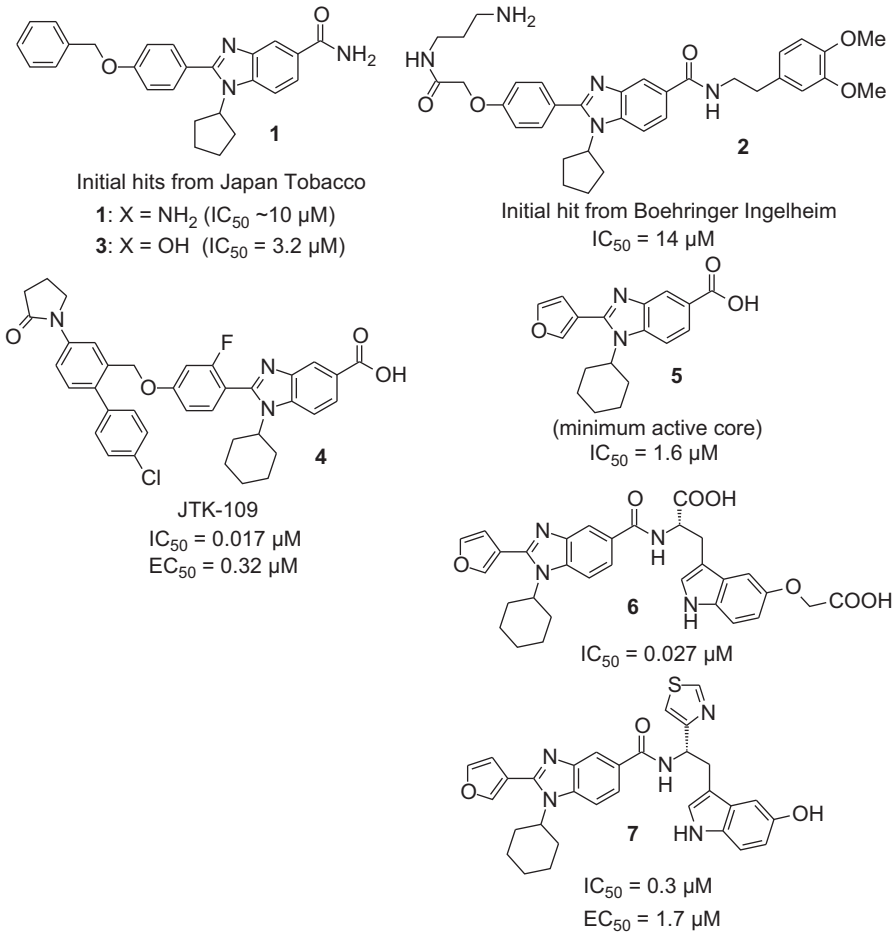

Figure 8.2 Non-nucleoside benzimidazole inhibitors from Japan Tobacco and Boehringer Ingelheim.

left-hand side aryloxy substituent interacted with protein. Guided by this information and using high-throughput-directed libraries, small benzimidazole-5-carboxylic acid analog **5** was initially established as the minimum core for biochemical activity.[13b] At the time these discoveries were made, cell culture systems were not yet available to establish whether the mechanism by which these benzimidazole derivatives were inhibiting NS5B function *in vitro* was relevant to HCV replication. Characterization of the biochemical profile of **2** indicated that inhibition by this compound was non-competitive with the process of nucleotide triphosphate incorporation on to the nascent RNA chain. Order of addition experiments suggested that the compounds lacked the ability to inhibit processive chain elongation, instead inhibiting the initiation phase of HCV polymerase activity.[14]