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Synthesis and Hydrophobic Properties of New 2-Aryl-5,7-di-*tert*-butylbenzoxazoles

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Abstract: The series of fifteen lipophilic 2-aryl-5,7-di-*tert*-butylbenzoxazoles substituted in the phenyl ring was prepared by the reaction of 2-amino-4,6-di-*tert*-butylphenol with the appropriated aldehydes. The general synthetic approach of all newly synthesized compounds is presented. All the substituted 5,7-di-*tert*-butylbenzoxazole 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 log *P* data calculated in various ways 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; 2-Aryl-5,7-di-*tert*-butylbenzoxazoles; Lipophilicity measurement; Structure-lipophilicity relationships.

Introduction

Benzoxazoles belong to biologically very active skeletons [1]. Benzoxazoles and their complexes with various di- and tri-valent metal ions have been studied as potential antibacterial and antifungal agents [2—10], antituberculotics [11, 12], as well as antineoplastic [13—16], and antiviral agents [17, 18]. Benzoxazoles are also interesting fluorescent compounds [19, 20], which interfere with the biosynthesis of coloured carotenoids by inhibiting the enzyme phytoene desaturase. They have been studied as potential herbicides [21]. Benzoxazoles can be considered as structural bioisosters of naturally occurring nucleotides such as adenine and guanine, which allow them to interact easily with the biopolymers of a living system. They have shown low toxicity in warm-blooded animals [22].

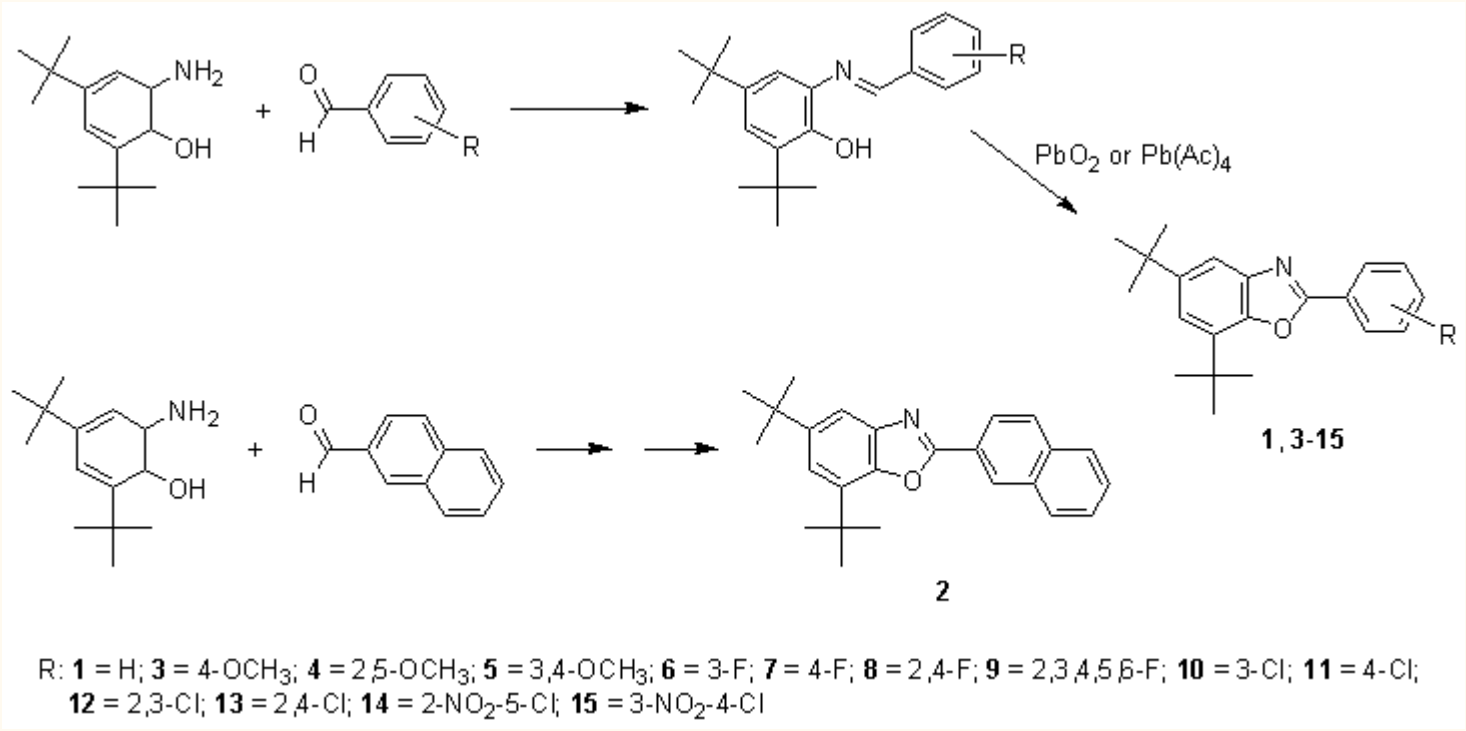
One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, *e.g.* the transport of a molecule through cellular membranes. Most frequently the drugs cross the biological barriers by the passive transport, which strongly depends on the lipophilicity. 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*) coefficient. Reversed phase high performance liquid chromatography (RP-HPLC) methods have used for lipophilicity measurement. 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*. Log *K*, calculated from the capacity factor *K*, is used as the lipophilicity index converted to log *P* scale [23].

