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Preparation and Herbicidal Activities of Substituted Amides of Quinoline Derivatives

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Abstract: The series of eight substituted amides of 5-hydroxy-2-methylquinoline-7-carboxylic acid 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.*) and the reduction of chlorophyll content in (*Chlorella vulgaris* Beij.). Several compounds showed the biological activity comparable with or higher than the standard 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU). 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.

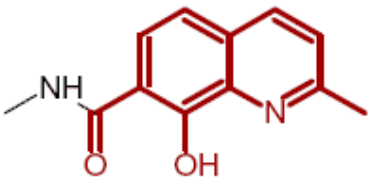
Keywords: Quinoline derivatives; Lipophilicity; OER inhibition; Spinach chloroplasts; Reduction of chlorophyll content; *Chlorella vulgaris*; Structure-activity relationships.

INTRODUCTION

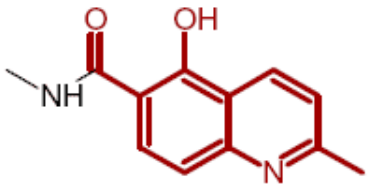
Various compounds possessing an amide -NHCO- functionality were found to inhibit photosynthetic electron transport. Although this has been discovered more than fifty years ago [1], there are still many unanswered questions about structural requirements for the activity of these compounds. Better understanding 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 [2]. A number of them showed antimicrobial activities [3-5]. Some quinoline analogues showed also antineoplastic activity [6,7]. Styrylquinoline derivatives have attracted strong attention recently due to their activity as prospective HIV integrase inhibitors [8,9].

As reported recently various quinoline derivatives inhibited oxygen evolution rate in spinach chloroplasts and they showed some antialgal properties [4,6,10-12]. In the current research, based on the analogy with the 8-hydroxy-2-methylquinoline-7-carboxamides (**I**) described in previous publications [11] we designed position isomers of the above mentioned derivatives – a series of 5-hydroxy-2-methylquinoline-6-carboxamides (**II**), which were evaluated as potential herbicides.



(I)



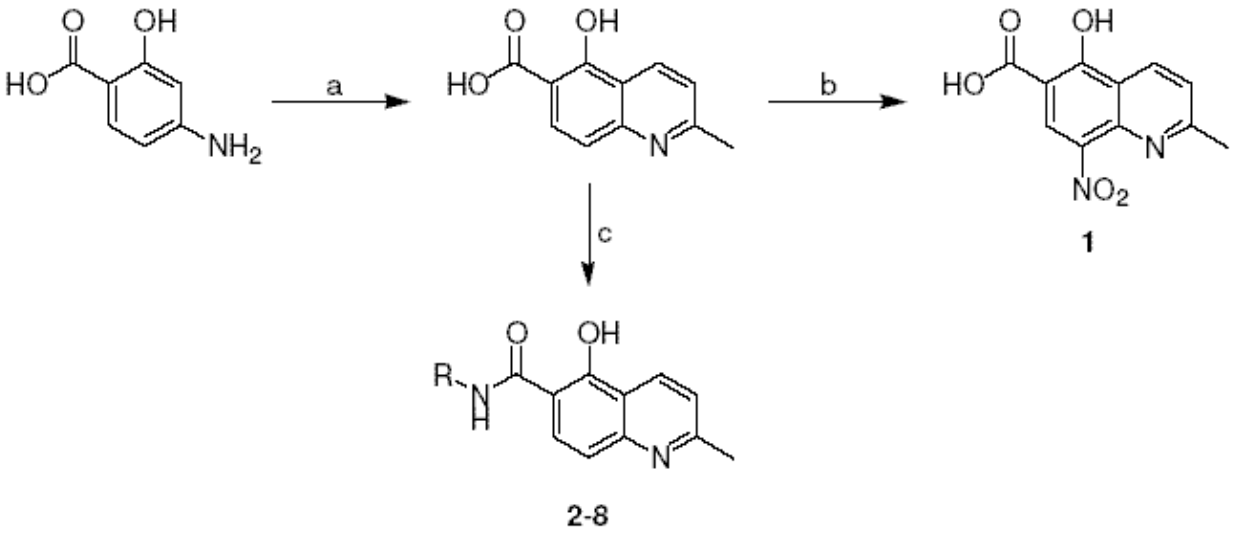
(II)

