Photosynthesis-Inhibiting Activity of 1-[(2-Chlorophenyl)carbamoyl]- and 1-[(2-Nitrophenyl)carbamoyl]naphthalen-2-yl Alkylcarbamates †

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† Preliminary results were presented at The 19th Electronic Conference on Synthetic Organic Chemistry (ECSOC-19, http://sciforum.net/conference/80/paper/3079), 1–30 November 2015 (paper b006) and The 20th Electronic Conference on Synthetic Organic Chemistry (ECSOC-20, http://sciforum.net/conference/94/paper/3535), 1–30 November 2016 (paper b004).

Received: 16 June 2017; Accepted: 14 July 2017; Published: 17 July 2017

Abstract: Eight 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates and eight 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates were tested for their activity related to the inhibition of photosynthetic electron transport (PET) in spinach (Spinacia oleracea L.) chloroplasts. The PET-inhibiting activity of the compounds was relatively low; the corresponding IC_{50} values ranged from 0.05 to 0.664 mmol/L; and the highest activity within the series of compounds was observed for 1-[(2-chlorophenyl)-carbamoyl]naphthalen-2-yl propylcarbamate. It has been proven that the compounds are PET-inhibitors in photosystem II. Despite rather low PET-inhibiting activities, primary structure-activity trends can be discussed.

Keywords: alkylcarbamates; hydroxynaphthalene-carboxamides; PET inhibition; spinach chloroplasts; structure-activity relationships

1. Introduction

Although naphthalene can be considered as the simplest compound from the group of arenes, it is one of the most interesting arenes. Naphthalene-based drugs include not only clinically used anti-infective chemotherapeutics—e.g., naftifine, terbinafine, tlnaftate, nafcillin—but also other compounds with significant antimicrobial effects, e.g., dye naftol [1–3]. The naphthalene scaffold can be found in many other bioactive compounds [1,3–8]; therefore, this scaffold can be considered a privileged structure [9–12].

Our research group prepared and tested naphthalencarboxamides and various positional isomers of hydroxynaphthalencarboxamides as potential antimicrobial and antiprotozoal compounds [13–22]. The presence of an amide (–CONH–) and/or a carbamate (–OCONH–) group(s) in the structure of
compounds enables interactions with various enzymes or enzymatic systems ([23–26] and references therein). In addition, these moieties can be found in many herbicides acting as photosynthesis inhibitors, e.g., [27–35]. Though currently about 20 mechanisms of action of herbicides are known [36], over 50% of marketed herbicides act by reversible binding to photosystem II (PS II) [37], resulting in interruption of the photosynthetic electron transport (PET) [38–40]. Various types of substituents modify properties of amide and carbamate moieties [41,42].

In the middle of the 1970s, it was found that salicylanilides belong to effective uncoupling agents of oxidative phosphorylation [43–45], and acceleration of the deactivation reactions of water splitting enzyme system Y by 3-tert-butyl-5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxybenzamide was observed [44]. Substituted salicylanilides or their bioisosteres inhibited PET in spinach chloroplasts [13–18,31–35] and reduced chlorophyll content in green alga, Chlorella vulgaris [31,35,46,47]. It is important to note that in addition to the above-mentioned herbicidal activity, the wide spectrum of biological effects of salicylanilides includes, for example, antibacterial, antimycobacterial, antifungal, and anthelmintic activity; however, their mechanism of action is still under investigation ([25,26] and references therein).

In the context of the above-mentioned facts, 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates and 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates were prepared [22] and tested for their photosynthesis-inhibiting activity—the PET inhibition in spinach chloroplasts (Spinacia oleracea L.). The structure–activity relationships are discussed.

2. Results and Discussion

2.1. Chemistry

A microwave-assisted synthesis [15] gave N-(2-chlorophenyl)-2-hydroxynaphthalene-1-carboxamide (1) and N-(2-nitrophenyl)-2-hydroxynaphthalene-1-carboxamide (2). Then these pattern compounds 1 and 2 with triethylamine and appropriate alkyl isocyanates yielded a series of eight 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl carbamates 1a–1h and eight 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl carbamates 2a–2h, see Scheme 1 [22].

![Scheme 1](image)

Scheme 1. Synthesis of 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl carbamates 1a–1h and 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl carbamates 2a–2h [22]. Reagents and conditions: (a) PCl₃, chlorobenzene, MW; (b) TEA, acetonitrile, room temperature.

