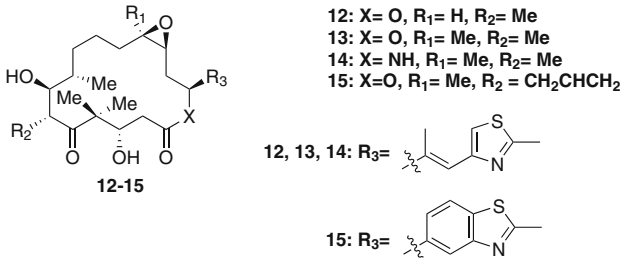

Fig. 6 Structures of cytotoxic natural products epothilone A (**12**) and B (**13**), semisynthetic derivative ixabepilone (**14**), and synthetic epothilone analogue sagopilone (**15**)

bacterial cell membrane, where it destabilizes the membrane by causing lipids to flip flop. This causes leakage and loss of membrane potential, leading to bacterial cell death (Silverman et al. 2003; Jung et al. 2004). During clinical trials, only a very small amount of patients displayed resistance towards daptomycin. For these cases, it has been shown to be the result of gene mutations which made the bacterial strains less susceptible, but not necessarily fully resistant (Arias et al. 2011). As a result of this, daptomycin will most likely retain an important role in clinics as last-resort antibiotic with a low risk of resistance for many years so come.

Epothilones

Originally isolated from the myxobacterial strain *Sorangium cellulosum* (Höfle et al. 1996), the epothilones (Fig. 6) are a group of macrolactones that were first thought to be useful antifungal compounds, until researchers at Merck showed that epothilones A and B had cytotoxic activity against multiple drug-resistant cancer cell lines (Bollag et al. 1995). This led to a fierce competition among Merck, Bristol-Myers Squibb, Schering-Plough (now merged with Merck), and Novartis, who all recognized the great potential of the epothilones as successors of the taxanes.

Although the epothilones showed great potential, it was soon discovered that their lactone ring was vulnerable to cleavage (Hunt 2009). To overcome these issues, extensive testing of semisynthetic derivatives was undertaken, which was made possible by learning from the total syntheses of epothilones A (**12**) and B (**13**) (Balog et al. 1996; Schinzer et al. 1997; Nicolaou et al. 1997). Ultimately, it was discovered that simply replacing the lactone for an amide solved the metabolic instability. This led to the development of epothilone analogue ixabepilone (**14**) by researchers at Bristol-Myers Squibb, after which approval was granted a few years ago. The development of synthetic epothilone by Bayer AG (formerly Schering AG), sagopilone (**15**), seems currently set on hold.

Carfilzomib (Kyprolis®)

Carfilzomib (**16**, Fig. 7) is a new small tetrapeptide (719.9 Da) with anticancer properties which has been approved in 2012 for the treatment of patients with relapsed and refractory multiple myeloma. It belongs to the new class of