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Architecture in the synthesis of steroidal inhibitors of NMDA receptors: Do built new or rebuilt old?

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Our main avenue of investigation is design and synthesis of steroidal inhibitors of N-methyl-D-aspartate receptors (NMDAR) that could serve as drug-like candidates for CNS disorders as these receptors are essential for synaptic plasticity, learning and memory. However, under pathological conditions, the over-excitation of the NMDAR can induce cell death. Our ongoing structure-activity relationship studies (SAR) are focused on structural modifications of steroidal skeleton that would afford potent inhibitors of NMDAR. In general, the inhibitory effect of neurosteroids on NMDAR is dependent upon the 5β-pregnane skeleton. To elucidate the SAR of the pregnane acetyl moiety, we have prepared a series of compounds with lipophilic D-ring modifications and showed that these analogues are more potent modulators of NMDA-induced currents (IC50 values varying from 90 nM to 5.4 μM) than the known endogenous neurosteroid- pregnanolone sulfate (IC50=24.6 μM). The obtained results emerged us to assess the structural motif of the steroidal D-ring. As such, a series of compounds with partially of fully degraded D-ring was synthesized (IC50 values varying from 15 μM to 224 μM). Finally, using the total synthesis of steroidal A, B and C-ring, we have prepared a series of compounds with non-steroidal structural characteristics of various types that allowed us to define new structural motifs for inhibitors of NMDA receptors.

Biography

Slavikova Barbora has received her Master's degree in 1983 from the Institute of Chemical Technology in Prague. She has been working at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic in Prague for almost 25 years with specialization in steroidal synthesis. During this period, she has synthesized thousands of compounds and is the author and co-author in 18 original papers and 4 patents.

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