We describe the synthesis of tetrahydroisoquinolines and tetrahydroisoquinolinium salts together with their pharmacological properties at various nicotinic acetylcholine receptors. In general, the compounds were α4β2 nAChR antagonists, with the tetrahydroisoquinolinium salts being more potent than the parent tetrahydroisoquinoline derivatives. The most potent α4β2 antagonist, 6c, exhibited submicromolar binding Ki and functional IC50 values and high selectivity for this receptor over the α4β4 and α3β4 nAChRs. Whereas the (S)-6c enantiomer was essentially inactive at α4β2, (R)-6c was a slightly more potent α4β2 antagonist than the reference β2-nAChR antagonist DHβE. The observation that the α4β2 activity resided exclusively in the (R)-enantiomer was in full agreement with docking studies. Several of tetrahydroisoquinolinium salts also displayed agonist activity at the α7 nAChR. Preliminary in vivo evaluation revealed antidepressant-like effects of both (R)-5c and (R)-6c in the mouse forced swim test, supporting the therapeutic potential of α4β2 nAChR antagonists for this indication.