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Letter

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

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KEYWORDS: Oxetan-3-ol, thetan-3-ol, carboxylic acid bio-isostere, cyclooxygenase, lipoxygenase, dual inhibitors

ABSTRACT: The oxetane ring serves as an isostere of the carbonyl moiety, suggesting that the oxetan-3-ol may be considered as a potential surrogate of the carboxylic acid functional group. To investigate this structural unit, as well as the thietan-3-ol and the corresponding sulfoxide and sulfone derivatives, as potential carboxylic acid bio-isosteres, 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 the oxetan-3-ol, thietan-3-ol and related structures hold promise as isosteric replacements of the carboxylic acid moiety.

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 bio-isosteres 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).

Given our ongoing interest in the area of carboxylic acid bio-isosteres,[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 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 bio-isosteres, 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 analogs comprising a wide selection of known carboxylic acid surrogates.[20] The properties evaluated here include acidity (pKa), 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 the oxetan-3-ol, the 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), were designed, synthesized and evaluated as inhibitors of eicosanoid formation in rat basophilic leukemia (RBL-1) cells.

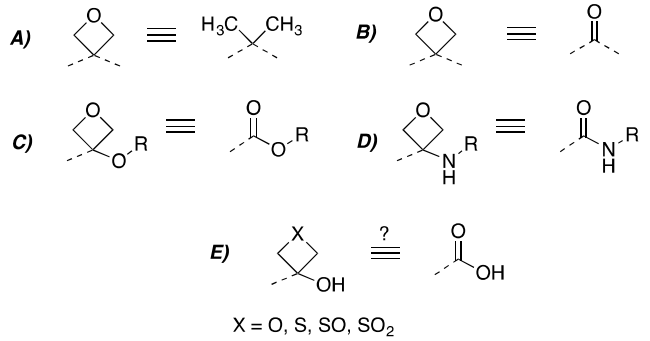
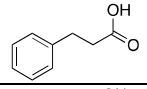
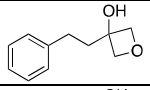
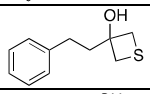
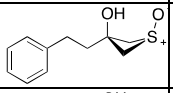
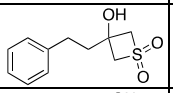
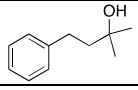


Figure 1. The oxetane ring holds promise as an isosteric replacement of the *gem*-dimethyl (A), and the carbonyl group in the context of ketones (B), esters (C), and amides (D); similar replacements may be of interest in the context of carboxylic acids (E).

Collectively, the data generated from these studies provide a characterization of a range of physicochemical properties of ox-

etan-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.

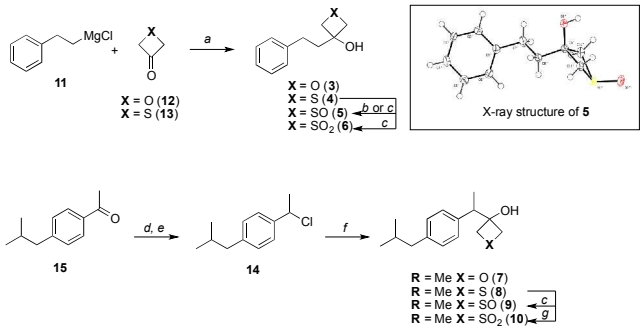
Table 1. Calculated and Experimental Properties of Test Compounds.

Cpd #	Structure	$logD_{7.4}$ [a]	$logD_{7.4}$ calc.[b]	PAMPA			pK_a [f]	pK_a calc.[b]	H bonding $ln(K_{eq})$[g]
				Pe (cm/s)[c]	% retention[d]	$logP_{app}$ [e]			
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 Analyza); [d] Membrane retention; [e] Log of the apparent permeability coefficient; [f] pK_a values determined by capillary electrophoresis (experiment run by Analyza); [g] ln of the 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

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 bromide **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 ^{1}H 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 pKa value of ~9.3, while all other derivatives were found to have pKa 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.

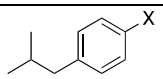
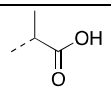
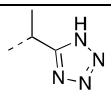
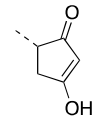
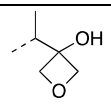
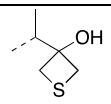
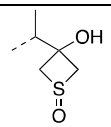
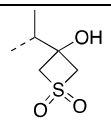


Scheme 1. *Reagents and Reaction conditions:* **a**) THF, –78 °C, 15 min, then rt, 1 h; **b**) UHP, AcOH, rt, 14 h; **c**) *m*-CPBA, CH_2Cl_2, –78 °C, 1 h; **d**) $NaBH_4$, MeOH, 0 °C to rt, 30 min; **e**) $SOCl_2$, CH_2Cl_2, 0 °C to rt, 18 h; f) (*i*) Mg, LiCl, $ZnCl_2$, THF, rt, 6 h, (*ii*) **12** 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 pKa 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 the PAMPA assay 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 amongst 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] and 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 analogs bearing a tetrazole[25] (**17**) and a cyclopentane-1,3-dione (**18**) were also constructed and tested for comparison. Typical assay conditions involved the co-incubation 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 Supporting Information. In initial concentration-response testing (Table 2), LTB_4, as well as combined PGD_2 and PGE_2, which co-eluted 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).

