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Discovery of ONO-7300243 from a Novel Class of Lysophosphatidic Acid Receptor 1 Antagonists: From Hit to Lead

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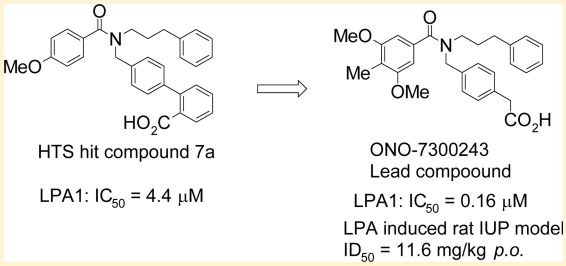
Supporting Information

ABSTRACT: Lysophosphatidic acid (LPA) evokes various physiological responses through a series of G protein-coupled receptors known as LPA_{1-6}. A high throughput screen against LPA_1 gave compound **7a** as a hit. The subsequent optimization of **7a** led to **ONO-7300243** (**17a**) as a novel, potent LPA_1 antagonist, which showed good efficacy *in vivo*. The oral dosing of **17a** at 30 mg/kg led to reduced intraurethral pressure in rats. Notably, this compound was equal in potency to the α_1 adrenoceptor antagonist tamsulosin, which is used in clinical practice to treat dysuria with benign prostatic hyperplasia (BPH). In contrast to tamsulosin, compound **17a** had no impact on the mean blood pressure at this dose. These results suggest that LPA_1 antagonists could be used to treat BPH without affecting the blood pressure. Herein, we report the hit-to-lead optimization of a unique series of LPA_1 antagonists and their *in vivo* efficacy.



KEYWORDS: *LPA1 antagonist, GPCR, benign prostatic hyperplasia, SAR, hit-to-lead optimization*

Lysophosphatidic acids (LPAs) are a bioactive class of phospholipids, which are produced by autotaxin from lysophosphatidylcholine in blood.[1−3] LPAs exerts a wide range of cellular responses, including intracellular Ca^{2+} mobilization, cell proliferation, cell survival, and cell motility. Based on their interesting properties, LPAs have been implicated in a wide range of complex physiological responses, including the contraction of smooth muscle, demyelization, wound healing, coagulation, and immunological competence.[4] Furthermore, these physiological functions can be related to a number of pathophysiological responses, such as cancer,[5] neuropathic pain,[6] and fibrosis.[7] The biological effects of LPAs are mediated through G protein-coupled receptors (GPCRs). Six LPA receptors (LPA_{1-6}) have been identified and characterized to date. $LPA_{1,2,3}$ (previously known EDG-2, 4, 7) belong to the EDG family of proteins because of their high sequence homology.[8,9]

Benign prostatic hyperplasia (BPH) is a chronic disease that affects around 30% of males over the age of 60 and is accompanied by the enlargement of prostate and difficulty urinating. Although the exact causes of BPH are not fully understood, the prostatic tissue mass and the smooth muscle tone are thought to be two of the major components of BPH. One option for the treatment of BPH is to reduce the prostatic smooth muscle tone using α_1 adrenoceptor antagonists such as tamsulosin or doxazosin, which are currently used in clinical practice to contract the urethra.[10,11] We previously reported that LPAs can induce the contraction of the urethra via LPA_1. Notably, LPAs have been reported to exhibit similar levels of contractile potency to the α_1 adrenoceptor agonist phenylephrine.[12,13] It is therefore envisaged that LPA_1 antagonist will show good potential for the treatment of BPH.

