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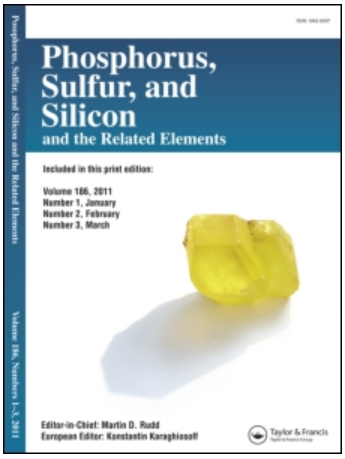

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Synthesis and Resolution of ATPO, a Potent and Selective Ampa Receptor Antagonist

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Synthesis and Resolution of ATPO, a Potent and Selective Ampa Receptor Antagonist

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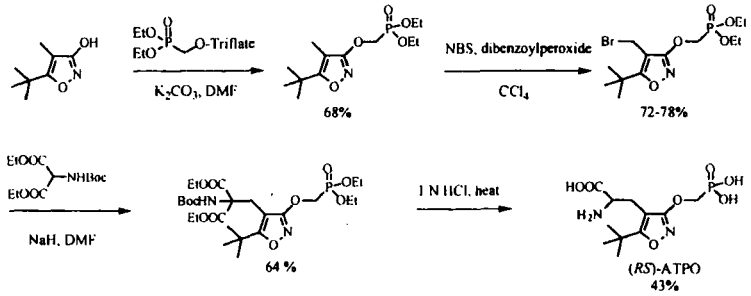
The excitatory amino acid (EAA) receptors mediate one of the major signaling systems in the central nervous system, and they are thought to be implicated in some neurodegenerative disorders, e.g. Alzheimer's disease and stroke. It is of key importance to design selective ligands for every group of EAA receptors. The AMPA receptors are one such group of EAA receptors. (*RS*)-ATPO is a potent antagonist at the AMPA receptors, but it has hitherto been pharmacologically characterized only as the racemate [1,2].



In order to explore the structure-activity relationship of the enantiomers, (*RS*)-ATPO was synthesized as shown and resolved by chiral HPLC using the Sumichiral OA-5000 column. The enantiomers had e.e. >98.5% (*S*) and >98.9% (*R*). An X-ray crystallographic analysis showed that (–)-ATPO has the *R* configuration. Pharmacological studies showed that (*S*)-(+)-ATPO is a potent AMPA receptor antagonist, twice as potent as the racemate, whereas (*R*)-(–)-ATPO is devoid of activity at AMPA receptors. Further pharmacological studies are in progress.

References

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[2] P. Wahl *et al., Mol. Pharmacol.* **53,** 590–596 (1998).