This study is a follow-up paper to the previous articles [11, 12, 24—37] and deals with the synthesis and physicochemical properties of the newly prepared *N*-heterocyclic compounds as potential drugs.

Results and Discussion

The formation of the target compounds **1**—**15** is a multistep process. Various synthetic pathways were reported in the previous paper [11, 12]. The compounds **1**—**15** could be obtained directly by 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 [4]. The general synthetic approach of the discussed compounds **1**—**15** is shown in Scheme 1.

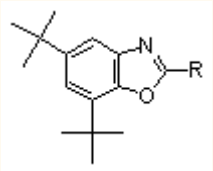
Scheme 1. Synthesis and structures of the substituted 2-aryl-5,7-di-*tert*-butylbenzoxazoles **1**—**15**.

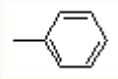
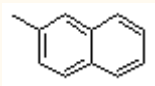
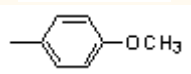
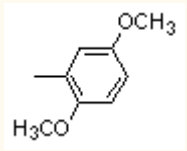
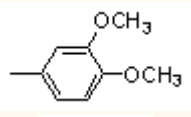
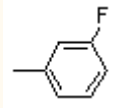


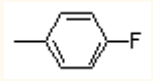
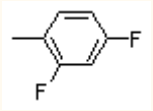
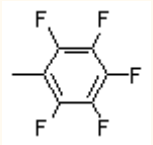
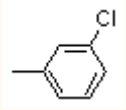
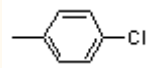
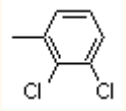
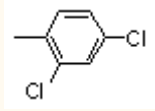
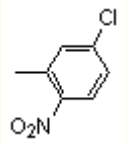
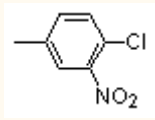
R: **1** = H; **3** = 4-OCH_3; **4** = 2,5-OCH_3; **5** = 3,4-OCH_3; **6** = 3-F; **7** = 4-F; **8** = 2,4-F; **9** = 2,3,4,5,6-F; **10** = 3-Cl; **11** = 4-Cl; **12** = 2,3-Cl; **13** = 2,4-Cl; **14** = 2-NO_2-5-Cl; **15** = 3-NO_2-4-Cl

Hydrophobicities (log *P* / Clog *P* data) 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. All the discussed hydrophobicity data of individual compounds are illustrated in Figure 1 and they are ordered according to the experimental log *K* values increase.

