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Preparation and Hydro-Lipophilic Properties of Methoxylated and Methylated 1-Hydroxynaphthalene-2-Carboxanilides †

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Abstract: A series of variously methoxylated and methylated *N*-aryl-1-hydroxynaphthalene-2-carboxanilides was prepared and characterized as potential anti-invasive agents. As it is known that lipophilicity significantly influences the biological activity of compounds, the hydro-lipophilic properties of these mono-, di- and tri-substituted 1-hydroxynaphthalene-2-carboxanilides are investigated in the study. All the discussed hydroxynaphthalene derivatives were analyzed using the reversed-phase, high-performance liquid chromatography method, to measure lipophilicity. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase, using an end-capped, non-polar C_{18} stationary reversed-phase column. The present study discusses the correlations between the logarithm of the capacity factor *k* and log *P*/Clog *P* values, calculated in various ways, as well as the relationships between the lipophilicity and the chemical structure of the studied compounds.

Keywords: hydroxynaphthalene carboxamides; synthesis; lipophilicity determinations; structure-lipophilicity relationships

1. Introduction

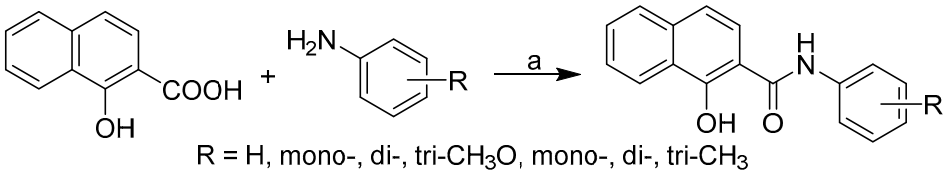
One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, e.g., the transport of a molecule through membranes. Drugs most frequently cross biological barriers by passive transport, which strongly depends on lipophilicity. Therefore, hydro-lipophilic properties are some of the most important physical characteristics of biologically-active compounds [1,2]. The thermodynamic parameter, characterized by the partition (log *P*)

coefficient, describes the partitioning of a compound between an aqueous and an organic phase [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 are widely used for lipophilicity measurements. 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 C_{18} stationary RP columns and calculating the capacity factor *k* [4–9]. Log *k*, calculated from the capacity factor *k*, is used as the lipophilicity index, and converted to log *P* scale [4].

Ring-substituted 1-hydroxynaphthalene-2-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 [10–13]. The new methoxy and methyl multisubstituted derivatives expand the spectrum of substitutions in the carboxanilide part of the molecule. As it was found that the lipophilicity of these significantly biologically-effective agents [10–13] determines their activity, this study investigated and compared the hydro-lipophilic properties of new methoxy and methyl multisubstituted 1-hydroxynaphthalene-2-carboxanilides with the hydro-lipophilic properties of recently-prepared monosubstituted *N*-alkoxy-1-hydroxy-naphthalene-2-carboxanilides and *N*-alkyl-1-hydroxy- naphthalene-2-carboxanilides. This contribution is a follow-up work to the previous papers [5–9; 14–24] aimed at the investigation of the physicochemical properties of new, biologically-active agents.

2. Results and Discussion

The condensation of 1-hydroxynaphthalene-2-carboxylic acid with the appropriately substituted anilines, using phosphorus trichloride in dry chlorobenzene, under microwave conditions, gave a series of methoxylated and methylated *N*-aryl-1-hydroxynaphthalene-2-carboxanilides **1–17**, as shown in Scheme 1.



Scheme 1. Synthesis of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1–17**. Reagents and conditions: (a) PCl_3, chlorobenzene, MW, 15 min. [10,11,13].

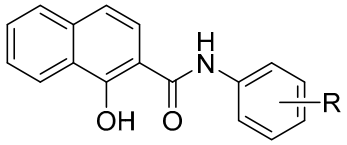
The lipophilicities (log *P*/Clog *P* data) of all seventeen anilides were calculated using two commercially-available programs: ACD/Percepta, ver. 2012, and ChemBioDraw Ultra 13.0. In addition, the lipophilicity of the studied compounds was investigated by means of the RP-HPLC determination of capacity factors *k*, with a subsequent calculation of log *k*. The results are shown in Table 1.

Log *P* values, calculated by the ChemBioDraw software for individual anilide positional isomers, except for unsubstituted compound **1** and trisubstituted compounds **7** and **14**, are not distinguished; therefore, these values are listed only in Table 1 without further discussion. Log *P* values of methylated *ortho*-, *meta*- and *para*-isomers/derivatives **8–10**, **11/13** and **15–17,** calculated by ACD/Percepta, were not distinguished as well. Clog *P* values, calculated by ChemBioDraw, provided the best results; these parameters are not distinguished for isomers **3**/**4** (R = 3-OCH_3, R = 4-OCH_3) and isomers **9**/**10** (R = 3-CH_3, R = 4-CH_3), as can be seen in Table 1.

