



Chromatographic and Computational Study of Hydro-lipophilic Properties of *N*-Alkoxyphenylhydroxynaphthalenecarboxamides

Iva Kapustikova¹, Tomas Gonec², Jiri Kos¹, Josef Jampilek^{1,*}

¹ Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Comenius University, Odbojarov 10, 832 32 Bratislava, Slovakia; e-mail: josef.jampilek@gmail.com

² Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackeho 1, 612 42 Brno, Czech Republic

* Authors to whom correspondence should be addressed.

Abstract: *N*-Alkoxy-3-hydroxynaphthalene-2-carboxanilides, *N*-alkoxy-1-hydroxynaphthalene-2-carboxanilides and *N*-alkoxy-2-hydroxynaphthalene-1-carboxanilides were recently reported as series of compounds with antimycobacterial, antibacterial and herbicidal activity. As it was found that the lipophilicity of these significantly biologically effective agents determined their activity, in this study hydro-lipophilic properties of all three series are investigated. All fifty-seven anilides were analysed using the reversed-phase high performance liquid chromatography method for lipophilicity measurement. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using an end-capped non-polar C₁₈ stationary reversed-phase column. In the present study, the correlation between the logarithm of capacity factor *k* and log *P*/Clog *P* values calculated in various ways is discussed as well as the relationships between the lipophilicity and the chemical structure of the studied compounds.

Keywords: Hydroxynaphthalenecarboxamides; Lipophilicity determinations; Structure-lipophilicity relationships.

INTRODUCTION

One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, e.g. the transport of a molecule through membranes. The drugs most frequently cross biological barriers by the passive transport, which strongly depends on the lipophilicity. Therefore hydro-lipophilic properties are one of the most important physical characteristics of biologically active compounds [1,2]. The thermodynamic parameter describes the partitioning of a compound between an aqueous and an organic phases and is characterized by the partition (log *P*) coefficient [3]. Classical methods for the determination of these constants are time consuming and not always sufficiently reliable. Therefore, reversed-phase high performance liquid chromatography (RP-HPLC) methods have become

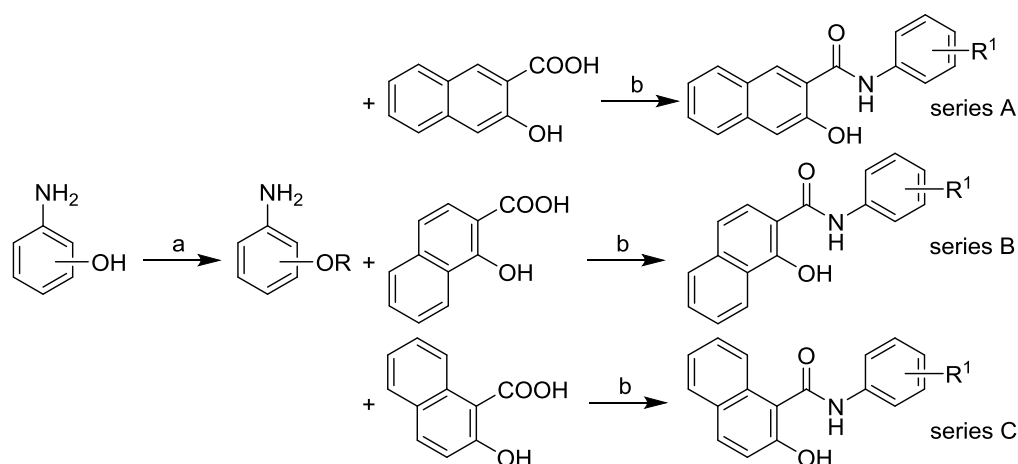
popular and widely used for lipophilicity measurement. A general procedure is the measurement of directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase using end-capped non-polar C₁₈ stationary RP columns and calculating the capacity factor *k* [4–8]. Log *k*, calculated from the capacity factor *k*, is used as the lipophilicity index converted to log *P* scale [4].

N-Alkoxy-3-hydroxynaphthalene-2-carboxanilides, *N*-alkoxy-1-hydroxynaphthalene-2-carboxanilides and *N*-alkoxy-2-hydroxynaphthalene-1-carboxanilides were recently synthesized and tested for their antibacterial and antimycobacterial activity as well as for their activity related to the inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts [9–14]. Since it was found that the lipophilicity of these significantly biologically effective agents determined their activity, in this study hydro-lipophilic properties of all three series are investigated. Thus this contribution is a follow-up work to the previous papers [5–8,15–25] aimed at the physicochemical properties of new biologically active agents.

