Preparation and Herbicidal Activity of Halogenated 8-Hydroxyquinoline-2-carboxanilides

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Abstract: In this study a series of twelve ring-substituted 8-hydroxyquinoline-2-carboxanilides was prepared and characterized. The discussed compounds were prepared by using microwave-assisted synthesis. The compounds were tested for their activity related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts. The compounds were found to inhibit PET in photosystem II. Significant PET-inhibiting activity was observed for *meta*-substituted compounds showing IC_{50} values close to that of photosystem II herbicide DCMU (3-(3,4-dichlorophenyl)-1,1-dimethylurea, IC_{50} = 1.9 μmol/L). *N*-(3-Fluorophenyl)-8-hydroxyquinoline-2-carboxamide showed the highest PET inhibition. The activity of *meta*- and *para*-substituted compounds strongly decreased with lipophilicity increase and electron-withdrawing effect. No influence of any of these parameters on PET-inhibiting activity of *ortho*-substituted compounds was observed.

Keywords: Hydroxyquinoline-2-carboxamides; PET inhibition; Spinach chloroplasts; Structure-activity relationships.

INTRODUCTION

A quinoline scaffold possesses unique physico-chemical properties and therefore it is present in many classes of biologically-active compounds expressing diverse effects [1–6]. In addition, according to the results reported recently, some quinoline derivatives and their analogues/isosteres also showed noteworthy herbicidal activities [7–20].

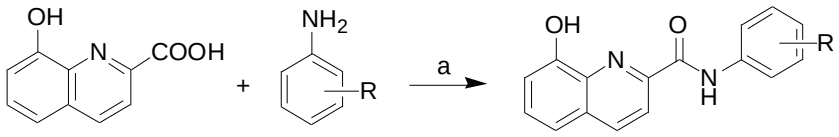
Although at present approximately 20 mechanisms of action of herbicides are known [21], over 50% of commercially available herbicides act by reversible binding to photosystem II (PS II), a membrane-protein complex in the thylakoid membranes, which catalyses the oxidation of water and the reduction of plastoquinone [22], and thereby inhibit photosynthesis [23–25]. Some organic compounds, possessing an amide (-NHCO-) group, e.g., substituted anilides [11,15–18,20], or a wide variety of compounds containing the quinoline system [9,10,12–14,19] were found to interact with tyrosine radicals Tyr_Z and Tyr_D (or their surroundings) which are situated in D_1 and D_2 proteins on the donor side of PS II. Due to this interaction, interruption of the photosynthetic electron transport occurs.

In the context of the previously-described azanaphtalenes and their isosteres [7–20], new simple modifications of quinoline that can possess interesting biological activity were investigated. The compounds were tested for their photosynthesis-inhibiting activity – the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.). Relationships between the structure and the inhibitory activity related to inhibition of photosynthetic electron transport (PET) in spinach chloroplasts of the new compounds are discussed.

RESULTS AND DISCUSSION

All the studied compounds were prepared according to Scheme 1. Microwave-assisted synthesis [17,18,20] facilitated the process of obtaining ring-substituted 8-hydroxyquinoline-2-carboxanilides, thus synthesis of the target compounds was carried out only by one step. At first the carboxyl group was activated with phosphorus trichloride. The final anilide was immediately formed by aminolysis of the acyl chloride by ring-substituted aniline in dry chlorobenzene. All the compounds were recrystallized from ethanol.

Scheme 1. Synthesis of ring-substituted 8-hydroxyquinoline-2-carboxanilides **1a**–**4c**: (a) PCl_3, chlorobenzene, MW.

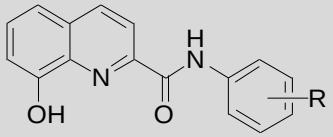


1-**4c**

R = F, Cl, Br, CF_3

Lipophilicity of all compounds **1a**–**4c** was calculated as log *P* using ACD/Percepta ver. 2012 (Advanced Chemistry Development, Inc., Toronto, ON, Canada). The results are shown in Table 1. Compounds showed a wide range of lipophilicities, with log *P* values from 2.59 (compounds **2a**, R = 2-F and **2c**, R = 4-F) to 3.44 (compound **4b**, R = 3-CF_3) within the series of ring-substituted 8-hydroxyquinoline-2-carboxanilides. For individual substituents in the aniline part of the discussed compounds also electronic Hammett's σ parameters were predicted using the same software; they ranged from 0.06 (compound **1a**, R = 2-F) to 0.51 (compounds **4a**, R = 2-CF_3 and **4c**, R = 4-CF_3).

