Bioorganic & Medicinal Chemistry Letters 28 (2018) 2279–2284

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Development of autotaxin inhibitors: A series of zinc binding triazoles

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ARTICLE INFO

Keywords:
Autotaxin inhibition
Idiopathic pulmonary fibrosis
PK/PD
Solubility
hERG inhibition

ABSTRACT

A series of inhibitors of Autotaxin (ATX) has been developed using the binding mode of known inhibitor, PF-8380, as a template. Replacement of the benzoxazolone with a triazole zinc-binding motif reduced crystallinity and improved solubility relative to PF-8380. Modification of the linker region removed hERG activity and led to compound **12** – a selective, high affinity, orally-bioavailable inhibitor of ATX. Compound **12** concentration-dependently inhibits autotaxin and formation of LPA *in vivo*, as shown in pharmacokinetic-pharmacodynamic experiments.

Introduction

Lysophosphatidic acid (LPA) is a key, serum-borne phospholipid, regulating a number of cellular processes such as proliferation, migration and differentiation through its interaction with G-protein coupled receptors.[1] LPA receptor signaling has been implicated in several disease states including fibrosis,[2] cholestatic pruritus[3] and tumour metastasis.[4] There are a number of forms of LPA, varying in length and unsaturation levels of the lipid sidechain, as well as at least six known receptors, whose roles are not all clearly understood.[2] Autotaxin (ATX), also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (eNPP2), is thought to be the predominant enzyme responsible for production of the various LPAs.[5] Autotaxin exhibits lysophospholipase D activity, which cleaves lysophosphatidylcholines (LPC) to the respective LPAs (Fig. 1).

Receptor mediated LPA signaling has been shown to be an important mechanism in lung fibrosis[6] and Bristol-Myers Squibb have been developing the selective LPA1 antagonist, BMS-986020,[7] for treatment of idiopathic pulmonary fibrosis (IPF). Another approach for blockade of this signaling pathway is inhibition of ATX, preventing formation of LPA. Galapagos are currently testing this approach with the autotaxin inhibitor GLPG-1690.[8] This paper is the first of two describing our discovery of autotaxin inhibitors for potential treatment of IPF.

PF-8380 (Fig. 2), characterised by Pfizer,[10] is a high affinity ATX inhibitor that has been shown by crystallization studies to occupy a similar binding pocket to LPA (Fig. 3). The benzyl carbamate occupies a hydrophobic pocket, similarly to the lipophilic chain of LPC, whilst the benzoxazolone is bound by the catalytic zinc.

Whilst PF-8380 is a potent autotaxin inhibitor and useful chemical probe for exploring ATX biology, its clinical utility is limited by a lack of solubility, which can lead to erratic oral exposure, and by activity at the hERG channel. In an attempt to design a safer and more soluble molecule, with consistent oral exposure, we began to explore the chemical space around PF-8380.

Initially, library work was carried out using the fragment **1**[10] (Scheme 1). In an attempt to improve solubility, a number of alternative alcohols (ROH) were used to reduce the number of aromatic rings via saturation.[15] Whilst **2b** and **2c** maintained the activity (Table 1) when compared with unsubstituted compound **2a**, none of these changes resulted in an improvement in thermodynamic solubility, which remained unmeasurable at physiological pH. Replacement of the dichlorophenyl moiety of PF-8380 with heterocycles such as pyridine led to a significant loss of activity (data not shown).

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https://doi.org/10.1016/j.bmcl.2018.05.030
Received 28 March 2018; Received in revised form 11 May 2018; Accepted 14 May 2018
Available online 21 May 2018
0960-894X/

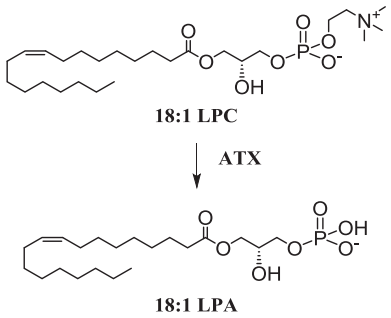


Fig. 1. Cleavage of 18:1 lysophosphatidylcholine (LPC) to 18:1 lysophosphatidic acid (LPA) by Autotaxin.

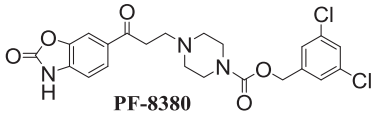
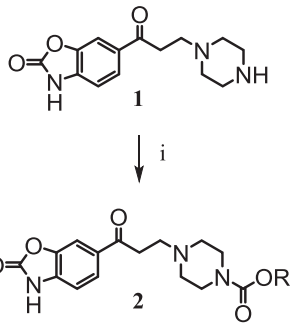


Fig. 2. Autotaxin inhibitor, PF-8380: structure and properties. ATX CR$^{\Psi}$ IC_{50} 1.1 nM, Rat *p.o.* pharmacokinetics10 F 43-83%, HT-Eq Solubility11 ($pH_{6.8}$) 0.011 mg/ml, Selectivity: hERG dofetilide12 IC_{50} 2700 nM. $^{\Psi}$Choline release assay.9 Assay values represent geometric means of 3–6 determinations.