RESULTS AND DISCUSSION

The condensation of hydroxynaphthalene-carboxylic acids with the appropriate alkoxy-substituted anilines using phosphorus trichloride in dry chlorobenzene under microwave conditions gave series A of *N*-substituted 3-hydroxynaphthalene-2-carboxanilides **1a–19a**, series B of *N*-substituted 1-hydroxynaphthalene-2-carboxanilides **1b–19b** and series C of *N*-substituted 2-hydroxynaphthalene-1-carboxanilides **1c–19c**. Unique commercially unavailable alkoxy-substituted anilines (i.e. except *o*-, *m*- and *p*-anisidine) were prepared by a modified procedure according to De Marco et al. [26] using direct alkylation of corresponding aminophenols by alkylbromides in the presence of sodium hydride, as reported recently [10], see Scheme 1.

Scheme 1. Synthesis of *N*-substituted 3-hydroxynaphthalene-2-carboxanilides **1a–19a** (series A), *N*-substituted 1-hydroxynaphthalene-2-carboxanilides **1b–19b** (series B) and *N*-substituted 2-hydroxynaphthalene-1-carboxanilides **1c–19c** (series C).



R = H (**1**), 2-OCH₃ (**2**), 3-OCH₃ (**3**), 4-OCH₃ (**4**), 2-OC₂H₅ (**5**), 3-OC₂H₅ (**6**), 4-OC₂H₅ (**7**), 2-OC₃H₇ (**8**), 3-OC₃H₇ (**9**), 4-OC₃H₇ (**10**), 2-OC₄H₉ (**11**), 3-OC₄H₉ (**12**), 4-OC₄H₉ (**13**), 2-OCH(CH₃)₂ (**14**), 3-OCH(CH₃)₂ (**15**), 4-OCH(CH₃)₂ (**16**), 2-OCH(CH₃)C₂H₅ (**17**), 3-OCH(CH₃)C₂H₅ (**18**), 4-OCH(CH₃)C₂H₅ (**19**)

Reagents and conditions: (a) R-Br, NaH, acetonitrile, room temperature, 24 h; (b) PCl₃, chlorobenzene, MW, 15 min. [10,13].

Lipophilicities ($\log P$ / $\text{Clog } P$ data) of all fifty-seven anilides were calculated using two commercially available programs: ACD/Percepta ver. 2012 and ChemBioDraw Ultra 13.0. In addition, the lipophilicity of the studied compounds was investigated by means of RP-HPLC determination of capacity factors k with a subsequent calculation of $\log k$. The results are shown in Tables 1–3.

The ChemBioDraw software does not distinguish the lipophilicity ($\log P$ and $\text{Clog } P$) values of neither individual anilide positional isomers within individual series nor lipophilicity among series A, B and C, and therefore these values are listed only in Tables 1–3 without other discussion. $\log P$ values of series A and B calculated by ACD/Percepta were not distinguished as well; nevertheless, the $\log P$ values of individual positional isomers differ. Therefore, the conformity of experimental and calculated $\log P$ (ACD) values are plotted in Figure 1. Based on these results, it can be stated that $\log P$ (ACD) values have a good match with experimentally determined $\log k$ of series A ($r = 0.9751$, $n = 19$); worse match can be observed for series B ($r = 0.8474$, $n = 19$); and the worst results are given by ACD/Percepta for series C ($r = 0.7939$, $n = 19$). These differences between experimental and calculated results can denote intramolecular interactions, i.e. the influence of spatially close second benzene nucleus of the naphthalene scaffold to the phenolic moiety (series B) or the amide moiety (series C).

Table 1. Structure of *N*-substituted 3-hydroxynaphthalene-2-carboxanilides **1a–19a** (series A), calculated lipophilicities ($\log P$ / $\text{Clog } P$) and determined $\log k$ of investigated compounds.