Table 1. Structure of ring-substituted 8-hydroxyquinoline-2-carboxanilides **1a**–**4c**, calculated values of log *P*, electronic Hammett's σ parameters (both calculated using ACD/Percepta ver. 2012), IC_{50} [μmol/L] values related to PET inhibition in spinach chloroplasts of compounds **1a**–**4c** in comparison with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) standard.



Comp.	R	log *P*	σ	PET inhibition IC_{50} [μmol/L]
1a	2-F	2.59	0.06	32.1
1b	3-F	2.76	0.34	2.3
1c	4-F	2.59	0.06	5.6
2a	2-Cl	3.07	0.22	46.0
2b	3-Cl	3.28	0.37	3.6
2c	4-Cl	3.05	0.23	42.5
3a	2-Br	3.16	0.22	38.9
3b	3-Br	3.31	0.39	3.4
3c	4-Br	3.19	0.23	72.7
4a	2-CF_3	3.36	0.51	51.2
4b	3-CF_3	3.44	0.43	21.3
4c	4-CF_3	3.27	0.51	477.6
DCMU	–	–	–	1.9

The evaluated quinoline derivatives showed a wide range of PET-inhibiting activity related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts, see Table 1. *N*-(3-Fluorophenyl)-8-hydroxyquinoline-2-carboxamide (**1b**) expressed the highest PET-inhibiting activity (IC_{50} = 2.3 μmol/L), while 8-hydroxy-*N*-[4-(trifluoromethyl)phenyl]quinoline-2-carboxamide (**4c**) showed the lowest PET inhibition (IC_{50} = 477.6 μmol/L). With respect to these small but specifically substituted groups of compounds some structure-activity relationships (SAR) can be proposed.

The PET-inhibiting activity was expressed by negative logarithm of IC_{50} value (compound concentration in mol/L causing 50% inhibition of PET). Correlations between log(1/IC_{50} [mol/L]) and the lipophilic or electronic properties of the individual anilide substituents in compounds **1a**–**4c** were performed, see Fig. 1 and Fig. 2. Based on the obtained results it is evident that *meta* substitution of aniline ring is preferred. Figure 1 (dependences between PET inhibition and electronic σ properties of the anilide substituents) illustrates the general trend: PET inhibition strongly decreases within individual *meta*- and *para*-series with electron-withdrawing substituent (F > Cl > Br > CF_3). On the other hand, the biological activity is also affected by the lipophilicity of studied compounds **1a**–**4c**, see Figure 2, where dependences of PET inhibition on log *P* are illustrated. In general, the dependences of log (1/IC_{50}) on log *P* show a similar trend as in case of electronic σ properties. The activity of the discussed compounds decreases with lipophilicity increase. It can be stated that both parameters had considerable influence on PET-inhibiting activity of *meta*- and *para*-substituted compounds, while in case of *ortho*-substituted compounds the influence of both observed parameters on PET inhibition was insignificant.

Figure 1. Relationships between PET-inhibiting activity log ($1/IC_{50}$) [mol/L] in spinach chloroplasts and anilide substituent electronic Hammett's σ parameters of studied compounds **1a**–**4c**.