RESULTS AND DISCUSSION

The Skraup synthesis gave 5-hydroxy-2-methylquinoline-6-carboxylic acid that was nitrated to yield 5-hydroxy-2-methyl-8-nitroquinoline-6-carboxylic acid (**1**). 5-Hydroxy-2-methylquinoline-6-carboxylic acid further reacted with the appropriate amine in the presence of ethyldimethylaminopropyl carbodiimid (EDCI) or dicyclohexyl carbodiimid (DCC) to provide an amide. In case of compound **7** diamine and twofold of quinaldic acid were used. Compound **8**

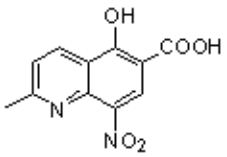
was prepared by reaction of twofold of 5-hydroxy-2-methyl-quinoline-6-carboxylic acid with urea. Synthetic pathways of all discussed quinoline derivatives **1-8** are shown in Scheme 1.

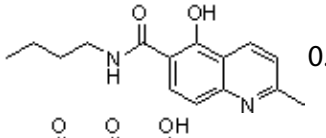
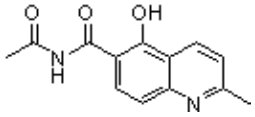
Scheme 1. Synthesis of compounds **1-8**: (a) Skraup synthesis; (b) HNO_3/H_2SO_4 5 °C; (c) amine, EDCI or DCC.



Hydrophobicities (log *P*/Clog *P* values) of the studied compounds **1-8** 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 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 and reduction of chlorophyll content in C. *vulgaris* of compounds **1-8** in comparison with standard DCMU.

