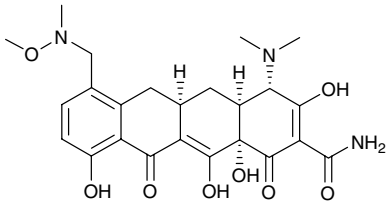
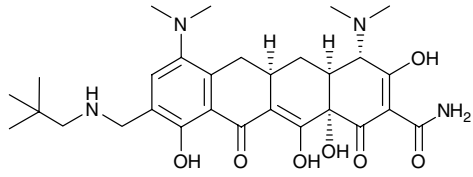


46; Sarecycline



47; Omadacycline

14.7 Erythromycin Macrolides

The basic compound erythromycin (**48**) was first reported by McGuire et al. (1952) following its discovery three years earlier. Its biosynthesis and *in vitro* establishment of the biosynthetic process were well described by workers at Abbott and led to significant attempts in the early days of what might be considered the "genomic revolution," to produce modified macrolide ring structures and use these to obtain novel agents. Though the process worked well on a small scale, attempts at scale up were not successful. *A case of being too early even though the ideas were feasible.*

The basic molecule and early variants rapidly met resistance, usually from one or more of the following: macrolide efflux, rRNA methylation, or ribosomal mutation. Macrolides and ketolides bind to the 23S rRNA of the 50S ribosomal subunit, which blocks the peptide exit channel and stimulates the dissociation of peptidyl-tRNA from the ribosome during the translocation process. In addition, these molecules also had the capability to interact with the precursors of a partially assembled 50S subunit, plus being capable of inhibiting the complete formation of bacterial ribosomes with the unassembled precursor particles undergoing nucleolytic degradation.

14.7.1 Recent Semisynthetic Macrolides

Although no new macrolides that were produced directly from nature have been utilized in the past 30 years, there have been some significant "modified macrolides" that have been successful. Only three will be mentioned, mainly because, even years after their original approval, they are still under active development in major countries. These will be discussed individually.

The first is clarithromycin (**49**), which was launched in 1990 in Europe and in 1991 in the United States, and it can be generically named as 6-*O*-methyl erythromycin A, with its initial synthesis reported in 1984 (Morimoto et al. 1984). Currently over 100 trials at phase IV are listed in the NIH website with one, NCT03516669, actively recruiting for study on a treatment for *Helicobacter pylori* infection in Taiwan, while others at phase III are recruiting in Egypt and Korea – just to give examples of the areas of the world that are currently involved.