

# CASE STUDY

## Drug Reprofilng - Inositol Monophosphate Dehydrogenases

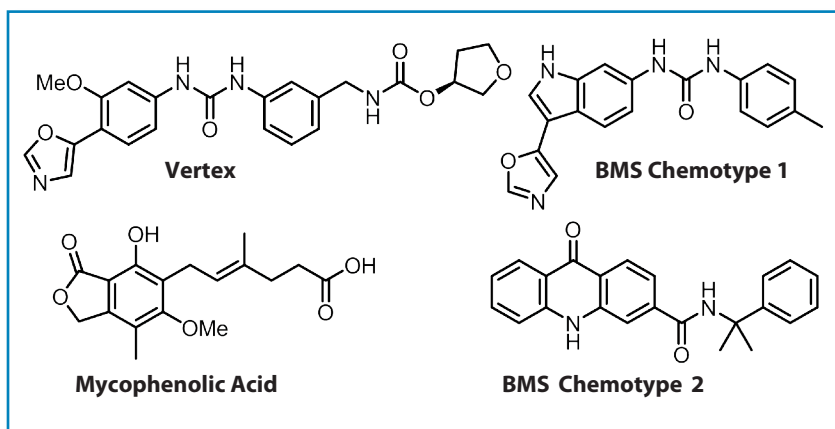


**cresset**

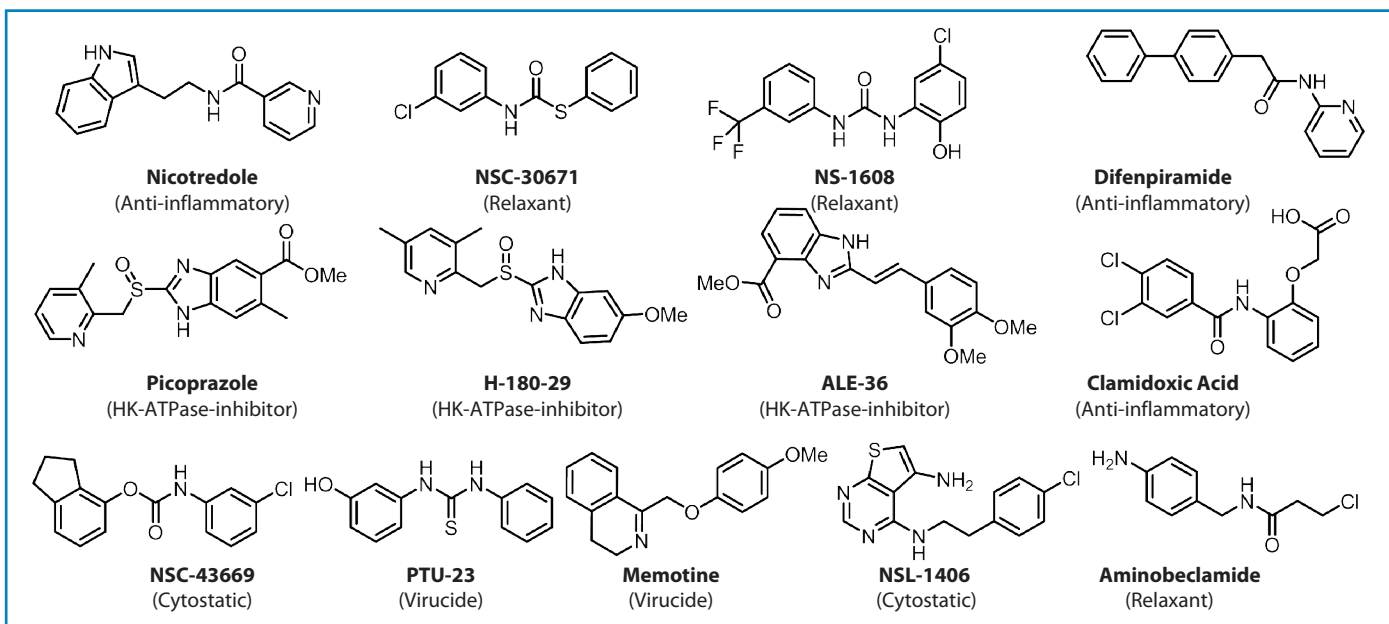
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Inositol monophosphate dehydrogenases (IMPDHs) are vital enzymes in the production of GMP, GDP and GTP. IMPDH is important for cell growth and its inhibition is potentially useful in immunosuppression, anticancer therapy, psoriasis, rheumatoid arthritis and antiviral chemotherapy. Our client, a small biotechnology company, wished to find new candidates for IMPDH from existing drugs that had been developed for other indications. Such compounds are more likely to be well tolerated and easily deliverable with good ADME and toxicity profiles, and were therefore lower risk candidates.

6 known human IMPDH inhibitors (4 shown right) were used to Field search the World Drug Index (WDI). The putative bioactive conformations of each ligand were derived using FieldTemplater to compare the 6 known ligands with ligands from available X-ray structures. 14 seed structures, covering all the putative bioconformers were then screened against the whole database using FieldScreen.



The top 1,000 results from each search were then analysed to find the drugs that were common to as many of the seeds as possible. 19 drugs were found that were common to 10 or more of the seeds. 13 of these are shown below:



It is striking that these drugs are associated with therapeutic actions that could be related to the known action of IMPDH (with the possible exception of the relaxants). Detailed investigation of a related series of IMPDH inhibitors has revealed that the oxazole moiety can act as a potential source of reactive metabolites, which can cause toxic side-effects<sup>1</sup>. Significant resource has been employed to replace this undesirable moiety by various groups. It is notable that none of the drugs identified by Cresset contains this moiety. Further investigation of this list has not been possible but one literature reference has been found that associates omeprazole and other HK-ATPase inhibitors with immunomodulation<sup>2</sup>.

<sup>1</sup> Beevers et al. Bioorganic & Medicinal Chemistry Letters 16 (2006) 2535-2538

<sup>2</sup> Peddicor T. E., Olsen K. M., Collier D. S. (1999) Crit. Care. Med. 27 (1): 90-4