Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 60 (2004) 5737–5750

Convenient access to substituted acridines by a Buchwald–Hartwig amination

René Csuk,* Alexander Barthel and Christian Raschke

Institut für Organische Chemie, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Str. 2, D-06120 Halle (Saale), Germany

Received 9 February 2004; revised 6 May 2004; accepted 7 May 2004

Abstract—A convenient, high yield procedure for the synthesis of anthranilic acids carrying a variety of different substituents as well as their straightforward transformation into the corresponding 9-chloroacridines could be established by using modified Buchwald–Hartwig amination conditions.

1. Introduction

Substituted acridines have been in use as antimalarials[1] for many years quite successfully and several of them[2–8] have exhibited excellent results in the chemotherapy of cancer. Quite recently, however, Prusiner et al. enlarged the scope of potential applications for these compounds dramatically due to their finding of quinacrine[9–12] (**1**) and related compounds[13] to show quite promising activity in vitro against prion based diseases. In addition, preliminary QSAR studies[14] attributed the observed activity both to the presence of an acridine ring and to the presence of a suitable spacer for the bisacridines **2**. Independent NMR binding studies[15] supported these conclusions by establishing a molecular interaction between the C-terminal helix of the prion protein and the quinacrine molecule. Up to now, however, no conclusive structure/activity relationships could be established due to the controversial interpretation of the biological data obtained in different biological screening systems[16–18] as well due to the lack of a sufficient large number of analogues synthesized and screened so far.

Acridines substituted at position C(9) are usually accessed from the corresponding 9-chloroacridines[19,20] the latter being prepared by the cyclization of suitably substituted *N*-phenylanthranilic acids. These compounds have been in the focus of synthetic interest in their own right due to the finding that flufenamic acid (**3**) has been used[21–24] quite successfully for the therapy of amyloidogenic diseases (Fig. 1).

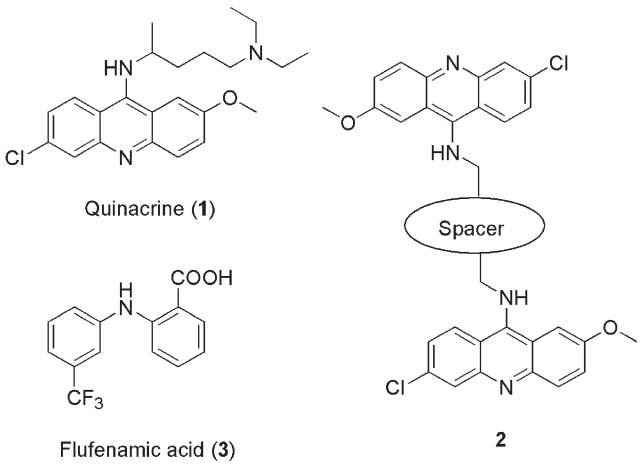


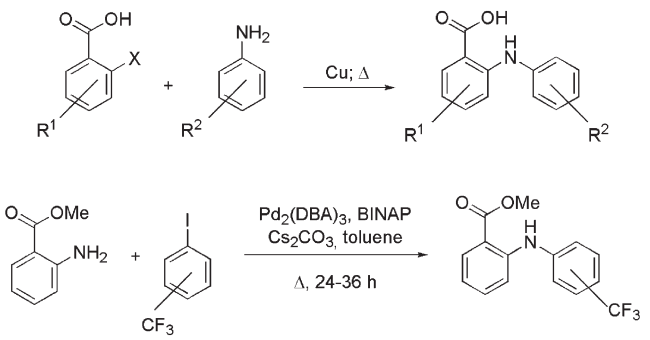
Figure 1. Structure of anti-Prion (**1**, **2**) or amyloidogenic (**3**) active compounds.

The majority of substituted *N*-phenylanthranilic acids have been synthesized using an Ullmann–Jourdan reaction[25–28] as the key step for establishing the C–N bond. These reactions despite the fact that several improvements[29–33] have been suggested over the years usually suffer from high reaction temperatures and from the need of using quite a large excess of copper or of copper salts. To obtain reasonably high yields electron withdrawing substituents are mandatory.[34] As an alternative the Pd(0) catalysed reaction of unsubstituted anthranilic acid with trifluoromethyl-iodobenzene has been suggested (Scheme 1).[21,35,36]

During our own investigations concerning the efficient synthesis of anti-prion active acridine derived compounds it became necessary to develop a reliable route providing these compounds in good yields even on a larger preparative

Keywords: Buchwald–Hartwig amination; Anthranilic acids; Acridines.
* Corresponding author. Tel.: +49-345-5525660; fax: +49-345-5527030; e-mail address: csuk@chemie.uni-halle.de

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.05.013

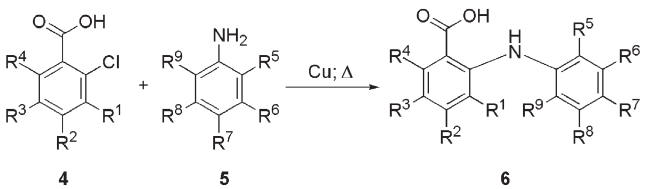


Scheme 1. Synthesis of *N*-phenyl-anthranilic acids.

scale. Thus, a more systematic investigation of the Ullmann–Jourdan reaction as well as of appropriate Pd(0)-mediated alternatives[21,35,36] was called for.

2. Results and discussion

In a first approach for the synthesis of substituted *N*-phenyl-anthranilic acids **6** we investigated their synthesis starting from substituted 2-chloro-benzoic acids **4** and aniline derivatives **5** in the presence of Cu or suitable Cu salts in more detail. Numerous variations concerning the choice of solvent (among these water,[37] ethanol, aqueous solution of sodium carbonate, DMF,[25] amyl alcohol as well as butane-2,3-diol), co-catalysts (Cu(I)[38] or Cu(II) salts, several diols, potassium iodide or pyridine[36]), the amount and particle size of the copper (or copper bronze) were performed in parallel



Scheme 2. Ullmann–Jourdan reactions.

synthesis technique. Finally the highest yields were obtained using copper–bronze (3%) in amyl alcohol as the solvent containing 15% of pyridine as a co-catalyst. Table 1 and Scheme 2 summarize our results for these Ullmann–Jourdan reactions under optimized conditions. Although the synthetic set-up is quite robust and the average yields for these couplings range between 40 and 60% this methodology is not optimal for scaling up and has to be optimized for each different substitution pattern.

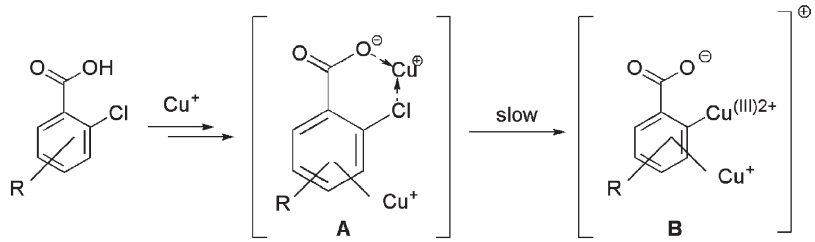
The problem usually arising with these reactions may be rationalized by the probable reaction mechanism[39] (cf. Scheme 3) for this reaction.

