RISE RESEARCH INNOVATION SCHOLARSHIP ENTREPRENEURSHIP

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Novel Approach to Synthesize $Na_v1.7$ Inhibitors as Analgesics for Neuropathic Pain

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Opportunity

Did you know? 1 in 5 people suffer from chronic pain in the US.[1]

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?

$Na_v1.7$ 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?

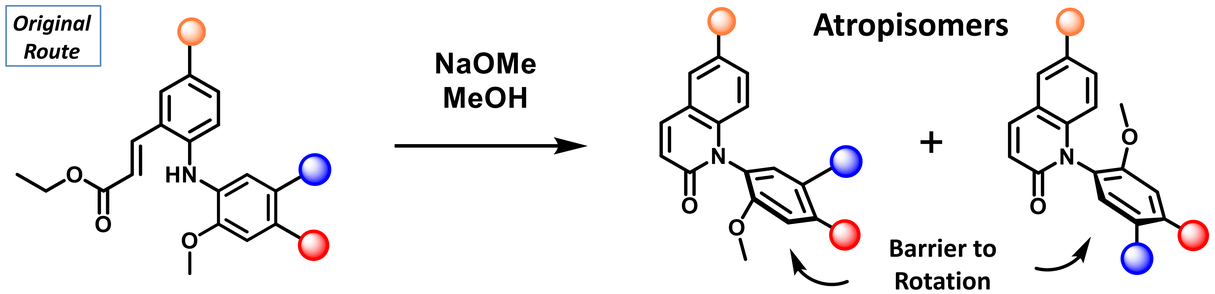
The chemistry team at Amgen used unconventional synthetic tools to selectively synthesize a non-opioid drug substance intermediate for $Na_v1.7$ and incorporated several principles of 'Green Chemistry' to stay eco-friendly.

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.

Original Route



Graceffa, R. F. et al. *J. Med.Chem.* (2017) *60*, 5990

50% Desired

50% Undesired

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:

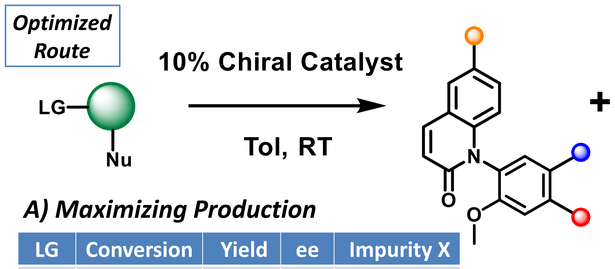
A) Maximize Production: Tested out reaction conditions to minimize impurities based on mechanistic understanding.

B) Shorten Delivery Time: Engineered fast-reacting substrates based on stereo-electronic principles.

C) Minimize Costs: Minimized formation of undesired isomer through catalyst screening and decreased loading.

Results

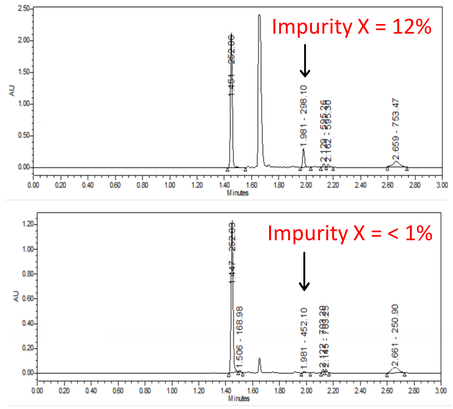
Optimized Route



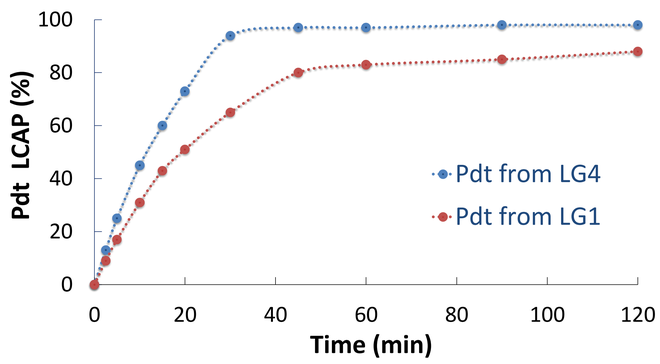
A) Maximizing Production

LG	Conversion	Yield	ee	Impurity X
LG1	100	67	90	12%
LG2	100	72	89	< 1%
LG3	100	71	92	0%
LG4	100	86	86	< 1%

An optimum leaving group on the substrate was identified which reduced impurity X from 12% to < 1%.



B) Shortening Delivery Time



Choice of leaving groups on substrate affects product yield and reaction rate differently.

C) Minimizing costs

Catalyst Loading	Conversion	q-NMR Yield	ee
10%	100	100	84
5%	100	82	89
2%	100	96	85
1%	100	98	88
0.5%	100	91	89

Catalyst loading can be reduced 20-fold with high quantitative yields and maintained selectivity.

R	Conversion	Isolated Yield	ee
MeO	100	86	86
R1	100	85	56
R2	100	84	72
R3	100	85	67

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

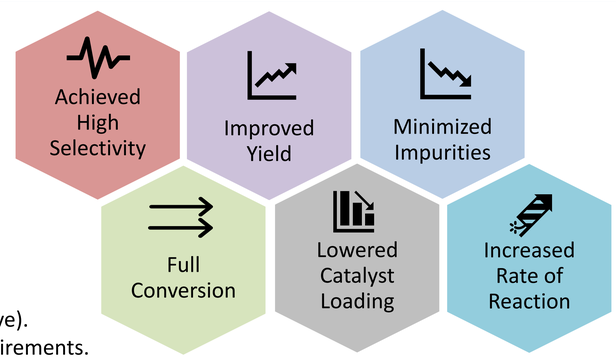
Impact

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 10% to 0.5%.
- 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.



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