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Inhibition of photosynthetic electron transport by 6-hydroxynaphthalene-2-carboxanilides

Matus Pesko[a], Jiri Kos[b], Katarina Kralova[c] & Josef Jampilek*[b]

[a]Department of Environmental Ecology, Faculty of Natural Sciences, Comenius University, Mlynska dolina Ch-2, 842 15 Bratislava, Slovakia

[b]Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackeho 1/3, 612 42 Brno, Czech Republic

[c]Institute of Chemistry, Faculty of Natural Sciences, Comenius University, Mlynska dolina Ch-2, 842 15 Bratislava, Slovakia
E-mail: josef.jampilek@gmail.com

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Inhibition of photosynthetic electron transport (PET) in spinach chloroplasts by 6-hydroxynaphthalene-2-carboxanilides has been investigated. The PET inhibiting activity of the studied compounds depends on compound lipophilicity, on the position of substituents on the anilide moiety as well as on electron-accepting and electron-donating properties of these substituents. The most active PET inhibitors are ***m***-substituted derivatives; the lowest activity is shown by the ***o***-substituted ones. The most potent PET inhibitor is 6-hydroxy-***N***-(3-trifluoromethylphenyl)naphthalene-2-carboxamide (IC_{50} = 10.8 μmol/L). Study of chlorophyll ***a*** fluorescence in the suspension of spinach chloroplasts in the presence of studied compounds confirms their site of action in PS II, and it can be assumed that the inhibitory site of action of the studied compounds is situated on the acceptor side of PS II at Q_B site.

Keywords: Chlorophyll ***a*** fluorescence, chloroplasts, hydroxynaphthalene carboxanilides, inhibition, photosynthetic electron transport, ***Spinacia oleracea*** L.

Herbicides are used routinely to control noxious plants. Urea- and triazine-based herbicides, with a common chemical structure of sp^2 hybrid bound to N, O, or =CH and attached to a lipophilic substituent, belong to the class of herbicides interacting with photosystem (PS) II. They have the same site of action but their activity is affected by the various side chains[1]. Shipman suggested that polar components of the herbicides bind ***via*** coulombic interactions at or near a highly polar protein site, probably a protein salt bridge or the terminus of an -helix on Q_B protein (denoted also as D_1 protein)[2]. Herbicides that target PS II compete with the native electron acceptor plastoquinone (PQ) for binding at the Q_B site in the D_1 subunit and thus block the electron transfer from Q_A to Q_B. Thus, the mechanism of action of these herbicides is displacement of Q_B from its binding site on Q_B protein, which is situated on the acceptor side of PS II. Binding sites of herbicides to Q_B protein were described[1,3]. On the other hand, some compounds could inhibit photosynthetic electron transport (PET) also on the donor side of PS II acting in $D^{\bullet}$ or $Z^{\bullet}/D^{\bullet}$ intermediates[4-6]. For several herbicides acting as PET inhibitors by reversible binding to PS II (a membrane-protein complex in the thylakoid membranes) that catalyses the oxidation of water and the reduction of PQ (Ref 7) and thereby inhibit photosynthesis[1,8,9], the presence of an amide-like moiety is characteristic[10-16]. The –NHCO– group is an important functional group that is able, due to its electronic properties, to interact and bind with a number of enzymes/receptors and affect the biological response by means of these target sites.

Recently it was found that ring-substituted 1-hydroxynaphthalene-2-carboxanilides[16], 2-hydroxynaphthalene-2-carboxanilides[17] and 3-hydroxynaphthalene -2-carboxanilides[18] showing antibacterial activity inhibited PET in PS II, and their PET-inhibiting activity depended on the position of the substituent on the anilide ring, its electronic parameters as well as on the compound lipophilicity. Structurally similar 6-hydroxynaphthalene-2-carboxanilides exhibited activity against ***Mycobacterium tuberculosis*** H37Ra, ***M. avium*** complex and ***M. avium*** subsp. ***paratuberculosis***, whereby compounds substituted in $C'_{(3)}$ and $C'_{(4)}$

preferentially inhibited growth of ***M. tuberculosis*** contrary to $C'_{(2)}$ and $C'_{(3)}$ substituted ones that showed potency against both nontuberculous mycobacteria. A significant decrease of mycobacterial cell metabolism (monitored as a viability of ***M. tuberculosis*** H37Ra) was also observed[19].