2.2. Inhibition of Photosynthetic Electron Transport (PET) in Spinach Chloroplasts

The PET-inhibiting activity was expressed by IC₅₀ value (compound concentration in mol/L causing 50% inhibition of PET), see Table 1. Both pattern anilides 1 and 2 showed higher PET-inhibiting activity than their carbamate counterparts. The highest activity within the series of the chlorinated carbamates 1a–1h (series I) was observed for 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl propylcarbamate (1b, IC₅₀ = 0.08 mM), while the highest PET-inhibiting activity within the series of the nitrated carbamates 2a–2h (series II) was observed for 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl pentylicarbamate (2e, IC₅₀ = 0.233 mM), Table 1. Despite rather low PET-inhibiting activities, primary dependences between structure of the compounds and their PET inhibition can be discussed.
Table 1. Structures of the discussed anilides 1, 2 and carbamates 1a–1h, 2a–2h; predicted clogP values, molar volume MV [cm$^{-3}$], Taft polar constants $\sigma^*$ of R$^2$ substituents of compounds and IC$_{50}$ [mmol/L] values related to PET inhibition in spinach chloroplasts of tested compounds in comparison with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) standard. IC$_{50}$ values are expressed as mean ± SD (n = 3 experiments), the means followed by different letters (a−j) are significantly different at p ≤ 0.05.

| Comp. | R$^1$ | R$^2$ | clogP ‡ | MV R$^2$ ‡ [cm$^3$] | $\sigma^*$ R$^2$ ‡ | PET Inhibition IC$_{50}$ [mmol/L] |
|-------|-------|-------|---------|-----------------|-----------------|-----------------|
| 1     | Cl    | —     | 5.03    | —               | —               | 0.049 ± 0.002 a |
| 1a    | Cl    | −C$_2$H$_5$ | 3.94    | 47.29          | −0.11           | 0.659 ± 0.046 f |
| 1b    | Cl    | −C$_3$H$_7$ | 4.41    | 63.80          | −0.12           | 0.080 ± 0.002 a |
| 1c    | Cl    | −CH(CH$_3$)$_2$ | 4.20    | 64.18          | −0.19           | 0.271 ± 0.010 d |
| 1d    | Cl    | −C$_4$H$_9$ | 4.71    | 80.31          | −0.25           | 0.589 ± 0.031 i |
| 1e    | Cl    | −C$_5$H$_{11}$ | 5.47    | 96.81          | −0.23           | 0.396 ± 0.017 f |
| 1f    | Cl    | −C$_6$H$_{13}$ | 6.03    | 113.32         | −0.25           | 0.358 ± 0.013 e |
| 1g    | Cl    | −C$_7$H$_{15}$ | 6.67    | 129.83         | −0.23           | 0.263 ± 0.009 cd |
| 1h    | Cl    | −C$_8$H$_{17}$ | 7.19    | 146.33         | −0.23           | 0.290 ± 0.010 d |
| 2     | NO$_2$ | —     | 4.45    | —              | —              | 0.121 ± 0.004 b |
| 2a    | NO$_2$ | −C$_2$H$_5$ | 3.58    | 47.29          | −0.11           | 0.450 ± 0.022 b |
| 2b    | NO$_2$ | −C$_3$H$_7$ | 3.96    | 63.80          | −0.12           | 0.365 ± 0.017 ef |
| 2c    | NO$_2$ | −CH(CH$_3$)$_2$ | 3.80    | 64.18          | −0.19           | 0.664 ± 0.041 f |
| 2d    | NO$_2$ | −C$_4$H$_9$ | 4.32    | 80.31          | −0.25           | 0.274 ± 0.012 d |
| 2e    | NO$_2$ | −C$_5$H$_{11}$ | 5.15    | 96.81          | −0.23           | 0.233 ± 0.008 e |
| 2f    | NO$_2$ | −C$_6$H$_{13}$ | 5.71    | 113.32         | −0.25           | 0.283 ± 0.012 d |
| 2g    | NO$_2$ | −C$_7$H$_{15}$ | 6.81    | 129.83         | −0.23           | 0.352 ± 0.018 e |
| 2h    | NO$_2$ | −C$_8$H$_{17}$ | 7.22    | 146.33         | −0.23           | 0.487 ± 0.027 h |
| DCMU  | —     | —     | —       | —              | —              | 0.002           |

† calculated using ACD/Percepta ver. 2012 (Advanced Chemistry Development, Toronto, ON, Canada).

