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Synthesis of 4-aryloxy-7-nitrobenzofurazan Derivatives from 4-chloro-7-nitrobenzofurazan and Various Phenoxide Anions (Including Pharmaceuticals) in the Presence of Crown Ethers

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Abstract: 4-Chloro-7-nitrobenzofurazan reacts by nucleophilic substitution with phenoxide anions derived from estriol (**2c**), ethynylestradiol (**2d**), phenol (**3e**), guaiacol (**3f**), 2,6-dimethoxyphenol (**3g**), eugenol (**3h**), isoeugenol (**3i**), the cytostatic Etoposide (**4**), and Reichardt's betaine (**5**) in the presence of crown ethers affording the corresponding 4-aryloxy-7-nitrobenzofurazan derivatives **6c**, **6d**, **7e** – **7i**, **8**, and **9**. The structure of these compounds was confirmed by NMR spectra. Hydrophobicity/hydrophilicity parameters were investigated by reverse phase thin-layer chromatography.

Keywords: 4-aryloxy-7-nitrobenzofurazan derivatives, phenoxide anions, 4-chloro-7-nitrobenzofurazan, crown ethers, NMR spectra, RPTLC

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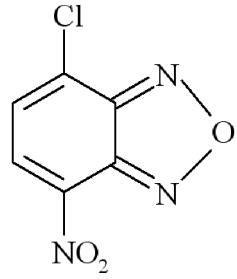
1 Introduction

Benzofurazan and benzofuroxan derivatives are routinely applied to the analytical determination of amino acids, primary or secondary amines, and polypeptides owing to the fluorescence of the corresponding products [1-21].

For nitrobenzofurazan derivatives the IUPAC numbering requires alphabetical ordering of substituents, which leads to structural non-uniformity. For convenience, we decided to fix the numbering in practically all formulas so that the nitro group is always numbered as 7, leaving the halogen or aryloxy group numbered as 4.

The activated chlorine atom in 4-chloro-7-nitrobenzofurazan (4-chloro-7-nitrobenzo-2-oxa-1,3-diazole, NBD chloride, **1**) can be substituted nucleophilically by primary or secondary amines and also by phenoxide [10,26,27,28] or tyrosine anions [22]. Some 4-substituted 7-nitrobenzofurazan and benzofuroxan derivatives were reported to possess antileukemic and immunosuppressing activity [1,22,23].Further data on benzofurazan derivatives have been published by Boulton, Katritzky and coworkers [29-34]. 4-Chloro-7-nitrobenzofurazan, or its more reactive and expensive 4-fluoro congener, are easily accessible [35] and are also commercially available under the names of NBD chloride or fluoride, respectively.



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In a previous paper [36] it was shown that in the presence of crown ethers (CEs), phenoxidic-type sodium salts of estrone (**2a**) and estradiol (**2b**) react with 1 affording diaryl ether compounds (4-aryloxy-7-nitrobenzofurazan derivatives) **6a** and **6b**, respectively. Interestingly, these weakly fluorescent ethers react fast and irreversibly with amino acids resulting in strongly fluorescent compounds. Biochemical implications are evident because the molecular design of 4-aryloxy-7-nitrobenzofurazan derivatives **6a**,**b** having biologically active structural fragments will allow their use in pharmacokinetics and pharmacodynamics. Their rapid reaction with amino acids or related compounds will lead to promising simple bioanalytical determinations of such compounds.

The present paper reports the synthesis and study of further novel 4-aryloxy-7-nitrobenzofurazan derivatives with potential biomedical and bioanalytical applications. For this purpose we investigated the reaction between NBD chloride (**1**) in the presence of CE with anions of the following phenols: phenol (**3e**), guaiacol or 2-methoxyphenol (**3f**), 2,6-dimethoxyphenol (**3g**), eugenol or 4-allyl-2-methoxyphenol (**3h**), *cis* + *trans*-isoeugenol or 2-methoxy-4-propenylphenol (**3i**), Reichardt's betaine or 2,6-diphenyl-4-