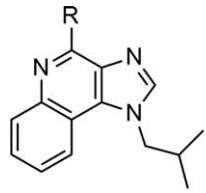
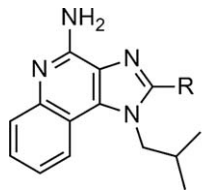


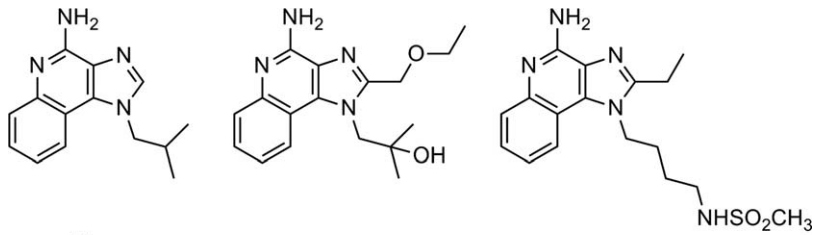
| | R | MEC (μg/mL) |
|---|---|---|
| **9** | $NH_2$ | 0.5 |
| **10** | OH | no induction |
| **11** | H | no induction |

**Figure 10.5** Effects of replacing the amino group.



| | R | MEC (μg/mL) |
|---|---|---|
| **11** | H | 0.5 |
| **12** | $CH_2CH_3$ | 0.05 |
| **13** | n-Bu | 0.01 |

**Figure 10.6** Substitution of imidazoquinolines at C2.




**11**
**Imiquimod**

**15**
**R-848**
**Resiquimod**

**16**
**R-852**
**PF-4878691**

**Figure 10.7** Imidazoquinolines evaluated clinically. Resiquimod and PF-4878691 were evaluated in HCV.

Compounds with small alkyl and substituted alkyl groups at C2 trended towards having greater potency relative to their unsubstituted parent compounds. Some representative examples are shown in Figure 10.6. Replacing the H at C2 of **11** with an ethyl group resulted in a 10-fold improvement in potency. A butyl group at C2 gave a 50-fold improvement in potency relative to H. Finally, a significant number of analogs with varying substituents at N1 had similar or improved potency.

This effort resulted in the discovery of imiquimod, **11** (Figure 10.7) now marketed under the trade-name Aldara for the treatment of genital warts associated with human papillomavirus infection.[34] Imiquimod is administered topically and, consistent with its mechanism of action, induces local production of IFN-α. Because it is topical, the antiviral effects also occur locally and the systemic exposure of the drug and systemic pharmacodynamic effects are minimal. Based on these IFN-α induction properties, 3M subsequently pursued