Published in final edited form as:

Bioorg Med Chem Lett. 2014 September 1; 24(17): 4171–4175. doi:10.1016/j.bmcl.2014.07.047.

Evaluation of the cyclopentane-1,2-dione as a potential bio-isostere of the carboxylic acid functional group

Carlo Ballatore^{a,b}, Bryant Gay^a, Longchuan Huang^a, Katie Herbst Robinson^b, Michael James^b, John Q. Trojanowski^b, Virginia M.Y. Lee^b, Kurt R. Brunden^b, and Amos B. Smith III^a

^aDepartment of Chemistry, School of Arts and Sciences, University of Pennsylvania, 231 South 34th St., Philadelphia, PA 19104-6323

^bCenter for Neurodegenerative Disease Research, Institute on Aging, University of Pennsylvania, 3600 Spruce Street, Philadelphia, PA 19104-6323

Abstract

Cycloalkylpolyones hold promise in drug design as carboxylic acid bio-isosteres. To investigate cyclopentane-1,2-diones as potential surrogates of the carboxylic acid functional group, the acidity, tautomerism, and geometry of hydrogen bonding of representative compounds were evaluated. Prototypic derivatives of the known thromboxane A₂ prostanoid (TP) receptor antagonist, 3-(3-(2-((4-chlorophenyl)sulfonamido)-ethyl)phenyl)propanoic acid, in which the carboxylic acid moiety is replaced by the cyclopentane-1,2-dione unit, were synthesized and evaluated as TP receptor antagonists. Cyclopentane-1,2-dione derivative **9** was found to be a potent TP receptor antagonist with an IC₅₀ value comparable to that of the parent carboxylic acid. These results indicate that the cyclopentane-1,2-dione may be a potentially useful carboxylic acid bio-isostere.

The carboxylic acid moiety is a privileged structure in drug design,¹ due to the fact that this functional group can establish relatively strong ionic and hydrogen-bond interactions with biological targets, leading to the formation of relatively stable complexes. The presence of this functional group in a drug or a drug candidate, however, can have undesired consequences, which typically include metabolic instability, toxicity, and often a reduced rate of passive diffusion across biological membranes. Under such circumstances, isosteric replacement strategies, in which the carboxylic acid moiety is substituted with a surrogate structure, can lead to derivatives with improved properties, relative to the parent carboxylic acid compound.²

© 2014 Elsevier Ltd. All rights reserved.

Correspondence to: Carlo Ballatore; Amos B. Smith, III.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Cyclic polyone systems comprise a promising source of carboxylic acid bio-isosteres. For example, squaric acid and related derivatives have been successfully employed as carboxylic acid surrogates in drug design.³⁻⁶ In similar fashion, cyclopentane-1,3-diones (Figure 1A) are effective substitutes for the carboxylic acid moiety of known thromboxane A₂ (TP) receptor antagonists (*e.g.*, **1**,⁷ Figure 1C), leading to potent derivatives.⁸

Cyclopentane-1,2-diones (Figure 1B) may also be considered as a potential carboxylic acid bio-isosteres, however, a systematic evaluation of this fragment as a carboxylic acid surrogate has not been reported. Like the cyclopentane-1,3-diones, the cyclopentane-1,2-dione system exists predominantly in enolketone form,^{9, 10} and presents two non-equivalent points of attachment (see Figure 1A and 1B). Notable differences in physicochemical properties however exist between the two cyclic diones, which may ultimately lead to important ramifications, particularly in the context of isosteric replacement of the carboxylic acid functional group. For example, the enol-ketone tautomers of the cyclopentane-1,2-dione, unlike those of the corresponding 1,3-dione system, are not vinylogous acid structures, thus resulting in relatively high pK_a values.¹¹ Moreover, whereas the cyclopentane-1,3-dione is known to undergo rapid exchange between enol-ketone tautomers, in the case of the corresponding 1,2-dione, depending on the substitution pattern, one tautomer may be considerably more stable than the other (Figure 1B).¹² Finally, given the structural differences, the two cyclic dione systems are likely to exhibit different geometries of hydrogen bonding.

Thus, to characterize the cyclopentane-1,2-diones as potential surrogates of the carboxylic acid functional group, we evaluated the acidity, tautomerism, and geometry of hydrogen bonding of representative model compounds **2** and **3**¹³ (Scheme 1), in which the cyclopentane-1,2-dione is substituted either at C3 (**2**) or C4 (**3**). The synthesis of **2** was achieved starting from 4-bromobenzylbromide (**4**) and the di-potassium salt **5**,¹⁴ which reacts to form the di-benzylated intermediate **6**. Next, following reported procedures,¹⁵ treatment of **6** with concentrated hydrochloric acid at 100 °C led to simultaneous decarboxylation and hydrolysis of the benzyl ether, resulting in the formation of 1,2-dione **2**. Compound **3**¹³ was synthesized via magnesium methoxide induced cyclization of α,β -unsaturated dione **7**, as described previously (Scheme 1).

