chemistry proceedings

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Proceeding Paper

Hydro-Lipophilic Properties of Chlorinated and Brominated 1-Hydroxynaphthalene-2-Carboxanilides †

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† Presented at the 28th International Electronic Conference on Synthetic Organic Chemistry (ECSOC 2024), 15-30 November 2024; Available online: https://sciforum.net/event/ecsoc-28.

Abstract: 1-Hydroxy-*N*-phenylnaphthalene-2-carboxamide and a series of other seventeen carboxanilides in the anilide part of dichlorinated, trichlorinated and dibrominated, tribrominated and chlorinated/brominated have recently been reported as biologically active compounds mainly with antibacterial, antimycobacterial and anticancer effects. Since lipophilicity is one of the factors influencing the bioavailability (absorption, distribution, metabolism, elimination) and activity and even toxicity of bioactive compounds, all the derivatives were investigated for their lipophilic and hydrophilic properties. All eighteen compounds were analyzed by reversed-phase high-performance liquid chromatography (RP-HPLC). The procedure was performed under isocratic conditions with methanol as the organic modifier in the mobile phase using an end-capped non-polar C18 stationary reversed-phase column. The lipophilicity values are expressed as the logarithm of the capacity factor *k* (for the mobile phase water: methanol) and the distribution coefficients *D* at pH values of 6.5 and 7.4 (for the mobile phase buffer: methanol), as well as the calculated values of log *P*/Clog *P* by various methods. 1-Hydroxy-*N*-(3,4,5-trichlorophenyl)naphtha- lene-2-carboxamide and *N*-(4-bromo-3-chlorophenyl)-1-hydroxynaphthalene-2-carboxamide are the most lipophilic compounds of the whole series, on the contrary, surprisingly unsubstituted 1-hydroxy-*N*-phenylnaphthalene-2-carboxamide is not the least lipophilic derivative. The mutual correlations between the experimental and predicted lipophilicity values are low, in addition, there are large deviations in the cross-correlations between log *k* and log *D*, which is due to the presence of a free ionizable phenolic group in the molecule.

Keywords: hydroxynaphthalene-carboxanilides; lipophilicity determinations; structure-lipophilicity relationships

Citation: Vrablova, L.; Gonec, T.; Jampilek, J. Hydro-Lipophilic Properties of Chlorinated and Brominated 1-Hydroxynaphthalene-2-Carboxanilides. *Chem. Proc.* **2024**, *6*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

Published: 15 November 2024

1. Introduction

Designing and optimizing the structure/properties of new drugs is one of the priorities of modern science. The relationships between the structure and effects of biologically active compounds are analyzed in each research [1,2]. Lipophilicity is an important property of all bioactive molecules. Determination of lipophilicity is a central step in studies devoted to the design of new agents with potential biological effects and is also useful in optimizing the effects of existing agents. Lipophilicity, a key property of compounds, is responsible for their solubility, transport across membranes, binding to plasma proteins, as well as interactions of molecules with receptors, which manifests the pharmacological action of drugs. It is one of the key properties for modeling the biological response,

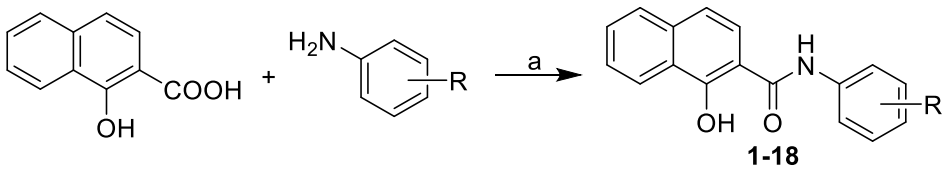
correlating with absorption, distribution, metabolism, excretion and toxicity (ADMET) processes [3–5].

A common quantitative descriptor of lipophilicity is the log *P* partition coefficient. Studies show that the optimal range of lipophilicity, expressed as the logarithm of the n-octanol/water partition coefficient (log *P*), for optimal gastrointestinal absorption by passive diffusion after oral administration is from 0 to 3 [3,4,6]. However, log *P* values include only the neutral form of the compound and are independent of ionization under physiological conditions. If the molecule contains basic or acidic groups, it can be ionized and its distribution in the n-octanol/water system depends on the pH. It is estimated that 95% of drugs are ionizable. Therefore, another descriptor of lipophilicity for ionizable molecules is expressed as the distribution coefficient *D* or its logarithm log *D*. Log *D* is dependent on the pH of the environment and its value includes the contribution of all ionized forms of the substance present at a given pH [3,6].

