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Ring-substituted 4-Hydroxy-1*H*-quinolin-2-ones: Preparation and Their Photosynthesis-inhibiting Activity

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Abstract: The series of twelve ring-substituted 4-hydroxy-1*H*-quinolin-2-one derivatives were prepared. The synthetic procedures of the compounds are presented. All the prepared quinoline derivatives were analyzed using RP-HPLC method for the lipophilicity measurement and their lipophilicity was determined. The prepared compounds were tested for their photosynthesis-inhibiting activity (the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.). The relationships between the lipophilicity and the chemical structure of the studied compounds are discussed as well as the structure-activity relationships (SAR) between the chemical structure and the biological activities of the evaluated compounds.

Keywords: Quinolinone derivatives; Lipophilicity; OER inhibition; Spinach chloroplasts; Structure-activity relationships.

INTRODUCTION

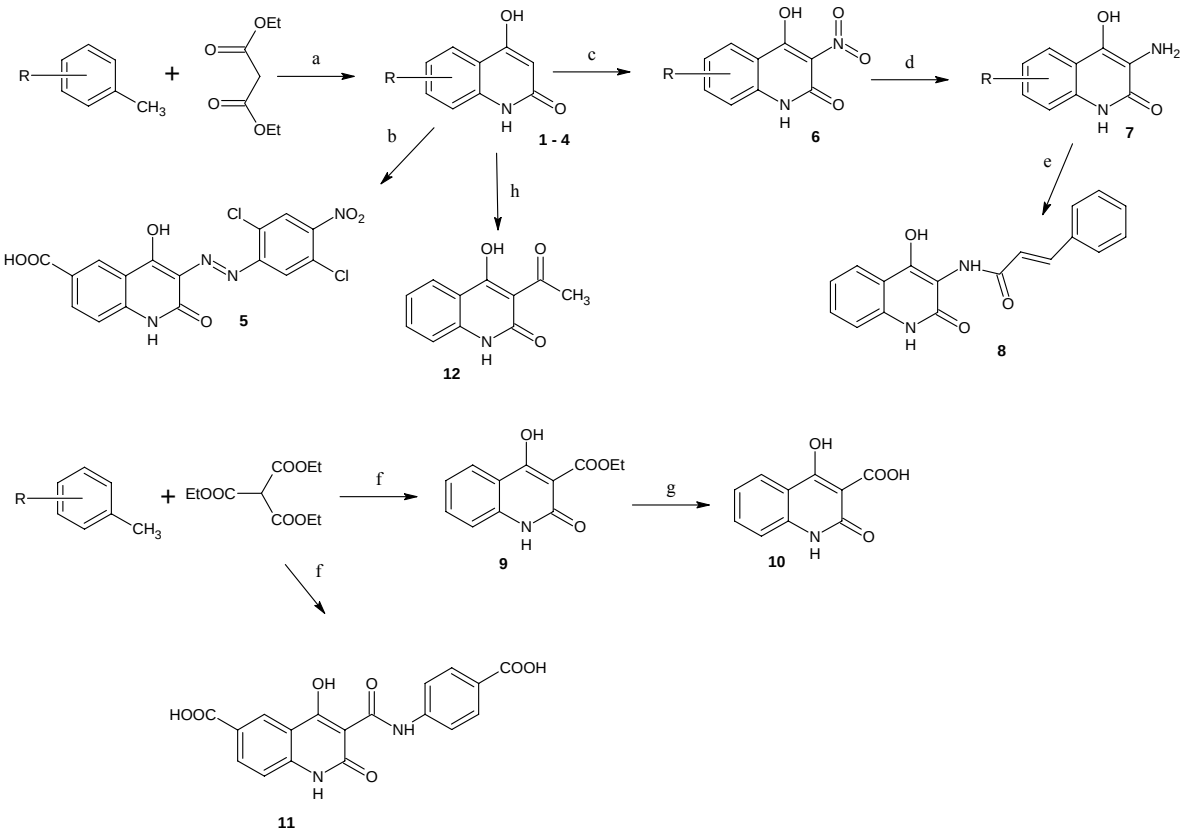
The Q_B quinone-binding site of photosystem II is an important target for herbicides including herbicides based on phenylurea moieties. It was found that a tail can be attached to the *para* position of phenylurea-type herbicides without loss of binding, provided that the tail is hydrophobic. This indicates that the herbicides must be oriented in the Q_B site so that these positions point toward the natural isoprenyl tail-binding pocket that extends out of the Q_B site. In turn, the requirement that the tail must extend out of the Q_B site constrains the size of the other herbicide substituents in the pocket [1]. In addition to these herbicides various compounds possessing an amide -NHCO- functionality were found to inhibit photosynthetic electron transport as well [2-5]. Better understanding of the SAR regularities are not only important for the design of modern agricultural agents but can also give the remarkable insight into the photosynthesis mechanisms of the green cells.
Quinoline scaffold is present in many classes of biologically active compounds [6]. A series of compounds derived from 8-hydroxyquinoline and styrylquinoline derivatives as potential HIV-1 integrase inhibitors were synthesized recently [7-10]. Our study dealing with 8-hydroxyquinoline and styrylquinoline derivatives showed that they could possess also strong antifungal activity [11-13]. According to the results reported recently some new hydroxyquinoline derivatives possess interesting herbicidal activities as well [12,14-18]. Some investigated compounds showed also antineoplastic activity [19].
This paper deals with synthesis and herbicidal activity of ring-substituted 4-hydroxy-1*H*-quinolin-2-one derivatives. All the compounds were tested for their photosynthesis-inhibiting activity (the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.). Lipophilicity (log *k*) of the compounds was determined using RP-HPLC. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP column. The structure-activity relationships of the studied compounds are discussed in the present study as well.