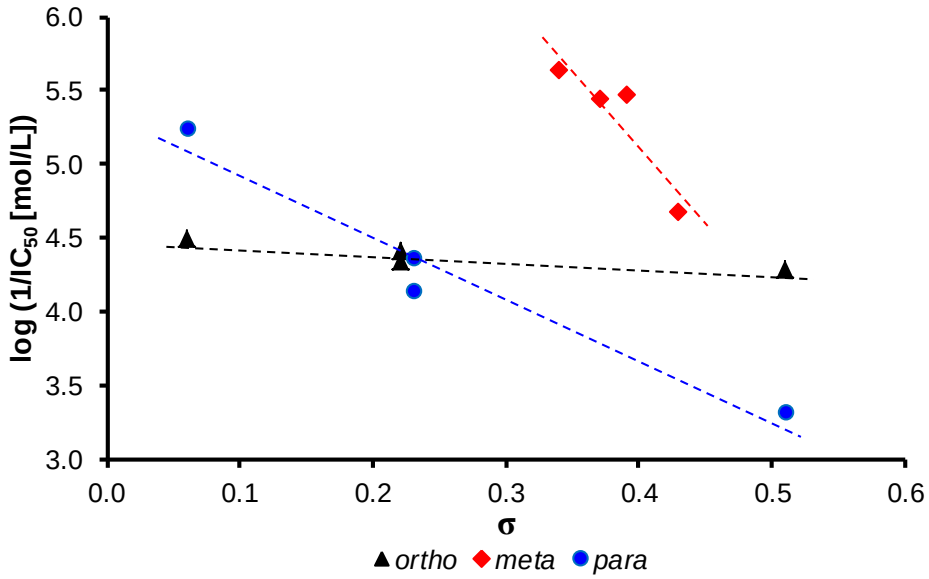
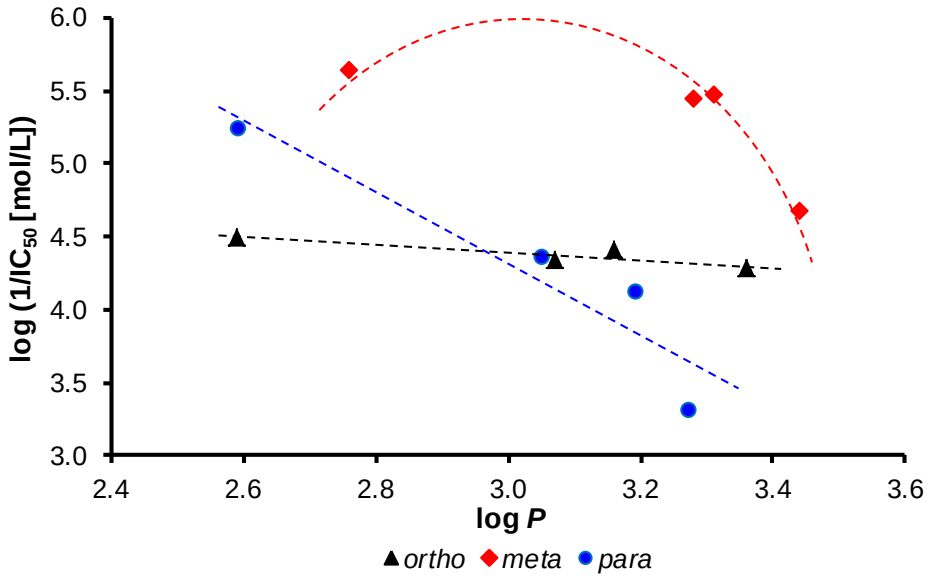


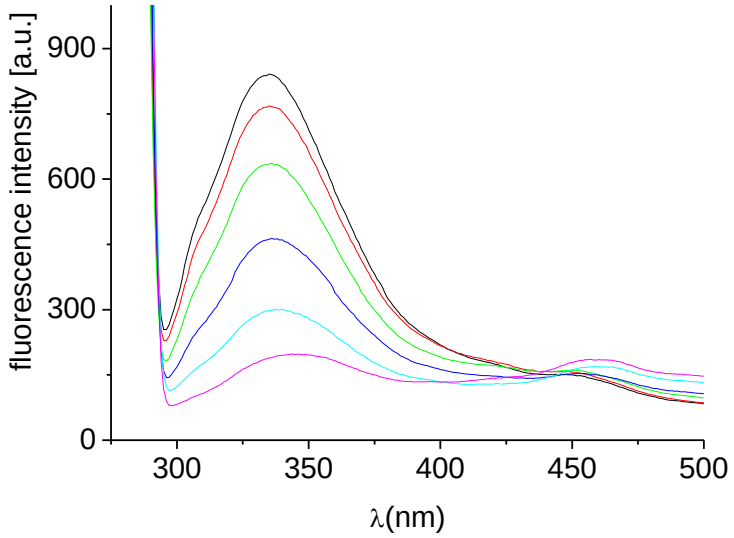
Figure 2. Relationships between PET-inhibiting activity log ($1/IC_{50}$ [mol/L]) in spinach chloroplasts and lipophilicity, expressed as log *P*, of studied compounds **1a**–**4c**.



Application of artificial electron donors allows specifying the section in the photosynthetic electron transport chain in which PET is stopped by an inhibitor [26]. One of such suitable artificial electron donors is 2,5-diphenylcarbazide (DPC) which supplies electrons in the site of $Z^{\bullet}/D^{\bullet}$ intermediate on the donor side of PS II. Consequently, in the presence of DPC the PET which was inhibited in the section between the oxygen evolving complex and the $Z^{\bullet}/D^{\bullet}$ intermediate can be restored. On the other hand, PET restoration by DPC does not occur if the site of PET inhibition is situated on the acceptor side of PS II, between P680 and secondary quinone acceptor Q_B. Because application of DPC to chloroplasts, the activity of which was inhibited (up to 15% of the control), caused practically complete PET restoration, it can be concluded that the site of studied halogenated 8-hydroxyquinoline-2-carboxanilides is situated on the donor side of PS II. The site of action situated on the donor side of PS II was found

