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3-Cyanoindole-Based Inhibitors of Inosine Monophosphate Dehydrogenase: Synthesis and Initial Structure–Activity Relationships

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Abstract—A series of novel small molecule inhibitors of inosine monophosphate dehydrogenase (IMPDH), based upon a 3-cyanoindole core, were explored. IMPDH catalyzes the rate determining step in guanine nucleotide biosynthesis and is a target for anticancer, immunosuppressive and antiviral therapy. The synthesis and the structure–activity relationships (SAR), derived from in vitro studies, for this new series of inhibitors is given.

Inosine monophosphate dehydrogenase (IMPDH), a key enzyme in the de novo synthesis of guanosine nucleotides, catalyzes the irreversible NAD-dependent oxidation of inosine-5′-monophosphate (IMP) to xanthosine-5′-monophosphate (XMP).[1] Two distinct cDNA's encoding IMPDH have been identified and isolated. These transcripts labeled type I and type II are of identical size (514 amino acids).[2,3] IMPDH II activity is markedly upregulated in actively proliferating cell types including cancers and activated peripheral blood lymphocytes.[4]

CellCept® (mycophenolate mofetil, MMF), a prodrug of mycophenolic acid (MPA), has clinical utility due to its inhibition of IMPDH, for the treatment of transplant rejection. Dose-limiting gastrointestinal (GI) toxicity exhibited from administration of either MMF or MPA limits this drug's potential for treatment of other autoimmune disorders, such as psoriasis and rheumatoid arthritis.[5]

Vertex reported in 2000 a structurally new chemical series exemplified by VX-497 shown in Figure 1.[6] We recently reported the discovery of BMS-337197 as a potent inhibitor of IMPDH.[7] The *N*-[3-methoxy-4-(5-

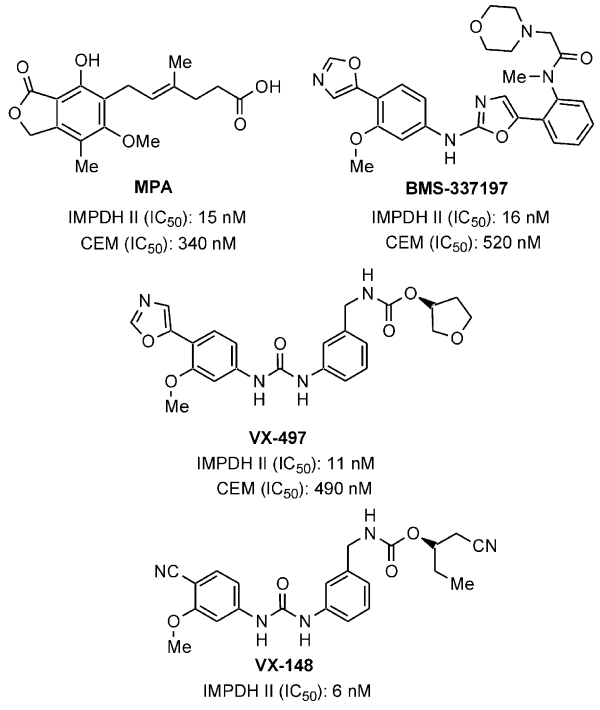

Figure 1. The chemical structures of MPA, BMS-337197 VX-497 and VX-148. IMPDH II inhibitory data for VX-148 as reported by Vertex.[8]

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oxazolyl)phenyl moiety is a common structural element that is present in both VX-497 and BMS-337197. Recently, Vertex disclosed the structure of VX-148, its second generation inhibitor that is conspicuously devoid of the terminal oxazole moiety.[8] This disclosure prompted us to reveal our efforts to replace the oxazole moiety with a nitrile residue for our key chemical series exemplified by BMS-337197.

A comparison of inhibitory values for VX-497 and **1** reveals that the carbamate side chain for this chemical series contributes little in the way of enhancing binding affinity to IMPDH II (Fig. 2). Similar inhibitory values are also seen for BMS-337197 and **3**. However, the carbamate side chain of VX-148 contributes significantly to the potency of this molecule (compare VX-148 and **2**). Without the side chain to enhance binding affinity, the two chemical series, exemplified by **2** and **4**, are of similar potency (Fig. 2). Our hypothesis was that the reduction in the binding affinity may be due to the non-optimal hydrogen bonding distance between the nitrile residue of compounds **2** and **4** (Fig. 2) and the N–H of Gly 326, in comparison to the complementary measurement for the oxazole moiety of compounds **1** and **3** (vide infra).