RESULTS AND DISCUSSION

Chemistry

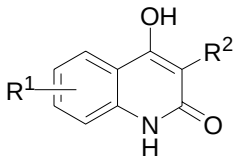
In most of described synthesis aniline derivatives were used as starting materials for their great availability from chemical vendors. Microwave assisted synthesis with malonic acid or its esters provide us compounds **1**-**4**. Further nitration and reduction according to known procedures appeared to be succeful in obtaining compounds **6** and **7**. Diazo derivative **5** was synthesised from **3** with dichloroaniline. Acylation of **7** with cinnamoyl chloride provide us compound **8**. Quinolines functionalized with carboxylic group at $C_{(3)}$ **9**, **10** and **11** were obtained in neat microwave assisted synthesis with moderate or good yield. Structure **12** was obtained according to modified procedure from 4-Hydroxyquinolin-2(1H)-one (**1**).

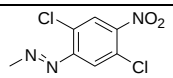
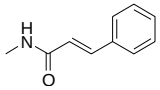
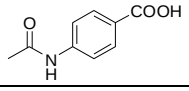
Scheme 1. Synthesis of quinoline derivatives **1-12**: (a) PPA, microwave irradiation; (b) (2,5-dichloro-4-nitrophenyl)diazonium chloride; (c) HNO_3; (d) Sn, HCl; (e) cinnamoyl chloride; (f) microwave irradiation; (g) hydrolysis; (h) NaH.



Hydrophobicities (log *P*/Clog *P* values) of the studied compounds **1-12** were calculated using two commercially available programs and also measured by means of the reversed phase high performance liquid chromatography (RP-HPLC) method for lipophilicity measurement. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using an end-capped non-polar C_{18} stationary RP column. The capacity factors *k* were determined and subsequent log *k* values were calculated. The results are shown in Table 1 and illustrated in Figure 1.

Table 1. Comparison of the calculated lipophilicities (log *P*/Clog *P*) with the determined log *k* values. IC_{50} values related to OER inhibition in spinach chloroplasts of compounds **1-12** in comparison with standard DCMU.