Several LPA_1 antagonists have been reported to date, and these compounds can be divided into two different categories: (i) lipid-like molecules containing a phosphoric acid moiety and a long alkenyl chain; and (ii) nonlipid-like small molecules (Figure 1). Compounds belonging to the first group generally exhibit poor bioavailability because of their high hydrophobicity. Furthermore, the behavior of these compounds can readily switch from agonist to antagonist depending upon the nature of the polar headgroup, making the design of antagonists particularly challenging. Most of the nonlipid small molecules developed to date as LPA_1 antagonists are phenylethoxy carbamoyl derivatives, such as Ki16425, which was the first reported compound to exhibit $LPA_{1,3}$ dual antagonist activities.[14] Several analogues of Ki16425 have been developed bearing a similar phenylethoxy carbamoyl moiety to the parent compound but with a wide variety of different five-membered

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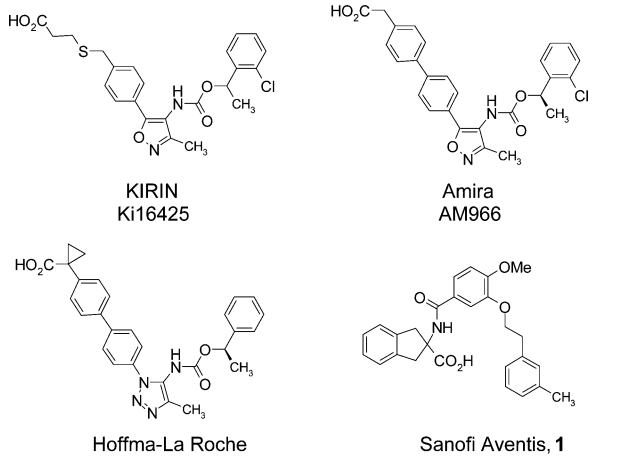
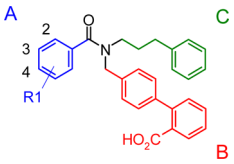


Figure 1. Structures of known LPA1 antagonists.

Table 1. Structure–Activity Relationship for Different Substituents on Section A



compd	R^1	LPA1 IC_{50} (μM)[a]
7a	4-MeO	4.4 (6.9–3.1)
7b	H	12.1 (15.0–9.7)
7c	2-MeO	3.3 (4.0–2.8)
7d	3-MeO	1.3 (1.9–0.9)
7e	3-F	5.5 (6.5–4.6)
7f	3-Me	1.7 (2.3–1.3)
7g	3,5-di-MeO	0.26 (0.32–0.21)
7h	3,4-di-MeO	3.7 (4.8–2.8)
7i	3,4,5-tri-MeO	0.39 (0.65–0.24)
7j	3,5-di-Me	0.26 (0.31–0.21)

[a]IC_{50} values were determined by nonlinear regression analysis of the dose–response curves (5 points) generated using GraphPad Prism ver.5.04 with 95% confidence intervals in parentheses.

rings to improve their subtype selectivity and/or *in vivo* efficacy.[14–18] It is noteworthy that some of these compounds are currently being evaluated in clinical trials for the treatment of idiopathic pulmonary fibrosis (IPF). Sanofi Aventis reported a structurally unique indan-2-carboxylic acid-containing antagonist **1**. This compound **1** is most likely an analogue of SAR100842, which is currently in Phase IIa trials for systemic sclerosis.[18]

At the beginning of our LPA_1 antagonist program, the only small molecule to have been reported in the literature as an LPA receptor antagonist was Ki16425 with no SAR data.[14] To obtain a good starting point, we carried out a high-throughput screening (HTS) campaign using a Chinese hamster ovarian (CHO) cell line stably expressing the human LPA_1 receptor. In this way, we identified compound **7a** as a weak LPA_1 antagonist (Table 1). Herein, we report the identification of a novel series of LPA_1 antagonists and the results of our structure and activity relationship (SAR) studies for the hit-to-lead optimization of this series for the treatment of BPH.

