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Abstract #830

Profound Hypouricemia Induced in Human Subjects by Novel Bifunctional Inhibitors of Xanthine Oxidase and URAT1

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Background/Purpose: A prototype anticancer drug (RLBN1001) induced marked hypouricemia in studies of > 350 human subjects. Preliminary exploration suggested dual effects on uric acid (UA) production and excretion, whereas studies by others showed the agent was a catalytic (Type 2) inhibitor of topoisomerase-II. Given the unusual clinical potency, we sought to: identify the hypouricemic mechanism(s); clarify structure-activity relationships (SARs) for both the uric acid and genotoxic targets; and develop novel analogs that would enhance the hypouricemic effect and eliminate genotoxicity, thereby discovering potentially useful treatments for gout.
Methods: We verified clinical proof-of-concept by examining biochemical effects in 50 human subjects treated with RLBN1001. We explored SARs in recursive chemical syntheses using four principal bioassays: renal UA transporters URAT1 (SLC22A12) and splice variants of GLUT9a/b (SLC2A9); xanthine oxidase (XO); and *in vitro* micronucleus (MN) (to detect genotoxicity).
Results: Over a 15-fold dosing range with RLBN1001, nadir levels of clinical hypouricemia (< 1.0 mg/dL) were not dose-related, indicating the minimal effective dose was below the lowest administered dose in this study (100 mg/m x/d x 5d). At both low and high doses, hypouricemia was associated with increased urinary excretion of both UA and total oxypurines, suggesting bifunctional equilibrium effects on both production and excretion. We found that the RLBN1001 prototype was a potent inhibitor of URAT1 but not GLUT9a, a very modest inhibitor of XO, and a potent clastogen in the MN assay. We iteratively synthesized a series of novel analogs and identified new compounds that are potent inhibitors of both XO (i.e., 4-fold more potent than allopurinol) and URAT1 (equipotent to lesinurad), but devoid of genotoxicity. One compound showed moderate inhibition of GLUT9b (data not shown), but other compounds showed minimal effects on this target. Data for reference and selected new compounds are shown in the table.
Conclusion: Having established compelling clinical POC with the RLBN1001 prototype, we have synthesized a library of unique compounds with strongly enhanced activities that both reduce UA production and enhance UA excretion. A lead compound is expected to enter initial clinical trials as a novel, potential first-line treatment for hyperuricemic patients with gout.

Compound	URAT1 Inhibition IC50 μM Mean ± SEM	XO Inhibition IC50 μM Mean ± SEM	MN
Allopurinol	> 300	2.8 ± 0.33	ND
Benzbromarone	0.2	ND	ND
Lesinurad	18.6	> 300	ND
RLBN1001	5.4 ± 1.0	274	+
RLBN2022	1.2	> 300	+
RLBN2027	6.3	243	+
RLBN2023	2.6 ± 0.6	1.1	Negative
RLBN2024	9.4 ± 0.6	0.7	Negative
RLBN3022	3.5	1.9	Negative
RLBN3050	9.5	0.6	Pending