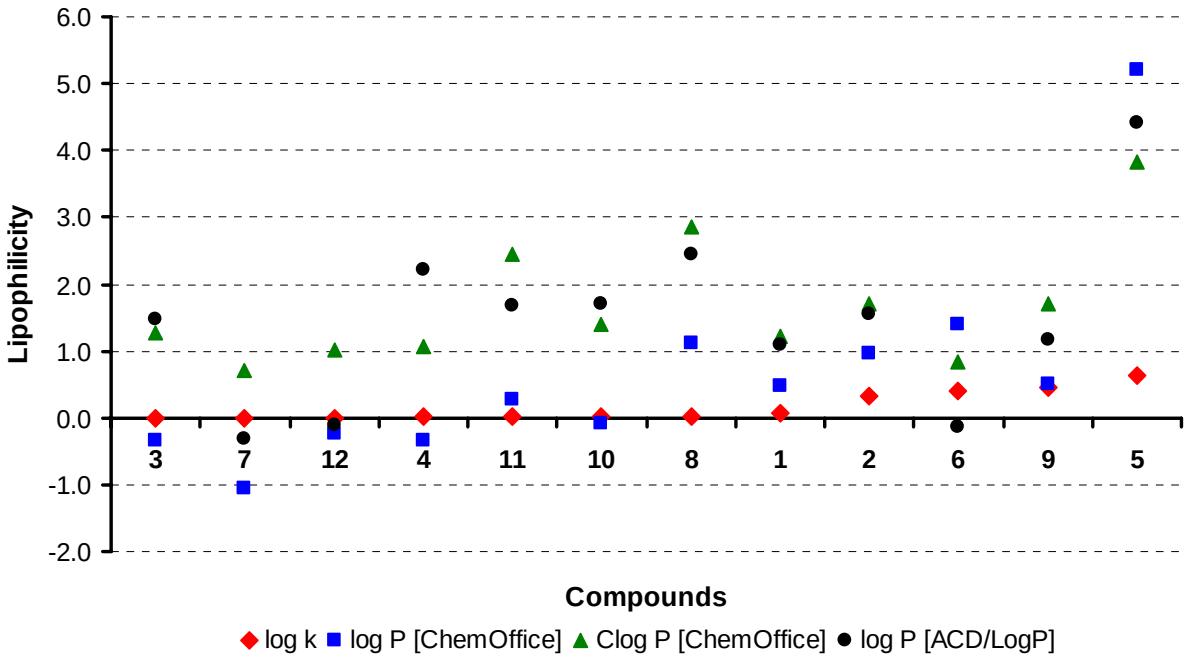


Comp.	R^1	R^2	log *k*	log *P*/Clog *P* ChemOffice	log *P* ACD/LogP	OER inhibition IC_{50} [μmol/L]
1	H	H	0.0664	0.49 / 1.216	1.10 ± 0.75	925
2	6-CH_3	H	0.3307	0.97 / 1.715	1.56 ± 0.75	157
3	6-COOH -5-OH	H	0.0002	-0.34 / 1.261	1.47 ± 0.75	346
4	6-COOH -7-OH	H	0.0080	-0.34 / 1.070	2.22 ± 0.75	538
5	6-COOH		0.6394	5.22 / 3.840	4.41 ± 1.00	126
6	H	-NO_2	0.4052	1.39 / 0.836	-0.14 ± 1.00	510
7	H	-NH_2	0.0004	-1.06 / 0.719	-0.32 ± 1.00	775
8	H		0.0128	1.11 / 2.848	2.45 ± 1.00	916
9	H	-$COOC_2H_5$	0.4595	0.51 / 1.694	1.17 ± 0.75	494
10	H	-COOH	0.0118	-0.09 / 1.409	1.71 ± 0.35	567
11	6-COOH		0.0081	0.27 / 2.445	1.67 ± 1.00	380
12	H	-$COCH_3$	0.0005	-0.24 / 1.012	-0.11 ± 1.00	[a]
DCMU	–	–	–	2.76 / 2.691	2.78 ± 0.38	1.9

[a] interacted with DCPIP.

The results obtained with all the compounds show that the experimentally determined lipophilicities (log *k* values) are lower than those indicated by the calculated log *P*/Clog *P*, see Figure 1. The results show that experimentally determined log *k* values correlate relatively poorly. As expected, compound **5** showed the highest lipophilicity, while compound **3** possessed the lowest hydrophobicity, which was unexpected. Compound **8** showed less hydrophobicity contrary to all the results of the lipophilicity calculated by software. If compared the lipophilicity data log *k* of both position analogues **3** and **4** it can be stated, that 7-hydroxy derivative **4** possessed higher hydrophobicity than 5-hydroxy analogue **3**. This fact is caused by intramolecular interactions [20].

Figure 1. Comparison of the computed log *P*/Clog *P* values using the two programs with the calculated log *k* values. The discussed compounds **1-12** are ordered according to the log *k* values increase.



All compounds were evaluated for their *in vitro* herbicidal efficiency. The results are showed in Table 1.

