Similar to the substitutions seen in the ketolide cethromycin, arylbutynyl substitutions at the C_6 position also show improved activity against erythromycin-resistant *S. aureus*, *S. pneumoniae*, and *S. pyogenes* relative to telithromycin (Keyes et al. 2003). Further compounds with higher levels of activity against methicillin-resistant *Staphylococcus epidermidis* and *S. pneumoniae* (compared with cethromycin) have been synthesized, which principally contain a variously substituted phenyl carbamate propyl chain to the 11-N ketolide backbone (Zheng et al. 2016). Novel macrolides with a 9-oxime ketolide structure have had mixed results in *in vivo* assays and led to further modification of 9-oxime-contianing macrolides (Agouridas et al. 1998). The successful 2-fluorination of ketolides such as solithromycin works in conjunction with aminopyridyl or carbamoylpyridyl groups to contribute to potency in the context of bactericidal 9-oxime erythromycins (Tian et al. 2017).

Further novel configurations of macrolides include bicyclolide oximes that have the 11,12-carbamate ring present in telithromycin with an additional 3,6-ring structure, which have been termed C-9 alkenylidine bridged macrolides (Poce et al. 2009; Tang et al. 2008). Bicyclolides including modithromycin and the oxime bicyclolide EDP-788 showed initial promising activity against macrolide-resistant *Mycobacterium avium* and *Neisseria gonorrhoeae* (Bermudez et al. 2007; Jacobsson et al. 2015).

5.3 Macrolide Mechanisms of Action

The primary mechanism of action of macrolide antibiotics is through binding to the bacterial ribosome to inhibit protein assembly and then translation. This is achieved through binding to the 50S subunit of the ribosome, specifically the 23s rRNA, which causes steric hindrance of peptide movement (Schlunzen et al. 2001). These interactions generally are bacteriostatic in nature, but for clarithromycin and azithromycin acting on *S. pyogenes*, *S. pneumoniae*, and *H. influenzae*, these interactions are bactericidal (Zuckerman 2000). Macrolides such as azithromycin accumulate to high levels in the primary space where bacterial infections occur, particularly the interstitial fluid of soft tissues (Kobuchi et al. 2016)

Macrolides and lincosamides such as clindamycin bind primarily to the peptidyl transferase ring of the 23s rRNA domain V and block the exit tunnel for nascent peptides (Schlunzen et al. 2001). The desosamine sugar and the lactone ring of the macrolide are responsible for mediating the hydrogen bond interactions with the peptidyl transferase cavity. In particular, the 2′ OH of the desosamine sugar interacts with a crucial nucleotide (A2058 of *Escherichia coli*) of the ribosome that is a target of resistance-mediating methylases and ribosomal mutations that mediate macrolide resistance (Weisblum 1995). This nucleotide and others that are involved with forming interactions with