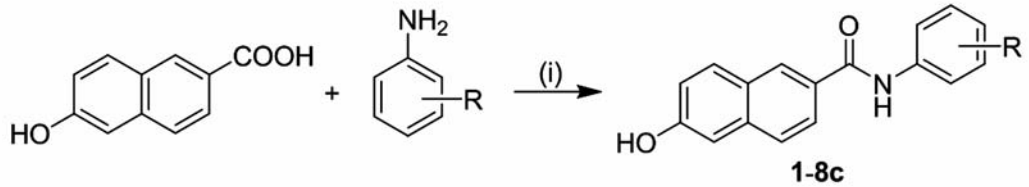
The goal of the present work is to investigate the inhibitory effect of twenty two 6-hydroxy-naphthalene-2-carboxanilides on the photosynthetic electron transport in spinach (***Spinacia oleracea*** L.) chloroplasts using the Hill reaction and fluorescence spectroscopy and to discuss the structure-activity relationships between the chemical structure, physical properties and PET-inhibiting activities of the tested compounds, the anilide moiety of which was modified by groups with electron-accepting and electron-donating properties. A good correlation between microbiological activity and herbicidal effect was described in previous studies[15-17,20-24]. This idea is based on the fact that both pharmaceuticals and pesticides are designed to target particular biological functions, and in some cases these functions overlap in their molecular target sites, or they target similar processes or molecules. Taking into the consideration that herbicides may also have molecular sites of action in mammals, until recently most pharmaceutical companies had pesticide divisions. All compounds generated by either division of the company were evaluated for both pesticide and pharmaceutical uses. In the past, some leading pesticides have become pharmaceuticals and ***vice versa***[25-28].

Results and Discussion

Ring-substituted 6-hydroxynaphthalene-2-carboxanilides **1**–**8c** were prepared by microwave-assisted synthesis in one step, see **Scheme I**. At first the carboxyl group was activated with phosphorus trichloride and the final amide was immediately formed by aminolysis of the acyl chloride with ring-substituted aniline in dry chlorobenzene[19].

Lipophilicity is a property that has a major effect on activity, because bioactive compounds mostly cross biological membranes through passive transport, which strongly depends on their lipophilicity. Lipophilicity has been studied and applied as an important drug property for decades. This parameter was measured by means of RP-HPLC and expressed as logarithm of capacity factor ***k*** (Ref 19). The experimentally estimated log ***k*** values of ring-substituted 6-hydroxynaphthalene-2-carboxanilides **1**–**8c** as well as log ***P*** values calculated using ACD/Percepta ver. 2012 (Advanced Chemistry Development, Inc., Toronto, ON, Canada, 2012) are listed in **Table I**.

The highest experimentally-determined lipophilicity was found for 6-hydroxy-***N***-(4-trifluoromethylphenyl)naphthalene-2-carboxamide (log ***k*** = 1.0133; **7c**), while 6-hydroxy-***N***-(4-methoxyphenyl)naphthalene-2-carboxamide (log ***k*** = 0.3313; **2c**) showed the lowest log ***k*** value. It could be noted that the experimentally-determined lipophilicity (log ***k***) of the discussed compounds poorly correlates with the calculated values of compounds **1**–**8c**, nevertheless these proven poor match between the experimentally-determined and calculated values of lipophilicity corresponds to observations described recently by Karabulut ***et al***.[29] Based on these facts it can be supposed that the differences between the predicted and the experimentally-determined lipophilicity values within the series of 6-hydroxynaphthalene-2-carboxanilides are caused by intermolecular interactions between phenolic and carbonyl moieties in individual molecules in a polar environment[29]. Strong intramolecular interactions of spatially close phenolic and carbonyl moieties were reported previously for structurally similar compounds[12,17]. It can be stated that the log ***k*** values better specify lipophilicity within the series of the studied compounds than the predicted log ***P*** values.



