10.2 Nucleoside Analogs and Prodrugs

Most of the published agonists of TLR-7 have chemical structures that are reminiscent of nucleoside bases. This is not unexpected, given that the native ligand is a nucleic acid (ssRNA). Some of the first TLR-7 agonists discovered were in fact nucleosides, although their mechanism of action was not realized until much later. Loxoribine[25] (**1**) and isatoribine[26] (**2**) are two examples of nucleoside analogs that originally attracted interest because they were found to have *in vivo* antiviral effects in animal infection models (Figure 10.1). Interestingly, they had little to no direct antiviral activity and the effects seemed to be indirect. Ultimately, the antiviral activity was determined to be due, for the most part, to IFN-α that was induced following *in vivo* administration of the compounds. It was subsequently discovered that the mechanism by which these compounds elicited IFN-α production was by agonist activity on TLR-7.[27]

Isatoribine was originally discovered at ICN,[26] and later became the basis of a discovery program at Anadys Pharmaceuticals. In a preliminary proof of concept clinical trial, intravenous administration of isatoribine to patients infected with HCV resulted in a dose-related reduction of viral levels.[28] The compound was administered at doses of 200, 400, 600 and 800 mg and a dose-related reduction in plasma HCV levels was observed, with maximum reduction at 800 mg. At the highest dose, 8/12 patients had a decrease of $>0.5\log_{10}$ in HCV RNA level. The decline in HCV level was correlated with an increase in plasma IFN-α and blood interferon-stimulated gene (ISG) levels. This clinical trial was informative; however, when dosed orally, isatoribine had poor bioavailability and was associated with gastrointestinal side effects.

Anadys subsequently undertook an effort to optimize isatoribine for oral delivery. The successful approach was the identification of an appropriate prodrug to enhance bioavailability, which also addressed the issue of gut side effects (Figure 10.2). The prodrug strategy was to block multiple sites on the structure.[29] The 2′- and 3′-hydroxyl groups of the ribose were converted to their acetate esters to increase the lipophilicity and therefore presumably increase the degree of absorption in the gastrointestinal tract. Additionally, the guanine oxo group at C4 was removed, further increasing lipophilicity and rendering the

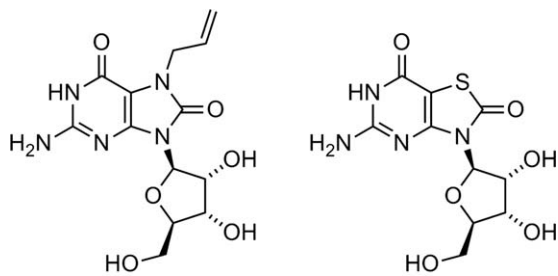

Figure 10.1 Examples of nucleoside TLR-7 agonists.