Our initial exploration of the HTS hit compound **7a** involved the modification of section A (blue in Table 1) to identify the

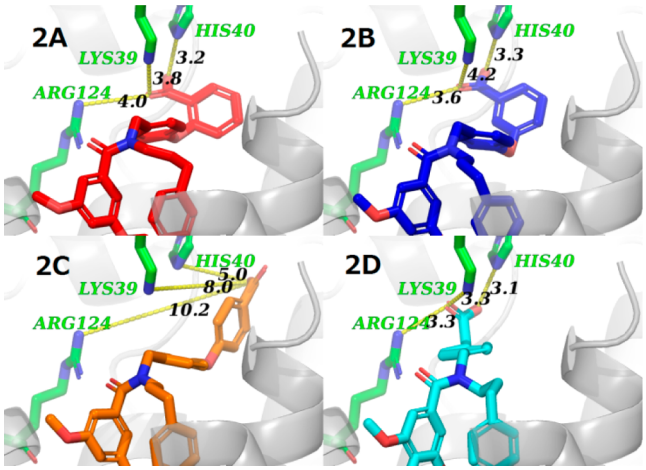


Figure 2. Docking results for some of our compounds using LPA1 crystal structure (PDB code 4z34).[19] Docking poses of compounds (2A) **10** (red), (2B) **13** (blue) (2C) **14** (orange), and (2D) **17a** (**ONO-7300243**). The hydrogen atoms have been omitted for clarity. The distances are highlighted by dashed lines (distances in Å).

optimum substituent at this position (Table 1). A variety of different substituted benzene rings were evaluated at this position, and the results are summarized in Table 1. The removal of the methoxy group from the benzoyl group resulted in a 2-fold decrease in the potency. Among the monosubstituted compounds (**7a**, **7c–f**), the 3-methoxy analogue **7d** is the most potent with an IC_{50} of 1.3 μM. Among the di- and trisubstituted compounds tested in the current study, the 3,5-dimethoxy analogue **7g** and 3,5-dimethyl analogue **7j** were found to be the most potent. Interestingly, the corresponding 3,4,5-trimethoxy analogue **7i** was equipotent with compound **7g**, whereas the mono- and disubstituted analogues **7c** and **7h** showed much lower antagonist activities. These results therefore highlight the importance of having electron-donating substituents at the 3- and 5-positions of the benzene ring for good potency.

We subsequently explored section B of hit compound **7a** by varying the substituents attached to the pendent benzoyl moiety. When the benzoic acid substituent from the original hit was replaced with phenylacetic acid (**8**) or dihydrocinnamic acid (**9**), the potency remained the same. In contrast, the introduction of an ether linker to give a biphenyl group (**10**) led to an increase in the antagonist activity (IC_{50} = 0.089 μM). Furthermore, the *ortho*- and *meta*-substituted carboxylic acid analogues **10** and **13** were more potent than the corresponding *para*-substituted derivatives (IC_{50} = 0.14 μM for **13**, 44% inhibition at 1 μM for **14**). These results therefore suggested that the carboxylic acid group needed to be placed in a specific position to interact as effectively as possible with specific basic residues on the target protein. An X-ray structure of LPA_1 bound to an antagonist was recently published in the literature.[19]

Docking studies were conducted using the X-ray crystal structure LPA_1 (PDB code 4z34)[19] to explore the binding mode of these prototype compounds (**10**, **13**, and **14**) and the importance of the positioning of the carboxylic group (Figure 2A–C). The results revealed that the phenyl ring of section A most likely formed a π-stacking interaction with the phenyl ring of section C. This phenyl ring of section C has a van der Waals contact with Trp271, Gly274, and Leu275 (see Supporting Information S36, Figure S1A). A similar stacking interaction to

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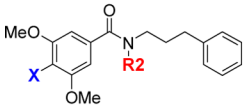
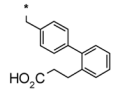
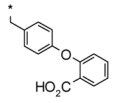
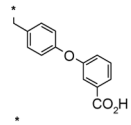
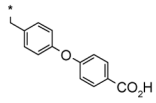
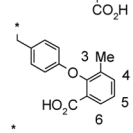
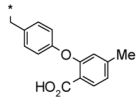
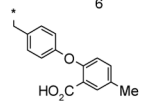
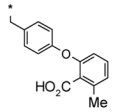
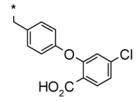
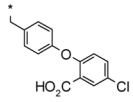
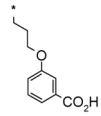
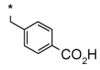
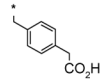
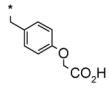
Table 2. Structure–Activity Relationship for Section B