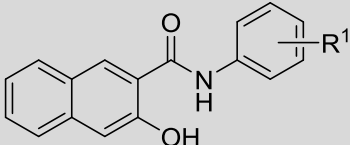
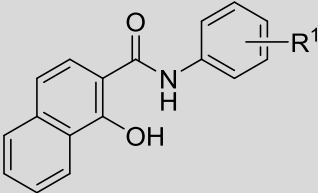
					
Comp.	R ¹	$\log k$	$\log P$ (ACD)	$\log P$ (ChemBioDraw)	$\text{Clog } P$ (ChemBioDraw)
1a	H	0.3927	4.52	3.45	4.4462
2a	2-OCH ₃	0.3982	4.61	3.32	3.9316
3a	3-OCH ₃	0.4055	4.56	3.32	4.5216
4a	4-OCH ₃	0.3374	4.37	3.32	4.5216
5a	2-OC ₂ H ₅	0.5570	4.92	3.66	4.4606
6a	3-OC ₂ H ₅	0.5682	4.88	3.66	5.0506
7a	4-OC ₂ H ₅	0.4916	4.67	3.66	5.0506
8a	2-OC ₃ H ₇	0.7221	5.26	4.14	4.9896
9a	3-OC ₃ H ₇	0.7672	5.21	4.14	5.5796
10a	4-OC ₃ H ₇	0.6963	5.27	4.14	5.5796
11a	2-OC ₄ H ₉	0.9136	5.60	4.56	5.5186
12a	3-OC ₄ H ₉	0.9711	5.54	4.56	6.1086
13a	4-OC ₄ H ₉	0.8961	5.60	4.56	6.1086
14a	2-OCH(CH ₃) ₂	0.6360	5.18	3.98	4.7696
15a	3-OCH(CH ₃) ₂	0.6723	5.13	3.98	5.3596
16	4-OCH(CH ₃) ₂	0.6017	5.11	3.98	5.3596
17a	2-OCH(CH ₃)CH ₂ CH ₃	0.7956	5.52	4.46	5.2986
18a	3-OCH(CH ₃)CH ₂ CH ₃	0.8670	5.47	4.46	5.8886
19a	4-OCH(CH ₃)CH ₂ CH ₃	0.7977	5.46	4.46	5.8886

Table 2. Structure of *N*-substituted 1-hydroxynaphthalene-2-carboxanilides **1b–19b** (series B), calculated lipophilicities ($\log P$ / $\text{Clog } P$) and determined $\log k$ of investigated compounds.

					
Comp.	R ¹	$\log k$	$\log P$ (ACD)	$\log P$ (ChemBioDraw)	$\text{Clog } P$ (ChemBioDraw)
1b	H	0.6755	4.52	3.45	4.4462
2b	2-OCH ₃	0.8593	4.61	3.32	3.9316
3b	3-OCH ₃	0.6828	4.56	3.32	4.5216
4b	4-OCH ₃	0.6239	4.37	3.32	4.5216
5b	2-OC ₂ H ₅	1.0940	4.92	3.66	4.4606
6b	3-OC ₂ H ₅	0.8353	4.88	3.66	5.0506
7b	4-OC ₂ H ₅	0.7700	4.67	3.66	5.0506
8b	2-OC ₃ H ₇	1.3103	5.26	4.14	4.9896
9b	3-OC ₃ H ₇	1.0215	5.21	4.14	5.5796
10b	4-OC ₃ H ₇	0.9588	5.27	4.14	5.5796
11b	2-OC ₄ H ₉	1.5122	5.60	4.56	5.5186
12b	3-OC ₄ H ₉	1.2088	5.54	4.56	6.1086
13b	4-OC ₄ H ₉	1.1537	5.60	4.56	6.1086
14b	2-OCH(CH ₃) ₂	1.2556	5.18	3.98	4.7696
15b	3-OCH(CH ₃) ₂	0.9355	5.13	3.98	5.3596
16b	4-OCH(CH ₃) ₂	0.8648	5.11	3.98	5.3596
17b	2-OCH(CH ₃)CH ₂ CH ₃	1.4424	5.52	4.46	5.2986
18b	3-OCH(CH ₃)CH ₂ CH ₃	1.1291	5.47	4.46	5.8886
19b	4-OCH(CH ₃)CH ₂ CH ₃	1.0518	5.46	4.46	5.8886