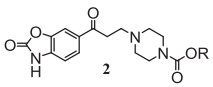
The linker region of PF-8380 was then modified, in an attempt to gain solubility via change in geometry or incorporation of heteroatoms, as shown in Scheme 2, to give a series of amide carbamates (**6**). Several potent compounds were identified (Table 2), but again, thermodynamic solubility remained unmeasurable at physiological pH.

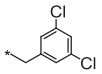
It became apparent at this time, that all compounds explored contained the benzoxazolone, and that all showed high crystallinity. We hypothesized that the crystallinity was due to the benzoxazolone, and that high crystal lattice energy was leading to poor dissolution, and hence poor solubility. In an attempt to reduce the crystal lattice energy, the benzoxazolone was truncated to the oxazolinone (**8**). Intermediates (**7**) were prepared analogously to **5**, then coupled to 2-oxo-2,3-dihydrooxazole-5-carboxylic acid (Scheme 3). We were pleased to find that this led to an improvement in solubility, despite a reduction in activity. Some activity could be recovered by replacing the piperazine with a



Scheme 1. Reagents and conditions: (i) ROH, CDI, DMF, overnight at RT, 30–70% yield.

Table 1



Compound	R	ATX CR$^{\Psi}$ IC_{50}/nM
PF-8380		1.1
2a		130
2b		240
2c		170

$^{\Psi}$ Choline release assay.9 Assay values represent geometric means of 3–6 determinations.

piperidine to give compound **8b**.

Within the series, it had been noted that hydrogen bond donor (HBD) count greatly affected permeability, as measured in artificial membrane experiments (PAMPA[16]). This was reflected in the permeability data (Table 3) for compounds **8a** and **8b** containing two HBDs.

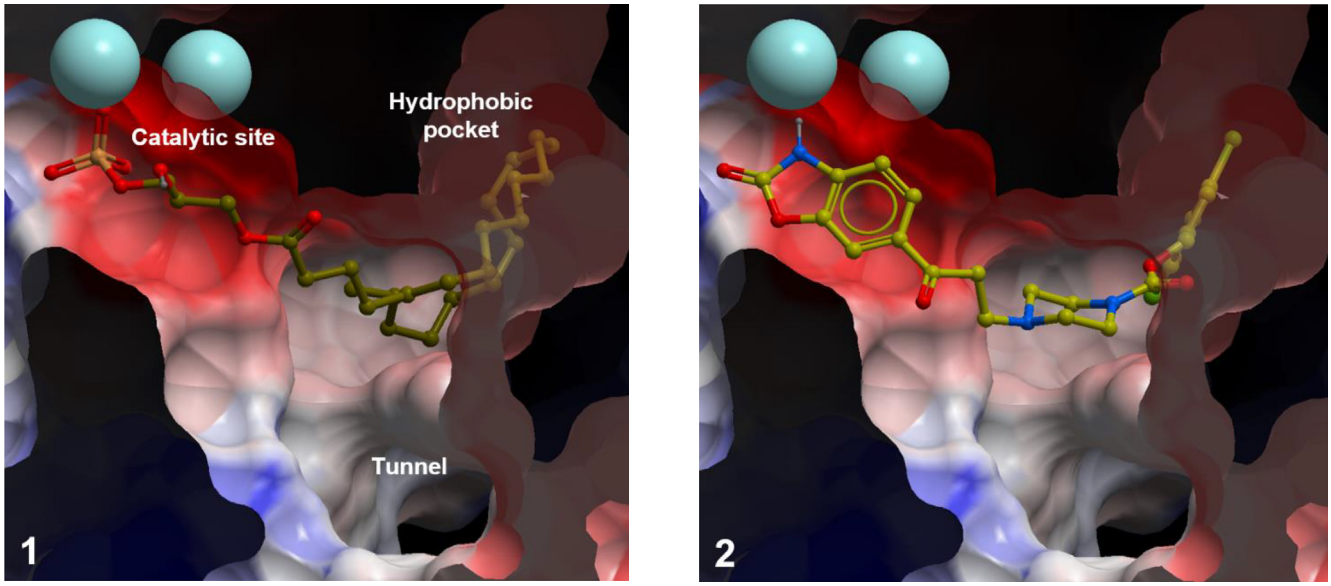


Fig. 3. 22:6 LPA and PF-8380 bound to Autotaxin. **1.** 22:6 Lysophosphatidic acid (LPA) bound to mouse Autotaxin (ATX) – the phosphate coordinated to Zn^{2+} (blue spheres) in the catalytic domain, and the lipophilic tail bound in the hydrophobic pocket. The tunnel is thought to deliver LPA to the receptor.13 [PDB ID 3NKR], **2.** Crystal structure of PF-8380 bound to rat ATX. The benzoxazolone is in close proximity to the catalytic site Zn^{2+} and the benzyl carbamate is bound in the hydrophobic pocket.14 [PDB ID 5LOK].