SL-51. $Na_V1.8$ Channel Modulators

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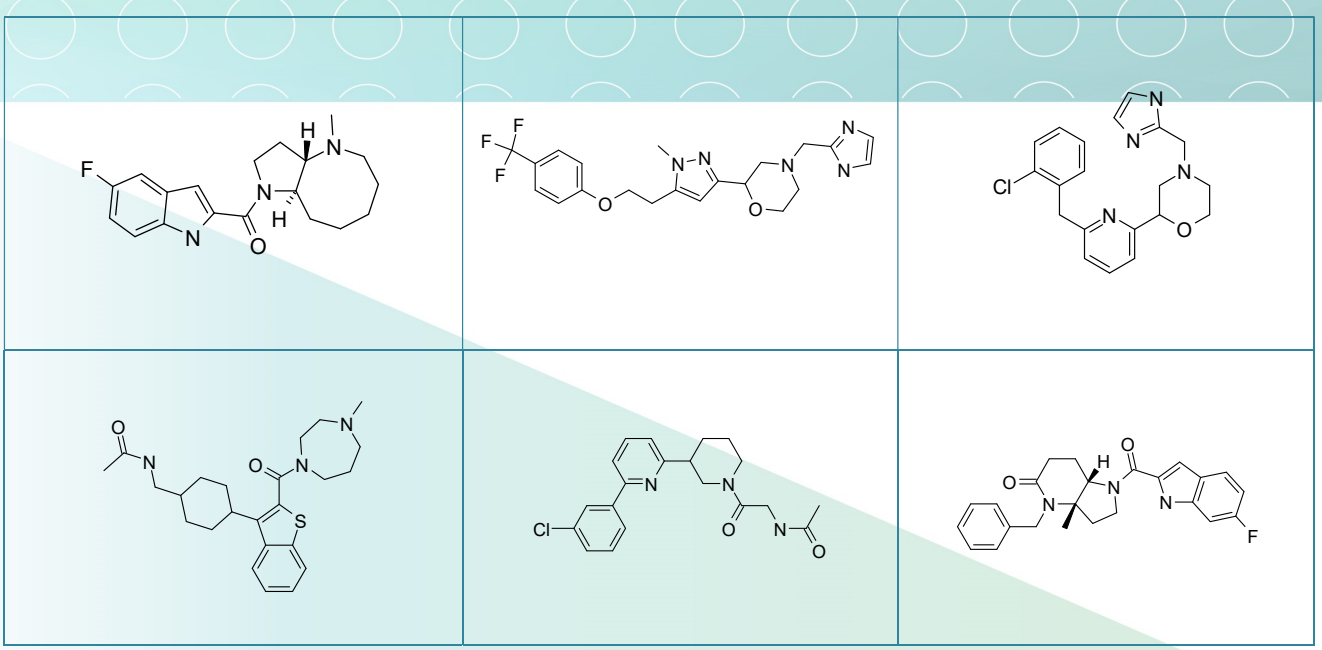
Voltage-gated sodium channels are involved in signal transduction in electrically excitable tissues such as those found in muscles, the heart, and nerves. Deregulated function of voltage-gated sodium channels is observed in various pathological and disease conditions including pain, CNS, and cardiac disorders. Specific channel isoforms, $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ are predominantly expressed in sensory neurons thus providing a strong rationale as anti-pain targets [1].

Based on the analysis of several known $Na_V1.8$-blockers we have developed a pharmacophore model which has been used to carry out an exhaustive search on a 20K+ set of natural product-like compounds. The highest scoring compounds were screened *in vitro* in the human $Na_v1.8/\beta3$ sodium channel cell line. The $Na_v1.8$ blocking effects were evaluated using the IonWorks™ Barracuda system. Blockage of the sodium channel was performed at 1 µM of a tested compound using a stimulus voltage pattern measuring peak current amplitudes for two test pulses TP1 (tonic inhibition) and TP2 (inactivated state inhibition).



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Formats	Supplementary Information
80 compounds per plate 0.1 mg; 1 mg; 2 mg dry film/powder 0.1 µmol; 1 µmol DMSO solutions	SL#51_SL#51_Nav18_ICh.sdf Supplementary Information Tonic block of $Na_v1.8$, at 1.0 µM – TP1 Inactivated state inhibition of $Na_v1.8$ at 1.0 µM – TP2

References:

1. Channels (Austin). 2015 Nov-Dec; 9(6): 360–366; doi: 10.1080/19336950.2015.1079674

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