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Low molecular weight indole fragments as IMPDH inhibitors

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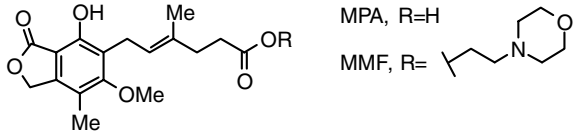
Abstract—The study of non-oxazole containing indole fragments as inhibitors of inosine monophosphate dehydrogenase (IMPDH) is described. The synthesis and in vitro inhibitory values for IMPDH II are discussed.

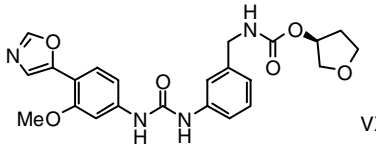
Proliferation of T and B lymphocytes is dependent on access to a large cellular pool of guanine nucleotides. Within the de novo purine biosynthetic pathway a key rate-limiting step is oxidation of inosine-5′-monophosphate to xanthosine-5′-monophosphate by the NAD-dependent enzyme inosine monophosphate dehydrogenase (IMPDH).[1] Two isoforms of the enzyme have been identified and designated type I and type II.[2] Of these it is IMPDH type II that is upregulated in actively proliferating cell types.[3,4] As a consequence inhibition of IMPDH II has become an attractive immunology target for the treatment of transplant rejection, psoriasis, systemic lupus erythematosus and rheumatoid arthritis.[5]

Mycophenolic acid (MPA) is a potent uncompetitive reversible inhibitor of both IMPDH I and II, which has been approved for clinical utility in transplant rejection in the form of Cellcept® or mycophenolate mofetil (MMF), an ester prodrug of MPA.[6]

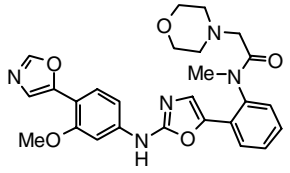
Despite clinical efficacy of Cellcept® its use in other disease end points is compromised by dose-limiting gastrointestinal (GI) side effects and efforts have focused on discovery of new IMPDH inhibitors with an improved therapeutic window.[7] Towards this end Vertex and BMS have reported *N*-[3-methoxy-4-(5-oxazolyl)phenyl-containing compounds, VX497[8] and BMS-337197[9] as potent IMPDH II inhibitors.



From protein/inhibitor crystallographic studies a binding model for VX497 complexed to IMPDH II has been reported.[8] Key interactions include formation of H-bonds between the NH of Gly 326 and the oxazole moiety, and carboxylate of Asp 274 with the urea NH's. In addition, favourable hydrophobic interactions result from binding of the methoxy in a pocket defined by the side chains of Asn 303 and Arg 332, and π-stacking of the phenyl oxazole with the bound nucleotide precursor. Based on this similar binding interactions have been suggested for BMS-337197 and used in the design of new IMPDH II inhibitors.[10]



VX-497



BMS-337197

Keywords: IMPDH; Inosine monophosphate dehydrogenase; Fragment.
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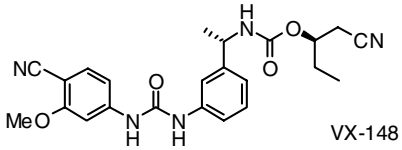
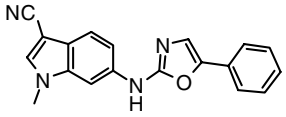
We have disclosed two new classes of oxazole-containing IMPDH II inhibitors.[11,12] Further detailed investigation of these series revealed the oxazole moiety as a potential source of reactive metabolites. Recently, a number of non-oxazole nitrile containing inhibitors have been reported in VX148[13] and indole **1**.[14] This report describes our preliminary efforts to discover non-oxazole containing IMPDH II inhibitors using a fragment optimisation approach.





In a fragment study, commercially available 3-cyanoindole (**2**) has been reported to inhibit IMPDH II at approximately 30 μM.[15] GOLD[16] docking of **2** using an in-house crystal structure of IMPDH II was undertaken to define potential binding modes. Interestingly, the best fit predicts the indole NH forming a H-bond to Asp 274 with the nitrile potentially forming a hydrogen bond with Gly 326 (Fig. 1).

To further explore this concept with a view to improving the potency of **2** for IMPDH II, a series of indole fragments containing hydrogen bond acceptor groups at the 3-position were synthesised as described in Schemes 1–4 or obtained from commercial sources. A number of fragments substituted on the indole core were also prepared, to establish precise structural requirements and to assess potential sites for further elaboration.