Cmpd	X	R2	LPA1: IC_{50} (μM) [a]	Cmpd	X	R2	LPA1: IC_{50} (μM) [a]
8	H		0.21 (0.28 - 0.16)	**9**	H		0.23 (0.30 - 0.18)
10	H		0.089 (0.12 - 0.066)				
11	OMe		0.13 (0.17 - 0.11)	**13**	H		0.14 (0.21 - 0.098)
12a	Me		0.071 (0.090 - 0.055)				
14	H		44% inh at 1 μM	**12b**	Me		0.14 (0.19 - 0.10)
12c	Me		0.015 (0.022 - 0.010)	**12d**	Me		0.042 (0.050 - 0.036)
12e	Me		0.10 (0.13 - 0.080)	**12f**	Me		0.0059 (0.0073 - 0.0048)
12g	Me		0.0035 (0.0050 - 0.0025)	**15**	Me		0.68 (0.98 - 0.47)
16	Me		> 1	**17a** (ONO-7300243)	Me		0.16 (0.19 - 0.13)
18a	Me		0.10 (0.12 - 0.086)				

[a] IC_{50} values were determined by nonlinear regression analysis of the dose–response curves (5 points) generated using GraphPad Prism ver.5.04 with 95% confidence intervals in parentheses.

this was also observed in the ligand in the LPA_1 X-ray crystal structure[19] and represents a common conformational feature of our LPA1 antagonists. The results of the docking experiments also revealed that compounds **10** and **13** could adopt conformations in which their carboxylic acid moieties interacted with Lys39, His40, and Arg124 in LPA_1. These two compounds would most likely show similar binding modes, which would explain why they exhibited similar levels of antagonist activity. In contrast, the docking experiments revealed that the carboxylic acid moiety of compound **14** could only interact with His40 in LPA1 (Figure 2C), explaining why this compound was less potent than compounds **10** and **13**.

Further investigation of section B was conducted by fixing section A as a 3,5-dimethoxy 4-methyl substituent and varying the nature of section B moiety. The 3,5-dimethoxy-4-methyl substituent was selected as the optimum section A group based on the potency of compound derivative **12a** being greater than that of the 3,4,5-trimethoxybenzamide derivative **11**. Compounds **12c** and **12d** bearing a methyl substituent at the 4- or 5-position of their benzoic acid moiety in section B, respectively, showed improved antagonist activity compared with compound **12a**. This result indicated that there was enough space around the benzoic acid group to accommodate additional substituents at the 4- and 5-positions of the benzene ring. In contrast, compounds **12b** and **12e** bearing a methyl group at the 3- or 6-position of the benzoic acid moiety did not improve the potency.

The introduction of an electron-withdrawing chloride at the 4- or 5-position of the benzene ring of the benzoic acid moiety afforded compounds **12f** and **12g**, respectively, with considerable increases in the activity compared with the methyl analogues. Based on these modifications, compound **12g** bearing a 3,5-dimethoxy-4-methylphenyl substituent on section A and a 5-chloro substituent on section B was determined to be the most potent antagonist of all of the compounds synthesized so far. However, the effect of the chloride atom on the benzoic acid moiety in section B currently remains unclear because compounds **12f** and **12g** exhibited almost identical activity, despite their different substitution pattern. It is noteworthy that both of these compounds are highly lipophilic (clogP = 8.24) and that increasing lipophilicity can lead to an increase in the activity.[20] The addition of a chloride substituent to give compound **12g** led to an increase in the lipophilicity compared with compound **12d**, as well as an increase in activity. In general, highly lipophilic compounds tend to behave in a promiscuous manner, hitting multiple targets, which can lead to unwanted side effects and poor pharmacokinetics.[21] With this in mind, we decided to investigate an alternative strategy for increasing the antagonist activity without increasing the lipophilicity to discover a lead compound.

