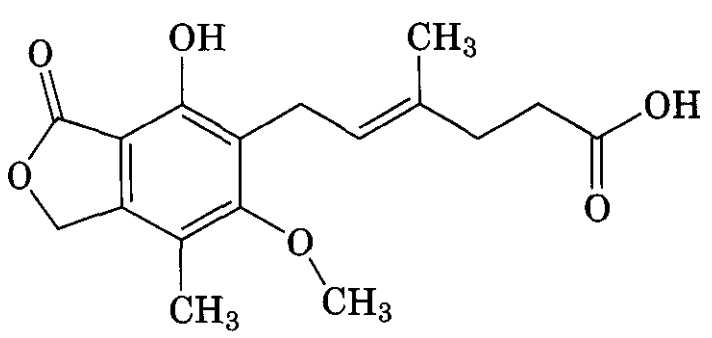
in human testing. The efforts with these two targets are described briefly below.

2.5.1 Inosine Monophosphate Dehydrogenase. Proliferative cells such as lymphocytes have high demands for the rapid supply of nucleotides to support DNA and RNA synthesis, as do viruses during their proliferative phase. The first dedicated step in the de *novo* biosynthesis of guanine nucleotides is conversion of inosinate to XMP, catalyzed by inosine monophosphate dehydrogenase (IMPDH).

$$\text{IMP} + \text{NAD}^+ \rightarrow \text{XMP} + \text{NADH}$$

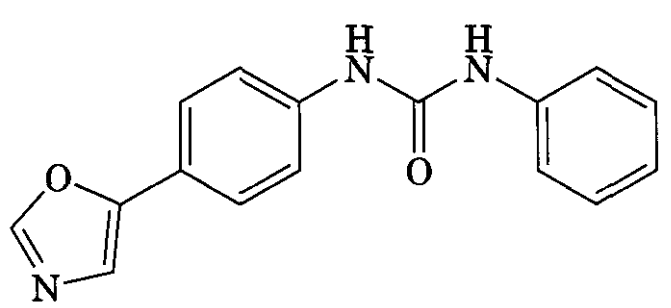
A prodrug form of (56) (mycophenolicacid), a noncompetitive inhibitor of IMPDH, is approved for human therapeutic use as an immunosuppressant (mycophenolate mofetil, CellCept). The use of this drug is hampered by gastrointestinal side effects probably related to the metabolism of the drug. A second class of IMPDH inhibitors is represented by the nucleoside analog mizoribine (also known as bredinin), a prodrug approved for human use in Japan. Such compounds competitively inhibit IMPDH in *vivo* after phosphorylation (128). These drugs validate the strategy of targeting IMPDH for the discovery of immunosuppressants. Other utilities that have been suggested for IMPDH inhibitors are antiviral and anticancer therapies.



(56) mycophenolic acid

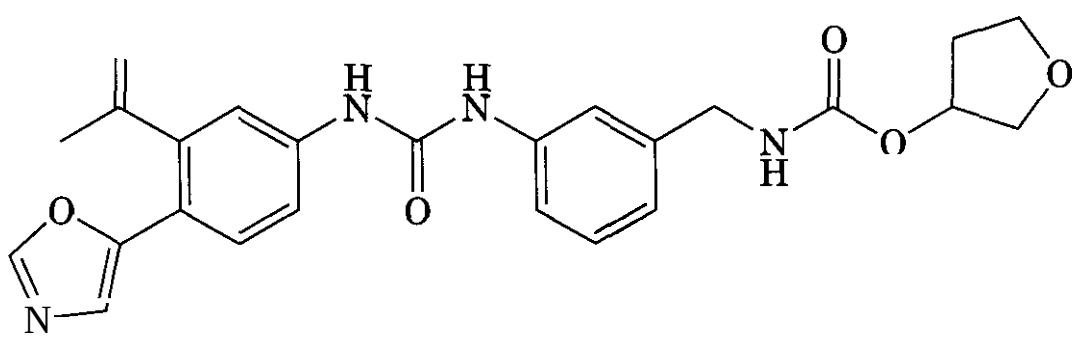
The structure of hamster IMPDH in complex with IMP and (56)was solved at Vertex in the mid-1990s (129). This allowed the visualization of a covalent intermediate, in which a cysteine thiol from the enzyme adds to C2 of the purine ring of the nucleotide substrate. An analogous covalent adduct is postulated to be a key catalytic intermediate during normal turnover (130). The structure was a key tool in the discovery of (57) (VX-497, merimepodip), a novel potent inhibitor of human IMPDH suitable for oral administration (131).

An experimental screen of a diverse library of commercially available compounds for inhibitors of IMPDH identified molecules with the phenyl, phenyloxazole urea scaffold (58) as weak inhibitors. Through use of the computational program DOCK (132), the initial inhibitors were built as models into the experimental structure of the crystalline complex of IMPDH, IMP, and (56). Structural analogs were generated to improve potency in an iterative process, guided by the structural modeling and the observed changes in potency for inhibition of human IMPDH.



(58)

After this process yielded compound (59), with nanomolar potency, an X-ray structure



(57) merimepodip