3-Formylindole (**3**) was commercially available. The 3-carbamoyl derivative **4** was prepared directly from **2**, by reaction with hydrogen peroxide and sodium hydroxide in methanol. A series of heteroaromatic derivatives were also prepared. The 4-pyridyl indole **5** was synthesised by dehydrogenation of a commercially available precursor (Scheme 1). 1-Phenylsulfonylindol-3-yl boronic acid was reacted with aromatic bromides to prepare,

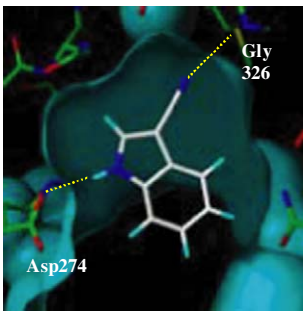
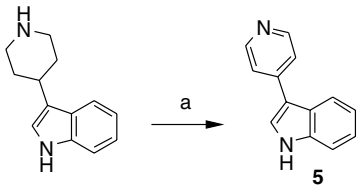
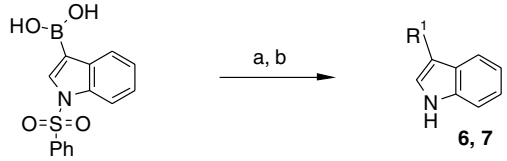


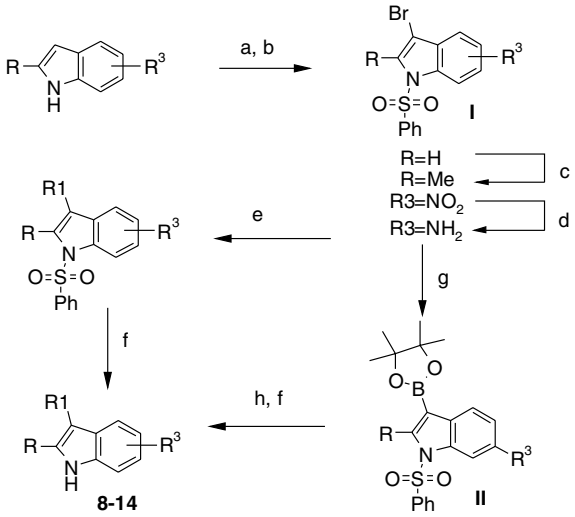
Figure 1. Indole **2** docked into IMPDH II, with potential H-bonds.



Scheme 1. Reagents and condition: (a) 1,1-Diphenylethylene, Pd/C, 250 °C (30%).



Scheme 2. Reagents and condition: (a) R^1-Br, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, microwave, 120–150 °C (74–81%); (b) NaOH, dioxane, reflux; or KOH, MeOH, reflux (86%).



Scheme 3. Reagents and conditions: (a) *N*-Bromosuccinimide, DCM, rt (77–93%); (b) $PhSO_2Cl$, TBAB, NaOH, toluene, H_2O; or NaH, THF; then $PhSO_2Cl$ (84–100%); (c) LDA, THF, −40 °C; then MeI, −40 °C to −20 °C; (d) $SnCl_2$, EtOH, H_2O, reflux (37–83%); (e) R^1-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, microwave, 120–150 °C (75–90%); (f) NaOH, dioxane, reflux; or, KOH, MeOH, reflux (12–86%); (g) bis(pinacolato)diboron, $Pd(dppf)Cl_2$, KOAc, DME, 80 °C (or THF, microwave, 150 °C) (46%); (h) R^1-Br or R^1-Cl, $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, microwave, 120–150 °C (51–90%).

after basic hydrolysis of the indole protecting group, indoles **6** and **7** (Scheme 2). Using similar chemistry, a set of related derivatives, additionally substituted on the indole core, were prepared starting from 6- and 7-nitroindole and 2-methylindole, (Scheme 3). The key step employed either Suzuki reaction of bromoindoles **I** with heteroaromatic boronic acids in the synthesis of **8**, **10**, **12** and **14**, or Suzuki reaction of the pinacolboronate ester **II** with heteroaromatic bromides (or chloride towards **11**) in the synthesis of **9**, **11** and **13**. The 2-methyl group of **14** was successfully introduced by deprotonation of the bromo nitroindole **I** followed by methyl iodide