Bioorganic & Medicinal Chemistry Letters 24 (2014) 4171–4175

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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

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ARTICLE INFO

Article history:
Received 20 June 2014
Revised 14 July 2014
Accepted 16 July 2014
Available online 23 July 2014

Keywords:
Carboxylic acid bio-isosteres
Cyclopentane-1,2-dione
Thromboxane A_2 receptor

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 A_2 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 IC_{50} 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]

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 (Fig. 1A) are effective substitutes for the carboxylic acid moiety of known thromboxane A_2 (TP) receptor antagonists (e.g., **1**,[7] Fig. 1C), leading to potent derivatives.[8]

Cyclopentane-1,2-diones (Fig. 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 enol-ketone form,[9,10] and presents two non-equivalent points of attachment (see Fig. 1A and B). 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,

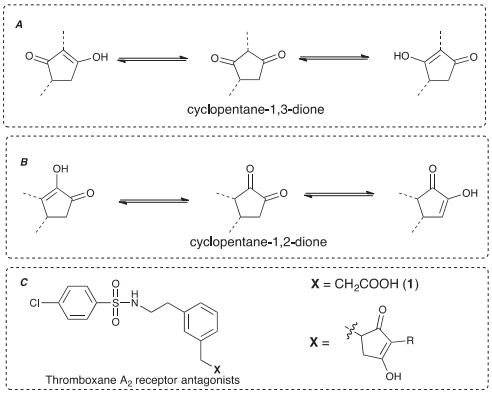

Figure 1. Tautomers of cyclopentane-1,3-dione (A) and cyclopentane-1,2-dione; (B) dotted lines indicate non-equivalent point of attachments on the two cyclic diones; (C) representative examples of TP receptor antagonists.

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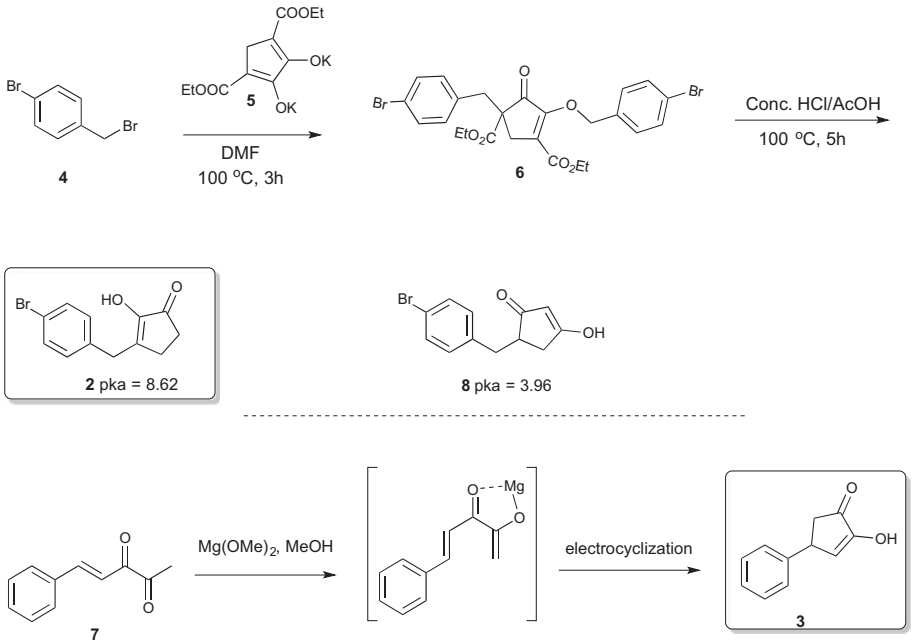
http://dx.doi.org/10.1016/j.bmcl.2014.07.047
0960-894X/

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 (Fig. 1B).[12] Finally, given the structural differences, the two cyclic dione systems are likely to exhibit different geometries of hydrogen bonding.