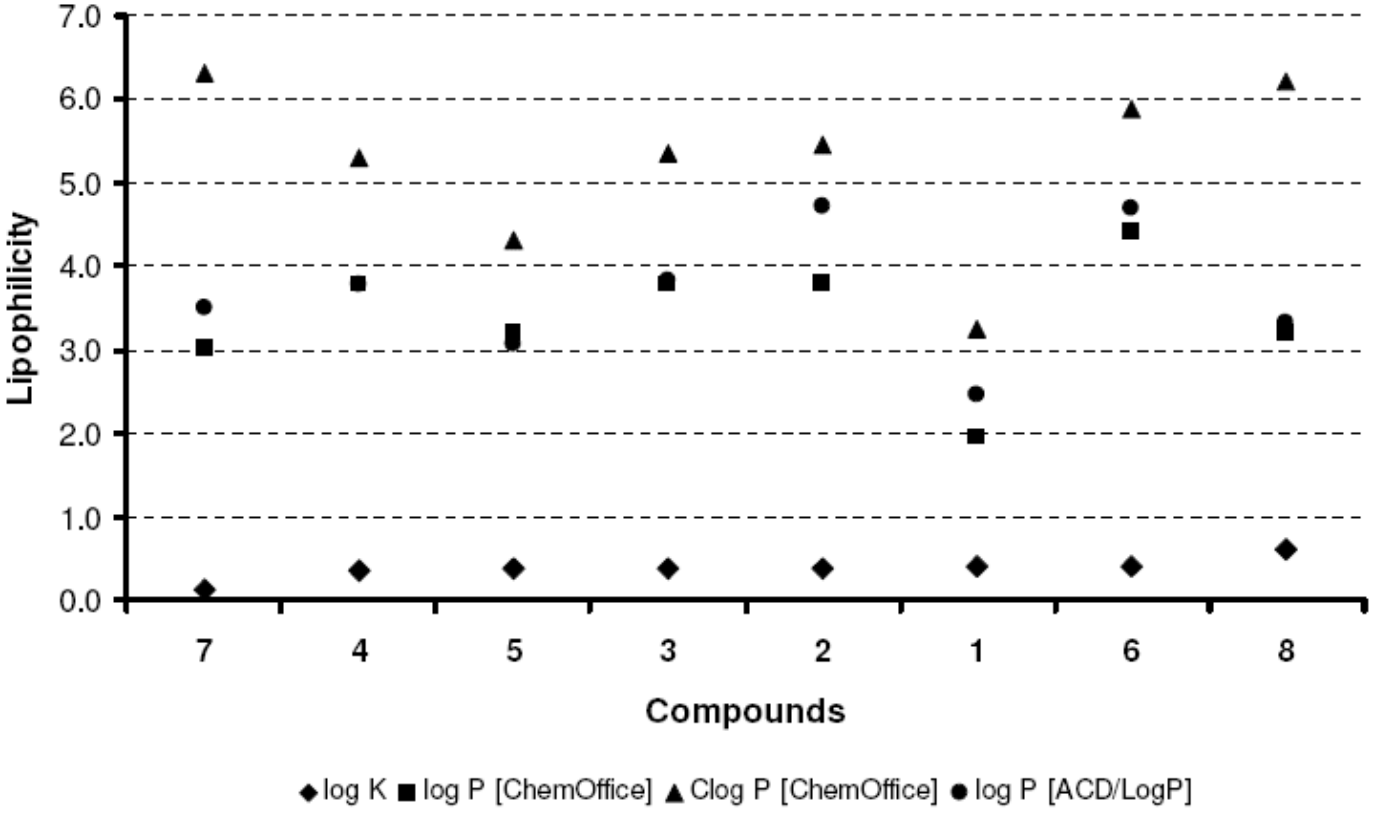
Comp.	R	log *K*	log *P*/Clog *P* ChemOffice	log *P* ACD/LogP	OER inhibition IC_{50} [µmol/L]	Chlorophyll reduction IC_{50} [µmol/L]
1		0.4072	1.95 / 3.235	2.47 ± 0.36	114.0	108.6 ± 11.3[a]
2	-Ph-4-Cl	0.3812	3.80 / 5.464	4.73 ± 0.42	265.0	23.8
3	$-CH_2Ph-4-CH_3$	0.3800	3.79 / 5.339	3.84 ± 0.41	468.0	97.2 ± 3.8
4	$-CH(CH_3)Ph-4-F$	0.3663	3.78 / 5.292	3.78 ± 0.47	426.0	100.0 ± 5.9[a]
5	$-C_2H_4Ph-4-OH$	0.3775	3.20 / 4.302	3.06 ± 0.40	16.0	102.5 ± 8.9[a]

6	-C_4H_8Ph	0.4173	4.42 / 5.877	4.68 ± 0.39	7.2	10.9
7		0.1203	3.01 / 6.303	3.51 ± 0.51	819.0	19.5
8		0.6120	3.20 / 6.223	3.31 ± 0.65	833.0	5.5
DCMU	-	-	2.76 / 2.691	2.78 ± 0.38	1.9	7.3

[a]IC_{50} was not determined for four compounds, an average decrease of Chl content related to the control for the concentration range of 0.83–100 µmol/L is indicated.

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 with calculated Clog *P* values, whereas log *P* data calculated using the ChemOffice software or ACD/Log P program do not agree with compounds **1-8**. As expected, dimmer **7** showed the lowest lipophilicity. Compound **8** possessed the highest hydrophobicity, which was unexpected. Acid **1** showed also high hydrophobicity contrary to all the results of the lipophilicity calculated softwares. If compared the lipophilicity results of position analogues presented in [11] it can be assumed, that 5-hydroxy derivatives **1-8** possessed higher hydrophobicity than 8-hydroxy analogues. This fact is caused by hydrogen bond between phenolic and carbonyl group [14] and/or ingeneration of hydrogen bond between phenolic and quinoline-nitrogen [4-6], due to their opposite positions.