The conformity of the experimental and calculated log *P* (ACD) values of methoxylated derivatives are plotted in Figure 1, while the conformity of the experimental and calculated Clog *P* (ChemBioDraw) values of the substituted compounds are illustrated in Figure 2. Based on these results, it can be stated that log *P* (ACD) values for methoxy derivatives **2–7** have a good match with experimentally-determined log *k* (r = 0.8983, n = 6), as shown in Figure 1. In addition, log *k* versus Clog *P* of the methoxy derivatives have a poor match (r = 0.2793, n = 6), seen in Figure 2A, contrary

to the dependence of log *k* on Clog *P* of methyl derivatives **8–14**, that have an excellent match (r = 0.9709, n = 7), as can be seen in Figure 2B. A poor match (r = 0.6652, n = 3) can also be observed for methoxymethyl derivatives **15–17**, shown in Figure 2C. In general, these differences between the experimental results of log *k* and the calculated log *P* values can denote intramolecular interactions, i.e., influences of the spatially-close phenolic moiety, the amide moiety, and substituents on the anilide ring.

Table 1. Structure of *N*-substituted 1-hydroxynaphthalene-2-carboxanilides **1–17**, calculated lipophilicities (*log P*/Clog *P*) and experimentally determined log *k* values of investigated compounds.



Comp.	R	log *k*	log *P* (ACD)	log *P* (ChemBioDraw)	Clog *P* (ChemBioDraw)
1	H	0.6769	4.52	3.45	4.4462
2	2-OCH_3	0.8584	4.61	3.32	3.9316
3	3-OCH_3	0.6713	4.56	3.32	4.5216
4	4-OCH_3	0.6284	4.37	3.32	4.5216
5	2,5-OCH_3	0.8712	4.77	3.19	3.95634
6	3,5-OCH_3	0.7048	4.49	3.19	4.54634
7	3,4,5-OCH_3	0.5603	4.30	3.07	3.80643
8	2-CH_3	0.5650	4.85	3.93	4.2952
9	3-CH_3	0.8235	4.85	3.93	4.9452
10	4-CH_3	0.8294	4.85	3.93	4.9452
11	2,5-CH_3	0.7155	5.03	4.42	4.7942
12	2,6-CH_3	0.5990	5.11	4.42	4.1442
13	3,5-CH_3	1.0030	5.03	4.42	5.4442
14	2,4,6-CH_3	0.7477	5.21	4.91	4.6432
15	2-OCH_3-5-CH_3	1.0603	4.89	3.81	4.4306
16	2-OCH_3-6-CH_3	0.4574	4.89	3.81	3.7806
17	5-OCH_3-2-CH_3	0.5362	4.99	3.81	4.3706

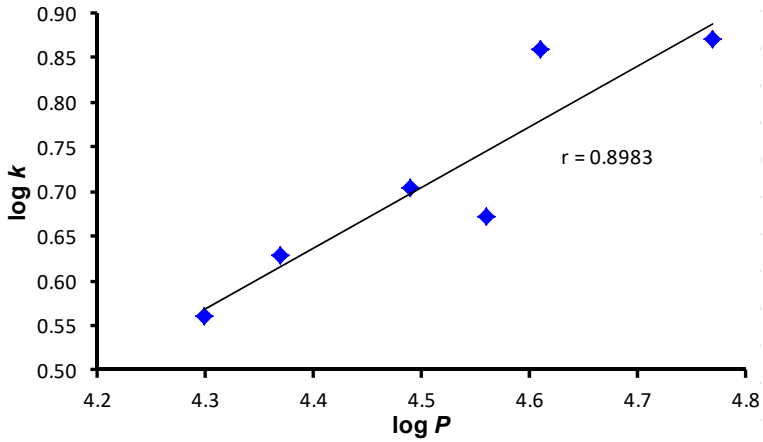


Figure 1. Comparison of experimentally-found log *k* values with calculated log *P* (ACD/Percepta) of *N*-methoxyphenyl-1-hydroxynaphthalene-2-carboxanilides **2–7**.

