

## Ion Channel Focused Library (Fingerprint Similarity)

Ion channels, a membrane proteins expressed in almost all living cells, are among the most important targets for treating a number of different pathophysiologies. Historically, however, the development of drugs targeting this protein class has been difficult. Several challenges associated with molecular-based drug discovery include validation of new channel targets and identification of acceptable medicinal chemistry leads. Despite some important drugs in clinical use today, as a class, ion channels remain underexploited in drug discovery and many existing drugs are poorly selective with significant toxicities or suboptimal efficacy.

Life Chemicals has applied a number of tools to predict ion channel blockers among compounds in its HTS Stock Collection. As a result, the Ion Channel Focused Library (Fingerprint Similarity) containing more than **5,000** compounds was designed (Fig. 1).

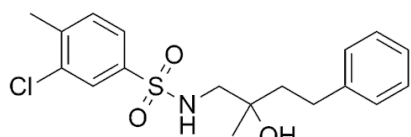
Initially, almost 19,000 referent compounds with known ion channel blocking activity were obtained from ChEMBL database. The compounds have been filtered to leave only those possessing moderate and high activity against ion channels. At the next step, a similarity search of the reference set has been done against Life Chemicals HTS Stock Collection of compounds employing 2D molecular fingerprints and two similarity metrics (Tanimoto > 0.85 and Tversky > 0.85). Compounds found in this search were filtered by Lipinski's Rule of Five to keep only drug-like compounds. Also, PAINS compounds as well as compounds with "bad" and reactive groups have been filtered out from the library.

The library contains compounds predicted to be active against the following Ion Channel targets:

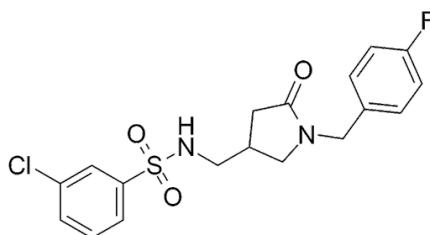
- Vanilloid receptor
- HERG
- Acetylcholine receptor; alpha1/beta1/delta/gamma
- Annexin A2/S100-A10
- Anoctamin-1
- Apoptosis regulator Bcl-2
- Calcium-activated potassium channel subunit alpha-1
- Cholesteryl ester transfer protein
- Cystic fibrosis transmembrane conductance regulator
- GABA A receptor alpha-2/beta-2/gamma-2
- GABA-A receptor; alpha-3/beta-3/gamma-2
- GABA-A receptor; anion channel
- Glutamate [NMDA] receptor subunit 3A
- Glutamate [NMDA] receptor subunit epsilon 2

- Glutamate NMDA receptor; GRIN1/GRIN2B
- Glutamate receptor ionotropic, AMPA 2
- Glutamate receptor ionotropic, AMPA 4
- Kir3.1/Kir3.4
- MCOLN3 protein
- Neuronal acetylcholine receptor protein alpha-4 subunit
- Neuronal acetylcholine receptor protein alpha-7 subunit
- Neuronal acetylcholine receptor; alpha3/beta4
- Neuronal acetylcholine receptor; alpha4/beta2
- P2X
- P2X purinoceptor 3
- P2X purinoceptor 7
- Perforin-1
- Potassium channel subfamily K member 3
- Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1
- Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4
- Presenilin er Ca<sup>2+</sup> leak channel
- Serotonin 3 (5-HT<sub>3</sub>) receptor
- Serotonin 3a (5-HT<sub>3a</sub>) receptor
- Short transient receptor potential channel 6
- Sodium channel alpha subunits; brain (Types I, II, III)
- Sodium channel protein type I alpha subunit
- Sodium channel protein type II alpha subunit
- Sodium channel protein type IX alpha subunit
- Sodium channel protein type V alpha subunit
- Sodium channel protein type X alpha subunit
- Sodium/potassium-transporting ATPase
- Sulfonylurea receptor 1, Kir6.2
- Transient receptor potential cation channel subfamily A member 1
- Transient receptor potential cation channel subfamily M member 8
- Transient receptor potential cation channel subfamily V member 4
- Voltage-gated L-type calcium channel
- Voltage-gated L-type calcium channel alpha-1C subunit
- Voltage-gated L-type calcium channel alpha-1D subunit
- Voltage-gated N-type calcium channel alpha-1B subunit
- Voltage-gated N-type calcium channel alpha-1B subunit/Amyloid beta A4 precursor protein- binding family A member 1
- Voltage-gated potassium channel subunit Kv1.3
- Voltage-gated potassium channel subunit Kv1.5
- Voltage-gated potassium channel subunit Kv7.1
- Voltage-gated potassium channel subunit Kv7.2
- Voltage-gated potassium channel subunit Kv7.4

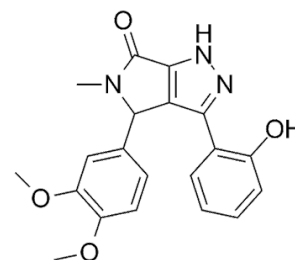
- Voltage-gated potassium channel, IKs; KCNQ1(Kv7.1)/KCNE1(MinK)
- Voltage-gated T-type calcium channel alpha-1G subunit
- Voltage-gated T-type calcium channel alpha-1H subunit
- Voltage-gated T-type calcium channel alpha-1I subunit



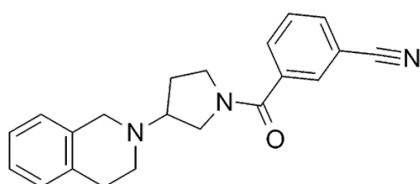
**F5857-4378**



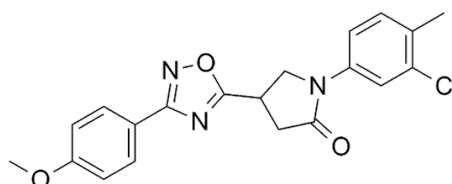
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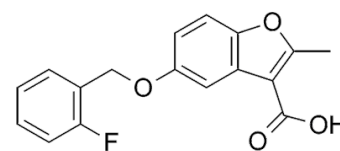
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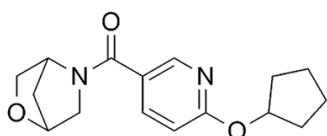
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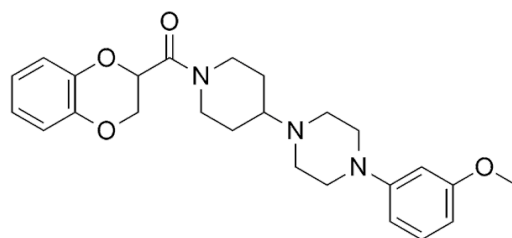
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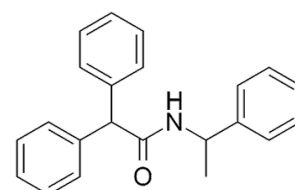
**F0821-0075**



**F6554-2101**



**F3395-0235**



**F0777-2178**

**Fig 1.** Some representative compounds from the Life Chemicals Ion Channel Focused Library (Fingerprint Similarity).