Scheme I

Table I — Calculated values of lipophilicity log ***P***, experimentally determined values of lipophilicity log ***k***, predicted values of electronic Hammett's σ parameters of R substituents and IC_{50} values related to PET inhibition in spinach chloroplasts in comparison with 3-(3,4-dichlorophenyl)-1, 1-dimethylurea (DCMU) standard

Compd	R	log ***P***[a]	log ***k***[19]	σ[a]	IC_{50} [μmol/L]
1	H	3.33	0.6612	0	108
2a	2-OCH_3	3.36	0.6039	–0.28	154
2b	3-OCH_3	3.37	0.4463	0.12	164
2c	4-OCH_3	3.29	0.3313	–0.27	ND
3a	2-CH_3	3.63	0.3690	–0.17	470
3b	3-CH_3	3.63	0.6086	–0.07	216
3c	4-CH_3	3.63	0.6227	–0.17	226
4a	2-F	3.36	0.4921	0.06	ND
4b	3-F	3.54	0.5766	0.34	25.7
4c	4-F	3.32	0.6726	0.06	234.5
5a	2-Cl	3.81	0.6777	0.22	184
5b	3-Cl	4.44	0.7684	0.37	37.6
5c	4-Cl	3.89	0.7947	0.23	62.3
6a	2-Br	4.10	0.7486	0.22	160
6b	3-Br	4.46	0.8767	0.39	21.0
6c	4-Br	4.22	0.8884	0.23	118
7a	2-CF_3	4.06	0.5623	0.51	353
7b	3-CF_3	4.17	0.9558	0.43	10.8
7c	4-CF_3	4.05	1.0133	0.51	55.0
8a	2-NO_2	3.44	0.8553	0.77	151
8b	3-NO_2	3.48	0.8533	0.71	41.2
8c	4-NO_2	3.34	0.5911	0.78	385
DCMU	–	–	–	–	1.9

[a]Calculated using ACD/Percepta ver. 2012; ND = not determined

Electronic parameters expressed as Hammett's σ parameters of substituents in the anilide part of compounds **1**–**8c** were predicted using ACD/Percepta ver. 2012, see **Table I**; they ranged from -0.28/-0.27 (compounds **2a**,**c** 2-OCH_3, 4-OCH_3) to 0.77/0.78 (compounds **8a**,**c** 2-NO_2, 4-NO_2).

Biological Evaluation (Inhibition of photosynthetic electron transport)

The PET inhibiting activity of the studied 6-hydroxynaphthalene-2-carboxanilides was evaluated and has been expressed by IC_{50} values, ***i.e.***, molar concentration of the compounds causing 50% inhibition relative to the untreated control. Due to low activity IC_{50} values could not be determined for compounds **2c** (R = 4-OCH_3) and **4a** (R = 2-F). The IC_{50} values of the rest of the tested compounds varied in wide concentration range, from 10.8 μmol/L (**7b**, R = 3-CF_3) to 470 μmol/L (**3a**, R = 2-CH_3), see **Table I**. The solubility of studied compounds in testing medium was satisfactory and the activity strongly depended on the position of the substituent on the phenyl ring. The most active compounds were ***m***-substituted; the less active were ***o***-substituted. The reduced activity of ***o***-substituted derivatives could be connected with intramolecular interactions of the substituent in position 2 with the amide group, which could adversely affect its possible interaction with constituents of the photosynthetic apparatus.

The dependence of the PET-inhibiting activity expressed as log(1/IC_{50}) on the lipophilicity of the compounds expressed as log ***P*** is illustrated in **Figure 1a**. The PET-inhibiting activity of ***o***-substituted derivatives was characterized by great variance, and no correlation between corresponding IC_{50} values and log ***P*** was observed. On the other hand, the IC_{50} values of ***m***- and ***p***-substituted derivatives were significantly affected by compound lipophilicity and the dependences of log(1/IC_{50}) on log ***P*** were bilinear (**Figure 1a**). The optimal lipophilicity for ***p***-substituted derivatives was found to be log ***P*** approx. 4.0 and for ***m***-substituted approx. 3.8. Further lipophilicity increase was reflected in declined PET inhibiting activity (**Figure 1a**). However, it could be noted that the PET-inhibiting activity of **3b** (R = 3-CH_3) was lower than expected. On the other hand, the PET inhibition linearly increases with increasing log ***k*** not only for ***o***- and ***p***-substituted compounds (r = 0.8571, n = 6 and r = 0.8769, n = 6), but also for more active ***m***-substituted ones (r = 0.7603, n = 7), see **Figure 1b**. The discrepancies between the presented dependences of log(1/IC_{50}) on log ***P*** and log(1/IC_{50}) on log ***k*** are likely due to intermolecular interactions of the studied compounds, which could modify the resulting compound lipophilicity and which are reflected only in experimentally-determined log ***k*** values. Such interactions were reported previously for structurally similar compounds[12,17].

