

Preparation and Herbicidal Properties of Ring-Substituted 4-Chloro-2-styrylquinazolines

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Abstract: In this study, a series of new seven ring-substituted 4-chloro-2-styrylquinazoline derivatives were prepared. The procedures for synthesis of the compounds are presented. The compounds were analyzed using RP-HPLC to determine lipophilicity. They were tested for their activity related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts. For all the compounds, the relationships between the lipophilicity and the chemical structure of the studied compounds are discussed, as well as their structure-activity relationships (SAR).

Keywords: 4-chloro-2-styrylquinazoline derivatives; Lipophilicity; PET inhibition; Spinach chloroplasts; Structure-activity relationships.

INTRODUCTION

A quinoline moiety is present in many classes of biologically-active compounds. A number of them have been clinically used as antifungal, antibacterial and antiprotozoic drugs [1,2] as well as antituberculotic agents [3-8]. Some quinoline-based compounds also showed antiasthmatic and antiplatelet activity [9-11]. A series of compounds derived from 8-hydroxyquinoline and styrylquinoline derivatives were recently synthesized as potential HIV-1 integrase inhibitors [12-15]. These compounds showed a significant similarity to some

novel antifungal agents, namely homoallylamines [16]. Our previous study dealing with 8-hydroxyquinoline and styrylquinoline derivatives showed that they could also possess strong antifungal activity [6-8,17,18]. According to the results reported recently, some new hydroxyquinoline derivatives also possess interesting herbicidal activities [6-8,17,19,20]. In addition, some of the quinoline derivatives investigated also showed antineoplastic activity [19,21,22].

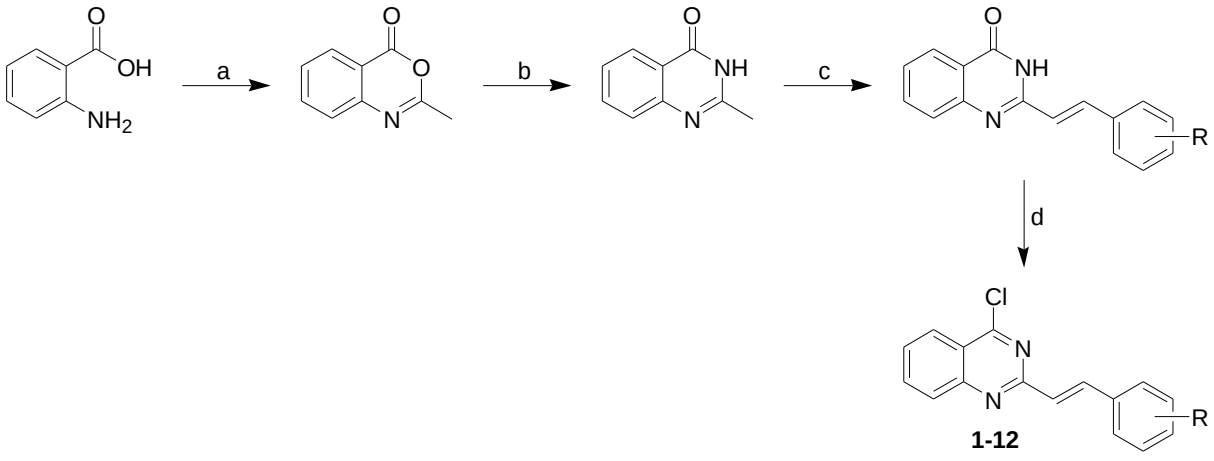
Over 50% of commercially available herbicides act by reversibly binding to photosystem II (PS II), a membrane-protein complex in the thylakoid membranes which catalyses the oxidation of water and the reduction of plastoquinone [23] and thereby inhibit photosynthesis [24-26]. Some organic compounds, e.g. substituted benzanilides [27] or pyrazine-2-carboxylic acids [28] were found to interact with tyrosine radicals Tyr_Z and Tyr_D which are situated in D_1 and D_2 proteins on the donor side of PS II and due to this interaction interruption of the photosynthetic electron transport occurred.

