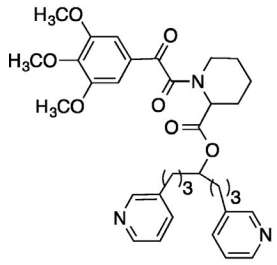
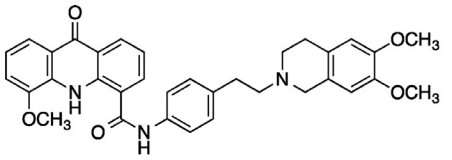
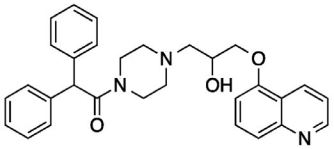
combination with etoposide or adriamycin, resulted in marked inhibition of metastases in refractory small cell lung cancer patients,[51] and another clinical study showed that it increases the antitumor efficiency of docetaxel.[52] The related compound MS-073 has been used to study the brain distribution of several neurokinin-1 antagonists, proving that some of them are effectively transported by Pgp across the blood–brain barrier.[53] Tariquidar (XR9576) underwent a phase II study in chemotherapy-resistant advanced breast cancer.[54] Zosuquidar (LY-335979), one of the most potent Pgp inhibitors described to date,[55] has fewer pharmacokinetic interactions than other MDR modulators because of its low affinity for P450 cytochromes, and advanced clinical studies on AML patients showed that it restores drug sensitivity.[56] Pharmacokinetic studies with ONT-093 (OC-144-093) showed that this compound does not interact significantly with the metabolism of paclitaxel because it is not a CYP3A substrate[57] and that it is selective toward Pgp, being a good candidate for a clinically useful MDR modulator.[58]



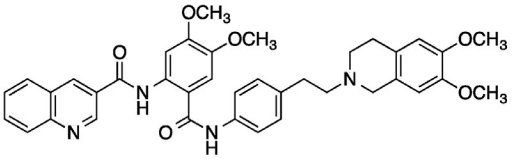
Biricodar (VX-710)



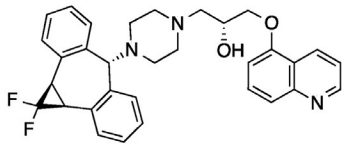
Elacridar (GF-120918)



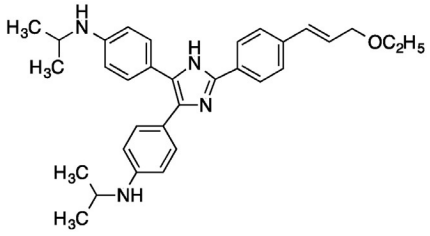
Dofequidar (MS-209)



Tariquidar (XR 9576)



Zosuquidar (LY-335979)



ONT-093
OC-144-093

Other members of the third-generation chemosensitizers are laniquidar, a potent orally active MDR inhibitor that entered phase II clinical trials in metastatic breast cancer in combination with taxols,[59] and the triazineaminopiperidine derivative S-9788, which inhibits Pgp specifically but showed cardiac toxicity in phase I clinical trials—a drawback that could be circumvented by combining it with verapamil or valspodar.[60]