chemistry proceedings

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Proceeding Paper

Preparation and Hydro-Lipophilic Properties of Monosubstituted *N*-Aryl-4-hydroxyquinoline-3-carboxanilides †

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† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 15–30 November 2022; Available online: https://ecsoc-26.sciforum.net.

Abstract: A series of twenty-two monosubstituted *N*-aryl-4-hydroxyquinoline-3-carboxanilides designed as dual anti-invasive agents was prepared and characterized. Lipophilicity significantly affects biological activities of compounds and ADME properties; therefore, the lipo-hydrophilic properties of these 4-hydroxyquinoline-3-carboxanilides were investigated. All the derivatives were analyzed using reversed-phase high-performance liquid chromatography. The procedure was carried out under isocratic conditions with methanol as the organic modifier in the mobile phase using an end-capped non-polar C18 stationary reversed-phase column. In this study, correlations between the logarithm of the capacity factor *k* and log *P*/Clog *P* values calculated using various methods are discussed, as well as the relationships between lipophilicity and chemical structure of the studied compounds.

Keywords: hydroxyquinoline-carboxanilides; synthesis; lipophilicity

Citation: Gonec, T.; Vrablova, L.; Pindjakova, D.; Strharsky, T.; Oravec, M.; Jampilek, J. Preparation and Hydro-Lipophilic Properties of Monosubstituted *N*-Aryl-4-hydroxyquinoline-3-carboxanilides. *Chem. Proc.* **2022**, *12*, 28. https://doi.org/10.3390/ecsoc-26-13548

Academic Editor: Julio A. Seijas

Published: 14 November 2022

1. Introduction

Many factors and parameters play an important role in the design and subsequent development of bioactive agents [1,2]. One of them is lipophilicity, which is among the most important of all investigated physicochemical properties, as it affects not only the ligand–target binding interaction, but also solubility and subsequent absorption (biological availability), binding to transporters, metabolism and excretion [3–5]. Lipophilicity is based on the distribution of a compound between two immiscible phases. It therefore represents the affinity of the compound to the lipophilic environment [6]. Lipophilicity can be expressed by the logarithm of the distribution coefficient log *P* or the distribution coefficient log *D* [5,7]. A number of methods have been developed to determine lipophilicity, which can be divided into experimental and computational [7,8]. The oldest and still frequently used experimental methods are chromatography, especially reversed-phase high-performance liquid chromatography (RP-HPLC) and reversed-phase thin-layer chromatography (RP-TLC), which can be used to determine a wide range of log *P* values [6,9,10].

Compounds that bind to multiple targets represent an innovative approach in designing anti-invasive compounds because they both prevent the emergence of resistant cells/pathogens and are able to destroy resistant cells/pathogens. Compounds based on quinoline scaffold (all azanaphthalenes) have a wide range of promising biological properties and can be considered privileged structures of multi-target agents [11–13]. Moreover, azanaphalene structures can be easily and rapidly synthesized, demonstrating the

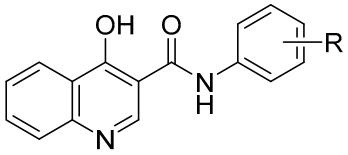
importance of these privileged structures. In addition, this simple scaffold has unique physicochemical properties and provides the possibility of a large number of modifications (through targeted- or diversity-oriented synthesis) and the preparation of many isomeric forms and bioisosteres. On the other hand, it is not easy to determine the exact mechanism of action of these compounds. For example, primaquine has celebrated more than 60 years of clinical application, but its mode of action has not been elucidated [14]. Hydroxyquinolines are known to be able to chelate not only iron (which is an essential nutrient), but also copper, manganese, magnesium, zinc and other vital metals [15]. Further research has led to the discovery that the mechanisms of action of these compounds are actually more complex. In addition to their bidentate properties causing metal chelation, substituted quinolines show different mechanisms of action, e.g., they inhibit mycobacterial gyrase, ATP synthase, FtsZ protein, glutathione *S*-transferase, enoyl-ACP reductase, decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1) or FadD32 [16–24].

Following on from previous ADMET studies dealing with (aza)naphthalenes [25–38], this contribution is devoted to the synthesis and structure–lipophilicity relationships of a series of monosubstituted anilides prepared from 4-hydroxyquinoline-3-carboxylic acid.

2. Results and Discussion

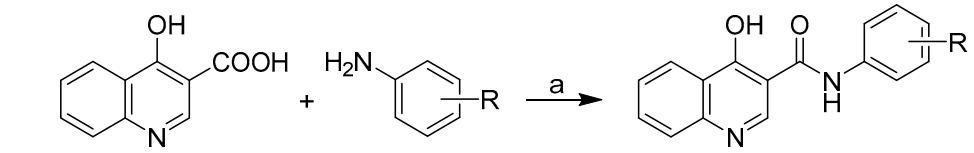
All studied compounds **1**–**8c** were prepared according to Scheme 1 using modified microwave-assisted (MW) synthesis [29,30]. Briefly: in dry chlorobenzene, the carboxyl group was activated with phosphorus chloride, and then the resulting acyl chloride was aminolyzed with a ring-substituted aniline. All the crude target compounds (see Table 1) were recrystallized from ethanol.

Table 1. Structure of ring-substituted 4-hydroxyquinoline-3-carboxanilides **1**–**8c**, experimentally determined log *k*, and predicted lipophilicities (log *P*/Clog *P*) values of investigated compounds.



