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Synthesis and Hydrophobic Properties of Benzoxazoles

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Abstract: A series of fourteen lipophilic 2-substituted 5,7-di-*tert*-butylbenzoxazoles was prepared by the reaction of 2-amino-4,6-di-*tert*-butylphenol with appropriated aldehydes. The general synthetic approach of all newly synthesized compounds is presented. All the substituted 5,7-di-*tert*-butylbenzoxazoles derivatives were analyzed using the reversed phase high performance liquid chromatography (RP-HPLC) method for the lipophilicity measurement. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP column. In the present study the correlation between RP-HPLC retention parameter Log *K* (the logarithm of capacity factor *K*) and various calculated Log *P* values is shown. The relationships between the lipophilicity and the chemical structure of the studied compounds are discussed as well.

Keywords: 2-amino-4,6-di-*tert*-butylphenol; 5,7-Di-*tert*-butylbenzoxazoles; Lipophilicity measurement; Structure-lipophilicity relationships

Introduction

Substituted benzoxazoles present a wide range of bioactivities, and their chemistry, pharmacological applications, and physicochemical properties have been extensively investigated [1]. Benzoxazoles and their complexes with various di- and tri-valent metal ions have been studied as potential antibacterial and antifungal agents [2-7], antituberculotics [8, 9], as well as antineoplastic [10-12], and antiviral agents [13, 14]. Benzoxazoles are also interesting fluorescent compounds [15], which interfere with the biosynthesis of coloured carotenoids by inhibiting the enzyme phytoene desaturase. They have been studied as potential herbicides [16].

One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, e. g. the transport of a molecule through cellular membranes. The drugs mostly (most frequently) cross the biological barriers by the passive transport, which strongly depends on the lipophilicity. Therefore hydrophobicity is the most important physical property of biologically active compounds. This thermodynamic parameter describes the partitioning of a soluble compound between an aqueous and an organic phase and is indicated as partition (Log *P*) or distribution (Log *D*) coefficient [17, 18].

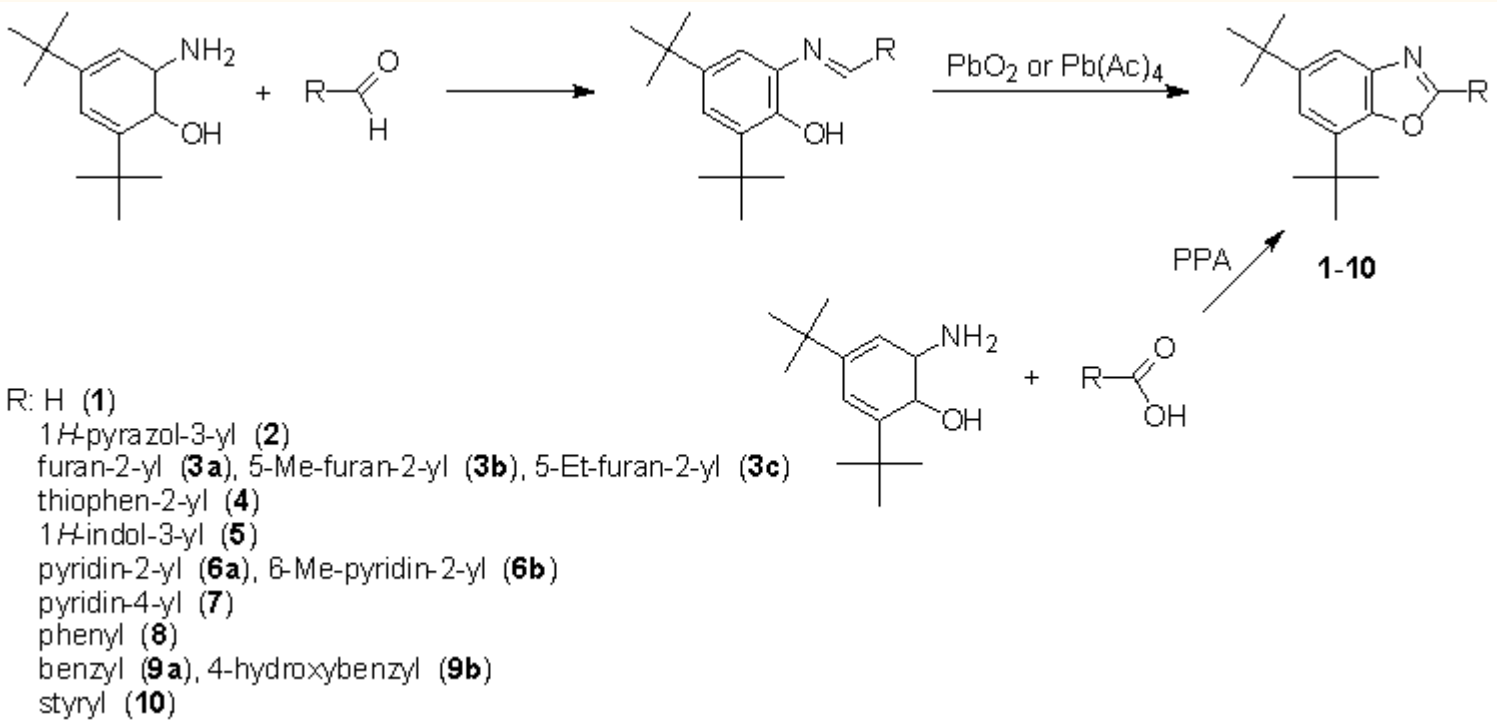
Classical methods for determination of these constants are time consuming and not always sufficiently reliable. Therefore, reversed phase high performance liquid chromatography (RP-HPLC) methods have become popular and widely used for lipophilicity measurement in spite of being more expensive. A general procedure is the measurement of the directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP columns and calculating the capacity factor K ($K = (T_R - T_D) / T_D$, where T_R is the retention time of the solute, whereas T_D denotes the dead time obtained via an unretained analyte). Log K, calculated from the capacity factor K, is used as the lipophilicity index converted to Log *P* scale [19].