The initially formed copper complex **A** is believed to afford in a rate determinating step the reactive species **B**; addition of Cu(I) salts (as well as of Cu(II) salts that give upon symproportion with Cu(0) in situ formed Cu(I) species) have previously been used to enhance the speed of several coupling reactions, but in our own experiments the addition of a broad variety of different Cu(I) salts did not show any effect on the rate of the reactions at all. The formation of several by-products is encountered during these reactions; this finding is well explained by the high reactivity of intermediate **C** (Scheme 4) that upon reaction with a molecule of aniline following path I affords the desired anthranilic acid. Reaction of **C** with protic solvents that are used most often for these coupling reactions, yield either ethers (upon reaction with primary alcohols, path II) or salicylates[40] (with water as the solvent). In addition, a single-electron transfer affords (reaction path III) the radical species **D** whose reaction with **C** consequently yields biphenylic diacids or after protonation the corresponding benzoic acid, respectively.

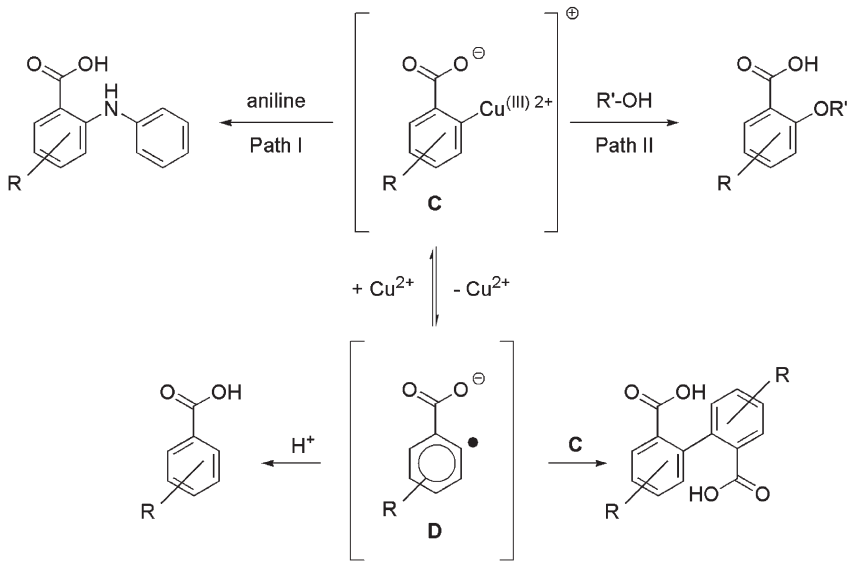
Due to these major drawbacks of the Ullmann–Jourdan reaction we focused our synthetic efforts on the investigation of Pd(0) catalysed reactions using the iodine-substituted benzoic acids as starting material. The latter have been accessed very easily by applying Sandmeyer

Table 1. Ullmann–Jourdan reactions (Scheme 2)

R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	R^9	Product	Yield (%)
H	NO_2	H	H	H	H	OMe	H	H	**6a**	54
H	NO_2	H	H	H	H	H	H	OMe	**6b**	65
H	NO_2	H	H	H	H	OMe	H	OMe	**6c**	57
H	NO_2	H	H	H	OMe	H	H	OMe	**6d**	40
H	H	NO_2	H	H	H	H	H	OMe	**6e**	49
H	H	NO_2	H	H	H	H	OMe	H	**6f**	40
H	H	NO_2	H	H	H	OMe	H	OMe	**6g**	58
H	H	H	H	H	H	OMe	H	H	**6h**	52
H	Cl	H	H	H	H	OMe	H	H	**6i**	58



Scheme 3. Probable reaction mechanism for Ullmann–Jourdan reactions.



Scheme 4. Possible side reactions occurring during Ullmann–Jourdan reactions.

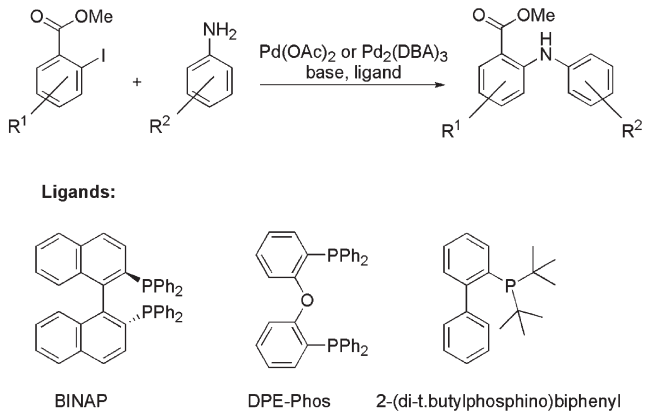


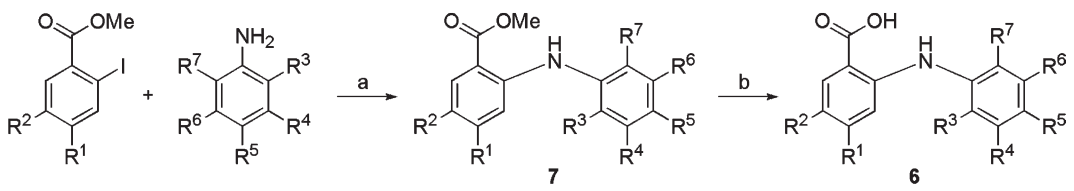
Figure 2. Pd(0) assisted synthesis of substituted *N*-phenyl-anthranilic acids.

reactions onto the corresponding 2-amino-benzoic acids[41] followed by esterification using the $SOCl_2$/methanol procedure.[42] Palladium-catalyzed coupling reactions are very important transformations both in academic and industrial laboratories. In order to establish optimised reaction conditions several model reactions were performed using potassium carbonate, potassium phosphate, cesium carbonate or potassium-*t*-butoxide as the base,[43] ±-BINAP, DPE-Phos[44] or 2-(di-*t*-butylphosphino)biphenyl as the phosphine ligand[45–48] and $Pd(OAc)_2$ as the source for the metal. From these preliminary screening experiments we deduced the reaction system DPE-Phos/$Pd(OAc)_2$/Cs_2CO_3 as best suited; these experiments also revealed that the premixing of $Pd(OAc)_2$ with the phosphine ligand and the aniline is a prerequisite for optimal reactions (Fig. 2).[49]

Table 2. Modified Buchwald–Hartwig aminations for the synthesis of substituted *N*-phenyl-anthranilic acids according to Scheme 5

R^1	R^2	R^3	R^4	R^5	R^6	R^7	Ester	Yield ester	Acid	Yield acid
H	H	H	H	OCF_3	H	H	**7j**	93	**6j**	95
H	H	H	Me	Me	H	NO_2	**7k**	89	**6k**	91
H	H	H	H	H	H	CO_2Me	**7l**	51	**6l**	80[a]
H	H	H	H	H	F	H	**7m**	94	**6m**	96
H	H	H	H	F	H	F	**7n**	98	**6n**	90
H	H	H	H	F	F	F	**7o**	94	**6o**	91
H	H	H	H	OMe	H	OMe	**7p**	97	**6p**	97
H	H	H	OMe	H	H	OMe	**7q**	73	**6q**	90
Cl	H	H	H	OCF_3	H	H	**7r**	90	**6r**	90
Cl	H	H	H	F	H	F	**7s**	86	**6s**	96
Cl	H	H	H	F	F	F	**7t**	54	**6t**	95
H	NO_2	H	H	OCF_3	H	H	**7u**	87	**6u**	95
H	NO_2	H	H	F	H	F	**7v**	85	**6v**	94
H	NO_2	H	H	F	F	F	**7w**	60	**6w**	93

[a] R^7=COOH.