also for 2-alkylthio-6-R-benzothiazoles (R = 6-formamido-, 6-acetamido-, and 6-benzoyl-amino-) [27], anilides of 2-alkylpyridine-4-carboxylic acids acting in the intermediates $Z^{\bullet}/D^{\bullet}$ [28] and 2-alkylsulphanyl-4-pyridinecarbothioamides acting in the $D^{\bullet}$ intermediate [29].
Interaction of the studied compounds with aromatic amino acids, which are present in the proteins of spinach chloroplasts situated in PS II, was documented by quenching their fluorescence at 340 nm. Figure 3 presents fluorescence emission spectra of aromatic amino acids of untreated spinach chloroplasts and of chloroplasts treated with increasing concentrations of compound **3c**. Binding of these compounds to aromatic amino acids occurring in photosynthetic proteins contributes to PET inhibition. Similar fluorescence quenching of aromatic amino acids present in PS II was observed for other tested halogenated 8-hydroxyquinoline-2-carboxanilides as well as previously studied *N*-benzylpyrazine-2-carboxamides [30] and 5-bromo- and 3,5-dibromo-2-hydroxy-*N*-phenylbenzamides [31].

Figure 3. Fluorescence emission spectra of aromatic amino acids in untreated spinach chloroplasts in presence of compound **3c**: 0, 5.5, 11, 22, 44 and 66 μmol/L (curves from top to bottom; λ_{ex} = 275 nm).



EXPERIMENTAL

General

All reagents were purchased from Aldrich (Sigma-Aldrich, St. Louis, MO, USA). TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and evaluated in iodine vapour. The melting points were determined on 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 FT-IR spectrometer (Thermo Electron Corporation, West Palm Beach, FL, USA). The spectra were obtained by accumulation of 256 scans with 2 cm^{-1} resolution in the region of 4000–600 cm^{-1}. All ^{1}H- and ^{13}C-NMR spectra were recorded on an Agilent VNMRS 600 MHz system (Agilent Technologies, Santa Clara, CA, USA) equipped with a triple resonance HCN probe at 25 °C in DMSO-d_6. ^{1}H and ^{13}C chemical shifts and ^{13}C-^{19}F coupling constants were determined from the standard ^{1}H and ^{13}C spectra with digital resolution 0.3 Hz or better. Chemical shifts (δ) are reported in ppm. When necessary, additional experiments were done: ^{13}C-APT (Attached Proton Test) for discrimination between CH and quaternary carbons; DQF COSY, HSQC and HMBC for through-bond ^{1}H-^{1}H and one- and multiple-bond ^{1}H-^{13}C correlations. Mass spectra were

measured using a LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Electron Corporation) with direct injection into an APCI source (400 °C) in the positive mode.

Synthesis

General procedure for synthesis of carboxamide derivatives (**1a**–**4c**): 8-Hydroxyquinoline-2-carboxylic acid (1.0 g, 5.3 mmol) was suspended in dry chlorobenzene (30 mL) at ambient temperature and phosphorus trichloride (0.23 mL, 2.7 mmol, 0.5 eq.), and the corresponding substituted aniline (5.3 mmol, 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 50 °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. Studied compounds **1a**–**4c** are presented in Table 1.

N-(2-Fluorophenyl)-8-hydroxyquinoline-2-carboxamide (**1a**). Yield 68%; Mp. 145 °C; IR (Zn/Se ATR, cm^{-1}): 3489w, 3376w, 1689s, 1618m, 1594w, 1537s, 1505s, 1455m, 1359w, 1327m, 1290w, 1252w, 1232m, 1194w, 1169w, 1121w, 1083w, 1031w, 887w, 848m, 757s, 722s; ^{1}H-NMR (DMSO-d_6), δ: 11.168 (s, 1H), 10.352 (s, 1H), 8.576 (d, 1H, *J*=8.5 Hz), 8.230 (d, 1H, *J*=8.5 Hz), 7.745 (td, 1H, *J*=7.8, 1.8 Hz), 7.608 (dd, 1H, *J*=7.7, 8.1 Hz), 7.523 (dd, 1H, *J*=8.2, 1.2 Hz), 7.40-7.28 (m, 3H), 7.219 (dd, 1H, *J*=7.7, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.54, 155.81 (*J*=247.4 Hz), 153.74, 146.76, 138.06, 136.46, 129.82, 129.73, 127.22 (*J*=9.2 Hz), 127.20, 125.05 (*J*=12.2 Hz), 124.45 (*J*=3.6 Hz), 118.92, 115.95(*J*=19.8 Hz), 117.60, 111.93; HR-MS: for $C_{16}H_{12}FN_2O_2$ $[M+H]^+$ calculated 283.0877 m/z, found 283.0872 m/z.