Comp.	R	log *k*	log *P* [1]	log *P* [2]	Clog *P* [2]
1	H	0.3655	3.93	2.53	4.5695
2a	2-OCH_3	0.4873	4.05	2.41	3.9533
2b	3-OCH_3	0.3956	3.98	2.41	4.5433
2c	4-OCH_3	0.3019	3.80	2.41	4.5433
3a	2-CH_3	0.5033	4.50	3.02	4.4185
3b	3-CH_3	0.5916	4.50	3.02	5.0685
3c	4-CH_3	0.5840	4.50	3.02	5.0685
4a	2-F	0.3591	3.95	2.69	4.2027
4b	3-F	0.5126	4.23	2.69	4.8027
4c	4-F	0.4383	4.14	2.69	4.8027
5a	2-Cl	0.5086	4.83	3.09	4.5227
5b	3-Cl	0.7499	5.12	3.09	5.3727
5c	4-Cl	0.7434	4.93	3.09	5.3727
6a	2-Br	0.5347	4.82	3.36	4.6427
6b	3-Br	0.5702	4.84	3.36	5.5227
6c	4-Br	0.8269	4.80	3.36	5.5227
7a	2-CF_3	0.4228	5.05	3.45	4.1603
7b	3-CF_3	0.8211	5.25	3.45	5.6103
7c	4-CF_3	0.8672	5.05	3.45	5.6103
8a	2-NO_2	0.1446	4.03	2.40	4.0457
8b	3-NO_2	0.4697	4.08	2.40	4.5057
8c	4-NO_2	0.5238	3.89	2.40	4.5057

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



R = H (**1**), OCH_3 (**2a-c**), CH_3 (**3a-c**), F (**4a-c**), Cl (**5a-c**), Br (**6a-c**), CF_3 (**7a-c**), NO_2 (**8a-c**)

Scheme 1. Synthesis of ring-substituted 4-hydroxyquinoline-3-carboxanilides **1**–**8c**. *Reagents and conditions:* (**a**) PCl_3, chlorobenzene, MW, 45 min [29,30].

The lipophilicity of the studied compounds was determined using RP-HPLC as capacity factors *k* with subsequent calculation of log *k*. 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 the individual triplets of positional isomers (a/b/c). The values are shown only in Table 1 without other discussion. According to the Clog *P* algorithm, which also includes possible chemical interactions of the molecule, lipophilicity values were the same only for *meta*- and *para*- isomers. Thus, only the log *P* values calculated by ACD/Percepta are unique for each isomer except for the methyl-substituted derivatives **3a**–**c**, where the software predicted log *P* = 4.50 for all three isomers.

Correlations between the experimentally determined values of log *k* and the predicted values of log *P* (ACD/Percepta) and Clog *P* (ChemBioDraw) are shown in Figures 1–3, with the *ortho*-, *meta*- and *para*-isomers separately illustrated for greater clarity and explanatory value.

As can be seen from the individual graphs, the correlations between the experimental and calculated values are quite poor, especially for *ortho*-isomers. The highest agreement is for *meta*-derivatives and data calculated using ACD/Percepta, where the correlation coefficient is *r* = 0.9531 (*n* = 7), see Figure 2A. As above-mentioned, the *ortho*-substituted derivatives gave the worst correlations (Figure 1). In addition, in graphs 1a and 1b (Figure 1), substituents capable of forming hydrogen bonds and/or other weak interactions with the aqueous environment or interactions within the molecule or with neighboring molecules are indicated. The spatially close the amide group, the hydroxyl group at $C_{(4)}$ and the quinoline nitrogen are of great importance for the overall poor correlation.

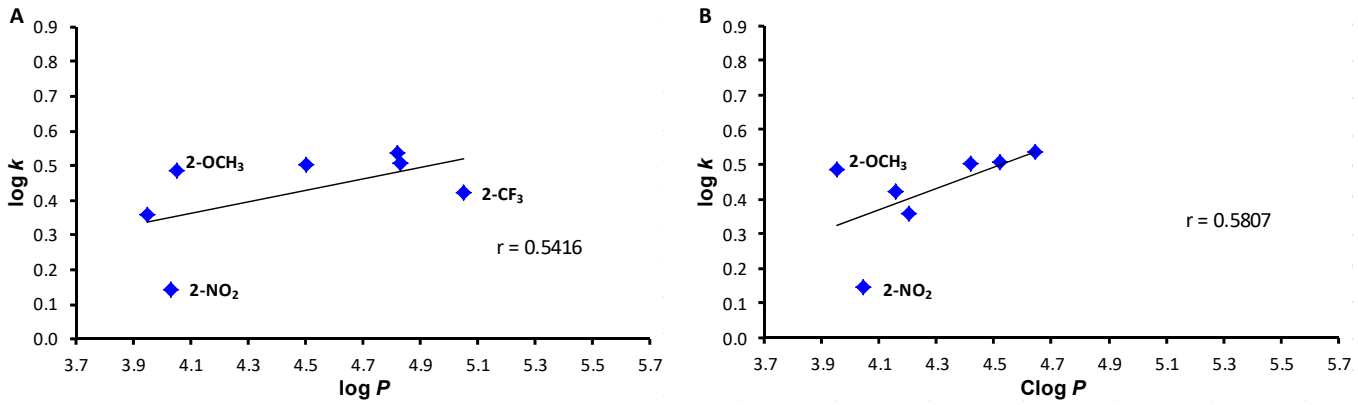


Figure 1. Comparison of experimentally found log *k* values with calculated log *P* (ACD/Percepta) (**A**), and Clog *P* (ChemBioDraw) (**B**) of *ortho*-substituted 4-hydroxyquinoline-3-carboxanilides **2a**, **3a**, **4a**, **5a**, **6a**, **7a**, **8a**.

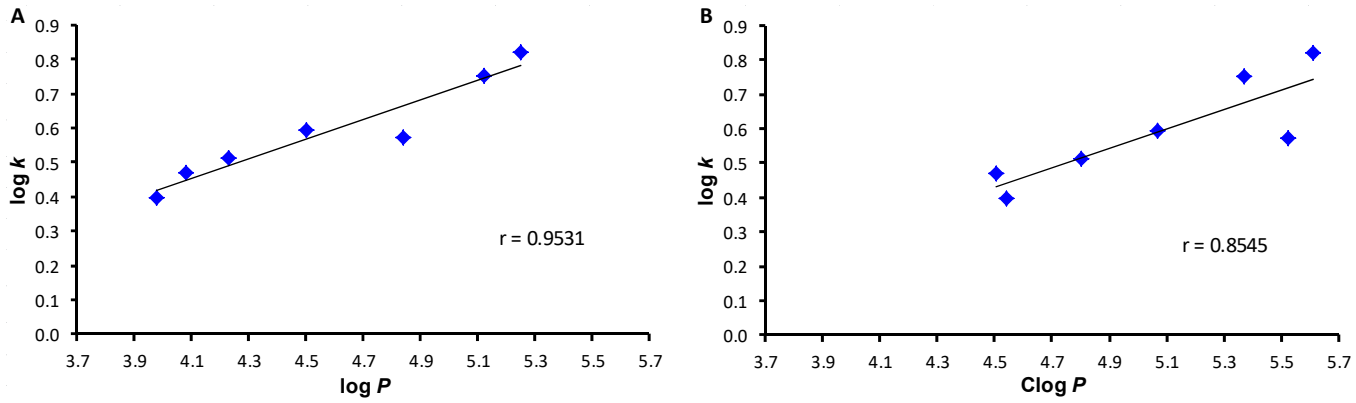


Figure 2. Comparison of experimentally found log *k* values with calculated log *P* (ACD/Percepta) (**A**), and Clog *P* (ChemBioDraw) (**B**) of *meta*-substituted 4-hydroxyquinoline-3-carboxanilides **2b**, **3b**, **4b**, **5b**, **6b**, **7b**, **8b**.