We recently reported the identification of the 3-(oxazol-5-yl) indole based IMPDH inhibitors (Fig. 2, **5**–**7**) and demonstrated that the 3-(oxazol-5-yl) indole group serves as a excellent replacement of the aniline moiety of the urea derivative (**1**) and BMS-337197.[9] Based on the reported protein/inhibitor crystallographic studies,[10] our strategy was to investigate an alternative spatial placement for the nitrile moiety allowing for a more effective engagement with the N–H of Gly 226 while maintaining the contribution to binding from the inhibitor/protein interactions at the methyl binding pocket (Fig. 3).

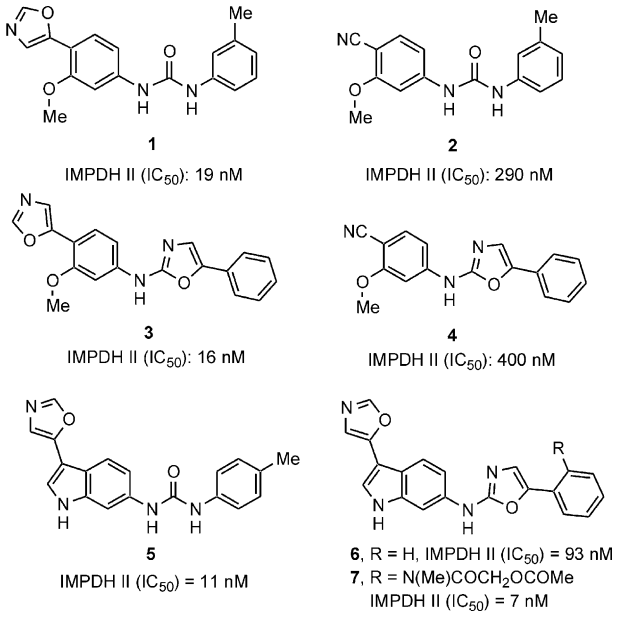


Figure 2. IC_{50} values for the oxazole- and nitrile-based IMPDH inhibitors.

The use of the indole core offered the opportunity to suitably position the terminal nitrile residue and the flexibility to probe the methyl binding pocket. We reasoned that by virtue of being one carbon removed from the phenyl group, the nitrile residue at the C-3 position on the indole will be spatially closer to the N–H of Gly 326 and thus will be able to more effectively engage this crucial interaction between the ligand and the protein (Fig. 3).

The synthetic pathways utilized in the preparation of 3-cyanoindole based inhibitors of IMPDH are outlined in Schemes 1–4. The ureas (**8**–**12**, Table 1) were prepared in a straightforward fashion by condensing 6-amino-3-cyanoindole with the corresponding isocyantes as outlined in Scheme 1. The 2-aminooxazole-cyanoindole series of compounds (**13**–**32**, Table 2) were synthesized via a tandem iminophosphorane/hetrocumelene mediated annulation as outlined in Schemes 2–4.[11] It is important to point out that the BOC and Fmoc groups that were used to protect the meta and para substituted benzylic amines prior to cyclization (Schemes 3 and 4) were not compatible for the benzylic amine that was *ortho* substituted. More specifically, polar products were obtained during the generationof the phenacyl bromide from the enolether (Scheme 2). This problem was cir-

