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Evaluation of Oxetan-3-ol, Thietan-3-ol, and Derivatives Thereof as Bioisosteres of the Carboxylic Acid Functional Group

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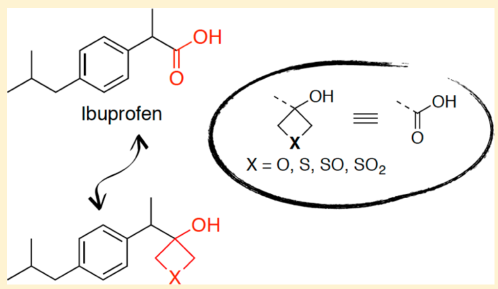
Supporting Information

ABSTRACT: The oxetane ring serves as an isostere of the carbonyl moiety, suggesting that oxetan-3-ol may be considered as a potential surrogate of the carboxylic acid functional group. To investigate this structural unit, as well as thietan-3-ol and the corresponding sulfoxide and sulfone derivatives, as potential carboxylic acid bioisosteres, a set of model compounds has been designed, synthesized, and evaluated for physicochemical properties. Similar derivatives of the cyclooxygenase inhibitor, ibuprofen, were also synthesized and evaluated for inhibition of eicosanoid biosynthesis in vitro. Collectively, the data suggest that oxetan-3-ol, thietan-3-ol, and related structures hold promise as isosteric replacements of the carboxylic acid moiety.



KEYWORDS: *Oxetan-3-ol, thietan-3-ol, carboxylic acid bioisostere, cyclooxygenase, lipoxygenase, dual inhibitors*

The (bio)-isosteric replacement of the carboxylic acid moiety of biologically active compounds is a common strategy in medicinal chemistry that is frequently employed to improve/modify the pharmacokinetic and/or pharmacodynamic properties of compounds of interest.[1−3] Although carboxylic acid isosteres are typically designed to mimic the carboxylic acid functional group, it is often the difference in structure and physicochemical properties of the isosteric replacement relative to the carboxylic acid that is critical to the success of this strategy. For this reason, and in consideration of the fact that the success of any isosteric replacement is typically context dependent, the evaluation and development of alternative surrogate structures that could complement and expand the existing set of bioisosteres continues to be a promising area of research.[4−9]

In recent years the oxetane ring has attracted considerable attention in medicinal chemistry[10] due to the fact that this four-membered ring heterocycle can be used to modulate important physicochemical properties of molecules, including aqueous solubility,[11] lipophilicity, and metabolic stability.[12] A series of publications[12−15] illustrated the potential of the oxetane ring as an isosteric replacement of the *gem*-dimethyl and the carbonyl group (Figure 1A,B). Importantly, 3-substituted oxetanes have been proposed as potential replacements of carboxylic esters and amides (Figure 1C,D).[14,16−19] These findings indicate that the oxetan-3-ol could be a potentially promising replacement of the carboxylic acid. Thus far, however, an evaluation of this fragment as a carboxylic acid surrogate has not been reported (Figure 1E).

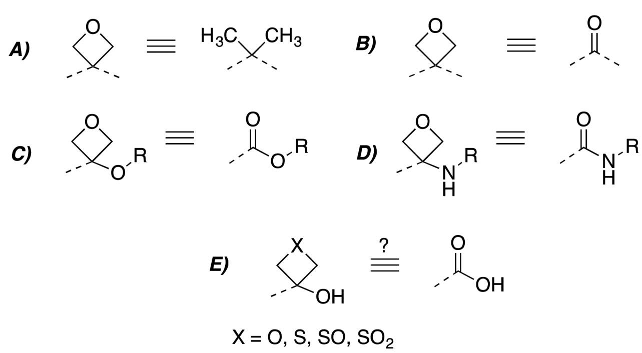


Figure 1. Oxetane ring holds promise as an isosteric replacement of the *gem*-dimethyl (A), and the carbonyl group in the context of ketones (B), esters (C), and amides (D); similar replacements may be of interest in the context of carboxylic acids (E).

Given our ongoing interest in the area of carboxylic acid bioisosteres,[6−8,20,21] we set out to investigate a range of physicochemical properties of the oxetan-3-ol, as well as the thietan-3-ol and the corresponding sulfoxide and sulfone

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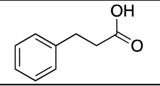
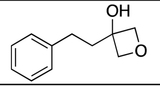
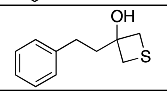
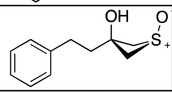
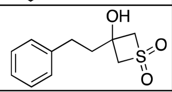
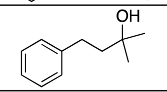
Table 1. Calculated and Experimental Properties of Test Compounds

