

# Design, Synthesis, and Pharmacological Characterization of Opioid Analgesics With Reduced Tolerance

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**Abstract:** For centuries, alkaloid secondary metabolites isolated from *Papaver somniferum* have provided clinicians with a powerful class of opioid analgesics that are considered the “gold standard” treatment for chronic, severe pain. Despite their considerable pharmacologic potential, mu opioid receptor (MOR) agonists such as morphine and oxycodone are limited significantly by the rapid development of analgesic tolerance. This necessitates escalating doses over weeks and months that results in exacerbated side effects of severe respiratory depression and constipation. Toward our overall goal of developing analgesics possessing an improved side effect profile, we have optimized the morphine structure to limit recognition by the multidrug resistance transporter, P-glycoprotein (P-gp), and to act as a dual-efficacy, MOR agonist/delta opioid receptor (DOR) antagonist probe. The molecular mechanisms underlying this activity have been evaluated using ligand-based and target-based pharmacophore models, and the next generation of analgesics lacking tolerance is currently in development.