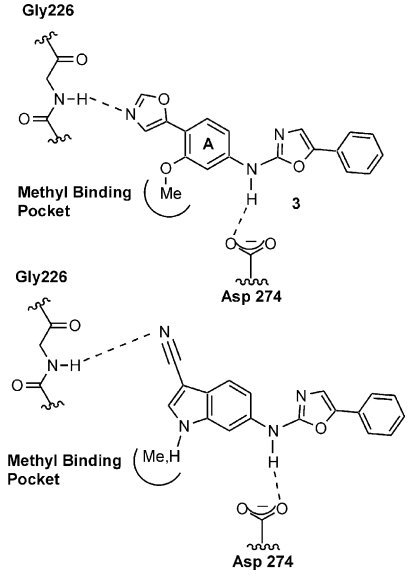
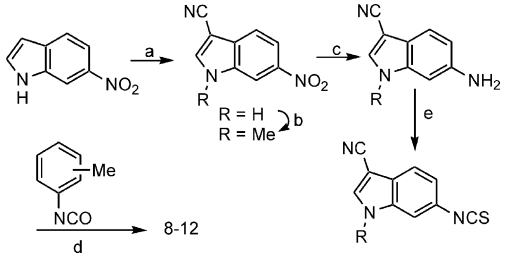
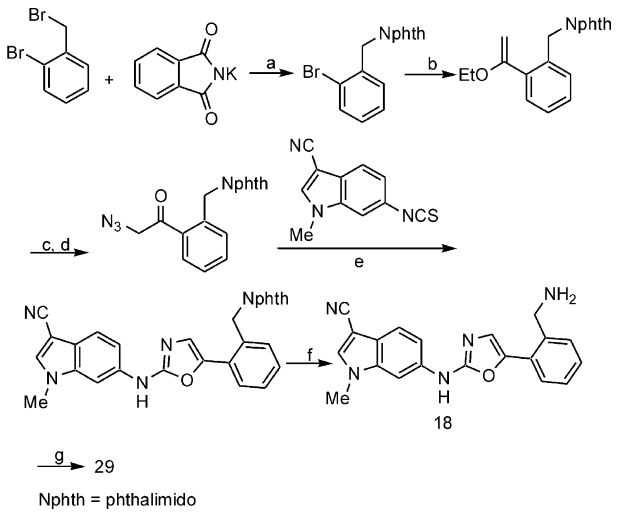


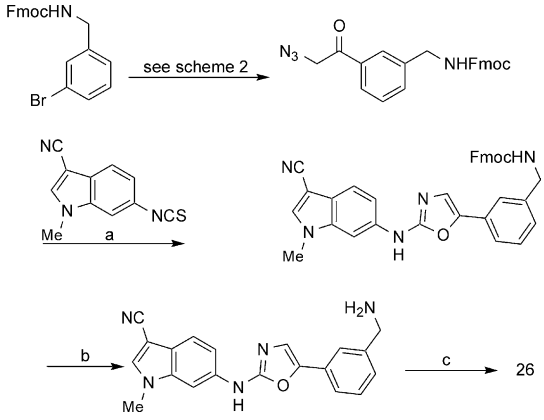
Figure 3. A comparison of binding modes for **3**, an analogue of BMS-337197 and an indole-based inhibitor.



Scheme 1. (a) $ClSO_2NCO$, CH_3CN, DMF, 90 °C (64%); (b) NaH, THF, MeI, 0 °C, (91%); (c) Pd/C, MeOH, 15 psi, 1 h (99%); (d) dioxane reflux, 15 min (75–85%); (e) 1,1′thiocarbonyldi-2(1H)-pyridone, CH_2Cl_2, rt, 90%.



Scheme 2. (a) DMF, 80 °C, 18 h, (79%); (b) $Pd(PPh_3)_2Cl_2$, $CH_2C(OEt)(Bu_3Sn)$, dioxane, 80 °C, 5 h (73%); (c) NBS, H_2O, THF, rt; (d) NaN_3, 90 min (79% for c, d); (e) PPh_3, dioxane, 100 °C, 40 min (60%); (f) NH_2NH_2, EtOH, 90 min (60%); (g) CDI, $OHCH_2CH_2CN$, DMF, rt, 90 min, (85%).

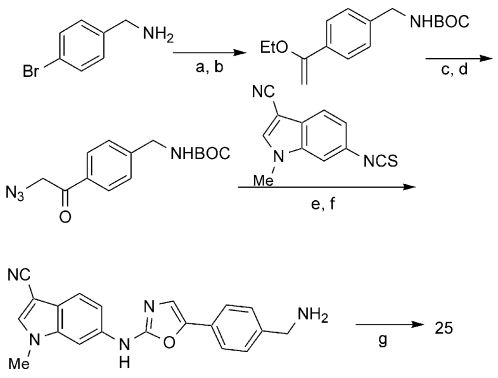


Scheme 3. (a) PPh_3, dioxane, 90 °C, 60 min (64%); piperidine, DMF, rt, (91%); 2-naphthoyl chloride, DMF, Et_3N, rt.

cumvented by using the phthalimido protecting group. A few representative examples are outlined in Schemes 2–4.