This study is a follow-up paper to the previous articles and deals with the synthesis and physicochemical properties of the newly prepared *N*-heterocyclic compounds as potential drugs [8, 9, 20-24].

Results and Discussion

The formation of the target compounds **1**-**10** is a multistep process. The characterization of these benzoxazole derivatives is described in papers [8, 9]. The discussed compounds could be obtained directly by condensation of 2-amino-4,6-di-*tert*-butylphenol and carboxylic acid under catalysis by polyphosphoric acid (PPA) [25]. Another pathway consists in reaction of 2-amino-4,6-di-*tert*-butylphenol with the appropriate aldehyde that formed Schiff bases. Their cyclization was done by equivalent amount of lead dioxide or lead tetraacetate, respectively [3]. The general synthetic approach of all discussed compounds **1**-**10** is shown in Scheme 1.

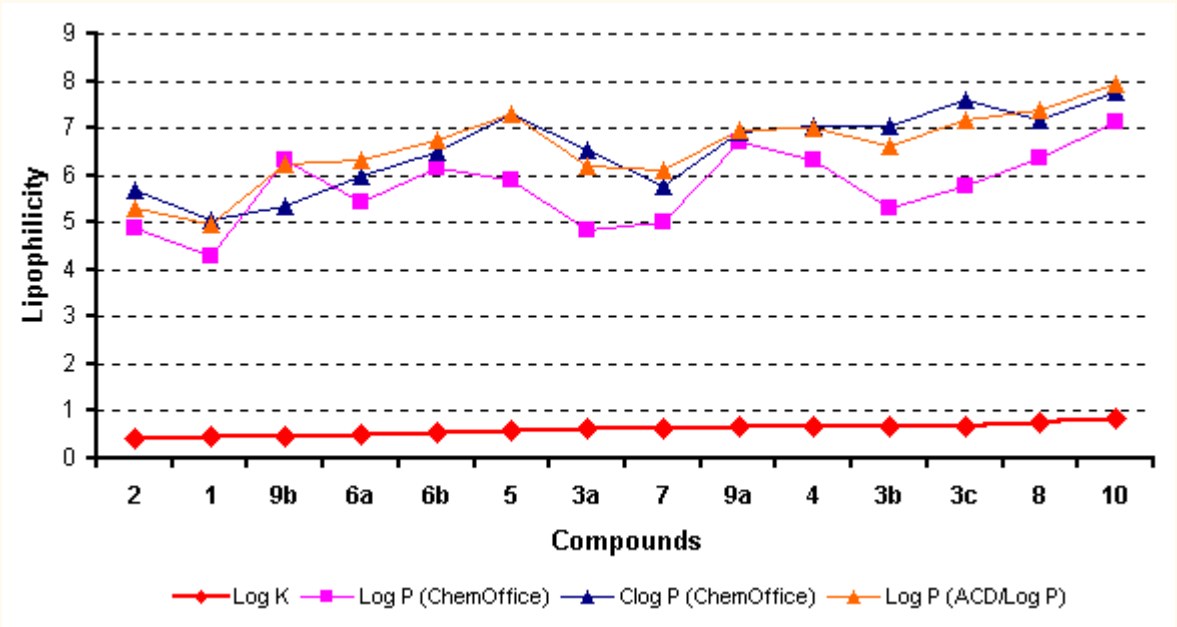
Scheme 1: Synthesis and structures of 2-substituted 5,7-di-*tert*-butylbenzoxazoles **1**-**10**.



