Investigation of a Bicyclo[1.1.1]pentane as a Phenyl Replacement within an LpPLA₂ InhibitorNicholas D. Measom,^{†,‡} Kenneth D. Down,[†] David J. Hirst,^{*,†,§} Craig Jamieson,[‡] Eric S. Manas,[§] Vipulkumar K. Patel,[†] and Don O. Somers[†][†]GlaxoSmithKline, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, U.K.[‡]Department of Pure and Applied Chemistry, University of Strathclyde, Thomas Graham Building, 295 Cathedral Street, Glasgow, G1 1XL, U.K.[§]GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, Pennsylvania 19426-0989, United States

Supporting Information

ABSTRACT: We describe the incorporation of a bicyclo[1.1.1]pentane moiety within two known LpPLA₂ inhibitors to act as bioisosteric phenyl replacements. An efficient synthesis to the target compounds was enabled with a dichlorocarbene insertion into a bicyclo[1.1.0]butane system being the key transformation. Potency, physicochemical, and X-ray crystallographic data were obtained to compare the known inhibitors to their bioisosteric counterparts, which showed the isostere was well tolerated and positively impacted on the physicochemical profile.

KEYWORDS: LpPLA₂, bicyclo[1.1.1]pentane, bioisostere, darapladib, cardiovascular disease, physicochemical

Lipoprotein-associated phospholipase A₂ (LpPLA₂) or platelet-activating factor acetylhydrolase (PAF-AH) has been extensively studied as a potential therapeutic target for the treatment of atherosclerosis^{1–6} and more recently in other diseases where vascular inflammation may play a role, e.g., diabetic macular edema and Alzheimer's disease.^{7,8} A range of epidemiological and genetic evidence suggests that increased LpPLA₂ concentration increases the risk of myocardial infarction (MI), ischemic stroke, and cardiac death in patients with stable cardiovascular disease (CVD).^{1,9–26} With considerable support for the hypothesis that LpPLA₂ is associated with atherosclerosis, a range of inhibitors has been developed, with darapladib 1^{27–29} and rilapladib 2³⁰ being well studied examples as both compounds have entered clinical trials (Figure 1).

Compound 1 (Figure 1) shows excellent potency against LpPLA₂ in *in vitro* assays with a pIC₅₀ of 10.2.²⁸ It is highly lipophilic (ChromLogD_{7.4}: 6.3) but does have good artificial membrane permeability (AMP) of 230 nm/s. *In vivo* studies have consistently shown inhibition of the hydrolysis of LpPLA₂ substrates in rats, dogs, rabbits, and pigs.²⁸ The *in vivo* effects of 1 include reduced content of lyso-phosphatidylcholines (lyso-PCs) within atherosclerotic lesions, which are pro-inflammatory mediators.³¹ Both compounds 1 and 2 (Figure 1) bind to

Figure 1. Darapladib and rilapladib structures.

LpPLA₂ in a similar manner with the cyclic amide/ketone mimicking the ester functionality of the enzyme substrates within the oxyanion hole.^{32,33} This blocks the active site where a Ser273, His351, and Asp296 form the catalytic triad and the backbone amide NHs of a Leu153 and Phe274 help to bind the substrate (Figure 4). The remaining functionality occupies lipophilic pockets adjacent to the active site. Compound 2 similarly displays excellent LpPLA₂ potency in *in vitro* assays.

Received: August 19, 2016

Accepted: November 15, 2016

Published: November 15, 2016

Both inhibitors, however, exhibit suboptimal physicochemical profiles. They have high molecular weights, low aqueous solubility, and high property forecast indices (PFI); a risk indicator of developability.³⁴ Improvement in the physicochemical properties of these compounds is therefore attractive. Methods of achieving this include introduction of polar functionality, removal of lipophilic groups, or replacement of suboptimal groups, such as aromatic rings with suitable bioisosteres, all of which were postulated to positively impact parameters such as PFI.³⁴

In this regard we targeted replacement of aromatic rings with saturated isosteres and became interested in the bicyclo[1.1.1]pentane system. There is a paucity of examples of the use of this template as a phenyl bioisostere^{35–37} including an mGluR1 receptor antagonist **3**^{38,39} and a γ -secretase inhibitor **4** (Figure 2).⁴⁰ This is possibly due to the lack of tractable routes to the

Figure 2. Drug compounds with bicyclo[1.1.1]pentane moiety.

desired analogues. Despite this, we reasoned it could serve as a useful isostere of the aryl unit in the darapladib chemotype (Figure 3).

