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 analysed 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. In the present study, 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 are discussed.

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

INTRODUCTION

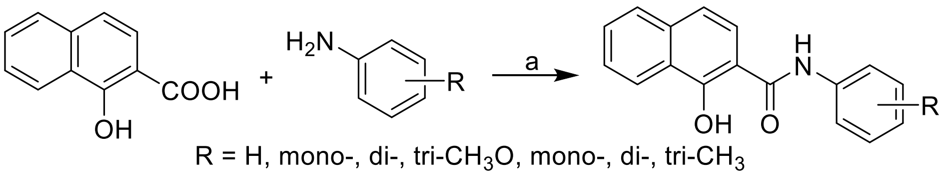
One of the major prerequisites for pharmacological screening and drug development is the prediction of absorption, e.g. the transport of a molecule through membranes. The drugs most frequently cross biological barriers by passive transport, which strongly depends on lipophilicity. Therefore, hydro-lipophilic properties are one 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 phases [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 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 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, in this study, the hydro-lipophilic properties of new methoxy and methyl multisubstituted 1-hydroxynaphthalene-2-carboxanilides are investigated and compared with hydro-lipophilic properties of recently prepared monosubstituted *N*-alkoxy-1-hydroxy-naphthalene-2-carboxanilides and *N*-alkyl-1-hydroxynaphthalene-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.

RESULTS AND DISCUSSION

The condensation of 1-hydroxynaphthalene-2-carboxylic acid with appropriate 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**, see Scheme 1.

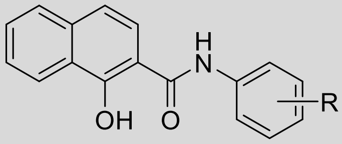
Scheme 1. Synthesis of ring-substituted 1-hydroxynaphthalene-2-carboxanilides **1**–**17**.



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 RP-HPLC determination of capacity factors *k* with a subsequent calculation of log *k*. The results are shown in Table 1.

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

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 other 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 only for isomers **3**/**4** (R = 3-OCH_3, R = 4-OCH_3) and isomers **9**/**10** (R = 3-CH_3, R = 4-CH_3), see Table 1.

The conformity of experimental and calculated log *P* (ACD) values of methoxylated derivatives are plotted in Figure 1, while the conformity of 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), see Figure 1, while log *k versus* Clog *P* of the methoxy derivatives have a poor match (r = 0.2793, n = 6), see Figure 2A, contrary to the dependence of log *k* on Clog *P* of methyl derivatives **8–14** with an excellent match (r = 0.9709, n = 7), see Figure 2B. A poor match (r = 0.6652, n = 3) can be also observed for methoxymethyl derivatives **15–17**, see Figure 2C. In general, these differences between experimental results of log *k* and 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.

