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Investigating biological activity spectrum for novel quinoline analogues 2: Hydroxyquinolinecarboxamides with photosynthesis-inhibiting activity

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Abstract—Two series of amides based on quinoline scaffold were designed and synthesized in search of photosynthesis inhibitors. The compounds were tested for their photosynthesis-inhibiting activity against *Spinacia oleracea* L. and *Chlorella vulgaris* Beij. The compounds lipophilicity was determined by the RP-HPLC method. Several compounds showed biological activity similar or even higher than that of the standard (DCMU). The structure–activity relationships are discussed.

1. Introduction

Designing new drugs is extremely complicated problem that attract much attention in current drug discovery strategies. With the novel methods and software tools for molecular modeling more and more molecular descriptors are available.[1,2] This does not always correspond to the number of biological data available. From the medicinal chemist point of view the availability of such data should significantly improve the performance of molecular design.

Quinoline is a system present in many classes of biologically active compounds. Recently, we have reported active herbicides based on such a scaffold.[3,4] A number of quinoline related compounds have been clinically used as antifungal, antibacterial, and antiprotozoic drugs[3,5–8] as well as antituberculotic agents.[9–11] Some quinoline analogues showed also antineoplastics activity.[12] Recently styrylquinoline derivatives have gained remarkable attention due to their activity as potential HIV integrase inhibitors.[13–17] Similar compounds could also possess strong antifungal activity.[7] The compounds containing 8-hydroxyquinoline pharmacophore seem to be especially interesting.[3,4,7]

Various compounds possessing an amide –NHCO– functionality were found to inhibit photosynthetic electron transport. Although this was discovered more than 50 years ago,[18] there are still many unanswered questions about the structural requirements for the activity of these compounds. In this particular case, a better understanding of the SAR trends are not only important for the design of the modern agricultural agents but can also give the remarkable insight into the photosynthesis mechanisms of the green cells. It has been reported recently that the amides of substituted pyridine-4-carboxylic acids[19] as well as anilides of the substituted pyrazine-2-carboxylic acids[20–24] inhibited oxygen evolution rate in spinach chloroplasts and they showed some antialgal properties. In the current research, we designed quinoline series containing the –NHCO– functionality

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in a hope to improve herbicidal activity. Figure 1 illustrates the design of the new analogues (**1**–**25**) that are based on structural analogies to active herbicides (**I**–**III**) having photosynthesis-inhibiting activity. New compounds contain (heterocyclic N)—C(=O)—N molecular fragment included in the quinoline moiety. In compounds **1**–**17**, two nitrogen atoms were separated by four carbon atoms to imitate a structure of **I** (four carbon atoms) or **II** (three carbon atoms). The nitro substitution in quinolines **III** is modified to the amide function.

2. Results and discussion

2.1. Chemistry

Compounds investigated in this work can be divided into two main series, as shown in Figure 1. The comparison of 8-hydroxyquinoline-7-carboxyamides **1**–**17** to the second series, that is, 8-hydroxyquinoline-7-carboxyamides **18**–**25,** indicates the reversed arrangement of heterocyclic nitrogen vs. the carboxyamide and hydroxyl functionality. The synthetic pathways of all discussed quinoline derivatives **1**–**25** are shown in Scheme 1.

The Kolbe–Schmidt reaction leads to 8-hydroxy-2-methylquinoline-7-carboxylic acid, whereas the Skraup synthesis gave 5-hydroxy-2-methylquinoline-6-carboxylic acid. These compounds were further reacted with the appropriate amine in the presence of ethyldimethylaminopropyl carbodiimid (EDCI) or dicyclohexyl carbodiimid (DCC) to afford an amide.

In the case of compounds **15**, **16**, **17**, and **24** diamine and salicylic acid or a twofold excess of quinaldic acid were used. Compound **25** was prepared by the reaction of a twofold excess of 5-hydroxy-2-methyl-quinoline-6-carboxylic acid with urea.

2.2. Lipophilicity

The drugs cross biological barriers most frequently through passive transport, which strongly depends on their lipophilicity; therefore lipophilicity of the drug molecules plays an important role in drug absorption, permeation, and disposition.[27] The lipophilicity of molecules is usually measured by their octanol/water partition coefficients ($\log P$) since the pioneering work of Hansch, Fujita and Leo.[28] $\log P$ is the logarithm of the partition coefficient in a biphasic system (e.g. *n*-octanol/water), defined as the ratio of a compound concentration in phase 1 and in phase 2. The $\log P$ is determined for the uncharged species of the drug. Note that it may exist preferably in the ionic or zwitterionic form(s).

