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SHORT
COMMUNICATIONSSynthesis of New 2*H*-Benzimidazole 1,3-Dioxide Derivatives
Analogous to Separase Inhibitor (Sepin-1)E. A. Chugunova^{a,b,*}, N. I. Akylbekov^c, M. R. Gaziev^c, V. A. Samsonov^d,
A. B. Dobrynin^a, and A. R. Burirov^a^a Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Center, Russian Academy of Sciences,
ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia

*e-mail: elena-chugunova@list.ru

^b Kazan Federal University, ul. Kremlevskaya 18, Kazan, 420008 Tatarstan, Russia^c Kazan National Research Technological University, ul. Karla Marksa 68, Kazan, 420015 Tatarstan, Russia^d Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences,
pr. Akademika Lavrent'eva 9, Novosibirsk, 630090 Russia

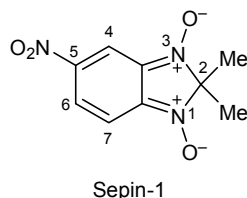
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Abstract—New biologically active 2*H*-benzimidazole 1,3-dioxide derivatives, analogs of Sepin-1, have been synthesized starting from benzofuroxan. Electrophilic substitution of hydrogen in the 2*H*-benzimidazole ring occurs at different positions, depending on the electrophile nature.

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2*H*-Benzimidazole 1,3-dioxides exhibit high biological activity. They can be used as antiparasitic agents against *Trypanosoma cruzi* and *Leishmania spp.* which, according to the WHO data, have infected about 30 million people; more than 400 million people are constantly under threat of infection [1].

Do et al. [2] recently reported that 2*H*-benzimidazole 1,3-dioxide derivatives inhibit separase, a cysteine protease important in the cell division process [2]. The most active separase inhibitor was 2,2-dimethyl-5-nitro-2*H*-benzimidazole 1,3-dioxide patented as Sepin-1 [3, 4].



Introduction of substituents other than methyl groups into the 2-position should enhance the inhibitory activity of 2*H*-benzimidazole 1,3-dioxides. Herein we describe the synthesis of new 2*H*-benzimidazole 1,3-dioxide derivatives that are analogs of Sepin-1.

Compound **2** was synthesized by reaction of benzofuroxane **1** with isobutyl alcohol in the presence of sulfuric acid. Presumably, the reaction involves rearrangement of primary carbocation generated from isobutyl alcohol into isomeric more stable secondary carbocation [5].

Taking into account that the inhibitory activity of compounds of this series is related to the presence of a nitro group in the 5-position of 2*H*-benzimidazole [2], 2*H*-benzimidazole 1,3-dioxide **2** was subjected to nitration with nitric acid in acetic acid. We thus obtained Sepin-1 analog **3**. Unlike the nitration, the bromination of **2** with molecular bromine in acetic acid gave 4-bromo derivative **4**. Thus, the direction of electrophilic substitution in 2*H*-benzimidazole 1,3-dioxide depends on the electrophile nature.

The structure of **4** was determined by X-ray analysis (see figure). The bond lengths in molecule **4** conform to the corresponding standard values. The heterocycle is planar, and the methyl and ethyl substituents are oriented in opposite directions with respect to the heterocycle.

2-Ethyl-2-methyl-2*H*-benzimidazole 1,3-dioxide (2). Isobutyl alcohol, 1 mL (0.01 mol), was added