Table 1. Calculated lipophilicities (log *P* / Clog *P*) and determined log *K* of the studied substituted 2-aryl-5,7-di-*tert*-butylbenzoxazoles **1**—**15**.



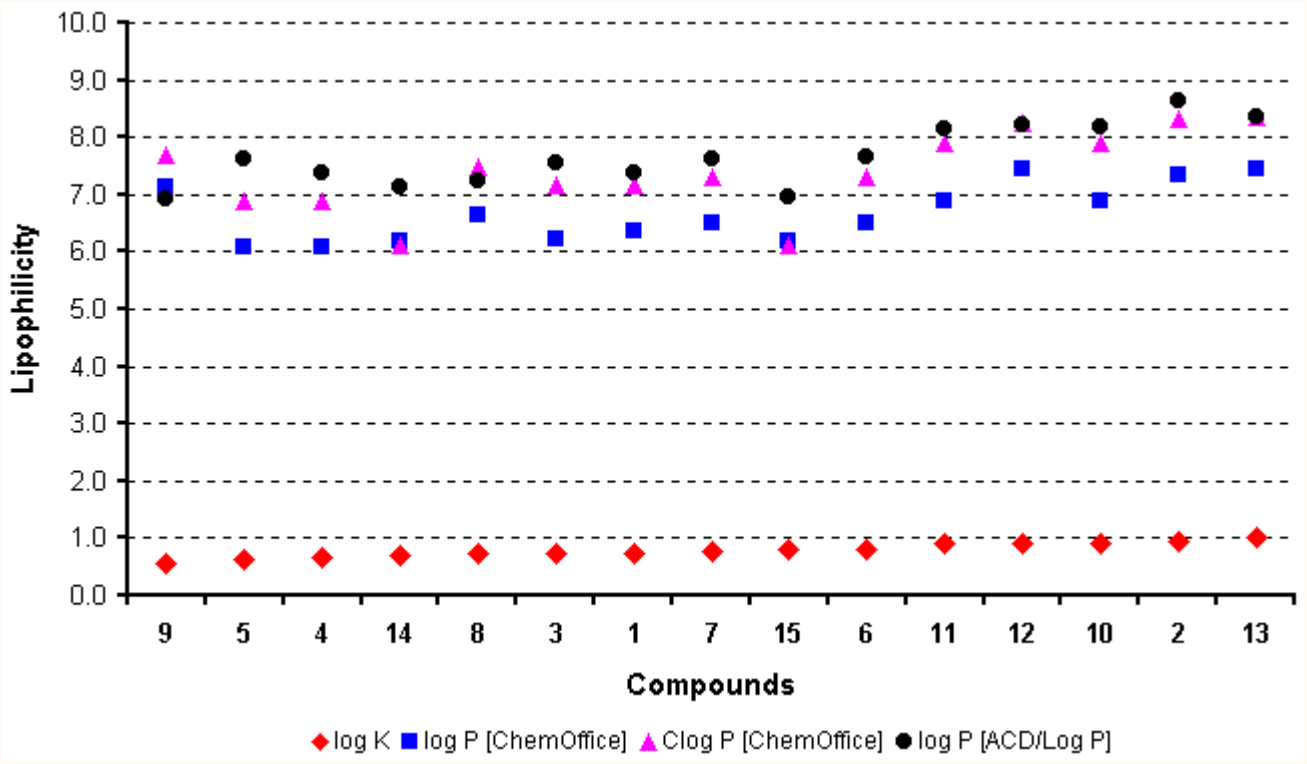
Compound	R	log *K*	log *P* / Clog *P* ChemOffice	log *P* ACD/LogP
1		0.7515	6.35 / 7.1650	7.39 ± 0.59
2		0.9464	7.34 / 8.3390	8.62 ± 0.59
3		0.7364	6.22 / 7.1842	7.55 ± 0.60
4		0.6482	6.09 / 6.8966	7.37 ± 0.61
5		0.6407	6.09 / 6.8966	7.63 ± 0.61
6		0.8027	6.50 / 7.3248	7.64 ± 0.63