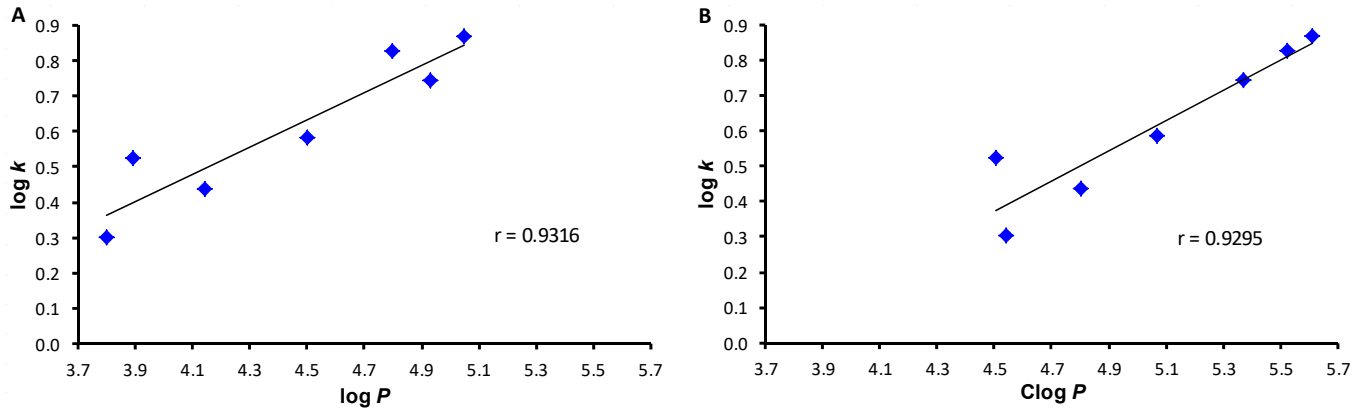


Figure 3. Comparison of experimentally found log *k* values with calculated log *P* (ACD/Percepta) (**A**), and Clog *P* (ChemBioDraw) (**B**) of *para*-substituted 4-hydroxyquinoline-3-carboxanilides **2c**, **3c**, **4c**, **5c**, **6c**, **7c**, **8c**.

According to the experimental values, it can be concluded that 4-hydroxy-*N*-(2-nitrophenyl)quinoline-3-carboxamide (**8a**) is the least lipophilic, and 4-hydroxy-*N*-[4-(trifluoromethyl)phenyl]quinoline-3-carboxamide (**7c**) is the most lipophilic. In general, *ortho*-derivatives have the lowest log *k* values. The exception is the methoxy substituents, where the *ortho*-isomer **2a** is the most lipophilic of the three. The *meta*- and *para*-derivatives in the triad mostly have close log *k* values, except for *N*-(4-bromophenyl)-4-hydroxyquinoline-3-carboxamide (**6c**), where there is a large "jump" between the log *k* values for the *para*- and *meta*-isomers. The order of compounds arranged according to increasing log *k* values is shown in Figure 4.

Regarding all these observations, it should be summarized that for these highly functionalized quinoline derivatives, standard commercially available lipophilicity calculation programs are unable to provide relevant data due to the high incidence of intra- and intermolecular interactions.

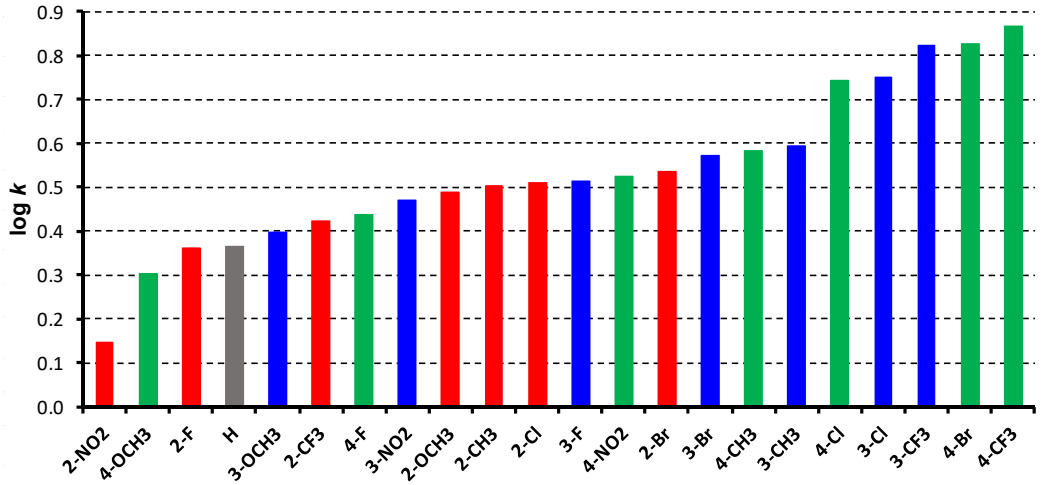


Figure 4. Order of individual derivatives arranged according to increasing log *k* values. (grey = unsubstituted derivative **1**, red = *ortho*-isomers, blue = *meta*-isomers, green = *para*-isomers).

