Macrolide is one of the most important classes of antibiotic that fermented by microorganism actinomycetes. Erythromycin A is the first generation of macrolide was discovered in 1952. Erythromycin A inhibits protein biosynthesis in the elongation step by binding to 50S bacterial ribosome. Compliance in taking this drug is relatively poor and severe gastric disturbance proves intolerable in a minority of patients owing to instability of erythromycin A in acidic environment. Various semi synthetic derivatives of erythromycin A have been synthesized. A molecular docking technique employing AutoDock version 3.0 was chosen to analyze the interaction of various derivatives of erythromycin A with their target macromolecule. In this study, erythromycin A and its derivatives were docked into 50S subunit of Deinococcus radiodurans. The results showed that the active derivatives of erythromycin A namely clarithromycin, roxithromycin, azithromycin, telithromycin and cethromycin interact with the 50S subunit via hydrogen and hydrophobic interactions. The hydrogen interactions were observed mainly between cladinose sugar and bases of guanine A2484 and urasil A2485, while the desosamine sugar was not involved in this interaction. However, the semi synthetic analogues showed additional hydrogen bonding via the erythronolide ring. With respect to hydrophobic interactions, cladinose and desosamine sugars interacted mainly to the bases of adenine A2482 and guanine A2484. Erythromycin A anhydrate which is the inactive form of erythromycin A does not posses any hydrogen or hydrophobic interaction with the macromolecule. This information is very useful when designing a new derivative to inhibit the protein biosynthesis.