Table 2. IC_{50} values of test compounds in the PGE_2/PGD_2 and LTB_4 assay.

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.

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 analogs (**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**, analogs **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 μM 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 bio-isosteric replacements of the carboxylic acid moiety of dif-

ferent non-steroidal anti-inflammatory drugs (NSAIDs), including **2**, can result in inhibitors of the 5-LOX pathway or multi-targeted derivatives capable of inhibiting concurrently multiple enzymes in the COX- and 5-LOX biosynthetic pathways. [26, 27]

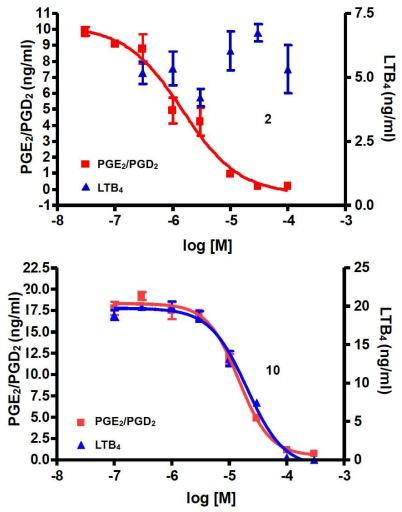


Figure 2. Concentration-response analyses of inhibition of 5-LOX-derived LTB_4 and COX-derived PGE_2/PGD_2 by compounds **2** (top) and **10** (bottom). Error bars represent standard error of the mean from triplicate samples.

Taken together, our results clearly suggest that the oxetan-3-ol as well as the thietan-3-ol and related sulfoxide and sulfone derivatives may be considered as alternative bio-isosteres 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.

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ASSOCIATED CONTENT

Supporting Information. Experimental details; NMR spectra of test compounds; X-ray crystal structures; Supplemental Table 1; Supplemental Figure 1; docking studies. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Contributions

The manuscript was written by CB, KRB, and ABS and was reviewed by all authors. PL, KO, VM, VT, LM, KV, LH, MJJ and MK made experimental contributions; CB and KB directed research; and VMYL and JQT provided resources. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

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

REFERENCES

1. Ballatore, C.; Huryn, D. M.; Smith, A. B., III, Carboxylic acid (bio)isosteres in drug design. *ChemMedChem* **2013,** 8, 385-395.
2. Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011,** 54, 2529-2591.
3. Herr, R. J. 5-Substituted-1H-tetrazoles as carboxylic acid isosteres: medicinal chemistry and synthetic methods. *Bioorg. Med. Chem.* **2002,** 10, 3379-93.
4. Duncton, M. A. J.; Murray, R. B.; Park, G.; Singh, R. Tetrazolone as an acid bioisostere: application to marketed drugs containing a carboxylic acid. *Org. Biomol. Chem.* **2016,** 14, 9343-9347.
5. Borhade, S. R.; Svensson, R.; Brandt, P.; Artursson, P.; Arvidsson, P. I.; Sandstrom, A. Preclinical characterization of acyl sulfonimidamides: potential carboxylic acid bioisosteres with tunable properties. *ChemMedChem* **2015,** 10, 455-60.
6. B Ballatore, C.; Soper, J. H.; Piscitelli, F.; James, M.; Huang, L.; Atasoylu, O.; Huryn, D. M.; Trojanowski, J. Q.; Lee, V. M.; Brunden, K. R.; Smith, A. B., III, Cyclopentane-1,3-dione: a novel isostere for the carboxylic acid functional group. application to the design of potent thromboxane (A2) receptor antagonists. *J. Med. Chem.* **2011,** 54, 6969-6983.
7. Ballatore, C.; Gay, B.; Huang, L.; Robinson, K. H.; James, M. J.; Trojanowski, J. Q.; Lee, V. M. Y.; Brunden, K. R.; Smith, A. B., III, Evaluation of the cyclopentane-1,2-dione as a potential bio-isostere of the carboxylic acid functional group. *Bioorg. Med. Chem. Lett.* **2014,** 24, 4171-4175.
8. Wang, X.; Liu, L.; Huang, L.; Herbst-Robinson, K.; Cornec, A.-S.; James, M. J.; Sugiyama, S.; Bassetto, M.; Brancale, A.; Trojanowski, J. Q.; Lee, V. M. Y.; Smith, A. B., III; Brunden, K. R.; Ballatore, C. Potent, long-acting cyclopentane-1,3-dione thromboxane (A_2)-receptor antagonists. *ACS Med. Chem. Lett.* **2014,** 5, 1015-1020.
9. Pemberton, N.; Graden, H.; Evertsson, E.; Bratt, E.; Lepistö, M.; Johannesson, P.; Svensson, P. H. Synthesis and functionalization of cyclic sulfonimidamides: a novel chiral heterocyclic carboxylic acid bioisostere. *ACS Med. Chem. Lett.* **2012,** 3, 574-578.
10. Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: recent advances in synthesis, reactivity, and medicinal chemistry. *Chem. Rev.* **2016,** 116, 12150-12233.
11. Skoda, E. M.; Sacher, J. R.; Kazancioglu, M. Z.; Saha, J.; Wipf, P. An uncharged oxetanyl sulfoxide as a covalent modifier for improving aqueous solubility. *ACS Med. Chem. Lett.* **2014,** 5, 900-904.
12. Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Fischer, H.; Wagner, B.; Schuler, F.; Polonchuk, L.; Carreira, E. M. Oxetanes as promising modules in drug discovery. *Angew. Chem. Int. Ed.* **2006,** 45, 7736-9.
13. Wuitschik, G.; Carreira, E. M.; Wagner, B. R.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Müller, K. Oxetanes in drug discovery: structural and synthetic insights. *J. Med. Chem.* **2010,** 53, 3227-3246.