In the context of the previously-described azanaphtalenes [6-8,17-22], new modifications of quinoline moiety that can trigger 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.). 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. Relationships among the structure and inhibitory activity related to inhibition of photosynthetic electron transport (PET) in spinach chloroplasts of the new compounds are discussed.

RESULTS AND DISCUSSION

All studied compounds were prepared according to Scheme 1. Microwave-assisted synthesis facilitated the process of obtaining quinazoline-related structures. 2-Methyl-4*H*-benzo[*d*][1,3]oxazin-4-one was synthesized from anthranilic acids and acetic anhydride. A further reaction with ammonia afforded 2-methylquinazolin-4(3*H*)-one. Ring-substituted 2-styrylquinazolin-4(3*H*)-ones were obtained from appropriate aldehydes using neat microwave-assisted synthesis [7,29]. Further aromatization with $POCl_3$ yielded 4-chloro-2-styrylquinazoline derivatives (**1-12**). Compounds **1-5** were described in Jampilek *et al.* [7] but for completeness' sake they are mentioned in Table 1.

Scheme 1. Synthesis of 4-chloro-2-styrylquinazoline **1-12**: (a) Ac_2O, microwave irradiation; (b) $NH_{3\ aq}$, microwave irradiation; (c) aldehyde, microwave irradiation; (d) $POCl_3$.

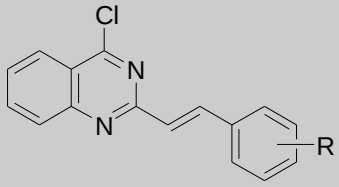


Hydrophobicities (log *P*/Clog *P*) of compounds **1-12** were calculated using two commercially available programs (ChemDraw Ultra 10.0 and ACD/LogP) and also measured by means of the RP-HPLC determination of capacity factors *k* with subsequent calculation of log *k*. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using an end-capped non-polar C_{18} stationary RP column. The program ChemDraw did not resolve the varying lipophilicity values of individual positional isomers, in that the same log *P*/Clog *P* data were calculated for **2-4**, **5**/**6** and **7-9**. The results are shown in Table 1 and illustrated in Figure 1.

The results show that experimentally determined log *k* values correlate relatively poorly with the calculated log *P*. Compound **5** showed the highest lipophilicity, while compound **12** possessed the lowest hydrophobicity within individual series of compounds. Surprisingly, 3,5-OCH_3 derivative **6** showed much lower lipophilicity than expected on the basis of calculated log *P* data and compared with 2,4-OCH_3 is its hydro/lipophilic properties diametrically opposed. If the lipophilicity data log *k* of three position isomers **2-4**, **7-9** are compared, it can be stated that 3-alkoxy derivative **3**/**8** possessed higher hydrophobicity than 2-alkoxy derivative **2**/**7** and 4-alkoxy derivative **4**/**9** showed the lowest lipophilicity. Due to the facts discussed above, it can be assumed that lipophilicity of individual compounds within both series is strongly influenced by intramolecular interactions.

It can be assumed, that the determined log *k* data specify lipophilicity within the individual series of compounds (2-$OCOCH_3$ (**12**) < 3,5-OCH_3 (**6**) < H (**1**) < 4-OCH_3 (**4**) < 2-OCH_3 (**2**) < 4-OC_2H_5 (**9**) < 2-OC_2H_5 (**7**) < 3-OCH_3 (**3**) < 4-OC_3H_7 (**10**) < 3-OC_2H_5 (**8**) < 3-CH_3 (**11**) < 2,4-OCH_3 (**5**)).

