DISCOVERY OF AN ADVANCED DUAL CHITINASE INHIBITOR OAT-870: A NEW POTENTIAL THERAPEUTIC IN THERAPY OF LUNG DISEASES

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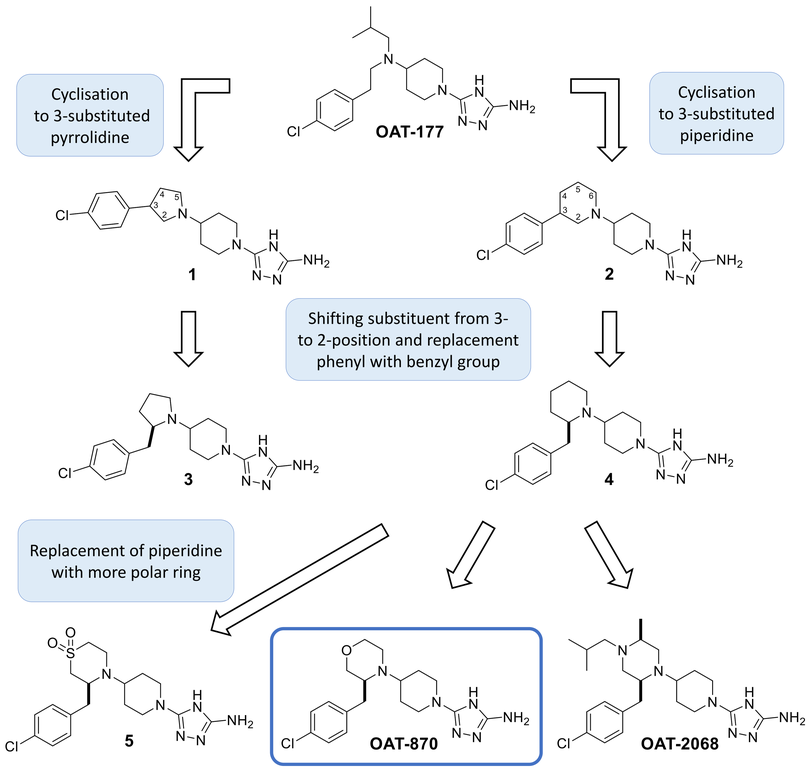
INTRODUCTION

Chitotriasidase 1 (CHIT 1) and acidic mammalian chitinase (AMCase) are the enzymatically active chitinases. They belong to the family of glycosidases including several chitinase-like proteins (CLPs) which lack the ability to degrade chitin[1].

It has been shown that elevated CHIT1 levels and activity were found in the plasma and bronchoalveolar lavage (BAL) fluid from patients suffering from orphan lung diseases (i.e. idiopathic pulmonary fibrosis – IPF or sarcoidosis)[1].

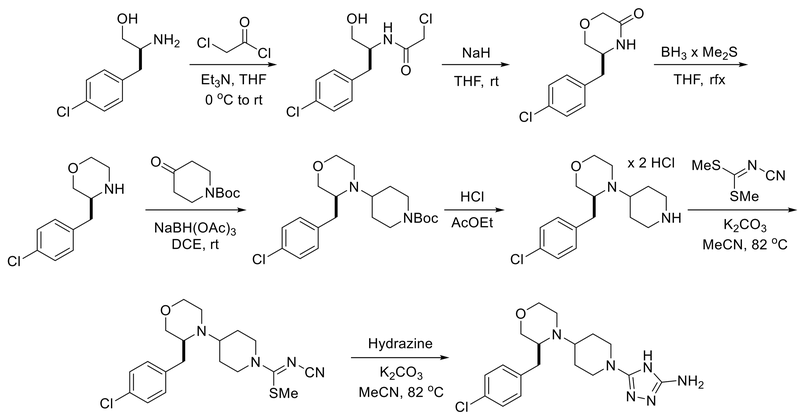
Given these observations we decided to design and prepare small-molecule chitinase inhibitors which would constitute a new class of orally administered therapeutics targeting the aforementioned lung diseases. Modification of the previously discovered in our laboratory **OAT-177**[2] led us to discovery of a potent dual chitinase inhibitor **OAT-870**[4].

