

PREPARATION OF LAVENDAMYCIN ANALOGUES

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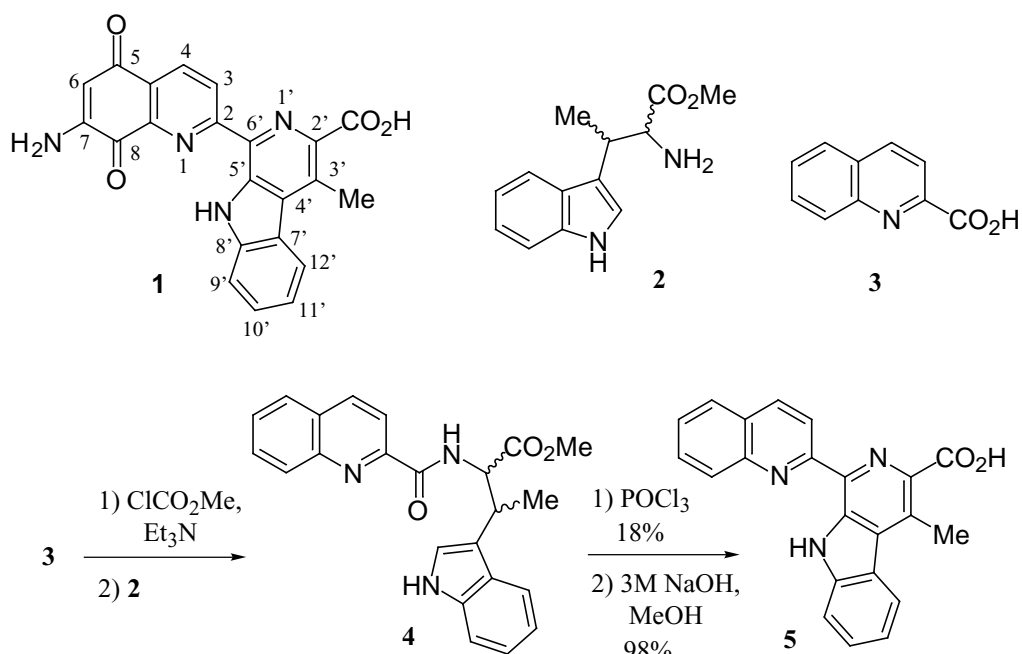
Abstract - A Pictet-Spengler type reaction conducted under modified conditions using a catalytic amount of pyridinium *p*-toluenesulfonate was used to prepare several lavendamycin (**1**) analogues.

Lavendamycin (**1**), a natural product produced by *Streptomyces lavendulae*, was first isolated in 1981^{1,2,3} and shown to possess antimicrobial and cytotoxic properties.² As part of our own research program on new topoisomerase I and topoisomerase II inhibitors, we investigated the ability of lavendamycin to induce topoisomerases I and II mediated cleavage of DNA in *in vitro* models. Thus we discovered that it displayed significant activity against topoisomerase I (MIC = 0.1 µg/mL).⁴ Since such types of inhibitors are scarcely found, we undertook a synthetic chemistry program on its analogues. Because the well established toxicity of lavendamycin seems to be linked to the presence of the quinone function, we focused our synthetic work on analogues of this natural product which do not possess the quinonic moiety. Such analogues were expected to maintain the biological properties of the parent molecule without its toxic side effects.

In order to determine the necessary structural features for the biological activity, we first synthesized the structurally simplified compound (**5**) by amidification of the methyl ester (**2**)⁵ of α -methyltryptophan with 2-quinolinecarboxylic acid (**3**), followed by cyclization in the presence of POCl₃^{5b} and alkaline hydrolysis. In our initial attempt to obtain the cyclized product (**5**) we used the experimental conditions^{5b} previously reported for similar cases (xylene, 4 h at reflux). Surprisingly enough, in our case, only degradation products were obtained. After several additional attempts under milder conditions (toluene, 16 h at reflux), we could isolate the expected compound but in poor yield (18%). Subsequent alkaline hydrolysis afforded acid (**5**). Since significant induction of topoisomerase I cleavable complex mediated by compound (**5**) was observed, this encouraging biological result led us to synthesize additional simplified analogues of lavendamycin, but by another and more efficient method.

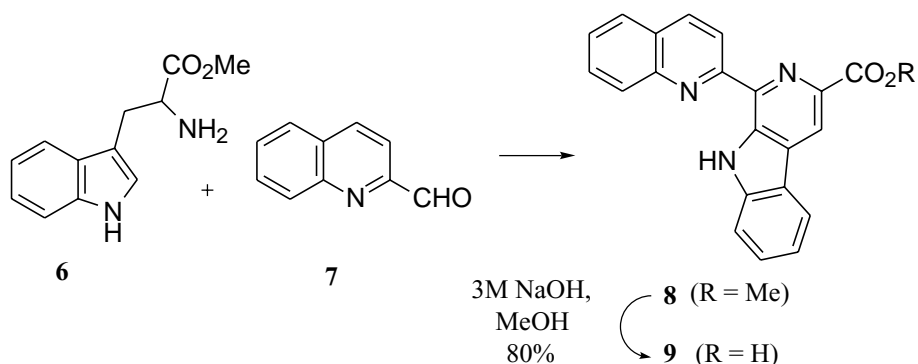
Thus we planned to use a Pictet-Spengler type reaction to prepare **9**, an analogue of **5** without the methyl at the 3' position.^{3a,6} The reaction of the methyl ester (**6**)⁷ of tryptophan with 2-quinolinecarboxaldehyde (**7**) without any catalyst and in refluxing xylene^{3a} led to the methyl ester of the expected product (**8**). The cyclization occurred in moderate yield because of the concomitant formation of

degradation products (see Table 1). We then tried to improve the yield by reducing the reaction time and the temperature and catalyzing the reaction by different acid catalysts. As reported in Table 1, significant



improvements were observed and the best result was obtained in refluxing toluene in the presence of pyridinium *p*-toluenesulfonate.⁸ Subsequent alkaline hydrolysis of compound (8) afforded acid (9) which was then submitted to biological testing. Compound (9) proved to have the same activity as 5 against

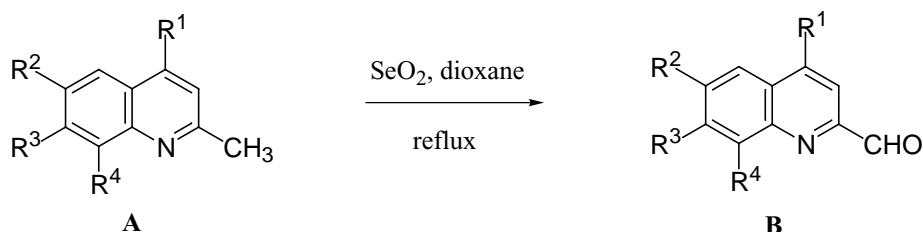
Table 1. Influence of Acid Catalysis in Preparation of Ester (8)



Experimental conditions	Isolated yield (%) of 8
16.5 h, xylene, reflux	35
14 h, toluene, reflux, <i>p</i> -TsOH (1.1 mol.eq.)	26
17 h, toluene, reflux, MeCO ₂ H (2 mol. eq.)	42
6.5 h, toluene, reflux, C ₆ H ₅ NHOTs (0.1 mol. eq.)	60

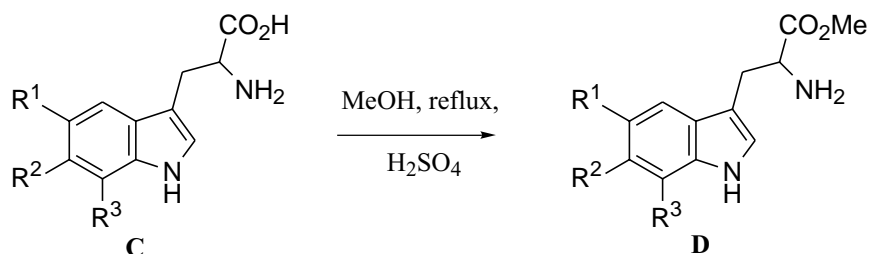
topoisomerase I. This very interesting result led us to pursue this work and to prepare, under identical experimental conditions, additional analogues of **9** with various substituents on the tryptophan and/or the quinoline moiety. The starting aldehydes (**14-17**) were prepared in good yields by oxidation of the suitable 2-methylquinolines using freshly sublimated selenium dioxide⁹ (Table 2). This reaction was efficient but suffered from the inconvenience of using this toxic oxidation reagent and from the difficulties to separate the products from selenium and its derivatives. In addition attempts to use catalytic amounts of selenium dioxide in the presence of *tert*-butyl hydroperoxide¹⁰ or to replace this oxidant by pyridinium chlorochromate¹¹ were fruitless leading to the recovery of the starting materials. Esters (**23-27**) were obtained by reaction of acids (**18-22**) with methanol (Table 3).

