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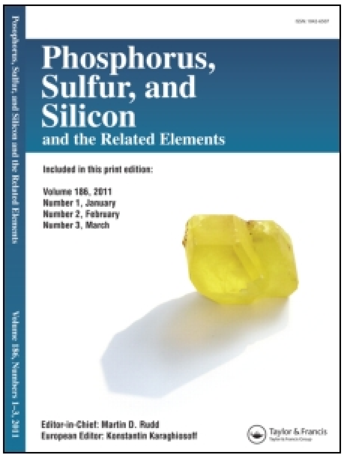

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To cite this Article Kinney, William A.(1996) 'The 3-Cyclobutene-1,2-Dione Group: Versatile Template for Bioisostere Construction', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 305 — 308

To link to this Article: DOI: 10.1080/10426509608545151

URL: http://dx.doi.org/10.1080/10426509608545151

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Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 305–308
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THE 3-CYCLOBUTENE-1,2-DIONE GROUP: VERSATILE TEMPLATE FOR BIOISOSTERE CONSTRUCTION

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Abstract The 3,4-diamino-3-cyclobutene-1,2-dione group was utilized as a unique α-amino carboxylic acid bioisostere in a series of *in vivo* active NMDA antagonists, which have potential as neuroprotectants. In order to investigate SAR in this series, a new free radical approach to alkyl substituted 3-cyclobutene-1,2-diones was developed utilizing 3-isopropoxy-4-tributyltin-3-cyclobutene-1,2-dione (Liebeskind's reagent). This methodology also allowed access to amino acids glycine, β-alanine, and GABA substituted with the 3-hydroxy-3-cylcobutene-1,2-dione group, which we had shown to be a carboxylic acid or tetrazole bioisostere in a series of angiotensin-II antagonists. The orally active hydroxycyclobutenedione derivative was prepared by a palladium catalyzed Stille cross-coupling of an iodobiphenyl moiety with Liebeskind's reagent.

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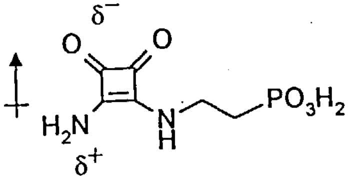
All chemical entities known to be competitive NMDA-receptor antagonists contain an α-amino carboxylic acid connected to a phosphonic acid through a variable length spacer. For instance, 2-amino-7-phosphonoheptanoic acid and 2-amino-5-phosphonopentanoic acid (AP7 and AP5) were early examples of this trend. No examples of NMDA antagonists have appeared in which the amino acid group is replaced by a bioisosteric group; in fact, there are few examples of such a bioisostere. It was our belief that in order to have a different efficacy and/or side effect profile versus existing NMDA antagonists, it was imperative to introduce novel functionalities.



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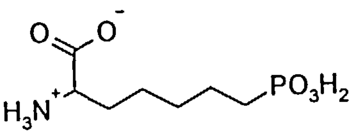
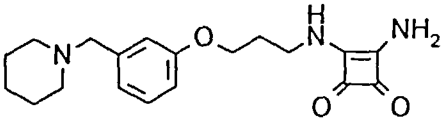


AP7

It was found that the 3,4-diamino-3-cyclobutene-1,2-dione functionality was such a bioisostere, and when connected to a phosphonic acid residue by an ethyl spacer, **1** was as effective as AP7 *in vitro* in a [^{3}H]CPP binding assay and *in vivo* in an NMDA induced lethality assay [1]. The equivalence was predicted based on the isoelectronic nature of an ammonium carboxylate to a dipolar diaminocyclobutenedione. Although these groups are isoelectronic, the diaminocyclobutenedione functionality is not acidic or basic and lacks a nucleophilic nitrogen. Therefore, this functional group would be less likely to have effects at other targets where such interactions are important; for example, a nucleophilic amine is necessary for amino acid decarboxylase enzymes. So this group might have advantages on selectivity grounds.



BMY-25,368

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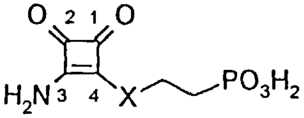
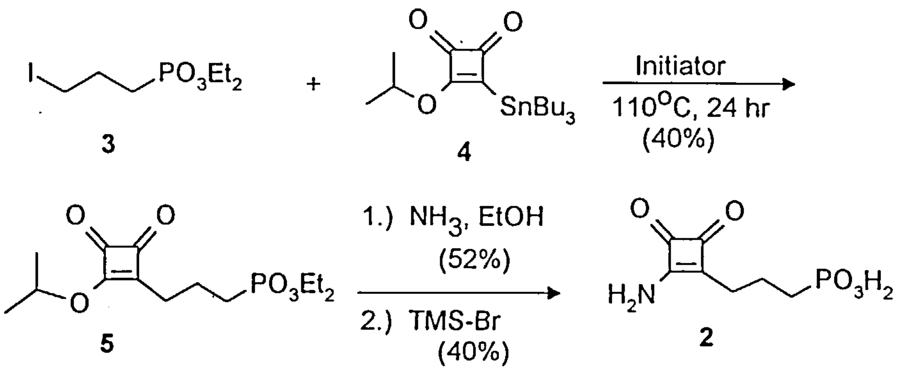
The 3,4-diamino-3-cyclobutene-1,2-dione group has been used in medicinal chemistry as a thiourea bioisostere in the potent histamine-2 receptor antagonist BMY-25,368. This compound advanced as far as phase III clinical studies for duodenal and gastric ulcers [2]. This demonstrates that the functionality has no apparent toxicity problems associated with it. Therefore, one has a novel functional group for NMDA antagonists with potential differences from known amino acid based drugs, and at the same time there is clinical safety experience with the group.