After synthesis, potentiometric titrations determined that the pK_a value of **2** is approximately 8.6, thus significantly higher than the pK_a of carboxylic acids and that of the corresponding 1,3-dione **8**⁸ (*i.e.*, pK_a ~4.0; see Scheme 1 and Supporting Information). Also of notice, comparison of infrared (IR) and NMR spectra of compound **2** and **8** clearly highlights the significant differences between the cyclic 1,2-dione and the corresponding 1,3-dione system in terms of rate of tautomeric exchange and relative stability of the tautomers (see Figure 2 and Figure S1, Supporting Information). Finally, single crystal X-ray analysis of model compounds **2** and **3** revealed that, unlike the 1,3-diones and similar to the carboxylic acids, the 1,2-diones can form dimers characterized by two-point interactions (see Figure 3 and Figure S2, Supporting Information), indicating that the 1,2-dione system may in fact provide hydrogen bond geometry that more closely mimics that of the carboxylic acids. By comparison, X-ray structure of the corresponding 1,3-dione system (**8**)

did not show dimer formation but rather multimeric structures characterized by linear head-to-tail H-bond interactions.⁸

Having established that the cyclopentane-1,3-diones can be effective bio-isosteres of the carboxylic acid moiety in the context of TP receptor antagonists,⁸ derivatives of the known TP receptor antagonist **1**⁷ (Figure 1C), in which the carboxylic acid moiety is replaced with a cyclopentane-1,2-dione linked at C3 or C4 (respectively **9**, Scheme 2; and **10**, Scheme 3), were designed and synthesized to be evaluated in a TP receptor functional assay.

The synthesis of 1,2-diones **9** and **10** followed similar strategies employed for the synthesis of model compounds **2** and **3**. Thus, central to the synthesis of dione **9** was the acid-mediated decomposition of intermediate **11** that could be obtained by reacting benzyl iodide **12** with the di-potassium salt **5**¹⁴ (Scheme 2), while dione **10** was obtained via magnesium methoxide promoted cyclization of α,β -unsaturated dione **13** (Scheme 3).

Test compounds were evaluated in a human TP (hTP) receptor functional assay, which measures receptor-stimulated production of the inositol triphosphate (IP₃) metabolite, inositol monophosphate (IP₁),⁸ in comparison with reference compound **1** and/or tetrahydronaphthalene derivative **14**¹⁶ (Figure 4), one of the most potent TP receptor antagonists reported to date. As shown in Table 1 and in Figure 4, both 1,2-dione derivatives were found to be active in the functional assay, with **9** exhibiting an IC₅₀ value comparable to that of carboxylic acid **1**. The results from the functional assay also suggest that the orientation of the 1,2-dione fragment within the receptor may be important for biological activity, as suggested by the fact that **10** was found to be approximately 20 times less potent than **9** (Table 1). A similar observation had been made with the corresponding 1,3-diones derivatives.⁸

Finally, to evaluate whether the cyclopentane-1,2-dione fragment might be a chemically reactive system that could lead to non-specific alkylation of proteins under physiological conditions, the stability of derivative **9** was determined *in vitro* by monitoring the disappearance of the compound, by LC/MS/MS, upon incubation in plasma at 37 °C. As shown in Figure 5, compound **9** was found to be essentially stable in plasma after 1h incubation.

Collectively, our data indicate that the cyclopentane-1,2-dione fragment, which is characterized by a relatively low intrinsic acidity and a geometry of hydrogen bonding that resembles that of carboxylic acids, holds promise as a potential carboxylic acid bio-isostere.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this work has been provided by NIH/NIA Grant AG034140, NSF Grant CHE-0840438 (X-ray facility), and the Marian S. Ware Alzheimer Program.