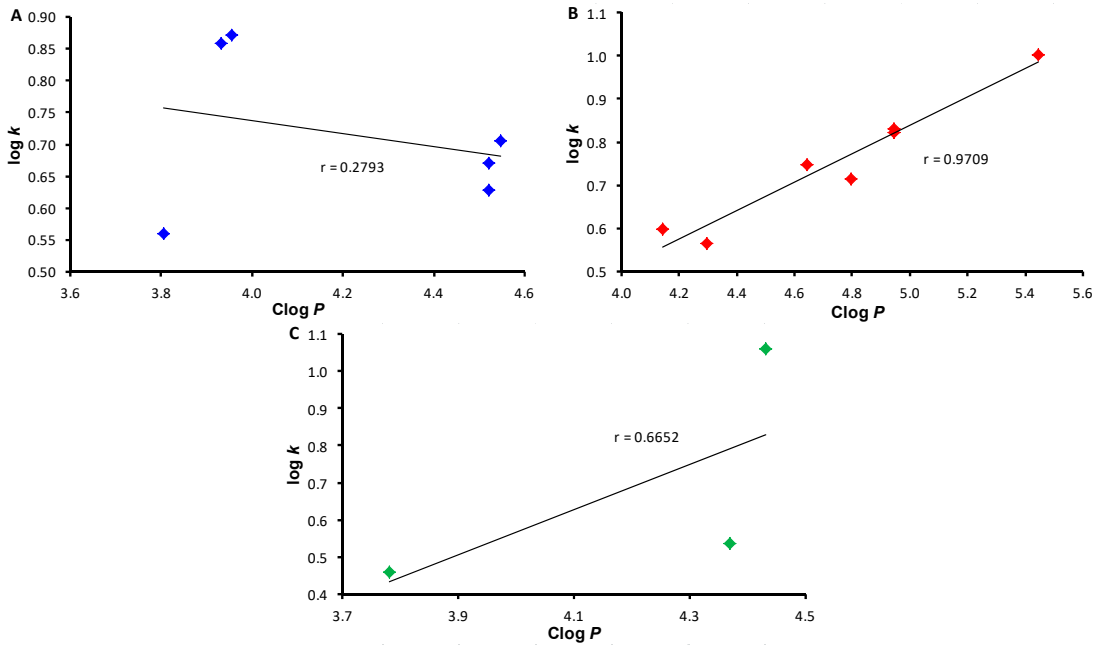


Figure 2. Comparison of experimentally-found log *k* values with calculated Clog *P* (ChemBioDraw) of *N*-methoxyphenyl-1-hydroxynaphthalene-2-carboxanilides **2–7** (**A**), *N*-methylphenyl-1-hydroxy-naphthalene-2-carboxanilides **8–14** (**B**) and methoxymethyl derivatives **15–17** (**C**).

The experimental results of lipophilicity expressed as log *k* are much more interesting and probably, more realistically, plot the influence of individual substituents on the overall lipophilicity of the individually discussed derivatives. Compound **15** (R = 2-OCH_3-5-CH_3, log *k* = 1.0603) showed the highest lipophilicity, while the lowest lipophilicity was demonstrated by compound **16** (R = 2-OCH_3-6-CH_3, log *k* = 0.4574). In the middle of the log *k* values of these two compounds, unsubstituted derivative **1** (log *k* = 0.6769) can be found, as seen in Figure 3. Although slightly higher than that of compound **16**, the second-lowest lipophilicity was observed for compound **17** (R = 5-OCH_3-2-CH_3). Based on these observations, it can be stated that the displacement of the methyl moiety from position 5 (*meta*) to 6 (*ortho*), or the preparation of "inverse" isomers (i.e., the elimination of the methoxy moiety from the *ortho* position; compare the compounds **15** and **17**), led to a sharp decrease of lipophilicity, which supports a theory about intramolecular interactions among substituents that are spatially close (especially in the *ortho* position) to the amide bond (-CONH–) and the phenolic moiety.

Within the series of monomethoxylated derivatives, the determined log *k* values decrease as follows: 2-OCH_3 (compound **2**) >> 3-OCH_3 (compound **3**) > 4-OCH_3 (compound **4**); while, within the series of monomethylated derivatives, an opposite trend can be observed, i.e., the lipophilicity decreases as follows: 4-CH_3 (compound **10**) > 3-CH_3 (compound **9**) >> 2-CH_3 (compound **8**). Only the 2-OCH_3 derivative showed a higher log *k* value than unsubstituted compound **1**, while the 4-CH_3 and 3-CH_3 derivatives showed higher log *k* values than unsubstituted compound **1**. 2,5-Dimethoxy derivative **5** possessed a higher log *k* value than compound **11** (R = 2,5-CH_3). On the other hand, compound **6** (R = 3,5-OCH_3) had a much lower log *k* value than compound **11** (R = 3,5-CH_3). Also, trimethyl derivative **14** showed a much higher lipophilicity than trimethoxy derivative **7**. In addition, 2,5-dimethoxy derivative **5** has a similar lipophilicity as monosubstituted 2-OCH_3 (compound **2**). In fact, the lipophilicity of di- and tri-methoxy derivatives decreases as follows: 2,5-OCH_3 (compound **5**) >> 3,5-OCH_3 (compound **6**) > 3,4,5-OCH_3 (compound **7**). These results also refer to the importance of *ortho*-placed methoxy moieties for the higher lipophilicity of the compounds. Among di- and tri-methyl substituted derivatives, the log *k* values decrease as follows: 3,5-CH_3 (compound **13**) >> 2,4,6-CH_3 (compound **14**) > 2,5-CH_3 (compound **11**) > 2,6-CH_3 (compound **12**). Contrary to the findings related to the methoxy moieties, *meta* and *para* substitution seems to be important for the higher lipophilicity of the methyl substituted derivatives.