R: H (**1**)
1*H*-pyrazol-3-yl (**2**)
furan-2-yl (**3a**), 5-Me-furan-2-yl (**3b**), 5-Et-furan-2-yl (**3c**)
thiophen-2-yl (**4**)
1*H*-indol-3-yl (**5**)
pyridin-2-yl (**6a**), 6-Me-pyridin-2-yl (**6b**)
pyridin-4-yl (**7**)
phenyl (**8**)
benzyl (**9a**), 4-hydroxybenzyl (**9b**)
styryl (**10**)

Hydrophobicities (Log *P* / CLog *P* values) of the studied compounds were calculated using two commercially available programs and measured by means of RP-HPLC determination of capacity factors *K* with a subsequent calculation of Log *K*. The results are shown in Table 1 and illustrated in Figure 1.

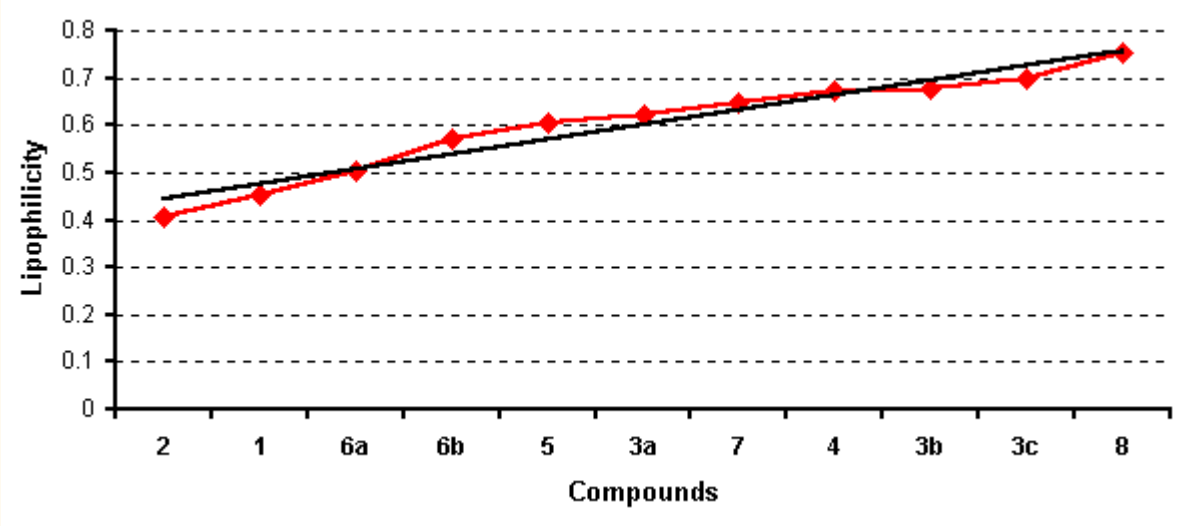
Figure 1: Comparison of the computed Log *P* / CLog *P* values using the two programs and the experimentally found Log *K* values.



The results show that the experimentally determined Log *K* values correlate relatively poorly with Log *P* data calculated either by ChemOffice Ultra software or ACD/Log *P* program, as well as with the calculated CLog *P* data, see Fig. 1. All the showed differences between experimental and calculated lipophilicity values are probably caused by interactions of the substituents with heteroatoms of benzoxazole nucleus in individual compounds.