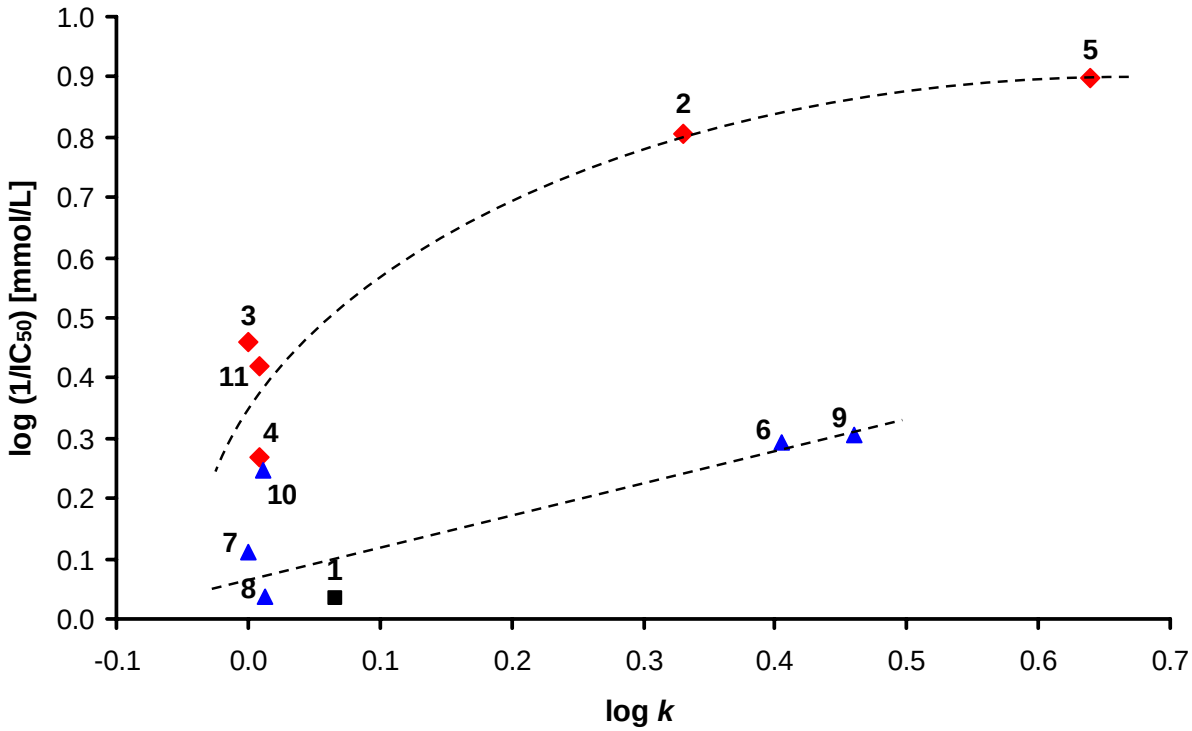
Quinoline derivatives **1-11** showed a wide range of activity related to OER inhibition in spinach chloroplasts activities. Two compounds showed interesting IC_{50} values: 126 µmol/L (**5**) and 157 µmol/L (**2**); nevertheless the studied activity of all the other compounds was very low.

Due to the medium and/or moderate activity of all the evaluated compounds **1-11** it is difficult to determine simple structure-activity relationships. However some observations seem to be interesting.

Unsubstituted structure (compound **1**) did not practically affect OER in chloroplasts. The studied compounds could be divided into two groups according to their chemical structure. Group 1 includes compounds **2-5** and **11**, and Group 2 compounds **6-10**.

Group 1 showed higher biological activity than Group 2. The activity related to OER inhibition seems to be positively influenced by substitution of ring B – especially the $C_{(6)}$ position, see compounds **2-4**, **11**. Comparison of the OER-inhibiting activities of compounds **2-5** and **11** also indicated, that the lipophilicity increase is connected with the quasi-parabolic increase of biological activity, see Figure 2. Interesting are great differences in inhibition of OER of position analogues **3** (6-COOH-5-OH) and **4** (6-COOH-7-OH). Higher inhibiting effect of **5** compared with **2** may be caused by higher lipophilicity (easier penetration of compound to cell) and/or redox properties of nitro moiety of 2,5-dichloro-4-nitrophenyldiazenyl substituent.

Figure 2. Relationships between the OER inhibition log ($1/IC_{50}$) [mmol/L] in spinach chloroplasts and lipophilicity (log *k*) of the studied compounds **1-12**.