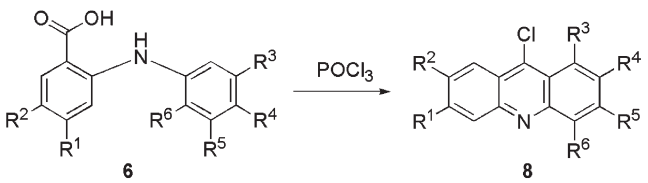
Scheme 5. Modified Buchwald–Hartwig aminations for the synthesis of substituted *N*-phenyl-anthranilic acids; (a) DPE-Phos, $Pd(OAc)_2$, Cs_2CO_3; (b) aqueous NaOH.

Following this procedure methyl anthranilates **7j–7w** were obtained in ca. 50–98% isolated yield (cf. Table 2 and Scheme 5).

Subsequent hydrolysis of these esters **7j–7w** resulted in the formation of the corresponding acids **6j–6w** that upon reaction with $POCl_3$ followed by work up under basic conditions furnished the corresponding 9-chloro-acridines **8** in good to excellent yields (cf. Table 3 and Scheme 6).

Table 3. Synthesis of the substituted 9-chloroacridines **8** according to Scheme 6

Starting material	R^1	R^2	R^3	R^4	R^5	R^6	Product	Yield (%)
6a	NO_2	H	H	OMe	H	H	**8a**	80
6b	H	NO_2	H	H	H	OMe	**8b**	75
6c	NO_2	H	H	OMe	H	OMe	**8c**	70
6f	NO_2	H	H	H	H	OMe	**8f**	79
6g	H	NO_2	H	OMe	H	OMe	**8g**	85
6h	H	H	H	OMe	H	H	**8h**	91
6i	Cl	H	H	OMe	H	H	**8i**	77
6j	H	H	H	OCF_3	H	H	**8j**	90
6m	H	H	H	H	F	H		
	H	H	F	H	H	H	**8m(2)**	37
	H	H	H	H	F	H	**8m(1)**	53
6n	H	H	H	F	H	F	**8n**	96
6o	H	H	H	F	F	F	**8o**	85
6p	H	H	H	OMe	H	OMe	**8p**	95
6q	H	H	OMe	H	H	OMe	**8q**	83
6r	Cl	H	H	OCF_3	H	H	**8r**	82
6s	Cl	H	H	F	H	F	**8s**	87
6t	Cl	H	H	F	F	F	**8t**	65
6u	H	NO_2	H	OCF_3	H	H	**8u**	84
6w	H	NO_2	H	F	F	F	**8w**	92



Scheme 6. Synthesis of the substituted 9-chloroacridines **8**.

In summary, a convenient, high yield procedure for the synthesis of anthranilic acids carrying a variety of different substituents as well as their straightforward transformation into the corresponding 9-chloroacridines could be established by using modified Buchwald–Hartwig amination conditions.

3. Experimental

3.1. General

Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin–Elmer 341 polarimeter (1 cm micro cell), NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, J in Hz, internal Me_4Si or internal CCl_3F), IR spectra (film or KBr pellet) on a Perkin–Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT TSQ 7000 (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used; TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV))}$ sulfate followed by gentle heating. The solvents were dried according to usual procedures.

3.2. General procedure for Ullmann–Jourdan reactions (GP1)

A mixture of the substituted chlorobenzoic acid (40.2 mmol) and the aniline derivative (79.6 mmol), potassium carbonate (6.9 g, 50.0 mmol) and Cu-powder (40 mesh, 0.24 g, 3 wt% with respect to the amount of benzoic acid used) was heated in amyl alcohol (40 ml) containing pyridine (1.21 g, 15 wt%) for 5 h under reflux. After cooling to room temperature, the solution was acidified with hydrochloric acid, the crude product was filtered off and recrystallized from ethanol to afford the product.

3.3. General procedure for Buchwald–Hartwig amination reactions (GP2)

Under argon a solution of $Pd(OAc)_2$ (40 mg, 2 mol%), DPEPhos (210 mg, 4 mol%) and the aniline derivative in dry toluene (15 ml) was stirred for 5 min. To this deep red solution the corresponding methyl 2-iodobenzoate (2.00 g, 7.60 mmol) and Cs_2CO_3 (3.48 g, 10.64 mmol) were added and stirring at 95 °C was continued until GC-MS and TLC showed the reaction to be completed (usually 2 days). The solid was filtered off and the filtrate concentrated in vacuo to afford a residue that was subjected to chromatography (silica gel, hexane/ethyl acetate 9:1→8:2) to afford the corresponding product.

3.4. General procedure for the saponification of the substituted methyl *N*-phenyl-anthranilates (GP3)

To a solution of the methyl anthranilate (2.0 g, 6.4 mmol) in acetone (100 ml) an aqueous solution of sodium hydroxide (5%, 20 ml) was added and the reaction mixture was stirred overnight at room temperature. After neutralization with diluted hydrochloric acid, the solvents were removed and the product was washed with water and dried to yield the corresponding acid.

3.5. General procedure for the synthesis of the substituted 9-chloroacridines (GP4)

The substituted *N*-phenyl-anthranilic acid (6.7 mmol) was dissolved in $POCl_3$ (15 ml) and heated under reflux for 6 h. After cooling to room temperature the reaction mixture was poured very carefully under vigorous stirring onto a mixture containing crushed ice (200 g), ammonia (100 ml) and chloroform (250 ml) keeping the pH during this operation always >8. The phases were separated and the aqueous phase was extracted with chloroform (2×100 ml), the organic phases were combined, dried ($CaCl_2$) and evaporated to yield the crude product that was pure enough for the further transformations. Analytically pure samples were obtained after flash-chromatography.

3.5.1. 2-(4-Methoxyanilino)-4-nitrobenzoic acid[50–52] (6a). Following GP1 from 2-chloro-4-nitrobenzoic acid (8.1 g, 40.2 mmol) and *p*-anisidine (9.8 g, 79.6 mmol) **6a** (6.2 g, 54%) was obtained as a red solid. Mp 241–245 °C (Lit.: 238–240 °C,[50] 235–237 °C,[51] 235–236 °C[52]). ^{1}H NMR (200 MHz, acetone-d_6): δ=3.78 (s, 3H, OCH_3), 6.96–7.07 (m, 2H, H_{arom}), 7.20–7.30 (m, 2H, H_{arom}), 7.42 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 7.54 (d, 1H, J=2.5 Hz, H_{arom}), 8.08 (d, 1H, J=8.3 Hz, H_{arom}), 9.58 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=55.2, 106.7, 109.6, 115.0, 115.9, 125.9, 131.5, 133.4, 149.3, 150.8, 156.9, 168.5. IR (KBr): ν=3357m, 2958m, 1678s, 1619w, 1584w, 1537s, 1516s, 1456w, 1426m, 1349s, 1251s, 1178w, 1144w, 1107w, 1070w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 282 nm (4.27). MS (ESI, MeOH): m/z=287.3 (100%, $(M-H)^-$), 597.4 (20% $[(M-H)_2Na]^-$).

3.5.2. 2-(2-Methoxyanilino)-4-nitrobenzoic acid (6b). Compound **6b** (7.5 g, 65%) was obtained from 2-chloro-4-nitrobenzoic acid (8.1 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 236–240 °C (Lit.: 187–189 °C[50]). ^{1}H NMR (400 MHz, acetone-d_6): δ=3.81 (s, 3H, OCH_3), 7.02 (ddd, 1H, J=7.9, 7.9, 1.7 Hz, H_{arom}), 7.13–7.22 (m, 2H, H_{arom}), 7.43 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 7.47 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 7.70 (d, 1H, J=2.1 Hz, H_{arom}), 8.09 (d, 1H, J=8.7 Hz, H_{arom}), 9.73 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=55.6, 107.3, 110.3, 112.2, 120.7, 122.2, 125.3, 127.6, 133.3, 147.5, 150.6, 151.4, 151.8, 168.4. IR (KBr): ν=1691s, 1622m, 1597m, 1543s, 1494m, 1437s, 1426m, 1349s, 1263s, 1114m, 1029m, 1107w, 1070w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 282 nm (3.90). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.2 (20% $[(M-H)_2Na]^-$).