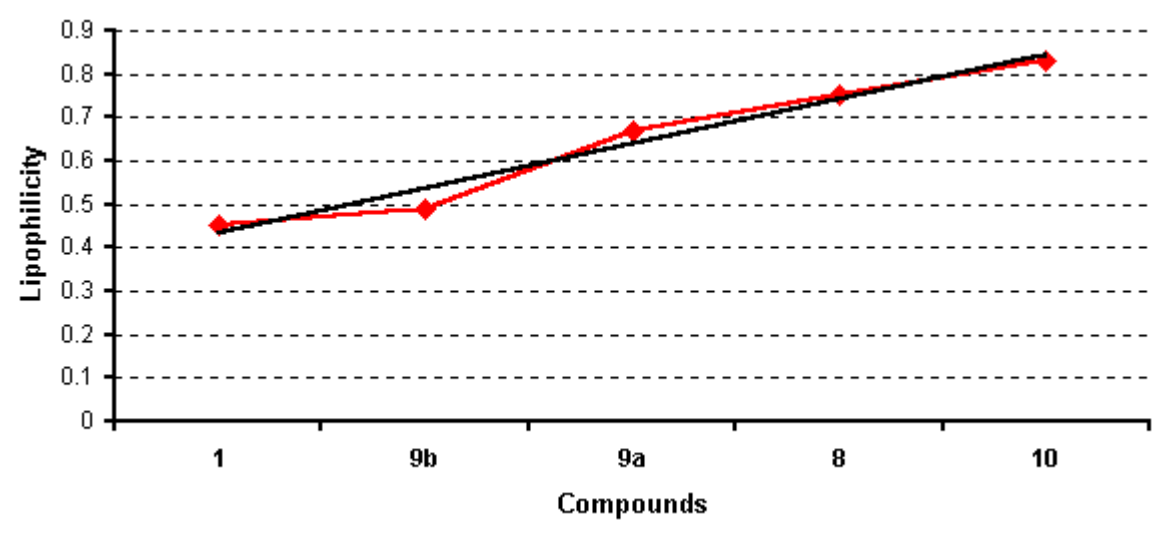
As expected, the dependence between Log *K* and the length of the alkyl substituents in compounds **3a**-**3c** and **6a**-**6b** (H, CH_3, C_2H_5) is approximately linear, see Fig. 2. 5,7-Di-*tert*-butyl-2-pyridin-2-yl-benzoxazole (**6a**) and its 6-methylpyridin-2-yl derivative (**6b**) are less lipophilic than 5,7-di-*tert*-butyl-2-pyridin-4-yl-benzoxazole (**7**). In contrast with our expectation the pyrazole derivative **2** shows less lipophilicity parameter (Log *K*) than 5,7-di-*tert*-butyl-benzoxazole (**1**), as well as all calculated data for 5,7-di-*tert*-butyl-2-(1*H*-indole-3-yl)-benzoxazole (**5**) show great differences with experimental Log *K* value. According to the calculation the compound **5** shows the highest lipophilicity of all heterocyclic substituents, but in accordance with the experiment the latter is situated between **6b** and **3a**, it means, that the compound **5** shows medium lipophilicity in the series of benzoxazole **1**-**8**. In contrast, at the compound **3c** Log *K* is higher than the calculated lipohilicity parameters. The lipophilicity of 5,7-di-*tert*-butyl-2-(5-ethylfuran-2-yl)-benzoxazole (**3c**) is the highest among heterocycle substituted benzoxazoles **2**-**7** discussed in Fig. 2.

Figure 2: The dependence between the lipophilicity (experimentally found Log *K* values) and the chemical structure of the heterocycles substituted benzoxazoles **2**-**7**, as well as 5,7-di-*tert*-butyl-benzoxazole (**1**) and 5,7-di-*tert*-butyl-2-phenyl-benzoxazole (**8**).



The dependence between the lipophilicity (Log *K*) and the chemical structure of the studied compounds **1**, **8**-**10** is illustrated in Fig. 3. The compounds **9b** showed the lowest lipophilicity, whereas the compound **10** the highest, as expected. Great differences between the experimental and calculated lipophilicity parameters could be observed at the compounds **8** and **9a**, see Fig. 3. For the compound **8** Log *K* is higher than the calculated lipohilicity parameters. The dependence between Log *K* and bulkiness of the substituents in the position $C_{(2)}$ of the compounds **1**, **8**, **9a**, **10** (H, Ph, Bz, styryl) is approximately linear, see Fig. 3.