As mentioned above, ACD/Percepta does not distinguish between $\log P$ values of series A and B. In general, both series are characterized by slightly higher calculated lipophilicity than series C with the exception of compound **7c** ($R = 4\text{-OC}_2\text{H}_5$) that has higher $\log P$ value than compounds **7a** and **7b**. Within individual series, the lipophilicity increases as follows: $\text{OCH}_3 < \text{OC}_2\text{H}_5 < \text{OCH}(\text{CH}_3)_2 < \text{OC}_3\text{H}_7 < \text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3 < \text{OC}_4\text{H}_9$. The *ortho*-substituted derivatives showed the highest calculated $\log P$ values, while *para*-substituted derivatives demonstrated the lowest $\log P$ values, except **10a–c** ($R = 4\text{-OC}_3\text{H}_7$) and **13a–c** ($R = 4\text{-OC}_4\text{H}_9$) that have the same calculated lipophilicity values as the *ortho*-substituted derivatives. Compounds **4a–c** ($R = 4\text{-OCH}_3$) showed lower $\log P$ values than unsubstituted anilides **1a–c**. Much more interesting and probably more precise are the experimental results of lipophilicity expressed as $\log k$. These confirmed that series C possesses the lowest lipophilicity within these 3 series, see Figure 2. On the other hand, series B showed the highest $\log k$ values. *ortho*-Substituted derivatives of series B and C are more lipophilic than *meta*- and *para*-alkoxy substituted derivatives, while within series A, *meta*-substituted derivatives are slightly more lipophilic than *ortho*- and *para*-substituted anilides.

Table 3. Structure of *N*-substituted 2-hydroxynaphthalene-1-carboxanilides **1c–19c** (series C), calculated lipophilicities ($\log P$ / $\text{Clog } P$) and determined $\log k$ of investigated compounds.

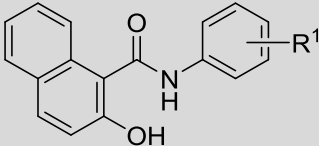
					
Comp.	R ¹	$\log k$	$\log P$ (ACD)	$\log P$ (ChemBioDraw)	$\text{Clog } P$ (ChemBioDraw)
1c	H	-0.0581	4.49	3.45	4.4462
2c	2-OCH ₃	0.2518	4.54	3.32	3.9316
3c	3-OCH ₃	0.1106	4.51	3.32	4.5216
4c	4-OCH ₃	-0.1149	4.30	3.32	4.5216
5c	2-OC ₂ H ₅	0.4759	4.88	3.66	4.4606
6c	3-OC ₂ H ₅	0.1175	4.83	3.66	5.0506
7c	4-OC ₂ H ₅	0.0542	4.76	3.66	5.0506
8c	2-OC ₃ H ₇	0.6639	5.22	4.14	4.9896
9c	3-OC ₃ H ₇	0.3209	5.14	4.14	5.5796
10c	4-OC ₃ H ₇	0.2622	5.21	4.14	5.5796
11c	2-OC ₄ H ₉	0.8578	5.53	4.56	5.5186
12c	3-OC ₄ H ₉	0.5161	5.49	4.56	6.1086
13c	4-OC ₄ H ₉	0.4604	5.54	4.56	6.1086
14c	2-OCH(CH ₃) ₂	0.6145	5.15	3.98	4.7696
15c	3-OCH(CH ₃) ₂	0.2214	5.06	3.98	5.3596
16c	4-OCH(CH ₃) ₂	0.1619	5.04	3.98	5.3596
17c	2-OCH(CH ₃)CH ₂ CH ₃	0.7927	5.47	4.46	5.2986
18c	3-OCH(CH ₃)CH ₂ CH ₃	0.4129	5.40	4.46	5.8886
19c	4-OCH(CH ₃)CH ₂ CH ₃	0.3621	5.40	4.46	5.8886

Figure 1. Comparison of experimentally found $\log k$ values with calculated $\log P$ (ACD/Percepta) of ring substituted *N*-alkoxyphenyl-3-hydroxynaphthalene-2-carboxanilides **1a–19a** (series A), *N*-alkoxyphenyl-1-hydroxynaphthalene-2-carboxanilides **1b–19b** (series B) and *N*-alkoxyphenyl-2-hydroxynaphthalene-1-carboxanilides **1c–19c** (series C).

