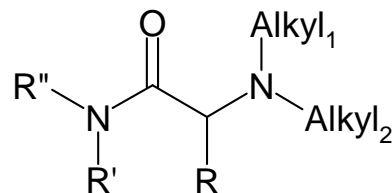


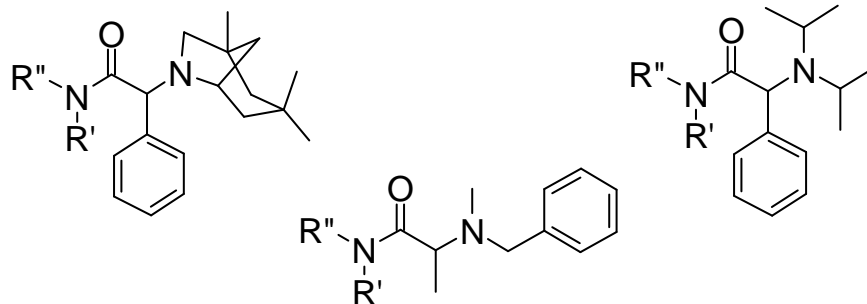
DIALKYLAMINOAMIDE

PEPTIDOMIMETIC / ION CHANNEL / GPCR

The scaffold:



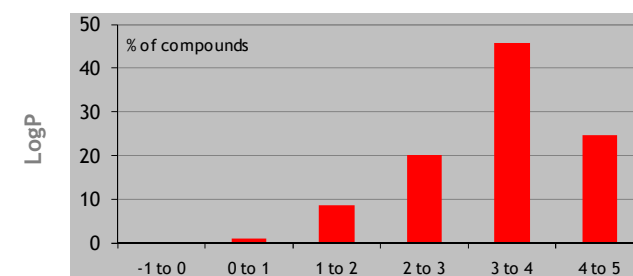
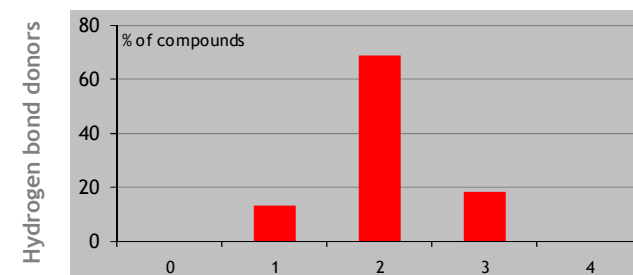
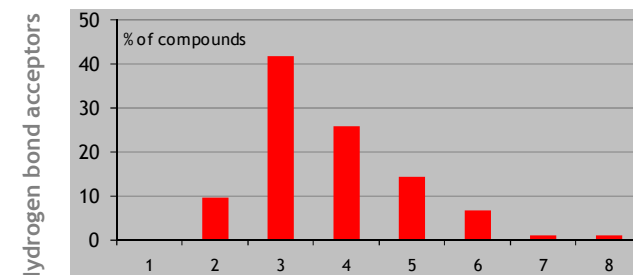
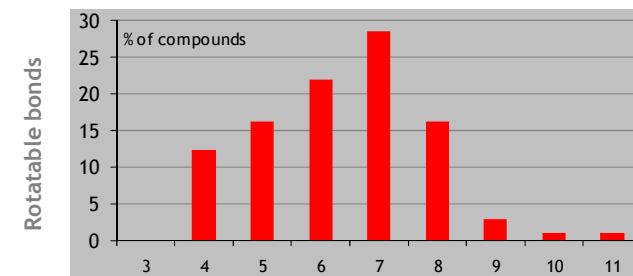
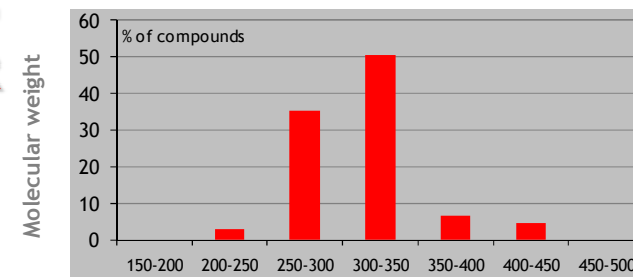
Example of selected intermediates:



Bullet points:

- * small peptidomimetics for the exploration of peptide receptors and enzymes
- * promiscuous linker with potent applications for the inhibition of ion channels, amine and peptide GPCRs
- * original molecules for fragment based drug discovery
- * 300+ compounds based on 10 intermediates
- * cherry-picking and custom format available