3. Experimental Section

3.1. General Methods

All reagents were purchased from Merck (Sigma-Aldrich, St. Louis, MO, USA) and Alfa (Alfa-Aesar, Ward Hill, MA, USA). Microwave-assisted reactions were performed using a StartSYNTH microwave lab station (Milestone, Sorisole, BG, Italy). The melting points were determined on a Kofler hot-plate apparatus HMK (Franz Kustner Nacht KG, Dresden, Germany) and are uncorrected. Infrared (IR) spectra were recorded on an ATR diamond iD7 for Nicolet™ Impact 410 Fourier-transform IR spectrometer (Thermo Scientific, West Palm Beach, FL, USA). The spectra were obtained through the accumulation of 64 scans with a 2 cm^{-1} resolution in the region of 4000–650 cm^{-1}. All ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL ECZR 400 MHz NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C, Jeol, Tokyo, Japan) in dimethyl sulfoxide-d_6 (DMSO-d_6). ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm. High-resolution mass spectra were measured using a high-performance liquid chromatograph Dionex UltiMate® 3000 (Thermo Scientific, West Palm Beach, FL, USA) coupled with an LTQ Orbitrap XL™ Hybrid Ion Trap-Orbitrap Fourier-transform mass spectrometer (Thermo Scientific) equipped with a HESI II (heated electrospray ionization) source in the positive mode.

3.2. Synthesis

General Procedure for Synthesis of Carboxamides **1**–**8c**

4-Hydroxyquinoline-3-carboxylic acid (0.5 g, 2.64 mM) was suspended in dry chlorobenzene (25 mL) at ambient temperature and phosphorus trichloride (0.12 mL, 1.32 mM, 0.5 eq.), and the corresponding substituted aniline (2.64 mM, 1 eq.) was added dropwise. The reaction mixture was transferred to the microwave reactor, where the synthesis was performed (1st phase: 10 min, 100 °C; 2nd phase: 15 min, 120 °C; 3rd phase: 20 min, 130 °C, 500 W). Then, the mixture was cooled to 60 °C, and the solvent was removed to dryness under reduced pressure. The residue was washed with hydrochloric acid and water. The crude product was recrystallized from diluted EtOH. All the studied compounds are presented in Table 1.

4-Hydroxy-N-phenylquinoline-3-carboxamide (**1**). Yield 48%; m.p. 260–267 °C; IR (cm^{-1}): 3061; 2944; 1662; 1610; 1594; 1558; 1515; 1474; 1441; 1357; 1315; 1297; 1281; 1255; 1214; 1187; 1174; 1146; 1076; 1026; 867; 828; 810; 754; 689; 682; ^{1}H-NMR (DMSO-d_6), δ: 12.96 (br. s, 1H); 12.49 (s, 1H); 8.88 (s, 1H); 8.33 (dd, J = 8.2 Hz, J = 1.4 Hz, 1H); 7.79–7.83 (m, 1H); 7.72–7.76 (m, 3H); 7.51–7.56 (m, 1H); 7.37 (t, J = 7.8 Hz, 2H); 7.09 (t, J = 7.3 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.35; 162.83; 144.18; 139.11; 138.84; 133.01; 129.04; 125.93; 125.48; 125.32; 123.39; 119.56; 119.20; 110.58; HR-MS: $[M - H]^-$ calculated 263.08260 m/z, found 263.08313 m/z.

4-Hydroxy-N-(2-methoxyphenyl)quinoline-3-carboxamide (**2a**). Yield 46%; m.p. 252–256 °C; IR (cm^{-1}): 2977; 2826; 1661; 1595; 1539; 1519; 1470; 1456; 1350; 1330; 1279; 1250; 1224; 1208; 1174; 1153; 1103; 1048; 1031; 828; 747; 680; ^{1}H-NMR (DMSO-d_6), δ: 12.83 (d, J = 4.1 Hz, 1H); 12.49 (s, 1H); 8.86 (d, J = 6.4 Hz, 1H); 8.52 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H); 8.34 (dd, J = 8.2 Hz, J = 0.9 Hz, 1H); 7.77–7.82 (m, 1H); 7.72–7.74 (m, 1H); 7.52 (ddd, J = 8.2 Hz, J = 6.9 Hz, J = 0.9 Hz, 1H); 7.03–7.10 (m, 2H); 6.92–6.97 (m, 1H); 3.93 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.03; 162.74; 148.42; 144.06; 139.03; 132.78; 128.34; 126.07; 125.56; 125.05; 123.27; 120.42; 119.85; 119.02; 110.99; 110.83; 55.90; HR-MS: $[M - H]^-$ calculated 293.09317 m/z, found 293.09378 m/z.

4-Hydroxy-N-(3-methoxyphenyl)quinoline-3-carboxamide (**2b**). Yield 53%; m.p. 256–259 °C; IR (cm^{-1}): 2949; 2832; 1659; 1623; 1592; 1554; 1516; 1475; 1457; 1427; 1358; 1337; 1280; 1206; 1170; 1160; 1137; 1051; 876; 815; 758; 743; 682; ^{1}H-NMR (DMSO-d_6), δ: 12.97 (br. s, 1H); 12.49 (s, 1H); 8.88 (d, J = 5.0 Hz, 1H); 8.32 (d, J = 7.3 Hz, 1H); 7.79–7.84 (m, 1H); 7.73–7.76 (m, 1H); 7.54 (t, J = 7.5 Hz, 1H); 7.47 (t, J = 1.8 Hz, 1H); 7.20–7.28 (m, 2H); 6.67 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H); 3.77 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.35; 162.89; 159.74; 144.21; 139.98; 139.11; 133.05; 129.82; 125.93; 125.48; 125.35; 119.22; 111.85; 110.54; 109.02; 105.24; 55.03; HR-MS: $[M - H]^-$ calculated 293.09317 m/z, found 293.09381 m/z.

4-Hydroxy-N-(3-methoxyphenyl)quinoline-3-carboxamide (**2c**). Yield 55%; m.p. 326–330 °C; IR (cm^{-1}): 3064; 2933; 2831; 1657; 1603; 1558; 1510; 1475; 1439; 1417; 1360; 1298; 1283; 1234; 1211; 1180; 1172; 1148; 1105; 1038; 819; 759; 747; 684; ^{1}H-NMR (DMSO-d_6), δ: 12.92 (s, 1H); 12.33 (s, 1H); 8.86 (s, 1H); 8.32 (d, J = 8.2 Hz, 1H); 7.78–7.83 (m, 1H); 7.72–7.76 (m, 1H); 7.66 (d, J = 9.1 Hz, 2H); 7.53 (t, J = 7.3 Hz, 1H); 6.94 (d, J = 8.7 Hz, 2H); 3.74 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.30; 162.39; 155.32; 143.96; 139.11; 132.95; 132.03; 125.92; 125.46; 125.24; 120.97; 119.18; 114.14; 110.72; 55.19; HR-MS: $[M - H]^-$ calculated 293.09317 m/z, found 293.09360 m/z.

