

Figure 7.10 Model of **4** bound to full-length NS3/4A with helicase C-terminus (white) restored and Glu628 highlighted with mesh surface.

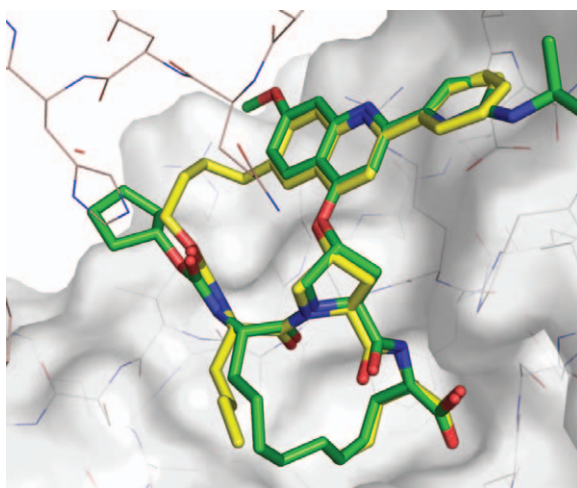


Figure 7.11 Target macrocycle **63** (yellow) overlaid with **4** (green).

The desired compounds were prepared as outlined in Scheme 7.3 *via* a synthetic sequence featuring a ring-closing metathesis (RCM)^{85,86} as the key macrocycle-forming event. Displacement of the brosylate of proline derivative **65**⁸⁷ with bromohydroxyquinoline **66** yielded ether **67**, which was vinylated *via* a palladium-catalyzed Stille reaction with tributylvinyltin to give **68**. Subsequent removal of the Boc protecting group and coupling with the appropriate norleucine carbamate derivatives **69a–d** afforded key RCM precursors **70a–d**. Ring closure was accomplished in excellent yield (84–93%) with the Zhan 1b catalyst⁸⁸ in 1,2-dichloroethane to give macrocyclic olefins **71a–d**. Conversion to