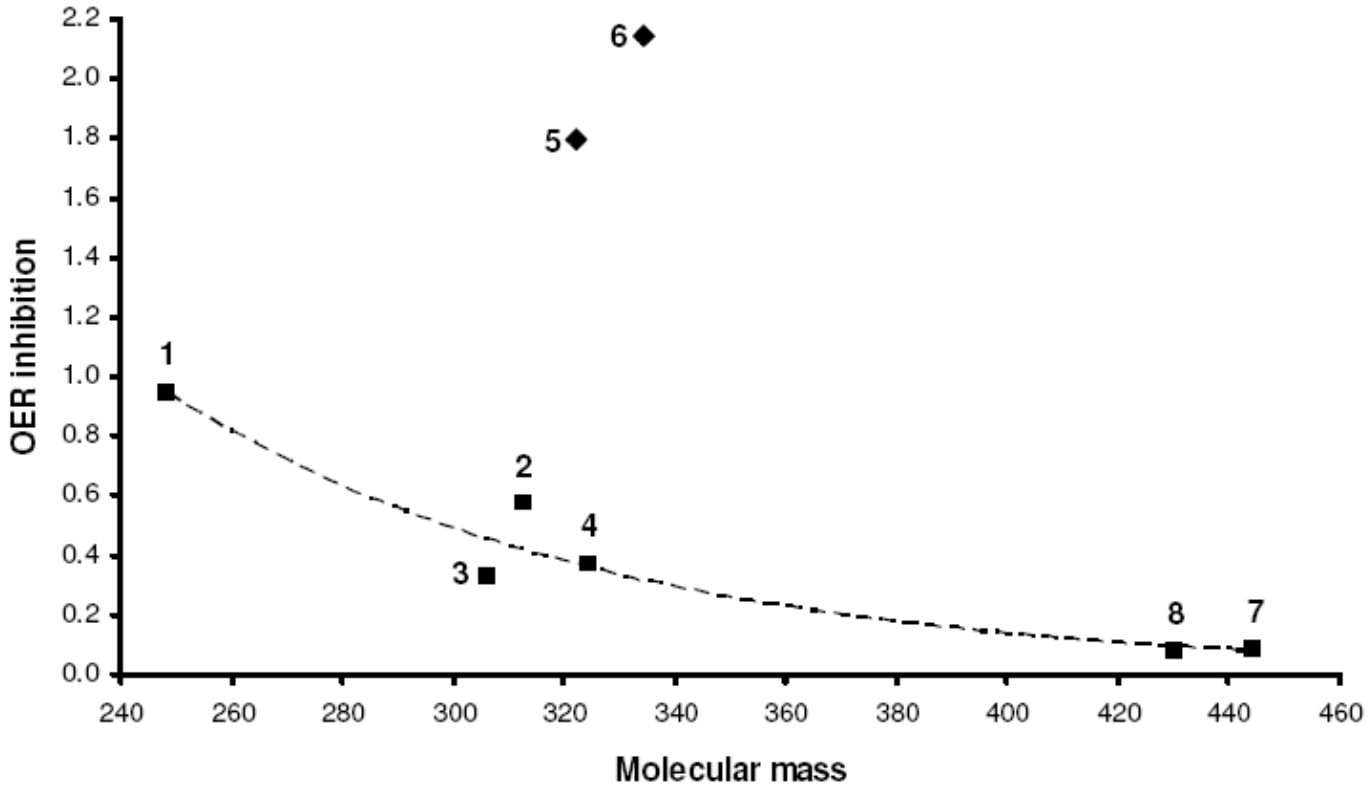
Figure 1. Comparison of log *P*/Clog *P* values using the two programs with the calculated log *K* values of the compounds **1-8**.



All compounds were evaluated for their *in vitro* herbicidal susceptibility. Some interesting results were obtained, see Table 1.

