Development of Dual AMCase and CHIT1 Inhibitor OAT-870 as a Potential Therapeutic for Interstitial Lung Diseases

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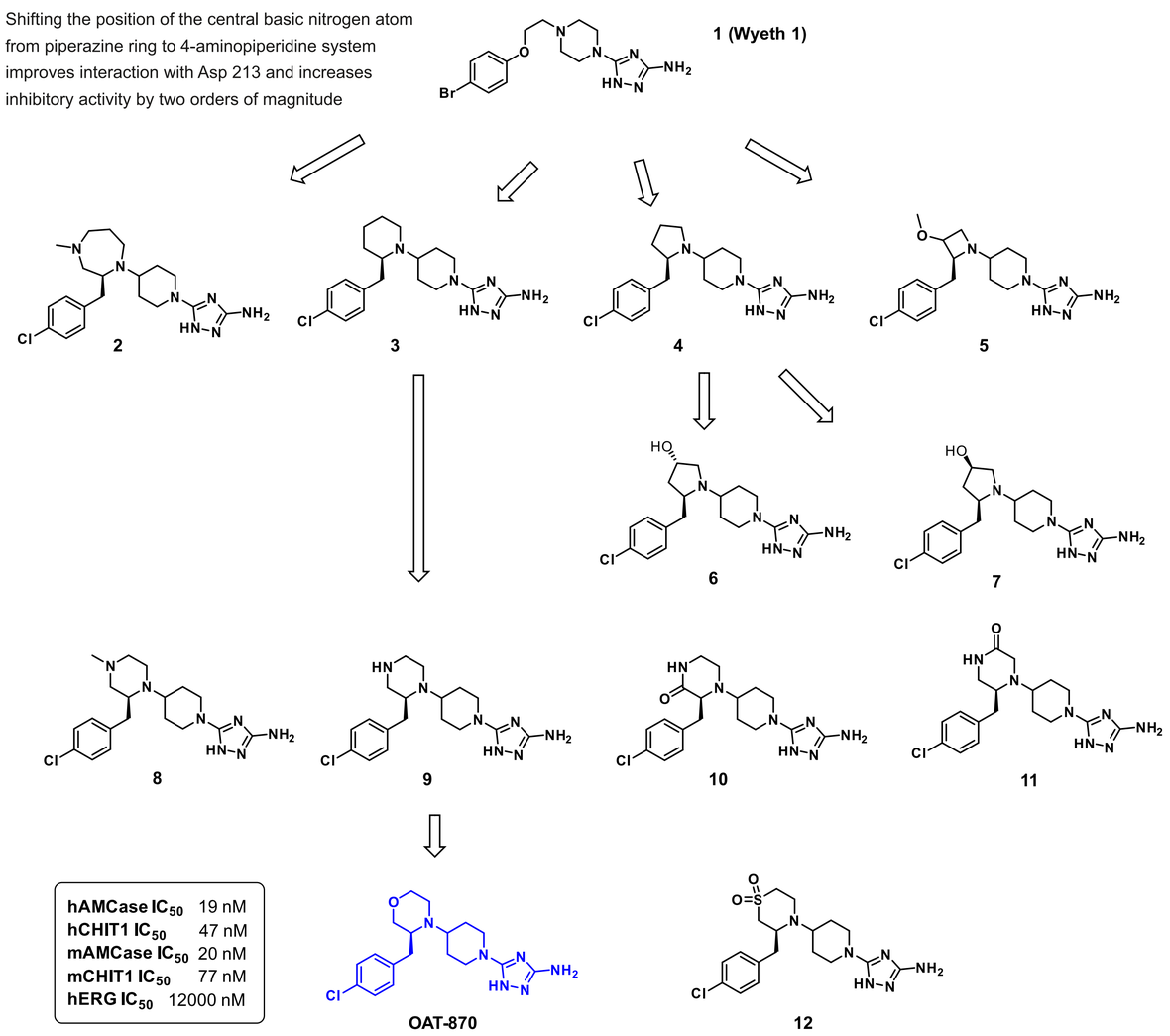
Introduction

Acidic mammalian chitinase (AMCase) and chitotriosidase (CHIT1) are the enzymatically active chitinases, which have been shown to be involved in various lung pathologies such as idiopathic pulmonary fibrosis, sarcoidosis, chronic obstructive pulmonary disease and asthma. AMCase is activated during type 2 inflammatory responses in both murine models of airway inflammation and in asthma patients. Elevated CHIT1 levels and activity were found in the plasma and bronchoalveolar lavage (BAL) fluids from patients with interstitial lung diseases such as sarcoidosis or idiopathic pulmonary fibrosis.

