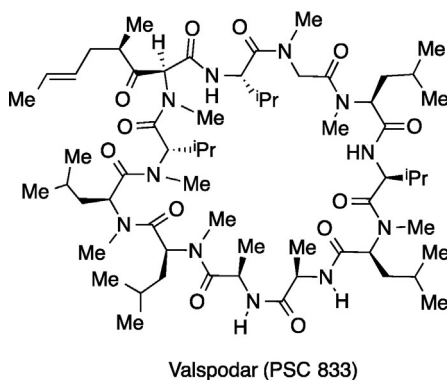
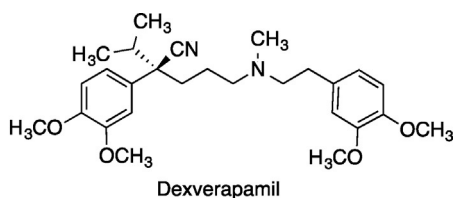


The second-generation compounds were analogs of the previously mentioned drugs, which were designed to reduce their toxicity by suppressing their additional pharmacological effects. Among them, the (*R*)-isomer of verapamil, named dexverapamil, lacks its cardiac effects while retaining the ability to inhibit Pgp, and valsopodar (PSC 833) is a structural analog of CsA that lacks its immunosuppressive effects. Unfortunately, both compounds are nonselective as Pgp inhibitors. For instance, valsopodar inhibits Pgp, MRP2, and other proteins of the ABC superfamily. In addition, its clinical value is uncertain because its specificity for Pgp is similar to that for cytochrome P450, which explains why valsopodar is involved in pharmacokinetic interactions with most anticancer drugs, requiring dose adjustment and leading to a high interpatient variability.<sup>46</sup> On the other hand, valsopodar and cyclosporin were thought to have an anticancer effect independently of their action on MDR,<sup>47</sup> but recent clinical results with valsopodar in patients with acute myeloid leukemia (AML) have been disappointing.<sup>48</sup>



For third-generation chemosensitizers, the development of compounds more specific and more potent as Pgp inhibitors than the earlier studied agents was attempted; however, most of these compounds showed unexpected toxic effects. Among those that have entered clinical trials, biricodar (Incel<sup>®</sup>, VX-710) and dofequidar (MS-209) inhibit Pgp and MRP1, elacridar (GF120918) inhibits Pgp and BCRP, tariquidar (XR9576) interacts with other ABC transporters rather than Pgp, and zosuquidar (LY335979) and ONT-093 (OC144-093) are selective inhibitors of Pgp. Biricodar is a simplified analog of tacrolimus, an immunosuppressive macrolactone that has an activity similar to that of cyclosporin. It has shown an optimal pharmacological profile in combination with paclitaxel,<sup>49</sup> and a phase II study has demonstrated its good safety and tolerability.<sup>50</sup> Dofequidar, in