4-Hydroxy-N-(2-methylphenyl)quinoline-3-carboxamide (**3a**). Yield 62%; m.p. 283–290 °C; IR (cm^{-1}): 3019; 2902; 1652; 1612; 1587; 1557; 1520; 1475; 1456; 1357; 1293; 1251; 1212; 1187; 1147; 1049; 833; 792; 771; 754; 711; 683; ^{1}H-NMR (DMSO-d_6), δ: 12.95 (d, J = 5.9 Hz, 1H); 12.35 (s, 1H); 8.90 (d, J = 6.4 Hz, 1H); 8.37 (d, J = 8.2 Hz, 1H); 8.35 (d, J = 8.7 Hz, 1H); 7.79–7.83 (m, 1H); 7.74–7.77 (m, 1H); 7.53 (ddd, J = 8.2 Hz, J = 6.9 Hz, J = 1.4 Hz, 1H); 7.26 (d, J = 7.3 Hz, 1H); 7.21 (t, J = 7.8 Hz, 1H); 7.01 (td, J = 7.3 Hz, J = 0.9 Hz, 1H); 2.41 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.47; 162.77; 144.21; 139.10; 137.47; 132.97; 130.27; 126.82; 126.34; 125.93; 125.56; 125.26; 123.24; 120.48; 119.17; 110.92; 18.14; HR-MS: $[M - H]^-$ calculated 277.09825 m/z, found 277.09872 m/z.

4-Hydroxy-N-(3-methylphenyl)quinoline-3-carboxamide (**3b**). Yield 56%; m.p. 299–307 °C; IR (cm^{-1}): 3061; 2906; 1667; 1615; 1592; 1574; 1558; 1514; 1474; 1441; 1358; 1303; 1265; 1214; 1192; 1165; 1137; 1029; 890; 867; 830; 817; 774; 752; 689; ^{1}H-NMR (DMSO-d_6), δ: 12.95 (br. s, 1H); 12.43 (s, 1H); 8.86 (s, 1H); 8.32 (dd, J = 8.2 Hz, J = 1.4 Hz, 1H); 7.78–7.83 (m, 1H); 7.72–7.75 (m, 1H); 7.50–7.58 (m, 3H); 7.23 (t, J = 7.5 Hz, 1H); 6.90 (d, J = 7.8 Hz, 1H); 2.31 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.33; 162.73; 144.07; 139.09; 138.76; 138.25; 132.97; 128.84; 125.93; 125.46; 125.27; 124.08; 120.06; 119.17; 116.69; 110.63; 21.15; HR-MS: $[M + H]^+$ calculated 279.11280 m/z, found 279.11295 m/z.

4-Hydroxy-N-(4-methylphenyl)quinoline-3-carboxamide (**3c**). Yield 65%; m.p. >330 °C; IR (cm^{-1}): 3066; 2914; 1661; 1602; 1557; 1515; 1476; 1439; 1359; 1315; 1300; 1254; 1212; 1176; 1026; 869; 811; 786; 755; 748; 682; ^{1}H-NMR (DMSO-d_6), δ: 12.88 (br. s, 1H); 12.39 (s, 1H); 8.86 (s, 1H); 8.32 (dd, J = 8.2 Hz, J = 0.9 Hz, 1H); 7.79–7.83 (m, 1H); 7.73–7.76 (m, 1H); 7.62 (d, J = 8.2 Hz, 2H); 7.53 (ddd, J = 8.2 Hz, J = 6.9 Hz, J = 1.4 Hz, 1H); 7.17 (d, J = 8.2 Hz, 2H); 2.28 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.30; 162.60; 144.04; 139.11; 136.31; 132.96; 132.32; 129.40; 125.92; 125.45; 125.25; 119.51; 119.17; 110.66; 20.47; HR-MS: $[M + H]^+$ calculated 279.11280 m/z, found 279.11273 m/z.

N-(2-Fluorophenyl)-4-hydroxyquinoline-3-carboxamide (**4a**). Yield 65%; m.p. 321–325 °C; IR (cm^{-1}): 2727; 1678; 1634; 1617; 1595; 1548; 1504; 1467; 1454; 1360; 1318; 1291; 1253; 1213; 1184; 1163; 1143; 1094; 1029; 934; 889; 837; 802; 770; 749; 679; ^{1}H-NMR (DMSO-d_6), δ: 12.99 (br. s, 1H); 12.75 (s, 1H); 8.89 (s, 1H); 8.53 (td, 1H, *J* = 8.2 Hz, *J* = 1.4 Hz); 8.34 (d, 1H, *J* = 7.3 Hz); 7.78–7.83 (m, 1H); 7.73–7.76 (m, 1H); 7.53 (t, 1H, *J* = 7.3 Hz); 7.32 (dd, 1H, *J* = 10.5 Hz, *J* = 8.7 Hz); 7.18–7.22 (m, 1H); 7.07–7.13 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.36; 163.11; 152.07 (d, *J* = 242.8 Hz); 144.34; 139.09; 133.06; 127.16 (d, *J* = 10.6 Hz); 125.94; 125.55; 125.37; 124.66 (d, *J* = 3.9 Hz); 123.72 (d, *J* = 7.7 Hz); 121.36 (d, *J* = 1.9 Hz); 119.20; 115.08 (d, *J* = 18.3 Hz); 110.39; HR-MS: $[M - H]^-$ calculated 281.07318 *m*/*z*, found 281.07370 *m*/*z*.