ACD/Percepta ver. 2012 was used for prediction of various physicochemical descriptors, from which only those that best characterize the influence of PET-inhibiting activity on compound structure are listed in Table 1. The lipophilicity of compounds 1a–1h, expressed as calculated log $P$ (clogP) values, ranged from 3.94 (compound 1a, R = C$_2$H$_5$) to 7.19 (compound 1h, R = C$_8$H$_{17}$), while the clogP values of compounds 2a–2h ranged from 3.58 (compound 2a, R = C$_2$H$_5$) to 7.22 (compound 2h, R = C$_8$H$_{17}$). Lipophilicity increases with the lengthening of the alkyl tail. Propyl showed a higher clogP value than isopropyl. In general, it can be stated that lipophilicity of these compounds is rather high. Recommended log $P$ value for drugs and agrochemicals is ≤ 5 [48]. The bulkiness of individual substituents R$^2$ expressed as molar volume MV [cm$^{-3}$] was calculated also for the hydrophobic N-alkyl tail; its values ranged from 47.29 to 146.33. This parameter represents the bulk of substituents (i.e., tail length/branching) of each compound relative to other members of the same series. Taft polar constants $\sigma^*$ representing electronic properties of individual alkyl substituents of the discussed compounds were also included in Table 1; they ranged from −0.25 to −0.11.

The dependence of the PET-inhibiting activity expressed as log(1/IC$_{50}$ [mol/L]) of compounds 1, 1a–1h and 2, 2a–2h in spinach chloroplasts on lipophilicity expressed as clogP is shown in Figure 1A,B, while Figure 1C illustrates this dependence for all investigated compounds 1–2h.
While ethyl derivative 2e was bilinear, pentyl derivative (Figure 1A). A slight increase of PET-inhibiting activity with further prolongation of the alkyl tail can be connected with the fact that a longer alkyl chain can be incorporated in the thylakoid membrane to a greater extent and subsequently cause membrane perturbation also at lower concentrations. The dependences of the PET-inhibiting activity log(1/IC\textsubscript{50} [mol/L]) of compounds 2a–2h on clogP was bilinear, pentyl derivative 2e being the most effective PET inhibitor (Figure 1B). The lower activity of isopropyl derivative 1c could be connected with its lower aqueous solubility. The dependence of log(1/IC\textsubscript{50} [mol/L]) on clogP for all the investigated compounds is illustrated in Figure 1C. It is evident that with the exception of compounds 1b and 1e of series I for compounds with clogP < 6.57 the activity of compounds of series II was slightly higher than that of compounds of series I with comparable lipophilicity. Lower PET-inhibiting activity of heptyl 2g and octyl 2h derivatives of series II compared to their analogues 1g, 1h of series I could be connected with their more significant solubility decrease with the elongation of the alkyl chain in the R\textsuperscript{2} substituent, resulting in precipitation from the solution during the experiment.

After exclusion of compounds 1a, 1b, and 1c, a bilinear course was found also for the dependences of the PET-inhibiting activity on log(1/IC\textsubscript{50} [mol/L]) of cabamate series I and II in spinach chloroplasts on bulkiness expressed as molar volume MV of the alkyl tails R\textsuperscript{2}, see Figure 2. The PET-inhibiting activity within the nitratated series II linearly increased with the increase of molar volume (influence of substituent R bulkiness, r = 0.9949, n = 4) up to pentyl derivative 2e (MV = 96.81 cm\textsuperscript{3}). After this
optimum, activity showed a strong linear decrease with the subsequent increase of molar volume up to $\text{MV} = 146.33 \text{ cm}^3$ ($2h$, $r = -0.9923$, $n = 4$). On the other hand, PET inhibition within the chlorinated series showed a moderate linear increase with the increase of molar volume ($r = 0.9577$, $n = 5$) up to heptyl derivative $1g$ ($\text{MV} = 129.83 \text{ cm}^3$) and, after that, slightly decreased to octyl derivative $1h$ ($\text{MV} = 146.33 \text{ cm}^3$).