Table 2. Oxidation of 2-Methylquinolines



A		B	React. Time	Isolated Yield (%)
10	R ¹ = Cl, R ² = R ³ = R ⁴ = H	14	2.5 h	98
11	R ² = F, R ¹ = R ³ = R ⁴ = H	15	3.5 h	98.5
12	R ³ = Cl, R ¹ = R ² = R ⁴ = H	16	2.5 h	84
13	R ⁴ = Cl, R ¹ = R ² = R ³ = H	17	3.5 h	99

Table 3. Esterification of Substituted Tryptophans

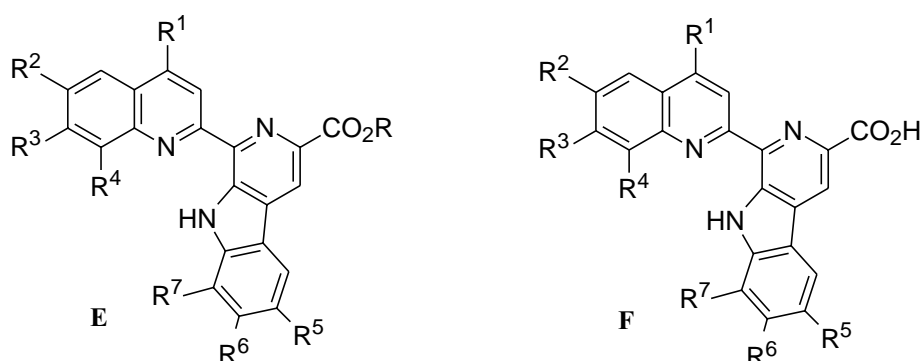


C		D	React. Time	Isolated Yield (%)
18	R ¹ = Me, R ² = R ³ = H	23	15 h	99
19	R ¹ = Ome, R ² = R ³ = H	24	15 h	99
20	R ¹ = F, R ² = R ³ = H	25	12 h	75

21	$R^2 = F, R^1 = R^3 = H$	26	15 h	91
22	$R^3 = Me, R^1 = R^2 = H$	27	8 h	90

The Pictet-Spengler reaction of aldehydes (**14-17**) with esters (**23-27**) in the presence of pyridinium *p*-toluenesulfonate as the catalyst gave esters (**28-38**) in satisfactory yields. Then alkaline hydrolysis of these esters provided lavendamycin analogues (**39-49**) generally in good yields (Table 4).

Table 4. Preparation of Lavendamycin Analogues



E		Time ^a	Yield ^b (%)	F	Time ^a	Yield ^b (%)
28	$R^1 = Cl, R^2 = R^3 = R^4 = R^5 = R^6 = R^7 = H$	8 h	42	39	3 h	90
29	$R^2 = F, R^1 = R^3 = R^4 = R^5 = R^6 = R^7 = H$	10 h	57	40	3.5 h	76
30	$R^3 = Cl, R^1 = R^2 = R^4 = R^5 = R^6 = R^7 = H$	10 h	60	41	4 h	68
31	$R^4 = Cl, R^1 = R^2 = R^3 = R^5 = R^6 = R^7 = H$	8 h	55	42	4 h	77
32	$R^5 = Me, R^1 = R^2 = R^3 = R^4 = R^6 = R^7 = H$	10 h	53	43	3.5 h	95
33	$R^5 = Ome, R^1 = R^2 = R^3 = R^4 = R^6 = R^7 = H$	10 h	52	44	3.5 h	95
34	$R^5 = F, R^1 = R^2 = R^3 = R^4 = R^6 = R^7 = H$	10 h	49	45	3.5 h	85
35	$R^6 = F, R^1 = R^2 = R^3 = R^4 = R^5 = R^7 = H$	10 h	57	46	4 h	60
36	$R^7 = Me, R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$	8 h	55	47	4 h	86
37	$R^1 = Cl, R^2 = R^3 = R^4 = R^5 = R^6 = H, R^7 = Me$	11 h	46	48	4 h	55
38	$R^3 = Cl, R^1 = R^2 = R^4 = R^5 = R^6 = H, R^7 = Me$	8 h	48	49	3.5 h	80

^a Reaction time; ^b Yield (%) of isolated product.

In conclusion, the optimized experimental conditions reported in this paper for the Pictet-Spengler reaction led to a very significant improvement in the yields of preparation of **28-38** with respect to the usual conditions. As illustrated above in the lavendamycin series, this method seems to be general and reproducible. It leads to the expected cyclization products in one step and in satisfactory to fairly good yields, not affected by the electronic effects of the various substituents.

EXPERIMENTAL

^1H (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were recorded on a Bruker AC 400 instrument unless otherwise stated. Multiplicities in the ^{13}C NMR spectra were determined by DEPT experiments. Elemental analyses were performed by the service of microanalyses, CNRS, ICSN, Gif sur Yvette. Most of the products here described are poorly soluble (lavendamycin analogues) or not very stable (**14-17**), and then, although NMR data were coherent, it was either difficult or impossible to get satisfying results for microanalyses. Therefore only high resolution MS are given for aldehydes (**14-17**) and the substituted analogues (**28-49**). They were obtained at the CRMPO (Rennes) with a Varian Mat 311 spectrometer.

Preparation of compounds (4) and (5)

Methyl chloroformate (0.55 mL, 7.20 mmol) was added with stirring and under argon to a cooled solution (0°C) of 2-quinolinecarboxylic acid (**3**) (1.25 g, 7.20 mmol) in a mixture of THF (30 mL) and Et_3N (1 mL). After 0.5 h, methyl ester of α -methyltryptophan, as a mixture of racemic both diastereomers (**2**)⁵ (2 g, 8.66 mmol), in THF solution (30 mL) was added quickly at the same temperature. The cooling bath was removed and the reaction was allowed to proceed for 4 h. Evaporation then column flash chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99:1) provided **4** as a white solid (2.7 g, 97%, for the mixture of both diastereomers in the 60/40 ratio, mp $70-73^\circ\text{C}$). ^1H NMR (CDCl_3) δ 1.54 and 1.61 (d, 3H, $J = 7.2$ Hz), 3.61 and 3.65 (s, 3H), 3.84 and 4.04 (m, 1H), 5.19 (m, 1H), 7.08-7.25 (m, 3H), 7.38 (dd, 1H, $J = 17.0, 8.1$ Hz), 7.58-7.80 (m, 4H), 7.88 (d, 1H, $J = 8.1$ Hz), 8.04-8.32 (m, 4H), 8.78 and 8.84 (br d, 1H, NH, $J = 9.3$ Hz); ^{13}C NMR (CDCl_3) δ 17.26 and 18.49 (CH_3), 34.07 and 34.15 (CH), 52.15 and 52.20 (CH_3), 57.16 and 57.61 (CH), 111.20-149.30 (17 arom. C), 164.34 and 164.66 (CO), 171.98 and 172.05 (CO); IR 3300, 1730, 1670 cm^{-1} ; HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3$: 387.1583. Found: 387.1571; Anal. Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_3 \cdot 0.2\text{H}_2\text{O}$: C, 70.65; H, 5.52; N, 10.75. Found: C, 70.65; H, 5.72; N, 10.61.

POCl_3 (7.5 mL, 80.5 mmol) was added at rt under argon and with stirring to a solution of compound (**4**) (740 mg, 1.91 mmol) in toluene (50 mL). Reaction mixture was heated to reflux and then stirred for 16 h at this temperature. Cooling, pouring into iced water (100 mL) with vigorous stirring, adding of aqueous saturated Na_2CO_3 to attain pH 8, decantation, extraction (CH_2Cl_2 , 3×50 mL) and evaporation yielded a brown oil that was heated with refluxing ethanol (5 mL). Cooling led to a solid. Filtration and washing with ethanol provided the expected methyl ester as brown crystals (124 mg, 18%, mp $196-198^\circ\text{C}$). ^1H NMR (CDCl_3) δ 3.22 (s, 3H), 4.09 (s, 3H), 7.37 (t, 1H, $J = 7.5$ Hz), 7.58-7.66 (m, 2H), 7.74-7.82 (m, 2H), 7.89 (d, 1H, $J = 8.0$ Hz), 8.27 (d, 1H, $J = 8.4$ Hz), 8.32 (d, 1H, $J = 8.7$ Hz), 8.37 (d, 1H, $J = 8.0$ Hz), 8.94 (d, 1H, $J = 8.7$ Hz), 12.00 (br s, 1H, NH); IR 1715 cm^{-1} ; HRMS Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2$ 367.1321. Found 367.1315; Anal. Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 73.39; H, 4.82. Found: C, 73.46; H, 4.95. This methyl ester (124 mg, 0.34 mmol) was added to 5 mL of MeOH and 1 mL of 3M aqueous solution of NaOH. Reaction mixture was stirred for 2 h at reflux and 12 h at rt. Aqueous 50% HCl was added and the crude solid was separated by filtration and then purified by washing with water. Drying provided pure **5** as white crystals (118 mg, 98%, mp $233-235^\circ\text{C}$). ^1H NMR ($\text{DMSO}-d_6$) δ 3.22 (s, 3H) 7.42 (m 1H), 7.71 (m, 2H), 7.92 (m, 1H), 8.09 (d, 1H, $J = 7.8$ Hz), 8.13 (d, 1H, $J = 8.2$ Hz), 8.43 (d, 1H, $J = 8.0$ Hz), 8.60 (d, 1H, $J = 8.7$ Hz), 8.75 (d, 1H, $J = 8.4$ Hz), 8.98 (d, 1H, $J = 8.7$ Hz), 12.40 (br s, 1H, NH), 12.70 (br s, 1H, OH); ^{13}C NMR ($\text{DMSO}-d_6$) δ 16.54, 113.73, 119.35, 120.82, 121.49, 123.85, 127.32, 127.65, 128.00, 128.35, 129.80, 129.88, 129.92, 131.19, 134.56 (2C), 136.80, 137.11, 142.53, 146.53, 156.64, 167.98; IR 3363, 1747 cm^{-1} ; HRMS Calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_2$: 353.1164, Found: 353.1152; Anal. Calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3\text{O}_2 \cdot 1.2\text{H}_2\text{O}$: C, 70.47; H, 4.68; N, 11.21. Found: C, 70.68; H, 4.54; N, 10.98.