3.5.3. 2-(2,4-Dimethoxyanilino)-4-nitrobenzoic acid (6c). Compound **6c** (7.3 g, 57%) was obtained from 2-chloro-4-nitrobenzoic acid (9.8 g, 79.6 mmol) and 2,4-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 235–240 °C (Lit.: 259–260 °C[27]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 6.60 (dd, 1H, J=8.7, 2.5 Hz, H_{arom}), 6.73 (d, 1H, J=2.5 Hz, H_{arom}), 7.27 (d, 1H, J=8.7 Hz, H_{arom}), 7.37–7.41 (m, 2H, H_{arom}), 8.06 (dd, 1H, J=6.6, 2.9 Hz, H_{arom}), 9.41 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.4, 55.7, 99.7, 104.9, 106.8, 109.3, 115.8, 120.0, 125.9, 133.2, 149.3, 150.8, 154.1, 158.2, 168.5. IR (KBr): ν=1690s, 1624m, 1584m, 1542s, 1438m, 1350s, 1250s, 1211s, 1160m, 1129w, 1033w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=286 nm (3.79). MS (ESI, MeOH): m/z=317.2 (100%, $(M-H)^-$), 657.5 (30% $[(M-H)_2Na]^-$).

3.5.4. 2-(2,5-Dimethoxyanilino)-4-nitrobenzoic acid (6d). Compound **6d** (5.1 g, 40%) was obtained from 2-chloro-4-nitrobenzoic acid (9.8 g, 79.6 mmol) and 2,5-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 206–209 °C (Lit.: 222–223 °C[53]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.69 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 6.53 (dd, 1H, J=8.7, 2.9 Hz, H_{arom}), 6.92 (d, 1H, J=2.9 Hz, H_{arom}), 6.95 (d, 1H, J=8.7 Hz, H_{arom}), 7.37 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 7.80 (d, 1H, J=2.5 Hz, H_{arom}), 8.02 (d, 1H, J= 8.3 Hz, H_{arom}), 11.95 (s, 1H, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ=56.0, 56.9, 106.0, 106.9, 110.1, 110.9, 113.6, 123.8, 124.8, 131.9, 133.0, 145.8, 148.5, 154.0, 168.5. IR (KBr): ν=1628s, 1533s, 1431m, 1347m, 1218s, 1008m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=292 nm (3.91). MS (ESI, MeOH): m/z=317.2 (100%, $(M-H)^-$), 657.5 (40% $[(M-H)_2Na]^-$).

3.5.5. 2-(2-Methoxyanilino)-5-nitrobenzoic acid (6e). Compound **6e** (5.9 g, 49%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 218–224 °C (Lit.: 215 °C[54]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.87 (s, 3H, OCH_3), 6.98–7.05 (m, 3H, H_{arom}), 7.28–7.32 (m, 1H, H_{arom}), 7.35 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 8.14 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.98 (d, 1H, J=2.5 Hz, H_{arom}), 9.88 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.7, 110.8, 112.2, 113.3, 120.6, 124.0, 126.4, 126.7, 128.2, 129.0, 136.4, 152.0, 152.4, 168.5. IR (KBr): ν=3308w, 2937m, 1674s, 1602s, 1578s, 1537s, 1503s, 1466m, 1439m, 1333s, 1296s, 1262s, 1182m, 1152m, 1132m, 1118m, 1067w, 1050w, 1031m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.43). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.3 (25% $[(M-H)_2Na]^-$).

3.5.6. 2-(3-Methoxyanilino)-5-nitrobenzoic acid (6f).[54,55] Compound **6f** (4.8 g, 40%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and *m*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 258–261 °C (Lit.: 253–254 °C[54]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.77 (s, 3H, OCH_3), 6.84 (dd, 1H, J=7.5, 2.0 Hz, H_{arom}), 6.90–6.96 (m, 2H, H_{arom}), 7.18 (d, 1H, J=9.5 Hz, H_{arom}), 7.36 (t, 1H, J=8.3 Hz, H_{arom}), 8.18 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.70 (d, 1H, J=2.9 Hz, H_{arom}), 10.31 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.2, 109.4, 111.0, 111.5, 113.4, 115.8, 128.3, 129.2, 130.4, 136.5, 139.3, 152.1, 160.2, 168.4. IR (KBr): ν=3306w, 3087w, 1670s, 1601s, 1578s, 1530m, 1496s, 1466w, 1439m, 1423m, 1335s, 1268m, 1237s, 1200m, 1173m, 1160m, 1132m, 1043w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (3.27). MS (ESI, MeOH): m/z=287.2 (100%, $(M-H)^-$), 597.6 (20% $[(M-H)_2Na]^-$).

3.5.7. 2-(2,4-Dimethoxyanilino)-5-nitrobenzoic acid (6g). Compound **6g** (7.75 g, 58%) was obtained from 2-chloro-5-nitrobenzoic acid (8.1 g, 40.2 mmol) and 2,4-dimethoxyaniline (12.3 g, 80.3 mmol) following GP1. Mp 236–242 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.59 (dd, 1H, J=8.3, 2.5 Hz, H_{arom}), 6.70–6.75 (m, 2H, H_{arom}), 7.26 (d, 1H, J=8.3 Hz, H_{arom}), 8.10 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.67 (d, 1H, J=2.9 Hz, H_{arom}), 9.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.4, 55.7, 100.2, 105.6, 110.6, 113.6, 119.6, 127.1, 128.8, 129.5, 136.3, 153.9, 154.8, 159.3, 169.0. IR (KBr): ν=3294w, 2938w, 2361m, 1689s, 1601s, 1582s, 1514s, 1438s, 1347s, 1307s, 1250s, 1209s, 1157m, 1131m, 1068w, 1030m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 398 nm (3.74). MS (ESI, MeOH): m/z=317.3 (100%, $(M-H)^-$), 657.5 (20% $[(M-H)_2Na]^-$). HRMS for $C_{15}H_{14}N_2O_4$: calcd: 318.0852; found: 318.0852.

3.5.8. 2-(4-Methoxyanilino)benzoic acid (6h).[56–59] Compound **6h** (5.3 g, 52%) was obtained from 2-chlorobenzoic acid (6.3 g, 40.2 mmol) and *o*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 196–199 °C (Lit.: 187 °C;[56,57] 181–183 °C[58]). ^{1}H NMR (400 MHz, DMSO-d_6): δ=3.74 (s, 3H,

OCH_3), 6.67 (ddd, 1H, J=7.1, 7.1, 1.7 Hz, H_{arom}), 6.88–6.96 (m, 3H, H_{arom}), 7.13–7.18 (m, 2H, H_{arom}), 7.30 (ddd, 1H, J=7.1, 7.1, 1.7 Hz, H_{arom}), 7.84 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 9.40 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.5, 111.3, 112.9, 114.8, 116.3, 125.0, 131.7, 133.0, 134.1, 148.9, 156.1, 170.0. IR (KBr): ν=3327m, 2954m, 2836w, 2643w, 2569w, 1665s, 1597s, 1577s, 1513s, 1452s, 1442s, 1425m, 1330m, 1296w, 1270s, 1245s, 1172s, 1110w, 1086w, 1032m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 225 nm (4.40). MS (ESI, MeOH): m/z=242.3 (100%, $(M-H)^-$), 507.4 (30% $[(M-H)_2Na]^-$).

