merely removing the tumor. Instead, multi-component treatment must be employed in an attempt to restore order to the disrupted. The conotoxins themselves have been shown to be useful in the treatment of cancer by blocking the N-type calcium channel. The k-conotoxins targeting the potassium channels, have a potential use in the therapy of hypertension, arrhythmia, ashma. Thus promising useful applications in epilepsy, parkinson's disease and stroke. Contulakins, targeting the neurotension receptor may be employed in the therapy of pain and disorders of the central nervous system (CNS). Cone snails may yield more medicine-and terms are looking at the venoms in different.

REFERENCE

1. Newcomb, R., and Miljanich, G. *Handbook Neurotoxicology*1, (2002) 617-651.
2. Pek I., Vašíček Z., Roček Z., Hajn. V. & Mikuláš R. *Základy zoopaleontologie*. Olomouc, (1996)264 pp.
3. Newman, D.J., Cragg, G.M., and Snader, K.M. Natural products as sources of new drugs over the period 1981–2002. J. Nat. Prod. 66, (2003)1022–1037.

4. ANI .Sea snail venom paves way for potent new painkiller. Compassionate health care network.(2007).
5. Olivera, B.M., Imperial, J.S., and Bulaj, G. Cone snails and conotoxins: evolving sophisticated neuropharmacology. In Perspectives in Molecular Toxinology (Menez, A., ed) (2002) pp. 143–158.
6. Louise Yeoman Venomous snails aid medical science BBC. (2006).
7. Hille, B. Ion channels of excitable membranes, Sinauer Associates (2001).
8. Alexander, S.P.H., Mathie, A., and Peters, J.A. Guide to receptors and channels. Br. J. Pharmacol., (2006).
9. Terlau, H., and Olivera, B.M. Conus venoms: A rich source of ion channel-targeted peptides. Physiol. Rev. 84, (2004)41–68.
10. Cruz LJ, White J. Clinical toxicology of Conus snail stings. In: Meier J, White J, (eds) Clinical Toxicology of Animal Venoms. (1995).
11. Jones RM, McIntosh JM. "Cone venom--from accidental stings to deliberate injection". *Toxicon* 39 (10): (2001)1447–1451.
12. Nicke A, Wonnacott S, Lewis RJ. "Alpha-conotoxins as tools for the elucidation of structure and function of neuronal nicotinic acetylcholine receptor subtypes". *Eur. J. Biochem.* 271 (12): (2004) 2305–19.
13. Leipold E, Hansel A, Olivera BM, Terlau H, Heinemann SH. "Molecular interaction of delta-conotoxins with voltage-gated sodium channels". *FEBS Lett.* 579 (18): (2005)3881–4.
14. Shon KJ, Stocker M, Terlau H, Stühmer W, Jacobsen R, Walker C, Grilley M, Watkins M, Hillyard DR, Gray WR, Olivera BM. J Biol Chem.Jan 2;273(1): (1998) 33-8.
15. Li RA, Tomaselli GF. "Using the deadly mu-conotoxins as probes of voltage-gated sodium channels". *Toxicon* 44 (2): (2004) 117–22.
16. Zeikus RD, Gray WR, Cruz LJ, Olivera BM, Kerr L, Moczydlowski E, Yoshikami D. "Conus geographus toxins that discriminate between neuronal and muscle sodium channels". *J. Biol. Chem.* 260 (16): (1985)9280–9288.
17. Nielsen KJ, Schroeder T, Lewis R. "Structure-activity relationships of omega-conotoxins at N-type voltage-sensitive calcium channels" (abstract). *J. Mol. Recognit.* 13 (2): (2000) 55–70.
18. Bowersox SS, Luther R. "Pharmacotherapeutic potential of omega-conotoxin MVIIA (SNX-111), an N-type neuronal calcium channel blocker found in the venom of Conus magus". *Toxicon* 36 (11): (1998) 1651–8.
19. Prommer E. "Ziconotide: a new option for refractory pain". *Drugs Today* 42 (6): (2006)369–78..
20. Miljanich GP. Ziconotide: neuronal calcium channel blocker for treating severe chronic pain. Current Medicinal Chemistry 11: (2004) 3029-3040,.
21. Shen GS, Layer RT, McCabe RT., Conopeptides: From deadly venoms to novel therapeutics., Drug Discov Today. Mar;5(3): (2000)98-106.
22. Olivera BM, Rivier J, Clark C, Ramilo C, Corpuz GP, Abogadie FC, Mena EE, Woodward SR, Hillyard DR, Cruz LJ.. Diversity of *Conus* neuropeptides. Science 249: (1990)257–263.
23. Balaji, R. A., Sasaki, T., Gopalakrishnakone, P., Sato, K., Kini, R. M., and Bay, B. H. *FEBS Lett.* 474, (2000)208–212
24. Gowd, K. H. *et al*., Novel peptides of therapeutic promise from Indian Conidae. *Ann. N. Y. Acad. Sci.*, 1056, (2005),462–473.