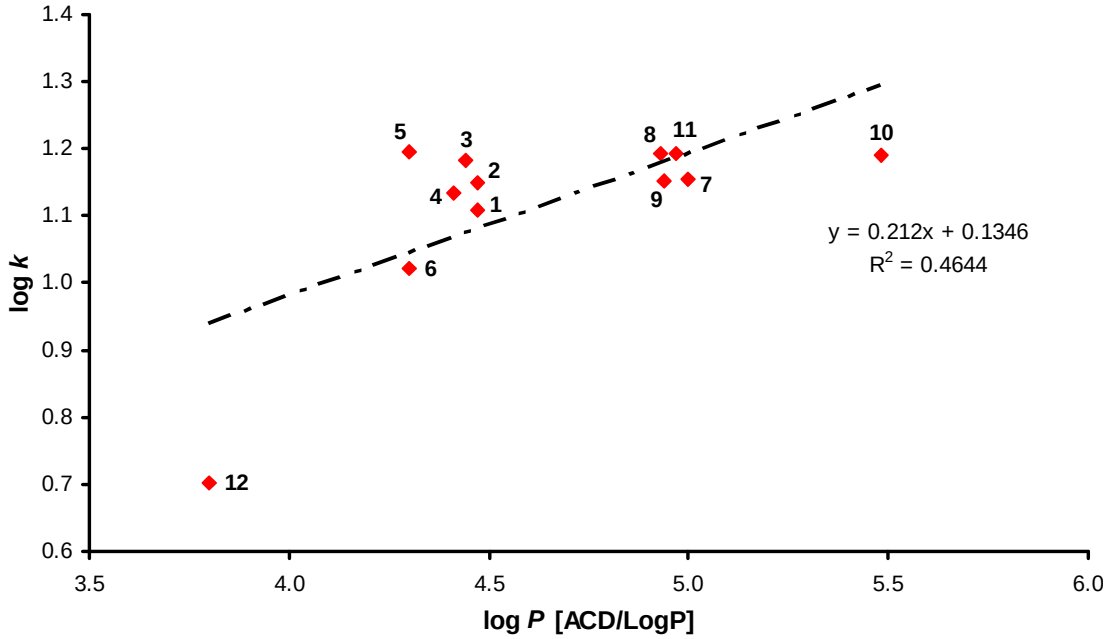
Table 1. Comparison of the experimentally determined log *k* values of compounds **1-12** with the calculated lipophilicities (log *P*/Clog *P*), electronic Hammett's σ parameters, and IC_{50} [μmol/L] values related to PET inhibition in spinach chloroplasts in comparison with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) standard.



Comp.	R	log *k*	log *P*/Clog *P* ChemOffice	log *P* ACD/LogP	σ [30]	PET inhibition IC_{50} [μmol/L]
1	H	1.1088	5.50/4.51522	4.47±0.56	0.0	285 [7]
2	2-OCH_3	1.1497	5.38/4.43422	4.47±0.57	-0.39 [31]	[a] [7]
3	3-OCH_3	1.1827	5.38/4.43422	4.44±0.57	0.12	303 [7]
4	4-OCH_3	1.1337	5.38/4.43422	4.41±0.57	-0.27	390 [7]
5	2,4-OCH_3	1.1953	5.25/4.52322	4.30±0.57	-0.66	508 [7]
6	3,5-OCH_3	1.0228	5.25/4.52322	4.30±0.57	0.24	862
7	2-OC_2H_5	1.1554	5.71/4.96322	5.00±0.57	0.02 [31]	287
8	3-OC_2H_5	1.1926	5.71/4.96322	4.97±0.57	0.10	218
9	4-OC_2H_5	1.1531	5.71/4.96322	4.94±0.57	-0.24	207
10	4-OC_3H_7	1.1911	6.20/5.49222	5.48±0.57	-0.25	208
11	3-CH_3	1.1939	5.99/5.01422	4.93±0.56	-0.07	115
12	2-$OCOCH_3$	0.7016	5.09/3.86422	3.80±0.56	–	224
DCMU	–	–	–	–	–	1.9

[a] precipitation during the experiment.

Figure 1. Relationship between calculated log *P* data (ACD/LogP) and experimentally found log *k* values of compounds **1**-**12**.