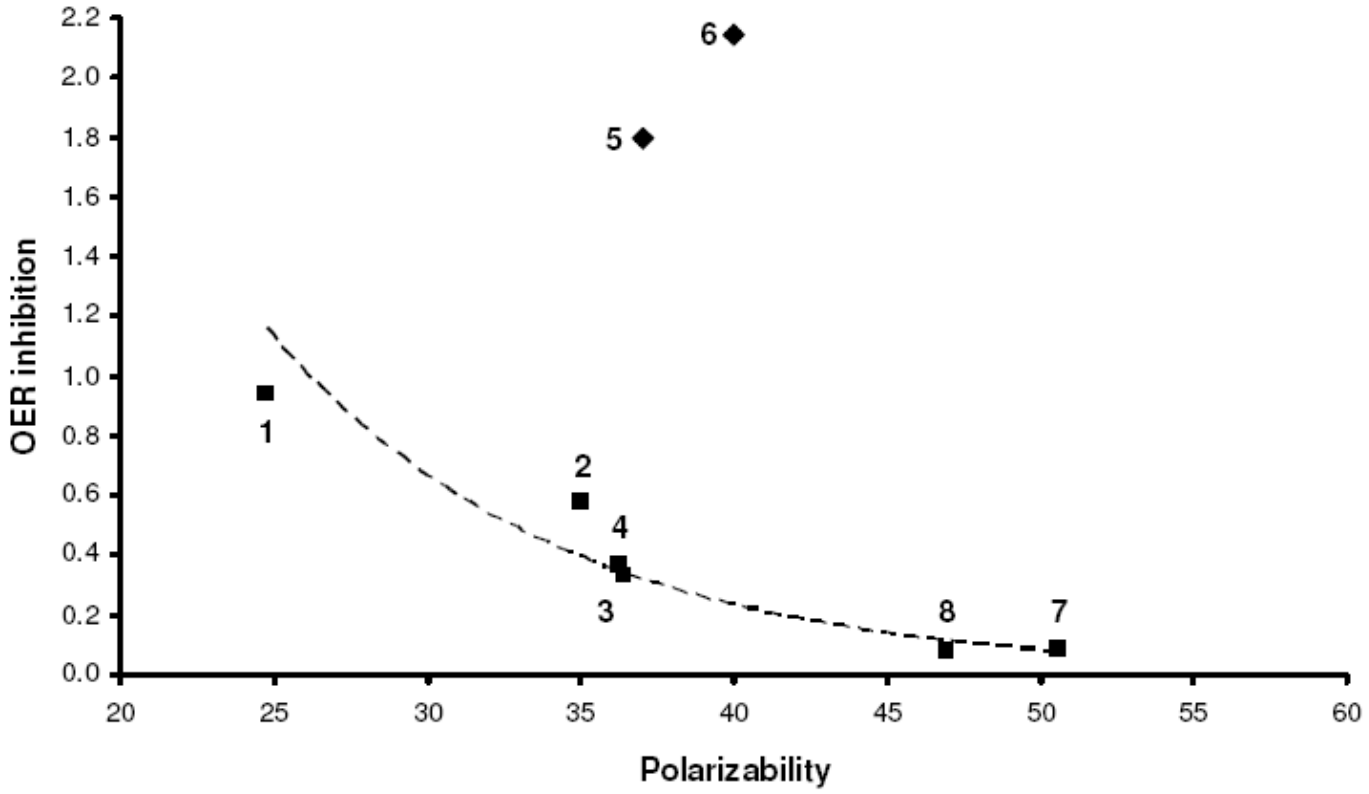
Derivatives of 5-hydroxy-2-methylquinoline-6-carboxylic acid **1-8** showed a wide range of OER-inhibiting activity in spinach chloroplasts activities. Two compounds showed interesting IC_{50} values: 7.2 μmol/L (**6**) and 16.0 μmol/L (**5**). The activity of compound **6** was comparable with DCMU. Both dimmers **7** and **8** possessed very low activity. Due to the small group and different structure types of the evaluated compounds **1-8** it is difficult to determine simple structure-activity relationships. However some observations seem to be interesting. It can be stated, that the lipophilicity is probably the secondary parameter for good activity as there is no good correlation between log *K* and the activity of compounds **1-8**. Poorly active compounds, when compared, showed some regularities between activity and structural properties, such as polarizability or molecular refraction, see Figure 2 and Figure 3.

Figure 2. OER inhibition {log ($1/IC_{50}$ [mmol/L])} versus molecular mass of the studied compounds. The active compounds **5**, **6** and the poorly active compounds **1-4**, **7**, **8**.



One can see that the activity dependence shown on Figure 2 is quite obvious as passive transport is important in fate of the active molecule in biological environment. Large molecules, usually highly lipophilic are less expected to achieve site of action. When compared molecular volume produces very similar changes in activity. Unfortunately the lack of compounds makes it difficult to predict the scope of preferable mass before further studies. Similar dependence can be observed for OER inhibition – polarizability/molecular refraction (Figure 3).