N-(3-Fluorophenyl)-8-hydroxyquinoline-2-carboxamide (**1b**). Yield 62%; Mp. 197 °C; IR (Zn/Se ATR, cm^{-1}): 3333w, 1686s, 1612s, 1599m, 1528s, 1504s, 1463m, 1443m, 1391w, 1365w, 1325w, 1295w, 1276w, 1237m, 1200w, 1174w, 1145s, 1111m, 1083w, 965m, 872w, 846s, 775s, 760s, 748s, 722s, 684s; ^{1}H-NMR (DMSO-d_6), δ: 11.265 (s, 1H), 10.376 (s, 1H), 8.572 (d, 1H, *J*=8.5 Hz), 8.263 (d, 1H, *J*=8.5 Hz), 7.866 (dt, 1H, *J*=11.6, 2.2 Hz), 7.698 (ddd, 1H, *J*=8.1, 1.9, 0.9 Hz), 7.611 (t, 1H, *J*=7.9 Hz), 7.522 (dd, 1H, *J*=8.2, 1.2 Hz), 7.484 (dt, 1H, *J*=6.8, 8.2 Hz), 7.233 (dd, 1H, *J*=7.6, 1.2 Hz), 7.012 (td, 1H, *J*=8.4, 2.5 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.35, 162.33 (*J*=241.6 Hz), 153.67, 146.87, 140.01(*J*=11.0 Hz), 138.20, 136.32, 130.43 (*J*=9.5 Hz), 129.87, 129.77, 118.95, 117.68, 116.33 (*J*=2.6 Hz), 112.10, 110.61 (*J*=20.9 Hz), 107.30 (*J*=26.1 Hz); HR-MS: for $C_{16}H_{12}FN_2O_2$ $[M+H]^+$ calculated 283.0877m/z, found 283.0876 m/z.

N-(4-Fluorophenyl)-8-hydroxyquinoline-2-carboxamide (**1c**). Yield 71%; Mp. 200 °C; IR (Zn/Se ATR, cm^{-1}): 3318w, 1677w, 1655m, 1609w, 1528s, 1528s, 1504s, 1464s, 1405m, 1359w, 1309w, 1286w, 1225m, 1189m, 1156m, 1133w, 1089w, 1083w, 932w, 886, 854m, 827s, 760m, 723, 678w; ^{1}H-NMR (DMSO-d_6), δ: 11.206 (s, 1H), 10.349 (s, 1H), 8.565 (d, 1H, *J*=8.5 Hz), 8.260 (d, 1H, *J*=8.5 Hz), 7.909 (m, 2H), 7.604 (dd, 1H, *J*=8.1, 7.7 Hz), 7.519 (dd, 1H, *J*=8.2, 1.2 Hz), 7.290 (m, 2H), 7.226 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.05, 158.57 (*J*=240.9 Hz), 153.64, 147.12, 138.12, 136.33, 134.60 (*J*=2.7 Hz), 129.74, 129.68, 122.56 (2C, *J*=8.0 Hz), 118.93, 117.65, 115.41(2C, *J*=22.4 Hz), 111.99; HR-MS: for $C_{16}H_{12}FN_2O_2$ $[M+H]^+$ calculated 283.0877 m/z, found 283.0877 m/z.

N-(2-Chlorophenyl)-8-hydroxyquinoline-2-carboxamide (**2a**). Yield 71%; Mp. 151-152 °C; IR (Zn/Se ATR, cm^{-1}): 3355w, 1695s, 1595s, 1581w, 1535s, 1505s, 1461m, 1433m, 1362w, 1328w, 1310w, 1290w, 1237s, 1198m, 1136w, 1115m, 1088w, 1052w, 1032m, 885w, 848s, 743s, 724s, 668s; ^{1}H-NMR (DMSO-d_6), δ: 11.224 (s, 1H), 10.322 (s, 1H), 8.571 (d, 1H, *J*=8.5 Hz), 8.229 (d, 1H, *J*=8.5 Hz), 7.746 (dd, 1H, *J*=7.9, 1.6 Hz), 7.630 (dd, 1H, *J*=8.0, 1.4 Hz), 7.610 (t, 1H, *J*=7.9 Hz), 7.528 (dd, 1H, *J*=8.2, 1.1 Hz), 7.458 (td, 1H, *J*=7.6, 1.5 Hz),

7.352 (td, 1H, *J*=7.8, 1.6 Hz), 7.233 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.57, 153.72, 146.77, 138.07, 136.50, 134.58, 129.80, 129.79, 129.67, 129.14, 128.09, 127.63, 127.59, 118.86, 117.62, 111.97; HR-MS: for $C_{16}H_{12}ClN_2O_2$ $[M+H]^+$ calculated 299.0582 m/z, found 299.0578 m/z.