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

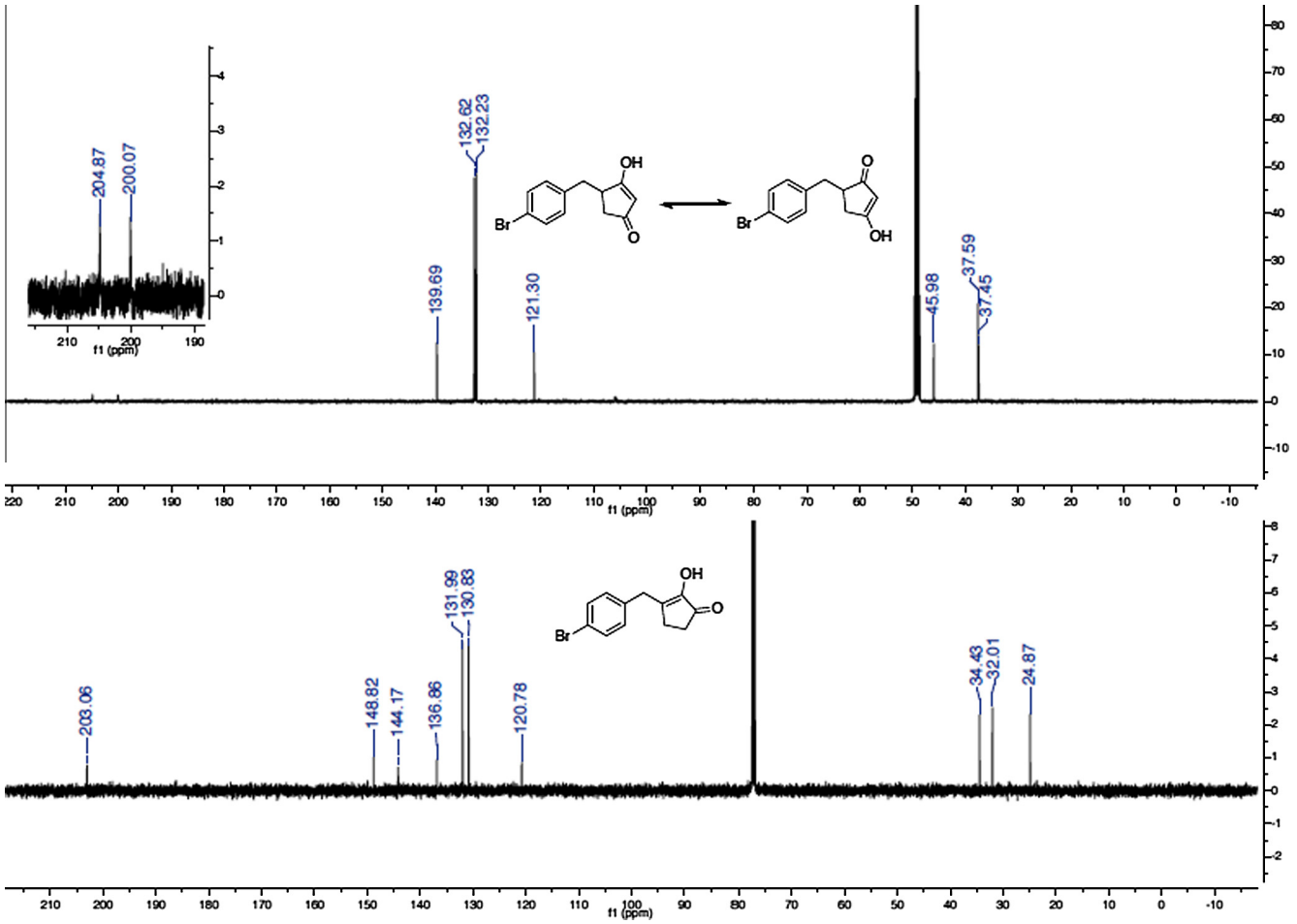


Figure 2. Rapid tautomeric exchange of **8** (top) results in weak ^{13}C NMR signals of the 1,3-dione system, while ^{13}C NMR spectrum of **2** (bottom) shows only one of the two enol-ketone tautomers.