The dependence of PET-inhibiting activity on the values of R substituent was found to be bilinear for the ***m***-substituted (r = 0.9447, n = 6) and the ***p***-substituted (r = 0.7967, n = 5) compounds (similarly as the above-discussed dependence of log(1/IC_{50}) on log ***P***), while no correlation between the corresponding IC_{50} values and was observed for

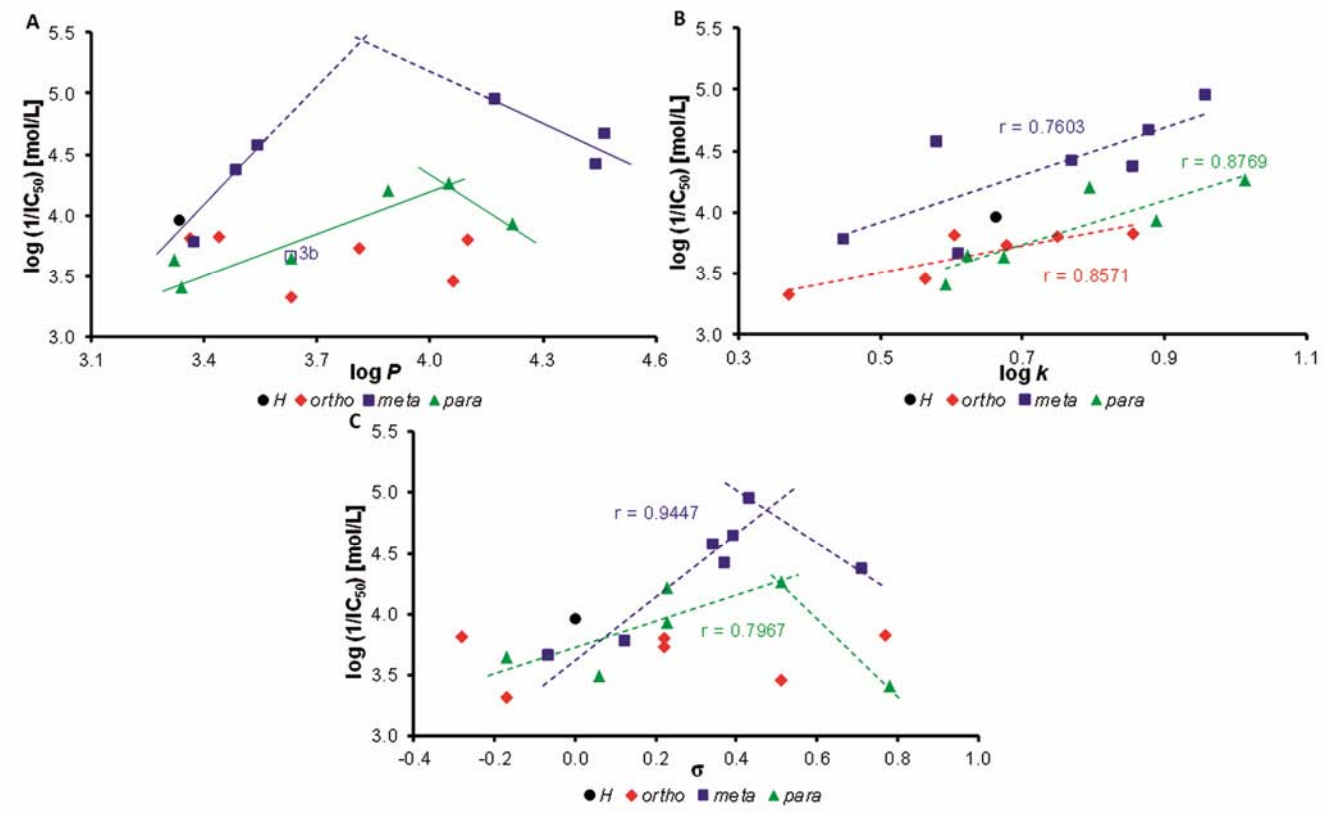


Figure 1 — Dependence of PET inhibiting activity log(1/IC_{50}) [mol/L] of tested compounds on lipophilicity expressed as log ***P*** (**A**) or log ***k*** (**B**) and on Hammett's σ constants of R substituent (**C**); (Eliminated compound 3-CH_3 (**3b**) in **A** is marked by empty square)

the ***o***-substituted ones, see **Figure 1c**. The optimal value for ***m***- and ***p***-substituted derivatives was similar, approximately 0.5; the activity decreased with further increase in values.

In the studied 6-hydroxynaphthalene-2-carboxanilides, due to the proximity of the ***o***-substituent on the aniline ring to the carboxamide group, the twist of the aniline ring plane towards the carboxamide group, ***i.e***. towards the whole naphthalene core, occurs[30]. The described process results in the violation of the molecule planarity, implying subsequent conjugation of the π-bonds of the phenyl ring through the NH fragment to the carbonyl group[31]. Consequently, the different electronic density (charge) at the carbonyl moiety appears, which can influence the potential binding of the carboxamide group to possible binding sites in the photosynthetic apparatus. In the case of ***m***- and ***p***-substituted derivatives, the described secondary steric effect did not manifest. ***p***-Substituted derivatives should have practically a linear/planar structure as was, for example, described for a similar type of molecule, where the X-ray analysis displayed a planar structure[32,33]. The lower PET-inhibiting activity of ***o***-substituted derivatives as compared to ***m***- and ***p***-substituted ones was also observed for several esters of 2-, 3- and 4-substituted alkoxyphenyl-carbamic acids[20,34] as well as for previously studied 