Preparation and Biological Properties of Ring-Substituted 3-Hydroxynaphthalene-2-carboxanilides

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Abstract: In this study a series of twenty-five ring-substituted 3-hydroxy-*N*-phenylnaphthalene-2-carboxanilides were prepared. The procedures for synthesis of the compounds are presented. The compounds were tested for their activity related to inhibition of photosynthetic electron transport (PET) in spinach (*Spinacia oleracea* L.) chloroplasts. Primary *in vitro* screening of the synthesized compounds was also performed against four *Staphylococcus* strains. Several compounds showed noteworthy biological activity especially against methicillin-resistant *Staphylococcus aureus* strains. For all the compounds structure-activity relationships (SAR) are discussed.

Keywords: Naphthalene-2-carboxanilides; PET inhibition; Spinach chloroplasts; *Staphylococcus aureus*; Structure-activity relationships.

INTRODUCTION

Salicylanilides (2-hydroxy-*N*-phenylbenzamides) are an important class of aromatic compounds with a wide range of pharmacological activities. A number of them show

anti-inflammatory [1], antimicrobial [2-7] or antineoplastic efficiency [8-10] as well as acetylcholinesterase-inhibiting activity [11].

Design of the presented compounds is based on salicylanilides, but one aromatic ring was extended to another, *i.e.* a naphthalene was used basic scaffold and various ring-substituted 3-hydroxy-*N*-phenylnaphthalene-2-carboxanilides were prepared. These compounds can be classified as analogues of salicylanilides or isosteres of quinoline-2-carboxanilides. Promising results of biological screening of some salicylanilides and quinaldanilides [2-7,11-14] inspired us to prepare and to evaluate these derivatives of naphthanilides. It was expected that ring-substituted 3-hydroxy-*N*-phenylnaphthalene-2-carboxanilides, compounds originating from biologically active salicylanilide/quinaldanilides (bioisosters), would have interesting biological properties.

Thus in the context of the previously-described amides [2-7,11,12,15-17] or various azanaphtalenes [13,14,18-25], a series of 3-hydroxynaphthalene-2-carboxanilides that can trigger interesting biological activity were investigated. These compounds were tested for their photosynthesis-inhibiting activity – the inhibition of photosynthetic electron transport in spinach chloroplasts (*Spinacia oleracea* L.). Primary *in vitro* screening of the synthesized compounds was also performed against four *Staphylococcus* strains, whereas three of them were methicillin-resistant *Staphylococcus aureus* strains. Relationships between the structure and *in vitro* antimicrobial activities or/and inhibitory activity related to inhibition of photosynthetic electron transport (PET) in spinach chloroplasts of the new compounds are discussed.

As the presence of an amide (-NHCO-) group [6,7,12-17] is characteristic of a number of herbicides acting as photosynthesis inhibitors, 3-hydroxy-*N*-phenylnaphthalene-2-carboxanilides were also evaluated for their PET-inhibiting activity in spinach chloroplasts (*Spinacia oleracea* L.). Many compounds possessing an amide (-NHCO-) group and a hydrophobic moiety in close vicinity to this group were found to act as photosynthesis inhibitors [26,27]. According to Shipman [28] the hydrophilic part of an herbicide binds electrostatically to the terminus of an alfa-helix at a highly charged amino acid, whereby the hydrophobic part of the inhibitors extends into the hydrophobic part of the membrane. Interruption of the photosynthetic electron transport can be connected with the displacement of plastoquinone from its binding pocket in one of the protein subunits of the photosystem (PS) II [29], with interaction of the inhibitor with tyrosine radicals Tyr_Z and Tyr_D which are situated in D_1 and D_2 proteins on the donor side of PS [30] II or with interaction with a membrane-protein complex in the thylakoid membranes, which catalyses oxidation of water and reduction of plastoquinone [31]. For example, in the presence of R' substituted salicylanilides the decreased intensity of the fluorescence emission band at 686 nm (belonging to the chlorophyll-protein complexes mainly in PS II [32]) suggested PS II as the site of action of the studied inhibitors [6].

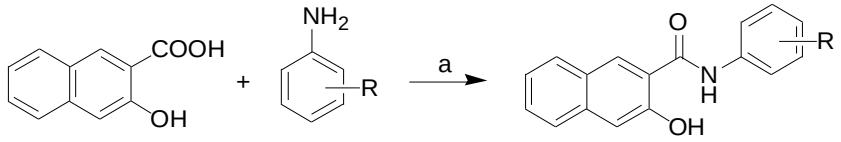
Both pharmaceuticals and pesticides are designed to target particular biological functions, and in some cases these functions overlap in their molecular target sites, or they target similar processes or molecules. Modern herbicides express low toxicity against mammals and one of the reasons is that mammals lack many of the target sites for herbicide action. At present, approximately 20 mechanisms of action of herbicides are known. It was determined that inhibitors of protoporphyrinogen oxidase, 4-hydroxyphenylpyruvate dioxygenase and glutamine synthetase inhibit these enzymes both in plants and mammals. However, the consequences of inhibition of the overlapping target site can be completely different for plants and animals. Therefore a compound that has lethal action on plants may be beneficial for mammals [33]. Such chemical compounds are characterized by low toxicity on mammals as a result of quick metabolism and/or elimination of herbicide from the mammal system. Taking into consideration that mammals may also have molecular sites of action of herbicides, most

pharmaceutical companies until recently had pesticide divisions, sometimes with a different name. 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*. However, little information of this type was published and must usually be deduced from patent literature. One of the exceptions is fluconazole, a fungicide product discovered by the pharmaceutical sector that is now used both as a pharmaceutical and patented as a crop production chemical [33–35].

RESULTS AND DISCUSSION

All the studied compounds were prepared according to Scheme 1. Microwave-assisted synthesis facilitated the process of obtaining 3-hydroxynaphthalene-2-carboxanilides, thus synthesis of the target compounds was carried out only by one step. At first the carboxyl group was activated with phosphorus trichloride. The final amide was immediately formed by aminolysis of the acyl chloride by ring-substituted aniline in dry chlorbenzene. This procedure is modification of method described recently by Bobal *et al.* [36].

Scheme 1. Synthesis of ring-substituted 3-hydroxy-*N*-phenylnaphthalene-2-carboxanilides **1**-**9c**: (a) PCl_3, chlorbenzene, MW.



1-**9c**

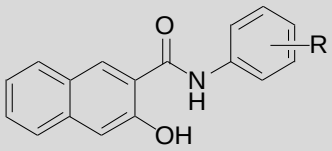
R = H, OH, OCH_3, CH_3, F, Cl, Br, CF_3, NO_2

Hydrophobicity of prepared compounds **1**-**9c** was expressed as distributive parameters π [37], *i.e.* lipophilicity contributions of individual substituents in the anilide part of the discussed compounds. Hammett's σ parameters [37,38] indicating electronic properties of individual substituents were used as other molecular descriptor. Both are listed in Table 1. Contributions of lipophilicity of individual substituents showed a wide range of distributive parameter π from -0.61 (compound **2c**, 4-OH) to 1.19 (compound **7c**, 4-Br). Hammett's σ parameters of individual substituents in the anilide part of the discussed compounds also possessed a wide range; from -0.37 (compound **2c**, 4-OH) to 1.72 (compound **9a**, 2-NO_2).