N-(3-Fluorophenyl)-4-hydroxyquinoline-3-carboxamide (**4b**). Yield 70%; m.p. 323–326 °C; IR (cm^{-1}): 2913; 1666; 1605; 1557; 1515; 1473; 1442; 1368; 1304; 1257; 1216; 1191; 1159; 1148; 1127; 1076; 1027; 993; 966; 868; 828; 813; 770; 755; 678; ^{1}H-NMR (DMSO-d_6), δ: 12.99 (br. s, 1H); 12.65 (s, 1H); 8.87 (s, 1H); 8.31 (dd, 1H, *J* = 8.2 Hz, *J* = 0.9 Hz); 7.78–7.85 (m, 2H); 7.72–7.75 (m, 1H); 7.53 (ddd, 1H, *J* = 8.1 Hz, *J* = 6.8 Hz, *J* = 0.9 Hz); 7.33–7.41 (m, 2H); 6.88–6.93 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.33; 163.18; 162.31 (d, *J* = 241.8 Hz); 144.31; 140.47 (d, *J* = 11.6 Hz); 139.07; 133.07; 130.56 (d, *J* = 9.6 Hz); 125.89; 125.45; 125.39; 119.22; 115.37 (d, *J* = 1.9 Hz); 110.20; 109.82 (d, *J* = 21.2 Hz); 106.49 (d, *J* = 26.0 Hz); HR-MS: $[M - H]^-$ calculated 281.07318 *m*/*z*, found 281,07373 *m*/*z*.

N-(4-Fluorophenyl)-4-hydroxyquinoline-3-carboxamide (**4c**). Yield 66%; m.p. 288–293 °C; IR (cm^{-1}): 3068; 2962; 1652; 1612; 1672; 1668; 1608; 1474; 1443; 1411; 1368; 1300; 1290; 1213; 1186; 1157; 1093; 1026; 989; 960; 872; 868; 821; 794; 770; 768; 749; 683; ^{1}H-NMR (DMSO-d_6), δ: 12.96 (br. s, 1H); 12.49 (s, 1H); 8.87 (s, 1H); 8.39 (d, 1H, *J* = 7.8 Hz); 7.73–7.83 (m, 4H); 7.53 (t, 1H, *J* = 7.5 Hz); 7.20 (t, 2H, *J* = 8.7 Hz); ^{13}C-NMR (DMSO-d_6), δ: 176.32; 162.79; 158.08 (d, *J* = 239.9 Hz); 144.15; 139.11; 135.23 (d, *J* = 1.9 Hz); 133.02; 125.89; 125.45; 125.33; 121.29 (d, *J* = 8.7 Hz); 119.21; 115.57 (d, *J* = 23.1 Hz); 110.42; HR-MS: $[M - H]^-$ calculated 281.07318 *m*/*z*, found 281,07370 *m*/*z*.

N-(2-Chlorophenyl)-4-hydroxyquinoline-3-carboxamide (**5a**). Yield 46%; m.p. 300–308 °C; IR (cm^{-1}): 3064; 3024; 2902; 1674; 1629; 1590; 1505; 1472; 1463; 1440; 1361; 1301; 1283; 1259; 1241; 1210; 1181; 1146; 1052; 1035; 876; 823; 805; 764; 747; 692; 681; ^{1}H-NMR (DMSO-d_6), δ: 12.80 (s, 1H); 8.86 (s, 1H); 8.57 (dd, *J* = 8.5 Hz, *J* = 1.6 Hz, 1H); 8.33 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H); 7.78–7.83 (m, 1H); 7.71–7.74 (m, 1H); 7.50–7.75 (m, 2H); 7.32–7.37 (m, 1H); 7.11 (td, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.51; 163.49; 144.65; 139.24; 136.06; 133.32; 129.54; 127.87; 126.10; 125.77; 125.65; 124.57; 122.50; 122.00; 119.37; 110.52; HR-MS: $[M - H]^+$ calculated 299.05818 *m*/*z*, found 299.05856 *m*/*z*.

N-(3-Chlorophenyl)-4-hydroxyquinoline-3-carboxamide (**5b**). Yield 60%; m.p. 300–312 °C; IR (cm^{-1}): 3059; 2906; 1668; 1610; 1590; 1553; 1516; 1473; 1443; 1425; 1358; 1302; 1253; 1213; 1184; 1152; 1076; 996; 905; 877; 828; 813; 773; 756; 749; 694; 680; ^{1}H-NMR (DMSO-d_6), δ: 12.99 (br. s, 1H); 12.64 (s, 1H); 8.86 (d, *J* = 1.8 Hz, 1H); 8.31 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H); 8.04 (t, *J* = 1.8 Hz, 1H); 7.79–7.83 (m, 1H); 7.73–7.76 (m, 1H); 7.48–7.56 (m, 2H); 7.38 (t, *J* = 8.0 Hz, 1H); 7.14 (ddd, *J* = 7.8 Hz, *J* = 1.4 Hz, *J* = 0.9 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.35; 163.21; 144.33; 140.20; 139.09; 133.34; 133.12; 130.65; 125.89; 125.48; 125.43; 123.09; 119.25; 119.13; 118.04; 110.18; HR-MS: $[M - H]^-$ calculated 297.04363 *m*/*z*, found 297.04437 *m*/*z*.

N-(4-Chlorophenyl)-4-hydroxyquinoline-3-carboxamide (**5c**). Yield 67%; m.p. 300–306 °C; IR (cm^{-1}): 3063; 2934; 1661; 1609; 1593; 1557; 1520; 1492; 1474; 1444; 1403; 1359; 1303; 1280; 1251; 1214; 1187; 1170; 1088; 1011; 872; 821; 760; 749; 678; ^{1}H-NMR (DMSO-d_6), δ: 12.96 (br. s, 1H); 12.57 (s, 1H); 8.87 (s, 1H); 8.31 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H); 7.73–7.83 (m, 4H); 7.51–7.55 (m, 1H); 7.38–7.42 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 176.31; 162.96; 144.22; 139.08; 137.73; 133.03; 128.86; 126.87; 125.88; 125.44; 125.34; 121.13; 119.21; 110.31; HR-MS: $[M + H]^+$ calculated 299.05818 *m*/*z*, found 299.05859 *m*/*z*.

N-(2-Bromophenyl)-4-hydroxyquinoline-3-carboxamide (**6a**). Yield 45%; m.p. 304–312 °C; IR (cm^{-1}): 3062; 3024; 2898; 1671; 1629; 1583; 1575; 1506; 1472; 1464; 1435; 1361; 1300; 1281; 1258; 1210; 1182; 1143; 1025; 876; 819; 805; 765; 746; 683; 666; ^{1}H-NMR (DMSO-d_6), δ: 12.95 (br. s, 1H); 12.68 (s, 1H); 8.89 (s, 1H); 8.54 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H); 8.34 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H); 7.79–7.83 (m, 1H); 7.73–7.76 (m, 1H); 7.69 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H); 7.53 (ddd, *J* = 8.2 Hz, *J* = 6.9 Hz, *J* = 0.9 Hz, 1H); 7.37–7.42 (m, 1H); 7.05 (td, *J* = 7.5 Hz, *J* = 1.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.19; 163.27; 144.52; 139.08; 137.23; 133.03; 132.66; 128.10; 125.97; 125.56; 125.34; 124.88; 122.47; 119.18; 112.97; 110.31; HR-MS: $[M + H]^+$ calculated 343.00766 *m*/*z*, found 343.00845 *m*/*z*.