Generally, Group 2 inhibited OER only slightly; nevertheless the compounds **6** and **9** were approximately twice as efficient as the compound **1**. All these compounds possess the substituted position $C_{(3)}$ of ring A, that caused decrease of OER inhibition compared to Group 1. The most active compound from Group 2 was ester **9**.

EXPERIMENTAL

General

All reagents were purchased from Aldrich. Kieselgel 60, 0.040-0.063 mm (Merck, Darmstadt, Germany) was used for column chromatography. 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 Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Elemental analyses were carried out on an automatic Perkin-Elmer 240 microanalyser (Boston, USA). The purity of the final compounds was checked by HPLC, see section 4.3. The detection wavelength 210 nm was chosen. The peaks in the chromatogram of the solvent (blank) were deducted from the peaks in the chromatogram of the sample solution. The purity of individual compounds was determined from the area peaks in the chromatogram of the sample solution. UV spectra (λ, nm) were determined on a Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, U.S.A.) in ca 6×10^{-4} mol methanolic solution and log ε (the logarithm of molar absorption coefficient ε) was calculated for the absolute maximum λ_{max} of individual target compounds. All ^{1}H NMR spectra were recorded on a Bruker AM-500 (499.95 MHz for ^{1}H), Bruker BioSpin Corp., Germany.

Chemicals shifts are reported in ppm (δ) to internal $Si(CH_3)_4$, when diffused easily exchangeable signals are omitted.

Synthesis

4-Hydroxyquinolin-2(1H)-one (1).
Aniline (7 mL, 5 mmol) and malonic acid (5.2 g, 5 mmol) was thoroughly mixed with 20 g PPA {P_2O_5 (287.9 g) was added to 85% phosphoric acid (200 g, 118.4 mL) with stirring and microwave heating. The mixture was then heated for next 15 min.} and heated with stirring in microwave reactor at 400 W during 2×20 min with 5 min interval. Temperature reached 210 °C. Then the mixture was pour into crushed ice and a cream solid was filtered and purified by extraction with EtOH and a white crystalline compound was obtained [21]. Yield 35%. Mp 340 °C. HPLC purity 97.12%. UV (nm), λ_{max}/log ε: 231.3 / 3.51.

4-Hydroxy-6-methylquinolin-2(1H)-one (2).
The product was obtained according to the described procedure [22, 23] as a light brown crystalline compound. Yield 54%. Mp 320 °C. HPLC purity 97.72%. UV (nm), λ_{max}/log ε: 232.4 / 3.55.

4,5-Dihydroxy-2-oxo-1,2-dihydroquinoline-6-carboxylic acid (3).
Naphthalene (15.4 g, 0.12 mol) and malonic acid (18.7 g, 0.18 mol) were melted with stirring at temperature control (<150 °C) to avoid decarboxylation of acid. $POCl_3$ (32.9 g, 0.36 mol) was then added dropwise during 30 min and *p*-aminosalicylic acid (15.3 g, 0.1 mol) was added. The resulted mixture was heated for next 30 min and left for cooling. Water (100 mL) was added to the warm mixture and the solution was alkalized with 20% NaOH to pH 9. After cooling on ice precipitated naphthalene was filtered and filtrate was acidified to pH 2. The product was filtered and crystallized from acetic acid as a bright yellow crystalline compound. Yield 36%. Mp 250 °C. Anal. Calc. for $C_{10}H_7NO_5$ (221.16): C 54.31%, H 3.19%; found: C 54.51%, H 4.11%. HPLC purity 98.74%. UV (nm), λ_{max}/log ε: 244.2 / 3.54. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.65 (s, 1H), 6.60 (d, *J*=8.3 Hz, 1H), 7.80 (d, *J*=8.3 Hz, 1H), 11.3 (bs, 1H), 12.20 (bs, 1H). IR [cm^{-1}] 3601, 2895, 1664, 1603, 1537, 1509, 1245

4,7-Dihydroxy-2-oxo-1,2-dihydroquinoline-6-carboxylic acid (4).
The product was obtained as isomer of **3** during its synthesis. Isolated by fractional crystalization as a white crystalline compound. Yield 36%. Mp 250 °C. Anal. Calc. for $C_{10}H_7NO_5$ (221.16): C 54.31%, H 3.19%; found: C 54.09%, H 3.52%. HPLC purity 98.51%. UV (nm), λ_{max}/log ε: 243.0 / 3.54. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.60 (s, 1H), 6.67 (s, 1H), 8.25 (s, 1H).