Given these observations we envisaged that effective inhibition of chitinases may pave the way for the new class of orally administered therapeutics against variety of pulmonary diseases. Structure-based optimization of compound **1**[1] led us to discovery of new class of potent dual chitinase inhibitors exemplified by compound **OAT-870**.

Structure Activity Relationship Study

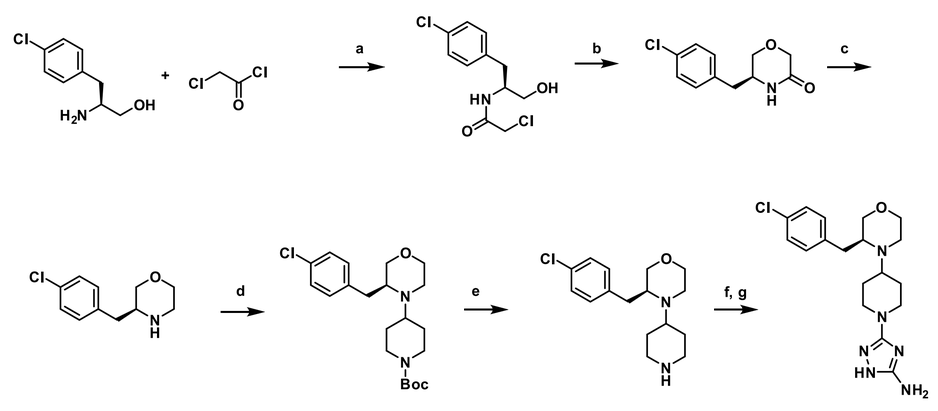
Shifting the position of the central basic nitrogen atom from piperazine ring to 4-aminopiperidine system improves interaction with Asp 213 and increases inhibitory activity by two orders of magnitude



Comp No. / IC_{50} [nM]	1	2	3	4	5	6	7	8	9	10	11	12	OAT 870
hAMCase	5450	8100	23	73	394	39	50	395	475	5400	1200	849	**19**
hCHIT1	6755	IA	75	58	521	82	87	17000	2000	IA	1400	4200	**47**
hERG	-	-	8300	4000	-	13000	55000	-	-	-	-	-	**12000**

OAT-870 was selected for further pharmacokinetics and *in vivo* study

Synthesis of OAT-870

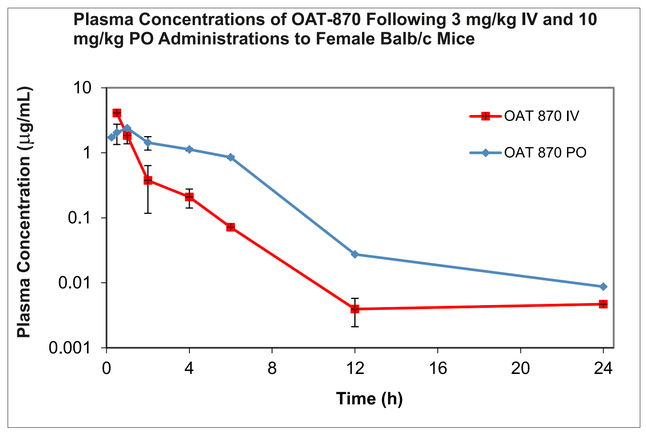


Reagents and conditions: (a) Chloroacetyl chloride, TEA, THF, 0°C to rt; (b) NaH, THF, rt; (c) BH_3xDMS, THF, rfx; (d) $NaBH(OAc)_3$, DCE, rt; (e) HCl, EtOAc, rt; (f) S,S'-Dimethyl N-Cyanodithioiminocarbonate, K_2CO_3, MeCN, 82°C; (g) Hydrazine, MeCN, 82°C.