Tryptophan methyl ester (6)

Sulfuric acid (1.5 mL of the 18 M reagent) was added dropwise and with stirring to a solution of L-(-)-tryptophan (2.04 g, 10 mmol) in MeOH (25 mL). Reaction mixture was heated to reflux and then stirred for 15 h at this temperature. Cooling, evaporation, adding of aqueous saturated NaHCO_3 to attain pH 7, decantation, extraction (CH_2Cl_2 , 4×20 mL), drying (MgSO_4) and evaporation left **6** as an oil which

crystallized slowly on standing thus leading to the pure product (1.85 g, 85%, mp 87°C (lit.,⁷ 89.5°C)). ¹H NMR (CDCl₃) δ 1.60 (br s, 2H, NH₂), 3.05 (dd, 1H, *J* = 14.3, 7.6 Hz), 3.28 (dd, 1H, *J* = 14.3, 4.9 Hz), 3.71 (s, 3H), 3.84 (dd, 1H, *J* = 7.6, 4.9 Hz), 7.05 (d, 1H, *J* = 2.0 Hz), 7.12 (m, 1H), 7.19 (m, 1H), 7.35 (d, 1H, *J* = 8.2 Hz), 7.62 (d, 1H, *J* = 7.9 Hz), 8.27 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 30.55 (CH₂), 51.81 (CH₃), 54.66 (CH), 110.15 (quat. C), 111.16 (CH), 118.33 (CH), 119.04 (CH), 121.65 (CH), 123.07 (CH), 127.14 (quat. C), 136.12 (quat. C), 175.54 (CO); IR 3456, 3344, 1731 cm⁻¹.

Preparation of compounds (8) and (9)

A solution of 2-quinolinecarboxaldehyde (**7**) (157 mg 1 mmol) in toluene (6 mL) was added with stirring and under argon to a solution of tryptophan methyl ester (**6**) (218 mg, 1 mmol) in toluene (6 mL). Pyridinium tosylate (25 mg, 0.1 mmol) was added and the reaction mixture was heated to reflux and then stirred for 6.5 h at this temperature. A yellow precipitate corresponding to **8** appeared on cooling and was separated from solution by filtration. Evaporation of the toluene solution led to an oil. Column flash chromatography (CH₂Cl₂) led to **8** as a yellow solid which was mixed to the previous one (212 mg, 60%, mp 221-222 °C). ¹H NMR (CDCl₃) δ 4.12 (s, 3H) 7.41 (dd, 1H, *J* = 7.9, 7.9 Hz), 7.61-7.69 (m, 2H), 7.76 (m, 1H), 7.83 (m, 1H), 7.93 (d, 1H, *J* = 8.1 Hz), 8.27 (d, 1H, *J* = 7.9 Hz), 8.32 (d, 1H, *J* = 8.4 Hz), 8.39 (d, 1H, *J* = 8.7 Hz), 9.00 (s, 1H), 9.05 (d, 1H, *J* = 8.7 Hz), 12.00 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 52.55 (CH₃), 112.25 (CH), 118.44 (CH), 119.48 (CH), 120.79 (CH), 121.41 (quat. C), 121.80 (CH), 126.88 (CH), 127.83 (CH), 127.92 (quat. C), 128.86 (CH), 129.03 (CH), 129.62 (CH), 130.44 (quat. C), 136.45 (quat. C), 136.52 (quat. C), 136.61 (CH), 137.23 (quat. C), 140.81 (quat. C), 147.03 (quat. C), 157.28 (quat. C), 166.62 (CO); IR 3326, 1731 cm⁻¹; HRMS Calcd for C₂₂H₁₅N₃O₂: 353.1164. Found: 353.1152; Anal. Calcd for C₂₂H₁₅N₃O₂·1.5H₂O: C, 69.46; H, 4.77. Found: C, 69.61; H, 5.09. This methyl ester was saponified in the same experimental conditions as for obtaining **5**. Pure acid (**9**) was thus obtained as a white solid (80%, mp 145-148 °C). ¹H NMR (DMSO-d₆) δ 7.44 (m, 1H), 7.75 (m 2H), 7.97 (m, 1H), 8.13 (m, 2H), 8.54 (d, 1H, *J* = 7.7 Hz), 8.66 (d, 1H, *J* = 8.7 Hz), 8.84 (d, 1H, *J* = 8.4 Hz), 9.12 (d, 1H, *J* = 8.7 Hz), 9.15 (s, 1H), 12.40 (br s, 1H, NH); IR 3363, 1747 cm⁻¹; HRMS Calcd for C₂₁H₁₃N₃O₂: 339.1008. Found: 339.1015; Anal. Calcd for C₂₁H₁₃N₃O₂·0.8H₂O: C, 71.30; H, 4.16; N, 11.88. Found: C, 71.26; H, 4.29; N, 11.72.

Preparation of aldehydes (14-17)

A mixture of 4-chloro-2-methylquinoline (**10**) (492 mg, 2.77 mmol), in dry dioxane solution (20 mL), and of freshly sublimated SeO₂ (369 mg, 3.32 mmol) was heated to reflux with stirring. Reaction was allowed to proceed for 2.5 h. Cooling, filtration, evaporation then column flash chromatography (CH₂Cl₂) led to **14** as a white solid (2.71 mg, 98 %, mp 145-146°C). ¹H NMR (CDCl₃) δ 7.73 (ddd, 1H, *J* = 8.4, 7.0, 1.3 Hz), 7.82 (ddd, 1H, *J* = 8.4, 7.0, 1.4 Hz), 8.02 (s, 1H), 8.21 (d, 1H, *J* = 8.4 Hz), 8.24 (d, 1H, *J* = 8.4 Hz), 10.11 (s, 1H); ¹³C NMR (CDCl₃) δ 117.50 (CH), 124.35 (CH), 127.97 (quat. C), 130.15 (CH), 130.80 (CH), 131.25 (CH), 144.12 (quat. C), 148.59 (quat. C), 152.27 (quat. C), 192.51 (CHO); IR 3091, 1708 cm⁻¹; MS (EI) *m/z* (rel. Int.) 193 (M⁺, 14), 191 (M⁺, 41), 165 (22), 163 (72), 128 (100), 127 (21), 126 (16), 101 (21); HRMS Calcd for C₁₀H₆NO³⁵Cl; 191.0138. Found: 191.0138.

Aldehydes (**15-17**) were obtained from **11-13** in the same experimental conditions as for **14** (reaction times are indicated in table 2). Data for **15**: white solid, yield: 98.5 %, mp 128.5-129.5°C; ¹H NMR (CDCl₃) δ 7.53 (dd, 1H, *J* = 8.7, 2.8 Hz), 7.61 (ddd, 1H, *J* = 9.0, 8.4, 2.8 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 8.26 (dd, 1H, *J* = 9.0, 5.4 Hz), 8.28 (d, 1H, *J* = 8.7 Hz), 10.21 (s, 1H); ¹³C NMR (CDCl₃) δ 111.01 (CH, *J*_{C/F} = 22.1 Hz), 118.11 (CH), 121.02 (CH, *J*_{C/F} = 26.0 Hz), 131.01 (quat. C, *J*_{C/F} = 9.9 Hz), 133.16 (CH, *J*_{C/F} = 9.1 Hz), 136.68 (CH, *J*_{C/F} = 5.3 Hz), 145.02 (quat. C), 152.15 (CH, *J*_{C/F} = 3.05 Hz), 162.01 (quat. C, *J*_{C/F} = 253.3 Hz), 193.36 (CHO); ¹⁹F NMR (CDCl₃) δ -108.89 (ddd, 1F, *J* = 8.4, 8.4, 5.4 Hz); IR 3050, 1698 cm⁻¹; MS (EI) *m/z* (rel. Int.) 175 (M⁺, 70), 148 (9), 147 (100), 146 (46), 126 (17), 120 (33), 119 (11), 99 (12); HRMS Calcd for C₁₀H₆NOF: 175.0433. Found: 175.0426. Data for **16**: white solid, yield: 84 %, mp 154°C; ¹H NMR (CDCl₃) δ 7.65 (dd, 1H, *J* = 8.7, 2.0 Hz), 7.86 (d, 1H, *J* = 8.7 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 8.26 (br d, 1H, *J* = 2.0 Hz), 8.31 (d, 1H, *J* = 8.4 Hz), 10.20 (s, 1H);

^{13}C NMR (CDCl_3) δ 117.48 (CH), 128.30 (quat. C), 128.97 (CH), 129.25 (CH), 130.13 (CH), 136.42 (quat. C), 137.24 (CH), 148.22 (quat. C), 153.23 (quat. C), 193.39 (CHO); IR 3073, 1698 cm^{-1} ; MS (EI) m/z (rel. Int.) 193 (M^+ , 19), 191 (M^+ , 64), 165 (29), 163 (100), 162 (31), 128 (43), 127 (19), 126 (18); HRMS Calcd for $\text{C}_{10}\text{H}_6\text{NO}^{35}\text{Cl}$: 191.0138. Found: 191.0138. Data for **17**: white solid, yield: 99 %, mp 148-149 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 7.60 (dd, 1H, $J = 8.4, 7.8$ Hz), 7.82 (dd, 1H, $J = 8.4, 1.4$ Hz), 7.92 (dd, 1H, $J = 7.8, 1.4$ Hz), 8.08 (d, 1H, $J = 8.4$ Hz), 8.33 (d, 1H, $J = 8.4$ Hz), 10.29 (s, 1H); ^{13}C NMR (CDCl_3) (50 MHz) δ 117.95 (CH), 126.84 (CH), 128.97 (CH), 130.51 (CH), 131.22 (quat. C), 134.68 (quat. C), 137.88 (CH), 144.09 (quat. C), 152.71 (quat. C), 193.27 (CHO); IR 3050, 1698 cm^{-1} ; MS (EI) m/z (rel. Int.) 193 (M^+ , 28), 191 (M^+ , 81), 165 (33), 163 (100), 162 (30), 128 (36), 127 (32), 126 (23); HRMS Calcd for $\text{C}_{10}\text{H}_6\text{NO}^{35}\text{Cl}$: 191.0138. Found: 191.0142.