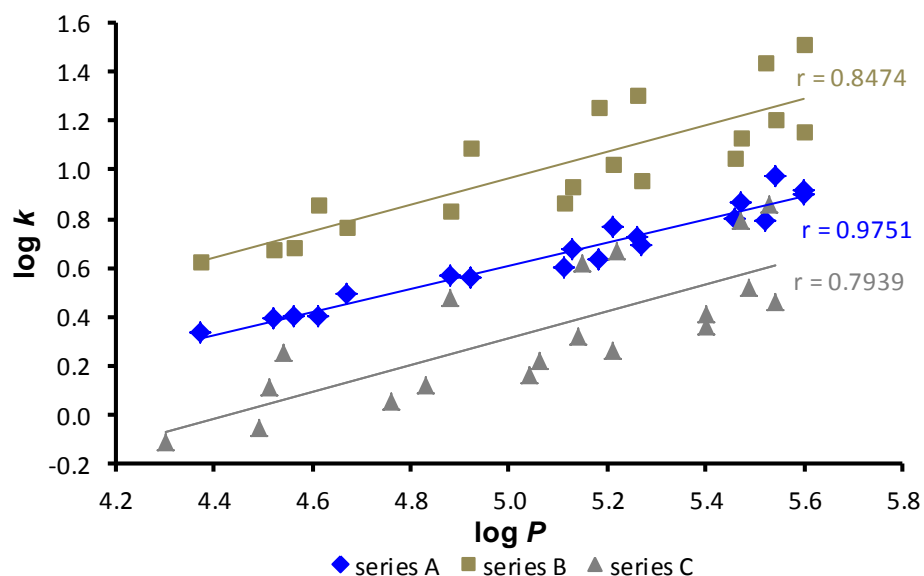
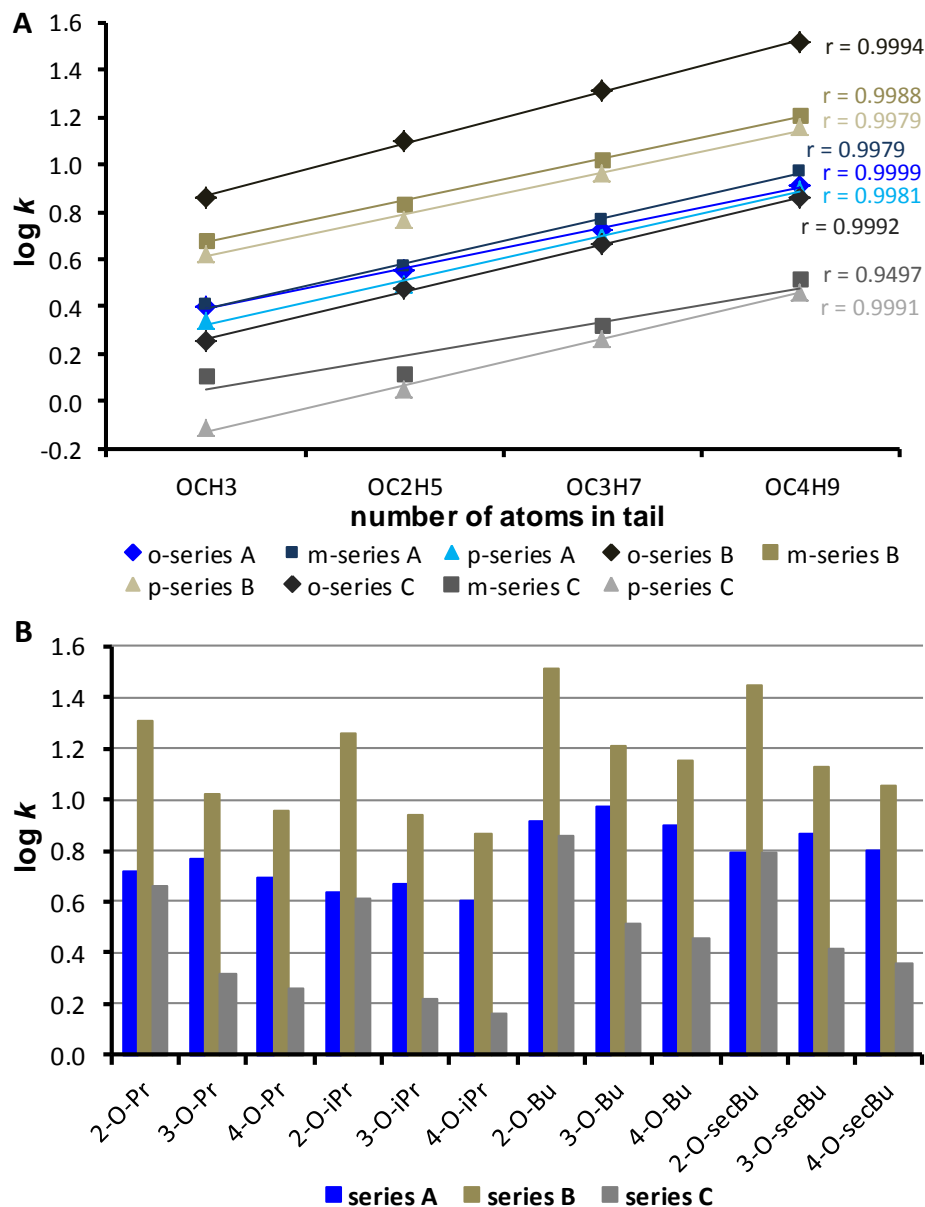


