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Structure-activity relationship of α-conotoxin Mr1.1 at the human α9α10 nicotinic acetylcholine receptor

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The short disulfide-rich α-conotoxins (α-CTxs) are peptides derived from the venom of the *Conus* marine snails and the majority antagonise the nicotinic acetylcholine receptors (nAChRs) that are involved in neurotransmission, and the non-neuronal cholinergic system. A handful of α-CTxs are drug leads for the treatment of cancer, chronic pain, and neuralgia. Here, we chemically synthesized a formerly defined rat α7 nAChR targeting α-CTx Mr1.1 from *C. marmoreus* and evaluated its activity at human nAChRs heterologously expressed in *Xenopus laevis* oocytes. Mr1.1 was most potent at the human (h) α9α10 nAChR with a half-maximal inhibitory concentration (IC_{50}) of 92.0 nM. Molecular dynamics simulations suggested Mr1.1 favourably binds at the α10(+)α9(–) and α9(+)α9(–) sites via hydrogen bonds and salt bridges, stabilizing the receptor in a closed conformation. Based on the Mr1.1-hα9α10 model, analogues were generated, and the more potent Mr1.1[S4Dap], antagonized hα9α10 with an IC_{50} of 4.0 nM. Furthermore, Mr1.1[S4Dap] displayed analgesic activity in the rat chronic constriction injury pain model and therefore presents a promising drug candidate.