unmasking of the phosphoramidate prodrug to give the 5′-monophosphate followed by hydrolysis of the C6-purine moiety employing adenosine deaminase-like protein 1 (ADAL-1).[52,53] Examples of guanosine nucleotide analogs where these prodrug strategies have been applied include the clinical candidates BMS-986094 (formerly INX-189)[54–56] (**21**, Figure 12.12), IDX-184[57,58] (**22**, Figure 12.12) and PSI-353661[59] (**24**, Figure 12.13). In each case, their corresponding nucleoside derivatives were weakly active in the HCV replicon whole cell system, yet their triphosphates were good inhibitors of the HCV polymerase *in vitro*. Preparation of these prodrug derivatives led to a 10- to >8000-fold improvement in whole cell replicon potency.[55,57,59] In the case of IDX-184 (**22**), the prodrug moiety incorporates a SATE unit. Decomposition of the IDX-184 promoiety is believed to proceed through both CYP450-dependent and -independent processes, releasing as one of its by-products episulfide. For IDX-184, the formation of intracellular 2′-*C*-methylguanosine triphosphate levels was 100-fold higher in both human and animal hepatocytes than that seen on exposure to 2′-*C*-methylguanosine.[57] Subsequent *in vivo* studies with rats and monkeys showed that oral IDX-184 resulted in a high liver-to-plasma (95% liver extraction) ratio with low plasma levels of the 2′-*C*-methylguanosine metabolite.[57,58] In human clinical studies, oral administration of IDX-184 resulted in low but dose-proportional exposure of the prodrug with a rapid disposition phase and an estimated oral bioavailability

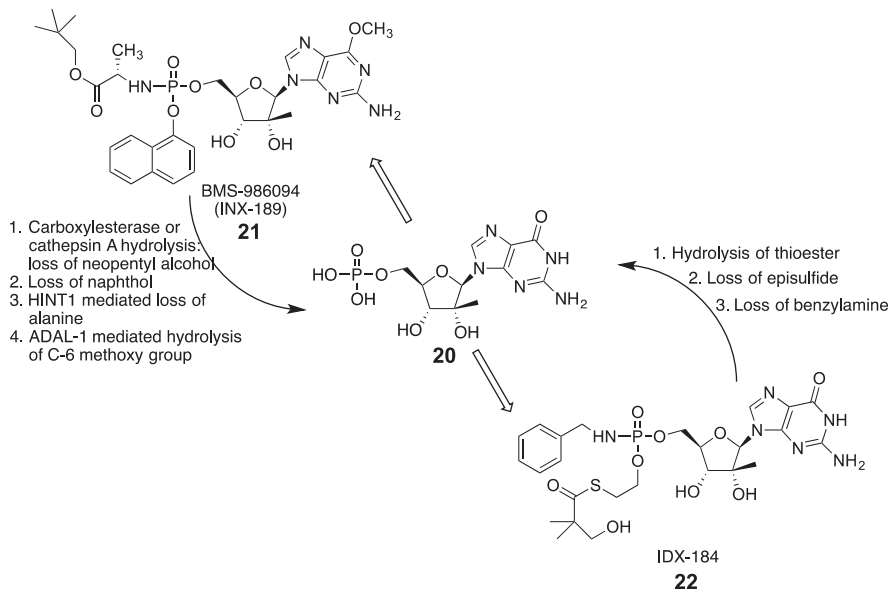

Figure 12.12 BMS-986094 (INX-189) (**21**) and IDX-184 (**22**) are phosphoramidate liver targeting produgs of 2′-*C*-methylguanosine 5′-monophosphate (**20**). BMS-986094 also employs a methoxy group at the C6 position of the purine base as a promoiety to mask the polar nature of the guanine base. Both agents were developed for the treatment of HCV infection.