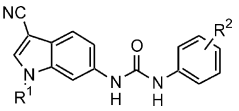
Preliminary SAR of the cyanoindole urea series (Table 1) suggested that there was no improvement in either the enzyme or cell potency when compared to the oxazole urea (**1**) or the cyanophenyl urea (**2**) class of compounds. Although these results were disappointing, one SAR trend is noteworthy. Unlike the 3-(oxazol-5-yl) indole urea series (**5**) the corresponding des-methyl analogue in the cyanoindole series **12** is inactive, suggesting that there are subtle differences in the orientations of these two classes of compounds with respect to interaction with N–H of Gly 326 and the methyl binding pocket.

The SAR trends in the 2-aminooxazole-cyanoindole series of compounds (**13**–**32**) is outlined in Table 2. Unlike the urea **8**, the parent compound in the 2-aminooxazole–cyanoindole series with no substituents on the phenyl ring (**13**) is a reasonably potent inhibitor of



Scheme 4. (a) (BOC)2O, DIPEA, CH_2Cl_2, rt (100%); (b) $Pd(PPh_3)_2Cl_2$, $CH_2C(OEt)(Bu_3Sn)$, dioxane, 100 °C, 5 h; (c) NBS, H_2O, THF, rt (20% for b, c); (d) NaN_3, acetone, H_2O, 50 °C (100%); (e) PPh_3, dioxane, 100 °C, 60 min (45%); (f) TFA, CH_2Cl_2, rt, (100%); (g) DMF, ClCO-*t*Bu, 0 °C to rt (60%).

Table 1. SAR of cyanoindole ureas

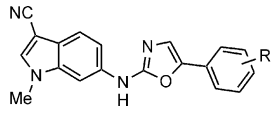


Compd	R^1	R^2	IMPDH II IC_{50}, μM	CEM IC_{50}, μM
1	NA	NA (UREA STD)	19	1.0
8	Me	H	0.63	—
9	Me	*o*-Me	>10,000	—
10	Me	*m*-Me	0.67	—
11	Me	*p*-Me	0.23	—
12	H	*p*-Me	>5000	—

IMPDH II with an IC_{50} of 33 nM. The potency of this compound is approximately 3-fold better than the corresponding analogue in the the 3-(oxazol-5-yl) indole aminooxazole series represented by compound **6**. The fact that the potency of this compound is approximately 10-fold better than the cyanophenyl oxazole compound **4**, supports our initial hypothesis about the importance of the distance between the nitrile and the N–H of Gly 326.

In order to improve both the enzyme and cell potency, a series of amines, amides and carbamates off the phenyl group of compound **13** were synthesized. As Table 2 indicates there were no clear SAR trends both in relation to the position or the nature of substitution (for example, compounds **18**–**20**, **23**–**25** and **28**–**32**). It is also interesting to note that analogue **17** is significantly less potent than the corresponding compound in the 3-(oxazol-5-yl) indole aminooxazole series represented by compound **7**. The carbamates **28** and **29**, the side chains of which are related to VX-148 are also significantly less potent both in terms of their ability to inhibit IMPDH II and the T-cell proliferation response. The most potent compound in this series was compound **26** with an IC_{50} of 40 nM against IMPDH II that was comparable to the parent compound **13** (IC_{50} = 33 nM). However, both compounds **26** and **13** were significantly less potent in inhibiting T-cell proliferation in a CEM cell

