

levels was correlated with dose-related increases in IFN markers. This study provided support to the viability of this prodrug strategy.

10.3 Imidazoquinoline Agonists

The imidazoquinoline class of TLR-7 agonists was discovered somewhat fortuitously at 3M Pharmaceuticals.³² The original program was directed toward finding inhibitors of herpes virus replication that were based on the known anti-herpes adenine derivative **5** (Figure 10.3). A series of adenine analogs based on the imidazoquinoline structures **6** and **7** were synthesized and found to inhibit replication of herpes virus in a mouse model of infection, but had no direct antiviral activity *in vitro*. The antiviral activity of these compounds *in vivo* was determined to result from induction of IFN- α by a specific mechanism that was unknown at the time. The *in vitro* assay used for subsequent compound optimization was based on IFN- α induction in human PBMCs. Ultimately this class of compounds was validated to act as agonists of TLR-7, which is consistent with their IFN-induction property.³³ Some analogs were found to be selective for TLR-7 and others were dual agonists of both TLR-7 and TLR-8.

A general overview of the SAR of this series is summarized in Figure 10.4. The amine group at C4 is required for activity. Comparing the series in Figure 10.5, the parent amine **9** has a minimum effective concentration (MEC) for IFN- α induction of $0.5 \mu\text{g mL}^{-1}$. Replacement of the amine with other groups, such as OH or H, in compounds **10** and **11**, respectively, among others, results in inactive compounds.

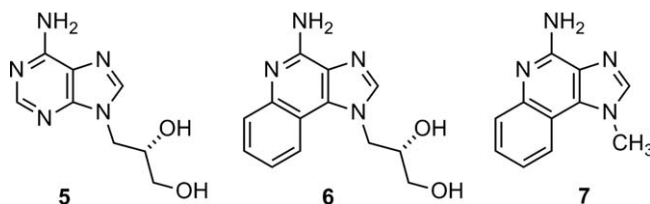


Figure 10.3 Basis for the discovery of imidazoquinolines.

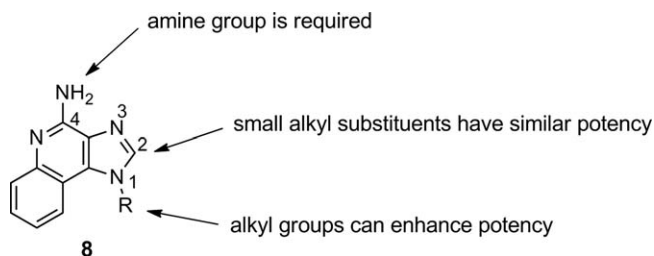


Figure 10.4 Overview of imidazoquinoline SARs.