The activity of the evaluated naphthanilide 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. Generally compounds showed poor-aqueous solubility. Only ten compounds from twenty-five tested compounds could be evaluated. PET inhibition by **1**, **3c**-**6c**, **7b**, **7c** and **8b**, **8c** could not be determined due to precipitation of the compounds during the experiments. With respect to these small but specifically substituted groups of compounds some structure-activity relationships (SAR) can be proposed. Compound **9b** (3-NO_2) expressed the highest PET-inhibiting activity (IC_{50} = 16.9 μmol/L), while compound **9c** (4-NO_2) expressed the lowest PET-inhibiting activity (IC_{50} = 187.5 μmol/L).
The PET-inhibiting activity was expressed by negative logarithm of IC_{50} value (compound concentration in mol/L causing 50% inhibition of PET). Despite the relatively low inhibitory activity of the studied compounds, correlations between log(1/IC_{50} [mol/L]) and the lipophilic or electronic properties of the individual anilide substituents in compounds **1**-**9c** were performed, see Fig. 1 and Fig. 2. Based on the obtained results it is not possible to decide, whether some of *ortho*-, *meta*- or *para*-positions are preferred from the point of view of

PET-inhibiting activity. PET inhibition increases with electron-withdrawing substituent to σ = 0.71 (3-NO_2, compound **9b**), where the optimum can be found and then decreases with subsequent increase of electron-withdrawing properties of substituents (σ = 0.71, 4-NO_2, compound **9c** and σ = 0.80, 2-NO_2, compound **9a**). Thus, when the activity of compound **8a** is not considered, the dependence of PET-inhibiting activity on the electronic σ properties of substituents showed bilinear dependence, see Figure 1, where correlations coefficients are r = 0.9908 (for the σ range from -0.39 to 0.71) and r = 0.8539 for σ > 0.71).

Table 1. Distributive π parameters, electronic Hammett's σ parameters, IC_{50} [μmol/L] values related to PET inhibition in spinach chloroplasts of compounds **1**-**9c** in comparison with 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) standard and *in vitro* anti-*Staphylococcus* activities (MIC) of compounds **1**-**9c** in comparison with standards ampicillin (APC) and ciprofloxacin (CPX).



Comp.	R	π [37]	σ [37]	PET inhibition IC_{50} [μmol/L]	MIC [μmol/L]			
					SA	*MRSA 63718*	*MRSA 630*	*MRSA 3202*
1	H	0	0	[b]	>972	>972	>972	>972
2a	2-OH	-0.41	-0.39 [38]	**165.9**	>917	>917	>917	>917
2b	3-OH	-0.50	0.12	**59.9**	**458**	**458**	**458**	**458**
2c	4-OH	-0.61	-0.37	**125.7**	>917	**458**	**917**	**458**
3a	2-OCH_3	-0.33	0	**59.5**	**55**	**55**	**55**	**55**
3b	3-OCH_3	0.12	0.12	**53.4**	>873	>873	>873	>873
3c	4-OCH_3	-0.03	-0.27	[b]	>873	>873	>873	>873
4a	2-CH_3	0.84	0.10	[b]	>923	>923	>923	**462**
4b	3-CH_3	0.52	-0.07	[b]	>923	>923	>923	**462**
4c	4-CH_3	0.60	-0.17	[b]	>923	>923	**462**	**231**
5a	2-F	0	0.47	[b]	>910	>910	**455**	**228**
5b	3-F	0.22	0.34	[b]	>910	>910	**455**	**228**
5c	4-F	0.15	0.06	[b]	>910	>910	**455**	**228**
6a	2-Cl	0.76	0.67	[b]	>860	>860	>860	**215**
6b	3-Cl	0.77	0.37	[b]	>860	>860	**430**	**215**
6c	4-Cl	0.76	0.23	[b]	>860	>860	>860	>860
7a	2-Br	0.84	0.71	**43.2**	>748	>748	>748	>748
7b	3-Br	0.96	0.39	[b]	>748	>748	>748	**187**
7c	4-Br	1.19	0.23	[b]	>748	>748	>748	**187**
8a	2-CF_3	1.04	0.40[a]	**105.2**	>773	>773	>773	**97**
8b	3-CF_3	1.10	0.43	[b]	>748	>748	**374**	**187**
8c	4-CF_3	1.04	0.74	[b]	>748	>748	**374**	**187**
9a	2-NO_2	-0.27[a]	0.80 [38]	**106.6**	>830	>830	**415**	415
9b	3-NO_2	0.11	0.71 [38]	**16.9**	>830	>830	>830	>830
9c	4-NO_2	0.22	0.78 [38]	**187.5**	>830	>830	>830	>830
DCMU	–	–	–	**1.9**	–	–	–	–
APC	–	–	–	–	**5.723**	>45.791	>45.791	>45.791
CPX	–	–	–	–	–	>48.287	>48.287	>48.287

[a]calculated using ACD/Percepta ver. 2012, [b]precipitation during the experiment, *SA* = *Staphylococcus aureus* ATCC 29213, *MRSA* = clinical isolates of methicillin-resistant *Staphylococcus aureus* 63718, SA 630 and SA 3202 (National Institute of Public Health, Prague, Czech Republic).

On the other hand, the biological activity is also affected by lipophilicity; distributive parameters π of the anilide substituents, see Table 1 and Fig. 2. In general, the dependence of log ($1/IC_{50}$) on π shows a similar trend as in case of electronic σ properties. When the least active anilide, *i.e.*, **9c**, was eliminated; similar bilinear dependence of PET inhibition (log $1/IC_{50}$, [mol/L]) on π, with the optimum π = 0.11 (3-NO_2, compound **9b**), can be observed. However, the corresponding correlation coefficients were significantly lower than those determined for the dependence of PET inhibiting activity on σ (r = 0.7146 and r = 0.9546, respectively). Application of artificial electron donor 1,5-diphenylcarbazide acting in $Z^{\bullet}/D^{\bullet}$ intermediate [39] to chloroplasts activity of which was inhibited by compound **2b** to 65.9% resulted in partial restoration of PET (up to 81.9 of the control), indicating that the site of action of the studied compound is situated at the donor side of PS II, before $Z^{\bullet}/D^{\bullet}$ intermediate as well as on the acceptor side of PS II, probably at Q_B.

Figure 1. Relationships between PET-inhibiting activity log ($1/IC_{50}$) [mol/L] in spinach chloroplasts and anilide substituent electronic Hammett's σ parameters of studied compounds **1**-**9c**.