References

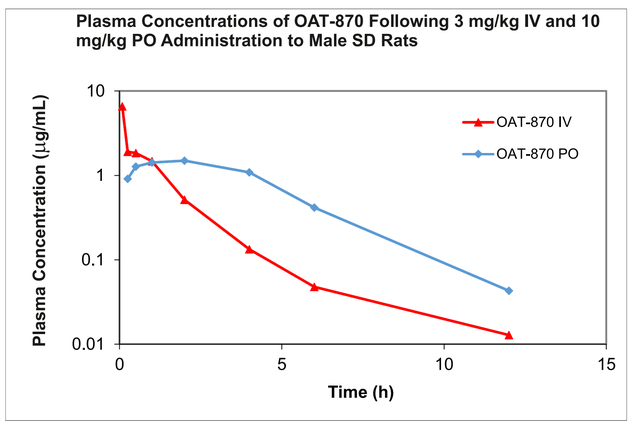
1. Cole, D. C.; Olland, A. M.; Jacob, J.; Brooks, J.; Bursavich, M. G.; Czerwinski, R.; DeClercq, C.; Johnson, M.; Joseph-McCarthy, D.; Ellingboe, J. W.; Lin, L.; Nowak, P.; Presman, E.; Strand, J.; Tam, A.; Williams, C. M.; Yao, S.; Tsao, D. H.; Fitz, L. J. Identification and characterization of acidic mammalian chitinase inhibitors. J. Med. Chem. 2010, 53, 6122-6128.

Pharmacokinetics in Mice



OAT-870 Pharmacokinetic Parameters		
Route	IV	PO
Dose [mg/kg]	**3**	**10**
$AUC_{0\text{-}inf}$ [mg*h/L]	4.76	11.09
C_0 or C_{max} [mg/L]	1.59	2.39
T_{max} [h]	n/a	1.00
CL [mL/min/kg]	10.51	n/a
V_{ss} [L/kg]	1.09	n/a
$T_{1/2}$ [h]	2.50	n/a
Bioavailability F [%]	n/a	70

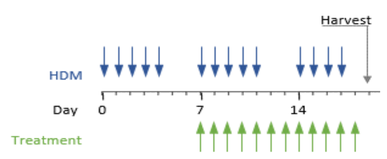
Pharmacokinetics in Rats



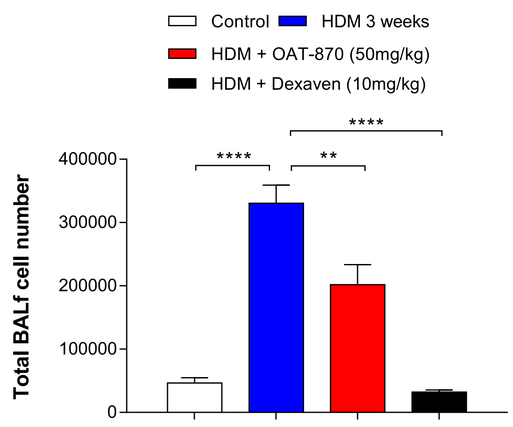
OAT-870 Pharmacokinetic Parameters		
Route	IV	PO
Dose [mg/kg]	**3**	**10**
$AUC_{0\text{-}inf}$ [mg*h/L]	4.98	8.01
C_0 or C_{max} [mg/L]	2.15	1.56
T_{max} [h]	n/a	1.5
CL [mL/min/kg]	2.02	n/a
V_{ss} [L/kg]	3.86	n/a
$T_{1/2}$ [h]	7.95	n/a
Bioavailability F [%]	n/a	48

Murine HDM-Induced Allergic Inflammation Model

A. Scheme of treatment



B. Results



Therapeutic efficacy of **OAT-870** was determined in a murine 3-week HDM-induced asthma model. Oral administration of OAT-870 (50 mg/kg) in curative treatment scheme (day 7-19) exhibited significant reduction of CD45-positive leukocytes influx into the lungs (Fig.B).

Therapeutic efficacy of **OAT-870** has been also evaluated in the bleomycin-induced pulmonary fibrosis model in mice showing promising results.

Conclusions

OAT-870 is a highly potent dual AMCase and CHIT1 small molecule inhibitor of low-nanomolar activity against both human and murine enzymes and with very good pharmacokinetic properties. Once daily 50 mg/kg oral doses in mice showed significant anti-inflammatory efficacy in acute HDM-induced allergic airway inflammation model. Additionally, **OAT-870** was further profiled in the AMES test (no genotoxicity observed). Also, potential off-target *in vitro* effects of **OAT-870** were evaluated in the CEREP Diversity panel consisting of 72 binding and 27 enzyme assays and the only significant interaction revealed was that with dopamine transporter (DAT; 95% inhibition at 10µM). These results led us to discovery of compound **OATD-01**, which, as of now, undergoes phase I of the clinical trials.

Financial Support

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

European Funds Smart Growth
European Union European Regional Development Fund