7		0.7617	6.50 / 7.3248	7.61 ± 0.63
8		0.7339	6.66 / 7.4737	7.24 ± 0.66
9		0.5563	7.14 / 7.6957	6.91 ± 0.78
10		0.9254	6.90 / 7.8948	8.18 ± 0.60
11		0.9118	6.90 / 7.8948	8.15 ± 0.60
12		0.9127	7.46 / 8.2437	8.23 ± 0.61
13		1.0010	7.46 / 8.3637	8.34 ± 0.61
14		0.6992	6.20 / 6.1348	7.13 ± 0.64
15		0.8021	6.20 / 6.1348	6.95 ± 0.64

The program ChemOffice has not resolved various lipophilicity values of individual positional isomers, *e.g.* the compounds **4**/**5**, **6**/**7**, **10**/**11**, or **14**/**15**, respectively.

The results show that the experimentally determined log *K* values correlate relatively poorly with log *P* / Clog *P* data calculated either by ChemOffice Ultra software or ACD/LogP program, as well as with the calculated data, see Figure 1. The results obtained concerning all the compounds **1**—**15** show that the experimentally determined lipophilicities (log *K* values) are lower than those indicated by the calculated log *P* / Clog *P*, see Figure 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 described in refs [12, 31]. But it can be stated, that the substitution in the $C_{(4)}$' position of phenyl ring shows the lowest influence of lipophilicity by interactions of substituents with heteroatoms of benzoxazole skeleton.

Figure 1. Comparison of log *P* / Clog *P* data calculated using the two programs with the experimentally found log *K* values. The discussed compounds are ordered according to the log *K* values increase.



5,7-Di-*tert*-butyl-2-(pentafluorophenyl)benzoxazole (**9**) possesses the lowest lipophilicity, as expected. Generally, it was expected, that the fluoro derivatives **6**—**9** show low lipophilicity. The lipophilicity decreases with the increase of the number of fluorine atoms in the molecule of benzoxazole.

Similarly, three discussed methoxy derivatives **3**—**5** show very low lipophilicity. Both 5,7-di-*tert*-butyl-2-(2,5-dimethoxyphenyl)benzoxazole (**4**) and 5,7-di-*tert*-butyl-2-(3,4-dimethoxyphenyl)benzoxazole (**5**) possess less lipophilicity than mono substituted methoxy derivative **3**, which shows less hydrophobicity than unsubstituted benzoxazole derivative **1**. This is in good agreement with our expectation.

On the other hand 5,7-di-*tert*-butyl-2-(naphthalen-2-yl)benzoxazole (**2**) and 5,7-di-*tert*-butyl-2-(2,4-dichlorophenyl)benzoxazole (**13**) show the highest hydrophobicity.

Experimentally observed dependence among chlorine substituted benzoxazoles **10**—**15** is very interesting. In the series of these compounds hydrophobicity increases 2-NO_2-5-Cl (**14**) < 3-NO_2-4-Cl (**15**) < 4-Cl (**11**) < 2,3-Cl (**12**) < 3-Cl (**10**) < 2,4-Cl (**13**). Nitro moiety decreases lipophilicity, as described in ref [12, 31]. The order of hydrophobicity of further chlorine derivatives **11**—**13** is influenced by intramolecular interactions.

These intramolecular interactions caused higher hydrophobicity of fluorine and/or chlorine 3-phenyl substituted benzoxazole derivatives **6** and **10** unlike 4-phenyl substituted benzoxazole derivatives **7** and **11**.

It can be assumed, that log *K* values evaluated from the capacity factor *K* specify lipophilicity within these individual series of the compounds.

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. Retention times (T_R) were measured in minutes.

The capacity factors *K* were calculated using the Millennium32® Chromatography Manager Software according to the formula $K = (T_R - T_D) / T_D$, where T_R is the retention time of the solute, whereas T_D denotes the dead time obtained via an unretained analyte. The log *K* values of the individual compounds, calculated from the capacity factor *K*, 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. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/LogP 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. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Table 1.

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