Figure 3. Potential isosteric replacement for darapladib.

Accordingly, in this letter we illustrate the successful incorporation of the bicyclo[1.1.1]pentane into both the darapladib and rilapladib structures. The crystal structure of darapladib bound to LpPLA₂, solved in-house and comparable to the structure recently published,³³ indicates the internal aromatic of the biaryl system acts as a spacer, to allow access to a lipophilic pocket occupied by the trifluoromethylphenyl group. Modeling of the bicyclo[1.1.1]pentane moiety within LpPLA₂ and comparison with the X-ray crystal structure of darapladib confirmed its potential viability as a replacement linker (Figure 4). It was envisaged that disrupting the planarity of the biaryl system would improve the physicochemical profile.

There are only two previously reported syntheses of the bicyclo[1.1.1]pentane moiety.^{41,42} These include utilizing a propellane as the key intermediate followed by a photochemical acetylation.⁴³ Alternatively, addition of a carbene derivative to a

Figure 4. X-ray crystal structure of darapladib (blue) in LpPLA₂ overlaid with modeled bioisosteric replacement (magenta).

bicyclo[1.1.0]butane followed by dechlorination can be employed.⁴² The latter was deemed more suitable for large scale chemistry and was therefore exploited in these syntheses.

The synthesis of key intermediate **13** commenced with an organometallic addition into the commercially available ketone **6** to furnish **7** as a ~2:1 ratio of diastereomers in good yield. Alcohol **7** was converted to the chloride, and subsequent esterification and cyclization gave intermediate **10** with all steps proceeding in good to excellent yield.⁴⁴ The bicyclo[1.1.0]butane derivative **10** was treated with a dichlorocarbene⁴² to generate **11** in a yield comparable with literature. Alternative carbene additions, including Simmons–Smith conditions, were investigated; however, these all proved unsuccessful. In a modification to the established process, dechlorination of the ring system was achieved utilizing a tin hydride replacement; tris(trimethylsilyl)silane (TTMSS).^{39,45} Dechlorination proceeded smoothly, and subsequent ester hydrolysis furnished the key carboxylic acid intermediate **13** in excellent yield (Scheme 1).

Intermediate **13** was then used in the synthesis of both LpPLA₂ analogues. Amide coupling of **13** with commercially available amine **14** followed by reduction of the resulting amide **15** furnished intermediate **16** in good yield. Subsequent amide coupling of **16** with fragment **17**²⁸ secured the darapladib analogue **5** (Scheme 2).

Analogue **22** was synthesized in a similar fashion starting with an amide coupling of **13** with commercially available amine **18**. Reduction⁴⁶ of the resulting amide **19** to give intermediate **20**, followed by amide coupling with fragment **21**⁴⁷ produced the desired compound **22** in moderate yield (Scheme 3).

With target compound **5** in hand, a comparison of its enzyme potency and physicochemical properties with that of **1** was undertaken. Data collected included LpPLA₂ potency, solubility, ChromLogD_{7.4} (and associated PFI³⁴), and AMP binding. Analogue **5** maintains high potency compared to that of its parent **1** with a pIC₅₀ of 9.4 (1 pIC₅₀ = 10.2). This suggested that the bioisosteric moiety was tolerated within the enzyme. In order to compare the binding mode of the bioisosteric analogue **5** with **1**, an X-ray crystal structure of **5** in the LpPLA₂ protein was generated.⁴⁸ The structure, solved at ~1.9 Å resolution, revealed a similar binding mode for both molecules (Figure 5), which is in agreement with the initial molecular modeling (Figure 4). The overlay of the two structures reveals that the bicyclo[1.1.1]pentane moiety slightly precludes the adjacent trifluorophenyl moiety extending as far toward Leu121 and Phe125, although these residues move slightly toward the inhibitor to fill the void. This suboptimal

Scheme 1. Synthesis of Key Intermediate 13^a

^aReagents and conditions: (i) 4-bromotrifluorotoluene, *n*BuLi, THF, -78°C to rt, 77%; (ii) conc. HCl, PhMe, rt, sonication, 75%; (iii) HCl, MeOH, 1,4-dioxane, rt, quant.; (iv) NaH, THF, rt, 98%; (v) sodium trichloroacetate, tetrachloroethylene, diglyme, 120 to 140°C , 38%; (vi) TTMSS, 1,1'-azobis(cyclohexanecarbonitrile), PhMe, 110°C , 74%; (vii) LiOH, 1,4-dioxane, rt, 95%.