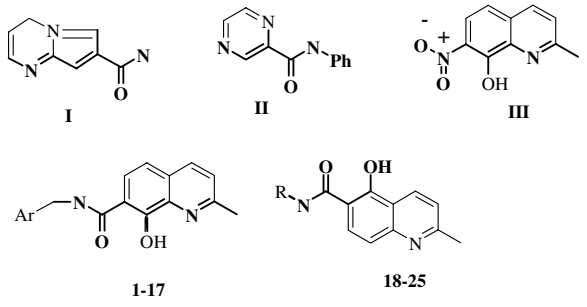
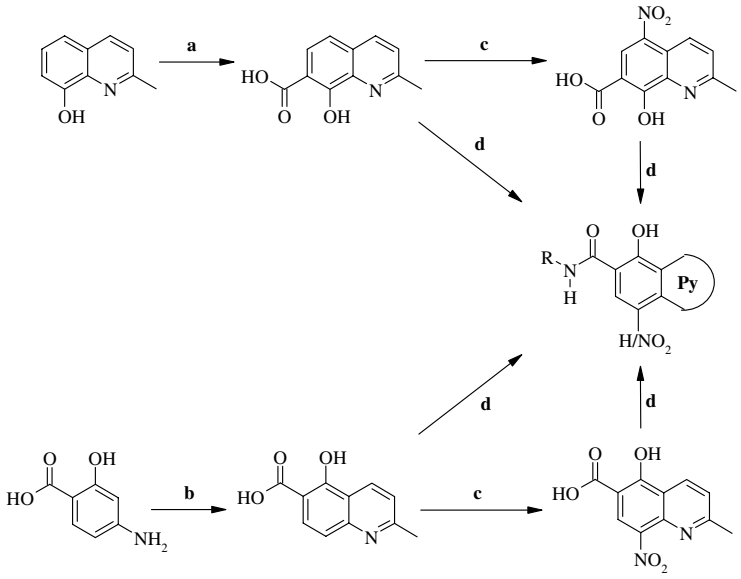


Figure 1. Design of compounds **1**–**25** on the basis of structural analogy to ALS (**I**),[25] heterocyclic amides (**II**)[20–24] and 8-hydroxy-7-nitroquinoline derivative (**III**).[4,26] In bold important molecular fragments included in **I**–**III** and in **1**–**25** are shown.

It has long been recognized that the retention of a compound in reversed-phase liquid chromatography is governed by its lipophilicity/hydrophobicity, and thus shows correlation with an octanol–water partition coefficient.[29] In reversed phase chromatography hydrophobic forces govern the retention, and it has been long recognized as a potential method for lipophilicity determination.[30] High performance liquid chromatography (HPLC) provides an excellent platform for computer controlled automated measurements with computerized data acquisition for a large number of research compounds. The other advantages in the use of the HPLC retention data for lipophilicity determination are that there is no need for concentration determination and method validation, small impurities are separated from the main component, a small amount of material is needed for the measurements, and the procedure can be completely automated. Therefore, the investigation of the true potential of this method is of great importance.[31]

An excellent review on the effect of stationary and mobile phase selection has been published by Pliska et al. and by Claessens et al.[27a,32] Reversed phase-high performance liquid chromatography (RP-HPLC) methods have become popular and widely used for lipophilicity measurement. The general procedure is the measurement of the directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase using RP columns and calculating the logarithm of the capacity factors ($\log K$). $\log K$ is the logarithm of the capacity factors in chromatographic approaches, which is related to the partitioning of a compound between a mobile and a (pseudo-)stationary phase. $\log K$ is used as the lipophilicity index converted to $\log P$ scale.[27a,31–33]

Lipophilicity computing software can usually calculate $\log P$ and $C\log P$. $C\log P$ values present the logarithm of *n*-octanol/water partition coefficient based on established chemical interactions. The software calculates $\log P$ values as lipophilicity contributions/increments of individual atoms, fragments, and the pairs of interacting fragments in the chemical structure, that is, increments of carbon and hetero atoms, aromatic systems, and functional groups. The software calculates lipophilicity contributions according to different internal databases/libraries. Therefore, the values of calculated lipophilicities are dependent on the used software, and the values for individual compounds may be different. This fact as well as various ionic/zwitterionic forms and intramolec-



Scheme 1. Synthesis of compounds **1**–**25**. Reagents and condition: (a) KOH, CO_2; (b) Skraup synthesis; (c) HNO_3/H_2SO_4 5 °C; (d) amine, EDCI or DCC.

ular interactions may cause differences between calculated and experimentally determined lipophilicities.[34]

Log *P*/*C*log *P* values were measured by means of the RP-HPLC and calculated using two commercially available programs. The RP-HPLC was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped nonpolar C_{18} stationary RP column. The capacity factors *K* were determined and subsequent log *K* values were calculated. The results are shown in Tables 1 and 2; Figure 2.

The overall correlation between the calculated and experimentally determined log *K* values is rather poor. The ACD/log *P* calculated data correlate relatively better with the measured values. In particular, log *P*/*C*log *P* values calculated by ChemOffice software do not agree well with the log *K* values measured for compounds **1**–**17**, see Figure 2.

This disagreement could be probably attributed to the presence of ionisable fragments in the molecules of hydroxyquinolines, which enhance intramolecular interactions. The commercially available chemical software (ChemOffice and ACD/log *P*) is not suitable for calculating the lipophilicity of similar highly functionalized molecules. The significant differences between the experimental and calculated parameters could be observed for compounds **6**, **7**, and **15**–**17**. This effect is caused probably by the interactions of the salicylamide hydroxyl and carboxamide functionalities as well as the interaction of this system with heterocyclic nitrogen.[35] Both dimers **16** and **17** showed the lowest log *K* value and compound **15** has the highest one within the series **1**–**17**, as expected.

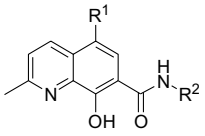
Compounds **10**–**14** substituted in the $C_{(5)}$ position of quinoline by nitro functionality showed higher experimental log *K* than the calculated log *P* values. In comparison to the unsubstituted compounds nitro group increases log *K*, see **1**–**5/10**–**14**. Moreover, the substitution pattern of the phenyl moiety can further explain the log *K* increase. This complied with the sequence $H < OCH_3 < F < CH_3$. The log *K* data followed also the aliphatic linker increase indicating the length-dependence of the chains: $C_2H_4Ph < CH_2Ph < C_4H_8Ph$.[36] Chain branching caused also the increase in lipophilicity, see **1/3** and **11/12**.

