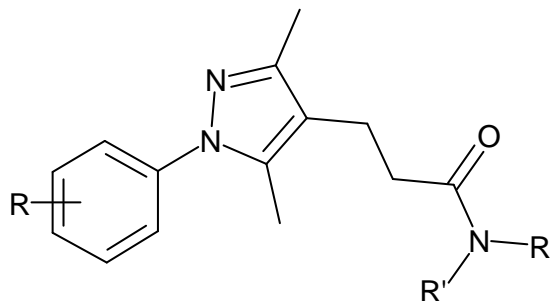


PYRAZOLE PROPIONAMIDE GPCR / NSAID LIBRARY

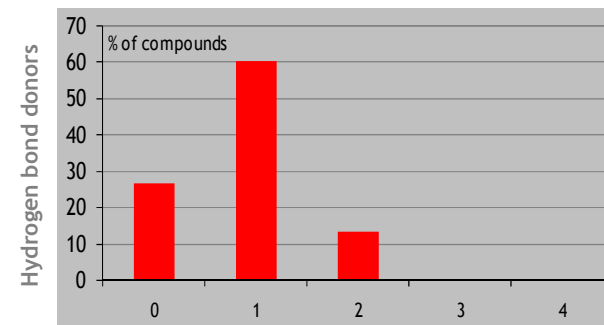
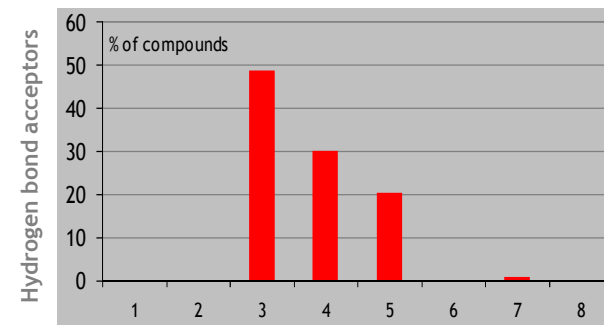
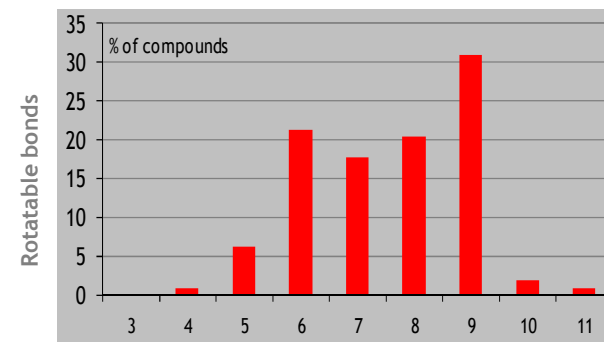
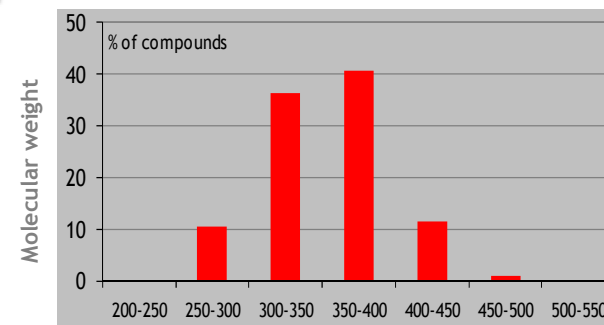
The scaffold:



Bullet points:

- * diverse exploration of pyrazole-4-propionamides
- * focused library for first intention screening
- * systematic variations for preliminary SAR establishment
- * flexible structures to optimize position in the active sites
- * privileged structures for GPCRs and for non steroidal anti-inflammatory agents
- * 600+ compounds based on 10 intermediates
- * cherry-picking and custom format available

CHARACTERISTIC CHARTS



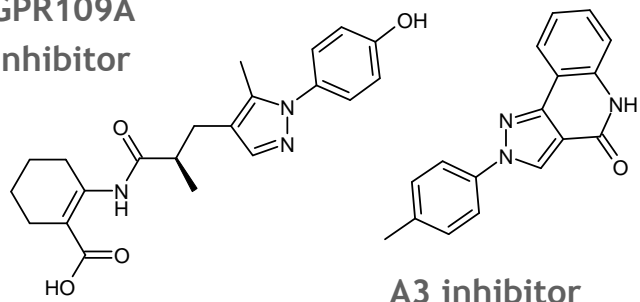
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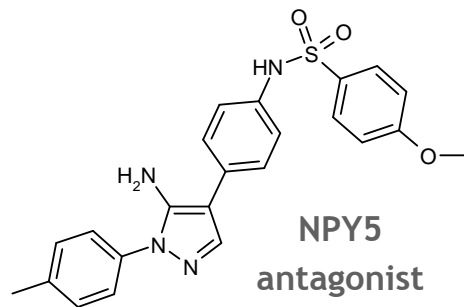
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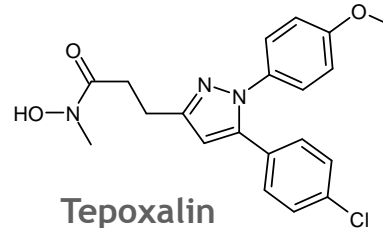
GPR109A inhibitor