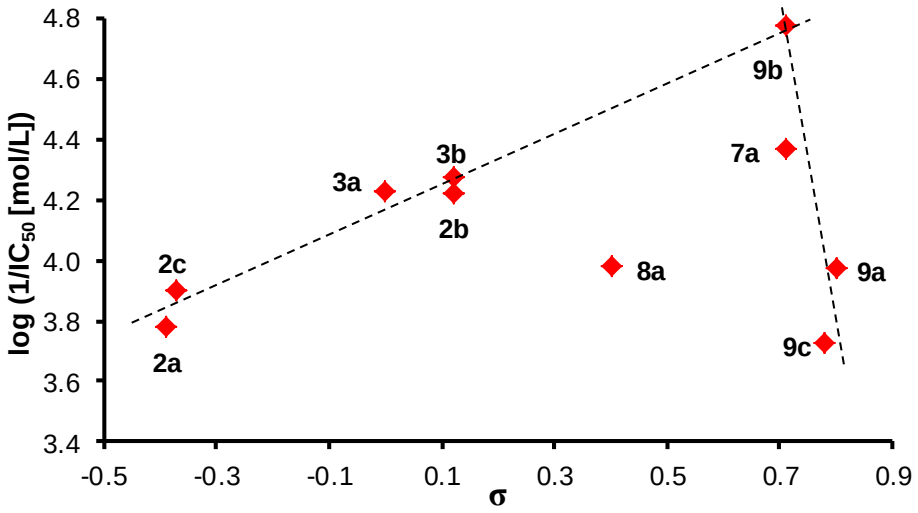
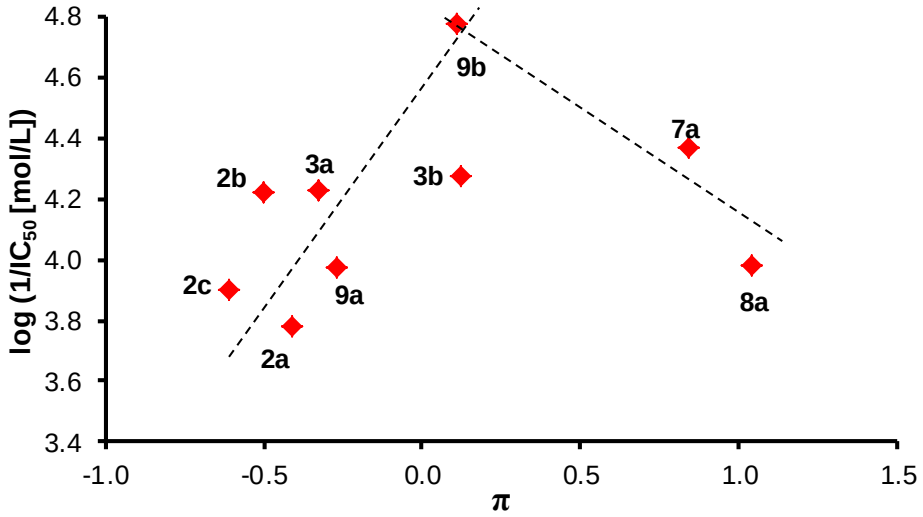


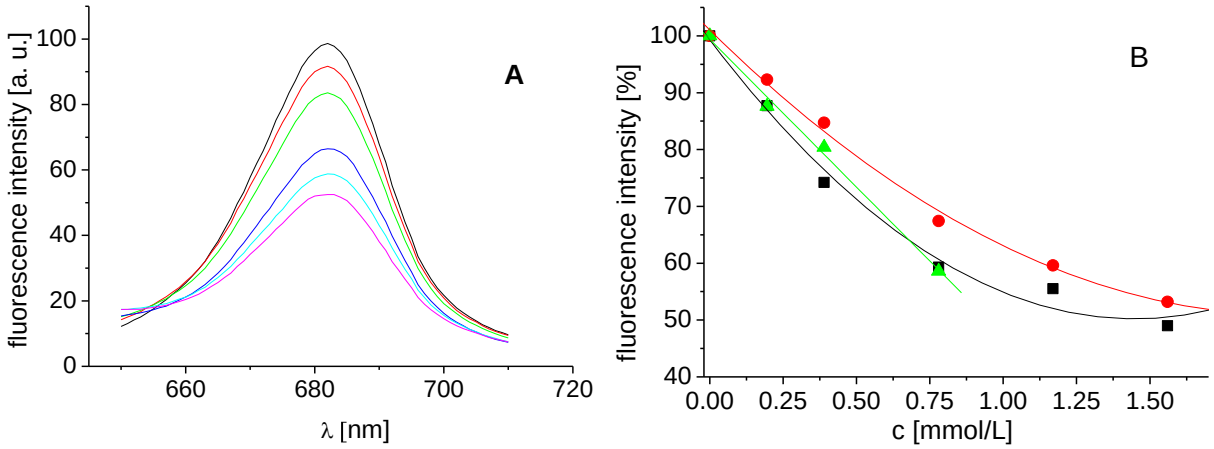
Figure 2. Relationships between PET-inhibiting activity log ($1/IC_{50}$ [mol/L]) in spinach chloroplasts and lipophilicity, expressed as distributive parameters π, of studied compounds **1**-**9c**. Compounds **9c** was excluded/are not plotted.



It can be assumed that the site of action of studied compounds is situated on the donor side of PS II in the section between the primary electron donor of PS II (H_2O) and $Z^{\bullet}/D^{\bullet}$ intermediate, probably in the vicinity of the oxygen evolving complex (OEC) situated on the luminal side of the thylakoid membrane. This assumption is also supported by the bilinear course of the dependence of log ($1/IC_{50}$) on σ, which indicates that for the PET-inhibiting activity not only sufficient lipophilicity (enabling easier penetration of the compounds into the lipids of photosynthetic membranes) but also sufficient electronegativity of the R substituent (enabling interactions with proteins located near oxygen evolving complex occurring in the polar region of photosynthetic membranes) is necessary. As 3-hydroxy-*N*-(3-nitrophenyl)naphthalene-2-carboxamide (**9b**) was the most active compound from the series, this result can indicate that PET inhibition can be associated with additional interaction of the nitro moiety with photosynthetic proteins. A strong dependence of PET-inhibiting activity on σ was also found for 2-benzylsulphanylbenzimidazoles [40]. 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-) [41], anilides of 2- alkylpyridine-4-carboxylic acids acting in intermediates $Z^{\bullet}/D^{\bullet}$ [42] and 2-alkylsulphanyl-4-pyridinecarbothioamides acting in the $D^{\bullet}$ intermediate [43].

The effects of the studied compounds on the photosynthetic apparatus of spinach chloroplasts were investigated by studying chlorophyll *a* (Chl*a*) fluorescence. The decreased intensity of the emission band at 686 nm belonging to the pigment-protein complexes in photosystem II [44] (Fig. 3A) suggested PS II as the site of action of the studied inhibitors. Lower solubility of compound **3b** did not allow to record fluorescence emission spectra of chloroplasts treated with compound concentration higher than 0.780 mmol/L. The extent of perturbation of chlorophyll *a*-protein complexes in the thylakoid membrane reflected as decreased fluorescence (Fig. 3B) correlated with PET inhibiting activity of compounds **2a**, **3b** and **8a** (IC_{50} = 59.9, 53.4 and 105.2 μmol/L, respectively). Similar decrease of Chl*a* fluorescence in plant chloroplasts was also observed after treatment with $HgCl_2$ [45], non-ionic surfactant Triton X 100 [46] as well as substituted benzanilides [47] and salicyanilides [48].