Preparation of esters (23-27)

Esters (**23-27**) were obtained from **18-22** in the same experimental conditions as for **6** (reaction times are indicated in Table 3). Data for **23**: pale brown oil, yield: 99 %; ^1H NMR (CDCl_3) δ 1.65 (br s, 2H, NH_2), 2.45 (s, 3H), 3.01 (dd, 1H, $J = 14.3, 7.8$ Hz), 3.26 (dd, 1H, $J = 14.3, 4.6$ Hz), 3.72 (s, 3H), 3.83 (dd, 1H, $J = 7.8, 4.6$ Hz), 6.97-7.02 (m, 2H), 7.22 (d, 1H, $J = 8.3$ Hz), 7.38 (s, 1H), 8.28 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 21.39 (CH_3), 30.67 (CH_2), 51.95 (CH_3), 54.83 (CH), 110.38 (quat. C), 110.86 (CH), 118.28 (CH), 123.10 (CH), 123.69 (CH), 127.60 (quat. C), 128.66 (quat. C), 134.56 (quat. C), 175.72 (CO_2Me); IR 3450-3363, 3108, 1739 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.51; H, 6.94; N, 12.04. Data for **24**: pale brown oil which crystallized slowly on standing, yield: 99 %, mp 109-110 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.62 (br s, 2H, NH_2), 3.03 (dd, 1H, $J = 14.4, 7.6$ Hz), 3.24 (dd, 1H, $J = 14.4, 4.9$ Hz), 3.72 (s, 3H), 3.83 (dd, 1H, $J = 7.6, 4.9$ Hz), 3.86 (s, 3H), 6.86 (dd, 1H, $J = 8.8, 2.4$ Hz), 7.03 (br d, 1H, $J = 2.2$ Hz), 7.05 (br d, 1H, $J = 2.4$ Hz), 7.24 (d, 1H, $J = 8.8$ Hz), 8.06 (br s, NH); ^{13}C NMR (CDCl_3) δ 30.63 (CH_2), 51.98 (CH_3), 55.84 (CH), 55.85 (CH_3), 100.44 (CH), 110.52 (quat. C), 111.92 (CH), 112.21 (CH), 123.73 (CH), 127.76 (quat. C), 131.37 (quat. C), 153.94 (quat. C), 175.73 (CO_2Me); IR 3367-3313, 3124, 1729 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.98; H, 6.74; N, 11.02. Data for **25**: pale brown solid, yield: 75 %, mp 86 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.65 (br s, 2H, NH_2), 3.03 (dd, 1H, $J = 14.4, 7.4$ Hz), 3.21 (dd, 1H, $J = 14.4, 4.9$ Hz), 3.72 (s, 3H), 3.81 (dd, 1H, $J = 7.4, 4.9$ Hz), 6.93 (ddd, 1H, $J = 9.2, 9.0, 2.5$ Hz), 7.09 (br d, 1H, $J = 2.3$ Hz), 7.24 (m, 2H), 8.27 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 30.55 (CH_2), 52.03 (CH_3), 54.73 (CH), 103.55 (CH, $J_{\text{C/F}} = 23.6$ Hz), 110.45 (CH, $J_{\text{C/F}} = 26.4$ Hz), 111.05 (quat. C, $J_{\text{C/F}} = 5.0$ Hz), 111.84 (CH, $J_{\text{C/F}} = 9.6$ Hz), 124.76 (CH), 127.77 (quat. C, $J_{\text{C/F}} = 9.7$ Hz), 132.71 (quat. C), 157.76 (quat. C, $J_{\text{C/F}} = 233.0$ Hz), 175.71 (CO_2Me); ^{19}F NMR (CDCl_3) δ -125.09 (ddd, 1F, $J = 9.2, 9.2, 4.4$ Hz); IR 3473-3376, 3018, 1733 cm^{-1} ; Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2\text{F}$: C, 61.01; H, 5.55; N, 11.86. Found: C, 61.15; H, 5.62; N, 11.67. Data for **26**: colorless oil that crystallized slowly on standing, yield: 91 %, mp 154 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.62 (br s, 2H, NH_2), 3.05 (dd, 1H, $J = 14.4, 7.5$ Hz), 3.24 (dd, 1H, $J = 14.4, 4.9$ Hz), 3.71 (s, 3H), 3.82 (dd, 1H, $J = 7.5, 4.9$ Hz), 6.89 (ddd, 1H, $J = 9.5, 8.8, 2.2$ Hz), 7.02-7.05 (m, 2H), 7.51 (dd, 1H, $J = 8.8, 5.3$ Hz), 8.13 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 30.60 (CH_2), 50.04 (CH_3), 67.05 (CH), 97.48 (CH, $J_{\text{C/F}} = 26.0$ Hz), 108.28 (CH, $J_{\text{C/F}} = 24.8$ Hz), 111.21 (quat. C), 119.46 (CH, $J_{\text{C/F}} = 10.2$ Hz), 123.12 (CH, $J_{\text{C/F}} = 3.4$ Hz), 124.04 (quat. C), 136.15 (quat. C, $J_{\text{C/F}} = 12.8$ Hz), 160.01 (quat. C, $J_{\text{C/F}} = 237.6$ Hz), 175.65 (CO_2Me); ^{19}F NMR (CDCl_3) δ -121.53 (ddd, 1F, $J = 9.5, 9.5, 5.3$ Hz); IR 3369-3305, 2952, 1733 cm^{-1} ; Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_2\text{F}$: C, 61.01; H, 5.55; N, 11.86; F, 8.04. Found: C, 60.86; H, 5.54; N, 11.91; F, 7.77. Data for **27**: pale brown oil that crystallized slowly on standing, yield: 90 %, mp 108-109 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 1.60 (br s, 2H, NH_2), 2.45 (s, 3H), 3.04 (dd, 1H, $J = 14.4, 7.7$ Hz), 3.28 (dd, 1H, $J = 14.4, 4.8$ Hz), 3.71 (s, 3H), 3.83 (dd, 1H, $J = 7.7, 4.8$ Hz), 6.98-7.06 (m, 3H), 7.46 (d, 1H, $J = 7.8$ Hz), 8.14 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 16.52 (CH_3), 30.84 (CH_2), 51.96 (CH_3), 54.91 (CH), 111.49 (quat. C), 116.38 (CH), 119.68 (CH), 120.39 (quat. C), 122.60 (CH), 122.65 (CH), 126.95 (quat. C), 135.84 (quat. C), 175.83 (CO_2Me); IR 3450-3378, 3150, 1735 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.34; H, 6.92; N, 11.99.

Preparations of esters (28-38) and of acids (39-49)