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

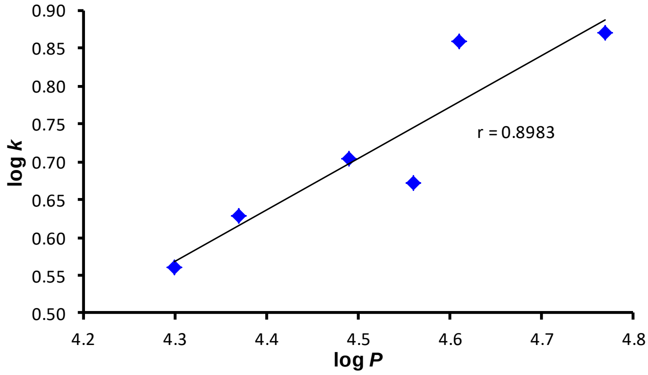
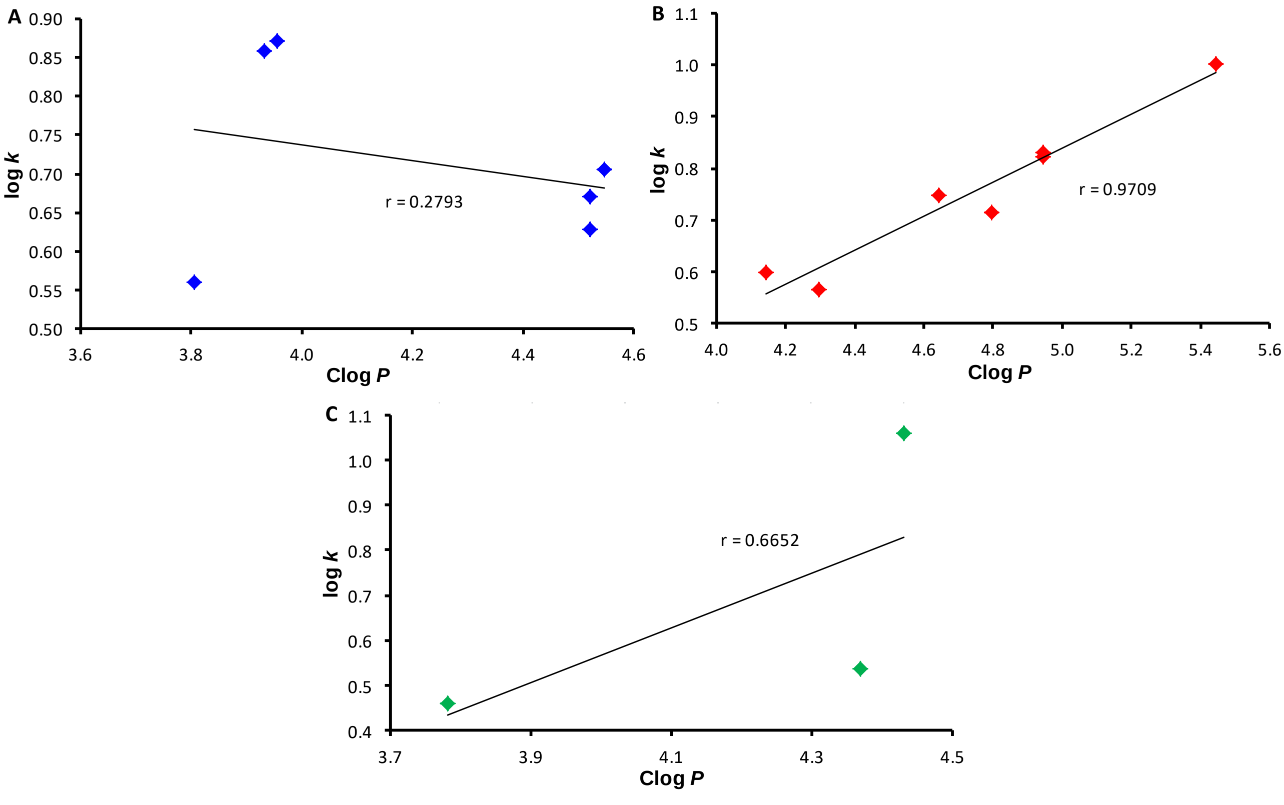