Figure 3. Fluorescence emission spectra of chlorophyll *a* in untreated spinach chloroplasts in presence of compound **8a**: 0, 0.195, 0.390, 0.780, 1.170 and 1.560 mmol/L (curves from top to bottom; λ_{ex} = 436 nm) (**A**) and dependence of fluorescence intensity of chlorophyll *a* on concentration of compounds **2b** (squares), **3b** (triangles) and **8a** (circles) (**B**).



All the discussed compounds were evaluated for their *in vitro* anti-*Staphylococcus* activity against *Staphylococcus aureus* as against three methicillin-resistant *Staphylococcus aureus* strains. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first described in 1961, and since then has become one of the most common clinically relevant bacterial pathogen isolated almost all over the world. Even though originally limited to the hospitals, MRSA is an increasing cause of infections in the community nowadays. Recent studies have shown that, despite antibacterial therapy, MRSA infections are still associated with serious clinical consequences (treatment failure, higher morbidity and mortality, prolonged hospitalization etc.). Because of changing features of MRSA, it is one of the most difficult bacteria for clinicians to treat. The emergence of resistance to currently available drugs, their toxicity and general lack of oral agents justify an urgent need for new anti-MRSA agents [49,50]
Although salicylanilides seem to be promising candidates of antibacterial agents [51,52], all the compounds showed only moderate activity except for 3-hydroxy-*N*-(2-methoxyphenyl) naphthalene-2-carboxamide (**3a**). As MIC = 55 μmol/L of compound **3a** was the same for all four strains, it can be speculated about specific mechanism of action. According to the results presented in Table 1, it can be concluded that compound **3a** exhibited activity comparable with the standards. Nevertheless due to moderate activity of the rest of the compound, therefore no thorough structure-activity relationships could be established.

EXPERIMENTAL

General

All reagents were purchased from Aldrich. Kieselgel 60, 0.040-0.063 mm (Merck, Darmstadt, Germany) was used for column chromatography. TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and evaluated in iodine vapour. The melting points were determined on Boetius PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and are uncorrected. Infrared (IR) spectra were recorded on a Smart MIRacle™ ATR ZnSe for Nicolet™ Impact 410 FT-IR Spectrometer (Thermo Scientific, USA). The spectra were obtained by accumulation of 256 scans with 2 cm^{-1} resolution in the region of 4000-600 cm^{-1}. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz FT-NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C, Bruker Comp., Karlsruhe, Germany). Chemicals shifts are reported in ppm (δ) using internal $Si(CH_3)_4$ as the reference with diffuse, easily exchangeable signals being omitted. Mass spectra were measured using a LTQ Orbitrap Hybrid Mass Spectrometer (Thermo Electron Corporation, USA) with direct injection into an APCI source (400 °C) in the positive mode.

Synthesis

General procedure for synthesis of carboxamide derivatives (**1**-**9c**): 1-Hydroxynaphtalene-2-carboxylic acid (1.0 g, 5.3 mmol) was suspended in dry chlorbenzene (30 mL) at ambient temperature and phosphorus trichloride (0.23 mL, 2.7 mmol, 0.5 eq.) and corresponding substituted aniline (5.3 mmol) were added dropwise. The reaction mixture was heated to 130 °C and stirred for 25 min at 130 °C in the microwave reactor. The mixture was cooled to 60 °C and then the solvent was removed to dryness under reduced pressure. The residue was washed with hydrochloride acid and water. The crude product was recrystallized from EtOH. The studied compounds **1**-**9c** are presented in Table 1.

3-Hydroxy-N-phenylnaphthalene-2-carboxamide (**1**) [54–56]. Yield 76%; Mp. 245-246 °C (Mp. 242-243 °C [55]); IR (Zn/Se ATR, cm^{-1}): 3291w, 1620m, 1556m,1494w, 1448w, 1396w, 1344m, 1250w, 1209m, 1173m, 1064w, 950w, 915w, 870m, 842m, 771w, 739s, 712m, 687m; ^{1}H-NMR (DMSO-d_6), δ: 11.36 (s, 1H), 10.60 (s, 1H), 8.53 (s, 1H), 7.93 (d *J*=8.1 Hz, 1H), 7.78, (d, *J*=8.1 Hz, 3H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H),

7.44-7.33 (m, 4H), 7.15 (t, *J*=7.26 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 165.67, 153.79, 138.37, 135.76, 130.42, 128.72, 128.66, 128.08, 126.83, 125.72, 124.03, 123.69, 121.55, 120.55, 110.57; HR-MS: for $C_{17}H_{14}NO_2[M+H]^+$ calculated 264.1019 m/z, found 264.1023 m/z.

3-Hydroxy-N-(2-hydroxyphenyl)naphthalene-2-carboxamide (**2a**) [56]. Yield 28%; Mp. 164-165 °C (Mp. 211-213 °C [56]); IR (Zn/Se ATR, cm^{-1}): 3120w, 3022w, 1645m, 1576w, 1539m, 1510w, 1452m, 1322w, 1296w, 1246m, 1211w, 1175w, 1146w, 1031m, 893m, 825m, 761s, 747s, 668m; HR-MS: for $C_{17}H_{14}NO_3$ $[M+H]^+$ calculated 280.0968 m/z, found 280.0974 m/z.

3-Hydroxy-N-(3-hydroxyphenyl)naphthalene-2-carboxamide (**2b**) [56] Yield 52%; Mp. 194-195 °C (Mp. 229-232 °C [56]); IR (Zn/Se ATR, cm^{-1}): 3280w, 1668m, 1634w, 1598w, 1509m, 1466s, 1355w, 1314w, 1283m, 1218m, 1149w, 1072w, 953w, 916w, 878m, 792m, 772m, 739s, 668m; HR-MS: for $C_{17}H_{14}NO_3$ $[M+H]^+$ calculated 280.0968 m/z, found 280.0973 m/z.

3-Hydroxy-N-(4-hydroxyphenyl)naphthalene-2-carboxamide (**2c**) [56]. Yield 35%; Mp. 199-200 °C (Mp. 268-270 °C [56]); IR (Zn/Se ATR, cm^{-1}): 3284w, 1653s, 1559w, 1507m, 1466s, 1280s, 1217m, 1146m, 1072m, 956w, 903w, 874m, 831m, 789s, 768w, 749s, 716w 668m; HR-MS: for $C_{17}H_{14}NO_3$ $[M+H]^+$ calculated 280.0968 m/z, found 280.0973 m/z.

