This article was downloaded by: [University of California, Berkeley] On: 21 October 2014, At: 19:43 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



# Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

http://www.tandfonline.com/loi/gpss20

## The 3-Cyclobutene-1,2-Dione Group: Versatile Template for Bioisostere Construction

William A. Kinney

<sup>a</sup> Wyeth-Ayerst Research , CN 8000, Princeton, NJ 08543-8000, USA Published online: 06 Aug 2008.

To cite this article: William A. Kinney (1996) The 3-Cyclobutene-1,2-Dione Group: Versatile Template for Bioisostere Construction, Phosphorus, Sulfur, and Silicon and the Related Elements, 109:1-4, 305-308

To link to this article: http://dx.doi.org/10.1080/10426509608545151

### PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sublicensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <a href="http://www.tandfonline.com/page/terms-and-conditions">http://www.tandfonline.com/page/terms-and-conditions</a>

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109-110, pp. 305-308 © 1996 OPA (Overseas Publishers Association) Reprints available directly from the publisher Photocopying permitted by license only

#### THE 3-CYCLOBUTENE-1,2-DIONE GROUP: VERSATILE TEMPLATE FOR BIOISOSTERE CONSTRUCTION

#### WILLIAM A. KINNEY\*

Wyeth-Ayerst Research, CN 8000, Princeton, NJ 08543-8000 USA

Abstract The 3,4-diamino-3-cyclobutene-1,2-dione group was utilized as a unique  $\alpha$ -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,  $\beta$ -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.

All chemical entities known to be competitive NMDA-receptor antagonists contain an  $\alpha$ -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.



305

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 [<sup>3</sup>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

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.



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 phosphonosubstituted 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.



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-3cyclobutene-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<sub>50</sub> 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 3hydroxy-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].



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.

\* Present address: Magainin Pharmaceuticals, 5110 Campus Drive, Plymouth Meeting, PA 19462, USA

#### REFERENCES

- W. A. Kinney, N. E. Lee, D. T. Garrison, E. J. Podlesney, Jr., J. T. Simmonds, D. Bramlett, R. R. Notvest, D. M. Kowal, R. P. Tasse, J. Med. Chem. 1992, 35, 4720-4726.
- 2. S. G. Chiverton, D. W. Burget, R. H. Hunt, Gut 1989, 30, 594-9.
- 3. W. A. Kinney, Tetrahedron Letters 1993, 2715-2718.
- 4. L. S. Liebeskind, R. W. Fengl, J. Org. Chem. 1990, 55, 5359.
- R. M. Soll, W. A. Kinney, J. Primeau, L. Garrick, R. J. McCaully, T. Colatsky, G. Oshiro, C. H. Park, D. Hartupee, V. White, J. McCallum, A. Russo, J. Dinish, A. Wojdan, *Biorg. Med. Chem. Lett.* 1993, 3, 757-760.
- 6. C. U. Kim, P. F. Misco, Tetrahedron Letters 1992, 3961-3962.
- E. F. Campbell, A. K. Park, W. A. Kinney, R. W. Fengl, L. S. Liebeskind, J. Org. Chem. 1995, 60, 1470-1472.
- W. H. W. Lunn, D. D. Schoepp, D. O. Calligaro, R. T. Vasileff, L. J. Heinz, C. R. Salhoff, P. J. O'Malley, J. Med. Chem. 1992, 35, 4608-4612.