Figure 3: The dependence between the lipophilicity (experimentally found Log *K* values) and the chemical structure of the non-heterocycles substituted benzoxazoles **8**-**10** as well as 5,7-di-*tert*-butyl-benzoxazole (**1**).



Experimetal

Lipophilicity HPLC determination (capacity factor K / calculated Log K)

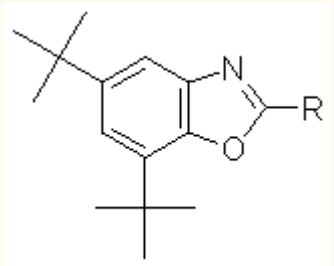
The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, U.S.A.) were used. The chromatographic column Symmetry® C_{18} 5 µm, 4.6 × 250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, U.S.A.) was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, U.S.A.). The mixture of MeOH p. a. (90.0%) and H_2O-HPLC -- Mili-Q Grade (10.0%) was used as a mobile phase. The total flow of the column was 1.0 ml/min, injection 30 µl, column temperature 45 °C and sample temperature 10 °C. The detection wavelength 210 nm was chosen. The KI methanolic solution was used for the dead time (T_D) determination.

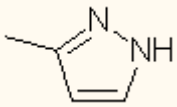
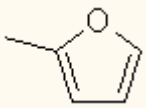
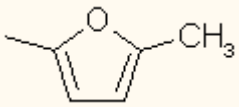
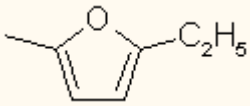
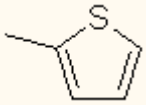
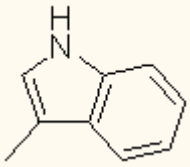
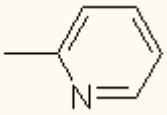
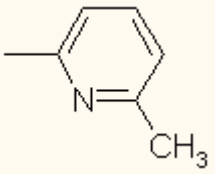
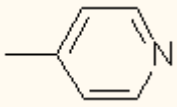
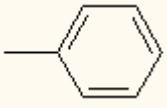
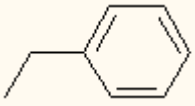
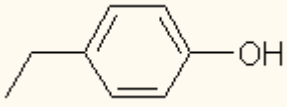
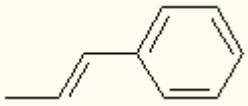
The capacity factors *K* were calculated using the Millennium32® Chromatography Manager Software. The Log *K* values of the individual compounds are shown in Table 1.

Lipophilicity calculations

Log *P*, *i. e.* the logarithm of the partition coefficient for *n*-octanol / water, was calculated using the programs CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/Log *P* ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). CLog *P* values (the logarithm of *n*-octanol / water partition coefficient based on established chemical interactions) were generated by means of CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Table 1.

Table 1: Comparison of calculated lipophilicities (log *P* / CLog *P*) and determined Log *K* of compounds **1**-**10**.



Compound	R	Log *K*	Log *P* ACD/Log P	Log *P* / CLog *P* ChemOffice
1	— H	0.4509	4.97 ± 0.34	4.29 / 5.067
2		0.4065	5.29 ± 0.61	4.87 / 5.669
3a		0.6234	6.18 ± 0.61	4.84 / 6.551
3b		0.6783	6.64 ± 0.61	5.30 / 7.050
3c		0.6972	7.17 ± 0.61	5.78 / 7.579
4		0.6723	6.99 ± 0.61	6.33 / 7.060
5		0.6064	7.31 ± 0.84	5.89 / 7.299
6a		0.5044	6.31 ± 0.60	5.43 / 5.986
6b		0.5726	6.77 ± 0.60	6.14 / 6.485
7		0.6473	6.13 ± 0.60	5.01 / 5.776
8		0.7515	7.39 ± 0.59	6.35 / 7.165
9a		0.6707	6.98 ± 0.58	6.72 / 6.904
9b		0.4880	6.24 ± 0.58	6.33 / 5.328
10		0.8325	7.93 ± 0.59	7.13 / 7.759

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