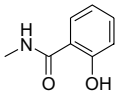
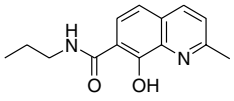
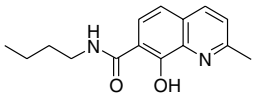
Similarly to the calculated log *P* data for compounds **1**–**17**, the overall data calculated for compounds **18**–**25** also do not agree well enough with the experimentally determined parameters (log *K* values correlate relatively better with calculated *C*log *P* values), see Figure 2. As expected, dimer **24** showed the lowest lipophilicity, the same as compound **17**. Compound **25** possessed the highest log *K* that was unexpected. Acid **18** showed also high hydrophobicity contrary to all the results of the lipophilicity calculated softwares. The comparison of compounds **3**–**21**, **7**–**23**, **4**–**20**, and **17**–**25** indicated a higher log *K* values within the series of **18**–**25** than those observed within **1**–**17**. This fact can be explained by hydrogen bond between phenolic and carbonyl group[37] and/or hydrogen bond between phenolic and quinoline–nitrogen[3,4,7] due to their opposite positions.[35]

2.3. Biological activities

All compounds were tested for their in vitro herbicidal susceptibility. The results obtained are shown in Tables 1 and 2. 8-Hydroxy-2-methyl-quinoline-7-carboxylic acid (2-hydroxyethyl)-amide (**6**) was found to be inactive in both tests, which seems to indicate the importance of the phenyl moiety.

Table 1. The PET inhibition in spinach chloroplasts and reduction of chlorophyll content in *C. vulgaris* of compounds **1**–**17** compared to that of the standard DCMU compound



Compound	R^1	R^2	Log *K*	Log *P*/*C*log *P* ChemOffice	Log *P* ACD/log *P*	PET inhibition IC_{50} (μmol/L)	Chlorophyll reduction IC_{50} (μmol/L)
1	H	$-CH_2Ph$	0.2812	3.31/4.840	3.75 ± 0.80	[b]	17.2
2	H	$-CH_2Ph$–4-F	0.3389	3.47/4.983	3.80 ± 0.85	[b]	158
3	H	$-CH(CH_3)Ph$–4-F	0.3720	3.78/5.292	4.15 ± 0.85	[b]	83.3
4	H	$-CH_2Ph$–4-CH_3	0.3793	3.79/5.339	4.21 ± 0.80	[b]	7.2
5	H	$-CH_2Ph$–4-OCH_3	0.2843	3.18/4.759	3.67 ± 0.81	[b]	4.8
6	H	$-C_2H_4OH$	0.2629	1.06/1.076	1.35 ± 0.81	[b]	[b]
7	H	$-C_2H_4Ph$	0.2404	3.59/4.969	4.17 ± 0.80	[b]	77.7 ± 6.3[a]
8	H	$-C_2H_4Ph$–4-F	0.3342	3.74/5.112	4.22 ± 0.84	[b]	15.9
9	H	$-C_4H_8Ph$	0.5075	4.00/5.348	5.06 ± 0.79	[b]	8.5
10	NO_2	$-CH_2Ph$	0.4021	2.96/3.531	4.07 ± 0.82	32.0	[b]
11	NO_2	$-CH_2Ph$–4-F	0.4136	3.10/3.674	4.12 ± 0.86	95.0	[b]
12	NO_2	$-CH(CH_3)Ph$–4-F	0.4283	3.42/5.224	4.47 ± 0.86	8.7	43.6
13	NO_2	$-CH_2Ph$–4-CH_3	0.4304	3.38/4.030	4.53 ± 0.82	107.0	[b]
14	NO_2	$-CH_2Ph$–4-OCH_3	0.4087	3.09/3.450	3.98 ± 0.82	137.0	[b]
15	H		0.6361	2.31/4.755	3.60 ± 0.87	[b]	[b]
16	H		0.1109	2.91/5.991	4.04 ± 1.13	[b]	93.7
17	H		0.1168	3.01/6.303	4.26 ± 1.12	[b]	149
DCMU	—	—	—	2.76/2.691	2.78 ± 0.38	1.9	7.3

The measured log *K* and calculated log *P*/*C*log *P* data are shown to illustrate lipophilicity.

[a] IC_{50} was not determined, a value referring to an average decrease of Chl content related to the control determined for the concentration range of 0.83–100 μmol/L ([%] ± SD) is indicated.

[b] Inactive compound.

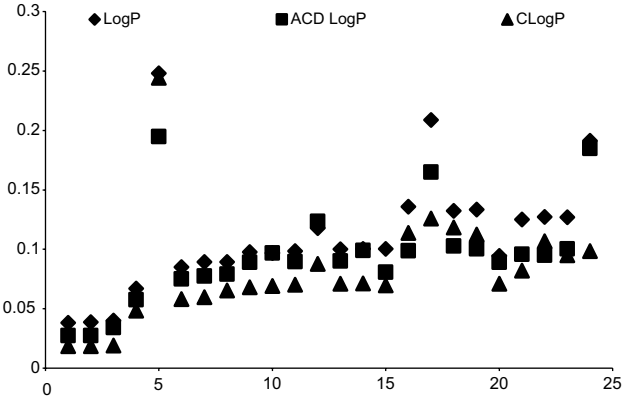


Figure 2. Comparison of the computed log *P*/*C*log *P* values using the two programs with the log *K* values of the compounds **1**–**25**.

