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Discovery of substituted lactams as novel dual orexin receptor antagonists. Synthesis, preliminary structure–activity relationship studies and efforts towards improved metabolic stability and pharmacokinetic properties. Part 1

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ABSTRACT

Starting from a thiazolidin-4-one HTS hit, a novel series of substituted lactams was identified and developed as dual orexin receptor antagonists. In this Letter, we describe our initial efforts towards the improvement of potency and metabolic stability. These investigations delivered optimized lead compounds with CNS drug-like properties suitable for further optimization.

The neuropeptides orexin-A and B (or hypocretin-1 and 2) are produced by a small population of neurons in the lateral hypothalamus. Both peptides are endogenous ligands for two G-protein-coupled receptors (GPCRs) known as orexin-1 (OX_1R) and orexin-2 (OX_2R) receptors.[1,2] The orexin receptors have been widely studied since their discovery in 1998, and the identification of potent antagonists is an active area of research as attested by the numerous chemotypes that have been disclosed in the patent and scientific literature.[3] Our interest in identifying orexin receptor antagonists began with the investigation of substituted tetrahydroisoquinolines[4] and related heterocyclic derivatives.[5] We have subsequently disclosed that the tetrahydroisoquinoline almorexant (ACT-078573), an orally-administered dual orexin receptor antagonist (DORA),[6] promoted robust sleep responses in rats, dogs, and humans.[7a] In the meantime, additional clinical proof-of-concept studies have substantiated the finding that DORAs offer potential as a novel therapy for the treatment of primary insomnia.[7b,c] GlaxoSmithKline has reported sleep efficacy for the structurally distinct investigational drug SB-649868, and Merck has recently completed Phase III clinical studies in insomnia with the drug candidate suvorexant. A pivotal finding emerging from these clinical studies is the absence of narcoleptic behaviour, including cataplexy.[7] The modulation of orexin receptor signaling has been implicated in the regulation of additional biological functions potentially influencing drug addiction, eating disorders, pain, anxiety, depression, and cancers.[3e] In addition to the key findings related to DORAs, investigators have also disclosed preclinical characterization of OX_1R and OX_2R-selective antagonists[8] but clinical efficacy has not been reported to date. With the discontinuation of the clinical development of almorexant for safety concerns, we sought to identify novel molecules that are devoid of adverse effects. The design of therapeutic agents that can cross the blood–brain barrier and achieve the drug concentrations required for appropriate target receptor occupancy represents a major challenge for medicinal chemists working on CNS targets. We have broadened our efforts by performing a high-throughput screening (HTS) of our corporate compound collection with the goal to identify novel structural classes that present affinities for the orexin receptors and potential for brain penetration. In this Letter, we describe our efforts towards the identification of substituted lactams as a novel series of DORAs, focusing on improving potency and metabolic stability.

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Thiazolidin-4-ones **1** emerged as micromolar hits and low molecular weight orexin receptor antagonists from a high-throughput screening of our chemical library (Fig. 1). Optimization of the compounds resulted in the identification of lead thiazolidin-4-one **2** that displayed improved in vitro potency towards both orexin receptors.[9] This derivative appeared suboptimal regarding metabolic stability, and early pharmacokinetic analyses indicated rapid clearance upon p.o. dosing in rats. The sulfur was predicted to be the most likely site of cytochrome P450-mediated oxidative metabolism[10] and further investigations have corroborated that sulfur was actually the major victim in presence of human liver microsomes (HLM).[11]

Oxidation of the sulfur atom to the corresponding sulfoxide/sulfone derivatives gave less active compounds. Additional efforts in this series of potential DORAs resulted in compounds with poor pharmacokinetic behaviour in rats. This prompted us to abandon the thiazolidin-4-one scaffold and to explore isosteric alternatives that might provide improved metabolic stability. Accordingly, we planned to switch the core structure from thiazolidin-4-ones **1** to lactams **3** by replacing the metabolically labile sulfur with methylene groups (Fig. 1).[12]