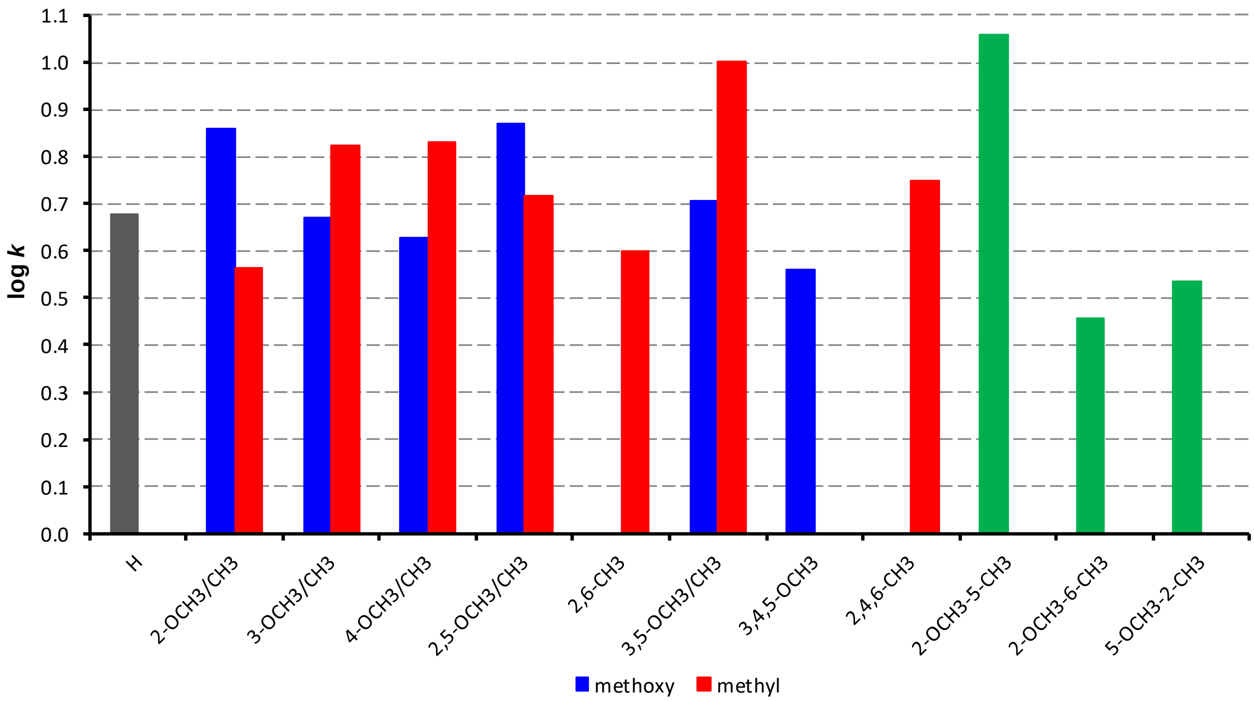
Figure 2. Comparison of experimentally found log *k* values with calculated Clog *P* (ChemBioDraw) of *N*-methoxyphenyl-1-hydroxynaphthalene-2-carboxanilides **2**–**7** (**A**), *N*-methylphenyl-1-hydroxynaphthalene-2-carboxanilides **8**–**14** (**B**) and methoxymethyl derivatives **15**–**17** (C).



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 individual 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, see Figure 3. Slightly higher lipophilicity than that of compound **16**, but the second lowest 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 compounds **15** and **17**), led to a sharp decrease of lipophilicity, which supports a theory about intramolecular interactions among substituents 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 2-OCH_3 derivative showed higher log *k* value than unsubstituted compound **1**, while 4-CH_3 and 3-CH_3 derivatives showed higher log *k* values than unsubstituted compound **1**. 2,5-Dimethoxy derivative **5** possessed higher log *k* value than compound **11** (R = 2,5-CH_3). On the other hand, compound **6** (R = 3,5-OCH_3) had much lower log *k* value than compound **11** (R = 3,5-CH_3). Also trimethyl derivative **14** showed much higher lipophilicity than trimethoxy derivative **7**. 2,5-Dimethoxy derivative **5** has 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**). Also these results refer to the importance of *ortho* placed methoxy moieties for the higher lipophilicity of the compounds. Among di- and tri-methyl substituted derivatives, log *k* values decreases 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 relating to the methoxy moieties, *meta* and *para* substitution seem 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.

EXPERIMENTAL

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) and evaluated in iodine vapour. 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 HPLC separation module Waters Alliance 2695 XE (Waters Corp., Milford, MA, USA). The 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 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 injection into HESI II in the positive or negative mode.

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; the solid residue was washed with 2 M HCl; and the crude product was recrystallized from aqueous ethanol. All 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.*

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%) as a mobile phase was used. The total flow of the column was 1.0 mL/min, injection 20 μL, column temperature 40 °C and sample temperature 10 °C. The detection wavelength 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.

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

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