It is important to note that a strong dependence of PET inhibition on the electron-withdrawing effect of substituents in individual series of many PET inhibitors was observed [14–16,34,49]. Therefore, it can be hypothesized that also a nitro moiety in the ortho position of the anilide ring (electronic Hammett’s parameter $\sigma = 1.72$ [50]) activates more strongly an amide bond—one of the structural motifs responsible for binding to PS II—and from this point of view, it is more advantageous than chlorine in the ortho position (electronic Hammett’s parameter $\sigma = 0.67$ [50]) of the anilide ring. In general, the $N$-alkyl tail of a suitable length facilitates penetration of a compound through hydrophobic regions of thylakoid membrane to the site of action in photosynthetic apparatus, as discussed below, but the electron-deficient amide bond is more important for the intrinsic effect of compounds [14–16,34,35,51]. Therefore, it is noteworthy that the PET-inhibiting activity of pentyl derivative $2e$ ($\text{IC}_{50} = 0.233 \text{ mM, MV} = 96.81 \text{ cm}^3$) is similar to the PET inhibition of heptyl derivative $1g$ ($\text{IC}_{50} = 0.263 \text{ mM, MV} = 129.83 \text{ cm}^3$) although MV value is significantly lower for compound $2e$.

The dependence of PET-inhibiting activity of studied compounds $1a–1h$ and $2a–2h$ on Taft polar constants $\sigma^*$ of the alkyl tail $R^2$ is shown in Figure 3. With the exception of compounds with the highest $\sigma^*$ values in both series belonging to compounds with short alkyl chains (ethyl $1a$ as well as ethyl $2a$ and propyl $2b$ derivatives), the observed trend for the two studied series was opposite. While for compounds of series $I$, the increasing $\sigma^*$ value resulted in increased inhibitory activity, for compounds of series $II$ it showed a decrease. Therefore, it can be hypothesized that these different properties/behaviour of compounds of series $I$ and $II$, as mentioned above, are caused by possible interactions and the electron activation of amide and carbamate groups (responsible also for interactions with the photosynthetic apparatus) with the spatially close NO$_2$ moiety in the ortho position of the anilide ring.
was inhibited by the most active compounds 2e and 1b. The application of 2,5-diphenylcarbazide (DPC, artificial electron donor) that supplies electrons to octyl, so called ‘cut-off’ effect—i.e., the loss/notable decrease of biological activity usually observed for amphiphilic compounds—was manifested [26,27,52–54].

Besides physicochemical parameters—for example, lipophilicity or electronic properties of substituents—an appropriate concentration of the compound at the site of action in the photosynthetic apparatus is also important for PET-inhibiting activity. A compound having very low aqueous solubility cannot pass through the hydrophilic regions of the thylakoid membrane to reach the site of action, which results in a significant decrease of inhibitory activity. The solubility of butyl derivative 1d and derivatives with longer alkyl chains was similar and significantly lower than that of propyl 1b and isopropyl 1c derivatives, which resulted in a notable activity decrease; a slight increase of PET-inhibiting activity with a further prolongation of the alkyl tail can be connected with the fact that a longer alkyl chain can be incorporated in the thylakoid membrane to a greater extent and subsequently cause membrane perturbation also at a lower concentration. This effect is connected with the surface activity of these compounds (they can be considered as non-ionic surfactants) and with the alkyl tail length (molar volume), which is again reflected by lipophilicity. From the aspect of PET-inhibiting activity, the lipophilicity optimum for C4–C8 alkyl chains can be found at C7 (compound 1g), and C5 (compound 2e), see Figures 1 and 2. With the further elongation of the alkyl chain (hydrophobic part) to octyl, so called ‘cut-off’ effect—i.e., the loss/notable decrease of biological activity usually observed for amphiphilic compounds—was manifested [26,27,52–54].

