The CDC and NIH estimate that around 65-80% of all bacterial infections involve biofilms. Bacterial biofilms are sticky matrix-enclosed bacterial populations that form when bacteria colonize foreign material, such as human tissue and medical devices. Exhibiting decreased antibiotic susceptibility, biofilm infections often require surgical removal of the infected tissue or replacement of the device—procedures that add dramatically to the morbidity and mortality associated with these infections. Of particular concern is the ease with which mutations confer resistance to the rifamycin antibiotics, inhibitors of the bacterial RNA polymerase that are first-line treatments for biofilm infections. Given that the bacterial RNA polymerase may be a favorable target for clearing biofilms, this study seeks to investigate the in vitro activity of synthetic phloroglucinol derivatives, novel inhibitors of the bacterial RNA polymerase that target the switch region with no overlap from the rifamycin target (and thus exhibit no cross-resistance), against biofilms of Staphylococcus epidermidis and Staphylococcus aureus. Susceptibility testing in a peg-lid biofilm reactor reveals that these compounds have antibiofilm activity comparable to that of the rifamycins and suppress rifamycin resistance emergence when utilized in combination. Serial passaging experiments also demonstrate that 1:1 combinations of rifamycin and a phloroglucinol derivative can prevent resistance emergence for at least 40 days. These combinations are promising candidates for the development of antimicrobial therapies for biofilm infections.