N-(3-Bromophenyl)-4-hydroxyquinoline-3-carboxamide (**6b**). Yield 60%; m.p. 317–327 °C; IR (cm^{-1}): 3065; 2904; 1662; 1609; 1589; 1549; 1516; 1472; 1440; 1421; 1359; 1302; 1252; 1213; 1184; 1165; 1147; 1068; 994; 876; 827; 812; 772; 756; 680; 672; ^{1}H-NMR (DMSO-d_6), δ: 12.98 (br. s, 1H); 12.62 (s, 1H); 8.86 (s, 1H); 8.31 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H); 8.18 (t, *J* = 1.8 Hz, 1H); 7.78–7.83 (m, 1H); 7.73–7.75 (m, 1H); 7.51–7.55 (m, 2H); 7.26–7.34 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 176.31; 163.14; 144.28; 140.31; 139.06; 133.07; 130.92; 125.96; 125.85; 125.42; 125.38; 121.94; 121.80; 119.22; 118.40; 110.17; HR-MS: $[M + H]^+$ calculated 343.00766 *m*/*z*, found 343.00839 *m*/*z*.

N-(4-Bromophenyl)-4-hydroxyquinoline-3-carboxamide (**6c**). Yield 60%; m.p. 310–319 °C; IR (cm^{-1}): 3061; 2905; 1662; 1604; 1586; 1553; 1516; 1487; 1473; 1443; 1398; 1359; 1314; 1281; 1249; 1214; 1187; 1172; 1073; 1007; 816; 759; 749; 683; ^{1}H-NMR (DMSO-d_6), δ: 12.97 (br. s, 1H); 12.58 (s, 1H); 8.87 (s, 1H); 8.32 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H); 7.79–7.83 (m, 1H); 7.70–7.76 (m, 3H); 7.51–7.56 (m, 3H); ^{13}C-NMR (DMSO-d_6), δ: 176.31; 162.98; 144.24; 139.08; 138.13; 133.05; 131.77; 125.88; 125.44; 125.36; 121.51; 119.22; 114.87; 110.31; HR-MS: $[M + H]^+$ calculated 343.00766 *m*/*z*, found 343.00824 *m*/*z*.

4-Hydroxy-N-[2-(trifluoromethyl)phenyl]quinoline-3-carboxamide (**7a**). Yield 56%; m.p. 240–244 °C; IR (cm^{-1}): 3035; 2898; 1688; 1664; 1613; 1590; 1549; 1524; 1472; 1456; 1352; 1318; 1274; 1250; 1168; 1143; 1109; 1058; 1034; 943; 866; 801; 763; 681; ^{1}H-NMR (DMSO-d_6), δ: 12.97 (d, *J* = 5.5 Hz, 1H); 12.74 (s, 1H); 8.89 (d, *J* = 6.9 Hz, 1H); 8.39 (d, *J* = 8.2 Hz, 1H); 8.33 (dd, *J* = 8.2 Hz, *J* = 0.9 Hz, 1H); 7.80–7.84 (m, 1H); 7.73–7.77 (m, 2H); 7.69 (t, *J* = 7.8 Hz, 1H); 7.51–7.55 (m, 1H); 7.32 (t, *J* = 7.5 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.42; 163.41; 144.58; 139.03; 135.93 (q, *J* = 1.9 Hz); 133.10; 132.02; 126.20; 125.97 (q, *J* = 5.8 Hz); 125.55; 125.36; 124.90 (q, *J* = 32.8 Hz); 124.75; 124.01; 123.93 (q, *J* = 273.6 Hz); 119.18; 109.99; HR-MS: $[M - H]^-$ calculated 331.06999 *m*/*z*, found 331.07043 *m*/*z*.

4-Hydroxy-N-[3-(trifluoromethyl)phenyl]quinoline-3-carboxamide (**7b**). Yield 75%; m.p. 280–285 °C; IR (cm^{-1}): 3064; 2911; 1669; 1622; 1599; 1580; 1515; 1475; 1451; 1360; 1336; 1308; 1284; 1269; 1250; 1212; 1165; 1147; 1117; 1092; 1069; 1026; 899; 822; 785; 761; 747; 695; 684; ^{1}H-NMR (DMSO-d_6), δ: 13.01(br. s, 1H); 12.57 (s, 1H); 8.87 (s, 1H); 8.30–8.33 (m, 2H); 7.79–7.83 (m, 2H); 7.72–7.75 (m, 1H); 7.58 (t, *J* = 7.8 Hz, 1H); 7.51–7.55 (m, 1H); 7.43 (d, *J* = 7.8 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.34; 163.40; 144.35; 139.50; 139.08; 133.11; 130.17; 129.68 (q, *J* = 31.8 Hz); 125.88; 125.44; 125.43; 124.13 (q, *J* = 272.6 Hz); 123.22; 119.70 (q, *J* = 3.9 Hz); 119.24; 115.70 (q, *J* = 3.9 Hz); 110.11; HR-MS: $[M - H]^-$ calculated 331.06999 *m*/*z*, found 331.07047 *m*/*z*.

4-Hydroxy-N-[4-(trifluoromethyl)phenyl]quinoline-3-carboxamide (**7c**). Yield 58%; m.p. 286–290 °C; IR (cm^{-1}): 3064; 2981; 2915; 1662; 1600; 1551; 1523; 1475; 1445; 1415; 1318; 1305; 1259; 1215; 1164; 1151; 1105; 1063; 1014; 821; 761; 749; 685; ^{1}H-NMR (DMSO-d_6), δ: 13.03 (br. s, 1H); 12.81 (s, 1H); 8.90 (s, 1H); 8.33 (dd, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H); 7.95 (d, *J* = 8.2 Hz, 2H); 7.80–7.85 (m, 1H); 7.74–7.77 (m, 1H); 7.72 (d, *J* = 8.7 Hz, 2H); 7.55 (ddd, *J* = 8.2 Hz, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 176.37; 163.38; 144.48; 142.30 (q, *J* = 1.9 Hz); 139.08; 133.15; 126.29 (q, *J* = 3.9 Hz); 125.88; 125.48; 125.45; 124.46 (q, *J* = 273.6 Hz); 123.31 (q, *J* = 31.8 Hz); 119.55; 119.27; 110.10; HR-MS: $[M - H]^-$ calculated 331.06999 *m*/*z*, found 331.07040 *m*/*z*.