3.5.9. 4-Chloro-2-(4-methoxyanilino)benzoic acid (6i). Compound **6i** (6.6 g, 58%) was obtained from 2,4-dichlorobenzoic acid (7.7 g, 40.1 mmol) and *p*-anisidine (9.8 g, 79.6 mmol) following GP1. Mp 206–208 °C (Lit.: 214–215 °C;[60,61] 213.5–214 °C;[62] 213–214 °C;[63] 202 °C;[64] 176–178 °C[65]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.76 (s, 3H, OCH_3), 6.69 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.75 (d, 1H, J=1.7 Hz, H_{arom}), 6.96–7.01 (m, 2H, H_{arom}), 7.17–7.22 (m, 2H, H_{arom}), 7.84 (d, 1H, J=8.3 Hz, H_{arom}), 9.49 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 110.0, 111.6, 114.9, 116.0, 125.9, 131.8, 133.5, 138.9, 150.0, 156.7, 169.2. IR (KBr): ν=3321m, 3008m, 2954m, 2833m, 1662s, 1596s, 1570s, 1515s, 1460s, 1426s, 1334w, 1250s, 1232s, 1178m, 1156m, 1102m, 1038w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.39). MS (ESI, MeOH): m/z=276.7 (100%, $(M-H)^-$).

3.5.10. 2-[4-(Trifluoromethoxy)anilino]benzoic acid (6j). Following GP3 from **7j** (2.0 g, 6.4 mmol) **6j** (1.8 g, 95%) was obtained as a solid. Mp 195–196 °C (Lit.: 175–176 °C[66]). ^{1}H NMR (500 MHz, DMSO-d_6): 6.75 (ddd, 1H, J=7.3, 0.9 Hz, H_{arom}), 7.23 (dd, 1H, J=8.0, 0.9 Hz, H_{arom}), 7.29–7.34 (m, 4H, H_{arom}), 7.40 (ddd, 1H, J=7.8, 6.9, 1.4 Hz, H_{arom}), 7.90 (dd, 1H, J=8.3, 1.8 Hz, H_{arom}), 9.63 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=113.4, 114.1, 118.1, 120.1 (q, J=253.2 Hz), 122.0, 122.2, 131.8, 134.0, 140.0, 143.2, 146.2, 169.7. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.9 (s, OCF_3). IR (KBr): ν=3338w, 3072w, 1660s, 1600s, 1580s, 1519s, 1450s, 1421m, 1330w, 1284s, 1253s, 1200s, 1164s, 1152s, 1108w, 1014w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=234 nm (3.94). MS (ESI, MeOH): m/z=296.1 (100%, $(M-H)^-$), 615.2 (85% $[(M-H)_2Na]^-$). HRMS for $C_{14}H_{10}F_3NO_3$: calcd: 297.0613; found: 297.0614.

3.5.11. 2-(4,5-Dimethyl-2-nitroanilino)benzoic acid (6k). Compound **6k** (0.86 g, 91%) was obtained from **7k** (1.0 g, 3.3 mmol) following GP3. Mp 241–246 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ=2.23 (s, 6H, CH_3) 7.03 (ddd, 1H, J=6.9, 6.9, 1.4 Hz, H_{arom}), 7.42 (s, 1H, H_{arom}), 7.45–7.52 (m, 2H, H_{arom}), 7.91 (s, 1H, H_{arom}), 7.94 (dd, 1H, J= 7.8, 1.8 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=18.4, 19.9, 117.7, 118.1, 119.8, 121.1, 125.8, 129.8, 131.7, 133.7, 135.2, 135.9, 142.6, 145.8, 168.7. IR (KBr): ν=2923m, 1689s, 1627m, 1583s, 1566s, 1505s, 1484s, 1453m, 1434m, 1405m, 1338s, 1291m, 1262s, 1247s, 1158w, 1085w, 1053w, 1020w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.17). MS (ESI, MeOH): m/z=285.6 (100%, $(M-H)^-$). HRMS for $C_{15}H_{14}N_2O_4$: calcd: 286.0954; found: 286.0954.

3.5.12. 2-(2-Carboxyanilino)benzoic acid (6l).[21,67–71] Compound **6l** (0.76 g, 80%) was obtained from **7l** (1.0 g, 3.5 mmol) following GP3. Mp 300–301 °C (Lit.: 314–316 °C;[67] 302–305 °C;[68] 295 °C[69,70]). ^{1}H NMR (400 MHz, DMSO-d_6): 6.94 (ddd, 2H, J=7.9, 6.2, 2.1 Hz, H_{arom}), 7.40–7.48 (m, 4H, H_{arom}), 7.89 (d, 2H, J=7.9 Hz, H_{arom}), 10.80 (s, 1H, NH) 13.00 (s, 2H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=117.5, 117.6, 119.9, 131.7, 133.2, 143.5, 168.2. IR (KBr): ν=2970m, 2630m, 1668s, 1602m, 1581s, 1521s, 1449s, 1414m, 1325m, 1274s, 1250s, 1230s, 1166m, 1086w, 1044w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=220 nm (4.49). MS (ESI, MeOH): m/z=256.3 (100%, $(M-H)^-$), 535.5 (302% $[(M-H)_2Na]^-$).

3.5.13. 2-(3-Fluoroanilino)benzoic acid (6m). Compound **6m** (1.4 g, 96%) was obtained from **7m** (1.5 g, 6.1 mmol) following GP3. Mp 190–192 °C (Lit.: 164 °C;[72] 162–164 °C[73]). ^{1}H NMR (400 MHz, DMSO-d_6): 6.57 (ddd, 1H, J=9.1, 9.1, 2.5 Hz, H_{arom}), 6.69 (ddd, 1H, J=7.5, 7.1, 1.3 Hz, H_{arom}), 6.84–6.88 (m, 2H, H_{arom}), 7.13–7.25 (m, 3H, H_{arom}), 7.90 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.43 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=104.0 (d, J=23.8 Hz), 106.5 (d, J=21.5 Hz), 114.0, 114.7, 118.3, 124.4, 130.4, 131.0 (d, J=10.0 Hz), 132.5, 144.2, 145.3 (d, J=10.0 Hz), 163.5 (d, J=240.9 Hz), 172.0. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−112.9 (m, F). IR (KBr): ν=1606s, 1578s, 1544m, 1509s, 1448m, 1387m, 1284w, 1150s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=231 nm (4.16). MS (ESI, MeOH): m/z=230.3 (100%, $(M-H)^-$), 483.5 (32% $[(M-H)_2Na]^-$).

