CHEM-X INFINITY

oriBase Pharma
innovative molecules

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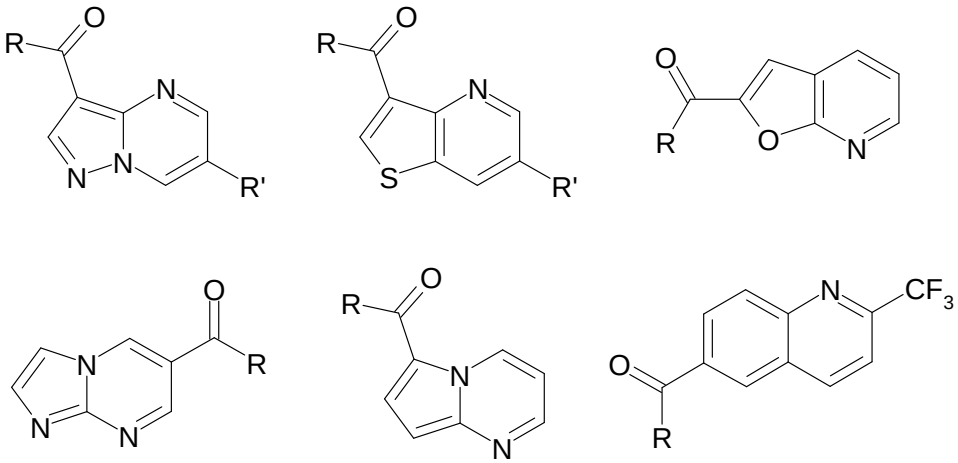
CHEMHIT3 KINASE LIBRARY

The scaffolds:

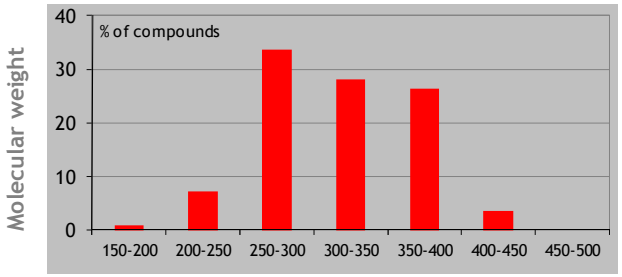
Pyrazolo[1,5-a]pyrimidines, Thieno[3,2-b]pyridines, Pyrrolo[1,2-a]pyrimidines, Imidazo[1,2-a]pyrimidines, Furo[2,3-b]pyridines and Quinoline-6-carboxamides

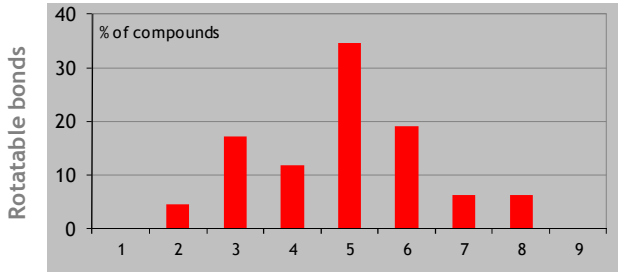


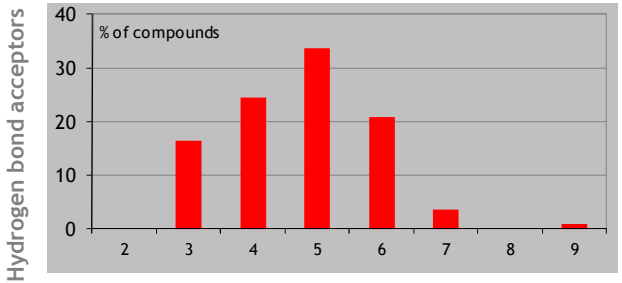
Bullet points:

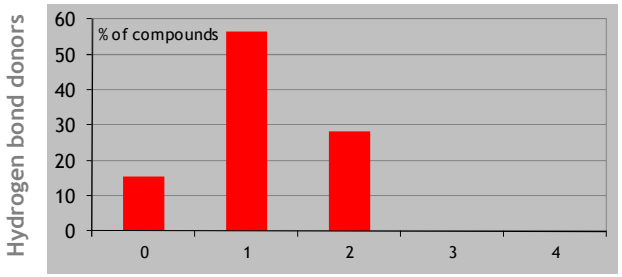
* diverse exploration of original small aza-heterocycles
* privileged structures for kinase inhibitions
* isosteric applications for indole analogs
* strictly respect of Lipinski's rules
* 600+ compounds based on 10 intermediates
* cherry-picking and custom format available

