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Photosynthesis-Inhibiting Activity of Fluorinated 2-Hydroxynaphthalene-1-carboxanilides †

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Abstract: 2-Hydroxy-*N*-phenylnaphthalene-1-carboxamide, three fluoro monosubstituted and five fluoro disubstituted 2-hydroxynaphthalene-1-carboxanilides were prepared by microwave-assisted synthesis and characterized. All the compounds were evaluated for their ability to inhibit photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts. The PET inhibitory activity of the discussed compounds proved to be in a wide range, from inactive *N*-(2,6-difluorophenyl)-2-hydroxynaphthalene-1-carboxamide with an IC_{50} = 904 μM to *N*-(2,5-difluorophenyl)-2-hydroxynaphthalene-1-carboxamide with an IC_{50} of 44.2 μM, which was the most potent isomer of the series of evaluated compounds. Based on previous studies, it can be assumed that the mechanism of PET inhibition of these compounds is the inhibition of photosystem II in the thylakoid membrane.

Keywords: Hydroxynaphthalene-carboxamides; PET inhibition; Spinach chloroplasts

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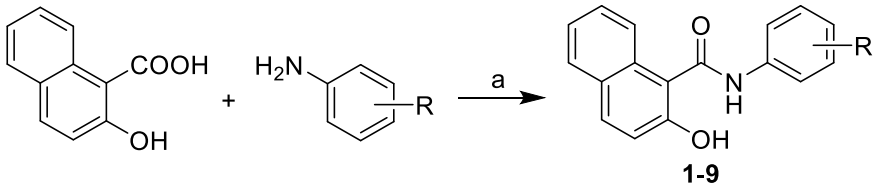
1. Introduction

Hydroxynaphthalene-carboxanilides are known for a wide range of biological activities. In addition to antibacterial and antituberculotic effects, it is also antiparasitic activity and has also been found to be able to inhibit photosynthesis by reversibly binding to photosystem II (PS II) in the thylakoid membrane [1–18]. The amide bond is important for this biological activity. The effect is enhanced by the presence of a hydroxyl group [1,4,19,20] and modified by substitution of the anilide part of the molecule [1,4–7,15]. The amide bridge connecting the two parts of the molecule simulates a peptide bond (–CONH–) and is crucial for this interaction inhibiting photosynthetic electron transfer (PET). There are over 50% of herbicides acting on the market [21–24].

Previously published monofluorinated anilides of 2-hydroxynaphthalene-1-carboxylic acid were added a series of difluorinated derivatives, and these new compounds were investigated for their ability to inhibit PET in spinach (*Spinacia oleracea* L.) chloroplasts.

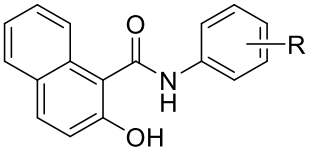
2. Results and Discussion

The studied compounds were prepared by the method described by Gonec et al. [1]. Briefly: 1-hydroxynaphthalene-2-carboxylic acid and the appropriate aniline were dissolved in dry chlorobenzene and provided the target 2-hydroxy-*N*-arylnaphthalene-1-carboxanilides in the presence of phosphorus trichloride in a microwave reactor, see Scheme 1 and Table 1.



Scheme 1. Synthesis of 2-hydroxy-*N*-arylnaphthalene-1-carboxanilides **1–9**. *Reagents and conditions*: (a) PCl_3, chlorobenzene, MW, 45 min.

Table 1. Structure of 2-hydroxynaphthalene-1-carboxanilides **1–9**, experimentally determined values of lipophilicity log *k*, calculated electronic σ parameters of anilide (Ar) substituents and IC_{50} [μM] values related to PET inhibition in spinach chloroplasts of tested compounds in comparison with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) standard.



Comp.	R	log *k*	$\sigma_{(Ar)}$ [b]	PET Inhibition IC_{50} [μM]
1 [a]	H	−0.0525	0	28.9
2 [a]	2-F	0.0521	0.06	243
3 [a]	3-F	0.0353	0.34	213
4 [a]	4-F	−0.0155	0.06	313
5	2,4-F	0.0775	1.04	215
6	2,5-F	0.1954	1.24	44.2
7	2,6-F	−0.2192	1.44	904
8	3,4-F	0.1299	1.22	243
9	3,5-F	0.2002	1.12	69.7
DCMU	–	–	–	2.1

[a] described in [1], [b] calculated using ACD/Percepta ver. 2012 (Advanced Chemistry Development, Toronto, ON, Canada).