Lipophilicity can be determined experimentally using several methods. They are usually divided into direct and indirect methods [7–9]. In this work, aimed at determining the lipophilicity of a series of anilides of 1-hydroxynaphthalene-2-carboxylic acid, an indirect chromatographic method using reversed-phase high-performance liquid chromatography (RP-HPLC) was used. Hydroxynaphthoic acid derivatives have a wide spectrum of biological effects, as recently described [10–20], and thus offer a source of promising molecules for drug development.

2. Results and Discussion

The discussed anilides were synthesized using microwave-assisted synthesis as illustrated in Scheme 1 and described by Gonec et al. [10,11]. The reaction of 1-hydroxynaphthalene-2-carboxylic acid with ring-substituted aniline using phosphorus trichloride in chlorobenzene provided a series of eighteen 1-hydroxynaphthalene- 2-carboxanilides **1–18**. All the target compounds are listed in Table 1.

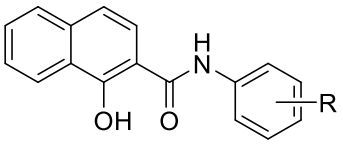


Scheme 1. Synthesis of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1–18**. *Reagents and conditions*: (a) PCl_3, chlorobenzene, microwave synthesis (500 W, 130 °C, 15 min) [10,11].

The lipophilicity of all eighteen compounds was determined using RP-HPLC as capacity factors *k* (with subsequent calculation of log *k*) and as the distribution coefficients *D* at pH values of 6.5 and 7.4 (with subsequent calculation of log $D_{6.5}$ and log $D_{7.4}$). The retention times of individual compounds were determined under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C18 stationary RP columns. In addition, the lipophilicities (log *P*/Clog *P* data) of all target anilides were calculated using two commercially available programs: ACD/Percepta ver. 2012, and ChemBioDraw Ultra 13.0. All results are shown in Table 1.

Log *P* and Clog *P* calculations in ChemBioDraw software are based on the fragment method, whereby the log *P* calculation algorithm in this software neglects the position of the substituents and therefore calculates the same log *P* values for individual positional isomers. According to the Clog *P* algorithm, which also includes possible chemical interactions of the molecule, the lipophilicity values were identical for the 2,4- and 2,5-disubstituted isomers (i.e., for derivatives **3**/**5**, **11**/**12**, **15**/**16**). For this reason, the lipophilicity values predicted by the ChemBioDraw software are only listed in Table 1 without further discussion. Thus, only the log *P* values calculated by ACD/Percepta are unique for each individual isomer.

Table 1. Structure of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1–18**, experimentally determined log *k*, log $D_{6.5}$, log $D_{7.4}$, and predicted lipophilicities (log *P*/Clog *P*) values of investigated compounds.



Comp.	R	log *k*	log $D_{6.5}$	log $D_{7.4}$	log *P* [1]	log *P* [2]	Clog *P* [2]
1	H	0.6084	0.5139	0.5487	4.52	3.45	4.44620
2	2,3-Cl	0.6838	0.4371	0.3870	5.76	4.56	5.24996
3	2,4-Cl	0.7387	0.5168	0.4680	5.78	4.56	5.36996
4	2,5-Cl	0.6717	0.3949	0.3938	5.82	4.56	5.36996
5	2,6-Cl	0.5729	0.4516	0.4594	5.52	4.56	4.51996
6	3,4-Cl	0.9304	0.9048	0.8909	5.99	4.56	6.09996
7	3,5-Cl	0.9704	0.9531	0.9306	6.01	4.56	6.21996
8	2,4,5-Cl	0.6894	0.5314	0.4864	6.31	5.12	5.99452
9	2,4,6-Cl	0.8398	0.7254	0.6825	6.15	5.12	5.26452
10	3,4,5-Cl	1.2387	1.0960	1.0561	6.28	5.12	6.72452
11	2,4-Br	0.8863	0.6991	0.6353	5.9	5.10	5.63996
12	2,5-Br	0.5551	0.5535	0.4888	5.81	5.10	5.63996
13	2,6-Br	0.5887	0.5951	0.4541	5.67	5.10	4.75996
14	2,4,6-Br	0.8911	0.8090	0.7648	6.34	5.93	5.65452
15	2-Cl-4-Br	0.8936	0.5442	0.5282	5.88	4.83	5.51996
16	2-Cl-5-Br	0.8004	0.4803	0.4275	5.82	4.83	5.51996
17	3-Cl-4-Br	1.2223	0.9317	0.8847	6.02	4.83	6.22996
18	2-Br-4-Cl	0.8320	0.6566	0.6174	5.80	4.83	5.48996