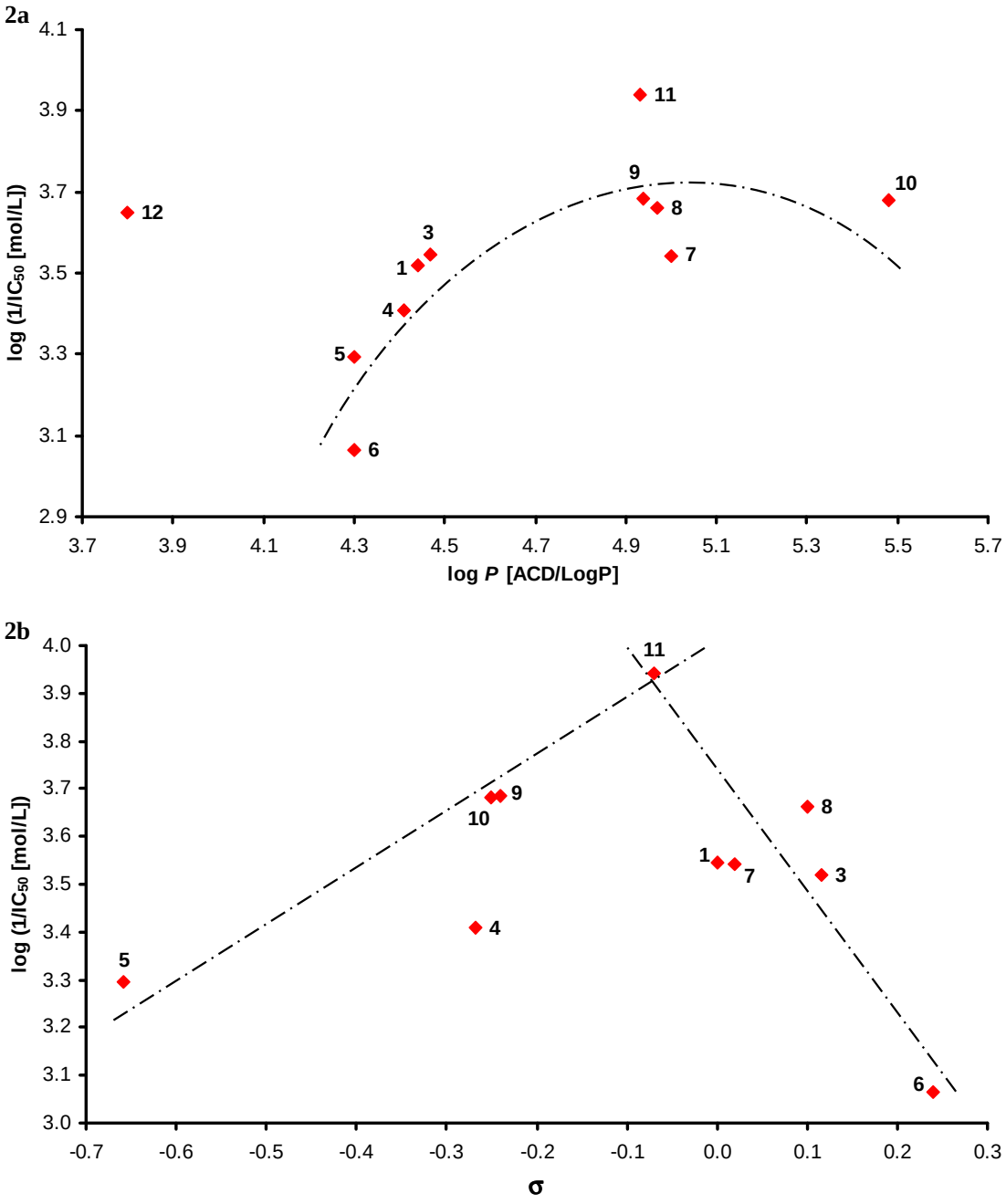
The activity of the evaluated quinazoline derivatives related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts was moderate or low relative to the standard, see Table 1. The PET-inhibiting activity was expressed by negative logarithm of IC_{50} value (compound concentration in mol/L causing 50% inhibition of PET). Compound **11** expressed the highest (IC_{50} = 115 µmol/L) and compound **6** the lowest PET-inhibiting activity (IC_{50} = 862 µmol/L).