The lipophilicity of all compounds was determined by reversed-phase high performance liquid chromatography (RP-HPLC) and expressed as the logarithm of the capacity factor *k*, see Table 1. The lowest lipophilicity value (log *k* = −0.2192) was determined for compound **7** (R = 2,6-F), while the highest lipophilicity was determined for compounds **6** (R = 2,5-F, log *k* = 0.1954) and **9** (R = 3,5-F, log *k* = 0.2002). The log *k* value of unsubstituted derivative **1** was −0.0525. The log *k* values of the remaining compounds ranged from −0.0155 to 0.1299. Electronic $\sigma_{(Ar)}$ parameters of individual substituted anilide rings (Table 1) were predicted using the ACD/Percepta ver. 2012 program (Advanced Chemistry Development, Toronto, ON, Canada). Electronic σ parameters ranged from 0 (**1**, R = H) to 1.44 (**7**, R = 2,6-F).

The PET inhibition in spinach (*Spinacia oleracea* L.) chloroplasts was expressed as a negative logarithm of IC_{50} value (compound concentration in μM causing 50% inhibition of PET). The ring-substituted 2-hydroxynaphthalene-1-carboxanilides showed rather moderate or low PET-inhibiting activity in the range of IC_{50} from 44.2 to 906 μM, see Table 1. Unsubstituted derivative **1**, which is included for comparison, had an activity of IC_{50} 28.9 μM. *N*-(2,5-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**6**) demonstrated the highest PET inhibition IC_{50} = 44.2 μM.

Although the set of evaluated compounds is limited in number and activity, some structure-activity relationships can be observed. The dependence of the PET-inhibiting

activity expressed as log(1/IC_{50} [M]) of the compounds in spinach chloroplasts on lipophilicity (log *k*) is illustrated in Figure 1A, while the dependence of PET inhibition on electronic $\sigma_{(Ar)}$ properties of the whole anilide substituents is plotted in Figure 1B. It is clear from Figure 1A that the activity within the series of fluorinated derivatives increases with increasing lipophilicity (correlation coefficient r = 0.9137, *n* = 8) of the compounds. It also seems that PET inhibition is influenced by the electron-withdrawing properties of combinations of fluorine substituents; monosubstitution shows rather weak/weaker and conversely $C_{(2,6)}$′ disubstitution (compound **7**) strong electron-withdrawing properties. The trend between PET inhibition and electronic properties seems to be bilinear with an optimum for a $\sigma_{(Ar)}$ value of approx. 1.24 (R = 2,5-F).

Thus, the mutual position of the fluorine substituents on the anilide ring plays a key role in the size of PET inhibition, although even the most potent derivative showed lower activity than unsubstituted compound **1**. On the other hand, it is clear that significant intra/intermolecular interactions can be observed in the individual combinations of substituents, which are manifested by different sizes of lipophilicity and electron-withdrawing properties of the individual derivatives. It can be stated that the difluorination of the 2,5 and 3,5 positions of the anilide ring seems to be the most advantageous and fully corresponds to the observation described in Kos et al. [16] and partially meets the results described in Gonec et al. [5].