The experimental conditions were the same as for **8** and **9** (reaction times are indicated in Table 4). Data for **28**: yellow solid, yield : 42 %, mp 225-227°C. ¹H NMR (CDCl₃) δ 4.20 (s, 3H), 7.37 (ddd, 1H, *J* = 7.9, 7.9, 1.2 Hz), 7.61-7.69 (m, 3H), 7.83 (ddd, 1H, *J* = 8.3, 8.3, 1.3 Hz), 8.18 (d, 1H, *J* = 7.9 Hz), 8.23 (d, 1H, *J* = 8.4 Hz), 8.27 (dd, 1H, *J* = 8.3, 1.0 Hz), 8.88 (s, 1H), 9.02 (s, 1H), 11.63 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 52.55 (CH₃), 112.20 (CH), 118.58 (CH), 119.34 (CH), 120.91 (CH), 121.25 (quat. C), 121.77 (CH), 124.25 (CH), 125.96 (quat. C), 127.70 (CH), 128.97 (CH), 129.25 (CH), 130.44 (CH), 130.55 (quat. C), 135.94 (quat. C), 136.23 (quat. C), 136.67 (quat. C), 140.69 (quat. C), 143.25 (quat. C), 147.71 (quat. C), 157.05 (quat. C), 166.39 (CO₂Me); IR 3363, 1716 cm⁻¹; MS (EI) *m/z* (rel. Int.) 389 (M⁺, 36), 388 (27), 387 (M⁺, 100), 331 (35), 329 (94), 330 (28), 327 (31), 293 (32); HRMS Calcd for C₂₂H₁₄N₃O₂³⁵Cl: 387.0774. Found: 387.0774. Data for **29**: pale yellow solid, yield: 57 %, mp 241°C. ¹H NMR (CDCl₃) δ 4.10 (s, 3H), 7.37 (dd, 1H, *J* = 7.8, 6.8 Hz), 7.61-7.69 (m, 3H), 7.47 (dd, 1H, *J* = 8.7, 2.6 Hz), 7.54 (ddd, 1H, *J* = 8.7, 8.7, 2.6 Hz), 7.61-7.68 (m, 2H), 8.19-8.24 (m, 3H), 8.88 (s, 1H), 8.97 (d, 1H, *J* = 8.7 Hz), 11.66 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 53.42 (CH₃), 111.08 (CH, *J*_{C/F} = 21.9 Hz), 112.27 (CH), 118.59 (CH), 119.91 (CH, *J*_{C/F} = 25.9 Hz), 120.34 (CH), 120.96 (CH), 121.46 (quat. C), 121.91 (CH), 128.66 (quat. C, *J*_{C/F} = 10.4 Hz), 129.03 (CH), 130.63 (quat. C), 131.45 (CH, *J*_{C/F} = 9.1 Hz), 136.10 (CH, *J*_{C/F} = 5.3 Hz), 136.39 (quat. C), 136.78 (quat. C), 137.08 (quat. C), 140.84 (quat. C), 144.13 (quat. C), 156.90 (quat. C, *J*_{C/F} = 2.8 Hz), 160.70 (quat. C, *J*_{C/F} = 248.9 Hz), 166.60 (CO₂Me); ¹⁹F NMR (CDCl₃) δ -112.84 (ddd, 1F, *J* = 8.7, 8.7, 5.3 Hz); IR 3351, 3054, 1714 cm⁻¹; MS (EI) *m/z* (rel. Int.) 372 (27), 371 (M⁺, 100), 314 (16), 313 (86), 312 (40), 311 (28), 28 (28); HRMS Calcd for C₂₂H₁₄N₃O₂F: 371.1070. Found: 371.1083. Data for **30**: pale yellow solid, yield: 60 %, mp 276-277°C. ¹H NMR (CDCl₃) δ 4.12 (s, 3H), 7.41 (dd, 1H, *J* = 7.8, 7.2 Hz), 7.57 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.68 (ddd, 1H, *J* = 7.4, 7.2, 0.9 Hz), 7.77 (d, 1H, *J* = 8.3 Hz), 7.85 (d, 1H, *J* = 8.6 Hz), 8.26 (d, 1H, *J* = 7.8 Hz), 8.31 (br d, 1H, *J* = 2.0 Hz), 8.35 (d, 1H, *J* = 8.7 Hz), 8.98 (s, 1H), 9.04 (d, 1H, *J* = 8.7 Hz), 11.76 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 52.62 (CH₃), 112.35 (CH), 118.68 (CH), 119.79 (CH), 120.99 (CH), 121.39 (quat. C), 121.87 (CH), 126.26 (quat. C), 127.81 (CH), 127.93 (quat. C), 129.04 (CH), 129.08 (CH), 130.70 (quat. C), 135.53 (quat. C), 136.43 (CH), 136.47 (CH), 136.72 (quat. C), 136.78 (quat. C), 140.84 (quat. C), 147.38 (quat. C), 158.28 (quat. C), 166.52 (CO₂Me); IR 3355, 3058, 1735 cm⁻¹; MS (EI) *m/z* (rel. Int.) 389 (M⁺, 35), 388 (20), 387 (M⁺, 100), 330 (17), 329 (64), 328 (31), 327 (22), 168.5 (17); HRMS Calcd for C₂₂H₁₄N₃O₂³⁵Cl: 387.0774. Found: 387.0770. Data for **31**: pale yellow solid, yield: 55 %, mp 237-240°C. ¹H NMR (CDCl₃) δ 4.12 (s, 3H), 7.39 (ddd, 1H, *J* = 8.4, 7.4, 1.0 Hz), 7.55 (dd, 1H, *J* = 7.9, 7.4 Hz), 7.66 (ddd, 1H, *J* = 6.9, 6.9, 1.0 Hz), 7.73 (d, 1H, *J* = 8.4 Hz), 7.86 (dd, 1H, *J* = 7.9, 1.0 Hz), 7.95 (dd, 1H, *J* = 7.4, 1.0 Hz), 8.26 (d, 1H, *J* = 7.9 Hz), 8.40 (d, 1H, *J* = 8.9 Hz), 9.00 (s, 1H), 9.08 (d, 1H, *J* = 8.9 Hz), 12.43 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 52.60 (CH₃), 112.35 (CH), 118.82 (CH), 119.98 (CH), 120.83 (CH), 121.35 (quat. C), 121.79 (CH), 126.69 (CH), 126.87 (CH), 128.93 (CH), 129.06 (quat. C), 129.43 (CH), 130.64 (quat. C), 133.07 (quat. C), 136.52 (quat. C), 136.57 (quat. C), 136.75 (quat. C), 136.91 (CH), 141.21 (quat. C), 143.03 (quat. C), 157.38 (quat. C), 166.58 (CO₂Me); IR 3326, 3046, 1714 cm⁻¹; MS (EI) *m/z* (rel. Int.) 389 (M⁺, 34), 387 (M⁺, 96), 331 (35), 330 (32), 329 (100), 328 (30), 293 (25), 292 (28); HRMS Calcd for C₂₂H₁₄N₃O₂³⁵Cl: 387.0774. Found: 387.0770. Data for **32**: pale yellow solid, yield: 53 %, mp 197-199°C. ¹H NMR (CDCl₃) δ 2.49 (s, 3H), 4.06 (s, 3H), 7.34 (dd, 1H, *J* = 8.3, 1.3 Hz), 7.45 (d, 1H, *J* = 8.3 Hz), 7.52 (ddd, 1H, *J* = 7.8, 7.0, 0.9 Hz), 7.71 (ddd, 1H, *J* = 8.3, 7.0, 1.3 Hz), 7.79 (d, 1H, *J* = 8.0 Hz), 7.84 (s, 1H), 8.11 (d, 1H, *J* = 8.3 Hz), 8.21 (d, 1H, *J* = 8.6 Hz), 8.72 (s, 1H), 8.87 (d, 1H, *J* = 8.6 Hz), 11.55 (br s, 1H, NH); ¹³C NMR (CDCl₃) δ 52.42 (CH₃), 53.40 (CH₃), 111.74 (CH), 118.27 (CH), 119.35 (CH), 121.32 (CH), 121.40 (quat. C), 126.71 (CH), 127.72 (CH), 127.77 (quat. C), 128.94 (CH), 129.47 (CH), 130.03 (quat. C), 130.12 (quat. C), 130.23 (CH), 136.19 (quat. C), 136.39 (quat. C), 136.46 (CH), 136.88 (quat. C), 138.89 (quat. C), 146.91 (quat. C), 157.22 (quat. C), 166.54 (CO₂Me); IR 3351, 1729 cm⁻¹; MS (EI) *m/z* (rel. Int.) 368 (24), 367 (M⁺, 100), 310 (15), 309 (68), 308 (27), 307 (33), 306 (25), 153 (26); HRMS Calcd for C₂₃H₁₇N₃O₂: 367.1321. Found: 367.1335. Data for **33**: pale yellow solid, yield: 52 %, mp 215-216°C. ¹H NMR (CDCl₃) δ 3.95 (s, 3H), 4.09 (s, 3H), 7.27