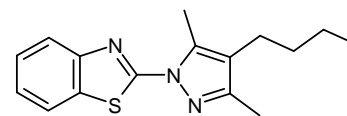
A3 inhibitor



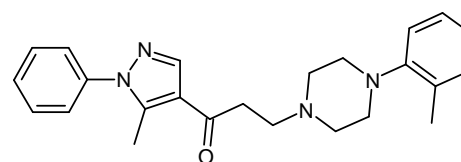
NPY5 antagonist



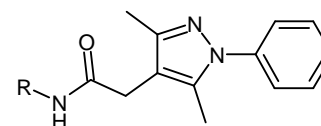
Tepoxalin



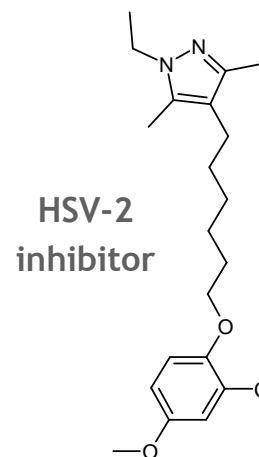
NSAID



Go-1002



Anti-alcoholic agents



HSV-2 inhibitor

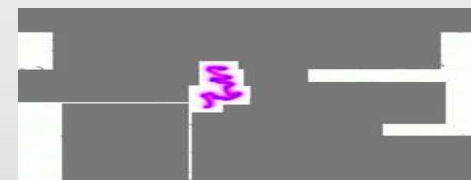
As other simple heterocycles classified as alkaloids, pyrazoles belong to the chemist's toolkit to design analogues of interesting molecules. It is important however to note that unlike imidazoles, pyrazoles are quite rare in nature and thus provide good starting points to identify new active compounds. This library of 1-aryl-3,5-dimethylpyrazole-4-propionamides is designed to offer flexible molecules having potent uses in several medicinal fields.

Several related active compounds are described in the GPCR area. A series of pyrazole-4-propionamide has shown good affinity against the recently described G-protein coupled receptor GPR109A for the treatment of coronary heart disease¹. Pyrazole propionamides could also be considered as flexible analogues of adenosine A3 inhibitors for potential antiasthmatic, anti-inflammatory and cerebroprotective agents². 1-aryl-5-aminopyrazoles have been described as NPY5 antagonists³.

Diphenylpyrazoles are known to have anti-inflammatory properties, like the anti-arthritis COX-2 inhibitor celecoxib. Another example closely related to our core structure is tepoxalin, a non-steroidal anti-inflammatory drug approved for veterinary use to reduce inflammation and relief of pain caused by musculoskeletal disorders. A simplest series of dimethylpyrazoles was also studied as new anti-inflammatory agents⁴.

Other potential uses include Go-1002, which was shown to have psychotropic effects with a pharmacological profile similar to reserpine⁵. Go-1002 is a potent orally active hypotensive agent, with epinephrine-, amphetamine- and tyramine-blocking properties. Series of dimethylpyrazole acetamides were also detected to have potent anti-alcoholic applications probably by inhibiting the activity of alcohol dehydrogenase (ADH)⁶. Finally, 4-alkylated-3,5-dimethylpyrazoles were studied for antiviral activity against HSV (herpes simplex virus) type 2 as pyrazole analogues of arildone⁷.

We then do believe that Chem-X-Infinity's pyrazole-4-propionamide library will be an efficient tool for the exploration of this pharmacophore as a typical privileged structure for interaction with GPCRs and for anti-inflammatory agents. This focused library should be of great help for the discovery of new leads with the potentiality to quickly generate preliminary SAR.



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¹ *Bioorg. Med. Chem. Lett.*, 2008, 18, 3163

² *J. Med. Chem.*, 2005, 48, 5001

³ *Bioorg. Med. Chem. Lett.*, 2001, 11, 2287

⁴ *Indian J. Chem. Sect. B*, 1986, 25, 288

⁵ *J. Med. Chem.*, 1972, 15, 875

⁶ *Pharm. Chem. J.*, 1989, 23, 684

⁷ *J. Med. Chem.*, 1981, 24, 735