(E)-3-[(2,5-Dichloro-4-nitrophenyl)diazenyl]-4-hydroxy-2-oxo-1,2-dihydroquinoline-6-carboxylic acid (5).
2,5-Dichloro-4-nitroaniline (0.92 g) was dissolved in Et_2O/EtOH : 2/1, then 15% HCl (0.91 mL) was added to this solution and the mixture was cooled to 5 °C. $NaNO_2$ (0.39 g, 5.7 mmol) and compound **3** (1.0 g, 5.7 mmol) were added slowly with temperature still at 5 °C and pH<7 (15% HCl). The resulting mixture was standing overnight in ice. The precipitated solid was then filtered and crystallized from Et_2O/EtOH. A reddish crystalline compound was obtained. Yield 64%. Mp 340 °C. Anal. Calc. for $C_{16}H_8Cl_2N_4O_6$ (423.16): C 45.41%, H 1.91%; found: C 45.26%, H 2.24%. HPLC purity 96.39%. UV (nm), λ_{max}/log ε: 271.4 /

3.61.^{1}H NMR (DMSO-d_6, 500 MHz) δ: 5.70 (s, 1H), 7.10-7.60 (m, 3H), 11.10 (s, 1H), 11.30 (s, 1H).

4-Hydroxy-3-nitroquinolin-2(1H)-one (6).
The product was obtained according to the described nitration procedure [24] as a yellow crystalline compound. Yield 71%. Mp 252-255 °C. HPLC purity 99.72%. UV (nm), λ_{max}/log ε: 336.8 / 3.57.

3-Amino-4-hydroxyquinolin-2(1H)-one (7).
Compound **6** (2.0 g, 0.0097 mol) and tin powder (3.8 g, 0.032 mol) were stirred with 36% HCl (8.1 mL). The mixture was warmed at 80-90 °C during 30 min. The brown solution was cooled to room temperature and filtered. The filtrate was alkalized with $NH_{3(aq)}$ and warmed for 20 min. Then Celite (1.3 g) was added and filtered. The solid was washed thoroughly with hot water. The combined filtrates were concentrated and acidified. After cooling a white crystalline compound was obtained. Yield 85%. Mp 300 °C [25]. HPLC purity 91.99%. UV (nm), λ_{max}/log ε: 232.8 / 3.53.

(2E)-N-(4-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-3-phenylprop-2-enamide (8).
Compound **7** (0.018 g, 0.001 mol) was mixed with water (5 mL), Et_2O (5 mL) and sodium bicarbonate (0.3 g). The resulted mixture was stirred in an ice bath (-3 °C) and 10 mL of Et_2O solution of cynamoyl chloride (0.017 g, 0.001 mol) was added slowly. The resulted mixture was stirred in room temperature during 2 days, cooled in fridge and filtered. Et_2O was added to the solid and dried. A white crystalline compound was obtained. Yield 50%. Mp 145 °C. Anal. Calc. for $C_{18}H_{14}N_2O_3$+H_2O (324.33): C 66.66%, H 4.97%; found: C 66.54%, H 5.27%. HPLC purity 99.79%. UV (nm), λ_{max}/log ε: 263.1 / 3.51.^{1}H NMR (DMSO-d_6, 500 MHz) δ: 3.30 (s, 1H), 6.50 (d, *J*=16.2 Hz, 2H), 7.10 (s, 1H), 7.38 (m, 9H), 7.5 (s, 1H).

Ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (9).
Aniline (0.46 mL, 0.005 mol) and triethyl methanetricarboxylate (2.12 mL, 0.01 mol) was heated in microwave reactor during 8 min at 60% power level. The mixture was then cooled to room temperature and 7 mL of Et_2O was added. The crude product was crystallized from MeOH. A white crystalline compound was obtained. Yield 50%. Mp 116-120 °C. TLC(SiO_2, R_f=0.71) Anal. Calc. for $C_{12}H_{11}NO_4$ (233.22): C 61.8%, H 4.75%; found: C 61.65%, H 4.39%. HPLC purity 95.01%. UV (nm), λ_{max}/log ε: 244.2 / 3.59.^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.19 (t, 3H), 4.17 (q, 2H), 4.70 (s, 1H), 7.09 (t, 2H), 7.32 (t, 1H), 7.52 (d, *J*=8.5 Hz, 1H), 10.30 (t, 1H).