3-Hydroxy-N-(2-methoxyphenyl)naphthalene-2-carboxamide (**3a**) [55]. Yield 80%; Mp. 165-166 °C (Mp. 164-166 °C [55]); IR (Zn/Se ATR, cm^{-1}): 3191w, 1624m, 1593s, 1549m, 1487w, 1435m, 1393w, 1393w, 1342m, 1284m, 1248w, 1227m, 1173m, 1115m, 1067m, 1031w, 922w, 864m, 837m, 801w, 771m, 735s, 685m; ^{1}H-NMR (DMSO-d_6), δ: 11.78 (s, 1H), 11.08 (s, 1H), 8.72 (s, 1H), 8.51 (d, *J*=7.7 Hz, 1H), 7.98 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=0.9, 1H), 7.40-7.32 (m, 2H), 7.11-6.92 (m, 3H), 3.92 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 162.27, 152.61, 148.64, 135.82, 132.50, 128.94, 128.22, 127.91, 127.19, 125.58, 123.94, 123.79, 121.29, 120.62, 120.19, 111.01, 110.71, 56.05; HR-MS: for $C_{18}H_{16}NO_3$ $[M+H]^+$ calculated 294.1124 m/z, found 294.1130 m/z.

3-Hydroxy-N-(3-methoxyphenyl)naphthalene-2-carboxamide (**3b**). Yield 75%; Mp. 194-195 °C; IR (Zn/Se ATR, cm^{-1}): 3316*w*, 3047w, 1642m, 1622s, 1593s, 1556s, 1456*m*, 1398w, 1365*w*, 1346w, 1266 *m*, 1225*m*, 1157*m*, 1134w, 1067m, 1046s, 962w, 913m, 873s, 799*w*, 770m, 752m, 682m; ^{1}H-NMR (DMSO-d_6), δ: 11.30 (s, 1H), 10.56 (s, 1H), 8.51 (s, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.55-7.47 (m, 2H), 7.40-7.24 (m, 4H), 6.76-6.70 (m, 1H), 3.78 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 165.64, 159.52, 153.67, 139.58, 135.73, 130.42, 129.50, 128.64, 128.06, 126.83, 125.72, 123.69, 121.75, 112.72, 110.54, 109.50, 106.28, 55.03; HR-MS: for $C_{18}H_{16}NO_3$ $[M+H]^+$ calculated 294.1124 m/z, found 294.1131 m/z.

3-Hydroxy-N-(4-methoxyphenyl)naphthalene-2-carboxamide (**3c**). Yield 66%; Mp. 235-236 °C; IR (Zn/Se ATR, cm^{-1}): 3283w, 3013w, 1636m, 1618s, 1564m, 1510m, 1393w, 1357m, 1303w, 1247m, 1170m, 1146w, 1116w, 1070m, 1030m, 950m, 878m, 856m, 830s, 795w, 775w, 737m; ^{1}H-NMR (DMSO-d_6), δ: 11.47 (s, 1H), 10.50 (s, 1H), 8.56 (s, 1H), 7.92 (d, *J*=7.7 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 1H), 7.71-7.64 (m, 2H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.40-7.33 (m, 2H), 7.01-6.93 (m, 2H), 3.77 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 165.65, 155.91, 154.18, 135.78, 131.25, 130.12, 128.62, 128.06, 126.75, 125.70, 123.64, 122.31, 120.87, 113.87, 110.59, 55.16; HR-MS: for $C_{18}H_{16}NO_3$ $[M+H]^+$ calculated 294.1124 m/z, found 294.1130 m/z.

3-Hydroxy-N-(2-methylphenyl)naphthalene-2-carboxamide (**4a**) [55]. Yield 74%; Mp. 195-196 °C (Mp. 194-196 °C [55]) IR (Zn/Se ATR, cm^{-1}): 3325w, 3115w, 1622s, 1586m, 1548m, 1456m, 1385w, 1355w, 1356w, 1248w, 1173m, 1065m, 954w, 915w, 873m, 844*w*,

803*w*, 773*w*, 742s, 679m; ^{1}H-NMR (DMSO-d_6), δ: 11.80 (s, 1H), 10.53 (s, 1H), 8.69 (s, 1H), 7.96 (d, *J*=7.7 Hz, 2H), 7.78 (d, *J*=8.1 Hz, 1H), 7.52 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.41-7.36 (m, 2H), 7.33-7.22 (m, 2H), 7.16-7.08 (m, 1H), 2.34 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 164,58, 153.57, 136.36, 135.87, 131.45, 130.29, 129.99, 128.82, 128.22, 126.99, 126.24, 125.67, 124.86, 123.76, 123.36, 120.60, 110.72, 17.73; HR-MS: for $C_{18}H_{16}NO_2$ $[M+H]^+$ calculated 278.1176 m/z, found 278.1182 m/z.

3-Hydroxy-N-(3-methylphenyl)naphthalene-2-carboxamide (**4b**). Yield 73%; Mp. 207-208 °C; IR (Zn/Se ATR, cm^{-1}): 3297w, 3048w, 1607s, 1557 *m*, 1489m, 1451w, 1397w, 1357w, 1344w, 1259m, 1210m, 1173w, 1076w, 951m, 923m, 859s, 836m, 783s, 744s, 689s; ^{1}H-NMR (DMSO-d_6), δ: 11.38 (s, 1H), 10.53 (s, 1H), 8.54 (s, 1H), 7.93 (d, *J*=8.6 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.60-7.47 (m, 3H), 7.40-7.32 (m, 2H), 7.27 (t, *J*=7.7 Hz, 1H), 6.97 (d, *J*=7.3 Hz, 1H), 2.34 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 165.62, 153.84, 138.26, 137.96, 135.77, 130.42, 128.66, 128.56, 128.08, 126.82, 125.71, 124.74, 123.69, 121.40, 121.06, 117.73, 110.59; 21.11; HR-MS: for $C_{18}H_{16}NO_2$ $[M+H]^+$ calculated 278.1176 m/z, found 278.1181 m/z.

3-Hydroxy-N-(4-methylphenyl)naphthalene-2-carboxamide (**4c**) [53] Yield 68%; Mp. 220-221 °C (Mp. 221 °C [53]); IR (Zn/Se ATR, cm^{-1}): 3290w, 3008w, 1619s, 1556m, 1516w, 1450w, 1357m, 1252m, 1208m, 1175m, 1121w, 1070m, 951m, 913m, 869s, 832m, 810s, 761w, 741s, 716s; ^{1}H-NMR (DMSO-d_6), δ: 11.46 (s, 1H), 10.57 (s, 1H), 8.55 (s, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 7.67 (d, *J*= 8.6 Hz, 2H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.40-7.32 (m, 2H), 7.19 (d, *J*=8.6 Hz, 2H), 2.29 (s, 3H); ^{13}C-NMR (DMSO-d_6), δ: 165.64, 154.01, 135.78, 133.12, 130.32, 129.10, 128.64, 128.06, 126.80, 125.70, 123.66, 121.16, 120.62, 110.60, 20.42; HR-MS: for $C_{18}H_{16}NO_2$ $[M+H]^+$ calculated 278.1176 m/z, found 278.1182 m/z.