(dd, 1H, $J = 8.8, 2.4$ Hz), 7.57-7.62 (m, 3H), 7.80 (ddd, 1H, $J = 7.0, 7.0, 1.2$ Hz), 7.89 (d, 1H, $J = 7.8$ Hz), 8.26 (d, 1H, $J = 8.4$ Hz), 8.34 (d, 1H, $J = 8.7$ Hz), 8.90 (s, 1H), 9.01 (d, 1H, $J = 8.7$ Hz), 11.78 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 52.56 (CH_3), 55.87 (CH), 103.41 (CH), 113.12 (CH), 118.54 (CH), 119.00 (CH), 119.56 (CH), 121.90 (quat. C), 126.92 (CH), 127.56 (CH and quat. C), 129.08 (CH), 129.68 (CH), 130.27 (quat. C), 135.71 (quat. C), 136.13 (quat. C), 136.66 (CH), 136.95 (quat. C), 137.38 (quat. C), 147.11 (quat. C), 154.71 (quat. C), 157.38 (quat. C), 166.69 (CO_2Me); IR 3355, 2950, 1704 cm^{-1} ; MS (EI) m/z (rel. Int.) 384 (45), 383 (M^+ , 100), 369 (14), 368 (61), 308 (45), 280 (21), 191.5 (12), 140.5 (12); HRMS Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2$: 383.1270. Found: 383.1285. Data for **34**: pale yellow solid, yield : 49 %, mp 228-230°C. ^1H NMR (CDCl_3) δ 4.08 (s, 3H), 7.35 (ddd, 1H, $J = 8.9, 8.9, 2.4$ Hz), 7.58 (m, 2H), 7.77 (m, 2H), 7.85 (d, 1H, $J = 8.0$ Hz), 8.18 (d, 1H, $J = 8.4$ Hz), 8.28 (d, 1H, $J = 8.7$ Hz), 8.78 (s, 1H), 8.92 (d, 1H, $J = 8.7$ Hz), 11.78 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 52.64 (CH_3), 107.33 (CH, $J_{\text{C/F}} = 23.8$ Hz), 113.16 (CH, $J_{\text{C/F}} = 8.9$ Hz), 117.24 (CH, $J_{\text{C/F}} = 25.9$ Hz), 118.67 (CH), 119.54 (CH), 121.98 (quat. C, $J_{\text{C/F}} = 9.5$ Hz), 127.08 (CH), 127.95 (CH), 128.05 (quat. C), 129.05 (CH), 129.80 (CH), 130.08 (quat. C, $J_{\text{C/F}} = 4.6$ Hz), 136.63 (quat. C), 136.81 (CH), 137.05 (quat. C), 137.45 (quat. C), 137.72 (quat. C), 147.08 (quat. C), 157.16 (quat. C), 158.01 (quat. C, $J_{\text{C/F}} = 236.8$ Hz), 166.48 (CO_2Me); ^{19}F NMR (CDCl_3) δ -122.31 (ddd, 1F, $J = 8.7, 8.7, 4.2$ Hz); IR 3357, 3070, 1720 cm^{-1} ; MS (EI) m/z (rel. Int.) 372 (27), 371 (M^+ , 100), 313 (63), 312 (27), 311 (40), 310 (13), 156 (34), 155.5 (31); HRMS Calcd for $\text{C}_{22}\text{H}_{14}\text{N}_3\text{O}_2\text{F}$: 371.1070. Found: 371.1083. Data for **35**: pale yellow solid, yield : 57 %, mp 246-247°C; ^1H NMR (CDCl_3) δ 4.12 (s, 3H), 7.13 (ddd, 1H, $J = 9.2, 8.7, 2.1$ Hz), 7.41 (dd, 1H, $J = 9.2, 2.1$ Hz), 7.63 (dd, 1H, $J = 7.6, 7.5$ Hz), 7.83 (dd, 1H, $J = 7.9, 7.8$ Hz), 7.92 (d, 1H, $J = 7.8$ Hz), 8.18 (dd, 1H, $J = 8.7, 5.3$ Hz), 8.29 (d, 1H, $J = 7.9$ Hz), 8.38 (d, 1H, $J = 8.7$ Hz), 8.91 (s, 1H), 9.02 (d, 1H, $J = 8.7$ Hz), 11.99 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 52.62 (CH_3), 98.92 (CH, $J_{\text{C/F}} = 26.6$ Hz), 109.59 (CH, $J_{\text{C/F}} = 24.9$ Hz), 117.90 (quat. C), 117.98 (CH), 119.46 (CH), 123.09 (CH, $J_{\text{C/F}} = 10.7$ Hz), 127.01 (CH), 127.90 (CH), 127.98 (quat. C), 129.00 (CH), 129.77 (CH), 130.14 (quat. C), 136.75 (CH), 136.97 (quat. C), 137.14 (quat. C), 137.24 (quat. C), 141.56 (quat. C, $J_{\text{C/F}} = 12.6$ Hz), 147.00 (quat. C), 157.12 (quat. C), 163.65 (quat. C, $J_{\text{C/F}} = 246.4$ Hz) 166.48 (CO_2Me); ^{19}F NMR (CDCl_3) δ -110.60 (ddd, 1F, $J = 9.2, 9.2, 5.3$ Hz); IR 3351, 3050, 1714 cm^{-1} ; MS (EI) m/z (rel. Int.) 372 (27), 371 (M^+ , 100), 314 (16), 313 (86), 312 (44), 311 (28), 28 (28); HRMS Calcd for $\text{C}_{22}\text{H}_{14}\text{N}_3\text{O}_2\text{F}$: 371.1070. Found: 371.1083. Data for **36**: yellow solid, yield: 55 %, mp 198-199°C; ^1H NMR (CDCl_3) δ 2.73 (s, 3H), 4.09 (s, 3H), 7.24 (dd, 1H, $J = 7.9, 7.1$ Hz), 7.38 (d, 1H, $J = 7.3$ Hz), 7.56 (dd, 1H, $J = 7.9, 7.1$ Hz), 7.75 (ddd, 1H, $J = 8.3, 7.1, 1.3$ Hz), 7.84 (d, 1H, 7.9 Hz), 7.99 (d, 1H, $J = 7.9$ Hz), 8.08 (d, 1H, $J = 8.3$ Hz), 8.27 (d, 1H, $J = 8.6$ Hz), 8.82 (s, 1H), 8.93 (d, 1H, $J = 8.6$ Hz), 11.89 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 16.69 (CH_3), 52.58 (CH_3), 118.73 (CH), 119.38 (CH), 119.47 (CH), 120.91 (quat. C), 120.98 (CH), 121.30 (quat. C), 126.94 (CH), 127.91 (quat. C), 127.95 (CH), 128.96 (CH), 129.19 (CH), 129.74 (CH), 130.86 (quat. C), 136.43 (quat. C), 136.65 (CH and quat. C), 137.15 (quat. C), 140.46 (quat. C), 146.96 (quat. C), 157.40 (quat. C), 166.67 (CO_2Me); IR 3342, 3050, 1710 cm^{-1} ; MS (EI) m/z (rel. Int.) 368 (28), 367 (M^+ , 100), 309 (34), 308 (18), 307 (28), 306 (10), 154 (13), 153 (21); HRMS Calcd for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2$: 367.1321. Found: 367.1315. Data for **37**: pale yellow solid, yield: 46 %, mp 240-241°C. ^1H NMR (CDCl_3) δ 2.76 (s, 3H), 4.12 (s, 3H), 7.31 (dd, 1H, $J = 7.6, 7.5$ Hz), 7.46 (d, 1H, $J = 7.1$ Hz), 7.70 (ddd, 1H, $J = 8.3, 7.0, 1.0$ Hz), 7.86 (ddd, 1H, $J = 8.3, 7.0, 1.3$ Hz), 8.06 (d, 1H, $J = 7.8$ Hz), 8.18 (d, 1H, $J = 8.3$ Hz), 8.32 (dd, 1H, $J = 8.3, 1.0$ Hz), 8.93 (s, 1H), 9.08 (s, 1H), 11.85 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 16.75 (CH_3), 52.70 (CH_3), 119.12 (CH), 119.51 (CH), 119.56 (CH), 119.60 (quat. C), 121.23 (CH), 121.37 (quat. C), 124.53 (CH), 126.21 (quat. C), 127.94 (CH), 129.30 (CH), 129.47 (CH), 130.74 (CH), 131.24 (quat. C), 136.21 (quat. C), 136.46 (quat. C), 136.88 (quat. C), 140.54 (quat. C), 143.56 (quat. C), 147.86 (quat. C), 157.38 (quat. C), 166.59 (CO_2Me); IR 3351, 2962, 1716 cm^{-1} ; MS (EI) m/z (rel. Int.) 403 (M^+ , 36), 402 (27), 401 (M^+ , 100), 345 (17), 343 (50), 341 (24), 306 (20), 170.5 (20); HRMS Calcd for $\text{C}_{22}\text{H}_{16}\text{N}_3\text{O}_2^{35}\text{Cl}$: 401.0931. Found: 401.0915. Data for **38**: pale yellow solid, yield: 48 %, mp 284-285°C. ^1H NMR (CDCl_3) δ 2.80 (s, 3H), 4.12 (s, 3H), 7.34 (dd, 1H, $J = 7.8, 7.3$ Hz), 7.48 (d, 1H, $J = 7.3$ Hz), 7.57 (dd, 1H, $J = 8.7, 2.0$, Hz), 7.86 (d, 1H, $J = 8.7$ Hz), 7.95 (d, 1H, $J = 7.8$ Hz), 8.16 (s, 1H), 8.34