Despite the relatively low inhibitory activity of the studied compounds as well as the relative scarcity of compounds for which PET-inhibiting activity could be determined, correlations between log ($1/IC_{50}$) and lipophilicity (expressed as log *P*) or electronic properties (expressed as Hammett's σ parameters [30,31]) of the benzylidene R substituent for compounds **1**-**12** were performed, see Fig 2A and Fig. 2B. It is not possible to perform clear conclusions from the dependence of log ($1/IC_{50}$) on log *k*, due to large variation of biological activity for compounds within narrow range of lipophilicity expressed by log *k*, therefore neither dependence nor any Figure can be presented.

According to Fig. 2A it can be stated that the dependence of PET-inhibiting activity on the lipophilicity expressed as log *P* (ACD/LogP) shows quasi-parabolic relation except compound **12**, which benzylidene substituent contains by one oxygen atom more than the other studied compounds and except compound **11** (R = CH_3), where benzylidene substituent does not contain any oxygen atom. On the other hand, the biological activity was expressively affected by electronic σ properties of these benzylidene substituents, see Fig. 2B. The dependence of log ($1/IC_{50}$) on σ was bilinear, for compounds with σ in the range of -0.66 (compound **5**) to -0.07 (compound **11**) the activity linearly raised with increasing value of σ, however further increase of σ led to sharp activity decrease. The most active compound from the series was **11** (R = 3-CH_3). The results indicate that PET inhibition depends not only on the lipophilicity but also on the σ values of electronic properties of individual benzylidene substituents whereby the effect of electronic properties of benzylidene R substituent is more important. The relatively high PET-inhibiting activity of compound **12** (R = 2-$OCOCH_3$) despite of low lipophilicity of this compound (log *k* = 0.7016, log *P* = 3.8) can be associated with additional interaction of the second oxygen atom in R substituent with photosynthetic proteins.

Within a series of alkoxy derivatives it can be concluded that introduction of methoxy group to benzylidene decreased activity compared with unsubstituted compound **1** analogous to 2-ethoxy moiety introduction. Contrary, substitution by longer chain (ethoxy or propoxy moeity) especially to the position 4 of the benzylidene ring (compounds **9** and **10**) caused significant PET inhibition increase.

Figure 2. The relationships between the PET-inhibiting activity log ($1/IC_{50}$) [mol/L] in spinach chloroplasts and lipophilicity (log *P*), see Fig. 2A or the electronic Hammett's σ parameters of benzylidene R substituents, see Fig. 2B, of the studied compounds **1-12**.



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 F_{254} plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and evaluated in iodine vapour. The melting points were determined on a Boetius PHMK 05 instrument (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Infrared spectra were recorded using KBr pellets on the FT-IR spectrometer Nicolet 6700 (Nicolet - Thermo Scientific, USA). All ^{1}H NMR spectra were recorded on a Bruker AM-500 (499.95 MHz for ^{1}H), Bruker BioSpin Corp., Germany. Chemical shifts are reported in ppm (δ) against the internal standard, $Si(CH_3)_4$. Easily exchangeable signals were omitted when diffuse. Syntheses were performed on Plazmatronika RM-800PC microwave reactor with monomode cavity, magnetic stirrer and external IR temperature measurements. Microwave power was automatically adjusted to achieve the desired temperature unless specified otherwise.

Synthesis

Synthesis of 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one, 2-methylquinazolin-4(3*H*)-one and ring-substituted 2-styrylquinazolin-4(3*H*)-ones was described in detail in ref. [7,22,29].

General method for synthesis of 4-chloro-2-styrylquinazoline derivatives (**1**-**12**): A mixture of ring-substituted 2-styrylquinazolin-4(3*H*)-ones (0.01 mol), *N*,*N*-dimethylaniline (0.02 mol) and phosphorus oxychloride (0.015 mol) in dry benzene (50 mL) was stirred and heated under reflux for 3 h. The reaction mixture was then cooled and filtered. The filtrate was diluted with benzene (30 mL) and the solution washed with water (50 mL), twice with 20% aqueous NaOH (50 mL) and finally twice with water. After drying with $MgSO_4$, the organic solvent was evaporated and the product obtained was crystallized from heptane [7,22,29].

Compounds **1-5** was described in detail in ref. [7,22,29].

