CHEM-X INFINITY

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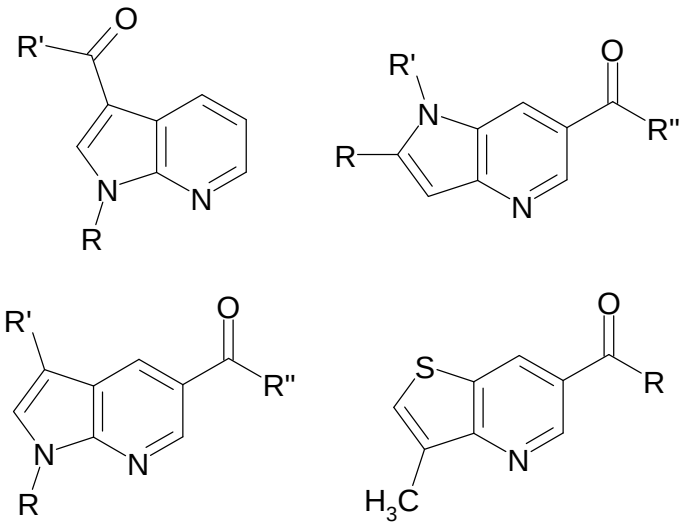
AZAINDOLE LIBRARY KINASE & GPCR

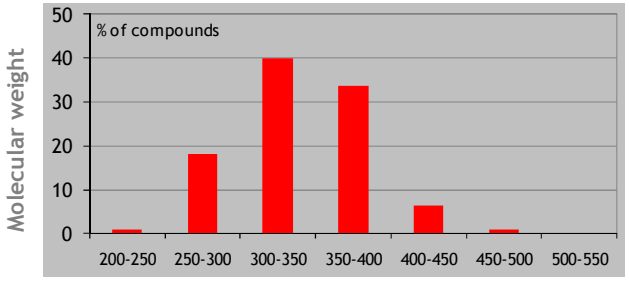
The scaffolds:

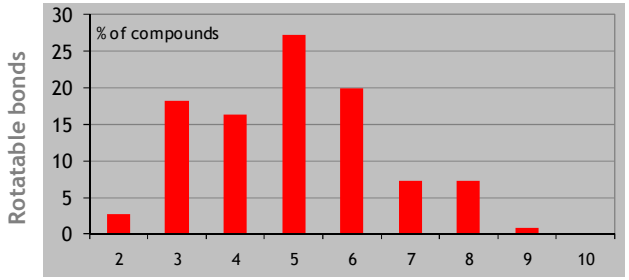


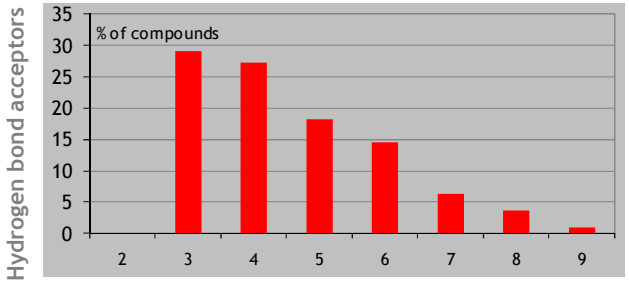
Bullet points:

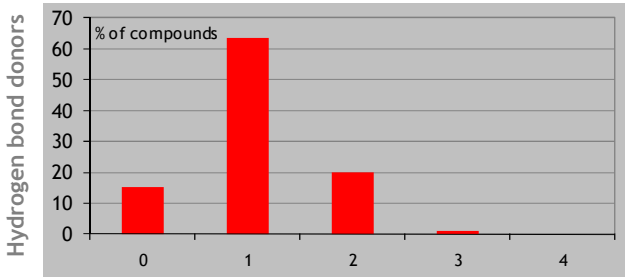
* highly diverse exploration of original azaindole scaffold
* privileged structures for kinase and enzyme inhibitors, peptide and amine GPCRs, DNA and DNA processing enzymes interactions
* many reports of better pharmacokinetics and oral activity for aza-isosters of indoles
* 700+ compounds based on 10 intermediates
* cherry-picking and custom format available

