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Photosynthesis-Inhibiting Activity of Methoxy-Substituted 3-Hydroxynaphthalene-2-Carboxanilides †

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Abstract: In this study, a series of six 3-hydroxynaphthalene-2-carboxanilides, substituted on the anilide ring by combinations of methoxy-methoxy, methoxy-fluoro and methoxy-chloro groups at different positions, was prepared by microwave-assisted synthesis and characterized. The compounds were tested for their activity related to the inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts. The PET-inhibiting activity of the compounds was within a wide range, but rather moderate; the highest activity within the series was determined for *N*-(3,5-dimehoxy-phenyl)-3-hydroxynaphthalene-2-carboxamide (IC_{50} = 24.5 μM). These compounds are supposed to inhibit PET in photosystem II.

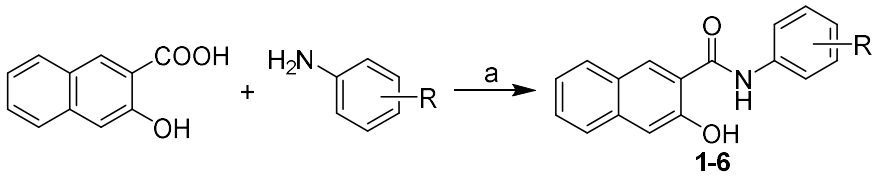
Keywords: hydroxynaphthalene-carboxamides; PET inhibition; spinach chloroplasts

1. Introduction

Although approx. 20 various mechanisms of actions of herbicides are known [1–3], over 50% of commercially available herbicides act by reversible binding to photosystem II (PS II) [1,2,4,5], and due to this interaction, the photosynthetic electron transport (PET) is interrupted [6–10]. In addition to allowing interactions with many other biological targets [11,12], the amide (–CONH–) moiety is essential for the effectiveness of many herbicides acting as inhibitors of photosynthesis [10,13–20]. A series of ring-monosubstituted anilides of 3-hydroxynaphtalene-2-carboxylic acid were published by Kos et al. [21,22] as compounds with an interesting spectrum of biological activities. Recently, disubstituted derivatives [23,24] have been published. Since monosubstituted derivatives of 3-hydroxy-*N*-arylnaphthalene-2-carboxanilides showed PET inhibition in spinach chloroplasts (*Spinacia oleracea* L.), selected new derivatives variously substituted by dimethoxy, fluoro-methoxy or chloro-methoxy groups were evaluated for their PET-inhibiting activity. Thus, this short paper builds on the previous work [21,23,25–33] aimed at investigating the PET-inhibiting activity of naphthalenecarboxamides. The relationships between structure and activity are briefly discussed.

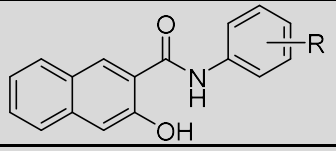
2. Results and Discussion

All the studied compounds were prepared according to Scheme 1 as described previously by Kos et al. [21,23,24]. The condensation of 3-hydroxynaphthalene-2-carboxylic acid with appropriate substituted anilines using phosphorus trichloride in dry chlorobenzene under microwave conditions gave a series of target 3-hydroxy-*N*-arylnaphthalene-2-carboxanilides **1–6**, see Table 1



Scheme 1. Synthesis of 3-hydroxy-*N*-arylnaphthalene-2-carboxanilides **1–6**. *Reagents and conditions*: (a) PCl_3, chlorobenzene, MW, 45 min.

Table 1. Structure of 3-hydroxynaphthalene-2-carboxanilides **1–6**, calculated values of log *P* of compounds, 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 *P* [a]	$\sigma_{(Ar)}$ [a]	PET Inhibition IC_{50} [μM]
1	2,5-OCH_3	4.77	0.08	183
2	3,5-OCH_3	4.49	0.93	**24.5**
3	3-F-5-OCH_3	4.88	0.99	31.6
4	2-F-6-OCH_3	4.69	0.16	507
5	2-OCH_3-5-F	4.89	0.14	79.1
6	2-Cl-5-OCH_3	5.20	1.13	171
DCMU	–	–	–	2.1

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

All the predicted molecular descriptors (lipophilicity and electronic σ parameters of individual anilides) were calculated using the ACD/Percepta ver. 2012 program (Advanced Chemistry Development, Toronto, ON, Canada), see Table 1. The lipophilicity of compounds **1–6**, expressed as log *P* values, ranged from 4.49 (compound **2**, R = 3,5-OCH_3) to 5.20 (compound **6**, R = 2-Cl-5-OCH_3). In general, it can be stated that the lipophilicity is rather high, but for agrochemicals, higher lipophilicity ($\log p \leq 5$) is recommended [34], because they have to permeate through the hydrophobic cuticle of the plants. As expected, both dimethoxy derivatives **1** and **2** showed lower lipophilicity expressed as log *P* values than the combinations of fluoro-methoxy substituents (compounds **3–5**), and the lipophilicity of the latter was lower than that of chlorinated derivative **6**, so that the order of log *P* values of all the derivatives discussed was as follows: **2** (R = 3,5-OCH_3) < **1** (R = 2,5-OCH_3) < **4** (R = 2-F-6-OCH_3) < **3** (R = 3-F-5-OCH_3) < **5** (R = 2-OCH_3-5-F) < **6** (R = 2-Cl-5-OCH_3).