3-Hydroxy-N-(2-fluorophenyl)naphthalene-2-carboxamide (**5a**) [57]. Yield 65%; Mp. 222-223 °C (Mp. 226-228 °C [57]); IR (Zn/Se ATR, cm^{-1}): 2981w, 1625s, 1605s, 1556m, 1488w, 1458*m*, 1345m, 1262*m*, 1219*m*, 1206*w*, 1191*w*, 1102*w*, 1065*m*, 1033m, 951*w*, 916e, 867m, 838w, 811*m*, 774w, 740s, 693w; ^{1}H-NMR (DMSO-d_6), δ: 11.86 (s, 1H), 10.95 (s, 1H), 8.69 (s, 1H), 8.36 (dt, *J*=7.7 Hz, *J*=2.2 Hz, 1H), 7.98 (d, *J*=8.1 Hz, 1H), 7.78 (d, *J*=7.7 Hz, 1H), 7.52 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.41-7.33 (m, 2H), 7.30-7.25 (m, 1H), 7.24-7.16 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 163.90, 153.08, (d, *J*=243.8 Hz), 152.88, 135.97, 132.17, 128.93, 128.03, 127.08, 126.27 (d, *J*=10.7 Hz), 125.66, 124.98 (d, *J*=6.9 Hz), 124.62 (d, *J*=3.4 Hz), 123.88, 122.87 (d, *J*=0.8 Hz), 120.46, 115.18 (d, *J*=19.1 Hz), 110.81; HR-MS: for $C_{17}H_{13}FNO_2$ $[M+H]^+$ calculated 282.0925 m/z, found 282.0931 m/z.

3-Hydroxy-N-(3-fluorophenyl)naphthalene-2-carboxamide (**5b**). Yield 67%; Mp. 248-249 °C; IR (Zn/Se ATR, cm^{-1}): 3305w, 3033w, 1622*s*, 1557w, 1516w, 1489w, 1449w, 1401w, 1361w, 1334w, 1253*m*, 1212s, 1178m, 952m, 915m, 872m, 840s 771m, 742s, 715m, 685m; ^{1}H-NMR (DMSO-d_6), δ: 11.19(s, 1H), 10.73 (s, 1H), 8.45 (s, 1H), 7.93 (d, *J*=7.7 Hz, 1H), 7.82 (t, *J*=2.1 Hz, 1H), 7.79-7.75 (m, 1H), 7.51 (t, *J*=7.1 Hz, 2H), 7.44-7.32 (m, 3H), 7.02-6.92 (m, 1H); ^{13}C-NMR (DMSO-d_6), δ: 165.70, 162.09 (d, *J*=241.5 Hz), 153.38, 140.24 (d, *J*=11.1 Hz), 135.73, 130.54, 130.48, 130.30 (d, *J*=9.5 Hz), 128.63, 128.08, 126.84, 125.73, 123.71, 122.09, 116.06 (d, *J*=2.7 Hz), 110.32 (d, *J*=18.7 Hz), 107.10 (d, *J*=25.9 Hz); HR-MS: for $C_{17}H_{13}FNO_2$ $[M+H]^+$ calculated 282.0925 m/z, found 282.0932 m/z.

3-Hydroxy-N-(4-fluorophenyl)naphthalene-2-carboxamide (**5c**) [57]. Yield 69%; Mp. 264-265 °C (Mp. 264.5-265.5 °C [57]); IR (Zn/Se ATR, cm^{-1}): 3289w, 2994w, 1615s, 1569m, 1505m, 1445w, 1409w, 1357m, 1250w, 1206m, 1171w, 1100m, 1068m, 1011w, 952w, 915m, 871m, 829s, 799m, 766m, 739m, 706m; ^{1}H-NMR (DMSO-d_6), δ: 11.31 (s, 1H), 10.64 (s, 1H), 8.49 (s, 1H), 7.93 (d, *J*=8.12 Hz, 1H), 7.83-7.75 (m, 3H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz,

J=1.3 Hz, 1H), 7.40-7.32 (m, 2H), 7.23 (t, *J*=9.0 Hz, 2H); ^{13}C-NMR (DMSO-d_6), δ: 165.71, 158.50 (d, *J*=240.7 Hz), 153.79, 135.76, 134.72 (d, *J*=2.7 Hz), 130.29, 128.62, 128.06, 126.79, 125.72, 123.68, 122.44 (d, *J*=8.0 Hz), 121.47, 115.28 (d, *J*=22.1 Hz), 110.55; HR-MS: for $C_{17}H_{13}FNO_2$ $[M+H]^+$ calculated 282.0925 m/z, found 282.0930 m/z.

3-Hydroxy-N-(2-chlorophenyl)naphthalene-2-carboxamide (**6a**) [53]. Yield 50%; Mp. 226-227 °C (Mp. 225 °C [53]); IR (Zn/Se ATR, cm^{-1}): 3164w, 1625m, 1591s, 1546s, 1439m, 1345m, 1293w, 1243w, 1192m, 1171m, 1034m, 840m, 740s, 668m;^{1}H-NMR (DMSO-d_6), δ: 11.91 (s, 1H), 11.13 (s, 1H), 8.73 (s, 1H), 8.51 (dd, *J*=8.1 Hz, *J*=1.3 Hz, 1H), 7.99 (d, *J*=7.69 Hz, 1H), 7.78 (d, *J*=8.12 Hz, 1H), 7.59-7.52 (m, 2H), 7.49-7.45 (m, 1H), 7.41-7.33 (m, 2H), 7.22-7.14 (m, 1H) ^{13}C-NMR (DMSO-d_6), δ: 163.49, 152.65, 135.99, 135.29, 132.62, 129.29, 128.99, 128.42, 127.77, 127.13, 125.62, 125.12, 123.88, 123.35, 122.69, 120.55, 110.78; HR-MS: for $C_{17}H_{13}ClNO_2$ $[M+H]^+$ calculated 298.0629 m/z, found 298.0637 m/z.

3-Hydroxy-N-(3-chlorophenyl)naphthalene-2-carboxamide (**6b**) [58]. Yield 69%; Mp. 257-258 °C (Mp. 258-261 °C [58]); IR (Zn/Se ATR, cm^{-1}): 3299w, 3054w, 1623s, 1545m, 1476w, 1426m 1364m, 1278w, 1248m, 1214m, 1174w, 1065w, 913w, 866m, 776m, 744m, 708m, 680m; ^{1}H-NMR (DMSO-d_6), δ: 11.16 (s, 1H); 10.68 (s, 1H), 8.46 (s, 1H), 7.99 (t, *J*=1.9 Hz, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.76 (d, *J*=7.7 Hz, 1H), 7.67 (d, *J*=8.1 Hz, 1H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.47-7.34 (m, 3H), 7.2 (d, *J*=8.1 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 165.77, 153.42, 139.95, 135.73, 133.06, 130.45, 130.35, 128.61, 128.09, 126.81, 125.73, 123.71, 123.60, 122.03, 119.80, 118.73, 110.52; HR-MS: for $C_{17}H_{13}ClNO_2$ $[M+H]^+$ calculated 298.0629 m/z, found 298.0637 m/z.