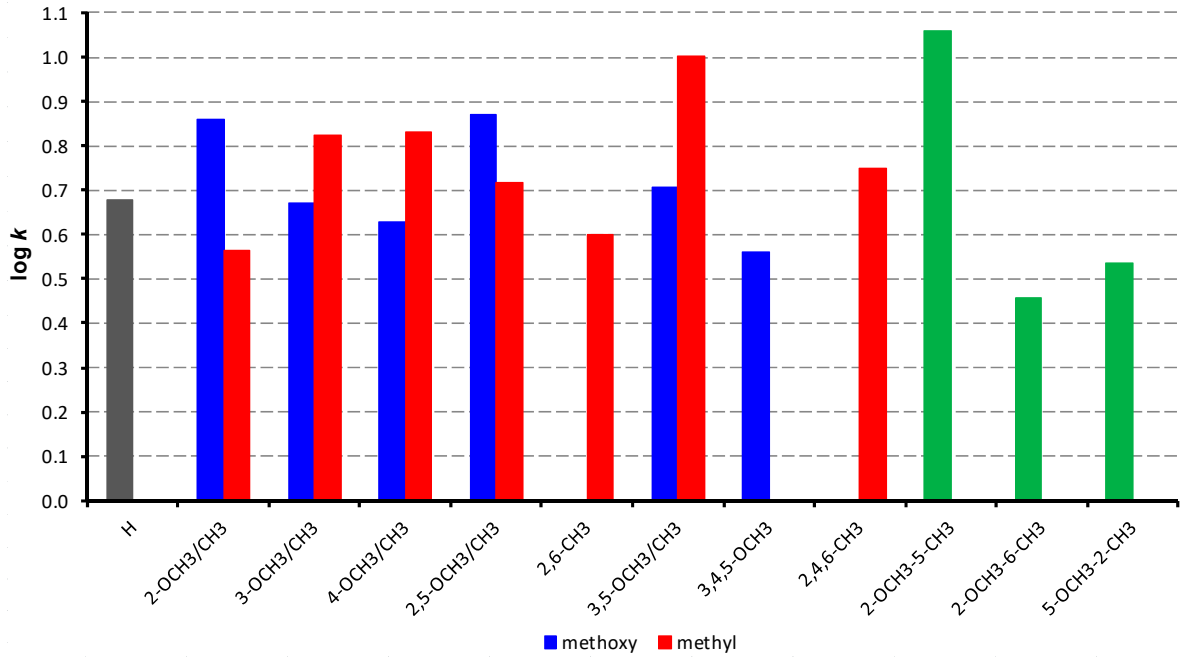


Figure 3. Comparison of experimentally-determined log *k* values of *N*-methoxy and *N*-methyl substituted compounds.

Thus, it can be assumed that experimentally-determined log *k* values specify lipophilicity within the individual series of compounds more precisely, and can be used as a useful tool for further investigation of structure-activity relationships within these methoxy/methyl substituted series of biologically-active compounds.

3. Experimental Section

3.1. General

All reagents were purchased from Merck (Sigma-Aldrich, St. Louis, MO, USA) and Alfa (Alfa-Aesar, Ward Hill, MA, USA). Reactions were performed using a CEM Discover SP microwave reactor (CEM, Matthews, NC, USA). Thin layer chromatography was performed on alumina-backed silica gel 40 F_{254} plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) light and evaluated in iodine vapor. Melting points were determined on a Kofler hot-plate apparatus (HMK Franz Kustner Nacht BG, Dresden, Germany) and are uncorrected. The purity of the final compounds was checked by a Waters Alliance 2695 XE HPLC separation module (Waters Corp., Milford, MA, USA). A detection wavelength of 210 nm was used. The peaks in the chromatogram of the solvent (blank) were deducted from the peaks in the chromatogram of the sample solution. The purity of the individual compounds was determined from the area peaks in the chromatogram of the sample solution. Infrared (IR) spectra were recorded on a Smart MIRacle™ ATR ZnSe for a Nicolet™ Impact 410 FT-IR spectrometer (Thermo Scientific, West Palm Beach, FL, USA). The spectra were obtained by the accumulation of 64 scans with 2 cm^{-1} resolution in the region of 4000–650 cm^{-1}. All ^{1}H and ^{13}C NMR spectra were recorded on an Agilent VNMRS 600 MHz system (600 MHz for ^{1}H and 151 MHz for ^{13}C; Agilent Technologies, Santa Clara, CA, USA) in DMSO-d_6. Chemical shifts are reported in ppm (δ) using the signal of the solvent (DMSO-d_6) as the reference (2.500, resp. 39.50) against the internal standard, $Si(CH_3)_4$. High-resolution mass spectra were measured using a Dionex UltiMate® 3000 high-performance liquid chromatograph (Thermo Scientific) coupled with a LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Fourier Transform Mass Spectrometer (Thermo Scientific), with an injection into a HESI-II Probe in the positive or negative mode.

3.2. Synthesis

General Procedure: 1-Hydroxynaphthalene-2-carboxylic acid (5.3 mmol), and the corresponding substituted aniline (5.3 mmol), were suspended in 30 mL of dry chlorobenzene. Phosphorous trichloride (2.65 mmol) was added dropwise, and the reacting mixture was heated using infrared flask-surface control of temperature at maximal allowed power 500 W and 130 °C in the microwave reactor for 15 min. The solvent was evaporated under reduced pressure. Subsequently, the solid residue was washed with 2 M HCl and the crude product was recrystallized from aqueous ethanol. All of the studied compounds are presented in Table 1.