To address this problem, we investigated the possibility of removing one of the phenyl rings from the bis aryl portion of the molecule (section B) to decrease the molecular weight (Table 2, **15**–**18a**). Although a benzylic phenyl ring was not

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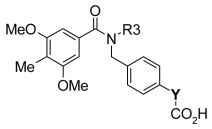
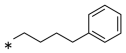
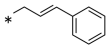
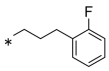
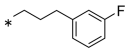
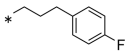
Table 3. Structure–Activity Relationship for Section C[a]



Cmpd	Y	R3	LPA1: IC_{50} (μM)
18b	$-OCH_2-$		> 10
18c	$-OCH_2-$		6.6 (9.1 - 4.8)
17b	$-CH_2-$		> 1
17c	$-CH_2-$		0.22 (0.30 - 0.16)
17d	$-CH_2-$		0.19 (0.23 - 0.15)
17e	$-CH_2-$		>1

[a]IC_{50} values were determined by nonlinear regression analysis of the dose–response curves (5 points) generated using GraphPad Prism ver.5.04 with 95% confidence intervals in parentheses.

essential for inducing antagonist activity in **15**, a linker was required to maintain some distance between the carboxylic acid and amide functional groups in **16**. The activity lost in **16** was recovered by the addition of a spacer, as shown in compounds **17a** and **18a**. The results of a docking experiment with compound **17a** using the X-ray crystal structure of LPA_1 suggested that basic residues in the active site of the protein could form interactions with acidic functional groups, as shown in compounds **10** and **13** (Lys39, His40, and Arg124, Figure 2D). This would explain why compounds **17a** and **18a** exhibited similar levels of antagonist activity against LPA_1. Notably, compounds **17a** and **18a** allowed for a considerable reduction in the molecular weight, as well as the lipophilicity (clogP = 5.29 for **17a**, 5.23 for **18a**).

Regarding section C, the replacement of the phenylpropyl chain in **18a** with a phenylethyl or phenylbutyl group gave compounds **18b** and **18c**, respectively, which both showed lower antagonist activities than **18a**, indicating that the chain length is critical to the activity (Table 3). Compounds **18b** and **18c** could not form a π-stacking interaction between the phenyl rings of section A and C so that their activities were lost. The introduction of an sp^2 carbon to this part of the molecule also led to a decrease in the potency, as demonstrated by **17b**. Notably, the introduction of a fluoro group at the *ortho* (**17c**) or *meta* (**17d**) position of the phenyl ring was tolerated, whereas the *para*-fluoro analogue **17e** ablated activity because of steric repulsion with Trp271 (see Supporting Information S36, Figure S1B). This phenyl propyl moiety is critical to the antagonist activity.

Three representative compounds (**12g**, **17a**, and **18a**) were studied in an LPA-induced rat intraurethral pressure (IUP) model (Table 4). This IUP model was conducted as previously described by the intraduodenal (i.d.) administration of the compounds.[22,23] Compound **12g**, which showed the strongest *in vitro* LPA_1 antagonist activity (IC_{50} = 0.0035 μM), showed 53% inhibition of LPA-induced IUP increase at 10 mg/kg i.d. administration. Although **ONO-7300243** (**17a**) showed only modest *in vitro* activity (IC_{50} = 0.16 μM), it showed much stronger effects *in vivo* (88% inhibition at 10 mg/kg i.d., 62% inhibition at 3 mg/kg i.d.) compared with compound **12g**. To develop a deeper understanding of this difference, we compared the *in vitro* physicochemical properties of these two compounds. The results revealed that **ONO-7300243** (**17a**) showed good membrane permeability and good metabolic stability against rat liver microsomes (MS). Furthermore, the molecular weight of **ONO-7300243** (**17a**) was much lower than that of compound **12g** (MW = 461 for **17a**, 574 for **12g**), leading to a lower lipophilicity (clog P = 5.29 for **17a**, 8.24 for **12g**). These data therefore indicate that the good physicochemical properties of compound **17a** led to its good *in vivo*