CHARACTERISTIC CHARTS

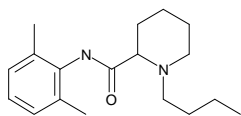
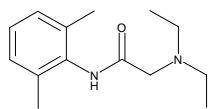
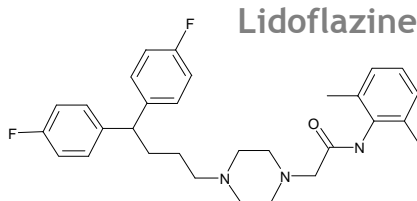
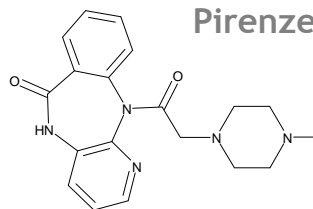
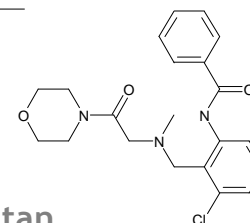
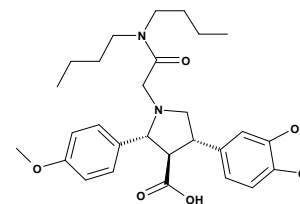
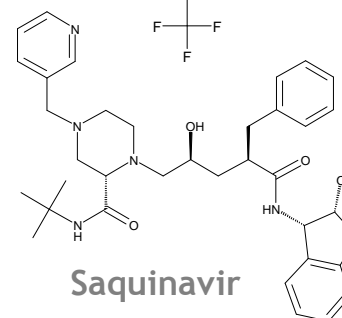
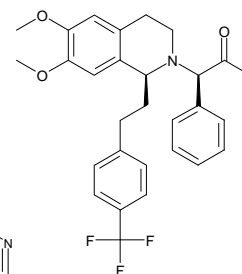
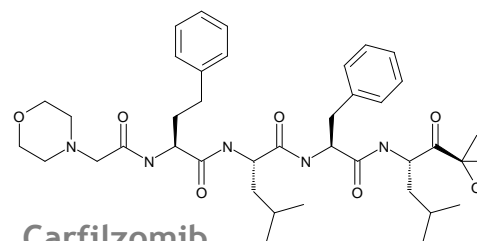
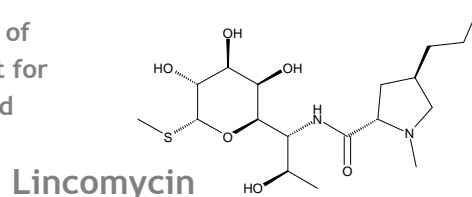


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102 avenue Gaston Roussel
93230 - ROMAINVILLE - France

+33 1 41 83 02 03
+33 1 41 83 02 04 (fax)

www.chem-x-infinity.com

Bupivacaine**Lidocaine****Lidoflazine****Pirenzepine****Fominoben****Atrasentan****Almorexant****Saquinavir****Carfilzomib****Lincomycin**

Most of the natural ligands are peptides. However, peptides are not suitable for drug generation since they are unstable in biological conditions and they are degraded by enzymes. Changing the amino acid sequence can fool the proteases and make the molecule stable enough to be used as a drug. One of the solutions to obtain those peptidomimetic molecules is to introduce tertiary amines in the peptide sequence. Following this strategy, we designed a series of dialkyl amino acids around glycine, alanine, phenylglycine and *beta*-alanine. Those small intermediates have been reacted with diverse amines to obtain small peptidomimetic structures for first intention screening and fragment based drug discovery.

The dialkylaminoamide linker can not be considered as a full scaffold. However it can be found in several classes of active molecules. Previously described examples are the anesthetic bupivacaine¹ and its analogs. These sodium channel blockers belonging to the aminoamide family are usually used topically. Belonging to the same family, lidocaine is also the most important class 1B antiarrhythmic drug² and is used intravenously for the treatment of ventricular arrhythmias. Other antiarrhythmic agents include lidoflazine, a calcium channel blocker³.

Aminoamides are also present in some GPCR inhibitors as pirenzepine⁴, a muscarinic M1 antagonist for the treatment of peptic ulcer and in the antitussive drug fominoben⁵. Atrasentan is an endothelin ET_A receptor antagonist that blocks endothelin induced cell proliferation and is developed for cancer treatment⁶. Almorexant is currently in Phase III clinical trials for the treatment of insomnia⁷. It is a competitive receptor antagonist of the OX₁ and OX₂ orexin receptor.

The substructure is also found in larger molecules for protein inhibition, including the protease inhibitors saquinavir, indinavir and nelfinavir antiretroviral drugs used for the treatment of HIV. A typical peptidomimetic structure is carfilzomib⁸, a proteasome inhibitor which recently showed promising overall response rates in Phase II testing when it was administered as a single agent in patients with relapsed or refractory multiple myeloma. Finally, some antibacterials have amidoamide linkers like the natural compound lincomycin and its synthetic analogs⁹.

We then believe that Chem-X-Infinity's library of dialkylaminoamides is an efficient starting point for the investigation of new ion channel, GPCR and protein inhibitors and provides original molecules for fragment based researches.



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¹ *Anesthesiology*, 1998, 88, 1071

² *Eur. Heart J.*, 1984, 5, 99

³ *J. of Pharm. and Exp. Ther.*, 1966, 152, 265

⁴ *Drugs*, 1985, 30, 85

⁵ *Eur. J. of pharmacology*, 1984, 97, 277

⁶ *Clinical Cancer Res.*, 2008, 14, 1464

⁷ *Molecular Pharmacology*, 2009, 76, 618

⁸ *Blood*, 2007, 110, 3281

⁹ EP1654268, 2006