Cpd #	Structure	$logD_{7.4}$[a]	$logD_{7.4}$ calc.[b]	PAMPA Pe (cm/s)[c]	PAMPA % retention[d]	PAMPA $logP_{app}$[e]	pK_a[f]	pK_a calc.[b]	H bonding $\ln(K_{eq})$[g]
1		−0.49 ± 0.19*	−0.56*	1.66E−06 ± 3.48E−7*	−6.8 ± 11*	−5.79 ± 0.10*	4.64*	4.7*	4.31*
3		2.07	1.7	8.27E−06	−11.9	−5.08	>12	13.5	2.53
4		2.99	2.28	1.32E−05	11.4	−4.88	>12	14.3	2.40
5		1.22	0.48	6.23E−06	10.0	−5.21	>12	14.2	3.46
6		1.24	0.58	1.22E−05	10.7	−4.91	9.31	13.6	3.76
16		ND	2.64	ND	ND	ND	ND	15.4	1.62

[a]Distribution coefficient between *n*-octanol and aqueous buffer (pH 7.4) determined by LC/MS (experiment run by WuXi AppTech). [b]Calculated values using ChemAxon. [c]Effective permeability (PAMPA assay run by Analiza, Inc.). [d]Membrane retention. [e]Log of the apparent permeability coefficient. [f]pK_a values determined by capillary electrophoresis (experiment run by Analiza, Inc.). [g]Equilibrium constants (K_{eq}) determined from a colorimetric assay that monitors the blue-shift of the maximum wavelength of a fluorescent pyrazinone HB acceptor upon complexation with the HB donor analyte. *Data previously reported.[20] ND = not determined.

structural units. To enable a more informative and rigorous comparison of the properties of these fragments relative to those of carboxylic acids and other known carboxylic acid bioisosteres, we constructed and evaluated a focused set of derivatives of the phenylpropionic acid (**1**, Table 1), as this carboxylic acid was already employed as a template structure in the synthesis and evaluation of a series of analogues comprising a wide selection of known carboxylic acid surrogates.[20] The properties evaluated here include acidity (pK_a), lipophilicity ($logD_{7.4}$), and permeability in the parallel artificial membrane permeability assay (PAMPA). Hydrogen-bonding studies were also conducted to evaluate these fragments as hydrogen bond (HB) donors. In addition, to evaluate the potential of oxetan-3-ol, thietan-3-ol, and related sulfoxide and sulfone derivatives as replacements of the carboxylic acid moiety in the context of biologically active compounds, a small set of derivatives of the cyclooxygenase (COX) inhibitor, ibuprofen (**2**, Table 2), was designed, synthesized, and evaluated as inhibitors of eicosanoid formation in rat basophilic leukemia (RBL-1) cells.

Collectively, the data generated from these studies provide a characterization of a range of physicochemical properties of oxetan-3-ol, thietan-3-ol, and related structures and, in turn, exemplify the possible utility of these fragments as replacements of the carboxylic acid functional group in drug design.

The synthesis of oxetane and thietane derivatives **3**−**6** and **7**−**10** was conducted as highlighted in Scheme 1. Model compounds **3**−**6** were constructed starting from phenethylmagnesium chloride **11** and the appropriate oxetan-3-one (**12**) or thietan-3-one (**13**) to give alcohols **3** and **4**, respectively. Treatment of the thietan-3-ol derivative **4** with urea-hydrogen peroxide complex (UHP) in acetic acid led to the corresponding sulfoxide as a mixture (6:4) of cis- and trans-isomers, as determined by ^1H NMR. When *m*-CPBA was used for the oxidation step, the cis/trans ratio was >98:2. Recrystallization of this mixture led to the formation of crystals of the cis-isomer **5** that were suitable for X-ray diffraction analysis (Scheme 1). Alternatively, oxidation of **4** with 2.2 equiv of oxone led to the formation of the fully oxidized sulfone derivative **6**, a crystalline material that enabled X-ray diffraction analysis (see Supporting Information). In a similar fashion, the synthesis of ibuprofen derivatives **7**−**10** was carried out starting from known alkyl chloride **14**, which was prepared in two steps from commercially available ketone **15**. Grignard addition to **12** or **13** yielded the oxetan-3-ol derivative **7** and thietan-3-ol derivative **8**, respectively. Oxidation of the latter compound with *m*-CPBA led to the sulfoxide derivative **9** (cis/trans ratio >20:1), while oxidation of **8** with oxone (2.2 equiv) resulted in sulfone derivative **10**.