References and notes

1. Hajduk PJ, Bures M, Praestgaard J, Fesik SW. Privileged molecules for protein binding identified from NMR-based screening. *J Med Chem.* 2000; 43:3443–3447. [PubMed: 10978192]
2. Ballatore C, Huryn DM, Smith AB III. Carboxylic acid (bio)isosteres in drug design. *ChemMedChem.* 2013; 8:385–95. [PubMed: 23361977]
3. Kinney WA, Abou-Gharbia M, Garrison DT, Schmid J, Kowal DM, Bramlett DR, Miller TL, Tasse RP, Zaleska MM, Moyer JA. Design and Synthesis of [2-(8,9- Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)- ethyl]phosphonic Acid (EAA-090), a Potent N-Methyl-d-aspartate Antagonist, via the Use of 3-Cyclobutene-1,2-dione as an Achiral α -Amino Acid Bioisostere. *J Med Chem.* 1998; 41:236–246. [PubMed: 9457246]
4. Campbell EF, Park AK, Kinney WA, Fengl RW, Liebeskind LS. Synthesis of 3-Hydroxy-3-cyclobutene-1,2-dione Based Amino Acids. *J Org Chem.* 1995; 60:1470–1472.
5. Soll RM, Kinney WA, Primeau J, Garrick L, McCaully RJ, Colatsky T, Oshiro G, Park CH, Hartupce D, White V, McCallum J, Russo A, Dinish J, Wojdan A. 3-hydroxy-3-cyclobutene-1,2-dione: Application of novel carboxylic acid bioisostere to an in-vivo active non-tetrazole angiotensin-II antagonist. *Bioorg Med Chem Lett.* 1993; 3:757–760.
6. Kinney WA, Lee NE, Garrison DT, Podlesny EJ, Simmonds JT, Bramlett D, Notvest RR, Kowal DM, Tasse RP. Bioisosteric replacement of the .alpha.-amino carboxylic acid functionality in 2-amino-5-phosphonopentanoic acid yields unique 3,4-diamino-3-cyclobutene-1,2-dione containing NMDA antagonists. *J Med Chem.* 1992; 35:4720–4726. [PubMed: 1361582]
7. Dickinson RP, Dack KN, Long CJ, Steele J. Thromboxane modulating agents. 3. 1H-imidazol-1-ylalkyl- and 3-pyridinylalkyl-substituted 3-[2-[(arylsulfonyl)amino]ethyl]benzenepropanoic acid derivatives as dual thromboxane synthase inhibitor/thromboxane receptor antagonists. *J Med Chem.* 1997; 40:3442–52. [PubMed: 9341919]
8. Ballatore C, Soper JH, Piscitelli F, James M, Huang L, Atasoylu O, Huryn DM, Trojanowski JQ, Lee VM, Brunden KR, Smith AB 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; 54:6969–83. [PubMed: 21863799]
9. Schwarzenbach G, Wittwer C. Über das Keto- EnolGleichgewicht bei cyclischen α -Diketonen. *Helv Chem Acta.* 1947; 30:663–69.
10. Hiraga K. Structures of cyclopentanepolyones. *Chem Pharm Bull (Tokyo).* 1965; 13:1300–6. [PubMed: 5864720]
11. Vittorelli P, Heimgartner H, Schmid H, Hoet P, Ghosez L. Addition of carboxylic acids and cyclic 1,3-diketones to 2-dimethylamino-3,3-dimethyl-1-azirine. *Tetrahedron.* 1974; 30:3737–3740.
12. Trost BM, Dong G, Vance JA. Cyclic 1,2-diketones as core building blocks: a strategy for the total synthesis of (–)-terpestacin. *Chemistry.* 2010; 16:6265–77. [PubMed: 20411537]
13. Muxfeldt H, Weigele M, Rheenen VV. Magnesium Methoxide Cyclization of Biacetyl Derivatives I. *J Org Chem.* 1965; 30:3573–3574.
14. Aqad E, Leriche P, Mabon G, Gorgues A, Allain M, Riou A, Ellern A, Khodorkovsky V. Base-catalyzed condensation of cyclopentadiene derivatives. Synthesis of fulvalene analogues: strong proaromatic electron acceptors. *Tetrahedron.* 2003; 59:5773–5782.
15. Jōgi A, Ilves M, Paju A, Pehk T, Kailas T, Müürisepp AM, Lopp M. Asymmetric synthesis of 4'-C-benzyl-2',3'-dideoxynucleoside analogues from 3-benzyl-2-hydroxy-2-cyclopenten-1-one. *Tetrahedron: Asymmetry.* 2008; 19:628–634.
16. Cimetiere B, Dubuffet T, Muller O, Descombes JJ, Simonet S, Laubie M, Verbeuren TJ, Lavielle G. Synthesis and biological evaluation of new tetrahydronaphthalene derivatives as thromboxane receptor antagonists. *Bioorg Med Chem Lett.* 1998; 8:1375–80. [PubMed: 9871769]

Figure 1. Tautomers of cyclopentane-1,3-dione (A) and cyclopentane-1,2- dione (B); dotted lines indicate non-equivalent point of attachments on the two cyclic diones; (C) representative examples of TP receptor antagonists.

Figure 2. Rapid tautomeric exchange of **8** (top) results in weak ^{13}C -NMR signals of the 1,3-dione system, while ^{13}C -NMR spectrum of **2** (bottom) shows only one of the two enol-ketone tautomers.

Figure 3.
X ray structure of compound **2** (CCDC 1009311), revealing inter-molecular H-bonding.

Figure 4.
Dose-response curves of test compounds in the hTP receptor IP₁ functional assay.

Figure 5.
In vitro plasma stability of **9**.

Scheme 1.

Synthesis of 1,2-dione model compounds **2** and **3** and structure of previously reported 1,3-dione **8**; pKa determinations were conducted by Sirius Analytical.

Scheme 2.
Synthesis of 1,2-dione derivative **9**.

Scheme 3.
Synthesis of 1,2-dione derivative **10**.

Table 1

IC₅₀ values of test compounds in the IP₁ hTP receptor assay.

Compound	IC ₅₀ μ M
1	0.190 $\pm$ 0.060
14	0.0026 $\pm$ 0.001
9	0.054 $\pm$ 0.016
10	1.140 $\pm$ 0.820

Values represent the average and SD of assays run in triplicate, utilizing 0.8 nM I-BOP as agonist.