1-hydroxynaphthalene-2-carboxanilides[16], while for ring-substituted 2-hydroxynaphthalene-1-carboxanilides the PET-inhibiting activity was not affected by the position of the substituent on the phenyl ring[17]. On the other hand, the dependence of PET-inhibiting activity on σ was found to be bilinear with the optimum σ = 0.51 for ***o***-, ***m***- and ***p***-substituted 2-hydroxynaphthalene-1-carboxanilides[17], σ = 0.43 for ***m***- and ***p***-substituted 1-hydroxynaphthalene-2-carboxanilides[16] and σ = 0.71 for ***o***-, ***m***- and ***p***-substituted 3-hydroxynaphthalene-2-carboxanilides[18].

By the addition of 1,5-diphenylcarbazide (DPC), an artificial electron donor acting in $Z^{\bullet}/D^{\bullet}$ intermediate on the donor side of PS II (Ref 35), to chloroplasts treated with the studied compounds, in which PET

was inhibited by about 90-93%, PET was practically completely restored, however only in the presence of very high DPC concentration, approximately 2 mmol/L. Based on the fact that DPC can alter the binding of compounds with herbicidal activity, ***e.g.***, atrazin or metribuzin, presumably because of overlapping of the binding domain in the Q_B pocket, but its effect on the Q_B site can affect PQ reduction only at relatively high concentrations (>2 mol/L)[36,37], it could be assumed that the inhibitory site of action of the studied compounds is situated on the acceptor side of PS II, in the section at Q_B site. However, for PS II herbicides such are DCMU or atrazin also a second binding site situated on the donor side of PS II near $Z^{\bullet}/D^{\bullet}$ intermediates and the high-affinity Mn-binding sites was reported[38-40]. Similarly, using EPR spectroscopy it was found that the site of action of 5-bromo- and 3,5-dibromo-2-hydroxy-***N***-phenylbenzamides[6], phenylcarbamates and phenylthiocarbamates[41] and ***N***-phenylpyrazine-2-carboxamides[5] in the photosynthetic apparatus is also situated on the donor side of PS 2, in $D^{\bullet}$ or in the $Z^{\bullet}/D^{\bullet}$ intermediates. Therefore the second site of action of the studied 6-hydroxynaphthalene-2-carboxanilides situated on the donor side of PS II could not be excluded.