Evaluation of physicochemical properties of model compounds **3**−**6** revealed that replacement of the carboxylic acid of **1** with these four-membered ring heterocycles results in a drastic reduction in acidic character (see Table 1). This is evident from the fact that sulfone derivative **6** exhibits a pK_a value of ∼9.3, while all other derivatives were found to have pK_a values >12 (i.e., above the range of the assay), with calculated values as high as ∼14. However, an evaluation of the hydrogen bond (HB) acidity of these compounds, which was conducted employing a previously reported colorimetric assay,[22] suggested that these replacements cause a far less dramatic reduction in the HB acidity scale relative to **1**. For example, compound **3** exhibited at least eight orders of magnitude lower acidity relative to **1**, but less than two orders of magnitude weaker binding via hydrogen bonding to the fluorescent HB acceptor used in the assay (see equilibrium constant, K_{eq}, values of test compounds **3**−**6**, Table 1). Also of interest, the K_{eq} values of **3**−**6** are significantly higher than that of alcohol **16**, confirming that the four-membered ring heterocycles found in compounds **3**−**6** play an important role in determining the HB-donating ability of the hydroxyl moiety. These observations, combined with prior studies that established the remarkable HB basicity of the oxetane ring,[23] suggest that the oxetan-3-ol **3** and related structures **4**−**6** have significant HB capacity.

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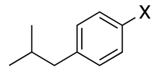
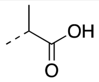
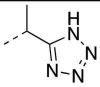
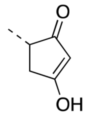
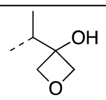
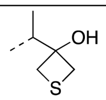
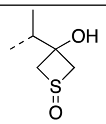
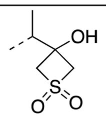
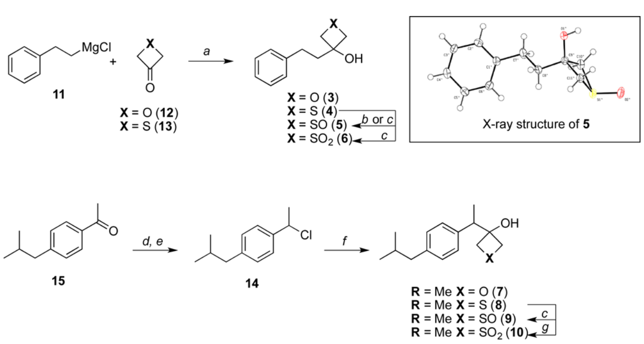
Table 2. IC_{50} Values of Test Compounds in the PGE_2/PGD_2 and LTB_4 Assays

Cpd		PGE_2/D_2 Assay IC_{50} (μM)[a]	LTB_4 Assay IC_{50} (μM)[b]
2		0.6 (0.3–1.1)*	>100
17		31.8 (24.6–41.0)*	>100
18		28.1 (10.6–74.5)*	>100
7		34.1 (25.9–44.9)*	8.4 (6.4–10.9)*
8		>100	7.6 (4.9–11.8)*
9		17.4 (5.7–53.5)*	11.7 (6.2–22.4)*
10		14.6 (12.1–17.5)*	20.2 (16.0–25.4)*

[a]Inhibition of COX pathway as determined by LC−MS/MS analyses of the combined production of COX-derived PGD_2 and PGE_2 in RBL-1 cells upon stimulation with arachidonic acid in the presence or absence of test compounds. [b]Inhibition of 5-LOX pathway as determined by LC−MS/MS analyses of the production of 5-LOX-derived LTB_4 in RBL-1 cells upon stimulation with arachidonic acid in the presence or absence of test compounds. *The data represent the calculated IC_{50} values and associated 95% confidence intervals as determined from triplicate samples at each concentration after a sigmoidal curve fit using GraphPad Prism software.

Scheme 1[a]



[a]Reagents and reaction conditions: (a) THF, −78 °C, 15 min, then rt, 1 h; (b) UHP, AcOH, rt, 14 h; (c) *m*-CPBA, CH_2Cl_2, −78 °C, 1 h; (d) $NaBH_4$, MeOH, 0 °C to rt, 30 min; (e) $SOCl_2$, CH_2Cl_2, 0 °C to rt, 18 h; (f) (i) Mg, LiCl, $ZnCl_2$, THF, rt, 6 h, (ii) **12** or **13**, THF, rt, 17 h; (g) oxone, acetone/H_2O, 0 °C to rt, 20 h.

The combination of limited acid character with the ability to establish HB may be a desirable feature of these structural units with respect to possible applications in drug design, especially in those circumstances where the presence of a negatively ionizable acid in a drug candidate may be responsible for an insufficient passive diffusion across biological membranes. Indeed, consistent with the relatively high pK_a values and with these molecules being mostly neutral at physiological pH, all of the model compounds were found to be comparatively more lipophilic and permeable in PAMPA compared to **1**. Furthermore, a comparison of physicochemical properties of model compounds **3**−**6** with 33 other phenylpropionic acid derivatives in which the carboxylic acid moiety was replaced by known carboxylic acid surrogates reveals that the four-membered ring heterocycles **3**−**6** are among the most permeable derivatives within the entire set (see Supplemental Figure 1, Supporting Information).

