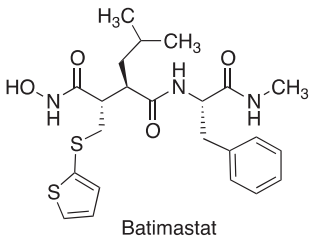
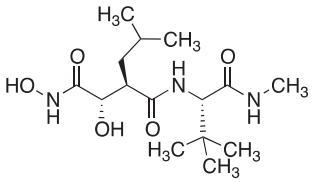
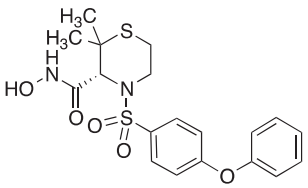
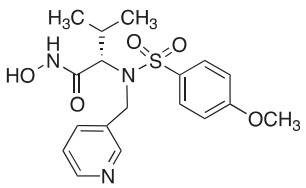
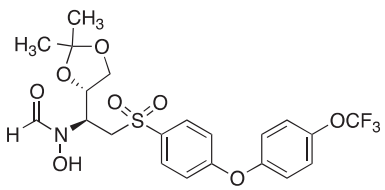

Batimastat


Marimastat

The second generation of MMP inhibitors includes non-peptidic compounds that are more specific, probably because they have been designed on the basis of structural studies of the MMP active site by nuclear magnetic resonance (NMR) and X-ray crystallography. Several of these compounds entered phase III clinical trials to treat many types of cancer, but those that showed only partial selectivity failed. In the first subgroup, bearing a hydroxamic function, are prinomastat (AG3340) and MMI-270 (CGS-27023A). Phase II clinical studies of prinomastat for early stage cancers are still ongoing, but phase III trials for advanced prostate and non-small cell lung cancer (NSCLC) were stopped because they did not show beneficial effects.[35] Clinical studies with MMI-270 were advanced to phase II, but they were interrupted because of poor patient tolerance. The reverse hydroxamate ABT-518 was designed to overcome the metabolic instability of hydroxamates, which is due to reduction of this group to an amide. This compound, which is a potent, orally bioavailable, selective inhibitor of MMP-2 and -9, entered phase I/II clinical trials for some solid tumors.[36]


Prinomastat (AG-3340)


MMI-270 (CGS-27023)


ABT-518

Other functional groups that can interact with the Zn^{2+} cation are the carboxy and mercapto moieties. Among the carboxylic acid-based specific inhibitors, the development of tanomastat (BAY 12-9566) was discontinued after phase III studies for treatment of several cancers, whereas S-3304 (a potent, orally active, non-cytotoxic inhibitor of MMP-2 and -9)[37] entered phase II trials for the treatment of some solid tumors. Rebimastat (BMS-275291) is a thiol-based inhibitor that selectively inhibits MMP-1, -2, -8, -9, and -14 and has entered phase II/III clinical trials in advanced NSCLC.