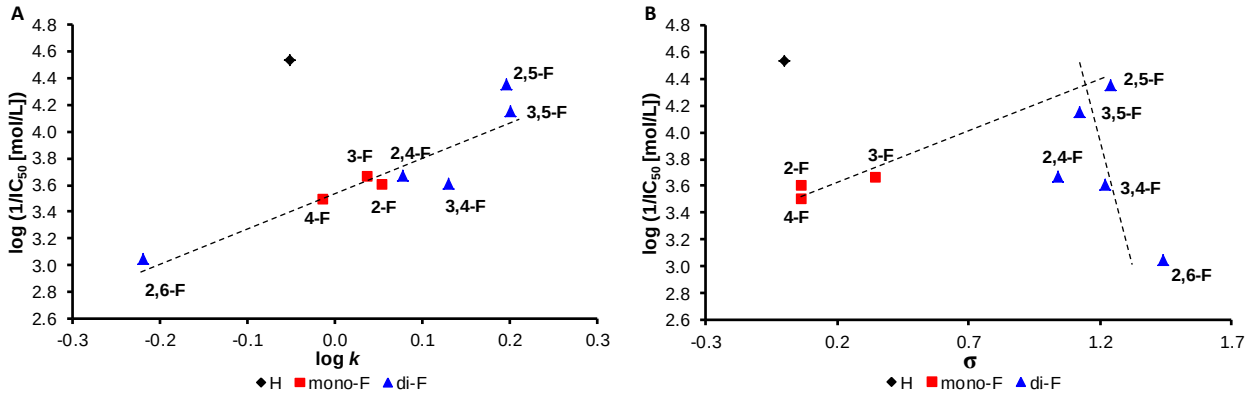


Figure 1. Graph of dependence of PET-inhibiting activity log(1/IC_{50} [M]) of compounds **1–7** in spinach chloroplasts on lipophilicity expressed as log *k* (**A**) and electronic $\sigma_{(Ar)}$ parameters of anilide substituents (**B**).

The close structural similarity (isomerism) of these derivatives with other recently described hydroxynaphthalene-carboxanilides and salicylanilides suggests that the site of inhibitory effect is located on the acceptor side of PS II, in the region between P680 (primary PS II donor) and plastoquinone Q_B [1,4,5,7,11,12,16,25,26].

3. Experimental

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 StartSYNTH microwave lab station (Milestone, Sorisole, 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 a iD7 diamond ATR optical system for Nicolet™ Impact 410 Fourier-transform 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 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 carboxamide derivatives **1–9**: 2-Hydroxynaphtalene-1-carboxylic acid (1.0 g, 5.3 mM) was suspended in dry chlorobenzene (30 mL) at ambient temperature and phosphorus trichloride (0.23 mL, 2.7 mM, 0.5 eq.), and the corresponding substituted aniline (5.3 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, 100 W; 2nd phase: 15 min, 120 °C, 500 W; 3rd phase: 20 min, 130 °C, 500 W). Then the mixture was cooled to 60 °C, and then the solvent was removed to dryness under reduced pressure. The residue was washed with hydrochloride acid and water. The crude product was recrystallized from EtOH.

Described anilides **1–4** were characterized by Gonec et al. [1].

N-(2,4-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**5**). Yield 83%; Mp 176–180 °C; IR (cm^{-1}): 3207, 1636, 1615, 1600, 1538, 1511, 1501, 1435, 1428, 1369, 1349, 1271, 1257, 1243, 1197, 1135, 1094, 1034, 971, 956, 901, 845, 819, 809, 754, 743, 727; ^{1}H-NMR (DMSO-d_6), δ: 10.19 (s, 1H), 10.16 (s, 1H), 7.90 (dd, 1H, *J* = 8.9 Hz, *J* = 6.2 Hz), 7.86 (d, 1H, *J* = 8.9 Hz), 7.85 (d, 1H, *J* = 8.2 Hz), 7.82 (d, 1H, *J* = 8.5 Hz), 7.49 (ddd, 1H, *J* = 8.5 Hz, *J* = 6.8 Hz, *J* = 1.3 Hz), 7.36 (ddd, 1H, *J* = 10.8 Hz, *J* = 9.1 Hz, *J* = 2.9 Hz), 7.34 (ddd, 1H, *J* = 8.2 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.24 (d, 1H, *J* = 8.1 Hz), 7.15 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 166.0, 159.0 (dd, *J* = 244.1 Hz, *J* = 11.4 Hz), 154.9 (dd, *J* = 249.3 Hz, *J* = 12.4 Hz), 151.9, 131.5, 130.4, 128.0, 127.4, 127.0, 126.8 (dd, *J* = 9.6 Hz, *J* = 3.0 Hz), 123.5, 123.0, 122.6 (dd, *J* = 12.4 Hz, *J* = 3.7 Hz), 118.3, 117.6, 111.1 (dd, *J* = 21.9 Hz, *J* = 3.5 Hz), 104.3 (dd, *J* = 26.6 Hz, *J* = 24.3 Hz); ^{19}F-NMR (DMSO-d_6), δ: −114.3 (m), −117.3 (m); HR-MS: $[M-H]^+$ calculated 298.067411 *m*/*z*, found 298.06796 *m*/*z*.