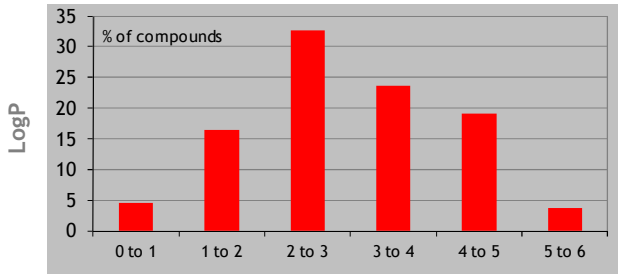
CHARACTERISTIC CHARTS

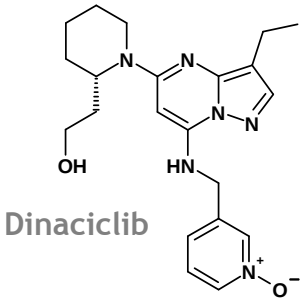






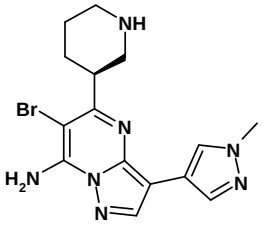


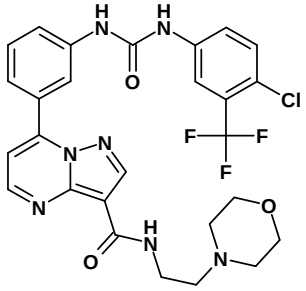




Dinaciclib

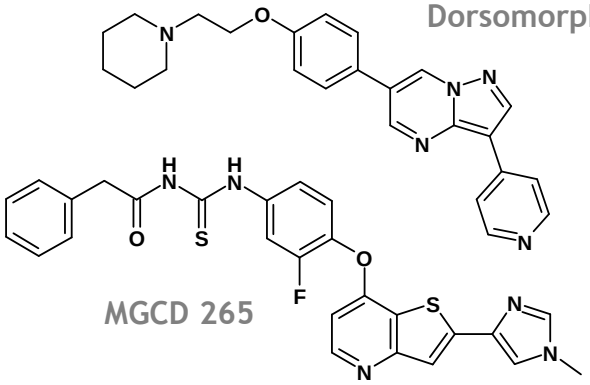
SCH 900776





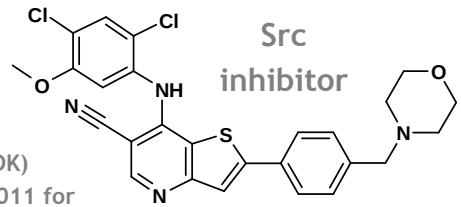
B-Raf inhibitor

Dorsomorphin



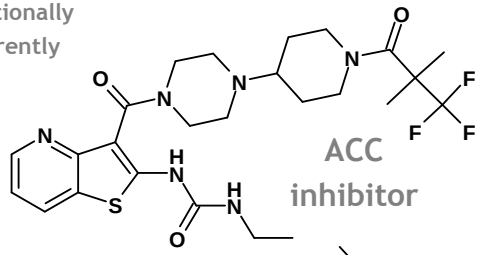
MGCD 265

Because of synthetic difficulties, several small heterocycles have been poorly represented in combinatorial libraries.
The replacement of one or two carbons by nitrogen in simple heterocycles like indoles, thiophenes or benzofurans can dramatically change the activity and the pharmacokinetic properties of the final compounds. In collaboration with ORIBASE PHARMA which specializes in the design and synthesis of kinase focused scaffolds, we built a diverse library of compounds having a wide range of applications.