4-Chloro-2-[(E)-2-(3,5-dimethoxyphenyl)vinyl]quinazoline (**6**). Yield 55 % of bright-pink ccrystals; MP 158 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 3.86 (s, 6H, 2·OCH_3); 6.54 (s, 1H, Ar-H); 6.81 (s, 1H, Ar-H); 6.84 (s, 1H, Ar-H); 7.01 (d, 1H, C=C-H); 7.48 (t, 1H, Ar-H); 7.65 (d, 1H, Ar-H); 7.78 (t, 1H, Ar-H); 7.89 (d, 1H, C=C-H); 8.13 (d, 1H, Ar-H).

4-Chloro-2-[(E)-2-(2-ethoxyphenyl)vinyl]quinazoline (**7**). Yield 64 % of orange crystalline compound; Mp 153 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 1.06 (t, 3H, CH_3); 3.78 (q, 2H, CH_2); 7.04 (t, 1H, Ar-H); 7.12 (d, 1H, Ar-H); 7.37 (d, 1H, C=C-H); 7.40 (t, 1H, Ar-H); 7.78 (t, 1H, Ar-H); 7.82 (d, 1H, Ar-H); 8.01 (d, 1H, Ar-H); 8.06 (t, 1H, Ar-H); 8.27 (d, 1H, Ar-H); 8.47 (d, 1H, C=C-H).

4-Chloro-2-[(E)-2-(3-ethoxyphenyl)vinyl]quinazoline (**8**). Yield 41 % orange crystalline bompound; Mp 93 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 1.05 (t, 3H, CH_3); 3.77 (q, 2H, CH_2); 6.98 (d, 1H, Ar-H); 7.32 (d, 1H, C=C-H); 7.35-7.39 (m, 2H, Ar-H); 7.37 (s, 1H, Ar-H); 7.81 (t, 1H, Ar-H); 8.03 (d, 1H, Ar-H); 8.07 (d, 1H, Ar-H); 8.11 (d, 1H, C=C-H); 8.26 (d, 1H, Ar-H).

4-Chloro-2-[(E)-2-(4-ethoxyphenyl)vinyl]quinazoline (**9**). Yield 66 % of yellow crystalline compoud; Mp 158 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 1.06 (t, 3H, CH_3); 3.78 (q, 2H, CH_2); 6.82 (d, 1H, C=C-H); 6.99 (d, 1H, Ar-H); 7.43 – 7.79 (m, 6H, Ar-H); 7.87 (d, 1H, C=C-H); 8.31 (d, 1H, Ar-H).

4-Chloro-2-[(E)-2-(4-propoxyphenyl)vinyl]quinazoline (**10**). Yield 49 % of yellow crystals; Mp 96 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 0.98 (t, 3H, CH_3); 1.76 (dd, 2H, CH_2);

3.98 (t, 2H, CH_2); 7.03 (d, 2H, Ar-H); 7.20 (d, 1H, C=C-H); 7.75 (d, 2H, Ar-H); 7.76 (t, 1H, Ar-H); 7.99 (d, 1H, Ar-H); 8.04 (t, 1H, Ar-H); 8.08 (d, 1H, C=C-H); 8.25 (d, 1H, Ar-H).

2-[(E)-2-(4-Chloroquinazolin-2-yl)vinyl]phenyl acetate (**12**). Yield 54 %; of a bright yellow crystalline compound; Mp 155 °C; ^{1}H NMR (400 MHz, DMSO-d_6), δ[ppm]: 2.15 (s, 3H, CH_3); 7.03 (t, 1H, Ar-H); 7.07 (d, 1H, C=C-H); 7.11 (d, 1H, Ar-H); 7.40 (t, 1H, Ar-H); 7.46 (t, 1H, Ar-H); 7.49 (t, 1H, Ar-H); 7.60 (d, 1H, Ar-H); 7.68 (d, 1H, Ar-H); 8.09 (d, 1H, Ar-H); 8.15 (d, 1H, C=C-H).

