Development of Bifunctional Peptidomimetic Ligands as Novel Opioid Analgesics

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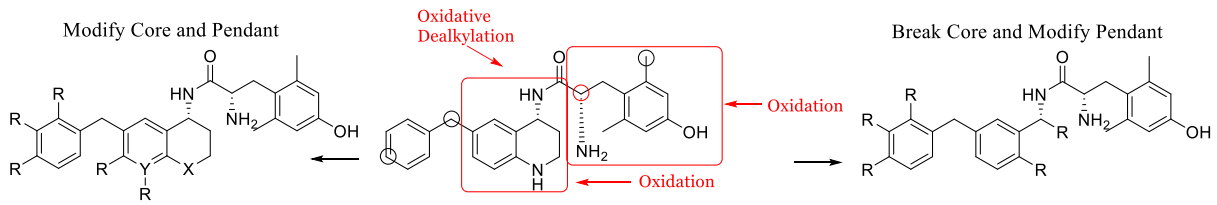
Opioids are among the most commonly prescribed analgesics used in the treatment of pain. Though highly efficacious, these opioids suffer from a number of undesirable side effects, including tolerance, dependence, addiction, respiratory depression, and constipation. Analgesia, in addition to these negative side effects, are attributed to activation of the μ-opioid receptor (MOR). Recent evidence has emerged that suggests that activation of the μ-opioid receptor with concomitant antagonism at the δ-opioid receptor (DOR) is capable of inducing analgesia without these negative side-effects *in vivo*. Our lab has developed a tetrahydroquinoline (THQ) based peptidomimetic lead that expresses this MOR agonist/DOR antagonist profile and is making derivatives of this lead to improve its pharmacodynamic and pharmacokinetic properties.

Currently, derivatives of our lead express active analgesia *in vivo*, of which some even express reduced tolerance, dependence, and drug seeking behavior. Despite these favorable attributes, our current compounds only work through intraperitoneal (ip.) injection. Unless we want this to be the primary method of drug administration, developing these compounds to be orally bioavailable will be necessary. With this goal in mind, we have subjected a series of our compounds to mouse-liver microsome (MLM) studies aimed at modeling our compound's stability in first pass metabolism. These studies indicated that our peptidomimetics have an *in vitro* half-life of less than ten minutes. Without accounting for gut metabolism or gut absorption, the liver metabolic stability must be improved if the goal of oral bioavailability is to be achieved.

Our MLM data indicate that our peptidomimetics are primarily metabolized via cytochrome p450 enzymes. An analysis of these metabolites indicates two major regions of metabolism, which are the THQ core and the 2',6'-dimethyltyrosine (DMT) pendant. Since metabolism at the THQ core frequently results in the bisection of the peptidomimetic, a series of analogs were synthesized that aimed at reducing metabolism at this position. This was performed in conjunction with modifications aimed at improving stability of the benzyl pendant. Direct modifications of the THQ core to improve their metabolic properties utilized two different approaches. The first is to retain the bicyclic structure of the THQ core while attempting to mitigate metabolism. This route is attractive because it is likely to retain much of our compounds current *in vitro* and *in vivo* activity. However, modifications in these regions may prove to be insufficient for improving metabolic stability. Alternatively, another approach involving elimination of part of the metabolically labile THQ core is also being pursued. This route has the advantage of directly impeding the bisection that occurs through aromatization of the THQ core. However, this would introduce an additional level of conformational flexibility which may harm our *in vitro* and *in vivo* activity profiles. Pursuit of analogs of both of these forms will be discussed.



Circles=Metabolic site predicted by SmartCYP, red indicates regions of greater likelyhood of metabolism than black