Figure 2. Comparison of experimentally determined $\log k$ values of all three discussed series of *N*-alkoxy substituted compounds: 3-hydroxynaphthalene-2-carboxanilides **2a–19a** (series A), 1-hydroxy-naphthalene-2-carboxanilides **2b–19b** (series B) and 2-hydroxynaphthalene-1-carboxanilides **2c–19c** (series C): only unbranched alkoxy chains (A), and branched alkoxy chains and their unbranched isomers (B).



Otherwise, lipophilicity logically linearly (correlation factors ranged from 0.9497 to 0.9999; $n=4$) increases with the lengthening of the unbranched alkoxy tail (see Fig. 2A). Nevertheless, it should be noted that unsubstituted compounds **1a–c** showed higher experimental lipophilicity than compounds **4a–c** ($R = 4\text{-OCH}_3$), see Table 1. Branched alkoxy substituents, i.e. compounds **14a–c**, **15a–c**, **16a–c** ($R = \text{OCH}(\text{CH}_3)_2$) and **17a–c**, **18a–c**, **19a–c** ($R = \text{OCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$) showed less lipophilicity than their unbranched *n*-alkoxy isomers **8a–c**, **9a–c**, **10a–c** and **11a–c**, **12a–c**, **13a–c** (see Fig. 2B), which corresponds to our previously reported results, e.g., [15,22].

All these observations correspond to biological activities; e.g., lipophilic *N*-(alkoxyphenyl)-1-hydroxynaphthalene-2-carboxamides of series B demonstrated higher potency against non-tuberculous mycobacteria *Mycobacterium smegmatis* and *M. kansasii* than compounds of

series A and C, but also stronger antiproliferative effect against the human monocytic leukemia THP-1 cell line [10,13]. In addition, compounds of series B significantly affected photosystem II, which resulted in the inhibition of photosynthetic electron transport in spinach (*Spinacia oleracea* L.) chloroplasts [14].

Thus, it can be assumed, that experimentally determined $\log k$ values specify lipophilicity within the individual series of compounds and can be used as a useful tool for other investigation of structure-activity relationships within these series of biologically effective compounds.

EXPERIMENTAL

Synthesis

The discussed *N*-alkoxyphenylhydroxy-naphthalenecarboxamides **1a–7c** were synthesized using microwave-assisted synthesis as described recently by Kos et al. [9] and Gonec et al. [10–13] The studied compounds are presented in Table 1.

Lipophilicity determination by HPLC (capacity factor k /calculated $\log k$)

The HPLC separation module Waters[®] e2695 equipped with Waters 2487 Dual λ Absorbance Detector 2487 (Waters Corp., Milford, MA, USA) were used. The chromatographic column Symmetry[®] C₁₈ 5 μ m, 4.6×250 mm, Part No. W21751W016 (Waters Corp.) was used. The HPLC separation process was monitored by Empower[™] 3 Chromatography Data Software (Waters Corp.). Isocratic elution by a mixture of MeOH p.a. (72%) and H₂O-HPLC Mili-Q grade (28%) as a mobile phase was used. The total flow of the column was 1.0 mL/min, injection 20 μ L, column temperature 40 °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 Empower[™] 3 Chromatography Data 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 using an unretained analyte. Each experiment was repeated three times. $\log k$, calculated from the capacity factor k , is used as the lipophilicity index converted to $\log P$ scale. The $\log k$ values of individual compounds are shown in Tables 1–3.