[1] calculated using ACD/Percepta ver. 2012 (Advanced Chemistry Development, Inc., Toronto, ON, Canada, 2012); [2] calculated using ChemBioDraw Ultra 13.0 (CambridgeSoft, PerkinElmer Inc., MA, USA).

Very poor agreement is evident from the graphs in Figure 1 where experimentally determined lipophilicity values (log *k*, log $D_{6.5}$, log $D_{7.4}$) are plotted against log *P* values; correlation coefficients *r* (*n* = 18) are 0.5225, 0.4774, 0.4084, respectively. These low correlations appear to be due to the phenolic moiety at the 1-position of naphthalene. It follows that predicted log *P* values cannot be used to search for structure–activity relationships.

Figure 2 shows the mutual correlations of all three measured experimental values. The best correlation was obtained when comparing the distribution parameters, i.e., log$D_{6.5}$ versus log$D_{7.4}$ (*r* = 0.9842, *n* = 18). Correlations of log *k* versus log$D_{6.5}$ or log$D_{7.4}$ were lower (r = 0.8506 and 0.8526, respectively). This fact again confirms the significant influence of the free phenolic group, which manifests itself in media with different pH.

This influence is also evidenced by the fact that the least lipophilic compound is not the unsubstituted 1-hydroxy-*N*-phenylnaphthalene-2-carboxamide (**1**), as expected (and as predicted by all the used programs), but *N*-(2,5-dibromophenyl)-1-hydroxynaphthalene- 2-carboxamide (**12**, log *k* = 0.5551). The above-mentioned differences between log *k* and log *D* lead to the fact that according to log $D_{6.5}$ *N*-(2,5-dichlorophenyl)-1-hydroxynaph- thalene-2-carboxamide (**4**) is the least lipophilic (log $D_{6.5}$ = 0.3949), while according to log$D_{7.4}$ *N*-(2,3-dichlorophenyl)- 1-hydroxynaphthalene-2-carboxamide (**2**) is the least lipophilic (log $D_{7.4}$ = 0.3870). 1-Hydroxy-*N*-(3,4,5-trichlorophenyl)naphthalene-2-carboxamide (**10**) is the most lipophilic derivative both based on the measurements performed under all three conditions, and this compound has the highest lipophilicity also according to predicted log *P*/Clog *P* values.