The PET-inhibiting activity was expressed by negative logarithm of IC_{50} value (compound concentration in μM causing 50% inhibition of PET). The evaluated disubstituted 3-hydroxynaphthalene-2-carboxanilides showed a wide range of PET inhibition in spinach (*Spinacia oleracea* L.) chloroplasts with IC_{50} values ranging from 9.8 to 1123 μM, see Table 1, while in general, the PET inhibition was rather moderate. *N*-(3,5-Dimethoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**2**) showed the highest PET-inhibiting activity (IC_{50} = 24.5 μM) within the whole investigated series, while positional isomer *N*-(2,5-dimethoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**1**) was completely inactive (IC_{50} = 183 μM). Also *N*-(2-chloro-5-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**6**) and *N*-(2-fluoro-6-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**4**) did not show PET activity (IC_{50} = 171 and 507 μM, respectively).

Due to the limited number of compounds, of which only 3 showed moderate activity, it is not possible to thoroughly evaluate the structure-activity relationships, it is not even possible to formulate trends, see Figure 1A,B, where the dependence of the PET-inhibiting activity expressed as

log (1/IC_{50} [M]) of compounds **1–6** in spinach chloroplasts on lipophilicity (log *p*) and electronic $\sigma_{(Ar)}$ properties of the whole anilide substituents is plotted. On the other hand, these limited observations are fully consistent with recently published results [23,28,29]. The position of anilide substitution is critical; the disubstitution of both *meta* positions, i.e., $C_{(3)}$' and $C_{(5)}$', is more preferred for higher PET-inhibiting activity and gives more active compounds than mono-*meta*-substitutions [23,28,29]. Any other combinations of positions led to a reduction or loss of PET inhibition [23,28,29]. If one methoxy moiety is replaced by fluorine, the PET activity is insignificantly changed, while the substitution by chlorine caused a decrease of PET inhibition [23,28,29]. This fact is also connected with the electron σ parameter, which was approx. 0.96 for active compounds **2** and **3** within this series; in previous studies, $\sigma_{(Ar)}$ of PET active compounds was approx. 1.1 [23,28,29]. Thus, it can be concluded that the complex electronic properties of anilide substituents affecting the electron density at the amide bond have a direct effect on PET-inhibiting activity.

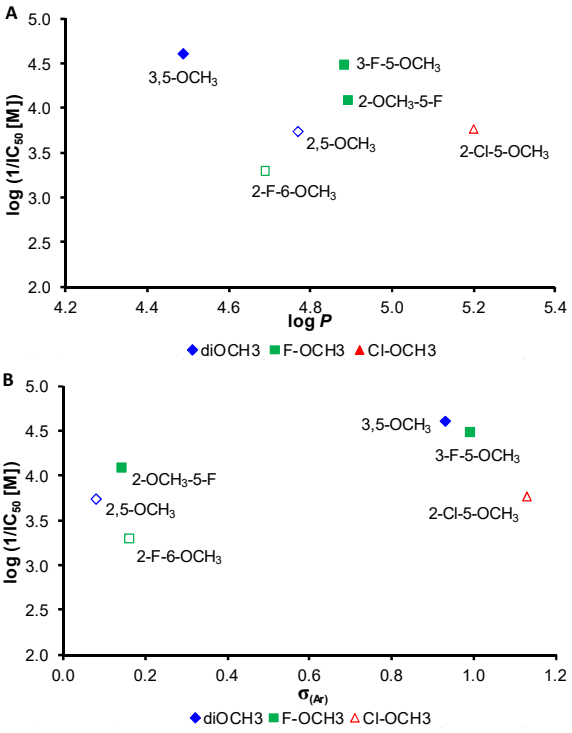


Figure 1. Graph of dependence of PET-inhibiting activity log(1/IC_{50} [M]) of compounds **1–6** in spinach chloroplasts on lipophilicity expressed as log *p* (**A**) and electronic $\sigma_{(Ar)}$ parameters of anilide substituents (**B**). Empty symbols indicate compounds with no or insignificant activity.