Table 4. Representative Properties of ONO-7300243 (17a), 18a, and 12g

compd	17a ONO-7300243	18a	12g
In Vitro Efficacy (μM)[a]			
LPA_1	0.16 (0.19–0.13)	0.10 (0.12–0.86)	0.0035 (0.0050–0.0025)
LPA_2	8.6 (10.3–7.2)	23 (96–5.4)	0.79 (1.9–0.33)
LPA_3	>10	>10	>10
In Vivo Efficacy			
Rat IUP (%)[b]	−88	−44	−53
Physicochemical Properties			
MW	461	477	574
clogP	5.29	5.23	8.24
solubility (μM) (pH 6.8 buffer)	73	84	69
Caco2 (Papp)	15.9×10^{-6}	3.2×10^{-6}	N.T.[c]
Metabolic Stability[d]			
$T_{1/2}$ (min)			
Human MS	28	22	<15
Rat MS	29	24	<15

[a]IC_{50} values were determined by nonlinear regression analysis of the dose–response curves (5 points) generated using GraphPad Prism ver.5.04 with 95% confidence intervals. [b]Maximal inhibition rate of LPA-induced increase of intraurethral pressure (IUP) in anesthetized rats. Each compound (10 mg/kg) in 0.5% methylcellulose was administered intraduodenally at 0 min, and LPA (300 μg/kg) was injected intravenously at pre, 5, 15, 30, and 60 min. [c]N.T. = not tested. [d]0.5 mg/mL, NADPH; MS, microsomes.

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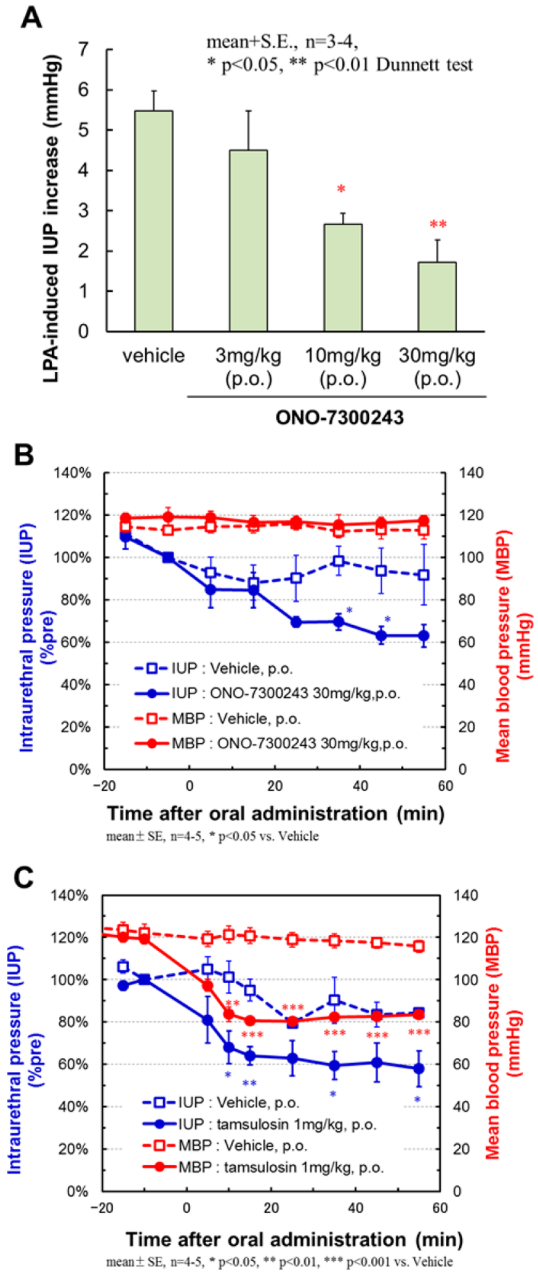