Described anilides **1–4** and **8–10** were characterized recently by Gonec et al. [10].

N-(2,5-Dimethoxyphenyl)-1-hydroxynaphthalene-2-carboxamide (**5**). Yield 75%; Mp. 116–119 °C; HPLC purity 97.60%; IR (cm^{-1}): 3433, 1634, 1604, 1595, 1538, 1489, 1453, 1413, 1387, 1325, 1276, 1248, 1208, 1200, 1172, 1150, 1125, 1045, 1021, 951, 866, 835, 806, 792, 762, 723, 711; ^{1}H-NMR (DMSO-d_6), δ: 13.66 (s, 1H), 10.34 (s, 1H), 8.33 (dd, 1H, *J* = 7.7, *J* = 1.3 Hz), 8.07 (d, 1H, *J* = 8.6 Hz), 7.91 (d, 1H, *J* = 8.1 Hz), 7.67 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.59 (ddd, 1H, *J* = 8.3, *J* = 7.0, *J* = 1.2 Hz), 7.53 (d, 1H, *J* = 8.8 Hz), 7.43 (d, 1H, *J* = 2.9 Hz), 7.06 (d, 1H, *J* = 8.8 Hz), 6.81 (dd, 1H, *J* = 8.8, *J* = 2.9 Hz), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 168.20, 158.43, 152.92, 146.22, 135.97, 128.90, 127.58, 126.54, 125.90, 124.84, 123.62, 123.09, 118.42, 112.35, 111.51, 110.69, 108.95, 56.24, 55.48; HR-MS: $[M - H]^+$ calculated 322.10739 *m*/*z*, found 322.10892 *m*/*z*.

N-(3,5-Dimethoxyphenyl)-1-hydroxynaphthalene-2-carboxamide (**6**). Yield 83%; Mp. 118–121 °C; HPLC purity 96.95%; IR (cm^{-1}): 3266, 2999, 2936, 2833, 2540, 1614, 1595, 1549, 1514, 1470, 1453, 1423, 1332, 1296, 1257, 1227, 1194, 1154, 1064, 985, 846, 813, 799, 711; ^{1}H-NMR (DMSO-d_6), δ: 13.93 (s, 1H), 10.35 (s, 1H), 8.31 (d, 1H, *J* = 8.2 Hz), 8.11 (d, 1H, *J* = 9.2 Hz), 7.91 (d, 1H, *J* = 8.2 Hz), 7.67 (ddd, 1H, *J* = 8.0, *J* = 6.8, *J* = 1.3 Hz), 7.58 (ddd, 1H, *J* = 8.3, *J* = 7.0, *J* = 1.2 Hz), 7.47 (d, 1H, *J* = 8.9 Hz), 7.05 (d, 2H, *J* = 2.3 Hz), 6.36 (t, 1H, *J* = 2.3 Hz), 3.77 (s, 6H); ^{13}C-NMR (DMSO-d_6), δ: 169.49, 160.37, 159.91, 139.34, 135.99, 129.14, 127.47, 125.93, 124.65, 123.07, 123.01, 117.79, 107.60, 100.13, 96.69, 55.22; HR-MS: $[M - H]^+$ calculated 322.10738 *m*/*z*, found 322.10788 *m*/*z*.

1-Hydroxy-N-(3,4,5-trimethoxyphenyl)-naphthalene-2-carboxamide (**7**). Yield 66%; Mp. 177–180 °C; HPLC purity 98.47%; IR (cm^{-1}): 3375, 1627, 1594, 1549, 1504, 1452, 1410, 1393, 1328, 1293, 1278, 1230, 1210, 1186, 1127, 1001, 989, 950, 836, 825, 814, 793, 760, 725; ^{1}H-NMR (DMSO-d_6), δ: 14.01 (s, 1H), 10.36 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.2 Hz, 1H), 7.56–7.61 (m, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.17 (s, 2H), 3.81 (s, 6H), 3.67 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 169.29, 159.93, 152.63, 135.97, 134.56, 133.64, 129.13, 127.49, 125.94, 124.68, 123.08, 122.92, 117.78, 107.53, 99.84, 60.12, 55.86; HR-MS: for $C_{20}H_{19}NO_5$ $[M + H]^+$ calculated 354.133599 *m*/*z* found 354.13376 *m*/*z*.

N-(2,5-Dimethylphenyl)-1-hydroxynaphthalene-2-carboxamide (**11**). Yield 70%; Mp. 92–95 °C; HPLC purity 95.71%; IR (cm^{-1}): 3445, 1627, 1575, 1538, 1447, 1410, 1387, 1358, 1330, 1286, 1246, 1209, 1025, 882, 840, 805, 791, 757; ^{1}H-NMR (DMSO-d_6), δ: 14.28 (br.s, 1H), 10.34 (s, 1H), 8.30 (dd, 1H, *J* = 7.7, *J* = 1.3, Hz), 8.10 (d, 1H, *J* = 8.6 Hz), 7.91 (d, 1H, *J* = 8.1 Hz), 7.67 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.58 (ddd, 1H, *J* = 8.3, *J* = 7.0, *J* = 1.2 Hz), 7.46 (d, 1H, *J* = 8.9 Hz), 7.20 (d, 1H, *J* = 8.1 Hz), 7.17 (s, 1H), 7.06 (dd, 1H, *J* = 7.8, *J* = 1.3 Hz), 2.31 (s, 3H), 2.21 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 169.57, 159.96, 135.96, 135.35, 134.93, 131.22, 130.22, 129.02, 127.76, 127.51, 127.50, 125.88, 124.70, 123.03, 122.94, 117.87, 107.16, 20.41, 17.35; HR-MS: $[M - H]^+$ calculated 290.11756 *m*/*z*, found 290.11859 *m*/*z*.