Figure 3. OER inhibition {log ($1/IC_{50}$ [mmol/L])} versus polarizability of compounds **1-4**, **7**, **8**. The active compounds **5**, **6** and the poorly active compounds **1-4**, **7**, **8**.



These regularities became even more important, if we compare them with two highly active compounds **5**, **6**. They are active despite the fact that all their properties suggest rather low OER activity. According to this we can guess that activity of two most active structures in OER measurements acts in different mechanism than the rest of the compounds.

Probably the more important parameter is the 2D distance between the quinoline nucleus and the $C_{(4)}$'-hydrogen/substituent in the phenyl ring.

5-Hydroxy-2-methylquinoline-6-carboxamides **2-8** possessed very interesting activity in reduction of chlorophyll content in *Chlorella vulgaris*. Compounds **2**, **6-8** (activity range 5.5-23.8 μmol/L) are potential herbicides with **8** the most active (IC_{50} = 5.5 μmol/L). According to Table 1 it seems, that there are better relationships between log *K* and the activity in series **1-8**. Anti-algal activity increased with the lipophilicity increase.

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 below. 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 6x10^{-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.

5-Hydroxy-2-methyl-8-nitroquinoline-6-carboxylic acid (**1**). Product was obtained according to the described procedure [13]. Yield 53%. Mp 280 °C (decomp.). HPLC purity 94.25%. UV (nm), λ_{max}/log ε: 284.4 / 3.67.

General procedure of compounds 2-8

To solution prepared hydroxyquinaldinecarboxylic acids (1.02 g, 5.0 mmol) in dry CH_2Cl_2 with EDCI or DCC (0.6 mmol) was added of appropriate amine (5.3 mmol) in dry CH_2Cl_2 during 4 h. After the reaction was completed, solid was filtered, washed with 5% $NaHCO_3$, water and diethyl ether.

5-hydroxyquinaldine-6-carboxylic acid 4-chlorophenylamide (**2**). An orange crystalline compound. Yield 35%. Mp 176-178 °C. Anal. Calc. for $C_{17}H_{13}ClN_2O_2$+2H_2O (348.76): C 61.82%, H 4.55%; found: C 61.79%, H 4.21%. HPLC purity 94.13%. UV (nm), λ_{max}/log ε: 265.5 / 3.57. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.76 (s, 3H), 7.46 (d, *J*=8.45 Hz, 1H), 7.45 (d, *J*=7.5 Hz, 2H), 7.58 (d, *J*=8.4 Hz, 1H), 7.75 (d, *J*=7.5 Hz, 2H), 8.37 (d, *J*=9.2 Hz, 1H), 8.56 (d, *J*=8.8 Hz, 1H).

5-Hydroxyquinaldine-6-carboxylic acid 4-methylbenzylamide (**3**). A beige crystalline compound. Yield 50%. Mp 184-186 °C. Anal. Calc. for $C_{18}H_{18}N_2O_2$+2H_2O (342.37): C 65.80%, H 6.49%; found: C 65.85%, H 6.77%. HPLC purity 98.95%. UV (nm), λ_{max}/log ε: 257.2 / 3.57. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.28 (s, 3H), 2.65 (s, 3H), 3.95 (s, 2H), 7.10 (d, *J*=7.5 Hz 1H), 7.20 (d, *J*=8.5 Hz, 1H), 7.30 (d, *J*=8.5 Hz, 1H), 7.40 (d, *J*=7.6 Hz, 2H), 7.90 (d, *J*=7.6 Hz, 2H), 8.0 (bs, 1H), 8.60 (d, *J*=8.2 Hz, 1H).

5-Hydroxy-2-methylquinoline-6-carboxylic acid [1-(4-fluorophenyl)-ethyl]-amide (**4**). A bright brown solid. Yield 31%. Mp 240 °C (decomp). Anal. Calc. for $C_{19}H_{17}FN_2O_2$+H_2O (342.36): C 66.66%, H 5.59%; found: C 67.02%, H 5.39%. HPLC purity 81.13%. UV (nm), λ_{max}/log ε: 260.7 / 3.56. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.65 (d, 3H), 2.7 (d, 3H), 4.6 (q, 1H), 7.35-7.5 (m, 11H), $[\alpha]^{20}$=5 °.