N-(2,5-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**6**). Yield 83%; Mp 148–151 °C; IR (cm^{-1}): 3245, 1621, 1609, 1581, 1532, 1504, 1462, 1418, 1408, 1334, 1249, 1236, 1223, 1203, 1161, 1145, 1103, 961, 870, 823, 784, 755, 740, 723, 673; ^{1}H-NMR (DMSO-d_6), δ: 10.36 (s, 1H), 10.29 (s, 1H), 8.03 (ddd, 1H, *J* = 10.1 Hz, *J* = 6.1 Hz, *J* = 3.2 Hz), 7.87 (d, 1H, *J* = 8.9 Hz), 7.85 (d, 1H, *J* = 8.2 Hz), 7.83 (d, 1H, *J* = 8.5 Hz), 7.48 (ddd, 1H, *J* = 8.5 Hz, *J* = 6.8 Hz, *J* = 1.4 Hz), 7.35 (ddd, 1H, *J* = 10.4 Hz, *J* = 9.5 Hz, *J* = 5.1 Hz), 7.34 (ddd, 1H, *J* = 8.2 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.24 (d, 1H, *J* = 8.9 Hz), 7.03–7.08 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 166.2, 157.7 (dd, *J* = 238.6 Hz, *J* = 1.4 Hz), 152.1, 149.9 (dd, *J* = 242.0 Hz, *J* = 2.3 Hz), 131.5, 130.7, 128.0, 127.5, 127.5 (dd, *J* = 13.9 Hz, *J* = 11.9 Hz), 127.1, 123.5, 123.0, 118.3, 117.2, 116.5 (dd, *J* = 22.3 Hz, *J* = 9.9 Hz), 111.2 (dd, *J* = 24.2 Hz, *J* = 7.6 Hz), 110.6 (dd, *J* = 28.4 Hz, *J* = 1.5 Hz); ^{19}F-NMR (DMSO-d_6), δ: −117.5 (m), −129.1 (m); HR-MS: $[M-H]^+$ calculated 298.067411 *m*/*z*, found 298.06796 *m*/*z*.

N-(2,6-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**7**). Yield 85%; Mp 167–169 °C; IR (cm^{-1}): 3242, 1630, 1609, 1584, 1526, 1465, 1403, 1331, 1290, 1236, 1209, 1162, 1147, 1135, 1010, 966, 899, 810, 776, 745, 707; ^{1}H-NMR (DMSO-d_6), δ: 10.18 (s, 1H), 10.08 (s, 1H), 7.88 (d, 1H, *J* = 3.3 Hz), 7.82–7.85 (m, 2H), 7.51 (ddd, 1H, *J* = 7.0 Hz, *J* = 3.7 Hz, *J* = 1.1 Hz), 7.20–7.40 (m, 5H); ^{13}C-NMR (DMSO-d_6), δ: 165.92, 158.07 (dd, *J* = 248.7 Hz, *J* = 5.4 Hz), 151.92, 131.56, 130.40, 128.05 (t, *J* = 9.9 Hz), 128.01, 127.40, 126.97, 123.44, 123.01, 118.26, 117.46, 114.62 (t, *J* = 17.2 Hz), 111.89 (m); HR-MS: $[M-H]^+$ calculated 298.06741 *m*/*z*, found 298.06805 *m*/*z*.

N-(3,4-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**8**). Yield 82%; Mp 213–217 °C; IR (cm^{-1}): 3307, 1642, 1615, 1589, 1559, 1512, 1435, 1410, 1353, 1289, 1258, 1237, 1210, 1157, 1106, 969, 850, 806, 779, 744, 671; ^{1}H-NMR (DMSO-d_6), δ: 10.62 (s, 1H), 10.18 (s, 1H), 8.02 (ddd, 1H, *J* = 13.3 Hz, *J* = 7.6 Hz, *J* = 2.5 Hz), 7.88 (d, 1H, *J* = 8.9 Hz), 7.85 (d, 1H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.5 Hz), 7.49–7.52 (m, 1H), 7.47 (ddd, 1H, *J* = 8.5 Hz, *J* = 6.8 Hz, *J* = 1.3 Hz), 7.43 (ddd, 1H, *J* = 10.5 Hz, *J* = 9.1 Hz, *J* = 9.1 Hz), 7.34 (ddd, 1H, *J* = 8.2 Hz, *J* = 6.8 Hz, *J* = 1.1 Hz), 7.26 (d, 1H, *J* = 8.9 Hz); ^{13}C-NMR (DMSO-d_6), δ: 165.9, 151.8, 149.0 (dd, *J* = 242.7