Lipophilicity calculations

$\log P$, i.e. the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs ACD/Percepta 2012 (Advanced Chemistry Development, Inc., Toronto, ON, Canada, 2012) and ChemBioDraw Ultra 13.0 (CambridgeSoft, PerkinElmer Inc. USA). $\log P$ values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were generated by means of ChemBioDraw Ultra 13.0 (CambridgeSoft, PerkinElmer Inc. USA) software. The results are shown in Tables 1–3.

ACKNOWLEDGEMENTS

This study was supported by grants FaF UK/13/2016, FaF UK/4/2017 and by SANOFI-AVENTIS Pharma Slovakia.

REFERENCES

1. Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **2001**, *46*, 3–26.

2. Lipinski, C.A. Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov. Today: Technologies*. **2004**, *1*, 337–341.
3. Kerns, E.H.; Di, L. *Drug-like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*. Academic Press: San Diego, CA, USA, 2008.
4. Pliska, V. In: *Lipophilicity in Drug Action and Toxicology* (Methods and Principles in Medicinal Chemistry, Vol. 4). Pliska, V., Testa, B., van der Waterbeemd, H. (Eds.). 1st Ed. Wiley-VCH: Weinheim, Germany, 1996, pp. 1–6.
5. Kucerova-Chlupacova, M.; Opletalova, V.; Jampilek, J.; Dolezel, J.; Dohnal, J.; Pour, M.; Kunes, J.; Vorisek, V. New hydrophobicity constants of substituents in pyrazine rings derived from RP-HPLC study. *Coll. Czech. Chem. Commun.* **2008**, *73*, 1–18.
6. Musilek, K.; Jampilek, J.; Dohnal, J.; Jun, D.; Gunn-Moore, Fr.; Dolezal, M.; Kuca, K. RP-HPLC determination of the lipophilicity of bispyridinium reactivators of acetylcholinesterase bearing a but-2-ene connecting linker. *Anal. Bioanal. Chem.* **2008**, *391*, 367–372.
7. Musiol, R.; Jampilek, J.; Podeszwa, B.; Finster, J.; Tabak, D.; Dohnal, J.; Polanski, J. RP-HPLC determination of drug lipophilicity in series of quinoline derivatives. *Cent. Eur. J. Chem.* **2009**, *7*, 586–597.
8. Tengler, J.; Kapustikova, I.; Stropnický, O.; Mokry, P.; Oravec, M.; Csollei, J.; Jampilek, J. Synthesis of New (arylcabonyloxy)aminopropanol derivatives and the determination of their physico-chemical properties. *Cent. Eur. J. Chem.* **2013**, *11*, 1757–1767.
9. Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Gonec, T.; Bobal, P.; Kauerovala, T.; Oravec, M.; Kollar, P.; Cizek, A.; Kralova, K.; Jampilek, J. Antibacterial and herbicidal activity of ring-substituted 3-hydroxynaphthalene-2-carboxanilides. *Molecules* **2013**, *18*, 7977–7997.
10. Gonec, T.; Zadrazilova, I.; Nevin, E.; Kauerovala, T.; Pesko, M.; Kos, J.; Oravec, M.; Kollar, P.; Coffey, A.; O'Mahony, J.; Cizek, A.; Kralova, K.; Jampilek, J. Synthesis and biological evaluation of *N*-alkoxyphenyl-3-hydroxynaphthalene-2-carboxanilides. *Molecules* **2015**, *20*, 9767–9787.
11. Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Bobal, P.; Kollar, P.; Cizek, A.; Kralova, K.; Jampilek, J. Antimycobacterial and herbicidal activity of ring-substituted 1-hydroxynaphthalene-2-carboxanilides. *Bioorg. Med. Chem.* **2013**, *21*, 6531–6541.
12. Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Govender, R.; Keltosova, S.; Chambel, B.; Pereira, D.; Kollar, P.; Imramovsky, A.; O'Mahony, J.; Coffey, A.; Cizek, A.; Kralova, K.; Jampilek, J. Antibacterial and herbicidal activity of ring-substituted 2-hydroxynaphthalene-1-carboxanilides. *Molecules* **2013**, *18*, 9397–9419.
13. Gonec, T.; Pospisilova, S.; Kauerovala, T.; Kos, J.; Dohanosova, J.; Oravec, M.; Kollar, P.; Coffey, A.; Liptaj, T.; Cizek, A.; Jampilek, J. *N*-Alkoxyphenylhydroxynaphthalene-carboxamides and their antimycobacterial activity. *Molecules* **2016**, *21*, 1068.
14. Gonec, T.; Kralova, K.; Pesko, M.; Jampilek, J. Antimycobacterial *N*-alkoxyphenylhydroxynaphthalenecarboxamides affecting photosystem II. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1881–1885.
15. Jampilek, J.; Opletalova, V.; Grafnetterova, T.; Dohnal, J. Thiosemicarbazones of acetylpyrazines: Preparation and their hydrophobic properties. *ECSOC-9*, November 1-30, **2005**, a001, <http://www.usc.es/congresos/ecsoc/9/GOS/a001/index.htm>.
16. Jampilek, J.; Vinsova, J.; Grafnetterova, T.; Dohnal, J. Synthesis and hydrophobic properties of benzoxazoles. *ECSOC-9*, November 1-30, **2005**, a008, <http://www.usc.es/congresos/ecsoc/9/GOS/a008/index.htm>.