Evaluation of ibuprofen derivatives was conducted employing a modified RBL-1 cell assay that was previously developed for the evaluation of 5-lipoxygenase (5-LOX) inhibition,[24] which we adapted to monitor for compound inhibition of both COX and 5-LOX biosynthetic pathways. In addition to oxetane and thietane derivatives (**7**−**10**), ibuprofen analogues bearing a tetrazole[25] (**17**) and a cyclopentane-1,3-dione (**18**) were also constructed and tested for comparison. Typical assay conditions involved the coincubation of RBL-1 cells in 24-well plates with different concentrations of test compounds for 2 h, followed by the addition of the calcium ionophore, A23187 (12 μM), for 15 min to induce arachidonic acid production. Culture supernatants were subsequently collected and assessed for COX-derived prostaglandins (PGs) and 5-LOX-derived leukotrienes (LTs) by LC−MS/MS, as described in the Supporting Information. In initial concentration−response testing (Table 2), LTB_4 and combined PGD_2 and PGE_2, which coeluted under the chromatographic conditions, were quantified. In subsequent studies, a refined LC−MS/MS protocol was employed that permitted separate analyses of PGD_2 and PGE_2, as well as LTB_4 and LTC_4 (see Supporting Information).

Interestingly, the RBL-1 cell assay results revealed that replacement of the carboxylic acid moiety of **2** with the comparatively less acidic and more permeable four-membered ring structures results in analogues (**7**−**10**) that, unlike **2** as well as the tetrazole (**17**) and the cyclopentane-1,3-dione (**18**) derivatives, inhibit 5-LOX-mediated synthesis of LTB_4. Furthermore, with the exception of thietan-3-ol derivative **8**, analogues **7**, **9**, and **10** were found to inhibit the formation of both COX- and 5-LOX-derived eicosanoids with **9** and **10** exhibiting balanced inhibition activity in the micromolar range (see Figure 2). Although the RBL-1 assay does not permit us to unambiguously determine the enzymes in the arachidonic acid cascade that are inhibited by the test compounds, the observation that **7**, **9**, and **10** effectively reduce the formation of multiple PGs and LTs (see supplemental Table 1, Supporting Information) suggests that such inhibition is likely to take place at the COX and 5-LOX enzymes. These findings appear to be generally consistent with prior reports showing that selected bioisosteric replacements of the carboxylic acid moiety of different nonsteroidal anti-inflammatory drugs (NSAIDs), including **2**, can result in inhibitors of the 5-LOX pathway or multitargeted derivatives capable of inhibiting concurrently multiple enzymes in the COX- and 5-LOX biosynthetic pathways.[26,27]

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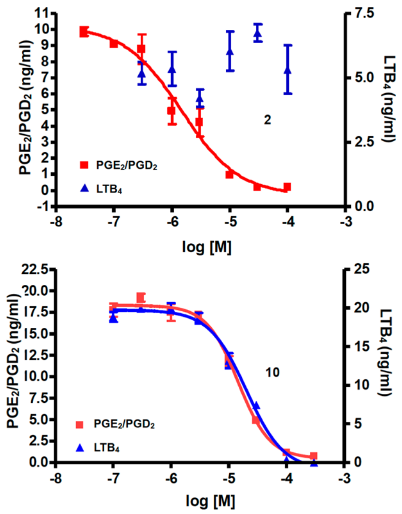

Figure 2. Concentration−response analyses of inhibition of 5-LOX-derived LTB_4 and COX-derived PGE_2/PGD_2 by compounds **2** (top) and **10** (bottom). Error bars represent standard error of the mean from triplicate samples.

Taken together, our results clearly suggest that oxetan-3-ol as well as thietan-3-ol and related sulfoxide and sulfone derivatives may be considered as alternative bioisosteres of the carboxylic acid functional group. Given the relatively low acidity and high permeability, these fragments may be considered especially in the context of CNS drug design, when isosteric replacement of the carboxylic acid is often needed to improve the brain penetration of a candidate compound.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchemlett.7b00212.

Experimental details; NMR spectra of test compounds; X-ray crystal structures; Supplemental Table 1; Supplemental Figure 1; docking studies (PDF)

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Author Contributions

The manuscript was written by C.B., K.R.B., and A.B.S. and was reviewed by all authors. P.L., K.O., V.M., V.T., L.M., K.V., L.H., M.J.J., and M.K. made experimental contributions; C.B. and K.R.B. directed research; and V.M.-Y.L. and J.Q.T. provided resources. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PG, prostaglandin; LT, leukotriene; HB, hydrogen bond

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