N-(3-Chlorophenyl)-8-hydroxyquinoline-2-carboxamide (**2b**). Yield 45%; Mp. 227 °C; IR (Zn/Se ATR, cm^{-1}): 3342w, 1689m, 1589m, 1524m, 1502m, 1481m, 1464w, 1405m, 1324w, 1296w, 1222w, 1191w, 1169w, 1118m, 1097w, 1078w, 977w, 881m, 855s, 817w, 786s, 765s, 722s, 685s; ^{1}H-NMR (DMSO-d_6), δ: 11.243 (s, 1H), 10.354 (s, 1H), 8.573 (d, 1H, *J*=8.5 Hz), 8.261 (d, 1H, *J*=8.5 Hz), 8.060 (t, 1H, *J*=2.1 Hz), 7.874 (ddd, 1H, *J*=8.2, 2.0, 0.9 Hz), 7.614 (dd, 1H, *J*=7.7, 8.1 Hz), 7.524 (dd, 1H, *J*=8.2, 1.1 Hz), 7.478 (t, 1H, *J*=8.1 Hz), 7.240 (ddd, 1H, *J*=8.0, 2.1, 0.9 Hz), 7.236 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.33, 153.65, 146.82, 139.74, 138.20, 136.30, 133.11, 130.50, 129.88, 129.76, 123.80, 119.98, 118.93, 118.90, 117.67, 112.07; HR-MS: for $C_{16}H_{12}ClN_2O_2$ $[M+H]^+$ calculated 299.0582 m/z, found 299.0582 m/z.

N-(4-Chlorophenyl)-8-hydroxyquinoline-2-carboxamide (**2c**). Yield 75%; Mp. 272-273 °C; IR (Zn/Se ATR, cm^{-1}): 3390w, 3316w, 1686m, 1651m, 1589m, 1528s, 1502s, 1466m, 1399m, 1362w, 1307w, 1283w, 1226m, 1187m, 1090m, 1008w, 889w, 839m, 804m, 748m, 722m, 671w; ^{1}H-NMR (DMSO-d_6), δ: 11.229 (s, 1H),10.356 (s, 1H), 8.563 (d, 1H, *J*=8.5 Hz), 8.255 (d, 1H, *J*=8.5 Hz), 7.938 (m, 2H), 7.605 (dd, 1H, *J*=8.1, 7.7 Hz), 7.515 (dd, 1H, *J*=8.1, 1.2 Hz), 7.502 (m, 2H, *J*=7.9 Hz), 7.226 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.19, 153.66, 146.98, 138.16, 137.22, 136.32, 129.81, 129.72, 128.71 (2C), 127.79, 122.17 (2C), 118.93, 117.66, 112.04; HR-MS: for $C_{16}H_{12}ClN_2O_2$ $[M+H]^+$ calculated 299.0582 m/z, found 299.0583 m/z.

N-(2-Bromophenyl)-8-hydroxyquinoline-2-carboxamide (**3a**). Yield 76%; Mp. 176-177 °C; IR (Zn/Se ATR, cm^{-1}): 3452w, 3336w, 1696s, 1592m, 1575m, 1532s, 1504s, 1460m, 1431m, 1362w, 1328w, 1305w, 1235m, 1196w, 1134w, 1109w, 1087w, 1045w, 1021m, 848m, 814w, 758s, 723s, 668m; ^{1}H-NMR (DMSO-d_6), δ: 11.208 (s, 1H), 10.306 (s, 1H), 8.571 (d, 1H, *J*=8.5 Hz), 8.223 (d, 1H, *J*=8.5 Hz), 7.786 (dd, 1H, *J*=8.0, 1.4 Hz), 7.700 (dd, 1H, *J*=7.9, 1.6 Hz), 7.610 (t, 1H, *J*=7.9 Hz), 7.528 (dd, 1H, *J*=8.2, 1.1 Hz), 7.499 (td, 1H, *J*=7.7, 1.4 Hz), 7.283 (td, 1H, *J*=7.7, 1.7 Hz), 7.219 (dd, 1H, *J*=7.7, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.56, 153.72, 146.80, 138.07, 136.50, 136.10, 132.80, 129.80, 129.78, 128.50, 128.24, 128.05, 120.10, 118.86, 117.62, 111.95; HR-MS: for $C_{16}H_{12}BrN_2O_2$ $[M+H]^+$ calculated 343.0077 m/z, found 343.0075 m/z.