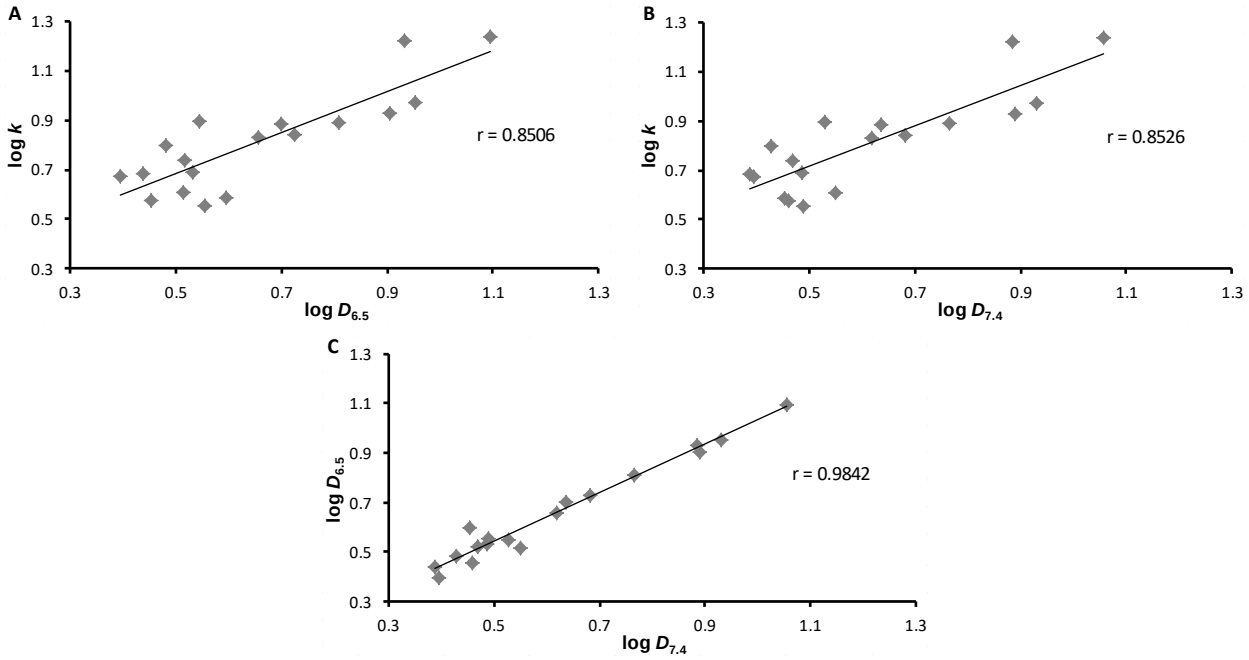


Figure 1. Comparison of experimentally determined values of log *k* (**A**), log $D_{6.5}$ (**B**), log $D_{7.4}$ (**C**) with calculated log *P* (ACD/Percepta) of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1–18**.

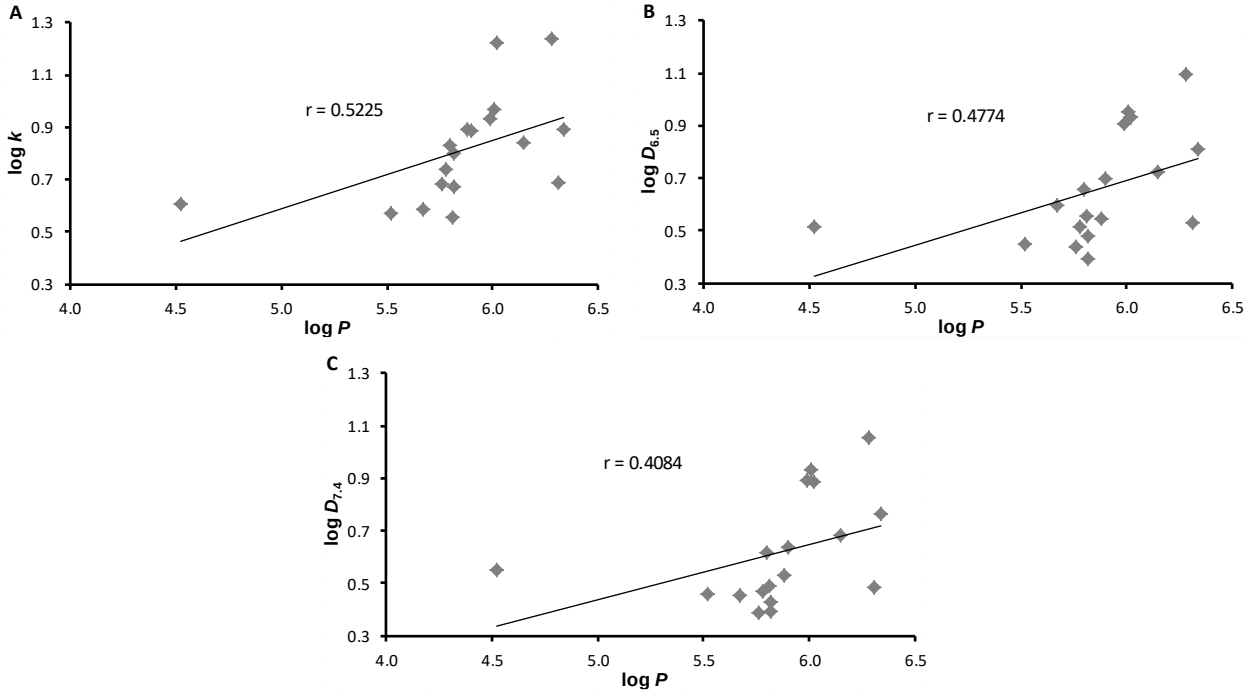


Figure 2. Cross-correlations of experimentally determined values of log *k*, log $D_{6.5}$ and log $D_{7.4}$ of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1–18**.