N-(2,6-Dimethylphenyl)-1-hydroxynaphthalene-2-carboxamide (**12**). Yield 80%; Mp. 102–105 °C; HPLC purity 98.10%; IR (cm^{-1}): 3413, 1615, 1587, 1577, 1508, 1493, 1408, 1379, 1325, 1274, 1247, 1203, 1147, 950, 877, 817, 795, 773, 765, 727, 714; ^{1}H-NMR (DMSO-d_6), δ: 14.36 (s, 1H), 10.26 (s, 1H), 8.29 (dd, 1H, *J* = 8.3, *J* = 1.0 Hz), 8.13 (d, 1H, *J* = 8.9 Hz), 7.92 (d, 1H, *J* = 8.2 Hz), 7.67 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.57 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.46 (d, 1H, *J* = 8.8 Hz), 7.18 (s, 3H), 2.22 (s, 6H); ^{13}C-NMR (DMSO-d_6), δ: 169.57, 160.10, 135.96, 135.69, 134.09, 129.04, 127.87, 127.51, 127.25, 125.91, 124.71, 123.00, 122.76, 117.90, 106.78, 17.92; HR-MS: $[M - H]^+$ calculated 290.11756 *m*/*z*, found 290.11847 *m*/*z*.

N-(3,5-Dimethylphenyl)-1-hydroxynaphthalene-2-carboxamide (**13**). Yield 69%; Mp. 88–90 °C; HPLC purity 94.30%; IR (cm^{-1}): 3420, 1614, 1579, 1543, 1465, 1412, 1388, 1355, 1327, 1280, 1243, 1206, 1183, 864, 840, 803, 755, 726, 685; ^{1}H-NMR (DMSO-d_6), δ: 14.10 (br. s, 1H), 10.33 (s, 1H), 8.31 (d, 1H, *J* = 8.2 Hz), 8.12 (d, 1H, *J* = 8.9 Hz), 7.91 (d, 1H, *J* = 8.2 Hz), 7.67 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.58 (ddd, 1H, *J* = 8.2, *J* = 6.9, *J* = 1.3 Hz), 7.45 (d, 1H, *J* = 8.9 Hz), 7.37 (s, 2H), 6.84 (s, 1H), 2.30 (s, 6H); ^{13}C-NMR (DMSO-d_6), δ: 169.37, 159.96, 137.66, 137.37, 135.94, 129.07, 127.44, 126.26, 125.87, 124.65, 123.04, 123.01, 119.84, 117.75, 107.51, 21.00; HR-MS: $[M - H]^+$ calculated 290.11756 *m*/*z*, found 290.11917 *m*/*z*.

1-Hydroxy-N-(2,4,6-trimethylphenyl)-naphthalene-2-carboxamide (**14**). Yield 52%; Mp. 160–163 °C; HPLC purity 100%; IR (cm^{-1}): 3306, 1616, 1590, 1520, 1498, 1456, 1409, 1383, 1320, 1277, 1255, 1210, 1141, 1081, 1033, 1021, 946, 933, 844, 799, 765, 716, 708, 667; ^{1}H-NMR (DMSO-d_6), δ: 14.40 (s, 1H), 10.15 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.55–7.60 (m, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 6.98 (s, 2H), 2.28 (s, 3H), 2.17 (s, 6H); ^{13}C-NMR (DMSO-d_6), δ: 169.66, 160.09, 136.29, 135.94, 135.30, 131.44, 129.00, 128.47, 127.50, 125.88, 124.74, 123.00, 122.78, 117.85, 106.83, 20.54, 17.86; HR-MS: for $C_{20}H_{19}NO_2$ $[M - H]^+$ calculated 304.133205 *m*/*z* found 304.13416 *m*/*z*.

1-Hydroxy-N-(2-methoxy-5-methylphenyl)-naphthalene-2-carboxamide (**15**). Yield 74%; Mp. 106–108 °C; HPLC purity 99.62%; IR (cm^{-1}): 3433, 1627, 1592, 1539, 1488, 1436, 1411, 1387, 1361, 1322, 1285, 1275, 1249, 1207, 1172, 1149, 1120, 1033, 1022, 938, 874, 800, 790, 759, 726; ^{1}H-NMR (DMSO-d_6), δ: 13.92 (s, 1H), 10.23 (s, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 8.07 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.66 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.56–7.60 (m, 1H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.01–7.08 (m, 2H), 3.82 (s, 3H), 2.29 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 168.74, 159.06, 150.54, 135.99, 129.16, 128.98, 127.61, 127.15, 126.59, 125.93, 125.23, 124.84, 123.42, 123.12, 118.22, 111.54, 108.34, 55.79, 20.24; HR-MS: for $C_{19}H_{17}NO_3$ $[M + H]^+$ calculated 308.12812 *m*/*z* found 308.12842 *m*/*z*.