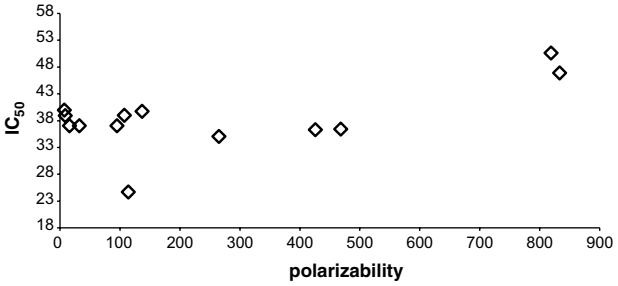
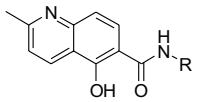
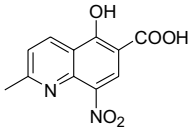
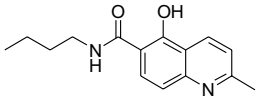
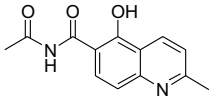


Figure 3. Activity (IC_{50}) of PET activity versus polarizability of studied compounds.

2.3.1. PET inhibition activity in spinach chloroplasts. An interesting activity rules can be deduced for the derivatives of 8-hydroxy-2-methylquinoline-7-carboxylic acid tested. Compounds lacking 5-NO_2 functionality are inactive if tested for the inhibition of oxygen evolution rate in spinach chloroplasts. This rule makes active compounds **10**–**14** that shows the PET inhibition activity ranging from 8.7 (**12**) to 137.0 μmol/L (**14**). The activity of compound **12** is comparable to that of DCMU. Thus, the most important requirement for high PET activity is the $C_{(5)}$ substitution by nitro moiety. Moreover, the activity increases with the electron accepting power of

Table 2. The PET inhibition in spinach chloroplasts and reduction of chlorophyll content in *C. vulgaris* of compounds **18**–**25** compared to that of the standard DCMU compound



Compound	R	Log *K*	log *P*/*C*log *P* ChemOffice	Log *P* ACD/log *P*	PET inhibition IC_{50} (μmol/L)	Chlorophyll reduction IC_{50} (μmol/L)
18		0.4072	1.95/3.235	2.47 ± 0.36	114.0	108.6 ± 11.3[a]
19	–Ph–4-Cl	0.3812	3.80/5.464	4.73 ± 0.42	265.0	23.8
20	$–CH_2Ph–4-CH_3$	0.3800	3.79/5.339	3.84 ± 0.41	468.0	97.2 ± 3.8
21	$–CH(CH_3)Ph–4-F$	0.3663	3.78/5.292	3.78 ± 0.47	426.0	100.0 ± 5.9[a]
22	$–C_2H_4Ph–4-OH$	0.3775	3.20/4.302	3.06 ± 0.40	16.0	102.5 ± 8.9[a]
23	$–C_4H_8Ph$	0.4173	4.42/5.877	4.68 ± 0.39	7.2	10.9
24		0.1203	3.01/6.303	3.51 ± 0.51	819.0	19.5
25		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

The measured log *K* and calculated log *P*/*C*log *P* data are shown to illustrate lipophilicity.

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

the $C_{(4)}$ substituent. However, only a poor correlation can be observed between the activity and polarizability as shown in Figure 3, or molar refractivity that was not shown here.

Among the amides of 5-hydroxy-2-methylquinoline-6-carboxylic acid **18**–**25** two compounds showed interesting IC_{50} values, compound **23** (IC_{50} = 7.2 μmol/L) and compound **22** (IC_{50} = 16.0 μmol/L). Moreover, the activity level of compound **23** was comparable to that of DCMU activity. Both dimers **24** and **25** possessed only very low activity. No simple structure–activity rule explaining the activity changes within the series **18**–**25** was revealed.

2.3.2. Reduction of chlorophyll content in *Chlorella vulgaris*. The derivatives of 8-hydroxy-2-methylquinoline-7-carboxylic acid indicated a high selectivity of herbicidal effect. Amides **1**–**9**, **15**–**17** inhibited selectively chlorophyll production in *C. vulgaris*, whereas amides possessing nitro functionality in the $C_{(5)}$ position, that is, compounds **10**–**14** are practically inactive against *C. vulgaris*. Compound **12** is the only exception in this trend.

Among the first series three compounds **1**, **8**, and **9** inhibited chlorophyll production in *C. vulgaris* comparable to DCMU. The inhibitory activity of compounds **4**, **5** even exceeded the activity of DCMU. In particular, IC_{50} values varied in the range from 4.8 (**5**) to 17.2 μmol/L (**1**), which makes compound **5** the most efficient inhibitor.

The inhibitory activity of 8-hydroxy-2-methylquinoline-7-carboxamides having the benzylamide functionality, compounds **1**,**2**, **4**, **5**, clearly depended on the electron-accepting properties of the benzyl substituent, which is illustrated in Figure 4.[38] This trend is contrary to that previously described for the PET activity.