Lipophilicity HPLC determination (capacity factor k / calculated log k)

A Waters Alliance 2695 XE HPLC separation module and a Waters Photodiode Array Detector 2996 (Waters Corp., Milford, MA, USA) were used. A Symmetry® C_{18} 5 μm, 4.6 × 250 mm, Part No. WAT054275 (Waters Corp., Milford, MA, USA) chromatographic column was used. The HPLC separation process was monitored by Empower™ 2 Chromatography Data Software, Waters 2009 (Waters Corp., Milford, MA, USA). A mixture of MeOH p.a. (55%) and H_2O-HPLC – Mili-Q Grade (45%) was used as a mobile phase. The total flow of the column was 0.9 mL/min, injection volume, 30 μL, column temperature, 30 °C and sample temperature, 10 °C. The detection wavelength of 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 Empower™ 2 Chromatography Data 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 using 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. 10.0 (CambridgeSoft, Cambridge, MA, USA) 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. 10.0 (CambridgeSoft, Cambridge, MA, USA) software. The results are shown in Table 1.

Study of inhibition photosynthetic electron transport (PET) 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, USA), 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) from 10 cm distance with a halogen lamp (250 W) using a 4 cm water filter to prevent warming of the samples. 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 [34]. The results are summarized in Table 1.

ACKNOWLEDGEMENTS

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REFERENCES

1. Roth, H.J.; Fenner, H. *Arzneistoffe* 3rd Ed.; Deutscher Apotheker Verlag: Stuttgart, Germany, 2000; pp. 51–114.
2. Harris, C.R.; Thorarensen, A. *Curr. Med. Chem.* **2004**, *11*, 2213.
3. Andries, K.; Verhasselt, P.; Guillemont, J.; Gohlmann, H.W.; Neefs, J.M.; Winkler, H.; Van Gestel, J.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V. *Science* **2005**, *307*, 223.
4. Vangapandu, S.; Jain, M.; Jain, R.; Kaur, S.; Singh, P.P. *Bioorg. Med. Chem.* **2004**, *12*, 2501.
5. Carta, A.; Piras, S.; Palomba, M.; Jabes, D.; Molicotti, P.; Zanetti, S. *Anti-Infective Agents Med. Chem.* **2008**, *7*, 134.
6. Jampilek, J.; Musiol, R.; Pesko, M.; Kralova, K.; Vejsova, M.; Carroll, J.; Coffey, A.; Finster, J.; Tabak, D.; Niedbala, H.; Kozik, V.; Polanski, J.; Csollei, J.; Dohnal, J. *Molecules* **2009**, *14*, 1145.
7. Jampilek, J.; Musiol, R.; Finster, J.; Pesko, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O'Mahony, J.; Coffey, A.; Dohnal, J.; Polanski, J. *Molecules* **2009**, *14*, 4246.
8. Musiol, R.; Jampilek, J.; Nycz, J.E.; Pesko, M.; Carroll, J.; Kralova, K.; Vejsova, M.; O'Mahony, J.; Coffey, A.; Mrozek, A.; Polanski, J. *Molecules* **2010**, *15*, 288.
9. Jampilek, J.; Dolezal, M.; Kunes, J.; Vichova, P.; Jun, D.; Raich, I.; O´Connor, R.; Clynes, M. *J. Pharm. Pharmacol.* **2004**, *56*, 783.
10. Jampilek, J.; Dolezal, M.; Kunes, J.; Vichova, P.; Jun, D.; Raich, I.; O´Connor, R.; Clynes, M. *Curr. Org. Chem.* **2004**, *8*, 1235.
11. Jampilek, J.; Dolezal, M.; Opletalova, V.; Hartl. J. *Curr. Med. Chem.* **2006**, *13*, 117.
12. Polanski, J.; Zouhiri, F.; Jeanson, L.; Desmaele, D.; d'Angelo, J.; Mouscadet, J.-F.; Gieleciak, R.; Gasteiger, J.; Le Bret. M. *J. Med. Chem.* **2002**, *45*, 4647.
13. 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.
14. Polanski, J.; Niedbala, H.; Musiol, R.; Podeszwa, B.; Tabak, D.; Palka, A.; Mencel, A.; Finster, J.; Mouscadet, J.F.; Le Bret, M. *Lett. Drugs Des. Disc.* **2006**, *3*, 175.
15. 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.
16. Musiol, R.; Serda, M.; Hensel-Bielowka, S.; Polanski, J. *Curr. Med. Chem.* **2010**, *17*, 1960.
17. Jampilek, J.; Dolezal, M.; Kunes, J.; Buchta, V.; Kralova, K. *Med. Chem.* **2005**, *1*, 591.
18. Musiol, R.; Jampilek, J.; Buchta, V.; Niedbala, H.; Podeszwa, B.; Palka, A.; Majerz-Maniecka, K.; Oleksyn, B.; Polanski, J. *Bioorg. Med. Chem.* **2006**, *14*, 3592.
19. 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.
20. Musiol, R.; Tabak, D.; Niedbala, H.; Podeszwa, B.; Jampilek, J.; Kralova, K.; Dohnal, J.; Finster, J.; Mencel, A.; Polanski, J. *Bioorg. Med. Chem.* **2008**, *16*, 4490.