4-Hydroxy-N-(2-nitrophenyl)quinoline-3-carboxamide (**8a**). Yield 51%; m.p. 306–310 °C; IR (cm^{-1}): 3066; 2965; 1680; 1623; 1558; 1539; 1498; 1475; 1451; 1439; 1345; 1265; 1149; 765; 739; 692; ^{1}H-NMR (DMSO-d_6), δ: 13.26 (s, 1H); 12.97 (br. s, 1H); 8.87 (s, 1H); 8.54 (d, 1H, *J* = 8.7 Hz); 8.33 (d, 1H, *J* = 8.2 Hz); 8.10 (d, 1H, *J* = 7.8 Hz); 7.79–7.83 (m, 1H); 7.72–7.77 (m, 2H); 7.53 (t, 1H, *J* = 7.5 Hz); 7.32 (t, 1H, *J* = 7.8 Hz); ^{13}C-NMR (DMSO-d_6), δ: 176.06; 163.69; 144.91; 139.50; 139.05; 134.53; 133.12; 132.96; 126.04; 125.57; 125.45; 125.27; 124.24; 123.87; 119.21; 110.02; HR-MS: $[M - H]^-$ calculated 308.06767 *m*/*z*, found 308.06824 *m*/*z*.

4-Hydroxy-N-(3-nitrophenyl)quinoline-3-carboxamide (**8b**). Yield 49%; m.p. 316–321 °C; IR (cm^{-1}): 3051; 1674; 1613; 1542; 1516; 1470; 1429; 1341; 1304; 1266; 1235; 1207; 1181; 1141; 1073; 960; 889; 834; 798; 762; 735; 712; ^{1}H-NMR (DMSO-d_6), δ: 13.05 (br. s, 1H); 12.86 (s, 1H); 8.88 (s, 1H); 8.87 (t, 1H, *J* = 2.3 Hz); 8.30 (dd, 1H, *J* = 8.2 Hz, *J* = 0.9 Hz); 7.91 (td, 2H, *J* = 7.4 Hz, *J* = 1.8 Hz); 7.79–7.83 (m, 1H); 7.72–7.75 (m, 1H); 7.62 (t, 1H, *J* = 8.0 Hz); 7.54 (t, 1H, *J* = 7.5 Hz); ^{13}C-NMR (DMSO-d_6). δ: 176.36; 163.56; 148.10; 144.47; 139.82; 139.09; 133.20; 130.35; 125.86; 125.73; 125.54; 125.45; 119.31; 117.95; 113.70; 109.94; HR-MS: $[M - H]^-$ calculated 308.06767 *m*/*z*, found 308.06842 *m*/*z*.

4-Hydroxy-N-(4-nitrophenyl)quinoline-3-carboxamide (**8c**). Yield 54%; m.p. 310–315 °C; IR (cm^{-1}): 3066; 2435; 1679; 1569; 1549; 1521; 1508; 1471; 1410; 1328; 1305; 1252; 1214; 1170; 1134; 1109; 1022; 975; 946; 846; 798; 758; 747; 690; ^{1}H-NMR (DMSO-d_6), δ: 13.07 (br. s, 1H); 13.04 (s, 1H); 8.90 (s, 1H); 8.32 (dd, 1H, *J* = 8.0 Hz, *J* = 1.1 Hz); 8.24 (d, 2H, *J* = 9.1 Hz); 7.97 (d, 2H, *J* = 9.2 Hz); 7.80–7.85 (m, 1H); 7.74–7.77 (m, 1H); 7.55 (ddd, 1H, *J* = 8.2 Hz, *J* = 6.9 Hz, *J* = 1.4 Hz); ^{13}C-NMR (DMSO-d_6), δ: 176.37; 163.55; 144.87; 144.62; 142.15; 139.04; 133.20; 125.81; 125.55; 125.45; 125.14; 119.34; 119.28; 109.84; HR-MS: $[M - H]^-$ calculated 308.06767 *m*/*z*, found 308.06821 *m*/*z*.

3.3. Lipophilicity Determination by HPLC

An HPLC system Agilent 1200 equipped with a DAD detector (Agilent, Santa Clara, CA, USA) was used. A chromatographic column Symmetry® C_{18} 5 μm, 4.6 mm × 250 mm, part No. WAT054275, (Waters Corp., Milford, MA, USA) was used. The HPLC separation process was monitored and evaluated with EZChrom Elite software ver. 3.3.2 (Agilent). Isocratic elution with 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. 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 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. Log *k*, calculated from the capacity factor *k*, is used as the lipophilicity index converted to log *P* scale. The log *k* values of the 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 ver. 2012 (Advanced Chemistry Development. Inc., Toronto, ON, Canada, 2012) and ChemBioDraw Ultra 13.0 (CambridgeSoft, PerkinElmer Inc., Cambridge, MA, USA). Clog *P* values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were calculated using ChemBioDraw Ultra 13.0 (CambridgeSoft) software. The results are shown in Table 1.

Author Contributions: Conceptualization, T.G. and J.J.; methodology, T.G., L.V., D.P. and M.O.; investigation, T.G., L.V., D.P., T.S. and M.O.; writing—original draft preparation, T.G. and J.J.; supervision, J.J.; funding acquisition, J.J. and M.O. 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-17-0373) and VEGA 1/0116/22. This work is based on the use of Large Research Infrastructure

CzeCOS supported by the Ministry of Education, Youth and Sports of the Czech Republic within the CzeCOS program, grant number LM2018123; M.O. was supported by SustES—Adaptation strategies for sustainable ecosystem services and food security under adverse environmental conditions, project no. CZ.02.1.01/0.0/0.0/16_019/0000797.

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 conflict of interest.

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