3.5.14. 2-(2,4-Difluoroanilino)benzoic acid (6n). Compound **6n** (1.5 g, 90%) was obtained from **7n** (1.8 g, 6.8 mmol) following GP3. Mp 202–204 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.79 (ddd, 1H, J=7.9, 7.9, 0.8 Hz, H_{arom}), 6.84 (d, 1H, J=8.7 Hz, H_{arom}), 7.04–7.12 (m, 1H, H_{arom}), 7.30–7.40 (m, 2H, H_{arom}), 7.45–7.52 (m, 1H, H_{arom}), 7.89 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.43 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ=104.9 (dd, J=24.9, 24.9 Hz), 111.8 (dd, J=21.2, 3.7 Hz), 112.5, 113.3, 117.7, 124.7 (dd, J=12.0, 2.8 Hz), 126.2 (dd, J=10.1, 2.8 Hz), 131.8, 134.5, 147.3, 155.8 (dd, J=246.7, 12.9 Hz), 158.6 (dd, J=243.5, 11.5 Hz), 170.1. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−115.4 (dd, J=15.2, 6.1 Hz, F), −120.1 (dd, J=15.2, 9.1 Hz, F). IR (KBr): ν=1661s, 1600m, 1582s, 1519s, 1450m, 1430m, 1334w, 1264s, 1210w, 1166m, 1142m, 1095w, 1043w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=234 nm (4.24). MS (ESI, MeOH): m/z=248.0 (100%, $(M-H)^-$). HRMS for $C_{14}H_9F_2NO_2$: calcd: 249.0601; found: 249.0600

3.5.15. 2-(2,3,4-Trifluoroanilino)benzoic acid (6o). Compound **6o** (1.6 g, 91%) was obtained from **7o** (1.8 g, 6.4 mmol) following GP3. Mp 210–215 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.83 (ddd, 1H, J=7.8, 7.8, 0.9 Hz, H_{arom}), 6.94 (d, 1H, J=8.3 Hz, H_{arom}), 7.24–7.34 (m, 2H, H_{arom}), 7.39 (ddd, 1H, J=7.3, 7.3, 1.8 Hz, H_{arom}), 7.97 (dd, 1H, J=8.3, 1.8 Hz, H_{arom}), 9.3 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): δ=112.2 (dd, J=17.5, 3.7 Hz), 113.1, 113.7, 118.3, 118.7 (d, J=6.5), 126.3 (dd, J=9.2, 2.8 Hz), 131.7, 134.3, 139.8 (ddd, J=248.6, 14.7, 14.7 Hz), 144.7 (ddd, J=247.6, 11.0, 3.7 Hz), 146.4, 147.6 (ddd,

J=243.9, 11.0, 2.8 Hz), 169.9. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−141.3 (m, F), −144.9 (m, F), −160.1 (m, F). IR (KBr): ν=3308m, 3082m, 1674s, 1616m, 1590s, 1535s, 1513s, 1489m, 1454s, 1446s, 1413w, 1313w, 1265s, 1238w, 1224w, 1165w, 1086w, 1056m, 1042m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.37). MS (ESI, MeOH): m/z=266.3 (100%, (M−H)$^-$), 555.7 (50% [(M−H)$_2$Na]$^-$). HRMS for $C_{13}H_8F_3NO_2$: calcd: 267.0507; found: 267.0509.

3.5.16. 2-(2,4-Dimethoxyanilino)benzoic acid (6p). Compound **6p** (1.9 g, 97%) was obtained from **7p** (2.0 g, 7.0 mmol) following GP3. Mp 180 °C (Lit.: 158–162 °C[25]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.53 (dd, 1H, J=8.7, 2.5 Hz, H_{arom}), 6.62–6.68 (m, 2H, H_{arom}), 6.80 (dd, 1H, J=8.3, 0.8 Hz, H_{arom}), 7.21 (d, 1H, J=8.3 Hz, H_{arom}), 7.28 (ddd, 1H, J=8.3, 7.1, 1.7 Hz, H_{arom}), 7.83 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), (s, 1H, NH), 12.8 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 55.6, 99.5, 104.4, 111.2, 112.5, 115.8, 121.5, 124.6, 131.4, 133.8, 148.6, 153.5, 156.9, 169.6. IR (KBr): ν=3333m, 2994s, 2968m, 2933m, 2641m, 1655s, 1611m, 1577s, 1518s, 1446s, 1421m, 1338w, 1314w, 1274s, 1256s, 1207s, 1155s, 1129s, 1039s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.66). MS (ESI, MeOH): m/z=272.4 (50%, (M−H)$^-$), 567.5 (100% [(M−H)$_2$Na]$^-$)

3.5.17. 2-(2,5-Dimethoxyanilino)benzoic acid (6q).[25,74,75] Compound **6q** (1.3 g, 90%) was obtained from **7q** (1.5 g, 5.2 mmol) following GP3. Mp 162–164 °C (Lit.: 167–168 °C;[74] 155–157 °C[25]). ^{1}H NMR (400 MHz, DMSO-d_6): 3.69 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.57 (dd, 1H, J=8.7, 2.9 Hz, H_{arom}), 6.78 (ddd, 1H, J=8.7, 6.6, 0.8 Hz, H_{arom}), 6.94 (d, 1H, J=2.9 Hz, H_{arom}), 6.97 (d, 1H, J=8.7 Hz, H_{arom}), 7.27 (d, 1H, J=8.3 Hz, H_{arom}), 7.40 (ddd, 1H, J=8.3, 7.1, 1.7 Hz, H_{arom}), 7.88 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.60 (s, NH), 13.0 (s, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=55.3, 56.1, 106.0, 106.7, 112.5, 113.1, 113.9, 117.3, 130.2, 131.6, 133.9, 144.7, 145.9, 153.1, 169.3. IR (KBr): ν=2953m, 2826m, 2640w, 1674s, 1605s, 1578s, 1537s, 1496m, 1448m, 1428m, 1410w, 1321w, 1260s, 1216s, 1201m, 1170m, 1133m, 1060w, 1028m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.40). MS (ESI, MeOH): m/z=272.3 (55%, (M−H)$^-$), 567.6 (100% [(M−H)$_2$Na]$^-$).

3.5.18. 4-Chloro-2-[4-(trifluoromethoxy)anilino] benzoic acid (6r). Compound **6r** (1.7 g, 90%) was obtained from **7r** (2.0 g, 5.8 mmol) following GP3. Mp 180–185 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ=6.83 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 7.09 (d, 1H, J=2.1 Hz, H_{arom}), 7.34–7.40 (m, 4H, H_{arom}), 7.89 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=111.7, 112.7, 117.6, 120.0 (q, J=255.5 Hz), 122.2, 123.4, 133.5, 138.7, 138.8, 143.9, 147.6, 168.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.7 (s, OCF_3). IR (KBr): ν=1661s, 1599s, 1571s, 1513s, 1455m, 1428s, 1401m, 1333m, 1290s, 1255s, 1217s, 1150s, 1104s, 1015w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=242 nm (3.99). MS (ESI, MeOH): m/z=330.7 (100%, (M−H)$^-$), 684.9 (70% [(M−H)$_2$Na]$^-$). Anal. calcd for $C_{14}H_9ClF_3NO_3$ (299.68): C, 50.70; H, 2.74; N, 4.22; found: C, 50.75; H, 2.88; N, 4.57.

3.5.19. 4-Chloro-2-(2,4-difluoroanilino)benzoic acid (6s). Compound **6s** (1.3 g, 95%) was obtained from **7s** (1.5 g, 5.0 mmol) following GP3. Mp 320 °C (decomp.). ^{1}H NMR (400 MHz, acetone-d_6): 6.54 (dd, 1H, J=8.3, 2.1 Hz, H_{arom}), 6.77 (t, 1H, J=1.7 Hz, H_{arom}), 6.95 (ddd, 1H, J=8.7, 2.9, 1.7 Hz, H_{arom}), 7.05 (ddd, 1H, J=9.1, 8.7, 2.9 Hz, H_{arom}), 7.37–7.45 (m, 1H, H_{arom}), 8.07 (d, 1H, J=8.3 Hz, H_{arom}), 11.42 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ=104.3 (t, J=25.0 Hz), 111.0, 111.3 (dd, J=21.5, 3.8 Hz), 116.1, 121.1, 123.2 (d, J=10.0 Hz), 126.1 (dd, J=13.0, 3.2 Hz), 133.3, 134.4, 146.7, 155.1 (dd, J=246.3, 12.3 Hz), 157.5 (dd, J=246.3, 12.3 Hz), 170.6. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−118.1 (m, F), −121.4 (m, F). IR (KBr): ν=1610m, 1584s, 1426m, 1373m, 1298w, 1259m, 1192w, 1141w, 1094w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=220 nm (4.14). MS (ESI, MeOH): m/z=282.6 (100%, (M−H)$^-$). HRMS for $C_{13}H_8ClF_2NO_2$: calcd: 283.0212; found: 283.0212.

