To design and synthesis a series of novel L-amino acid esters prodrugs of acyclic nucleoside phosphonates with more potent anti-HBV activity, adefovir dipivoxil was used as lead compound, according to the results of enhanced oral bioavailability and antiviral activities of nucleoside L-amino acid ester prodrugs. Eleven novel L-amino acid ester prodrugs of acyclic nucleoside phosphonates were designed and synthesized, their anti-HBV activities were evaluated in HepG2 2.2.15 cells. Eight compounds exhibited antiviral activity, and compounds 11 showed the most potent anti-HBV activity and highest elective index in vitro (EC₅₀ 0.095 μmol L⁻¹, SI 69523). Moreover, by analyzing the primary structure and activity relationship of these compounds, it could be suggested that L-amino acid ester strategy has significant potential in the acyclic nucleoside phosphonates prodrug design.