5-hydroxyquinaldine-6-carboxylic acid 2-(4-hydroxyphenyl)-ethylamide (**5**). Product was obtained according to the described procedure [13]. Yield 47%. Mp 114-117 °C. HPLC purity 95.83%. UV (nm), λ_{max}/log ε: 258.4 / 3.54.

5-hydroxyquinaldine-6-carboxylic acid (4-phenylbuthyl)-amide (**6**). A beige crystalline compound. Yield 52%. Mp 156-159 °C. Anal. Calc. for $C_{21}H_{22}N_2O_2$+H_2O (352.42): C 71.60%, H 6.82%; found: C 71.38%, H 7.34%. HPLC purity 98.63%. UV (nm), λ_{max}/log ε: 257.2 / 3.52. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.48-1.60 (m, 4H), 2.60 (m, 5H); 2.75 (t, 2H), 6.95 (d, *J*=8.5 Hz, 1H), 7.15 (d, *J*=7.9 Hz, 1H), 7.20-7.30 (m, 5H), 760 (bs, 1H); 7.88 (d, *J*=8.5 Hz, 1H), 8.48 (d, *J*=8.6 Hz, 1H).

bis-(5-Hydroxy-2-methylquinoline-6-carboxylic acid)-1,3-propylamide (**7**). A light brown crystalline compound. Yield 24%. Mp 226 °C. Anal. Calc. for $C_{25}H_{24}N_4O_4$+2H_2O (480.49): C 61.35%, H 5.93%; found: C 61.65%, H 6.05%. HPLC purity 92.56%. UV (nm), λ_{max}/log ε: 248.9 / 3.56. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.85 (s, 2H), 2.35 (s, 6H), 2.90 (t, 4H), 6.95 (d, *J*=8.65 Hz, 2H), 7.10 (d, *J*=9.35 Hz, 2H), 7.85 (d, *J*=8.6 Hz, 2H), 7.94 (bs, 1H), 8.55 (d, *J*=7.5 Hz, 2H), 18.15 (s, 2H).

1,3-bis-(5-Hydroxyquinaldine-6-carboxyl)-urea (**8**). A yellow crystalline compound. Yield 29%. Mp 206 °C. Anal. Calc. for $C_{23}H_{18}N_4O_5$+H_2O (448.42): C 60.99%, H 4.53; found: C 60.84%, H 4.95%.HPLC purity 94.75%. UV (nm), λ_{max}/log ε: 263.1 / 3.55. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.63 (s, 6H), 7.15 (d, *J*=8.1 Hz, 2H), 7.35 (d, *J*=8.15 Hz, 2H), 8.05 (d, *J*=8.75 Hz, 2H), 8.70 (d, *J*=8.65 Hz, 2H).

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, 4.6x250 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 by the procedure of Walker from spinach (*Spinacia oleracea* L.) [15]. 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. [16] 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 [17]. The results are summarized in Table 1.

Reduction of chlorophyll content in the green algae Chlorella vulgaris Beij.

The green algae C. *vulgaris* Beij. was cultivated statically at room temperature according to Kralova et al. [18] (photoperiod 16 h light/8 h dark; photosynthetic active radiation 80 μmol/m^2.s; pH 7.2). The effect of the compounds on algal chlorophyll (Chl) content was determined after 7-day cultivation in the presence of the tested compounds. The Chl content in the algal suspension was determined spectrophotometrically (Kontron Uvikon 800, Kontron, Muenchen, Germany) after extraction into methanol according to Wellburn [19]. The Chl content in the suspensions at the beginning of the cultivation was 0.01 mg/L. The applied compound concentrations were as follows: 100, 75, 50, 25, 8.3, 4.2 and 0.83 μmol/L. Because of the low solubility of the studied compounds in water, these were dissolved in DMSO. DMSO concentration in the algal suspensions did not exceed 0.25% and the control samples contained the same DMSO amount as the suspensions treated with the tested compounds. The antialgal activity of the compounds was expressed as IC_{50} (the concentration of the inhibitor causing a 50% decrease in content of chlorophyll as compared with the control sample) or as a percentage of the control determined for the studied concentration range (100-0.83 μmol/L) with a corresponding standard deviation (S.D.). Comparable IC_{50} value for a selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diurone®) was about 7.3 μmol/L [17]. The results are summarized in Table 1.

