SL-09. Cell Permeable Macrocycles

ASINEX
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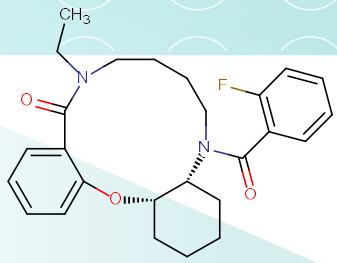
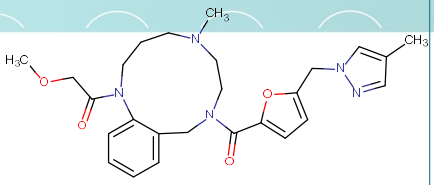
Macrocyclic chemotypes are unique due to their size, complexity, and ability to interact with so called “difficult targets”. Additionally, cyclization makes a molecule more drug-like, improving membrane permeability and metabolic stability. Analysis of 68 marketed macrocyclic drugs reveals that most are either cyclic peptides or macrolides. Furthermore, only 19 (<30%) of these 68 macrocycles are orally available, and all orally available macrocycles except for cyclosporine A belong to the macrolide class.

To overcome poor bioavailability, ASINEX has designed new chemical scaffolds with ring sizes ranging from 12 to 14 members, containing 1-3 aromatic cycles incorporated either into the macrocycle or added on a side chain. Macrocyclic fragments generally include 2-3 oxygen or nitrogen atoms that constitute amide, ether, or amine moieties. We have made special effort to minimize the number of hydrogen donors which can be favorable for bioavailability [1].

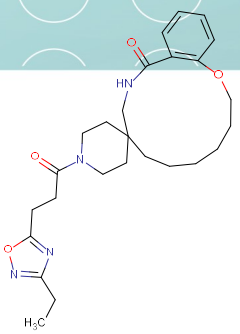
Compounds from our library have been tested in PAMPA assays and show permeability Pe greater than 4-16*10^{-6} cm/s. Generally, such compounds have excellent cellular permeability.



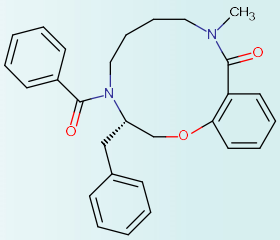
Pe = 11 x 10^{-6} cm/s



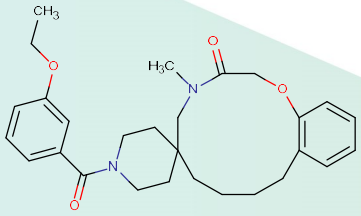
Pe = 7 x 10^{-6} cm/s



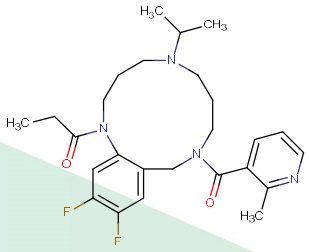
Pe = 6 x 10^{-6} cm/s



Pe = 13 x 10^{-6} cm/s



Pe = 7 x 10^{-6} cm/s



Pe = 11 x 10^{-6} cm/s

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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	PAMPA, Pe SL#9_MacroPAMPA_04-16.sdf

References:

1. *J. Med. Chem.*, 2015, 58 (11), pp 4581–4589, doi: 10.1021/acs.jmedchem.5b00128.

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