1-Hydroxy-N-(2-methoxy-6-methylphenyl)-naphthalene-2-carboxamide (**16**). Yield 58%; Mp. 177–179 °C; HPLC purity 99.96%; IR (cm^{-1}): 3400, 1616, 1595, 1575, 1511, 1498, 1472, 1412, 1389, 1328, 1309, 1267, 1252, 1208, 1147, 1080, 1033, 1023, 946, 846, 802, 791, 771, 759, 730, 720; ^{1}H-NMR (DMSO-d_6), δ: 14.40 (s, 1H), 10.07 (s, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 8.8 Hz, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.65–7.69 (m, 1H), 7.55–7.60 (m, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 3.77 (s, 3H), 2.20 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 169.80, 160.06, 155.24, 137.03, 135.93, 129.00, 128.01, 127.50, 125.87, 124.71, 123.73, 123.01, 122.98, 121.98, 117.77, 109.31, 106.96, 55.60, 17.68; HR-MS: for $C_{19}H_{17}NO_3$ $[M + H]^+$ calculated 308.12812 *m*/*z* found 308.12842 *m*/*z*.

1-Hydroxy-N-(5-methoxy-2-methylphenyl)-naphthalene-2-carboxamide (**17**). Yield 60%; Mp. 128–130 °C; HPLC purity 98.88%; IR (cm^{-1}): 3317, 1608, 1593, 1575, 1521, 1498, 1464, 1409, 1377, 1320, 1279, 1251, 1208, 1196, 1176, 1156, 1110, 1033, 1021, 962, 954, 868, 841, 807, 791, 757, 733, 712, 897; ^{1}H NMR (DMSO-d_6) δ 14.19 (s, 1H), 10.37 (s, 1H), 8.31 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.85 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.76 (s, 3H), 2.19 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 169.47, 159.88, 157.57, 135.97, 135.92, 130.93, 129.04, 127.52, 126.06, 125.90, 124.70, 123.05, 123.02, 117.90, 112.67, 112.53, 107.27, 55.23, 16.94; HR-MS: for $C_{19}H_{17}NO_3$ $[M + H]^+$ calculated 308.12812 *m*/*z* found 308.12842 *m*/*z*.

3.3. Lipophilicity Determination by HPLC (Capacity Factor k/Calculated log k)

The HPLC separation module Waters® e2695 equipped with a Waters 2996 PDA Detector (Waters Corp., Milford, MA, USA) was used. A chromatographic column Symmetry® C18 5 μm, 4.6 × 250 mm, Part No. W21751W016 (Waters Corp.) was used. The HPLC separation process was monitored by the Empower™ 3 Chromatography Data Software (Waters Corp.). Isocratic elution, by a mixture of MeOH p.a. (72%) and H_2O-HPLC Mili-Q grade (28%), was used as a mobile phase. The total flow of the column was 1.0 mL/min, the injection was 20 μL, the column temperature was 40 °C, and the sample temperature was 10 °C. A detection wavelength of 210 nm was chosen. A 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 and t_D is 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 [4]. The log k values of individual compounds are shown in Table 1.

3.4. 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., Waltham, MA, USA). Clog P values, i.e., the logarithm of the n-octanol/water partition coefficient based on established chemical interactions, were calculated by means of the ChemBioDraw Ultra 13.0 (CambridgeSoft) software. The results are shown in Table 1.

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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 Technol.* **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. Volume 4 Methods and Principles in Medicinal Chemistry. In *Lipophilicity in Drug Action and Toxicology*, 1st ed.; Pliska, V., Testa, B., van der Waterbeemd, H., Eds.; 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. Czechoslov. Chem. Commun.* **2008**, *73*, 1–18.
6. Musilek, K.; Jampilek, J.; Dohnal, J.; Jun, D.; Gunn-Moore, F.; 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.; Stropnicky, O.; Mokry, P.; Oravec, M.; Csollei, J.; Jampilek, J. Synthesis of New (arylcarbonyloxy)aminopropanol derivatives and the determination of their physico-chemical properties. *Cent. Eur. J. Chem.* **2013**, *11*, 1757–1767.
9. Kapustikova, I.; Bak, A.; Gonec, T.; Kos, J.; Kozik, V.; Jampilek, J. Investigation of Hydro-Lipophilic Properties of *N*-Alkoxyphenylhydroxynaphthalenecarboxamides. *Molecules* **2018**, *23*, 1635.
10. Gonec, T.; Kos, J.; Zadrazilova, I.; Pesko, M.; Keltosova, S.; Tengler, J.; Bobal, P.; Kollar, P.; Cizek, A.; Kralova, K.; et al. Antimycobacterial and herbicidal activity of ring-substituted 1-hydroxynaphthalene-2-carboxanilides. *Bioorg. Med. Chem.* **2013**, *21*, 6531–6541.
11. Gonec, T.; Pospisilova, S.; Kauerova, T.; Kos, J.; Dohanosova, J.; Oravec, M.; Kollar, P.; Coffey, A.; Liptaj, T.; Cizek, A.; et al. *N*-Alkoxyphenylhydroxynaphthalene-carboxamides and their antimycobacterial activity. *Molecules* **2016**, *21*, 1068.
12. Gonec, T.; Kralova, K.; Pesko, M.; Jampilek, J. Antimycobacterial *N*-alkoxyphenyl-hydroxynaphthalene-carboxamides affecting photosystem II. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1881–1885.