Scheme 2. Synthesis of Bioisosteric Darapladib Analogue 5^a

^aReagents and conditions: (i) 14, T3P, Et₃N, EtOAc, rt, 99%; (ii) LiAlH₄, THF, rt, 56%; (iii) 17, T3P, Et₃N, rt, CH₂Cl₂, 60%.

occupancy of the pocket could be an important factor in the slight drop-off in potency. Furthermore, the moiety has no effect on the key interactions within the oxyanion hole; retaining the carbonyl to backbone amide NH bonds with Leu153 and Phe274 residues and subsequently blocking the catalytic triad.

With the binding mode of both progenitor compound 1 and analogue 5 confirmed, a comparison of the physicochemical profiles of both was conducted (Table 1).

Analogue 5 showed an improved permeability of 705 nm/s from 230 nm/s⁴⁹ over 1 and a 9-fold increase in kinetic solubility (74 vs 8 μM , respectively). However, this was accompanied by an undesired increase in lipophilicity, as determined by measured ChromLogD_{7.4}, from 6.3 to 7.0.

Scheme 3. Synthesis of Bioisosteric Rilapladib Analogue 22^a

^aReagents and conditions: (i) 18, T3P, Et₃N, CH₂Cl₂, rt, 74%; (ii) [Ir(COE)₂Cl]₂, Et₂SiH₂, CH₂Cl₂, rt, 59%; (iii) 21, T3P, Et₃N, CH₂Cl₂, rt, 53%.

Calculation of Property Forecast Index (PFI), which is a summation of ChromLogD_{7.4} and number of aromatic rings,³⁴ consequently indicated that compounds 1 and 5 have equivalent PFIs due to the removal of one aromatic ring. Thermodynamic fasted state simulated intestinal fluid (FaSSIF) solubility was also obtained with analogue 5 exhibiting an approximately 3-fold improvement (>1000 $\mu\text{g/mL}$ compared to 399 $\mu\text{g/mL}$). This data is echoed by the comparison of 2 and 22, with 22 displaying improved solubility at pH 7.4 in both

Figure 5. X-ray crystal structure overlays of bound darapladib (blue) and analogue **5** (magenta) in LpPLA₂.

Table 1. Summary of Physicochemical Data

	1	5	2	22
pIC ₅₀	10.2	9.4	9.6 ⁵²	NT ^a
CLND (μM)	8	74	<1	32
FaSSIF (μg/mL)	399	>1000	203	635
AMP (nm/s) ⁴⁹	230	705	NT ^a	NT ^a
ChromLogD _{7.4}	6.3	7.0	6.74	7.06
PFI	10.3	10.0	11.74	11.06

^aNT = Not tested.

kinetic and thermodynamic measures as well as equivalent PFIs. Additionally, low clearance was observed for both **5** and **22** in a human liver microsomal assay, 1.22 and 0.76 mL/min/g, respectively. These data lend weight to the hypothesis that disrupting molecular planarity^{40,50,51} and reducing aromatic ring count³⁴ can be beneficial to solubility and the overall pharmacokinetic profile.

In summary, the incorporation of the bioisoteric bicyclo[1.1.1]pentane replacement, within LpPLA₂ analogues **5** and **22**, respectively, has been enabled through a challenging synthesis. High potency was maintained for **5**, and the binding mode was confirmed by X-ray crystallography.⁴⁸ The bicyclo[1.1.1]pentane moiety imparts improved physicochemical properties compared to the known inhibitor. This confirms the utility of this group as a phenyl bioisostere in the context of LpPLA₂ inhibition.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acsmmedchemlett.6b00281](https://doi.org/10.1021/acsmmedchemlett.6b00281).

Experimental procedures and analytical data for **5**–**22**;
X-ray crystallographic data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

N.D.M. is grateful to GlaxoSmithKline R&D, Stevenage for Ph.D. studentship funding. We would also like to thank Sean

Lynn for his help with the NMR assignments; Florent Potvain, Pascal Grondin, and Marie-Hélène Fouchet for running of the Lp-PLA₂ assay; the Physicochemical Analysis Team; and Storm Hart and Thomas Clohessy for their intellectual input.

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