The studied compounds affected chlorophyll ***a*** (Chl***a***) fluorescence in spinach chloroplasts indicating their interactions with constituents of the photosynthetic apparatus. The fluorescence emission spectra of Chl***a*** in spinach chloroplasts treated with compound **7b** are shown in **Figure 2a**. The decreased intensity of the emission band at 686 nm belonging to the Chl***a***–protein complexes occurring mainly in photosystem II (Ref 42) suggested PS II as the site of action of the studied inhibitors. The extent of perturbation of Chl***a***–protein complexes in the thylakoid membrane is reflected in the sharpness of the decreased fluorescence of the pigment (see **Figure 2b**). As shown in **Figure 2b**, the rate of the decline of Chl***a*** fluorescence with increasing concentration of the compound correlated with its PET inhibiting activity expressed by IC_{50} value. Perturbation of Chl***a***–protein complexes increased in the following order: **3b** (IC_{50} = 289 mol/L) < **5a** (IC_{50} = 80.4 mol/L) < **7b** (IC_{50} = 10.8 mol/L). A similar decrease of Chl***a*** fluorescence in plant chloroplasts was also observed previously after treatment with ring-substituted 1-hydroxynaphthalene-2-carboxanilides[16] and 2-hydroxynaphthalene-1-carboxanilides[17], 5-bromo- and 3,5-dibromo-2-hydroxy-***N***-phenylbenzamides[6] or ring-substituted 4-arylamino-7-chloroquinolinium chlorides[43]. Hsu and Lee who examined the effect of DCMU on the fluorescence of PS II preparations reported that the lowering of the fluorescence yield was not due to an inhibition on the donor side of PS II but to a non-photochemical quenching by oxidized PQ (Ref 44). The ability of the PQ pool in the oxidized form to quench the fluorescence of isolated thylakoids was described by Vernotte ***et al***.[45] and Thielen and van Gorkom[46]; however PQ acts more effectively as a deexcitation trap only for certain chlorophyll species responsible for fluorescence emission, such as those emitting at 687, 665 and 650 nm[44].

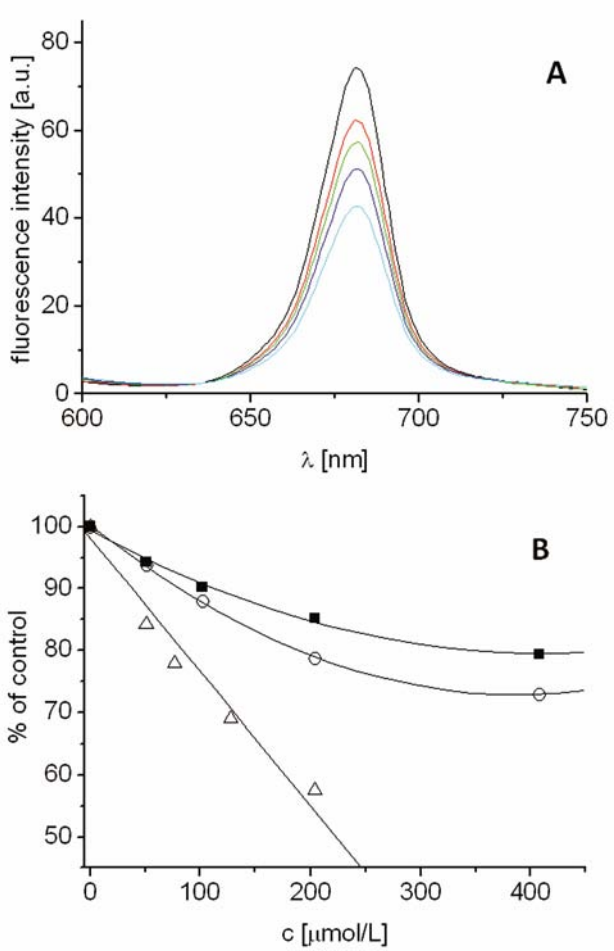


Figure 2 — Fluorescence emission spectra of chlorophyll ***a*** in untreated spinach chloroplasts in presence of compound **7b**: 0 μmol/L (black line), 51 μmol/L (red line), 76.5 μmol/L (green line), 127.5 μmol/L (blue line) and 204 μmol/L (cyan line) (ex = 436 nm) (**A**) and dependence of fluorescence intensity of chlorophyll ***a*** expressed as % of control on concentration of compounds **3b** (squares), **5a** (circles) and **7b** (triangles) (**B**)