Based on close structural similarity to other salicylanilides or hydroxynaphthanilides, the same mechanism of action of the investigated compounds can be assumed. The site of inhibitory action of the 3-hydroxynaphthalene-2-carboxanilides is situated on the acceptor side of PS II, at the section between P_{680} (primary donor of PS II) and plastoquinone Q_B [19,21,25–33,35,36].

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 CEM Discover SP microwave reactor (CEM, Matthews, NC, USA). 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 Smart MIRacle™ ATR ZnSe for Nicolet™ Impact 410 Fourier-transform IR

spectrometer (Thermo Scientific, West Palm Beach, FL, USA). The spectra were obtained by the accumulation of 256 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 JNM-ECA 600II device (600 MHz for ^{1}H and 150 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 **1–6**: 3-Hydroxynaphtalene-2-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, 500W; 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.

N-(2,5-Dimethoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**1**). Yield 57%; Mp 186-188 °C; IR (cm^{-1}): 3425, 2934, 2836, 1604, 1592, 1538, 1490, 1445, 1434, 1280, 1217, 1183, 1144, 1050, 1024, 872, 862, 785, 751, 737, 711; ^{1}H-NMR (DMSO-d_6), δ: 11.79 (s, 1H), 11.13 (s, 1H), 8.70 (s, 1H), 8.24 (s, 1H), 7.98 (d, 1H, *J* = 8.1 Hz), 7.78 (d, 1H, *J* = 8.1 Hz), 7.52 (t, 1H, *J* = 7.1 Hz), 7.37 (t, 1H, *J* = 7.3 Hz), 7.36 (s, 1H), 7.03 (dd, 1H, *J* = 9.2 Hz, *J* = 1.5 Hz), 6.66 (ddd, 1H, *J* = 9.2 Hz, *J* = 7.7 Hz, *J* = 1.5 Hz), 3.87 (s, 3H), 3.74 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.78, 153.24, 152.52, 142.74, 135.86, 132.74, 129.04, 128.78, 128.34, 127.23, 125.62, 123.86, 121.25, 111.74, 110.72, 107.52, 106.90, 56.63, 55.33; HR-MS: $[M-H]^+$ calculated 322.10738 *m/z*, found 322.10800 *m/z*.

N-(3,5-Dimethoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**2**). Yield 80%; Mp 179-181 °C; IR (cm^{-1}): 3115, 1645, 1623, 1606, 1558, 1478, 1455, 1341, 1318, 1269, 1227, 1198, 1156, 1061, 948, 838, 811, 799, 767, 678; ^{1}H-NMR (DMSO-d_6), δ: 11.26 (s, 1H), 10.52 (s, 1H), 8.46 (s, 1H), 7.92 (d, 1H, *J* = 8.1 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 7.51 (t, 1H, *J* = 7.5 Hz), 7.36 (t, 1H, *J* = 7.3 Hz), 7.32 (s, 1H), 7.04 (d, 2H, *J* = 1.8 Hz), 6.31 (t, 1H, *J* = 1.8 Hz), 3.76 (s, 6H); ^{13}C-NMR (DMSO-d_6), δ: 165.65, 160.51, 153.57, 140.16, 135.73, 130.45, 128.69, 128.13, 126.87, 125.77, 123.76, 122.07, 110.53, 98.71, 96.02, 55.16; HR-MS: $[M-H]^+$ calculated 322.10738 *m/z*, found 322.10809 *m/z*.

N-(3-Fluoro-5-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**3**). Yield 59%; Mp 228-230 °C; IR (cm^{-1}): 3147, 1644, 1622, 1595, 1557, 1520, 1456, 1448, 1359, 1261, 1224, 1212, 1191, 1141, 1129, 1063, 999, 987, 872, 858, 816, 767, 745, 690; ^{1}H-NMR (DMSO-d_6), δ: 11.12 (s, 1H), 10.64 (s, 1H), 8.41 (s, 1H), 7.93 (d, 1H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.1 Hz), 7.51 (t, 1H, *J* = 7.0 Hz), 7.32-7.40 (m, 3H), 7.21 (s, 1H), 6.62 (d, 1H *J* = 11.0 Hz), 3.78 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 165.74, 162.92 (d, *J* = 238.5 Hz), 160.71 (d, *J* = 12.9 Hz), 153.28, 140.61 (d, *J* = 13.7 Hz), 135.70, 130.46, 128.66, 128.11, 126.85, 125.77, 123.77, 122.51, 110.45, 101.95 (d, *J* = 2.0 Hz), 99.39 (d, *J* = 27.3 Hz), 96.97 (d, *J* = 25.0 Hz), 55.58; HR-MS: $[M-H]^+$ calculated 310.08740 *m/z*, found 310.08817 *m/z*.