Table 2. SAR of 2-aminooxazole-cyanoindole series



Compd	R	IMPDH II IC_{50}, μM	CEM IC_{50}, μM
13	H	0.033	8.0
14	*o*-Me	0.44	—
15	*m*-Me	0.49	>10
16	*p*-Me	>0.55	—
17	*o*-$NMeCOCH_2OAc$	0.266	—
18	*o*-CH_2NH_2	0.28	1.1
19	*m*-CH_2NH_2	0.18	3.5
20	*p*-CH_2NH_2	0.26	2.8
21	*m*-NHC(O)Ph	0.20	3.5
22	*m*-$CH_2NHC(O)Ph$	0.13	5.3
23	*p*-$CH_2NHC(O)Ph$	0.10	>10
24	*p*-$CH_2NHC(O)Me$	0.094	>10
25	*p*-$CH_2NHC(O)t$-Bu	0.18	4.9
26	*m*-$CH_2NHC(O)$2-napthyl	0.040	4.4
27	*m*-$CH_2NHC(O)$1-napthyl	0.084	2.5
28	*m*-$CH_2NHC(O)O(CH_2)_2CN$	0.24	>10
29	*o*-$CH_2NHC(O)O(CH_2)_2CN$	0.420	>10
30	*m*-$CH_2NHC(O)O(CH_2)_2NMe_2$	0.21	1.4
31	*m*-$CH_2NHC(O)O$-3-THF	0.260	>10
32	*o*-$CH_2NHC(O)O$-3-THF	0.420	>10

line when compared to BMS-337197 (BMS-337197 CEM $IC_{50} = 520$ nM vs 4 μM for compound **26**).

In summary, a series of cyanoindole based IMPDH inhibitors have been designed and synthesized as replacements for the *N*-[3-methoxy-4-(5-oxazolyl)phenyl moiety of VX-497 and BMS-337197. The SAR trends for this series differ significantly with respect to both BMS-337197 and the 3-(oxazol-5-yl) indole (**5**–**7**) series of IMPDH inhibitors.

References and Notes

1. Jackson, R. C.; Weber, G. *Nature* **1975**, *256*, 331.
2. Collart, F. R.; Huberman, E. *J. Biol. Chem.* **1988**, *263*, 15769.
3. Natsumeda, Y.; Ohno, S.; Kawasaki, H.; Kanno, Y.; Weber, G; Suzuki, K. *J. Biol. Chem.* **1990**, *265*, 5292.
4. Jayaram, H. N.; Grusch, M.; Cooney, D. A.; Krupitza, G. *Curr. Med. Chem.* **1999**, *6*, 561.
5. Sievers, T. M.; Rossi, S. J.; Ghobrial, R. M.; Arriola, E.; Nishimura, P.; Kawano, M.; Holt, ?. *Pharmacotherapy* **1997**, *17*, 1178.
6. Jain, J.; Almquist, S. J.; Shlyakhter, D.; Harding, M. W. *J. Pharm. Sci.* **2001**, *90*, 625.
7. Dhar, T. G. M.; Shen, Z.; Guo, J.; Liu, C.; Watterson, S. H.; Gu, H. H.; Pitts, W. J.; Fleener, C. A.; Rouleau, K. A.; Sherbina, N. Z.; McIntyre, K. W.; Witmer, M. R.; Tredup, J. A.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Cheney, D. L.; MacMaster, J. F.; Miller, L. M.; Berry, K. K.; Harper, T. W.; Barrish, J. C.; Hollenbaugh, D. L.; Iwanowicz, E. J. *J. Med. Chem.* **2002**, *45*, 2127.
8. Jain, J.; Almquist, S. J.; Heiser, A. D.; Shlyakhter, D.; Leon, E.; Memmott, C.; Moody, C. H.; Nimmesgern, E.; Decker, J. *Pharm. Exper. Ther.* **2002**, *302*, 1272.
9. Dhar, T. G. M.; Shen, Z.; Fleener, C. A.; Rouleau, K. A.; Barrish, J. B.; Hollenbaugh, D. A.; Iwanowicz, E. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3305.
10. Sintchak, M. D.; Nimmesgern, E. *Immunopharmacology* **2000**, *47*, 163.
11. Dhar, T. G. M.; Guo, J.; Shen, Z.; Pitts, W. J.; Gu, H. H.; Chen, B.-C.; Zhao, R.; Bednarz, M. S.; Iwanowicz, E. *J. Org. Lett.* **2002**, *4*, 2091, and references cited therein.