**INTRODUCTION**

Human acidic mammalian chitinase (hAMCase) is a 52kDa enzyme expressed in the stomach, salivary gland and lungs (the other chitinolytically-active protein found in mammals is chitinase-3-like protein 1 (CHI3L1)). Elevated levels of AMCase have been detected during type 2 inflammation in both murine asthma models and allergic asthma patients. Preliminary studies have shown that inhibition of the enzymatic activity of AMCase with the allosamidin or demethylallosamidin resulted in suppression of IL-13 mediated allergic inflammation and ovalbumin (OVA) induced allergy in mice.

Our ongoing studies are focused on finding selective and potent compounds towards each of chitinases mentioned above. Recently we have reported a highly selective mouse CHIT1 inhibitor OAT-177 and selective mouse AMCase inhibitor OAT-177. The latter was effective in house dust mite (HDM)-induced allergic airway inflammation model in mice. Herein, we report the synthesis and structure-based optimization of a new series of compounds that led us to the discovery of OAT-1441. The introduction of the benzoxazepine moiety resulted in high activity and selectivity along with improved in vitro and pharmacokinetic profile make OAT-1441 a suitable candidate for further preclinical development.

**Synthesis of OAT-1441**

Reagents and conditions for the synthesis of OAT-1441: (a) DEAD, Ph3P, THF, -15 °C → RT, 14 h; (b) LiAlH4, 0 °C → RT; (c) HCl in AcOEt 0 °C → RT then Et2O; (d) 1,2-DCE, NaBH(OAc)3, RT, overnight; (e) after step 4, piperidine, AcOH, 1,2-DCE, 70 °C, then NaH,DMSO, RT, overnight; (f) HCl in AcOEt 0 °C → RT, overnight; (g) 1,2-DCE, NaBH(OAc)3, 30 °C, 2 h then NaH,DMSO, RT, overnight; (h) 1,2-DCE, NaBH(OAc)3, 70 °C, 2 h then NaH,DMSO, RT, overnight; (i) 1,2-DCE, NaBH(OAc)3, 70 °C, 2 h then NaH,DMSO, RT, overnight; (j) 1,2-DCE, NaBH(OAc)3, 70 °C, 2 h then NaH,DMSO, RT, overnight; (k) 1,2-DCE, NaBH(OAc)3, 70 °C, 2 h then NaH,DMSO, RT, overnight; (l) 1,2-DCE, NaBH(OAc)3, 70 °C, 2 h then NaH,DMSO, RT, overnight.

**Plasma Concentrations of OAT-1441 Following 3 mg/kg IV and 10 mg/kg PO Administrations to Male Sprague-Dawley Rats**

**Structure Activity Relationship Leading to OAT-1441**

**Pharmacokinetic Parameters of OAT-1441 in Rats**

**CONCLUSIONS**

In summary, the SAR for N-benzylic analogues of OAT-377 was established. Further optimization generated a compound possessing high activity and selectivity as well as improved in vivo and pharmacokinetic profile make OAT-1441 a suitable candidate for further preclinical development.

**Plasma Concentrations of OAT-1441 Following 3 mg/kg IV and 10 mg/kg PO Administrations to Male Sprague-Dawley Rats**

**Pharmacokinetic parameters**

**FINANCIAL SUPPORT**

*Fund for research and development of new preclinical candidates in therapy of allergies and inflammatory bowel diseases*