Lipophilicity can be the second important factor affecting the activity of the compounds investigated. Compound **3** differed from **2** by linker branching to carboxamido group and phenyl moiety. The log *K* value of **3** was higher than that of **2** and the activity of **3** was much higher than **2**. Compounds **1**, **7**, **9**, and **2**, **8** as well as **16**, **17** differed from each other in the linker length connecting two aromatic moieties within the molecule, that is, a number of CH_2 groups in this linker. The comparison of compounds **1** and **9** having similar unsubstitued aromatic group showed that the increase of the compound lipophilicity caused by the prolongation of the linker by two CH_2 groups led to a moderate increase

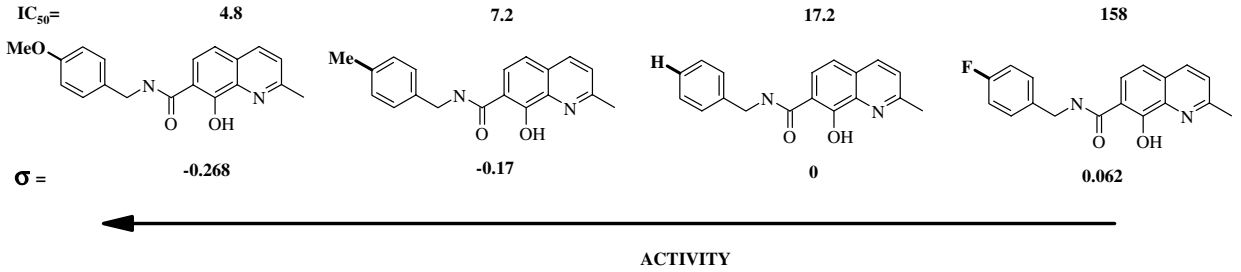


Figure 4. The IC_{50} ([μmol/L]) values decreases with the increase of the Hammett σ constant of the benzyl substituent of 8-hydroxy-2-methylquinoline-7-carboxyamides (**1**,**2**, **4**, and **5**).

of inhibitory activity. On the other hand, the prolongation of the linker in compound **1** by a single CH_2 group decreased the activity of compound **7** and the similar prolongation of the linker in compound **2** (4-fluorobenzylamide derivative) increased the activity of compound **8**. Moreover, the addition of a single CH_2 group to the linker of bis-[8-hydroxy-2-methylquinoline-7-carboxylic acid]-1,2-ethylamide (**16**) slightly decreased the activity of **17**. This indicates that lipophilicity alone cannot explain the activity changes within the first series of compounds **1**–**17**. Thus, the distance between the quinoline nucleus and the $C'_{(4)}$-hydrogen substituent in phenyl ring is probably also an important parameter influencing the activity.

The derivatives of 5-hydroxy-2-methylquinoline-6-carboxylic acid did not show similar selectivity as compounds **1**–**17**. The activity of 5-hydroxy-2-methylquinoline-6-carboxamides **19**–**25** is relatively high. Compounds **19**, **23**–**25** have advantageous IC_{50} values in the range of 5.5–23.8 μmol/L, and compound **25** is the most active analogue (IC_{50} = 5.5 μmol/L). Compound **24** showed higher activity than **17** and **23** was comparable to **9**. The comparison of the individual values listed in Table 2 indicates that the relationships between $\log K$ and the activity of the series **18**–**25** are slightly better than that for compounds **1**–**17**. Improved antialgal activity correlated with increased lipophilicity.

3. Conclusion

The comparison of antialgal activity to the oxygen evolution rate in spinach chloroplasts for the novel quinoline compounds indicated that the derivatives of 8-hydroxy-2-methylquinoline-7-carboxylic acid showed selective antialgal activity, whereas the derivatives of 8-hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid inhibited a better PET in spinach chloroplasts. 5-Hydroxy-2-methylquinoline-6-carboxamides showed unselective activity in both tests.

As we presented here quinoline based scaffolds can be successfully used for the design of new active electron transfer inhibitors. High to moderate activity of compounds **4**, **5**, **12**, and **23** makes these molecular fragments valuable for further study and modifications. Although there is no clear structure activity relationship for the series, we have shown some trends. Lipophilicity and the electron-accepting or electron-withdrawing power of the substituents are probably the most important among molecular features discussed. The inactivity of compound **18** suggests that the carboxamide function is the attribute that limits the activity.

4. Experimental

4.1. 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. 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. Peaks in the chromatogram of the solvent (blank) were deducted from peaks in the chromatogram of the sample solution. A purity of the individual compounds was determined from 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, USA) in ca 6×10^{-4} mol methanolic solution and $\log \epsilon$ (the logarithm of molar absorption coefficient ϵ) was calculated for the absolute maximum λ_{max} of individual target compounds. All ^1H NMR spectra were recorded on a Bruker AM-500 (499.95 MHz for ^1H), Bruker BioSpin Corp., Germany. Chemical shifts are reported in ppm (δ) to internal $Si(CH_3)_4$, when diffused easily exchangeable signals are omitted.

4.2. Synthesis

4.2.1. General procedure of substituted amides of quinoline derivatives 1–25 syntheses. To the solution prepared hydroxyquinaldinecarboxylic acids (1.02 g, 5.0 mmol) in dry CH_2Cl_2 with EDCI or DCC (0.6 mmol) was added 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.

4.2.2. 8-Hydroxy-2-methylquinoline-7-carboxylic acid benzylamide (1). A white crystalline compound. Yield 86%. Mp 215–218 °C. Anal. calcd for $C_{18}H_{16}N_2O_2$ (292.34): C 73.95%, H 5.52%; found: C 74.12%, H 5.68%. HPLC purity 91.17%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.62. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.57 (s, 3H), 4.06 (s, 2H), 6.94 (d, 1H, J = 8.4 Hz), 7.3 (d, 1H, J = 8.4 Hz), 7.35–7.37 (m, 3H), 7.45 (d, 2H, J = 7.3 Hz), 7.73 (d, 1H, J = 8.4 Hz), 8.0 (d, 1H, J = 8.4 Hz), 8.58 (bs, 2H).

