Vol. 4, No. 20 20 October 1994 NOO9 '34 ISSN 0960-894X

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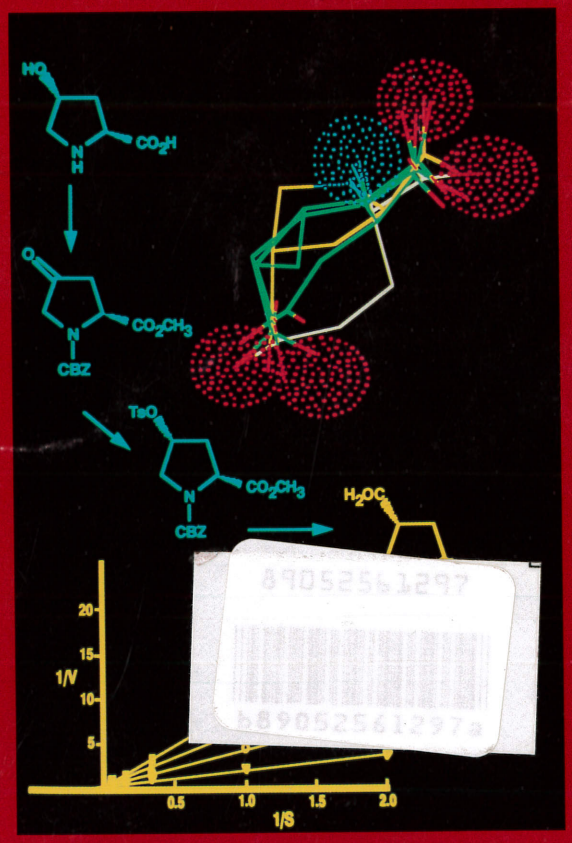

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BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

PUBLISHED TWICE MONTHLY

Publishing, Subscription and Advertising Office:
Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, Oxford, OX5 1GB, UK (Tel: (0865) 843000; Fax: (0865) 843010)

Subscription Rates
Annual Institutional Subscription Rates 1995: North, Central and South America, U.S.$ 984.00, Rest of World £ 660.00. Associated Personal Subscription Rates are available on request for those whose institutions are library subscribers. Sterling prices exclude VAT. Non-VAT registered customers in the European Community will be charged the appropriate VAT in addition to the price listed. Prices include postage and insurance and are subject to change without notice. Subscription enquiries from customers in North America should be sent to: Elsevier Science Inc., 660 White Plains Road, Tarrytown, New York 10591-5153, USA, and for the remainder of the world to: Elsevier Science Ltd, The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, UK.
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Bioorganic & Medicinal Chemistry Letters Vol. 4, No. 20, 1994

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0960-894X(1994)4:20;1-I

BMCLE8 4 (20) 2365–2490 (1994)

Indexed/Abstracted in: Chemical Abstracts, Current Contents, Science Citation Index, SciSearch, Research Alert, Excerpta Medica Database EMBASE

Pergamon

Printed in Great Britain by Nuffield Press Ltd.

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[*Continued from outside back cover*]

Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 20, pp. 2417-2420, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00350-5

DIPHENYLBORINIC ACID IS A STRONG INHIBITOR OF SERINE PROTEASES≠

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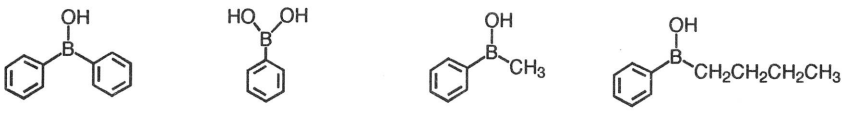
Abstract. Diphenylborinic acid, a commercially available and reasonably air stable compound, was found to be a strong competitive inhibitor of three serine proteases. Compared to phenylboronic acid, it was a thirty-fold better inhibitor of α-chymotrypsin, a fifteen-fold better inhibitor of subtilisin BPN', and a sixty-fold better inhibitor of bovine trypsin. The pK_a and inhibitory ability of methylphenylborinic acid was also determined.

Boronic acids have been studied as competitive inhibitors of serine proteases for more than twenty-five years.[1] Nonetheless, interest in these compounds remains high due to their potential clinical uses,[2] and their ability to act as structural probes of enzyme binding sites.[3] Despite numerous X-ray and NMR studies, some of the details concerning the structures of the enzyme/inhibitor complexes remain controversial, particularly when the inhibitors are simple, "non substrate-like" boronic acids.[4] In some cases there is clear evidence for a covalent tetrahedral adduct with the active-site serine hydroxyl.[4,5] In other cases there is no doubt that the boron is coordinated to the active-site histidine.[6]

Our interest in this area stems from our recent efforts to develop molecular transport devices using boron acids.[7] While conducting experiments with diphenylborinic acid, **1**, we became curious about its ability to inhibit serine proteases. Inhibition with asymmetric borinic acids has been reported before,[8] the most recent study by the Jones research group.[9] In general, borinic acids are better inhibitors than boronic acids. The major detraction with borinic acids is their susceptibility to air oxidation. Diarylborinic acids, however, are reasonably air stable compounds. For example, a solution of **1** in phosphate buffer, at pH 7.4, was found to be > 90 % pure after standing on the bench top for 24 hours. Compound **1** has a pK_a of 6.2.[10] At neutral pH it readily combines with vicinal diols to form anionic, tetrahedral "ate" complexes.[7] The expected inhibitory ability of **1** was hard to predict, *a priori*, since it was difficult to estimate the relative importance of various opposing factors such as increased acidity, enzyme binding site specificity, inhibitor hydrophobicity, loss of a potential active-site hydrogen, etc. We felt that if **1** were a good protease binder then it may have utility in clarifying some of the structural and mechanistic ambiguities concerning this class of transition-state-analogue inhibitors.



1 **2** **3** **4**

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