(d, 1H, $J = 8.7$ Hz), 8.95 (s, 1H), 9.05 (d, 1H, $J = 8.7$ Hz), 10.84 (br s, 1H, NH); ^{13}C NMR (CDCl_3) δ 16.91 (CH_3), 52.67 (CH_3), 119.08 (CH), 119.49 (CH), 119.94 (CH), 120.99 (quat. C), 121.23 (CH), 121.48 (quat. C), 126.41 (quat. C), 127.90 (CH), 127.99 (CH), 129.22 (CH), 129.48 (CH), 131.50 (quat. C), 132.06 (quat. C), 135.70 (quat. C), 136.56 (quat. C), 136.64 (CH), 136.91 (quat. C), 140.05 (quat. C), 147.49 (quat. C), 158.05 (quat. C), 166.63 (CO_2Me); IR 3342, 2921, 1725 cm^{-1} ; MS (EI) m/z (rel. Int.) 403 (M^+ , 37), 402 (27), 401 (M^+ , 100), 345 (26), 343 (74), 342 (32), 341 (36), 170 (29); HRMS Calcd for $\text{C}_{23}\text{H}_{16}\text{N}_3\text{O}_2^{35}\text{Cl}$: 401.0931. Found: 401.0928. Data for **39**: pale yellow solid, yield: 90 %, mp 278-279°C. ^1H NMR (DMSO-d_6) δ 7.40 (dd, 1H, $J = 7.5, 7.5$ Hz), 7.71 (dd, 1H, $J = 7.8, 7.4$ Hz), 7.85 (dd, 1H, $J = 7.8, 7.4$ Hz), 8.04 (m, 2H), 8.29 (d, 1H, $J = 8.4$ Hz), 8.49 (d, 1H, $J = 7.8$ Hz), 8.87 (d, 1H, $J = 8.4$ Hz), 9.10 (s, 1H), 9.26 (s, 1H), 12.31 (br s, 1H, NH), 12.87 (br s, 1H, CO_2H); ^{13}C NMR (DMSO-d_6) δ 113.69 (CH), 118.61 (CH), 119.31 (CH), 120.91 (CH), 120.91 (quat. C), 122.29 (CH), 123.63 (CH), 125.26 (quat. C), 128.76 (CH), 129.26 (CH), 130.56 (CH), 130.96 (CH), 131.06 (quat. C), 135.45 (quat. C), 135.78 (quat. C), 136.68 (quat. C), 141.78 (quat. C), 142.34 (quat. C), 148.11 (quat. C), 156.69 (quat. C), 166.51 (CO_2H); IR 3369, 3077, 1752 cm^{-1} ; MS (EI) m/z (rel. Int.) 375 (M^+ , 25), 374 (17), 373 (M^+ , 70), 331 (36), 330 (19), 329 (100), 328 (19), 294 (17); HRMS Calcd for $\text{C}_{21}\text{H}_{12}\text{N}_3\text{O}_2^{35}\text{Cl}$: 373.0618. Found: 373.0634. Data for **40**: pale yellow solid, yield: 76 %, mp 281-282°C. ^1H NMR (DMSO-d_6) δ 7.38 (dd, 1H, $J = 7.5, 7.5$ Hz), 7.69 (dd, 1H, $J = 7.5, 7.5$ Hz), 7.82 (m, 2H), 8.05 (d, 1H, $J = 8.5$ Hz), 8.49 (d, 1H, $J = 7.8$ Hz), 8.60 (d, 1H, $J = 8.8$ Hz), 8.88 (dd, 1H, $J = 9.1, 5.1$ Hz), 9.07 (d, 1H, $J = 8.5$ Hz), 9.08 (s, 1H), 12.34 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 111.38 (CH, $J_{\text{C/F}} = 22.1$ Hz), 113.94 (CH), 118.36 (CH), 120.10 (CH, $J_{\text{C/F}} = 25.2$ Hz), 120.46 (CH), 121.09 (quat. C), 121.22 (CH), 122.46 (CH), 128.80 (quat. C, $J_{\text{C/F}} = 10.7$ Hz), 129.39 (CH), 131.03 (quat. C), 133.09 (CH, $J_{\text{C/F}} = 9.1$ Hz), 135.60 (quat. C), 136.95 (CH, $J_{\text{C/F}} = 5.3$ Hz), 137.02 (quat. C), 137.20 (quat. C), 142.00 (quat. C), 144.66 (quat. C, $J_{\text{C/F}} = 2.3$ Hz), 156.51 (quat. C, $J_{\text{C/F}} = 2.3$ Hz), 160.63 (quat. C, $J_{\text{C/F}} = 245.7$ Hz), 166.96 (CO_2H); ^{19}F NMR (DMSO-d_6) δ -112.13 (ddd, 1F, $J = 8.8, 8.8, 5.5$ Hz); IR 3363, 3068, 1752 cm^{-1} ; MS (EI) m/z (rel. Int.) 358 (14), 357 (M^+ , 59), 314 (20), 313 (100), 312 (47), 287 (11), 155 (25), 28 (23); HRMS Calcd for $\text{C}_{21}\text{H}_{12}\text{N}_3\text{O}_2\text{F}$: 357.0913. Found: 357.0914. Data for **41**: pale yellow solid, yield: 68 %, mp > 295°C. ^1H NMR (DMSO-d_6) δ 7.44 (dd, 1H, $J = 7.4, 7.3$ Hz), 7.75 (m, 2H), 8.12 (d, 1H, $J = 8.2$ Hz), 8.17 (d, 1H, $J = 8.7$ Hz), 8.54 (d, 1H, $J = 7.8$ Hz), 8.69 (d, 1H, $J = 8.7$ Hz), 9.04 (s, 1H), 9.11 (d, 1H, $J = 8.7$ Hz), 9.14 (s, 1H), 12.39 (br s, 1H, NH), 12.87 (br s, 1H, CO_2H); ^{13}C NMR (DMSO-d_6) δ 113.74 (CH), 118.58 (CH), 119.84 (CH), 120.91 (CH), 120.97 (quat. C), 122.30 (CH), 126.37 (quat. C), 127.88 (CH), 128.64 (CH), 129.24 (CH), 129.96 (CH), 130.95 (quat. C), 134.53 (quat. C), 135.53 (quat. C), 136.70 (quat. C), 136.89 (quat. C), 137.25 (CH), 141.86 (quat. C), 147.70 (quat. C), 157.77 (quat. C), 166.70 (CO_2H); IR 3359, 3058, 1681 cm^{-1} ; MS (EI) m/z (rel. Int.) 375 (M^+ , 17), 373 (M^+ , 48), 331 (32), 330 (30), 329 (100), 328 (34), 146 (18); HRMS Calcd for $\text{C}_{21}\text{H}_{12}\text{N}_3\text{O}_2^{35}\text{Cl}$: 373.0618. Found: 373.0615. Data for **42**: pale yellow solid, yield: 77 %, mp > 295°C. ^1H NMR (DMSO-d_6) δ 7.38 (dd, 1H, $J = 7.3, 7.1$ Hz), 7.66-7.70 (m, 2H), 7.87 (d, 1H, $J = 7.9$ Hz), 8.07-8.10 (m, 2H), 8.48 (d, 1H, $J = 7.6$ Hz), 8.69 (d, 1H, $J = 8.4$ Hz), 9.06-9.08 (m, 2H), 12.18 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 112.59 (CH), 118.64 (CH), 119.82 (CH), 120.84 (quat. C), 121.08 (CH), 122.51 (CH), 127.53 (CH), 127.57 (CH), 128.95 (quat. C), 129.35 (CH), 130.02 (CH), 130.59 (quat. C), 131.88 (quat. C), 135.66 (quat. C), 135.88 (quat. C), 137.20 (quat. C), 138.03 (CH), 140.73 (quat. C), 142.36 (quat. C), 156.88 (quat. C), 166.39 (CO_2H); IR 3407, 3326, 3054, 1758 cm^{-1} ; MS (EI) m/z (rel. Int.) 375 (M^+ , 19), 374 (13), 373 (M^+ , 53), 331 (35), 330 (40), 329 (100), 328 (42), 164.5 (23); HRMS Calcd for $\text{C}_{21}\text{H}_{12}\text{N}_3\text{O}_2^{35}\text{Cl}$: 373.0618. Found: 373.0620. Data for **43**: pale yellow solid, yield: 95 %, mp 256-257°C. ^1H NMR (DMSO-d_6) δ 2.53 (s, 3H), 7.51 (dd, 1H, $J = 8.8, 1.4$ Hz), 7.70 (dd, 1H, $J = 6.9, 6.4$ Hz), 7.91 (ddd, 1H, $J = 8.3, 6.9, 1.4$ Hz), 7.95 (d, 1H, $J = 8.3$ Hz), 8.08 (d, 1H, $J = 7.4$ Hz), 8.26 (s, 1H), 8.61 (d, 1H, $J = 8.8$ Hz), 8.77 (d, 1H, $J = 8.3$ Hz), 9.01 (s, 1H), 9.04 (d, 1H, $J = 8.8$ Hz), 12.29 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 21.29 (CH_3), 113.49 (CH), 118.25 (CH), 119.56 (CH), 121.15 (quat. C), 121.76 (CH), 127.50 (CH), 127.79 (quat. C), 128.05 (CH), 129.86 (CH), 129.91 (quat. C), 129.99 (CH), 130.56 (CH), 130.71 (quat. C), 135.66 (quat. C), 136.59 (quat. C), 136.99 (quat. C), 137.30 (CH), 140.08 (quat. C), 147.19 (quat. C), 156.70 (quat. C), 166.76