STRUCTURE ACTIVITY RELATIONSHIP STUDY

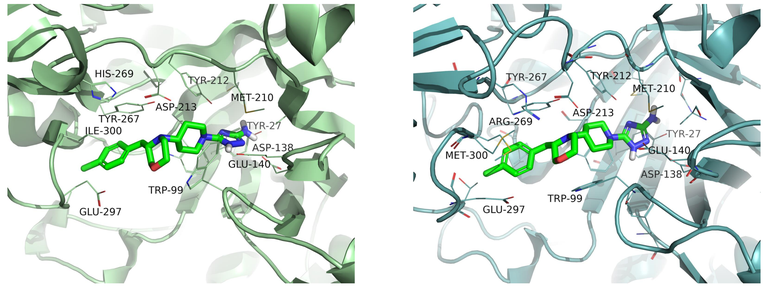


		OAT-177	1	2	3	4	5	OAT-2068	OAT-870
hAMCase	[nM]	14	5950	1350	73	23	849	67	22
hCHIT1	[nM]	232	19500	1850	59	41	4200	1300	48
mAMCase	[nM]	19	2600	335	120	81	IA	4200	30
mCHIT1	[nM]	2955	37000	19000	430	87	1900	30	74
hERG	[nM]	4000	NT	NT	4000	8300	NT	2400	39000

SYNTHESIS OF OAT-870



STRUCTURAL DATA FOR OAT-870

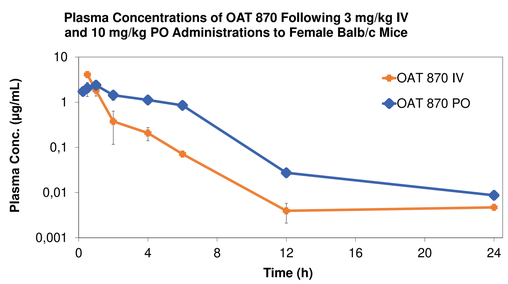


A Docking of **OAT-870** in the binding site of hAMCase

B Docking of **OAT-870** in the binding site of hCHIT1

Molecular docking was performed using rDock to AMCase (PDB ID: 3RM4 and 3RM8) and CHIT1 (PDB ID: 5NR8). For each ligand, 100 poses were generated, and top scoring 10 models were inspected visually in PyMOL. Poses with a binding mode most similar to the native ligands were accepted for further analysis.

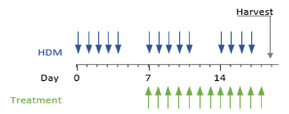
PHARMACOKINETIC PROFILE IN MICE



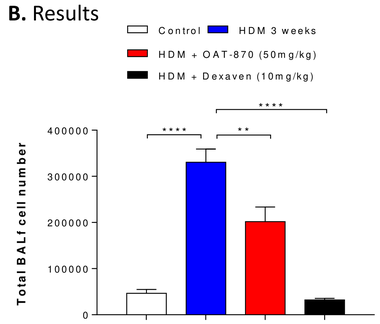
Route	IV	PO
Dose (mg/kg)	3	10
AUC_{0-inf}(mg*h/L)	4.8	11.1
C_0 or C_{max}(mg/L)	1.6	2.4
T_{max}(h)	n/a	1,0
CL (mL/min/kg)	10.5	n/a
Vss (L/kg)	1.1	n/a
$T_{½}$ (h)	2.5	2.7
Bioavailability (F%)	n/a	70

MURINE HDM-INDUCED ALLERGIC INFLAMMATION MODEL

A. Scheme of treatment



B. Results



Flow cytometry analysis of total infiltrating leukocyte numbers in BAL recovered from mice challenged with PBS or HDM with or without **OAT-870** (50 mg/kg; PO; qd) or after dexamethasone (10 mg/kg, IP, qd) dosed in therapeutic regimen was performed.
Oral administration of **OAT-870** exhibited a significant reduction (37 %) of CD45-positive leukocytes influx into the lungs.

CONCLUSIONS

OAT-870 is a potent dual AMCase and CHIT1 inhibitor with very good pharmacokinetic profile. Significant anti-inflammatory effect in HDM-induced airway inflammation model in mice was observed when dosing once daily (50 mg/kg).

Together with **OAT-177**[2] (selective mAMCase) and **OAT-2068**[3] (selective mCHIT1) **OAT-870**[4] constitutes a unique set of potent inhibitors which can be used as valuable tool compounds for the studies concerning the role chitinases in various pathologies.

Further profiling revealed no genotoxicity in the AMES test, but data from the CEREP Diversity panel (including 72 binding and 27 enzyme assays) indicated dopamine transporter (DAT) as a significant off-target (95% inhibition at 10 µM). These results led us to discovery of compound **OATD-01** - a first-in-class chitinase inhibitor currently in clinical trials (see Poster **MEDI 272**).

ACKNOWLEDGEMENTS

„Development of a first-in-class small molecule drug candidate for treatment of idiopathic pulmonary fibrosis through chitotriosidase inhibition”

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[1] A review on human chitinases see Kumar A., Zhang K.Y.J. *Human Chitinases: Structure, Function, and Inhibitor Discovery*. In: Yang Q., Fukamizo T. (eds) *Targeting Chitin-containing Organisms. Advances in Experimental Medicine and Biology*, vol 1142. Springer 2019, Singapore.

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