14. Burkhard, J. A.; Wuitschik, G.; Rogers-Evans, M.; Müller, K.; Carreira, E. M. Oxetanes as versatile elements in drug discovery and synthesis. *Angew. Chem. Int. Ed.* **2010,** 49, 9052-9067.
15. Croft, R. A.; Mousseau, J. J.; Choi, C.; Bull, J. A. Structurally Divergent Lithium Catalyzed Friedel–Crafts Reactions on Oxetan-3-ols: Synthesis of 3,3-Diaryloxetanes and 2,3-Dihydrobenzofurans. *Chemistry* **2016,** 22, 16271-16276.
16. McLaughlin, M.; Yazaki, R.; Fessard, T. C.; Carreira, E. M. Oxetanyl peptides: novel peptidomimetic modules for medicinal chemistry. *Org. Lett.* **2014,** 16, 4070-4073.
17. Möller, G. P.; Müller, S.; Wolfstädter, B. T.; Wolfrum, S.; Schepmann, D.; Wünsch, B.; Carreira, E. M. Oxetanyl amino acids for peptidomimetics. *Org. Lett.* **2017**, 19 , 2510–2513.
18. Beadle, J. D.; Knuhtsen, A.; Hoose, A.; Raubo, P.; Jamieson, A. G.; Shipman, M. Solid-Phase Synthesis of Oxetane Modified Peptides. *Org. Lett.* **2017,** DOI: 10.1021/acs.orglett.7b01466
19. Powell, N. H.; Clarkson, G. J.; Notman, R.; Raubo, P.; Martin, N. G.; Shipman, M. Synthesis and structure of oxetane containing tripeptide motifs. *Chem. Commun.* **2014,** 50, 8797-8800.
20. Lassalas, P.; Gay, B.; Lasfargeas, C.; James, M. J.; Tran, V.; Vijayendran, K. G.; Brunden, K. R.; Kozlowski, M. C.; Thomas, C. J.; Smith, A. B., III; Huryn, D. M.; Ballatore, C. Structure property relationships of carboxylic acid isosteres. *J. Med. Chem.* **2016,** 59, 3183-203.
21. Soper, J. H.; Sugiyama, S.; Herbst-Robinson, K.; James, M. J.; Wang, X.; Trojanowski, J. Q.; Smith, A. B., III; Lee, V. M.; Ballatore, C.; Brunden, K. R. Brain-penetrant tetrahydronaphthalene thromboxane A_2-prostanoid (TP) receptor antagonists as prototype therapeutics for Alzheimer's disease. *ACS Chem. Neurosci.* **2012,** 3, 928-940.
22. Huynh, P. N. H.; Walvoord, R. R.; Kozlowski, M. C. Rapid Quantification of the activating effects of hydrogen-bonding catalysts with a colorimetric sensor. *J. Am. Chem. Soc.* **2012,** 134, 15621-15623.
23. Berthelot, M.; Besseau, F.; Laurence, C. The hydrogen-bond basicity pKHB scale of peroxides and ethers. *Eur. J. Org. Chem.* **1998,** 1998, 925-931.
24. Tries, S.; Neupert, W.; Laufer, S. The mechanism of action of the new antiinflammatory compound ML3000: inhibition of 5-LOX and COX-1/2. *Inflamm. Res.* **2002,** 51, 135-143.
25. Valenti, P.; Rampa, A.; Fabbri, G.; Giusti, P.; Cima, L. Tetrazole analogs of ibuprofen and flurbiprofen. *Arch. Pharm. (Weinheim, Ger.)* **1983,** 316, 752-5.
26. Elkady, M.; Niess, R.; Schaible, A. M.; Bauer, J.; Luderer, S.; Ambrosi, G.; Werz, O.; Laufer, S. A. Modified acidic nonsteroidal anti-inflammatory drugs as dual inhibitors of mPGES-1 and 5-LOX. *J. Med. Chem.* **2012,** 55, 8958-62.
27. Boschelli, D. H.; Connor, D. T.; Hoefle, M.; Bornemeier, D. A.; Dyer, R. D. Conversion of NSAIDS into balanced dual inhibitors of cyclooxygenase and 5-lipoxygenase. *Bioorg. Med. Chem. Lett.* **1992,** 2, 69-72.

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