X = NH (**1**), CH_2 (**2**)

The necessity of the 4-amino substituent of the novel amino acid bioisostere contained in **1** was investigated by preparing **2**, which contains a carbon for nitrogen replacement. In order to avoid organometallic approaches, which were incompatible with the phosphonic acid ester functionality, a novel approach was devised [3]. The alkyl radical, generated from the alkyl iodide **3** (Scheme I) with azobiscyclohexylnitrile in toluene, added to Liebeskind's reagent **4** [4] with the elimination of tributyltin radical to afford the desired phosphono-substituted cyclobutenedione **5**. It was converted in two steps to the desired analog **2**, which was devoid of activity at the NMDA receptor, demonstrating the necessity of the 4-amino group for this amino acid bioisostere.

Scheme I



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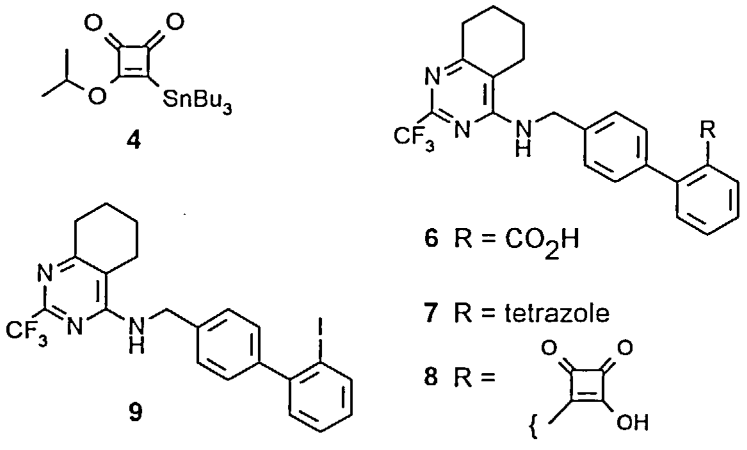
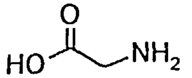
In the course of our investigations into novel angiotensin II antagonists, it became of interest to explore novel carboxylic acid bioisosteres, which might have broad application in drug design (Scheme II) [5]. We felt the 3-hydroxy-3-cyclobutene-1,2-dione had potential, because of its marked acidity and structural similarity to a carboxylic acid. The target to investigate this new carboxylic acid bioisostere relative to the carboxylic acid (**6**) and tetrazole derivatives (**7**) was **8**. Due to the work of Liebeskind [4], the palladium-catalyzed Stille cross coupling of aryl halides to Liebeskind's reagent **4** was well precedented. The elaborate aryl iodide **9** was coupled with **4** with catalytic *trans*-benzyl(chloro)bis(triphenylphosphine)palladium (II) and CuI in acetonitrile at 70°C to afford the arylhydroxycyclobutenedione isopropyl ester in 71% yield. Acid hydrolysis yielded the desired derivative **8** in 83% yield. The IC_{50} values for the three derivatives **6**, **7**, and **8** at the AII-receptor were 275 nM, 3 nM, and 25 nM respectively, demonstrating the utility of the 3-hydroxy-3-cyclobutene-1,2-dione group as a

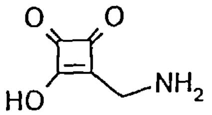
Scheme II



carboxylic acid or tetrazole bioisostere; others have also shown this at a different biological target [6]. Importantly, compound **8** also demonstrated *in vivo* activity as an antihypertensive in rats, even when administered orally, further suggesting the utility of cyclobutenedione based groups in medicinal chemistry.

Because of our interest in inhibiting the NMDA receptor, we thought 3-hydroxy-3-cyclobutene-1,2-dione group could be further investigated as a carboxylic acid bioisostere in the glycine derivative **10**; it was expected that it might inhibit the strychnine-insensitive glycine modulatory site on the NMDA receptor by mimicking glycine [7]. The target was synthesized utilizing the free radical method described above with a phthalimido protecting group. However, derivative **10** was found to be inactive at the glycine receptor, as **11** was shown to be by others [8].





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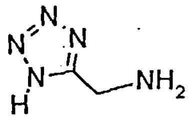

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In summary, we and others have demonstrated many uses of cyclobutenediones as bioisostere frameworks for construction of medicinally useful agents. Additionally, new chemistry has be elucidated allowing for the ready introduction of cyclobutenediones into target structures.

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