Hz, *J* = 13.1 Hz), 145.3 (dd, *J* = 241.7 Hz, *J* = 12.6 Hz), 136.6 (dd, *J* = 9.0 Hz, *J* = 2.6 Hz), 131.3, 130.4, 128.0, 127.4, 127.1, 123.3, 123.1, 118.3, 118.0, 117.5 (d, *J* = 17.7 Hz), 115.5 (dd, *J* = 5.7 Hz, *J* = 3.0 Hz), 108.1 (d, *J* = 21.7 Hz); ^{19}F-NMR (DMSO-d_6), δ: −137.3 (ddd, *J* = 22.7 Hz, *J* = 13.2 Hz, *J* = 8.7 Hz), −144.8 (m); HR-MS: $[M-H]^+$ calculated 298.067411 *m*/*z*, found 298.06799 *m*/*z*.

N-(3,5-Difluorophenyl)-2-hydroxynaphthalene-1-carboxamide (**9**). Yield 70%; Mp 219–223 °C; IR (cm^{-1}): 3328, 1646, 1614, 1549, 1514, 1476, 1442, 1425, 1349, 1312, 1267, 1241, 1210, 1152, 1112, 999, 987, 891, 835, 804, 743, 665; ^{1}H-NMR (DMSO-d_6), δ: 10.78 (s, 1H), 10.26 (s, 1H), 7.89 (d, 1H, *J* = 8.8 Hz), 7.86 (d, 1H, *J* = 7.3 Hz), 7.66 (d, 1H, *J* = 8.1 Hz), 7.56–7.59 (m, 2H), 7.48 (td, 1H, *J* = 8.1 Hz, *J* = 1.5 Hz), 7.34 (td, 1H, *J* = 7.3 Hz, *J* = 1.1 Hz), 7.26 (d, 1H, *J* = 8.8 Hz), 6.96 (tt, 1H, *J* = 9.3 Hz, *J* = 2.3 Hz); ^{13}C-NMR (DMSO-d_6), δ: 166.38, 162.51 (dd, *J* = 242.6 Hz, *J* = 15.3 Hz), 151.84, 141.98 (t, *J* = 13.7 Hz), 131.21, 130.61, 128.05, 127.35, 127.22, 123.18, 123.16, 118.29, 117.81, 102.33–101.77 (m), 98.43 (t, *J* = 26.3 Hz); HR-MS: $[M-H]^+$ calculated 298.06741 *m*/*z*, found 298.06808 *m*/*z*.

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

A HPLC system Agilent 1200 equipped with DAD detector (Agilent, Santa Clara, CA, USA) was used. A chromatographic column Symmetry® C_{18} 5 μm, 4.6 × 250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, USA) was used. The HPLC separation process was monitored and evaluated by EZChrom Elite software ver. 3.3.2 (Agilent). 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. 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 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. Study of Photosynthetic Electron Transport (PET) Inhibition in Spinach Chloroplasts

Chloroplasts were prepared from spinach (*Spinacia oleracea* L.) according to Kralova et al. [27]. The inhibition of photosynthetic electron transport (PET) in spinach chloroplasts was determined spectrophotometrically (Genesys 6, Thermo Scientific), using an artificial electron acceptor 2,6-dichlorophenol-indophenol (DCIPP) according to Kralova et al. [27], and the rate of photosynthetic electron transport was monitored as a photoreduction of DCPIP. The measurements were carried out in phosphate buffer (0.02 M, pH 7.2) containing sucrose (0.4 M), $MgCl_2$ (0.005 M), and NaCl (0.015 M). The chlorophyll content was 30 mg/L in these experiments, and the samples were irradiated (~100 W/m^2 with 10 cm distance) with a halogen lamp (250 W) using a 4 cm water filter to prevent warming of the samples (suspension temperature 22 °C). The studied compounds were dissolved in DMSO due to their limited water solubility. The applied DMSO concentration (up to 4%) did not affect the photochemical activity in spinach chloroplasts. The inhibitory efficiency of the studied compounds was expressed by IC_{50} values, i.e., by molar concentration of the compounds causing a 50% decrease in the oxygen evolution rate relative to the untreated control. The comparable IC_{50} value for the selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diuron®) was about 2.1 μM. The results are shown in Table 1.

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