3.5.20. 4-Chloro-2-(2,3,4-trifluoroanilino)benzoic acid (6t). Compound **6t** (0.92 g, 95%) was prepared from **7t** (1.0 g, 3.2 mmol) according to GP3 followed by column chromatography (silica gel, $CHCl_3$). Mp 280–287 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 6.64 (dd, 1H, J=8.3, 2.1 Hz, H_{arom}), 6.88 (d, 1H, J=0.9 Hz, H_{arom}), 7.14–7.24 (m, 2H, H_{arom}), 7.84 (d, 1H, J=8.0 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=111.9, 112.1 (d, J=3.1 Hz), 115.5, 116.9 (m), 122.1 (m), 128.4, 133.6, 134.6, 139.9 (ddd, J=247.0, 16.1, 16.1 Hz), 143.7 (ddd, J=245.7, 7.8, 3.1 Hz), 145.0 (ddd, J=245.7, 9.3, 3.2 Hz), 146.4, 170.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−144.2 (m, F), −147.4 (m, F), −160.6 (ddd, J=21.4, 21.4, 4.7 Hz, F). IR (KBr): ν=1607s, 1518s, 1485s, 1430m, 1371m, 1265m, 1168w, 1050s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.03). MS (ESI, MeOH): m/z=300.1 (100%, (M−H)$^-$), 623.1 (95% [(M−H)$_2$Na]$^-$). HRMS for $C_{13}H_7ClF_3NO_2$: calcd: 301.0117; found: 301.0119.

3.5.21. 5-Nitro-2-[4-(trifluoromethoxy)anilino] benzoic acid (6u). Compound **6u** (1.6 g, 95%) was prepared from **7u** (1.8 g, 5.1 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): 6.00 (d, 1H, J=9.9 Hz, H_{arom}), 6.77–6.82 (m, 2H, H_{arom}), 7.08–7.12 (m, 2H, H_{arom}), 7.37 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.09 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=112.2, 120.3 (q, J=253.9 Hz), 121.6, 123.4, 125.7, 126.6, 128.3, 128.4, 141.7, 154.1, 159.5, 173.8. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−57.7 (s, OCF_3). IR (KBr): ν=1630s, 1598s, 1531s, 1508s, 1482s, 1443s, 1385s, 1332s, 1296s, 1270s, 1204s, 1147s, 1133s, 1066m, 1015m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=404 nm (3.97). MS (ESI, MeOH): m/z=341.3 (100%, (M−H)$^-$), 705.4 (40% [(M−H)$_2$Na]$^-$). HRMS for $C_{14}H_9F_3N_2O_4$: calcd: 342.0464; found: 342.0465.

3.5.22. 2-(2,4-Difluoroanilino)-5-nitro-benzoic acid (6v). Compound **6v** (1.4 g, 94%) was prepared from **7v** (1.5 g, 4.9 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, acetone-d_6): δ=5.86 (dd, 1H, J=10.0, 2.1 Hz, H_{arom}), 6.80–6.93 (m, 2H, H_{arom}), 7.01 (ddd, 1H, J=9.1, 9.1, 2.1 Hz, H_{arom}), 7.39 (dd, 1H, J=10.0, 2.9 Hz, H_{arom}), 8.08 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): δ=110.8 (dd, J=21.5, 3.0 Hz), 112.3, 124.8

(m), 125.5, 126.8, 128.1, 128.4, 138.7 (d, J=12.3 Hz), 154.1 (dd, J=241.7, 11.5 Hz), 155.8 (dd, J=237.9, 11.5 Hz), 160.5, 173.7. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−122.3 (m, F) IR (KBr): ν=1638s, 1537s, 1451s, 1341s, 1289m, 1264m, 1194m, 1143m, 1096m, 1070m cm^{-1}. UV–vis (methanol): λ_{max} (log ε) 395 nm (3.82). MS (ESI, MeOH): m/z=293.3 (100%, $(M-H)^-$), 609.3 (30% $[(M-H)_2Na]^-$). HRMS for $C_{13}H_8F_2N_2O_4$: calcd: 294.0452; found: 294.0452.

3.5.23. 2-(2,3,4-Trifluoroanilino)-5-nitro-benzoic acid (6w). Compound **6w** (0.90 g, 93%) was prepared from **7w** (1.0 g, 3.1 mmol) following GP3. Mp 300 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6): 5.88 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 6.63–6.71 (m, 1H, H_{arom}), 6.94–7.04 (m, 1H, H_{arom}), 7.41 (dd, 1H, J=9.5, 2.9 Hz, H_{arom}), 8.12 (d, 1H, J=2.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, DMSO-d_6): 111.1 (dd, J=16.1, 3.1 Hz), 112.3, 118.3(m), 125.5, 127.4, 128.1, 128.2, 139.6 (ddd, J=245.2, 16.1, 16.1 Hz), 140.5 (m), 143.9 (dd, J=242.5, 5.8 Hz), 143.3 (dd, J=236.7, 11.1 Hz), 160.5, 173.6. ^{19}F NMR (188 MHz, DMSO-d_6): δ=−147.2 (dd, J=22.9, 9.2 Hz, F), −147.9 (m, F), −162.4 (ddd, J=22.9, 22.9, 9.2 Hz, F). IR (KBr): 1615s, 1456s, 1413m, 1381m, 1340s, 1294m, 1265m, 1150m, 1133w, 1071w, 1049m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=389 nm (3.94). MS (ESI, MeOH): m/z=311.2 (100%, $(M-H)^-$). HRMS for $C_{13}H_7F_3N_2O_4$: calcd: 312.0358; found: 312.0359.

3.5.24. Methyl 2-[4-(trifluoromethoxy)anilino]benzoate (7j). Following GP2 from 4-trifluoromethoxyaniline (1.61 g, 9.12 mmol) and methyl 2-iodo-benzoate (2.00 g, 7.60 mmol) **7j** (2.2 g, 93%) was obtained as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.75 (t, 1H, J=7.5 Hz, H_{arom}), 7.15–7.24 (m, 5H, H_{arom}), 7.32 (ddd, 1H, J=8.5, 7.1, 1.5 Hz, H_{arom}), 7.95 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.8, 112.3, 113.9, 117.6, 120.4 (q, J=256.2 Hz, OCF_3), 122.0, 123.1, 131.6, 134.0, 139.5, 144.6, 147.3, 168.7. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.8 (s, OCF_3). IR (film): ν=3318m, 3037w, 2954m, 1690s, 1601s, 1584s, 1518s, 1456s, 1438s, 1406m, 1325s, 1254s, 1202s, 1163s, 1085s, 1048w, 1015w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 237 nm (4.38). MS (ESI, MeOH+TFA): m/z=312.1 (100%, $(M+H)^+$). HRMS for $C_{15}H_{12}F_3NO_3$: calcd: 311.0777; found: 311.0770

3.5.25. Methyl 2-(4,5-dimethyl-2-nitroanilino)benzoate (7k). Compound **7k** (2.0 g, 89%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 4,5-dimethyl-2-nitroaniline (1.5 g, 9.1 mmol) following GP2. Mp 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.23 (s, 6H, CH_3), 3.94 (s, 3H, OCH_3), 6.98 (ddd, 1H, J=7.3, 7.8, 1.4 Hz, H_{arom}), 7.36 (s, 1H, H_{arom}), 7.41 (ddd, 1H, J=7.3, 8.3, 1.4 Hz, H_{arom}), 7.47 (dd, 1H, J=8.3, 1.4 Hz, H_{arom}), 7.92 (s, 1H, H_{arom}), 8.00 (dd, 1H, J=7.8, 1.4 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=18.8, 20.3, 52.2, 118.1, 118.6, 119.4, 121.1, 126.5, 129.3, 132.0, 133.3, 135.4, 136.8, 142.9, 145.2, 167.5. IR (KBr): ν=2922m, 1701s, 1628m, 1583s, 1566s, 1507s, 1457m, 1425m, 1336s, 1295m, 1273s, 1249s, 1180w, 1164w, 1080m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.34). MS (ESI, MeOH): m/z=301.1 (100%, $(M+)^+$). HRMS for $C_{16}H_{16}N_2O_4$: calcd: 300.1110; found: 300.1111.