N-(2-Fluoro-6-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**4**). Yield 66%; Mp 140-142 °C; IR (cm^{-1}): 3259, 2836, 1651, 1622, 1596, 1532, 1515, 1506, 1466, 1438, 1279, 1249, 1216, 1167, 1146, 1087, 900, 873, 834, 789, 767, 747, 728; ^{1}H-NMR (DMSO-d_6), δ: 11.76 (s, 1H), 10.22 (s, 1H), 8.69 (s, 1H), 7.93 (d, 1H, *J* = 8.8 Hz), 7.78 (d, 1H, *J* = 8.4 Hz), 7.54 (t, 1H, *J* = 7.3 Hz), 7.30-7.40 (m, 3H), 6.99 (d, 1H, *J* = 8.4 Hz), 6.94 (t, 1H, *J* = 9.0 Hz), 3.84 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 166.28, 158.06 (d, *J* = 246.4 Hz), 155.80 (d, *J* = 5.3 Hz), 154.64, 136.20, 130.97, 128.90, 128.51, 128.22 (d, *J* = 10.7 Hz), 126.75, 125.82, 123.88, 118.74, 113.67 (d, *J* = 15.3 Hz), 110.91, 107.91 (d, *J* = 26.4 Hz), 107.71, 56.25; HR-MS: $[M-H]^+$ calculated 310.08740 *m/z*, found 310.08801 *m/z*.

N-(5-Fluoro-2-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**5**). Yield 80%; Mp 199-201 °C; IR (cm^{-1}): 3194, 1640, 1625, 1615, 1601, 1538, 1488, 1432, 1393, 1356, 1346, 1249, 1214, 1176, 1148, 1065, 1038, 975, 866, 838, 786, 731, 711; ^{1}H-NMR (DMSO-d_6), δ: 11.86 (s, 1H), 11.25 (s, 1H), 8.70 (s, 1H), 8.40

(dd, 1H, *J* = 11.0 Hz, *J* = 3.3 Hz), 7.93 (d, 1H, *J* = 8.1 Hz), 7.78 (d, 1H, *J* = 8.4 Hz), 7.53 (t, 1H, *J* = 7.5 Hz), 7.37 (s, 1H), 7.36 (t, 1H, *J* = 7.5 Hz), 7.12 (dd, 1H, *J* = 9.2 Hz, *J* = 5.1 Hz), 6.92 (td, 1H, *J* = 8.6 Hz, *J* = 3.3 Hz), 3.92 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.96, 156.01 (d, *J* = 232.2 Hz), 152.43, 144.77 (d, *J* = 1.8 Hz), 135.96, 132.88, 129.08, 128.95 (d, *J* = 12.9 Hz), 128.46, 127.23, 125.65, 123.94, 120.95, 111.72 (d, *J* = 9.1 Hz), 110.78, 109.01 (d, *J* = 22.8 Hz), 106.91 (d, *J* = 29.6 Hz), 56.96; HR-MS: $[M-H]^+$ calculated 310.18740 *m*/*z*, found 310.08807 *m*/*z*.

N-(2-Chloro-5-methoxyphenyl)-3-hydroxynaphthalene-2-carboxamide (**6**). Yield 58%; Mp 187-188 °C; IR (cm^{-1}): 3177, 2954, 2834, 1638, 1624, 1598, 1539, 1462, 1447, 1427, 1358, 1305, 1274, 1262, 1220, 1167, 1147, 1135, 1063, 1028, 960, 916, 866, 845, 787, 771, 745, 719; ^{1}H-NMR (DMSO-d_6) δ: 11.97 (s, 1H), 11.17 (s, 1H), 8.73 (s, 1H), 8.25 (d, 1H, *J* = 2.9 Hz), 7.99 (d, 1H, *J* = 8.2 Hz), 7.78 (d, 1H, *J* = 8.3 Hz), 7.53 (ddd, 1H, *J* = 8.3 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.46 (d, 1H, *J* = 8.8 Hz), 7.38 (ddd, 1H, *J* = 8.2 Hz, *J* = 6.8 Hz, *J* = 1.2 Hz), 7.38 (s, 1H), 6.78 (dd, 1H, *J* = 8.8 Hz, *J* = 3.0 Hz), 3.80 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 163.4, 158.5, 152.5, 136.1, 132.9, 129.6, 129.1, 128.6, 127.2, 125.7, 124.0, 120.6, 114.2, 110.8, 110.4, 108.0, 55.5; HR-MS: $[M+H]^+$ calculated 328.0735 *m*/*z*, found 328.0737 *m*/*z*.

3.3. Study of Photosynthetic Electron Transport (PET) Inhibition in Spinach Chloroplasts

Chloroplasts were prepared from spinach (*Spinacia oleracea* L.) according to Kralova et al. [37]. 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. [37], 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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