Figure 3. *In vivo* efficacy of **ONO-7300243** (**17a**). (A) Dose responsibility of **ONO-7300243** (**17a**). The compound was orally administered at each dose in conscious rats. After 60 min, LPA (300 μg/kg) was injected intravenously and IUP was measured in short-term anesthetized rats. (B,C) Change of IUP and mean blood pressure (MBP) without LPA stimulation in conscious rats. Vehicle, **ONO-7300243** (**17a**), or tamsulosin (α_1 adrenoceptor antagonist) was orally administered at 0 min, and IUP and MBP were measured continuously for 60 min. The mean pressure was calculated at 10 min intervals.

efficacy. It is noteworthy that **ONO-7300243** (**17a**) and compound **18a** exhibited good selectivity toward LPA_1 over LPA_2, most likely because low molecular weight and low lipophilicity lead to reduced compound promiscuity and increased selectivity.[20] Compounds **17a** and **18a** exhibited almost identical levels of antagonist activity *in vitro*. However, the *in vivo* potency of compound **18a** was lower than that of compound **17a**. These two compounds have showed similar physicochemical properties except for their Caco2 permeability. The main difference between compounds **17a** and **18a** is the acidity of their carboxylic acid group (i.e., the pK_a value of phenyl acetic acid is 4.3, whereas that of phenoxyacetic acid is 3.1). This increased acidity could contribute to decreased membrane permeability and could explain the reduced *in vivo* activity (44% inhibition at 10 mg/kg i.d.).

We subsequently investigated the oral administration of **ONO-7300243** (**17a**) to determine its effect on rat IUP. Compound **17a** inhibited the LPA-induced IUP increase in a dose-dependent manner (ID_{50} = 11.6 mg/kg p.o.) up to 1 h after dosing (Figure 3A). Significant effects were observed at 10 and 30 mg/kg ($p < 0.05$ vs vehicle). We also assessed whether or not this LPA_1 antagonist influenced in blood pressure in conscious rats (Figure 3B). **ONO-7300243** (**17a**) (30 mg/kg, p.o.) led to a significant decrease in the IUP in conscious rats without LPA stimulation compared with the vehicle without affecting the mean blood pressure (MBP). These results therefore suggested that the LPA_1 receptor was constantly activated to some extent *in vivo*, exhibiting LPA_1 antagonist effects in normal rats without exogenous LPA stimulation. For comparison, tamsulosin (α_1 adrenoceptor antagonist), which is used in clinical practice for the treatment of BPH, was tested in the same *in vivo* model (Figure 3C). Tamsulosin significantly reduced IUP at 1 mg/kg oral administration with the same potency for reducing IUP as **ONO-7300243** (**17a**). This compound also led to a significant reduction in MBP at the same dose.[22] This difference in the effect on blood pressure distinguishes LPA_1 antagonists from α_1 adrenoceptor antagonists. Tamsulosin has been optimized for once daily administration. In contrast, the results of a rat pharmacokinetic study of **ONO-7300243** (**17a**) showed that this material had a rapid clearance (CL_{tot} = 15.9 mL/min/kg at 3 mg/kg i.v.) and a short half-life (0.3 h) (see Supporting Information S35, Table S1). The main goal of the lead optimization stage for this compound would therefore involve making improvements to its pharmacokinetic profile to yield a promising compound.

In conclusion, we have successfully obtained the orally effective lead compound **ONO-7300243** (**17a**) as the result of modification of sections A and B of hit compound **7a**. The oral administration of compound **17a** in rats led to a significant reduction in IUP in a dose-dependent manner without affecting MBP. When dosed at 30 mg/kg p.o., the potency of **ONO-7300243** was the same as tamsulosin dosed at 1 mg/kg p.o. The lead optimization of this compound will focus on improving its pharmacokinetic profile and should lead to a promising candidate for the treatment of BPH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.6b00225.

Experimental procedures, pharmacokinetic parameters of ONO-7300243, LPA1 receptor antagonist assay, and van der Waals contact of Section C (PDF)

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Notes

The authors declare no competing financial interest.

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