13. Gonec, T.; Kos, J.; Pesko, M.; Dohanosova, J.; Oravec, M.; Liptaj, T.; Kralova, K.; Jampilek, J. Halogenated 1-Hydroxynaphthalene-2-carboxanilides Affecting Photosynthetic Electron Transport in Photosystem II. *Molecules* **2017**, *22*, 1709.
14. Jampilek, J.; Opletalova, V.; Grafnetterova, T.; Dohnal, J. Thiosemicarbazones of acetylpyrazines: Preparation and their hydrophobic properties. In Proceedings of the ECSOC-9, Basel, Switzerland, 1–30 November 2005; p. a001. Available online: http://www.usc.es/congresos/ecsoc/9/GOS/a001/index.htm (accessed on 10 October 2018).
15. Jampilek, J.; Vinsova, J.; Grafnetterova, T.; Dohnal, J. Synthesis and hydrophobic properties of benzoxazoles. In Proceedings of the ECSOC-9, Basel, Switzerland, 1–30 November 2005; p. a008. Available online: http://www.usc.es/congresos/ecsoc/9/GOS/a008/index.htm (accessed on 10 October 2018).
16. 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. In Proceedings of the ECSOC-9, Basel, Switzerland, 1–30 November 2005; p. c004. Available online: http://www.usc.es/congresos/ecsoc/9/BOCNP/c004/index.htm (accessed on 10 October 2018).
17. Jampilek, J.; Vinsova, J.; Dohnal, J. Synthesis and hydrophobic properties of substituted 2-aryl-5,7-di-*tert*-butylbenzoxazoles. In Proceedings of the ECSOC-10, Basel, Switzerland, 1–30 November 2006; p. a003. Available online: http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm (accessed on 10 October 2018).
18. Jampilek, J.; Opletalova, V.; Dohnal, J. *N*,*N*-Dimethylthiosemicarbazones of acetylpyrazines: Preparation and their hydrophobic properties. In Proceedings of the ECSOC-10, Basel, Switzerland, 1–30 November 2006; p. a004. Available online: http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm (accessed on 10 October 2018).
19. Jampilek, J.; Palek, L.; Dolezal, M. Synthesis and hydrophobic properties of some substituted 3-arylaminopyrazine-2,5-dicarbonitriles. In Proceedings of the ECSOC-10, Basel, Switzerland, 1–30 November 2006; p. a019. Available online: http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm (accessed on 10 October 2018).
20. Jampilek, J.; Vinsova, J.; Kaderavkova, Z.; Dohnal, J. Synthesis and hydrophobic properties of new 2-aryl-5,7-di-tert-butylbenzoxazoles. In Proceedings of the ECSOC-11, Basel, Switzerland, 1–30 November 2007; p. a009. Available online: http://www.usc.es/congresos/ecsoc/11/hall_aGOS/a009/index.htm (accessed on 10 October 2018).
21. Jampilek, J.; Opletalova, V.; Dolezel, Jan and Dohnal, J. Preparation and hydrophobic properties of 5-arylalkylidenerhodanines. In Proceedings of the ECSOC-11, Basel, Switzerland, 1–30 November 2007; p. a012. Available online: http://www.usc.es/congresos/ecsoc/11/hall_aGOS/a012/index.htm (accessed on 10 October 2018).
22. Dolezal, M.; Jampilek, J.; Bielesz, S.; Kunes, J. Substituted pyrazine-2,5-dicarboxamides: Synthesis, hydrophobicity parameters, and antimycobacterial evaluation. In Proceedings of the ECSOC-11, Basel, Switzerland, 1–30 November 2007; p. c005. Available online: http://www.usc.es/congresos/ecsoc/11/hall_cBCNP/c005/index.htm (accessed on 10 October 2018).
23. 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. In Proceedings of the ECSOC-12, Basel, Switzerland, 1–30 November 2008; p. c0006. Available online: http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm (accessed on 10 October 2018).
24. Kapustikova, I.; Gonec, T.; Kos, J.; Jampilek, J. Chromatographic and computational study of hydro-lipophilic properties of N-alkoxyphenylhydroxynaphthalenecarboxamides. In Proceedings of the ECSOC-12, Basel, Switzerland, 1–30 November 2008; p. 4719. Available online: http://sciforum.net/conference/ecsoc-21/paper/4719 (accessed on 10 October 2018).