N-(3-Bromophenyl)-8-hydroxyquinoline-2-carboxamide (**3b**). Yield 55%; Mp. 235 °C; IR (Zn/Se ATR, cm^{-1}): 3445w, 3279w, 3057w, 1626w, 1584s, 1536m, 1504m, 1504m, 1478, 1409w, 1329w, 1306w, 1230w, 1190w, 1163w, 1123w, 1072w, 994w, 881w, 850w, 722w, 747s, 725m, 677m; ^{1}H-NMR (DMSO-d_6), δ: 11.228 (s, 1H), 10.347 (s, 1H), 8.572 (d, 1H, *J*=8.5 Hz), 8.257(d, 1H, *J*=8.5 Hz), 8.183 (t, 1H, *J*=2.0 Hz), 7.924 (ddd, 1H, *J*=8.1, 1.9, 1.0 Hz), 7.612 (dd, 1H, *J*=7.8, 8.1 Hz), 7.522 (dd, 1H, *J*=8.3, 1.2 Hz), 7.415 (t, 1H, *J*=8.0 Hz), 7.368 (ddd, 1H, *J*=7.9, 1.9, 1.1 Hz), 7.233 (dd, 1H, *J*=7.7, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.31, 153.65, 146.82, 139.88, 138.21, 136.30, 130.81, 129.88, 129.76, 126.70, 122.81, 121.54, 119.28, 118.94, 117.68, 112.08; HR-MS: for $C_{16}H_{12}BrN_2O_2$ $[M+H]^+$ calculated 343.0077 m/z, found 343.0079 m/z.

N-(4-Bromophenyl)-8-hydroxyquinoline-2-carboxamide (**3c**). Yield 65%; Mp. 283-284 °C; IR (Zn/Se ATR, cm^{-1}): 3386w, 3316w, 1686m, 1650m, 1585s, 1524s, 1500s, 1393m, 1305w, 1280w, 1224m, 1179m,1161m, 1111w, 1072m, 1005m, 933w, 887w, 837m, 822m, 811m, 801m, 720m; ^{1}H-NMR (DMSO-d_6), δ: 11.221 (s, 1H), 10.356 (s, 1H), 8.565 (d, 1H, *J*=8.5 Hz), 8.255 (d, 1H, *J*=8.5 Hz), 7.888 (m, 2H), 7.631 (m, 2H), 7.607 (t, 1H, *J*=7.9 Hz),

7.519 (dd, 1H, *J*=8.2, 1.2 Hz), 7.227 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.19, 153.65, 146.96, 138.16, 137.63, 136.32, 131.62 (2C), 129.82, 129.72, 122.51 (2C), 118.93, 117.66, 115.87, 112.04; HR-MS: for $C_{16}H_{12}BrN_2O_2$ $[M+H]^+$ calculated 343.0077 m/z, found 343,0082 m/z.

8-Hydroxy-N-[2-(trifluoromethyl)phenyl]quinoline-2-carboxamide (**4a**). Yield 71%; Mp. 142-143 °C; IR (Zn/Se ATR, cm^{-1}): 3312w, 1666m, 1590m, 1524m, 1505s, 1483m, 1459s, 1365w, 1315s, 1280m, 1240m, 1202w, 1170m, 1117s, 1056m, 1032m, 935w, 894w, 857s, 817w, 754s, 733s, 668m; ^{1}H-NMR (DMSO-d_6), δ: 11.221 (s, 1H), 10.269 (s, 1H), 8.569 (d, 1H, *J*=8.5 Hz), 8.208 (d, 1H, *J*=8.5 Hz), 7.867 (dm, 1H, *J*=7.9 Hz), 7,807 (t, 1H, *J*=7.8 Hz), 7.706 (dm, 1H, *J*=7.8 Hz), 7.612 (dd, 1H, *J*=7.7, 8.2 Hz), 7.592 (tm, 1H, *J*=7.7 Hz), 7.529 (dd, 1H, *J*=8.2, 1.2 Hz), 7.218 (dd, 1H, *J*=7.6, 1.2 Hz); ^{13}C-NMR (DMSO-d_6), δ: 163.49, 153.69, 146.62, 138.07, 136.49, 135.36 (q, *J*=2.9 Hz), 133.32, 130.53, 129.83, 129.78, 127.49, 126.61 (q, *J*=4.9 Hz), 126.03 (q, *J*=29.4 Hz), 123.60 (q, *J*=273.5 Hz), 118.80, 117.60, 111.91; HR-MS: for $C_{17}H_{12}F_3N_2O_2$ $[M+H]^+$ calculated 333.0845 m/z, found 333.0839 m/z.