The application of 2,5-diphenylcarbazide (DPC, artificial electron donor) that supplies electrons in the site of Z*/D*/ intermediate, i.e., tyrosine radicals Tyr2 and Tyr13 (or their surroundings) that are situated in D1 and D2 proteins on the donor side of PS II [40] in chloroplasts, the activity of which was inhibited by the most active compounds 1b or 2e (up to 30% of the control), caused practically complete PET restoration already at the addition of three-fold DPC concentration with regard to the applied concentration of compound 2e. Therefore, it can be concluded that the site of action of studied alkylcarbamates, 1a–1h and 2a–2h, is situated mainly on the donor side of PS II. The site of action situated on the donor side of PS II was found also for 2-alkylthio-6-R-benzothiazoles (R = 6-formamido-, 6-acetamido-, and 6-benzoylamino-) [55], anilides of 2-alkylpyridine-4-carboxylic acids [56], cationic surfactants [57,58] acting in the intermediates Z*/D* and 2-alkylsulphonyl-4-pyridinecarbothioamides acting in the D* intermediate [59].
3. Experimental Section

3.1. Synthesis

Both pattern compounds \( N-(2\text{-chlorophenyl})-2\text{-hydroxynaphthalene-1-carboxamide} (1) \) and \( N-(2\text{-nitrophenyl})-2\text{-hydroxynaphthalene-1-carboxamide} (2) \) as well as all carbamates 1a–1h and 2a–2h were described recently by Gonec et al. [15,22].

3.2. Study of Photosynthetic Electron Transport (PET) Inhibition in Spinach Chloroplasts

Chloroplasts were prepared from spinach (Spinacia oleracea L.) according to Masarovicova and Kralova [60]. The PET inhibition in isolated spinach chloroplasts was performed as described recently [15] using the artificial electron acceptor 2,6-dichlorophenol-indophenol (DCPIP). The rate of photosynthetic electron transport was monitored as a photoreduction of DCPIP. The inhibitory efficiency of the studied compounds was expressed by IC
\( _{50} \) values, i.e., by the molar concentration of the compounds causing a 50% decrease in the oxygen evolution rate relative to the untreated control. The comparable IC
\( _{50} \) value for the selective herbicide 3-(3,4-dichlorophenyl)-1,1-dimethylurea, DCMU (Diuron®), was about 0.002 mmol/L. The results are summarized in Table 1.

3.3. Statistical Analysis

Statistical analyses were performed using a Statgraphics PlusCenturion XV (Herndon, VA, USA). All measurements were performed in triplicate. Data was expressed as mean ± standard deviation (SD). Analysis of variance (ANOVA) and the least significant difference (LSD) test were applied to determine differences between means. Differences were considered to be significant at \( p \leq 0.05 \) confidence level. The one-way analysis of the variance (ANOVA) test was complemented by the Bonferroni’s multicomparison test.

4. Conclusions

A series of prepared and characterized eight 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates 1a–1h and eight 1-[(2-nitrophenyl)carbamoyl]naphthalen-2-yl alkylcarbamates 2a–2h were tested for their activity related to the inhibition of PET in spinach (Spinacia oleracea L.) chloroplasts. The highest activity within both series of carbamates was observed for 1-[(2-chlorophenyl) carbamoyl]naphthalen-2-yl propylcarbamate (1b, IC
\( _{50} = 80 \mu M) \). In spite of the rather low PET-inhibiting activity of the compounds, it was found that they inhibit PET in PS II. Lipophilicity and bulkiness of \( N \)-alkyl substituent \( R_2 \) seem to be important factors that influence PET-inhibiting activity, as trends for both series are similar. In addition to these parameters, PET-inhibiting activity was also affected by the electronic properties of \( R_2 \) substituent (whereas the influence of PET inhibition on electronic properties for the two series was opposite), and by possible interactions and electron activation of amide and carbamate groups (responsible also for interactions with photosynthetic apparatus) with the spatially close NO\(_2\) and Cl moieties in the ortho position of the anilide ring.

Acknowledgments: This study was supported by IGA VFU Brno 320/2015/FaF and by the Slovak Research and Development Agency (Grant No. APVV-0516-12). The HPLC/HRMS system forms a part of the National Infrastructure CzeCOS ProCES CZ.02.1.01/0.0/0.0/16_013/0001609; Michal Oravec was supported by the National Sustainability Program (NPU I; Grant No. LO1415).

Author Contributions: Tomas Gonec, Josef Stranik, Jiri Kos, Josef Jampilek—design, synthesis of the compounds, SAR, writing of the paper. Michal Oravec—HPLC, HRMS, NMR analyses characterizations of the compounds. Matus Pesko and Katarina Kralova—PET evaluation.

Conflicts of Interest: The authors declare no conflict of interest.
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**Sample Availability:** Samples of compounds 1–2h are available from author T. Gonec.