3-Hydroxy-N-(4-chlorophenyl)naphthalene-2-carboxamide (**6c**) [53,55]. Yield 71%; Mp. 263-264 °C (Mp. 260 °C [55]); IR (Zn/Se ATR, cm^{-1}): 3283w, 3052w, 1612s, 1549m, 1488m, 1400m, 1359w, 1334w, 1252w, 1209m, 1170m, 1116w, 1068w, 1012m, 749s, 711m, 680m;^{1}H-NMR (DMSO-d_6), δ: 11.24 (s, 1H), 10.68 (s, 1H), 8.47 (s, 1H), 7.93 (d, *J*=7.7 Hz, 1H), 7.8 (t, *J*=9.6 Hz, 2H), 7.54-7.46 (m, 2H), 7.42-7.32 (m, 4H); ^{13}C-NMR (DMSO-d_6), δ: 165.69, 153.56, 137.42, 135.74, 130.45, 130.40, 128.61, 128.08, 127.61, 126.81, 125.73, 123.70, 121.97, 121.83, 110.53; HR-MS: for $C_{17}H_{13}ClNO_2$ $[M+H]^+$ calculated 298.0629 m/z, found 298.0636 m/z.

3-Hydroxy-N-(2-bromophenyl)naphthalene-2-carboxamide (**7a**). Yield 61%; Mp. 215-216 °C; IR (Zn/Se ATR, cm^{-1}): 3158w, 1623s, 1582s, 1537s, 1446w, 1434m, 1388w, 1343*m*, 1312w, 1291*w*, 1193*w*, 1071w, 1047*w*, 1024*m*, 916m, 873m, 845m, 750s, 698*m*; ^{1}H-NMR (DMSO-d_6), δ: 11.88 (s, 1H), 11.00 (s, 1H), 8.72 (s, 1H), 8.42 (dd, *J*=8.1 Hz, *J*=1.3 Hz, 1H), 7.98 (d, *J*=8.1 Hz 1H), 7.80-7.70 (m, 2H), 7.57-7.50 (m, 2H), 7.45-7.34 (m, 2H), 7.13 (dt *J*=7.7 Hz, *J*=1.7 Hz, 1H); ^{13}C-NMR (DMSO-d_6), δ: 163.67, 152.77, 136.53, 136.02, 132.59, 132.54, 128.99, 128.45, 128.28, 127.10, 125.82, 125.64, 123.88, 123.50, 120.47, 114.35, 110.76; HR-MS: for $C_{17}H_{13}BrNO_2$ $[M+H]^+$ calculated 342.0124 m/z, found 342.0133 m/z.

3-Hydroxy-N-(3-bromophenyl)naphthalene-2-carboxamide (**7b**). Yield 73%; Mp. 251-252 °C; IR (Zn/Se ATR, cm^{-1}): 3295w, 3075w, 1622*m*, 1583*m*, 1553w, 1479m, 1403w, 1239*w*, 1209*m*, 1095*w*, 1073*w*, 992w, 953w, 923w, 867m 852s, 837m, 780s, 745s, 667m; ^{1}H-NMR (DMSO-d_6), δ: 11.16 (s, 1H), 10.00 (s, 1H), 8.46 (s, 1H), 8.13 (s, 1H), 7.92 (d, *J*=7.69 Hz, 1H), 7.78-7.68 (m, 2H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.40-7.33 (m, 4H); ^{13}C-NMR (DMSO-d_6), δ: 165.79, 153.44, 140.08, 135.74, 130.66, 130.43, 128.62, 128.09, 126.80, 126.51, 125.74, 123.72, 122.66, 122.00, 121.48, 119.14, 110.52; HR-MS: for $C_{17}H_{13}BrNO_2$ $[M+H]^+$ calculated 342.0124m/z, found 342.0130 m/z.

3-Hydroxy-N-(4-bromophenyl)naphthalene-2-carboxamide (**7c**). Yield 69%; Mp. 261-262 °C; IR (Zn/Se ATR, cm^{-1}): 3288w, 3052w, 1605*s*, 1544*m*, 1486*s*, 1447w, 1394m, 1360w, 1251*w*, 1209*m*, 1169*w*, 1075*m*, 1010m, 955*w*, 915w, 871m, 828*s*, 810s, 785m, 749s, 712m; ^{1}H-NMR

(DMSO-d_6), δ: 11.22 (s, 1H), 10.67 (s, 1H), 8.46 (s, 1H) 7.92 (d, *J*=7.7 Hz, 1H), 7.76 (d, *J*=8.6 Hz, 3H), 7.59-7.46 (m, 3H), 7.39-7.32 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 165.66, 153.51, 137.83, 135.72, 131.52, 130.39, 128.60, 128.06, 126.80, 125.70, 123.69, 122.30, 121.87, 115.63, 110.52; HR-MS: for $C_{17}H_{13}BrNO_2$ $[M+H]^+$ calculated 342.0124m/z, found 342.0132 m/z.

3-Hydroxy-N-(2-trifluoromethylphenyl)naphthalene-2-carboxamide (**8a**). Yield 49%; Mp. 209-210 °C; IR (Zn/Se ATR, cm^{-1}): 3274w, 1660w, 1626w, 1597w, 1515m, 1466s, 1352w, 1278s, 1217w, 1198*w*, 1146m, 1071w, 956*m*, 874*m*, 833*m*, 788*m*, 748*w*, 722m; HR-MS: for $C_{18}H_{13}NO_2F_3$ $[M+H]^+$ calculated 332.0893 m/z, found 332.0898 m/z.

3-Hydroxy-N-(3-trifluoromethylphenyl)naphthalene-2-carboxamide (**8b**). Yield 64%; Mp. 239-240 °C; IR (Zn/Se ATR, cm^{-1}): 3296w, 3108w, 1626s, 1575m, 1494m, 1428w, 1399w, 1361w, 1327s, 1207m, 1178s, 1148m, 1118s, 1100m, 1076m, 925w, 893m, 867s, 840m, 803s, 771m, 750s, 696s, 680m; ^{1}H-NMR (DMSO-d_6), δ: 11.16 (s, 1H), 10.83 (s, 1H), 8.45 (s, 1H), 8.29 (s, 1H), 7.96 (t, *J*=8.1 Hz, 2H), 7.97 (d, *J*=8.1 Hz, 1H), 7.62 (t, *J*=7.9 Hz, 1H), 7.55-7.47 (m, 2H), 7.40-7.32 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 166.06, 153.46, 139.32, 135.79, 130.45, 129.93, 129.51 (q, *J*=31.3 Hz), 128.63, 128.13, 126.84, 125.76, 124.11 (q, *J*=277.7 Hz), 123.94, 123.76, 122.09, 120.21 (q, *J*=3.8 Hz), 116.47 (q, *J*=3.8 Hz), 110.54; HR-MS: for $C_{18}H_{13}NO_2F_3$ $[M+H]^+$ calculated 332.0893 m/z, found 332.0900 m/z.