4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (10).
The product was obtained according to the described procedure [26,27] as a white crystalline compound. Yield 25%. Mp 225 °C. HPLC purity 99.51%. UV (nm), λ_{max}/log ε: 250.1 / 3.52.

3-(4-Carboxyphenylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-6-carboxylic acid(11).
4-Aminobenzoic acid (0.7 g, 0.005 mol) was mixed with triethyl methanetricaroxylate (2.12 ml, 0.01 mol) and heated in microwave reactor at 50% of power during 15 min and 3 min at 90%. Temperature reached 231 °C during heating. Et_2O was added to the cooled mixture and the precipitate was washed with hot MeOH to obtain the pure product as a yellow crystalline compound. Yield 62%. Mp 340-350 °C. Anal. Calc. for $C_{18}H_{12}N_2O_7$ (368.29): C 58.7%, H 3.28%; found: C 58.09%, H 3.54%. HPLC purity 97.52%. UV (nm), λ_{max}/log ε: 251.3 / 3.53.^{1}H NMR (DMSO-d_6, 500 MHz) δ: 7.41 (d, *J*=8.5 Hz, 1H), 7.70 (d, *J*=9.1 Hz,

2H), 7.90 (d, *J*=9.1 Hz, 2H), 8.15 (d, *J*=8.5 Hz, 1H), 8.50 (s, 1H), 12.40 (s, 1H), 12.95 (s, 1H), 16 (s, 1H). IR [cm^{-1}]: 3645, 1780, 1705, 1640, 1594, 1547, 1471, 1115

3-Acetyl-4-hydroxyquinolin-2(1H)-one (12).
NaH (2.4 g, 0.06 mol) was added to anhydrous benzene (180 mL) and then ethyl acetylacetate (7.6 mL, 0.06 mol) was added dropwise. The mixture was stirred for 1 h at ambient temperature and 2-methyl-3,1-benzoxazin-4-one (3.2 g, 0.02 mol) was added and stirred overnight. Water (180 mL) and Et_2O (150 mL) was added to the resulted mixture and the product was isolated from inorganic layer as a white crystalline compound. Yield 78%. Mp 254-257 °C. Anal. Calc. for $C_{11}H_9NO_3$ (203.19): C 65.12%, H 4.52%; found: C 65.02%, H 4.46%. HPLC purity 99.03%. UV (nm), λ_{max}/log ε: 252.5 / 3.57.^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.12 (s, 3H, CH_3), 7.13 (t, 1H, Ar-H), 7.56 (t, 1H, Ar-H), 7.95 (d, *J*=7.17 Hz, 1H, Ar-H), 8.44 (d, *J*=8.34 Hz, 1H, Ar-H), 11.04 (s, 1H, NH), 13.58 (s, 1H, OH).

Lipophilicity HPLC determination (capacity factor k / calculated log k)
The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, U.S.A.) were used. The chromatographic column Symmetry® C_{18} 5 μm, 4.6×250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, U.S.A.) was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, U.S.A.). The mixture of MeOH p.a. (55.0%) and H_2O-HPLC – Mili-Q Grade (45.0%) was used as a mobile phase. The total flow of the column was 0.9 mL/min, injection 30 μl, column temperature 30 °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 using the Millennium32® Chromatography Manager Software 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 via 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.

Lipophilicity calculations
Log *P*, *i.e.* the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs CS ChemOffice Ultra ver. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/LogP ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). Clog *P* values (the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions) were generated by means of CS ChemOffice Ultra ver. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Table 1.

Study of inhibition of oxygen evolution rate (OER) in spinach chloroplasts
Chloroplasts were prepared from spinach (*Spinacia oleracea* L.) according to Masarovicova and Kralova [28]. The inhibition of photosynthetic electron transport (PET) in spinach chloroplasts was determined spectrophotometrically (Kontron Uvikon 800, Kontron, Muenchen, Germany) using an artificial electron acceptor 2,6-dichlorophenol-indophenol (DCIPP) according to Kralova et al. [29] 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) from 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 (PET). The inhibitory efficiency of the studied compounds has been expressed by IC_{50} values, *i.e.* by molar concentration of the compounds causing 50% decrease in the oxygen evolution 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 [30]. The results are summarized in Table 1.

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