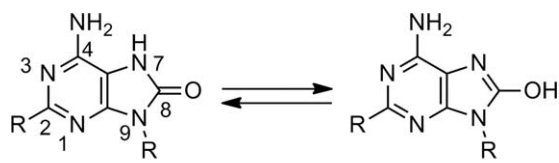
replicon activity in serum from subjects in the 6 and 9 mg groups. The conclusion was that the subjects in the 6 and 9 mg doses had significant pharmacologic activation of TLR-7. Subjects in all groups experienced adverse events and one subject in the 9 mg group experienced serious adverse events. The side effects were generally consistent with flu-like symptoms that result from administration of interferon and PEG-IFN. Given that the serum antiviral activity was only observed at doses that also resulted in adverse events, the investigators concluded that the therapeutic window would provide a substantial challenge to PF-4878691 for use in HCV therapy. An unanswered question from this study is whether doses of PF-4878691 that are below the threshold for systemic pharmacologic activity and therefore below levels that cause adverse events would have beneficial antiviral effects in HCV patients.

10.4 8-Oxopurine and 8-Oxodeazapurine Agonists

With the knowledge that the imidazoquinoline interferon inducers identified by 3M bear a resemblance to purine nucleoside bases, Dainippon Sumitomo Pharmaceuticals together with Gifu University sought to identify compounds that induce interferon by screening purine and pyrimidine derivatives in their compound library. From this exercise, a class of 8-oxopurine derivatives (**17a**), also referred to as their alternative tautomer 8-hydroxyadenines (**17b**), was identified (Figure 10.8).[38,39] The initial compounds were weak inducers of IFN-α *in vitro* in mouse splenocytes. This series became the basis of an optimization program to reach potent and selective TLR-7 agonists.

Initially, a systematic exploration of the SARs of substituents around the 8-oxopurine core was undertaken using an assay that measured production of IFN-α in mouse splenocytes as a function of compound concentration.[38] The carbonyl group at C8 was found to be important for activity and was a key feature of future analogs. Small alkyl groups at N9 were found to improve potency, as illustrated in Figure 10.9. The unsubstituted parent **18** was inactive at or below 10 μM, whereas the *n*-butyl (**19**) and benzyl substituents (**20**) had measurable interferon induction activity with an MEC of 10 μM. For comparison, the MEC for imiquimod in this assay was 1 μM. A benzyl group at N9 was generally found to provide good activity, so **20** was used as the basis for the next round of optimization.



17a **17b**

Figure 10.8 The 8-oxopurine/8-hydroxyadenine series identified by Dainippon Sumitomo Pharmaceuticals.