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REFERENCES

1. Roberts, D.H.; Hutson, T.R. (Eds.), *Herbicides*, Vol. 6, **1987**.
2. Roth, H.J.; Fenner, H. In *Arzneistoffe* 3rd ed.; Deutscher Apotheker Verlag: Stuttgart, **2000**; pp. 51-114.
3. Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V. *ECSOC-8* **2004**, c005, http://www.lugo.usc.es/%7Eqoseijas/ECSOC-8/BOCNP/005/index.htm.

4. Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Kralova, K. *Med. Chem.* **2005**, 1, 591.
5. Musiol, R.; Jampilek, J.; Buchta, V.; Silva, L.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. *Bioorg. Med. Chem.* **2006**, *14*, 3592.
6. Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D.R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. *Bioorg. Med. Chem.* **2007**, *15*, 1280.
7. Podeszwa, B.; Niedbala, H.; Polanski, J.; Musiol, R.; Tabak, D.; Finster, J.; Serafin, K.; Milczarek, M.; Wietrzyk, J.; Boryczka, S.; Mol, W.; Jampilek, J.; Dohnal, J.; Kalinowski, D.S.; Richardson, D.R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, in press.
8. Polanski, J.; Zouhiri, F.; Jeanson, L.; Desmaele, D.; d'Angelo, J.; Mouscadet, J.; Gieleciak, R.; Gasteiger, J.; Bret, M. L. *J. Med. Chem.* **2002**, *45*, 4647.
9. Polanski, J.; Niedbala, H.; Musiol, R.; Tabak, D.; Podeszwa, B.; Gieleciak, R.; Bak, A.; Palka, A.; Magdziarz, T. *Acta Poloniae Pharm. Drug Res.* **2004**, *61*, 3.
10. Musiol, R.; Jampilek, J.; Kralova, K.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, J. *ECSOC-9* **2005**, c005, http://www.usc.es/congresos/ecsoc/9/BOCNP/c005/index.htm.
11. Musiol, R.; Jampilek, J.; Kralova, K.; Tabak, D.; Podeszwa, B.; Finster, J.; Polanski, J. *ECSOC-10* **2006**, c007, http://www.usc.es/congresos/ecsoc/10/ECSOC10.htm.
12. Musiol, R.; Jampilek, J.; Kralova, K.; Tabak, D.; Finster, J.; Podeszwa, B.; Polanski, J. *Bioorg. Med. Chem.* **2007**, submitted.
13. Polanski, J.; Niedbala, H.; Musiol, R.; Podeszwa, B.; Tabak, D.; Palka, A.; Mencel, A.; Mouscadet, J.F.; Le Bret, M. *Lett. Drugs Des. Disc.* **2007**, *4*, 99.
14. Dolezal, M.; Jampilek, J.; Osicka, Z.; Kunes, J.; Buchta, V.; Vichova, P. *Farmaco* **2003**, *58*, 1105.
15. Walker, D. A. In *Methods in Enzymology* Part C; Colowick, S.P.; Kaplan, N.O. Ed.; Academic Press: New York, **1980**; Vol. 69, pp. 94-104.
16. Kralova, K.; Sersen, F.; Sidoova, E. *Chem. Pap.* **1992**, *46*, 348.
17. Fedke, C. *Biochemistry and Physiology of Herbicide Actio*n; Springer Verlag: Berlin-Heidelberg-New York, **1982**.
18. Kralova, K.; Sersen, F.; Melnik, M. *J. Trace Microprobe Techn.*, **1998**, *16*, 491.
19. Wellburn, A.R. *J. Plant. Physiol.*, **1994**, *144*, 307.