4.2.3. 8-Hydroxy-2-methylquinoline-7-carboxylic acid 4-fluorobenzylamide (2). Product was obtained according to the described procedure.[26] Yield 26%. Mp 190–196 °C. HPLC purity 91.48%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.60.

4.2.4. 8-Hydroxy-2-methylquinoline-7-carboxylic acid [1-(4-fluorophenyl)-ethyl]-amide (3). A white crystalline compound. Yield 36%. Mp 208–210 °C. Anal. calcd for $C_{19}H_{17}FN_2O_2$+2H_2O (360.36): C 63.32%, H 5.87%; found: C 63.55%, H 5.61%. HPLC purity 98.91%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.4/3.55. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.47 (d, 3H, J = 6.7 Hz), 2.6 (s, 3H), 4.46 (q, 1H), 5.59 (d, 1H, J = 7.8 Hz), 7.95 (d, 1H, J = 8.3 Hz), 7.22–7.33 (m, 3H), 7.50–7.57 (m, 2H), 7.75 (d, 1H, J = 8.4 Hz), 8.01 (d, 1H, J = 8.4 Hz), 8.37 (s, 1H).

4.2.5. 8-Hydroxy-2-methylquinoline-7-carboxylic acid 4-methylbenzylamide (4). Product A white crystalline compound. Yield 36.4%. Mp 192–200 °C (dec). Anal. calcd for $C_{19}H_{18}N_2O_2$ (306.37): C 74.49%, H 5.92%; found: C 74.32%, H 6.10%. HPLC purity 91.30%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.59. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.3 (s, 3H), 2.6(s, 3H), 4.02 (s, 2H), 6.9 (d, 1H, J = 8.4 Hz), 7.2 (d, 2H, J = 7.5 Hz), 7.31–7.35 (m, 3H), 7.75 (d, 1H, J = 8.3 Hz), 8.04 (d, 1H, J = 8.3 Hz), 8.43 (bs, 2H).

4.2.6. 8-Hydroxy-2-methylquinoline-7-carboxylic acid 4-methoxybenzylamide (5). A white crystalline compound. Yield 34.5%. Mp 180–190 °C (dec). Anal. calcd for $C_{19}H_{18}N_2O_3$ (322.37): C 70.79%, H 5.63%; found: C 70.65%, H 5.49%. HPLC purity 91.22%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.64. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.59 (s, 3H), 3.73 (s, 3H), 4.00 (s, 2H), 6.94 (d, 2H, J = 8.4 Hz), 6.97 (d, 1H, J = 8.3 Hz), 7.32 (d, 1H, J = 8.3 Hz), 7.40 (d, 2H,J = 8.4 Hz), 7.75 (d, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 8.3 Hz), 8.4 (bs, 2H).

4.2.7. 8-Hydroxy-2-methyl-quinoline-7-carboxylic acid (2-hydroxyethyl)-amide (6). A white crystalline compound. HPLC purity 99.59%. Yield 78.5%. Mp 228–229 °C. UV (nm), $\lambda_{max}/\log\epsilon$: 258.7/3.59.[39]

4.2.8. 8-Hydroxy-2-methylquinoline-7-carboxylic acid phenethylamide (7). A white crystalline compound. Yield 62%. Mp 228–235 °C. Anal. calcd for $C_{19}H_{18}N_2O_2$ (306.37): C 74.49%, H 5.93%; found: C 74.63%, H 6.05%. HPLC purity 90.81%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.62. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.61 (s, 3H), 2.89 (t, 2H), 3.09 (t, 2H), 6.98 (d, 1H, J = 8.4 Hz), 7.21–7.25 (m, 3H), 7.29–7.33 (m, 3H), 7.77 (d, 1H, J = 8.3 Hz), 8.03 (d, 1H, J = 8.3 Hz), 8.19 (bs, 2H).

4.2.9. 8-Hydroxy-2-methylquinoline-7-carboxylic acid [2-(4-fluorophenyl)-ethyl]-amide (8). A white crystalline compound. Yield 52%. Mp 189–193 °C. Anal. calcd for $C_{19}H_{17}FN_2O_2$ (324.36): C 70.36%, H 5.28%; found: C 70.23%, H 5.46%. HPLC purity 91.56%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.61. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.61 (s, 3H), 2.88 (t, 2H), 3.09 (t, 2H), 6.98 (d, 1H, J = 8.2 Hz), 7.12 (t, 2H), 7.28 (t, 2H), 7.33 (d, 1H, J = 8.3 Hz), 7.77 (d, 1H, J = 8.2 Hz), 8.03 (d, 1H, J = 8.2 Hz), 8.21 (bs, 2H).

4.2.10. 8-Hydroxy-2-methylquinoline-7-carboxylic acid (3-phenylbuthyl)-amide (9). A white crystalline compound. Yield 73%. Mp 196–201 °C. Anal. calcd for $C_{21}H_{22}N_2O_2$ (334.42): C 75.42%, H 6.63%; found: C 75.36%, H 6.78%. HPLC purity 93.31%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.61. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.61 (s, 4H), 2.55 (s, 2H), 2.64 (s, 3H), 2.83 (s, 2H), 6.96 (d, 1H, J = 8.4 Hz), 7.10 (d, 3H, J = 6.7 Hz), 7.18 (t, 2H), 7.26 (d, 1H, J = 8.2 Hz), 7.81 (d, 1H, J = 8.3 Hz), 7.94 (d, 1H, J = 8.2 Hz), 8.15 (bs, 2H).