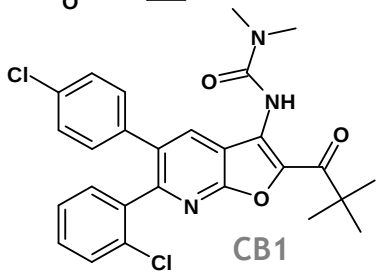
Src inhibitor

The heterocycle pyrazolo[1,5-a]pyrimidine can be found in dinaciclib, a potent cyclin dependant kinase (CDK) inhibitor currently in Phase III for several type of cancer. An orphan designation was granted by the EC in 2011 for the treatment of chronic lymphocytic leukemia[1]. The related molecule SCH 900776 is a potent and functionally selective inhibitor targeting cell cycle checkpoint kinase 1 (CHK1) with IC_{50} of 3 nM. The molecule is currently in Phase II as a new anticancer therapy[2]. Replacing the amino side chain by an aromatic led to promising B-Raf protein kinase inhibitors[3] that could be of great interest considering the recent approval of vemurafenib, also a B-Raf kinase inhibitor. Other kinases could be addressed with this heterocycle, like the inhibitor of AMP-activated protein kinase (AMPK) dorsomorphin, a reference compound[4]. Finally, Zaleplon and the related Indiplon, which are GABA-A receptor agonists for insomnia treatment, show that the pyrazolopyrimidine compounds could also be used for ion channel modulation[5].



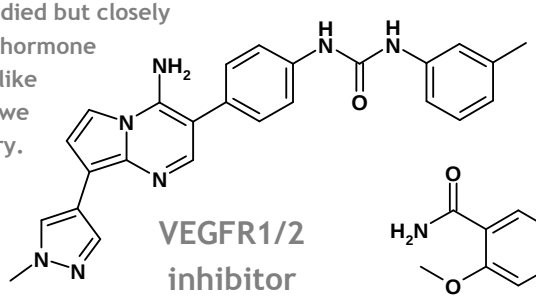
ACC inhibitor

Thieno[3,2-b]pyridines could also have many applications: MGCD 265 is a c-MET, VEGFR1 to 3, Ron and Tie-2 receptor tyrosine kinase inhibitor currently in Phase II for solid tumors and non-small-cell lung carcinoma[6]. Closely related 7-aminothienopyridines have been found to have high affinities either against EGFR kinase[7] or Src kinase[8]. Moreover, thienopyridine-3-carboxamides have been found to inhibit acetyl coenzyme-A carboxylase (ACC) which opens the use of the heterocycle for metabolic diseases[9]. Some related furo[2,3-b]pyridine were also introduced in the library despite few activities on kinases are reported. Those compounds could also have applications for GPCRs, particularly for cannabinoid receptor CB1 [10].

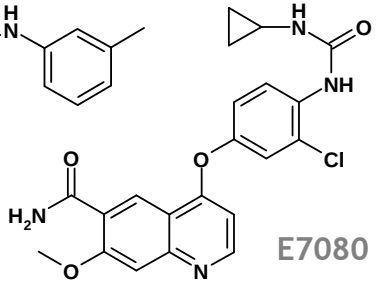


CB1 inhibitor

The pyrrolo[1,2-a]pyrimidines and the imidazo[1,2-a]pyrimidines were less studied but closely related analogs have activities against VEGFR1/2 [11] and gonadotropin-releasing hormone receptor[12]. Finally, since some quinolines are currently tested in clinical trials like E7080, a potent dual inhibitor of VEGFR-2 and 3 tyrosine kinase in Phase III [13], we added some original trifluoromethylated quinoline-6-carboxamides to the library.



VEGFR1/2 inhibitor



E7080

We then do believe that our CHEMHIT3 library will be a useful tool for first Intention screenings against kinases and should help for the identification of new classes of active structures.

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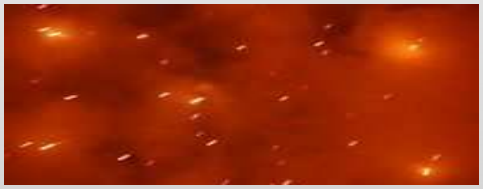

[1] *Mol. Cancer Ther.*, **2010,** *9,* 2344
[2] *Mol. Cancer Ther.*, **2011,** *10,* 591
[3] *Bioorg. Med. Chem. Lett.*, **2009,** *19,* 2735
[4] *Nat. Chem. Biol.*, **2008,** *4,* 33
[5] *J. Clin. Psychiatry*, **1999,** *60,* 536
[6] *Clin. Transl. Oncol.*, **2010,** *12,* 253
[7] *Bioorg. Med. Chem. Lett.*, **2004,** *14,* 21
[8] *J. Med. Chem.*, **2004,** *27,* 6666
[9] *Bioorg. Med. Chem.*, **2011,** *19,* 1580
[10] *Bioorg. Med. Chem. Lett.*, **2010,** *20,* 1448
[11] *J. Med. Chem.*, **2008,** *51,* 3777
[12] *Bioorg. Med. Chem. Lett.*, **2002,** *12,* 399
[13] *Clin. Cancer Res.*, **2009,** *15,* 7229