17. Opletalova, V.; Jampilek, J.; Chlupacova, M.; Dolezel, J.; Grafnetterova, T.; Dohnal, J. Chromatographic and computational study of hydrophobic properties of ring substituted pyrazinecarbonitriles and acetylpyrazines. *ECSOC-9*, November 1-30, **2005**, c004, <http://www.usc.es/congresos/ecsoc/9/BOCNP/c004/index.htm>.
18. Jampilek, J.; Vinsova, J.; Dohnal, J. Synthesis and hydrophobic properties of substituted 2-aryl-5,7-di-*tert*-butylbenzoxazoles. *ECSOC-10*, November 1-30, **2006**, a003, <http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm>.
19. Jampilek, J.; Opletalova, V.; Dohnal, J. *N,N*-Dimethylthiosemicarbazones of acetylpyrazines: Preparation and their hydrophobic properties. *ECSOC-10*, November 1-30, **2006**, a004, <http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm>.
20. Jampilek, J.; Palek, L.; Dolezal, M. Synthesis and hydrophobic properties of some substituted 3-arylaminopyrazine-2,5-dicarbonitriles. *ECSOC-10*, November 1-30, **2006**, a019, <http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm>.
21. Jampilek, J.; Vinsova, J.; Kaderavkova, Z.; Dohnal, J. Synthesis and hydrophobic properties of new 2-aryl-5,7-di-*tert*-butylbenzoxazoles. *ECSOC-11*, November 1-30, **2007**, a009, http://www.usc.es/congresos/ecsoc/11/hall_aGOS/a009/index.htm.
22. Jampilek, J.; Opletalova, V.; Dolezel, Jan and Dohnal, J. Preparation and hydrophobic properties of 5-arylalkylidenerhodanines. *ECSOC-11*, November 1-30, **2007**, a012, http://www.usc.es/congresos/ecsoc/11/hall_aGOS/a012/index.htm.
23. Dolezal, M.; Jampilek, J.; Bielez, S.; Kunes, J. Substituted pyrazine-2,5-dicarboxamides: Synthesis, hydrophobicity parameters, and antimycobacterial evaluation. *ECSOC-11*, November 1-30, **2007**, c005, http://www.usc.es/congresos/ecsoc/11/hall_cBCNP/c005/index.htm.
24. Opletalova, V.; Jampilek, J.; Dolezel, J.; Hirsova, P.; Dohnal, J. Rhodanineacetic acid derivatives as potential drugs: Preparation and hydrophobic properties of 5-arylalkylidene-3-carboxymethylrhodanines. *ECSOC-12*, November 1-30, **2008**, c0006, <http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm>.
25. Dolezal, M.; Osicka, Z.; Zitko, J.; Kunes, J.; Jampilek, J.; Vejsova, M.; Buchta V.; Kralova, K. Substituted *N*-phenylpyrazine-2-carboxamides, their synthesis, hydrophilic properties and evaluation of their antimycobacterial, antifungal and photosynthesis-inhibiting activity. *ECSOC-14*, November 1-30, **2010**, B380, <http://www.sciforum.net/conference/ecsoc-14/paper/380>.
26. De Marco, A.; De Candia, M.; Carotti, A.; Cellamare, S.; De Candia, E.; Altomare, C. Lipophilicity-related inhibition of blood platelet aggregation by nipecotic acid anilides. *Eur. J. Pharm. Sci.* **2004**, 22, 153–164.