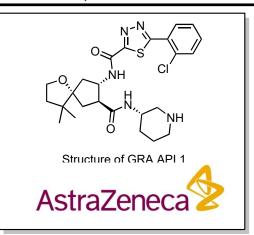
Process of the Week: Ghrelin Receptor Agonist



Background:

- -Ghrelin (Growth-Hormone Releasing Peptide) is a peptide hormone involved in the regulation of appetite and homeostatic processes. 1,3
- -Commonly associated with regulation of hunger, circulating ghrelin levels are lower in obese phenotypes compared to lean phenotypes. although these levels do not recede upon food intake.3
- -Cachexia (Wasting Syndrome), characterized by reduced food intake, loss of muscle and fat tissue, and increased metabolism, is a prevalent factor in the treatment-related symptoms for cancer and uremia patients⁴. This condition leads to both increased mortality and reduced quality of life.4
- -Substantial evidence exists to suggest these symptoms may be treatable through ghrelin modulation.⁴
- -GRA API 1 (CAS 2243167-93-1) has been shown to act as a potent agonist of the ghrelin receptor in vitro, prompting the need for a process route to produce ~0.8 kg. of material.²
- 1. Nature. 402 (6762): 656
- 3. Physiology & Behavior 2014, 136, 121
- 4. Expert Opinion on Biological Therapy 2013, 13 (4), 465

EDC. DMAP

BnOH Column

Process Drawbacks:

90%

- -Annulation is exothermic, and problematic on scale.
- -Zn-mediated alkylation requires excess metal and bromide.
- -Numerous columns and two chiral columns would dramatically increase scaled reaction expense.
- -Curtius rearrangement could result in buildup of azide intermediate.
- -Final amide formed is labile, and must be performed late in the synthesis.
- Short project timeline led to choice to refine discovery route,
- rather than find a new synthesis optimized for scale.

94%

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