Novel Approach to Synthesize Naᵥ1.7 Inhibitors as Analgesics for Neuropathic Pain

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Opportunity

What is Neuropathic Pain?
Neuropathic pain is a chronic pain condition wherein the body sends unprompted pain signals to the brain. Patients with this condition experience spontaneous shooting or burning pain in the body. Other symptoms include numbness, loss of sensation and swelling.

What Causes Neuropathic Pain?
Naᵥ1.7 is a channel found in sensory neurons that modulates the transfer of sodium ions.[2] These neurons control signaling of pain sensations. Unfortunately, mutations on the gene SCN9A which encodes this channel, causes pain disorders including Cognitive Insensitivity to pain (CIP), Paroxysmal extreme pain disorder (PEPD) & Erythromelalgia.

What is unique about our therapeutic solution?
The chemistry team at Amgen used unconventional synthetic tools to selectively synthesize a non-opioid drug substance intermediate for Naᵥ1.7 and incorporated several principles of ‘Green Chemistry’ to stay eco-friendly.

Approach

Goal: Process Development & Optimization
The biopharmaceutical industry is always investing in innovation to accelerate industrialization and delivery to patients. To optimize the reaction developed by Amgen shown on the right, an alternative route was investigated to minimize costs, maximize production and shorten delivery times.

Using Innovation to Drive a Key Transformation
Previously, the atropisomeric product was synthesized in a racemic fashion. The group discovered an asymmetric chiral catalyst to selectively synthesize the desired product without the need to purify it or discard unwanted material. For further optimization, a substrate scope was developed.

Incorporating Green Chemistry
Decreasing costs and staying eco-friendly for biopharmaceutical companies is a vital part of process development.

The team achieved these goals by successfully synthesizing the product: • Asymmetrically • Minimizing use of catalyst • Using relatively less harmful solvents • Diminishing need for purification

Exploring Scientific Approaches to:
A) Maximize Production: Tested out reaction conditions to minimize impurities based on mechanistic understanding.
B) Shorten Delivery Time: Engineered fast-reacting substrates based on stereo-electronic principles.
C) Minimize Costs: Minimized formation of undesired isomer through catalysis screening and decreased loading.

Results

Optimized Route

10% Chiral Catalyst

Optimal Leaving Group on R

Impurity X = 12%

100% Yield

Impurity X = <1%

A) Maximizing Production

B) Shortening Delivery Time

C) Minimizing costs

Different R groups (except MeO) adversely affected the enantioselectivity of the desired product.

Conclusions from Research
• Developed a chiral route for key drug substance intermediate.
• Identified new chiral catalyst to synthesize the atropisomer.
• Catalyst loading decreased 20-fold i.e. from 12% to < 1%.
• Achieved 90% enantioselectivity.
• Isolated yields were also high i.e. ~ 85%.
• Pdt LCAP reaches 95% in 35 minutes at RT.
• Shut down impurity X pathway.

Impact on Patients
• Synthesized a non-opioid pain killer (theoretically non-addictive).
• Accelerated delivery to patients by removing purification requirements.

Impact

References
[3] https://science.sciencemag.org/content/363/6424/aab0805

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