

New Product Highlights

2,6-Difluoro-4-[2-(phenylsulfonylamino)ethylthio]phenoxyacetamide (PEPA): A novel, allosteric modulator of AMPA glutamate receptors *Exclusively* available from Sigma-RBI

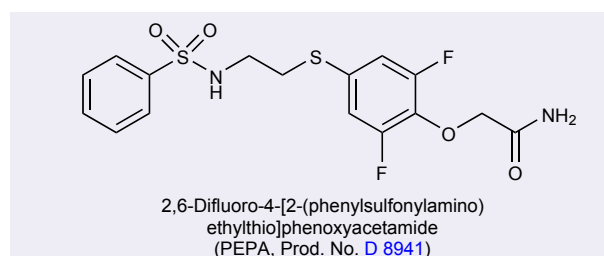
The α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptor subtype is a hetero-oligomer that is formed from combinations of four subunits referred to as GluR1-4. Each of these subunits exists in flip and flop isoforms that are produced by alternative mRNA splicing [1]. Two well-known and structurally distinct modulators of the AMPA receptor, **aniracetam** (Prod. No. [A 9950](#)) and **cyclothiazide** (Prod. No. [C 9847](#)) potentiate excitatory synaptic transmission by preferentially modulating the flop and flip splice variants respectively [2] and possess therapeutic potential as cognitive enhancers [3].

Sigma-RBI is pleased to introduce **2,6-difluoro-4-[2-(phenylsulfonylamino)ethylthio]phenoxyacetamide** (PEPA, Prod. No. [D 8941](#)), a structurally novel, selective, allosteric modulator of AMPA glutamate receptors. Using two-electrode voltage clamp recordings, PEPA potentiated glutamate-evoked currents in *Xenopus* oocytes by attenuating the extent of AMPA receptor desensitization expressing flop isoforms of GluR3 and GluR4 subunits, exhibiting an EC_{50} value of approximately 50 μ M. PEPA also reduced AMPA receptor desensitization in HEK293 cells transfected with all four GluR subunits, as measured by whole cell patch clamp recordings [3-5].

Although PEPA and aniracetam have similar subunit and splice-variant selectivity, at a concentration of 10 μ M PEPA was 100 times more potent than aniracetam in enhancing AMPA receptor currents in

Xenopus oocytes. PEPA and cyclothiazide have opposite splice-variant selectivity and at 25 μ M PEPA potentiated glutamate responses in *Xenopus* oocytes to a much greater extent than cyclothiazide at the same concentration [3]. PEPA (1, 3, 10 mg/kg/day for 10 days) also ameliorated ischemia-induced impairment of performance produced by occlusion of the middle cerebral artery in rats, as assessed by Morris water maze test. In contrast, comparable doses of aniracetam did not significantly improve performance [6].

PEPA is therefore a structurally novel allosteric modulator of AMPA glutamate receptors and appears to be a highly selective tool with which to investigate the physiology of GluR subunits and their involvement in cognitive processes.



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References

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