4.2.11. 8-Hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid benzylamide (10). A yellow crystalline compound. Yield 61%. Mp 219–228 °C. Anal. calcd for $C_{18}H_{15}N_3O_4$ (337.33): C 64.09%, H 4.48%; found: C 63.95%, H 4.42%. HPLC purity 99.37%. UV (nm), $\lambda_{max}/\log\epsilon$: 427.7/3.64. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.58 (s, 3H); 4.05 (s, 2H); 7.37–7.45 (m, 5H); 7.52 (d, 1H, J = 8.6 Hz); 8.18 (bs, 2H); 9.07 (d, 1H, J = 8.6 Hz); 9.13 (s, 1H).

4.2.12. 8-Hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid 4-flourobenzylamide (11). A yellow crystalline compound. Yield 44%. Mp 202–206 °C. Anal. calcd for $C_{18}H_{14}FN_3O_4$ (355.34): C 60.84%, H 3.97%; found: C 60.68%, H 3.80%. HPLC purity 96.22%. UV (nm), $\lambda_{max}/\log\epsilon$: 427.7/3.66. DMSO-$d_6$, 500 MHz) δ: 2.57 (s, 3H); 4.05 (s, 2H); 7.25 (t, 2H); 7.50 (t, 2H); 7.51 (d, 1H); 8.21 (bs, 2H); 9.07 (d, 1H, J = 8.6 Hz); 9.13 (s, 1H).

4.2.13. 8-Hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid [1-(4-fluorophenyl)-ethyl]-amide (12). An orange crystalline compound. Yield 54%. Mp 220–222 °C (dec). Anal. calcd for $C_{19}H_{16}FN_3O_4$+2H_2O (405.36): C 56.29%, H 4.97%; found: C 55.92%, H 5.06%. HPLC purity 99.09%. UV (nm), $\lambda_{max}/\log\epsilon$: 427.7/3.58. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.49 (d, 3H, J = 6.8 Hz), 2.56 (s, 3H), 4.46 (q, 1H), 7.18–7.27 (m, 2H), 7.49–7.56 (m, 3H), 8.3 (d, 1H, J = 8.7 Hz), 9.12 (s, 1H).

4.2.14. 8-Hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid 4-methylbenzylamide (13). A yellow crystalline compound. Yield 78%. Mp 228–232 °C. Anal. calcd for $C_{19}H_{17}N_3O_4$ (351.35): C 64.95%, H 4.88%; found: C 65.12%, H 4.96%. HPLC purity 99.30%. UV (nm), $\lambda_{max}/\log\epsilon$: 427.7/3.65. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.28 (s, 3H); 2.57 (s. 3H); 3.99 (s, 2H); 7.20 (d, 2H,

J = 7.7 Hz); 7.31 (d, 2H, J = 7.7 Hz); 7.51 (d, 1H, J = 8.6 Hz); 8.16 (bs, 2H); 9.06 (d, 1H, J = 8.7 Hz); 9.13 (s, 1H).

4.2.15. 8-Hydroxy-2-methyl-5-nitroquinoline-7-carboxylic acid 4-methoxybenzylamide (14). A yellow crystalline compound. Yield 63%. Mp 211–214 °C. Anal. calcd for $C_{19}H_{17}N_3O$ (367.35): C 62.12%, H 4.66%; found: C 61.83%, H 4.71%. HPLC purity 98.74%. UV (nm), $\lambda_{max}/\log\epsilon$: 430.2/3.58. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.58 (s, 3H); 3.74 (s, 3H); 3.96 (s, 2H); 6.96 (d, 2H, J = 8.6 Hz); 7.36 (d, 2H, J = 8.6 Hz); 7.52 (d, 1H, J = 8.7 Hz); 8.05 (bs, 2H); 9.08 (d, 1H, J = 8.7 Hz); 9.13 (s, 1H).

4.2.16. 2-Hydroxybenzoic acid *N*′-(8-hydroxy-2-methylquinoline-7-carbonyl)-hydrazide (15). A yellow crystalline compound. Yield 37.6%. Mp 147–150 °C. Anal. calcd for $C_{18}H_{15}N_3O_4$ (337.33): C 64.09%, H 4.48%; found: C 63.92%, H 4.38%. HPLC purity 94.17%. UV (nm), $\lambda_{max}/\log\epsilon$: 290.3/3.56. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.75 (s, 3H); 6.96–7.00 (m, 2H); 7.36 (d, 1H, J = 8.6 Hz); 7.46 (t, 1H); 7.60 (d, 1H, J = 8.4 Hz); 7.95–7.97 (m, 2H); 8.34 (d, 1H, J = 8.4 Hz); 11.07 (bs, 1H); 11.44 (bs, 1H).

4.2.17. Bis-[8-hydroxy-2-methylquinoline-7-carboxylic acid]-1,2-ethylamide (16). Product was obtained according to the described procedure.[26] Yield 7%. Mp 254–257 °C. HPLC purity 91.47%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.60.