3-Hydroxy-N-(4-trifluoromethylphenyl)naphthalene-2-carboxamide (**8c**) [41,44]. Yield 58%; Mp. 281-282 °C; IR (Zn/Se ATR, cm^{-1}): 3292w, 3021w, 1623s, 1548m, 1450m, 1410m, 1324m, 1255w, 1212m, 1175m, 1112s, 1065s, 1016m, 960w, 916w, 873m, 841s, 822m, 791w, 752s, 707m; ^{1}H-NMR (DMSO-d_6), δ: 11.17 (s, 1H), 10.85 (s, 1H), 8.45 (s, 1H), 8.03-7.91 (m, 3H), 7.79-7.72 (m, 3H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.40-7.32 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 165.87, 153.28, 142.15 (d, *J*=1.5 Hz), 135.76, 130.61, 128.64, 128.12, 126.86, 125.98 (q, *J*=3.8 Hz), 125.74, 124.30 (q, *J*=271.2Hz), 123.88 (q, *J*=32.0 Hz), 123.74, 122.28, 120.18, 110.53; HR-MS: for $C_{18}H_{13}NO_2F_3$ $[M+H]^+$ calculated 332.0893 m/z, found 332.0899 m/z.

3-Hydroxy-N-(2-nitrophenyl)naphthalene-2-carboxamide (**9a**). Yield 29%; Mp. 174-175 °C (Mp. 179.5-180 °C [39]); IR (Zn/Se ATR, cm^{-1}): 3240w, 1627m,1581m, 1557w, 1494m, 1450w, 1434w, 1393w, 1341m, 1270m, 1203w, 1147m, 870w, 840m, 771w, 736s, 691w; ^{13}C-NMR (DMSO-d_6), δ: 164.21, 155.98, 152.85, 137.18, 136.17, 132.97, 132.43, 129.16, 128.94, 127.04, 126.62, 125.89, 125.63, 123.75, 120.74, 115.27, 110,75; HR-MS: for $C_{17}H_{13}N_2O_4$ $[M+H]^+$ calculated 309.0870 m/z, found 309.0875 m/z.

3-Hydroxy-N-(3-nitrophenyl)naphthalene-2-carboxamide (**9b**) [55]. Yield 58%; Mp. 250-251 °C; (Mp. 242-244 °C [55]); IR (Zn/Se ATR, cm^{-1}): 3394w, 1658m, 1586m, 1525m, 1463m, 1345s, 1297s, 1230m, 1209m, 1145m, 1033w, 911w, 876m, 808m, 747m, 738s, 668m; ^{1}H-NMR (DMSO-d_6), δ: 11.12 (s, 1H), 10.93 (s, 1H), 8.83 (t, *J*=2.14 Hz, 1H), 8.45 (s, 1H), 8.11 (dd, *J*=8.12 Hz, *J*=1.28 Hz, 1H), 8.01-7.91 (m, 2H), 7.77 (d, *J*=8.1 Hz, 1H), 7.66 (t, *J*=8.1 Hz, 1H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.40-7.32 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ: 166.08, 153.30, 147.95, 139.72, 135.76, 130.48, 130.08, 128.61, 128.12, 126.80, 126.24, 125.76, 123.76, 122.22, 118.32, 114.35, 110.50; HR-MS: for $C_{17}H_{13}N_2O_4$ $[M+H]^+$ calculated 309.0870 m/z, found 309.0876 m/z.

3-Hydroxy-N-(4-nitrophenyl)naphthalene-2-carboxamide (**9c**) [59]. Yield 72%; Mp. 265-266 °C (Mp. 258-259 °C [59]); IR (Zn/Se ATR, cm^{-1}): 3285w, 2981w, 1618s, 1599m, 1568w, 1513s, 1449w, 1407w, 1337s, 1260w, 1210m, 1171m, 1147w, 1112m, 1033m, 916w, 851s, 772w, 747s, 704w; ^{1}H-NMR (DMSO-d_6), δ: 11.10 (s, 1H), 11.03 (s, 1H), 8.41 (s, 1H), 8.28 (d, *J*=9.4 Hz, 2H), 8.03 (d, *J*=9.0 Hz, 2H), 7.93 (d, *J*=8.1Hz, 1H), 7.77 (d, *J*=8.6 Hz, 1H), 7.51 (ddd, *J*=8.1 Hz, *J*=6.8 Hz, *J*=1.3 Hz, 1H), 7.39-7.32 (m, 2H); ^{13}C-NMR (DMSO-d_6), δ:

165.89, 152.98, 144.80, 142.58, 135.76, 130.73, 128.63, 128.15, 126.85, 125.75, 124.82, 123.76, 122.68, 119.79, 110.49; HR-MS: for $C_{17}H_{13}N_2O_4$ $[M+H]^+$ calculated 309.0870 m/z, found 309.0875 m/z.

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

Chloroplasts were prepared from spinach (*Spinacia oleracea* L.) according to Masarovicova and Kralova [60]. 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*. [61], 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 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 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. The results are summarized in Table 1.

Study of chlorophyll a fluorescence in spinach chloroplasts

The fluorescence emission spectra of chlorophyll *a* (Chl*a*) in spinach chloroplasts were recorded on fluorescence spectrophotometer F-2000 (Hitachi, Tokyo, Japan) using excitation wavelength λ_{ex} = 436 nm for monitoring fluorescence of Chl*a*, excitation slit 20 nm and emission slit 10 nm. The samples were kept in the dark for 2 min before measuring. The phosphate buffer used for dilution of the chloroplast suspension was the same as described above. The chlorophyll concentration in chloroplast suspension was 10 mg/L.

In vitro anti-bacterial susceptibility testing

The synthesized compounds were evaluated for *in vitro* antibacterial activity against representatives of multidrug-resistant bacteria, clinical isolates of methicilin resistant *Staphylococcus aureus* (MRSA) 63718, SA 630 and SA 3202 that were obtained from the National Institute of Public Health, Prague, Czech Republic. *Staphylococcus aureus* ATCC 29213 (SA) was used as reference and quality control strain. The broth dilution micro-method modified according to NCCLS guidelines [62,63] in Mueller-Hinton broth (Oxoid, UK) was used to determine the minimum inhibitory concentration (MIC). The evaluated compounds were dissolved in dimethylsulfoxide (DMSO) (Sigma, Germany) and the final concentrations ranging from 256 μg/mL to 0.008 μg/mL were obtained by twofold serial dilution of the stock solution. Ampicillin (APC) and ciprofloxacin (CPX) were used as reference antibacterial drugs. Bacterial inoculum in sterile phosphate buffered saline (pH 7.2–7.3) was prepared to match 0.5 McFarland scale and diluted 1:20. Drug-free controls and sterility controls were included. The determination of results was performed visually after 24 h of static incubation in the darkness at 37°C in an aerobic atmosphere. The MIC was defined as the lowest concentration of the compound at which no visible bacterial growth was observed. The results are shown in Table 1.

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