In general, lipophilicities represented by log *k* values are nominally the highest with a great distance are log$D_{6.5}$ values and then log$D_{7.4}$ values, which are the lowest. The order of compounds arranged according to increasing log *k* values and their overall comparison is shown in Figure 3. The greatest mutual differences can be observed for compounds **2** (R = 2,3-Cl), **15** (R = 2-Cl-4-Br), **16** (R = 2-Cl-5-Br) and **4** (R = 2,5-Cl).

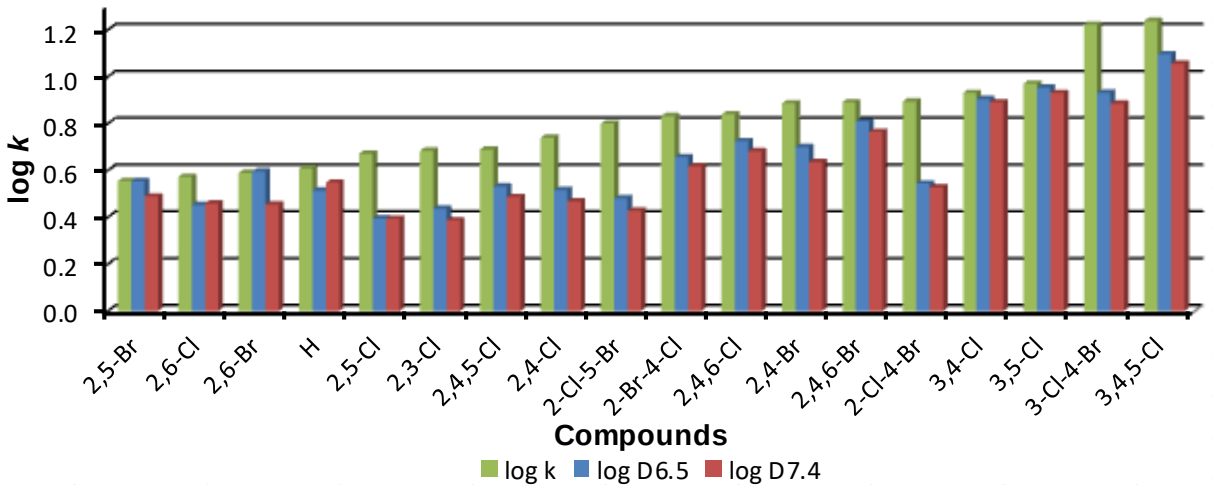


Figure 3. Order of individual derivatives arranged according to increasing log *k* values.

Regarding all these observations, it should be summarized that for these 1-hydroxynaphthalene-2-carboxamides on the anilide ring multisubstituted, standard commercially available lipophilicity prediction programs are unable to provide relevant data due to the high incidence of intra- and intermolecular interactions. Due to the presence of an ionizable acidic phenolic group in the vicinity of the amide bond, there are also differences in the experimental values obtained for different mobile phase properties/compositions.

3. Experimental Section

Detailed synthesis and characterization of 1-hydroxy-*N*-phenylnaphthalene- 2-carboxamide (**1**) was reported by Gonec et al. [10], while characterization of ring-substituted chlorinated and brominated carboxanilides **2–17** is provided in [11].

Experimental determination of lipophilicity values (log *k*, log $D_{6.5}$, and log $D_{7.4}$) was performed under the same conditions and on the same device as described by Strharsky et al. [21].

Author Contributions: Conceptualization, T.G. and J.J.; methodology, T.G. and L.V.; investigation, L.V.; writing—original draft preparation, T.G., L.V. and J.J.; supervision, J.J.; funding acquisition, J.J. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Slovak Research and Development Agency (project APVV-22-0133) and by grant GUK/1143/2024.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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