

Process Development of a Topical Trk Inhibitor



 Partnership between BenevolentAl Ltd and Concept Life Sciences

Tropomyosin-related kinases (Trks)

 Trks implicated in pathologies relevant to diseases of the skin including pain sensation, itch, inflammation, and tumor cell growth and survival

Medicinal chemistry efforts identified pan-Trk inhibitor 1 along with two other candidates to be developed for clinical trials

 Process route described herein has enabled the first in human clinical trials of this bioactive compound

1

Ashwood, et al. Org. Process Res. Dev. 2024, Articles ASAP https://doi.org/10.1021/acs.oprd.4c00325



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Some discovery route shortcomings:

- nickel poses challenges related to cost, toxicity, and residual metal removal
- key decarboxylative coupling step gave low yield
- Low overall yield of 3%

Process Route

Process route highlights:

- successful GMP campaign to deliver 1.4 kg of the API in two batches
- 18% overall yield
- · 6-fold increase in overall yield versus discovery route
- decarboxylative cross-coupling was successfully carried out on seven batches on 0.6–0.7 kg scale and yields one diastereomer

2

2