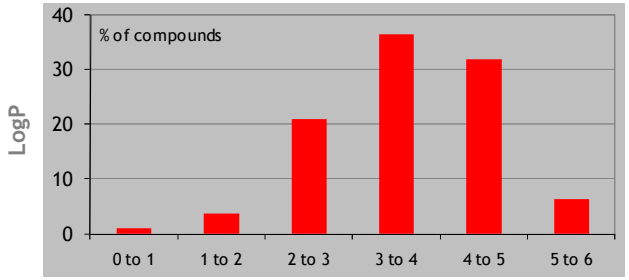
CHARACTERISTIC CHARTS

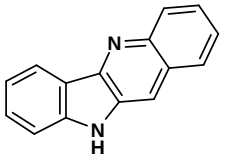




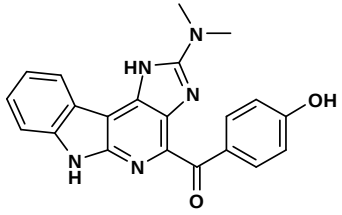




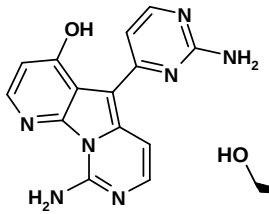




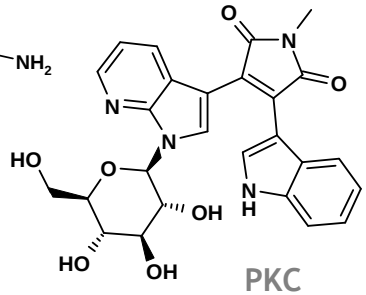
Quindoline



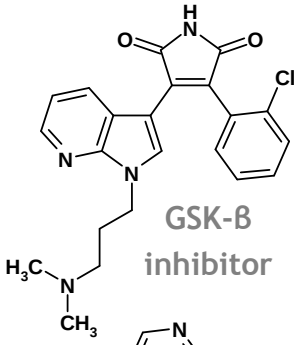
Grossularine II



Variolin B

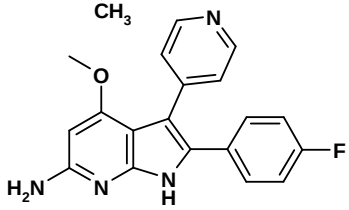


PKC inhibitor



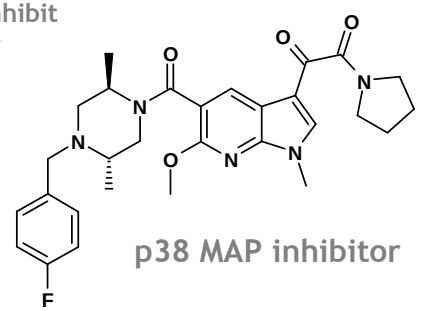
GSK-β inhibitor

4 and 7-azaindole structural fragments are rather uncommon in natural compounds. Quindoline and the related cryptolepine have been isolated from a West African medicinal plant and have been found to have anti-malarial activity. Grossularine II and variolin B are two marine anti-tumoral compounds; the activity of variolin B seems to result from cyclin-dependant kinase inhibition[1].



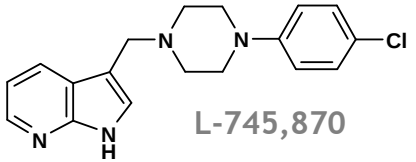
p44/42 MAP inhibitor

Azaindole analogues of the anti-tumoral antibiotic rebeccamycin were found to have potent and more selective antiproliferative properties than the original compound, with significant inhibition of topoisomerase I and protein kinase C[2]. Unsymetrical azaindole maleinimides have been found to inhibit selectively GSK3-β kinase[3]. Biaryl derivatives of 7-azaindoles were found to be potent inhibitors of p44/42 MAP kinase[4]. Azaindole pyruvic amide derivatives have also been recently patented as selective p38 MAP kinase inhibitors[5].



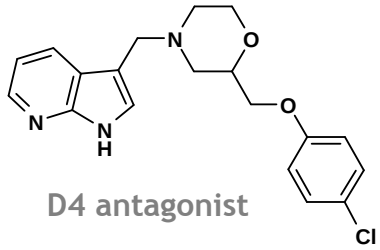
p38 MAP inhibitor

Simple morpholine[6] and piperazinyl[7] derivatives of 7-azaindole such as L-745,870 have been identified as dopamine D4 receptor antagonists with excellent oral bioavailability and brain penetration. Piperidine derivatives have been disclosed as orally active H1 antagonists without sedative properties[8]. Other GPCR inhibitors containing the azaindole substructure include 5HT1B agonists, mixed serotonin reuptake inhibitors, 5HT1a antagonists, CRFR-1 antagonists and 5HT1-F selective antagonists.



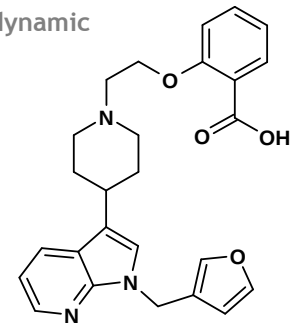
L-745,870

The obtention of arginine mimetics with good oral absorption has represented a difficult and long sought challenge. Incorporation of 4-azaindole structure in peptidomimetic patterns has finally yielded orally active factor Xa inhibitors[9] and thrombin inhibitors[10] with pharmacodynamic properties better than for benzamidines and their usual isosters.

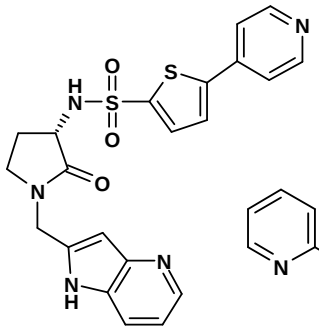


D4 antagonist

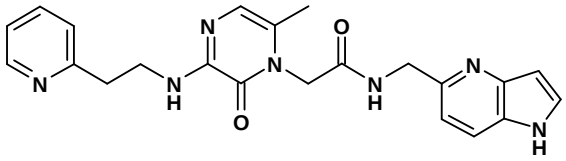
We then do believe that our azaindole library will be a useful tool for the exploration of the rich pharmacological spectrum of indoles, to identify specific leads for an extended range of receptors or enzymes.



H1 antagonist



Factor Xa inhibitor



Thrombin inhibitor

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[1] *Eur. J. Cancer.*, **2005,** *41,* 2366
[2] *Eur. J. Med. Chem.*, **2003,** *38,* 123
[3] *Bioorg. Med. Chem. Lett.*, **2004,** *14,* 3245
[4] *Biochem. Pharmacol.*, **2001,** *62,* 283
[5] WO4032874
[6] *Bioorg. Med. Chem.*, **1998,** *6,* 1
[7] *J. Med. Chem.*, **1996,** *39,* 1941
[8] *Bioorg. Med. Chem. Lett.*, **2005,** *15,* 1165
[9] *Bioorg. Med. Chem. Lett.*, **2000,** *10,* 1033
[10] *Bioorg. Med. Chem. Lett.*, **2003,** *13,* 795