

# Sevanol and its analogues: chemical synthesis, biological effects and molecular docking

Olga Belozerova<sup>1</sup>, Dmitry Osmakov<sup>2</sup>, Andrey Vladimirov<sup>1</sup>, Sergey Koshelev<sup>2</sup>, Anton Chugunov<sup>1</sup>, Yaroslav Andreev<sup>2</sup>, Viktor Palikov<sup>3</sup>, Yulia Palikova<sup>3</sup>, Elvira Shaykhutdinova<sup>3</sup>, Artem Gvozdz<sup>4</sup>, Igor Dyachenko<sup>3</sup>, Roman Efremov<sup>2</sup>, Vadim Kublitski<sup>1</sup>, and Sergey Kozlov<sup>1</sup>

<sup>1</sup>Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry Russian Academy of Sciences

<sup>2</sup>Institut bioorganiceskoj himii RAN

<sup>3</sup>Pushchino Branch of the Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry Russian Academy of Sciences

<sup>4</sup>FMBA Rossii

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## Abstract

Among acid-sensing ion channels (ASICs), ASIC1a and ASIC3 subunits are the most widespread and prevalent in physiological and pathophysiological conditions. They participate in synaptic plasticity, learning and memory as well as in the perception of inflammatory and neurological pain, making these channels attractive pharmacological targets. Sevanol, a natural lignan isolated from *Thymus armeniacus*, inhibits the activity of ASIC1a and ASIC3 isoforms and has a significant analgesic and anti-inflammatory effect. In this work, we described the efficient chemical synthesis scheme of sevanol and its analogues, which allows us to analyze the structure-activity relationships of different parts of this molecule. We found that the inhibitory activity of sevanol and its analogues on ASIC1a and ASIC3 channels depends on the number and availability of carboxyl groups of the molecule. At the structural level, we predicted the presence of sevanol binding site based on the presence of molecular docking in the central vestibule of the ASIC1a channel. We predicted that this site could also be occupied in part by the FRRF-amide peptide, and the competition assay of sevanol with this peptide confirmed this prediction. Intravenous (i.v.), intranasal (i.n.) and, especially, oral (p.o.) administration of synthetic sevanol in animal models produced significant analgesic and anti-inflammatory effects. Both non-invasive methods of sevanol administration (i.n. and p.o.) showed greater efficacy than invasive (i.v.) one, thus opening new horizons for medicinal uses of sevanol.

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