The above presented results indicate a significant effect of lipophilicity and the electron properties of the R substituent on the biological activity of the tested compounds. It is important to note that a correlation between the antitubercular (***M. tuberculosis*** H37Ra ATCC 25177)[19] and the PET-inhibiting activity (expressed by MIC and IC_{50} [μmol/L], respectively) of compounds substituted in ***m***-position of aniline ring, ***i.e.*** compounds showing the highest activity in both tests, was found, for example: **7b** (R = 3-CF_3, MIC = 24 mol/L, IC_{50} = 10.8 mol/L), **6b** (R = 3-Br, MIC = 23 mol/L, IC_{50} = 21.0 mol/L) and **4b** (R = 3-F, MIC = 28 mol/L, IC_{50} = 25.7 mol/L). This fact supports the hypothesis that for high activity of the discussed compounds transport through the mycobacterial or thylakoid membrane and suitable distribution of electron charge in the molecule, ***i.e.*** rather an electron-deficiency system, are preferable.

Experimental Section

Chemistry

The detailed synthetic pathway and complete characterization of compounds **1**–**8c** as well as lipophilicity determination using HPLC (capacity factor ***k*** /calculated log ***k***) are provided in Kos ***et al***.[19] All the studied compounds are presented in **Table I**.

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

Chloroplasts were prepared from spinach (***Spinacia oleracea*** L.) according to Masarovicova and Kralova[47]. 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***.[48], 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, ***p***H 7.2) containing sucrose (0.4 mol/L), $MgCl_2$ (0.005 mol/L) and NaCl (0.015 mol/L). The chlorophyll content was 30 mg/L in these experiments and the samples were irradiated (~100 W/m^2 with 10 cm distance) with a halogen lamp (250 W) using a 4 cm water filter to prevent warming of the samples (suspension temperature 22°C). The studied compounds were dissolved in DMSO due to their limited aqueous 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% inhibition relative to the untreated control. The comparable IC_{50} value for a selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diuron®) was about 1.9 μmol/L. The results are summarized in **Table I**.

The emission fluorescence spectra were recorded on a fluorescence spectrophotometer F-2000 (Hitachi, Tokyo, Japan) at RT (24°C). The samples of chloroplast suspension (10 mg chlorophyll/L) with and without the studied inhibitor were excited at 436 nm using a slit width of 10 nm and were kept in the dark for 2 min prior to the measurement. Due to low aqueous solubility the compounds were added to a chloroplast suspension in DMSO solution. The DMSO concentration in all samples was the same as in the control (10%).

Conclusion

Twenty-two new antimycobacterially effective ring-substituted 6-hydroxynaphthalene-2-carboxanilides were investigated for their ability to inhibit photosynthetic electron transport (PET) in spinach (***Spinacia oleracea*** L.) chloroplasts. The most active PET inhibitors were ***m***-substituted derivatives, the lowest activity was shown by the ***o***-substituted ones. The most potent PET inhibitor was 6-hydroxy-***N***-(3-trifluoromethylphenyl)naphthalene-2-carboxamide (**7b**, IC_{50} = 10.8 μmol/L). The PET inhibiting activity of the studied compounds depended on the position of substituents on the anilide moiety, on compound lipophilicity (linear increase with increasing lipophilicity expressed as log ***k***), as well as on electron-accepting and electron-donating properties of these substituents (bilinear for ***m***- and ***p***-substituted compounds with optimum approx. ≈ 0.5). The study of chlorophyll ***a*** fluorescence in the suspension of spinach chloroplasts in the presence of the studied compounds confirmed their site of action in PS II, and it could be assumed that the inhibitory site of action of the studied compounds is situated on the acceptor side of PS II at Q_B site.

Acknowledgments

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