For our SAR studies, we envisaged to develop a synthetic route giving access to five-, six-, and seven-membered ring lactams **3**, allowing the exploration of a wide range of phenyl group substitution patterns, and the presence of a chiral center in the final compounds required the preparation of enantiopure compounds. Therefore, the synthesis was based on the addition of metalated aromatic rings into activated *N*-sulfinyl imines by achieving asymmetric induction with Ellman's chiral *tert*-butanesulfinamide chemistry.[13] A representative preparation of the target molecules is described in Scheme 1. Starting from the unsaturated ester **4**, this sequence of reactions could deliver either pyrrolidin-2-ones ($n = 1$), piperidin-2-ones ($n = 2$), or azepan-2-ones ($n = 3$). Thus, oxidative cleavage of olefins **4** (OsO_4, $NaIO_4$, 2,6-lutidine)[14] afforded smoothly the corresponding aldehydes **5**. A subsequent condensation of crude aldehydes **5** with *tert*-butanesulfinamide (t-Bu–S(O)–NH_2, $CuSO_4$, CH_2Cl_2)[15] gave the expected *N*-*tert*-butanesulfinyl imines **6**. Nucleophilic addition of metalated aromatic rings into the activated *N*-sulfinyl imines **6** delivered the protected primary amines **8**. For this reaction, the organometallic reagents were prepared from the corresponding aryl halides **7** (halogen/metal exchange) or directly from the aromatic rings (regioselective proton/metal exchange). Removal of the *tert*-butylsulfinyl moiety in **8** under acidic conditions provided quantitatively the primary amine building blocks **9** which were further converted into secondary amines **10** via reductive amination. Finally, saponification of **10** followed by ring closure (HATU, DMF) led to the lactams **11**. Alternatively, a similar two-step saponification–

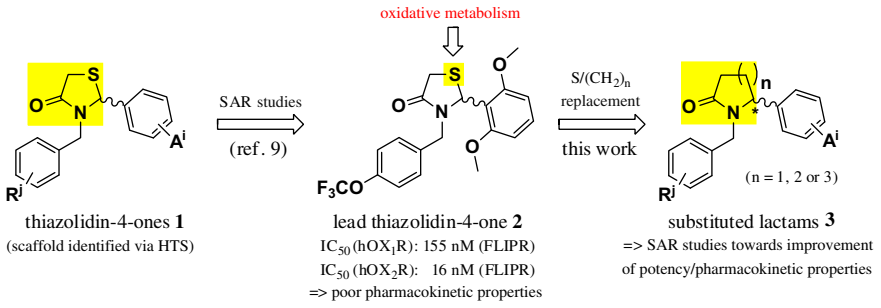
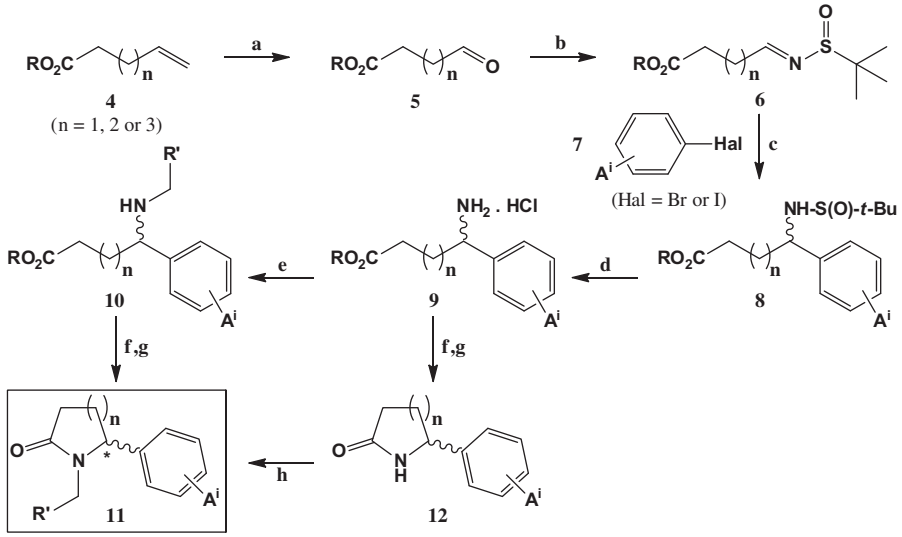


Figure 1. Investigation of substituted lactams as dual orexin receptor antagonists: overall transformation from initial thiazolidin-4-one HTS hit to the modified lactam template.



Scheme 1. General preparation of substituted lactams **11**. Reagents and conditions: (a) OsO_4 (0.04 equiv), $NaIO_4$ (4 equiv), 2,6-lutidine (2 equiv), dioxane/H_2O (3/1), rt (quantitative); (b) *tert*-butanesulfinamide (1 equiv), $CuSO_4$ (2 equiv), CH_2Cl_2, rt (59–79% over 2 steps); (c) aryl halide **7** (1.25 equiv), *n*-BuLi (1.25 equiv), THF, −78 °C, then **6** (1 equiv), −78 °C (54–80%); (d) 4 M HCl in dioxane (2 equiv), MeOH, 0 °C to rt (quantitative); (e) R′CHO (1 equiv), $NaBH(OAc)_3$ (1.4 equiv), DIPEA (2 equiv), 1,2-dichloroethane, rt (30–92%); (f) 1 N aq NaOH (2 equiv), MeOH, rt (quantitative); (g) HATU (1.25 equiv), DIPEA (1.25 equiv), DMF, rt (32–81% over 2 steps); (h) NaH (6 equiv), R′CH_2Br (1.1 equiv), DMF, rt to 60 °C (20–49%).