

**IMPROVING THE EFFICIENCY OF HALOGENATED
BENZIMIDAZOLE INHIBITORS OF PROTEIN KINASE CK2**

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Protein kinase CK2 is a ubiquitous Ser/Thr-specific protein kinase whose holoform is composed of two catalytic (α and/or α') and two regulatory (β) subunits [1,2]. The formers are constitutively active either alone or in combination with the β subunits and their overexpression correlates with abnormal cell proliferation. The physiological role of CK2 is still poorly understood although more than 300 physiological substrates of CK2 have been already committed with signal transduction, gene expression and development, metabolism, DNA repair and apoptosis [3]. It has been also suggested that CK2 plays a role as a transducer of survival signals in the cell [4,5]. Given these premises it is not surprising that the search of compounds usable in vivo to block the activity of CK2 recently received a strong impulse. Among ATP site-directed CK2 inhibitors polyhalogenated benzimidazole and benzotriazole compounds proved quite effective [6]. In particular tetrabromo-benzotriazole (TBB) has been shown to represent a very selective and fairly powerful inhibitor of CK2 with a K_i value of about 0.4 μ M [7]. The structural features underlying such a remarkable selectivity have been investigated by solving the crystal structure of a complex between *Zea mays* CK2 α and TBB. TBB fills a hydrophobic pocket that is found in all protein kinases but whose shape and size in the case of CK2 are perfectly fitting to the inhibitor molecule [8]. The elucidation of the molecular details of the interaction of CK2 with TBB has consequently prompted the development of more potent inhibitors of CK2.

Here we present a series of new benzimidazole derivatives carrying two or more halogen atoms on the benzene ring and additional derivatization at positions 1 and 2 of the imidazole ring. Their inhibitory activity has been determined toward CK2 and other "casein kinases". The type of N-1-alkyl substituent as well as the introduction of a polyfluoroalkyl moiety at position 2 did not improve the inhibitory efficacy toward CK2. In contrast, 4,5,6,7-tetrabromobenzimidazoles substituted at position 2 with either halogens or sulfur atoms, or, even more, with secondary and tertiary amines, while displaying a negligible activity toward CK1 and G-CK, proved more efficient toward CK2 as compared to the unsubstituted compounds, with K_i values, in some cases, in the low nanomolar range. Computer-aided modelization based on the coordinates of the crystal

structure of the TBB-CK2 α complex provides the rationale for the increased efficiency of these compounds as well as hints for the design of new inhibitors even more selective and powerful.

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