8-Hydroxy-N-[3-(trifluoromethyl)phenyl]quinoline-2-carboxamide (**4b**). Yield 68%; Mp. 213-214 °C; IR (Zn/Se ATR, cm^{-1}): 3293w, 1691w, 1657w, 1614w, 1541m, 1493s, 1393w, 1329s, 1224m, 1161s, 1111s, 1096s, 880m, 854m, 794m, 754m, 724m, 694m; ^{1}H-NMR (DMSO-d_6), δ: 11.373 (s, 1H), 10.343 (s, 1H), 8.575 (d, 1H, *J*=8.5 Hz), 8.267 (d, 1H, *J*=8.5 Hz) 8.321 (t, 1H, *J*=2.2 Hz), 8.199 (dm, 1H, *J*=8.1 Hz), 7.689 (t, 1H, *J*=8.0 Hz), 7.613 (t, 1H, *J*=7.9 Hz), 7.527 (dm, 1H, *J*=7.6 Hz), 7.522 (dd, 1H, *J*=8.3, 1.2 Hz), 7.237 (dd, 1H, *J*=7.6, 1.1 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.54, 153.66, 146.75, 139.08, 138.22, 136.31, 130.05, 129.91, 129.79, 129.54 (q, *J*=31.5 Hz), 124.11 (q, *J*=272.2 Hz), 124.08, 120.40 (q, *J*=3.9 Hz), 118.94, 117.69, 116.57 (q, *J*=4.0 Hz), 112.08; HR-MS: for $C_{17}H_{12}F_3N_2O_2$ $[M+H]^+$ calculated 333.0845 m/z, found 333.0839 m/z.

8-Hydroxy-N-[4-(trifluoromethyl)phenyl]quinoline-2-carboxamide (**4c**). Yield 72%; Mp. 253 °C; IR (Zn/Se ATR, cm^{-1}): 3315w, 1692w, 1662m, 1614w, 1595w, 1530s, 1501s, 1464m, 1409m, 1360w, 1318s, 1228m, 1183m, 1108s, 1063s, 1016w, 933w, 852s, 837s, 755m, 722m; ^{1}H-NMR (DMSO-d_6), δ: 11.378 (s, 1H), 10.398 (s, 1H), 8.577 (d, 1H, *J*=8.5 Hz), 8.273 (d, 1H, *J*=8.5 Hz), 8.146 (m, 2H), 7.818 (m, 2H), 7.617 (t, 1H, *J*=7.9 Hz), 7.526 (dd, 1H, *J*=8.2, 1.3 Hz), 7.238 (dd, 1H, *J*=7.6, 1.3 Hz); ^{13}C-NMR (DMSO-d_6), δ: 162.57, 153.69, 146.75, 141.89, 138.23, 136.32, 129.95, 129.81, 126.07 (q, 2C, *J*=3.8 Hz), 124.34 (q, *J*=271.3 Hz), 124.05 (q, *J*=32.2 Hz), 120.45 (2C), 118.98, 117.69, 112.13; HR-MS: for $C_{17}H_{12}F_3N_2O_2$ $[M+H]^+$ calculated 333.0845 m/z, found 333.0840 m/z.

Study of photosynthetic electron transport (PET) inhibition in spinach chloroplasts

Chloroplasts were prepared from spinach (*Spinacia oleracea* L.) according to Masarovicova and Kralova [32]. 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*. [33], and the rate of photosynthetic electron transport was monitored as a photoreduction of DCPIP. The measurements were carried out in phosphate buffer (0.02 mol/L, pH 7.2) containing sucrose (0.4 mol/L), $MgCl_2$ (0.005 mol/L) and NaCl (0.015 mol/L). 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 ~4 °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 50% decrease in the oxygen evolution rate relative to

the untreated control. The comparable IC_{50} value for a selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diurone®) was about 1.9 μmol/L. The results are summarized in Table 1.

Study of fluorescence of aromatic amino acids in spinach chloroplasts

The fluorescence emission spectra of aromatic amino acids in spinach chloroplasts were recorded on fluorescence spectrophotometer F-2000 (Hitachi, Tokyo, Japan) using excitation wavelength λ_{ex} = 275 nm for monitoring fluorescence of aromatic amino acids, excitation slit 20 nm and emission slit 10 nm. The phosphate buffer used for dilution of the chloroplast suspension was the same as described above. Due to low aqueous solubility the compounds were added to chloroplast suspension in DMSO solution. The DMSO concentration in all samples was the same as in the control (10%). The chlorophyll concentration in chloroplast suspension was 10 mg/L.

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