HIT OPTIMISATION AND SAR OF 3-PHENOXYPROPYL PIPERIDINE ANALOGUES AS ORL1 (NOP) RECEPTOR AGONISTS

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For several decades the focus of the field of pain has been to find an analgesic with the efficacy of morphine (μ opioid) but without the adverse side effect profile (e.g. respiratory depression, nausea, constipation, dysphoric effects and abuse potential). The ORL-1 receptor is the most recently discovered member of the opioid receptor family. It purportedly plays an important role in pain transmission, cognition and anxiety and carries a high degree of sequence homology with the other opioid receptors μ, κ and δ, but does not bind typical opioid ligands with high affinity.

Organon therefore initiated a program to develop potent ORL-1 receptor agonists as potential sedative analgesics for perioperative pain following surgery, which could replace the currently used combination of opioids (analgesic) with midazolam (sedative).

High throughput screening followed by hit optimisation led to a lead candidate that bound to the ORL1 receptor. This demonstrated full agonist activity and reversed hyperalgesia in a variety of animal models.

A successful lead optimisation program was initiated focusing on this compound to improve bio-activity (Ki <10 nM), selectivity (>20-fold selectivity over other opioid receptors) and solubility (~2mg/ml).

This poster will cover the hit optimisation phase of the project from screening hit to lead candidate, and will include details of the SAR developed within the 3-phenoxypropyl piperidine series during lead optimsation.