21. Podeszwa, B.; Niedbala, H.; Polanski, J.; Musiol, R.; Tabak, D.; Finster, J.; Serafin, K.; Wietrzyk, J.; Boryczka, S.; Mol, W.; Jampilek, J.; Dohnal, J.; Kalinowski, D.; Richardson, D.R. *Bioorg. Med. Chem. Lett.* **2007**, 17, 6138.
22. Mrozek-Wilczkiewicz, A.; Kalinowski, D.; Musiol, R.; Finster, J.; Szurko, A.; Serafin, K.; Knas, M.; Kamalapuram, S.K.; Kovacevic, Z.; Jampilek, J.; Ratuszna, A.; Rzeszowska-Wolny, J.; Richardson, D.R.; Polanski, J. *Bioorg. Med. Chem.* **2010**, *18*, 2664.
23. Draber, W.; Tietjen, K.; Kluth, J.F.; Trebst, A. *Angewandte Chemie* **1991**, *3*, 1621.
24. Tischer, W.; Strotmann, H. *Biochim. Biophys. Acta* **1977**, *460*, 113.
25. Trebst, A.; Draber, W. *Structure activity correlations of recent herbicides in photosynthetic reactions*. In *Advances in Pesticide Science*; Greissbuehler H. Ed.; Pergamon Press: Oxford, 1979; pp. 223–234.
26. Bowyer, J.R.; Camilleri, P.; Vermaas, W.F.J. In *Herbicides, Topics in Photosynthesis*, vol. 10. Baker N.R., Percival M.P. Eds.; Elsevier: Amsterdam, The Netherlands, 1991; pp. 27–85.
27. Kralova, K.; Sersen, F.; Kubicova, L.; Waisser, K. *J. Trace Microprobe Techn.* **2000**, *18*, 251-256.
28. Dolezal, M.; Kralova, K. *Synthesis and evaluation of pyrazine derivatives with herbicidal activity*. In *Herbicides, Theory and Applications*; Soloneski S.; Larramendy, M.L. Eds.; InTech: Rijeka, Croatia, 2011; pp.581–610.
29. Musiol, R.; Podeszwa, B.; Finster, J.; Niedbala, H.; Polanski; J. *Monatsh. Chem.* **2006**, *137*, 1211.
30. Norrington, F.E.; Hyde, R.M.; Williams, S.G.; Wotton, R. *J. Med. Chem.* **1975**, *18*, 604.
31. Takahata, Y.; Chong, D.P. *Int. J. Quantum Chem.* **2005**, *103*, 509.
32. Masarovicova, E.; Kralova, K. *Approaches to measuring plant photosynthesis activity*. In *Handbook of Photosynthesis* 2nd Ed.; Pessarakli M. Eds.; Taylor & Francis Group: Boca Raton, London-New York-Singapore, USA, 2005; pp. 617–656.
33. Kralova, K.; Sersen, F.; Sidoova, E. *Chem. Pap.* **1992**, *46*, 348.
34. Fedke, C. *Biochemistry and Physiology of Herbicide Action*. Springer Verlag: Berlin-Heidelberg-New York, 1982.