Unique among macrolide antibiotics, fidaxomicin has an 18-membered ring (Venugopal and Johnson 2012). Non-antibiotic macrolides have quite varied structures and fall into two general classes: antifungal polyene macrolides with an amphipathic structure containing active lipophilic polyene chains and immunosuppressive/immunomodulatory macrolides such as the 23-membered macrolide lactone tacrolimus (Hirokazu Tanaka et al. 1987; Mesa-Arango et al. 2012; Tevyashova et al. 2013).

Many additional modifications of existing macrolides have been created but have not yet been tested clinically. Many of these compounds have shown effectiveness against previously macrolide-resistant bacterial strains such as *S. pneumoniae*, *S. pyogenes*, *S. aureus*, and *H. influenzae*, among others, *in vitro*, and some are detailed below.

Some modifications of erythromycin have resulted in alkylides and carbamolides. The alkylides are derivatives of 3-*O*-alkyl-6-*O*-methylerythromycin and possess a 3-*O*-arylalkyl group instead of the 3-*O*-cladinose (Liang et al. 2012). 3-*O*-Modifications of erythromycin with carbamoyl groups combined with 6-*O*-methyl and the fusion across the carbons at ring positions 11 and 12 (similar to ketolides) with a carbamate (to form an oxycarbonylimino) create the carbamolide macrolide group (Magee et al. 2013).

Modifications of clarithromycin have resulted in acylides. The acylides have an added acyl group at the 3-*O* position of clarithromycin, which are effective *in vitro* against both methylase- and efflux-based erythromycin-resistant *S. pneumoniae* and *H. influenzae* (Tanikawa et al. 2001, 2003). The acylide backbone improves activity against efflux and inducible macrolide resistance (Pavlovic et al. 2017). Independent of the acylide modifications, fusion of a five-membered lactone ring to the 11- and 12-positions of the clarithromycin carbon ring results in products that have similar antibacterial properties to telithromycin (Hunziker et al. 2004).

Modifications of azithromycin result in several compounds, including 3-*O*-declandinosylazithromycin derivatives that have increased antibacterial activity against resistant *S. pneumoniae* and *S. pyogenes* strains (Yan et al. 2017). Additional active antibacterial compounds have been synthesized through modification of azithromycin at position four with arylalkyl side chains, such as the addition of an arylcarbamate moiety, yielding compounds that show promising activity against macrolide-resistant *S. pneumoniae* strains (Ma et al. 2009). Similarly, introducing a novel arylalkylcarbamoyl side chain at position 4 results in improved activity against erythromycin-resistant *S. pneumoniae* (Wang et al. 2017). Macrolones have been engineered by adding ligand groups to conventional macrolides, particularly being successful with the addition of a quinolone moiety onto an azithromycin scaffold (Cipcic Paljetak et al. 2016). Characterization of macrolones has shown that they too show promising activity against macrolide-resistant strains of *S. pneumoniae*, *S. pyogenes*, *S. aureus*, and *H. influenzae* (Cipcic Paljetak et al. 2016).