Innovations
UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

Urate Transport Inhibitors: Compounds Designed for Their Uricosuric Action

Category

Therapeutics – Novel Chemical Entity

Problem

Need for new urate transport inhibitors with higher efficacy and lower toxicity

Technology Overview

Novel chemical structures which exhibit high urate transporter inhibition

IP Status

- Patents issued in United States and Japan
- Available for Exclusive or Non-Exclusive Licensing

Value Proposition

- Potent inhibition of urate transport proteins with low nanomolar IC_{50} values
- Fast clearance and oral administration shown in *in vivo* mouse models

Market Attractions

- Increasing demand for treatment of diseases like gout with a market reaching $1870M with a CAGR of 8.3%.
- Opportunity to develop potentially disruptive drug for treating hyperuricemia in a rapidly expanding space

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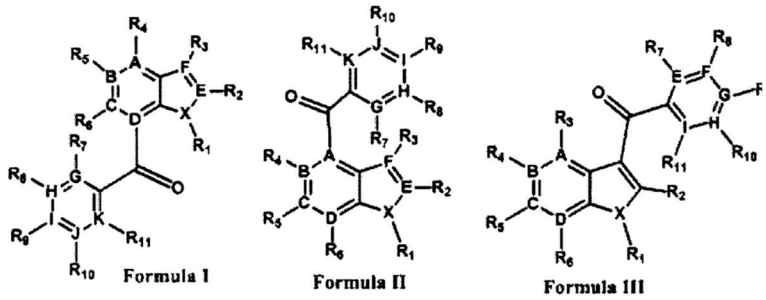
Problem: Renal urate (uric acid) excretion becomes dependent upon the balance between re-absorption and secretion. When uric acid is reabsorbed the kidneys, it is then released back into the blood stream; however, elevated urate levels are prevalent in a variety of disease states, including gout, hypertension, diabetes, chronic renal disease, diabetic renal disease, and cardiovascular disease. Renal urate re-absorption occurs via two proximal tubular transporters, but, to date, there are only a few drugs in the USA that lower blood urate levels. The most common, allopurinol, while effective, occasionally causes severe Stevens Johnson syndrome and may be fatal. A second drug, febuxostat, has been associated with cardiovascular complications leading to the FDA requiring a caution statement on the drug insert. The only other drug, probenecid, has weak uricosuric activity and requires twice daily dosing with limited use in reduced renal function. Hence, there is a major need to develop new agents.

Technical Solution and Key Value Propositions:

Efforts at the University of Colorado have generated various chemical structures which exhibit an array of urate transporter inhibitor potential. Three novel species were identified in a probe for structures which could have potential to replace current standards for urate transporter inhibition. The three structures are depicted below:



Formula I Formula II Formula III

The chemicals and their various derivatives were tested both *in vitro* and *in vivo* in mice to determine percentage of transporter inhibition. *In vitro* studies observed the inhibition of URAT1, URAT2, and URATv1 transporters by monitoring urate uptake in *Xenopus* oocytes. One halogenated compound yields a 99.9% ± 0.1 inhibition of URAT1 with an IC_{50} of only approximately 26 nM. The group also developed a procedure for probing affordable compounds by summing the percent inhibition of the three mentioned transport proteins. A percent sum of ≥160% is designated as a preferred compound. *In vivo* experiments illustrated that the compounds are bio-available and showed proof-of-concept oral administration of compounds chosen for their uricosuric action.

Key Documents and Sources:

"Developing Potent Urate Transporter Inhibitors: Compounds Designed For Their Uricosuric Action." US 10005750B2 issued June 26, 2018.