

**SELECTIVITY OF 4,5,6,7-TETRABROMOBENZIMIDAZOLE (TBBZ)
AS AN ATP-COMPETITIVE POTENT INHIBITOR OF PROTEIN
KINASE CK2 FROM VARIOUS SOURCES**

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The previously reported 4,5,6,7-tetrabromobenzotriazole (TBBt, also known as TBB) was shown to be a potent and selective ATP-competitive inhibitor of protein kinase CK2 [1], further supported by assays against an array of more than 30 other kinases [2]. The corresponding 4,5,6,7-tetrachlorobenzotriazole (TCBt) is a much weaker inhibitor [1]. The mode of binding of TBBt by *Zea mays* CK2 α in the crystal structure of the complex [3] showed that it is the N(2)-H prototropic tautomer that is selectively bound. This prompted the synthesis of the structurally related 4,5,6,7-tetrabromobenzimidazole (TBBz) and 4,5,6,7-tetrachlorobenzimidazole (TCBz). TBBz was, in fact, found to be an equally potent inhibitor of CK2 from such widely divergent sources as yeast, rat liver, *Neurospora crassa* and *Candida tropicalis*, with K_i values in the range 0.5 – 1 μ M, while TCBz was a much weaker inhibitor, like TCBt relative to TBBt [1]. Bearing in mind the similarity of the van der Waals radii of Br (1.95 Å) and CH₃ (2.0 Å), the corresponding much less hydrophobic 4,5,6,7-tetramethylbenzotriazole (TMeBt) was prepared, and found to be a very weak inhibitor of CK2, as well as CK1. An unexpected, and significant, difference between TBBt and TBBz is their inhibitory activity vs. yeast protein kinase PK60S, which phosphorylates, both *in vitro* and in intact yeast cells, three of the five pp13 kDa ribosomal acidic proteins in yeast cells [4]. TBBt was previously reported as a more effective inhibitor of PK60 ($K_i \approx 0.1 \mu$ M) than of yeast CK2 ($K_i \approx 0.6 \mu$ M) [1]. By contrast, TBBz proved to be a relatively feeble inhibitor of PK60, hence more selective than TBBt vs. CK2 in yeast cells. TMeBt was also virtually inactive vs. PK60. Like TBBt, TBBz is an additional lead compound for possible development of more potent inhibitors of CK2.

Partially supported by EC grant FP5 RTD No. QLRT-2001-01079.

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