(CO₂H); IR 3305, 1702 cm⁻¹; MS (EI) m/z (rel. Int.) 354 (14), 353 (M⁺, 54), 310 (25), 309 (100), 308 (60), 153.5 (31), 122 (11); HRMS Calcd for C₂₂H₁₅N₃O₂: 353.1164. Found: 353.1165. Data for **44**: yellow solid, yield: 95 %, mp 278-280°C. ¹H NMR (DMSO-d₆) δ 3.91 (s, 3H), 7.32 (dd, 1H, *J* = 8.9, 2.0 Hz), 7.70 (dd, 1H, *J* = 7.8, 7.1 Hz), 7.91 (dd, 1H, *J* = 8.0, 7.1 Hz), 7.96 (d, 1H, *J* = 8.9 Hz), 8.07 (m, 2H), 8.59 (d, 1H, *J* = 8.7 Hz), 8.76 (d, 1H, *J* = 8.4 Hz), 9.05 (d, 1H, *J* = 8.7 Hz), 9.09 (m, 1H), 12.21 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 55.85 (CH₃), 104.01 (CH), 114.56 (CH), 118.51 (CH), 119.08 (CH), 119.53 (CH), 121.61 (quat. C), 127.38 (CH), 127.74 (quat. C), 128.02 (CH), 129.89 (CH), 129.97 (CH), 130.60 (quat. C), 135.76 (quat. C), 136.52 (quat. C), 137.09 (CH), 137.09 (quat. C), 137.32 (quat. C), 147.30 (quat. C), 154.47 (quat. C), 156.97 (quat. C), 167.20 (CO₂H); IR 3363, 3079, 1764 cm⁻¹; MS (EI) m/z (rel. Int.) 370 (12), 369 (M⁺, 56), 326 (16), 325 (67), 311 (19), 310 (100), 282 (13), 280 (12); HRMS Calcd for C₂₂H₁₅N₃O₃: 369.1113. Found: 369.1110. Data for **45**: pale yellow solid, yield: 85 %, mp 290°C. ¹H NMR (DMSO-d₆) δ 7.56 (ddd, 1H, *J* = 9.2, 9.2, 2.6 Hz), 7.70 (dd, 1H, *J* = 7.6, 7.2 Hz), 7.91 (ddd, 1H, *J* = 7.6, 7.6, 1.2 Hz), 8.07 (m, 2H), 8.38 (dd, 1H, *J* = 9.0, 2.5 Hz), 8.61 (d, 1H, *J* = 8.6 Hz), 8.76 (d, 1H, *J* = 8.6 Hz), 9.03 (d, 1H, *J* = 8.6 Hz), 9.12 (s, 1H), 12.39 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 107.76 (CH, *J*_{CF} = 24.5 Hz), 115.09 (CH, *J*_{CF} = 8.8 Hz), 117.34 (CH, *J*_{CF} = 26.0 Hz), 118.97 (CH), 119.44 (CH), 121.58 (quat. C, *J*_{CF} = 10.6 Hz), 127.53 (CH), 127.81 (quat. C), 128.05 (CH), 129.95 (CH), 129.98 (CH), 130.40 (quat. C, *J*_{CF} = 4.4 Hz), 136.29 (quat. C), 136.70 (quat. C), 137.26 (quat. C), 137.59 (CH), 138.24 (quat. C), 147.25 (quat. C), 156.60 (quat. C), 157.48 (quat. C, *J*_{CF} = 235.1 Hz), 166.70 (CO₂H); ¹⁹F NMR (DMSO-d₆) δ -121.76 (ddd, 1F, *J* = 9.2, 9.2, 4.6 Hz); IR cm⁻¹ 3342, 3058, 1756; MS (EI) m/z (rel. Int.) 358 (12), 357 (M⁺, 45), 314 (26), 313 (100), 312 (50), 311 (23), 155 (18); HRMS Calcd for C₂₁H₁₂N₃O₂F: 357.0913. Found: 357.0920. Data for **46**: pale yellow solid, yield: 60 %, mp 295°C; ¹H NMR (DMSO-d₆) δ 7.24 (ddd, 1H, *J* = 9.8, 8.7, 2.1 Hz), 7.71 (dd, 1H, *J* = 7.9, 7.2 Hz), 7.82 (dd, 1H, *J* = 9.8, 2.1 Hz), 7.93 (dd, 1H, *J* = 8.0, 7.2 Hz), 8.09 (d, 1H, *J* = 7.9 Hz), 8.55 (dd, 1H, *J* = 8.7, 5.6 Hz), 8.62 (d, 1H, *J* = 8.7 Hz), 8.75 (d, 1H, *J* = 8.2 Hz), 9.03 (d, 1H, *J* = 8.7 Hz), 9.08 (s, 1H), 12.44 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 99.82 (CH, *J*_{CF} = 26.7 Hz), 109.62 (CH, *J*_{CF} = 24.4 Hz), 118.05 (quat. C), 118.45 (CH), 119.69 (CH), 124.43 (CH, *J*_{CF} = 10.7 Hz), 127.76 (CH), 128.02 (quat. C), 128.28 (CH), 130.11 (CH), 130.21 (CH), 130.72 (quat. C), 136.30 (quat. C), 137.32 (CH), 137.55 (quat. C), 137.64 (quat. C), 142.85 (quat. C, *J*_{CF} = 13.7 Hz), 147.42 (quat. C), 156.78 (quat. C), 163.23 (quat. C, *J*_{CF} = 242.6 Hz), 166.90 (CO₂H); ¹⁹F NMR (DMSO-d₆) δ -110.25 (ddd, 1F, *J* = 9.8, 9.8, 5.6 Hz); IR 3357, 3253, 3056, 1716 cm⁻¹; MS (EI) m/z (rel. Int.) 358 (18), 357 (M⁺, 72), 314 (18), 313 (100), 312 (37), 287 (13), 155.5 (28), 36 (56); HRMS Calcd for C₂₁H₁₂N₃O₂F: 357.0913. Found: 357.0914. Data for **47**: pale yellow solid, yield: 86 %, mp > 295°C; ¹H NMR (DMSO-d₆) δ 2.70 (s, 3H), 7.30 (dd, 1H, *J* = 7.6, 6.9 Hz), 7.48 (d, 1H, *J* = 6.9 Hz), 7.71 (dd, 1H, *J* = 7.6, 6.1 Hz), 7.91 (dd, 1H, *J* = 7.9, 6.9 Hz), 8.08 (d, 1H, *J* = 7.9 Hz), 8.28 (d, 1H, *J* = 8.0 Hz), 8.36 (d, 1H, *J* = 8.5 Hz), 8.62 (d, 1H, *J* = 8.6 Hz), 9.01 (m, 2H), 11.94 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 16.70 (CH₃), 118.47, 119.43, 119.97, 120.69, 121.24, 122.05, 127.60, 127.81, 128.20, 129.47, 129.64, 130.42, 131.02, 135.65, 136.71, 137.43, 138.00, 140.44, 146.80, 156.94, 166.89 (CO₂H); IR 3349, 3048, 1683 cm⁻¹; MS (EI) m/z (rel. Int.) 353 (M⁺, 40), 310 (24), 309 (100), 308 (37), 153.5 (20), 140.5 (14); HRMS Calcd for C₂₂H₁₅N₃O₂: 353.1164. Found: 353.1152. Data for **48**: pale yellow solid, yield: 55 %, mp > 295°C. ¹H NMR (DMSO-d₆) δ 2.60 (s, 3H), 7.03 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.22 (d, 1H, *J* = 7.2 Hz), 7.58 (dd, 1H, *J* = 7.9, 7.3 Hz), 7.74 (dd, 1H, *J* = 7.9, 7.2 Hz), 7.99 (m, 2H), 8.15 (d, 1H, *J* = 8.4 Hz), 8.70 (s, 1H), 8.91 (s, 1H), 11.40 (br s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 16.71 (CH₃), 118.37 (CH), 119.28 (CH), 119.85 (CH), 120.68 (quat. C), 121.13 (CH), 121.97 (quat. C), 123.85 (CH), 125.26 (quat. C), 128.84 (CH), 129.61 (CH), 130.08 (CH), 131.24 (quat. C), 131.46 (CH), 135.05 (quat. C), 135.29 (quat. C), 140.34 (quat. C), 140.41 (quat. C), 142.43 (quat. C), 147.71 (quat. C), 157.15 (quat. C), 167.14 (CO₂H); IR 3361, 3052, 1758 cm⁻¹; MS (EI) m/z (rel. Int.) 389 (M⁺, 20), 387 (M⁺, 53), 345 (35), 344 (22), 343 (100), 306 (23), 171.5 (14), 170.5 (14); HRMS Calcd for C₂₂H₁₄N₃O₂³⁵Cl: 387.0774. Found: 387.0770. Data for **49**: pale yellow solid, yield: 80 %, mp > 295°C. ¹H NMR (DMSO-d₆, at 71°C) δ 2.80 (s, 3H), 7.31 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.50 (d, 1H, *J* = 7.1 Hz), 7.73 (dd, 1H, *J* = 8.7, 2.2 Hz), 8.13 (d, 1H, *J* = 8.7 Hz), 8.29 (d, 1H, *J*

= 7.7 Hz), 8.46 (s, 1H), 8.65 (d, 1H, $J = 8.7$ Hz), 9.03 (s, 1H), 9.04 (d, 1H, $J = 8.7$ Hz), 11.76 (br s, 1H, NH); ^{13}C NMR (DMSO- d_6 , at 71°C) δ 16.42 (CH₃), 118.04 (CH), 119.43 (CH), 119.63 (CH), 120.42 (quat. C), 120.98 (CH), 121.88 (quat. C), 126.13 (quat. C), 127.64 (CH), 127.76 (CH), 129.45 (CH), 129.69 (CH), 131.02 (quat. C), 134.55 (quat. C), 135.54 (quat. C), 136.16 (quat. C), 136.99 (quat. C), 137.17 (CH), 140.29 (quat. C), 147.00 (quat. C), 157.64 (quat. C), 166.11 (CO₂H); IR 3351, 1679 cm^{-1} ; MS (EI) m/z (rel. Int.) 389 (M^+ , 22), 388 (17), 387 (M^+ , 62), 345 (35), 344 (29), 343 (100), 342 (42), 170.5 (20); HRMS Calcd for C₂₂H₁₄N₃O₂³⁵Cl: 387.0774. Found: 387.0770.

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