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A new antagonist of *Caenorhabditis elegans* glutamate-activated chloride channels with anthelmintic activity

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Nematode parasitosis causes mortality and morbidity in humans and losses in livestock and domestic animals. The acquisition of resistance to current anthelmintic drugs has prompted the search for new compounds for which the nematode *Caenorhabditis elegans* has emerged as a valuable platform. We have previously synthetized a library of compounds and determined that dibenzo[b,e]oxepin-11(6H)-one (doxepinone) reduces swimming rate, induces paralysis, and decreases the rate of pharyngeal pumping on *C. elegans*. To identify the drug targets, we performed a screening of strains carrying mutations in Cys-loop receptors involved in worm locomotion for determining resistance to doxepinone effects. A mutant strain that lacks subunit genes of the glutamate-gated chloride channels (GluCl), which are targets of the antiparasitic ivermectin, is resistant to doxepinone effects. To unravel the molecular mechanism, we measured whole-cell currents from GluClα1/β receptors expressed in mammalian cells. Glutamate elicits macroscopic currents whereas no responses are elicited by doxepinone, indicating that it is not an agonist of GluCls. Preincubation of the cell with doxepinone produces a significant decrease of the decay time constant and net charge of glutamate-elicited currents, indicating that it inhibits GluCls. Thus, we identify doxepinone as an attractive scaffold with promising anthelmintic activity and propose the inhibition of GluCls as a potential anthelmintic mechanism of action.

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