4.2.18. Bis-[8-hydroxy-2-methylquinoline-7-carboxylic acid]-1,3-propylamide (17). Product was obtained according to the described procedure.[26] Yield 23%. Mp 293–297 °C. HPLC purity 92.06%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.3/3.60.

4.2.19. 5-Hydroxy-2-methyl-8-nitroquinoline-6-carboxylic acid (18). Product was obtained according to the described procedure.[26] Yield 53%. Mp 280°C (dec). HPLC purity 94.25%. UV (nm), $\lambda_{max}/\log\epsilon$: 284.4/3.67.

4.2.20. 5-Hydroxyquinaldine-6-carboxylic acid 4-chlorophenylamide (19). An orange crystalline compound. Yield 35%. Mp 176–178 °C. Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 265.5/3.57. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.76 (s, 3H), 7.46 (d, 1H, J = 8.4 Hz), 7.45 (d, 2H, J = 7.5 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.75 (d, 2H, J = 7.5 Hz), 8.37 (d, 1H, J = 9.2 Hz), 8.56 (d, 1H, J = 8.8 Hz).

4.2.21. 5-Hydroxyquinaldine-6-carboxylic acid 4-methylbenzylamide (20). A beige crystalline compound. Yield 50%. Mp 184–186 °C. Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 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, 1H, J = 7.5 Hz), 7.20 (d, 1H, J = 8.5 Hz), 7.30 (d, 1H, J = 8.5 Hz), 7.40 (d, 2H, J = 7.6 Hz), 7.90 (d, 2H, J = 7.6 Hz), 8.0 (bs, 1H), 8.60 (d, 1H, J = 8.2Hz).

4.2.22. 5-Hydroxy-2-methylquinoline-6-carboxylic acid [1-(4-fluorophenyl)-ethyl]-amide (21). A bright brown solid. Yield 31%. Mp 240 °C (dec). Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 260.7/3.56. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 1.65 (d, 3H), 2.7 (s, 3H), 4.6 (q, 1H), 7.35–7.5 (m, 8H).

4.2.23. 5-Hydroxyquinaldine-6-carboxylic acid 2-(4-hydroxyphenyl)-ethylamide (22). Product was obtained according to the described procedure.[26] Yield 47%. Mp 114–117 °C. HPLC purity 95.83%. UV (nm), $\lambda_{max}/\log\epsilon$: 258.4/3.54.

4.2.24. 5-Hydroxyquinaldine-6-carboxylic acid (4-phenylbuthyl)-amide (23). A beige crystalline compound. Yield 52%. Mp 156–159 °C. Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 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, 1H, J = 8.5 Hz), 7.15 (d, 1H, J = 7.9 Hz), 7.20–7.30 (m, 5H), 7.60 (bs, 1H); 7.88 (d, 1H, J = 8.5 Hz), 8.48 (d, 1H, J = 8.6 Hz).

4.2.25. Bis-(5-hydroxy-2-methylquinoline-6-carboxylic acid)-1,3-propylamide (24). A light brown crystalline compound. Yield 24%. Mp 226 °C. Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 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, 2H, J = 8,65 Hz), 7.10 (d, 2H, J = 9.35 Hz), 7.85 (d, 2H, J = 8.6 Hz), 7.94 (bs, 2H), 8.55 (d, 2H, J = 7.5 Hz), 18.15 (s, 2H).

4.2.26. 1,3-Bis-(5-hydroxyquinaldine-6-carboxyl)-urea (25). A yellow crystalline compound. Yield 29%. Mp 206 °C. Anal. calcd 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), $\lambda_{max}/\log\epsilon$: 263.1/3.55. ^{1}H NMR (DMSO-d_6, 500 MHz) δ: 2.63 (s, 6H), 7.15 (d, 2H, J = 8.1 Hz), 7.35 (d, 2H, J = 8.15 Hz), 8.05 (d, 2H, J = 8.75 Hz), 8.70 (d, 2H, J = 8.65 Hz).

4.3. 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, USA) were used. The 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 by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, USA). 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 the 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 Tables 1 and 2.

4.4. Lipophilicity and physicochemical calculations

Log$P$, that is, the logarithm of the partition coefficient for *n*-octanol/water, was calculated using the programs CS ChemOffice Ultra ver. 9.0 (CambridgeSoft, Cambridge, MA, USA) and ACD/log$P$ 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, USA) software. The results are shown in Tables 1 and 2.

Molar refractivity, polarizability, and other simple physicochemical constants were calculated using ACD labs software. The Hammett constants were taken from Hansh and Leo.[38] Polarizabilty was calculated according to Lorentz–Lorenz equation.

$$\text{Polarizability} = 0.3964308 \cdot \frac{(n^2-1)}{(n^2+2)} \cdot \frac{M_W}{d}$$

4.5. Biological activities

4.5.1. PET inhibition in spinach chloroplasts. Chloroplasts were prepared by the procedure of Walker from spinach (*Spinacia oleracea* L.).[40] 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.[41–43] 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, that is, by molar concentration of the compounds causing a 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.[42] The results are summarized in Tables 1 and 2.

4.5.2. Reduction of chlorophyll content in the green algae *C. vulgaris* Beij. The green algae *C. vulgaris* Beij was cultivated statically at room temperature according to Kralova et al.[43] (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.[44] 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 percentage of the control determined for the studied concentration range (100–0.83 μmol/L) with the corresponding standard deviation (SD). Comparable IC_{50} value for a selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diurone®) was about 7.3 μmol/L.[42] The results are summarized in Tables 1 and 2.

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