3.5.26. Methyl 2-[2-(methoxycarbonyl)anilino]benzoate (7l). Compound **7l** (1.1 g, 51%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and methyl 2-amino-benzoate (1.4 g, 9.1 mmol) following GP2; the crude product was recrystallized from ethanol. Mp 90–95 °C (Lit.: 102–103 °C;[76] 96–98 °C[77]). ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.93 (s, 6H, OCH_3), 6.88 (t, 2H, J=7.5 Hz, H_{arom}), 7.35 (ddd, 2H, J=7.5, 7.5, 1.6 Hz, H_{arom}), 7.52 (d, 2H, J=8.3 Hz, H_{arom}), 7.97 (dd, 2H, J=7.9, 1.7 Hz, H_{arom}), 11.0 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.1, 117.1, 117.6, 119.8, 131.7, 133.2, 144.1, 167.6. IR (KBr): ν=3030w, 2940w, 1698s, 1609m, 1582s, 1523s, 1449s, 1432m, 1320m, 1266s, 1221s, 1193m, 1161w, 1085s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=237 nm (4.37). MS (ESI, MeOH): m/z=308.2 (100%, $(M+Na)^+$).

3.5.27. Methyl 2-(3-fluoroanilino)benzoate (7m). Compound **7m** (1.8 g, 94%) was obtained as an oil from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and *m*-fluoroaniline (1.0 g, 9.0 mmol) following GP2. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.60–6.70 (m, 2H, H_{arom}), 6.96 (m, 2H, H_{arom}), 7.20–7.38 (m, 3H, H_{arom}), 7.96 (dd, 1H, J=7.5, 1.7 Hz, H_{arom}), 9.50 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.9, 108.2 (d, J=24.2 Hz), 109.6 (d, J=24.2 Hz), 112.8, 114.5, 117.0, 117.9, 130.3 (d, J= 9.6 Hz), 131.6, 134.0, 142.6(d, J=10.0 Hz), 146.7, 163.4(d, J=244.7 Hz), 168.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ= −112.5 (m, F). IR (film): ν=3318w, 2952w, 1690s, 1602s, 1580s, 1521s, 1492m, 1455s, 1437m, 1328m, 1263s, 1250s, 1231s, 1192m, 1164m, 1141m, 1085m, 1047w, 1002w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=236 nm (4.36). MS (ESI, MeOH): m/z=246.3 (100%, $(M+H)^+$). HRMS for $C_{14}H_{12}FNO_2$: calcd: 245.0852; found: 245.0865.

3.5.28. Methyl 2-(2,4-difluoroanilino)benzoate (7n). Compound **7n** (2.0 g, 98%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,4-difluoroaniline (1.2 g, 9.3 mmol) following GP2. Mp 62–63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.90 (s, 3H, OCH_3), 6.74 (ddd, 1H, J=7.1, 1.2 Hz, H_{arom}), 6.82–6.94 (m, 3H, H_{arom}), 7.27–7.36 (m, 2H, H_{arom}), 7.95 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 9.23 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=51.8, 104.8 (t, J=9.6 Hz), 111.2 (dd, J=22.1, 3.7 Hz), 112.1, 113.4, 117.5, 124.7 (dd, J=12.0, 3.7 Hz), 126.1 (dd, J=2.8, 9.2 Hz), 131.6, 134.2, 147.9, 156.5 (dd, J=246.7, 11.0 Hz), 159.3 (dd, J=250.4, 12.0 Hz), 168.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−115.2 (m, F), −119.3 (m, F). IR (KBr): ν=3307w, 2953w, 1683s, 1587s, 1529s, 1458m, 1435m, 1332m, 1288m, 1254s, 1229s, 1190m, 1170m, 1148m, 1088s, 1054w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)= 236 nm (4.17). MS (ESI, MeOH): m/z=264.1 (100%, $(M+H)^+$). HRMS for $C_{14}H_{11}F_2NO_2$: calcd: 263.0758; found: 263.0759

3.5.29. Methyl 2-(2,3,4-trifluoroanilino)benzoate (7o). Compound **7o** (1.9 g, 91%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,3,4-trifluoroaniline (1.3 g, 9.1 mmol) according to GP2 followed by column chromatography (silica gel, $CHCl_3$). Mp 70–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.90 (s, 3H, OCH_3), 6.79 (ddd, 1H, J=7.9, 7.0, 1.2 Hz, H_{arom}), 6.91–6.95 (m, 2H, H_{arom}), 7.05–7.15 (m, 1H, H_{arom}), 7.32 (ddd, 1H, J=9.1, 7.1, 1.2 Hz, H_{arom}), 7.97 (dd, 1H, J=7.8, 1.2 Hz, H_{arom}), 9.3 (s,

1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 111.2 (dd, J=18.4, 4.6 Hz), 112.7, 113.7, 118.0, 118.1, 126.3 (dd, J=9.2, 3.1 Hz), 131.6, 134.1, 140.7 (ddd, J=250.9, 16.1, 16.1 Hz), 145.7 (ddd, J=247.1, 10.7, 2.3 Hz), 147.0, 147.4 (ddd, J=247.1, 10.7, 2.3 Hz), 145.7 (ddd, J=247.1, 10.7, 2.3 Hz), 168.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−140.0 (m, F), −143.7 (d, J=20.1 Hz, F), −158.6 (ddd, J=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=3304m, 2997w, 2955m, 1682s, 1615s, 1589s, 1536s, 1514s, 1491s, 1455m, 1436s, 1330m, 1315m, 1293m, 1255s, 1221s, 1191m, 1168m, 1141m, 1090s, 1060m, 1042m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.47). MS (ESI, MeOH): m/z=282.0 (100%, $(M+H)^+$). HRMS for $C_{14}H_{10}F_3NO_2$: 281.0664; found: 281.0664.

3.5.30. Methyl 2-(2,4-dimethoxyanilino)benzoate (7p). Compound **7p** (2.1 g, 97%) was obtained from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,4-dimethoxyaniline (1.4 g, 9.1 mmol) following GP2. ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.46 (dd, 1H, J=8.5, 3.1 Hz, H_{arom}), 6.54 (d, 1H, J=3.1 Hz, H_{arom}), 6.64 (ddd, 1H, J=7.9, 6.7, 1.2 Hz, H_{arom}), 6.95 (d, 1H, J=8.5 Hz, H_{arom}), 7.21–7.26 (m, 2H, H_{arom}), 7.92 (dd, 1H, J=8.5, 1.2 Hz, H_{arom}), 9.13 (s, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ=51.6, 55.5, 55.7, 99.6, 103.9, 111.3, 113.4, 116.1, 122.7, 124.8, 131.5, 134.0, 149.1, 154.2, 157.4, 168.9. IR (kap.): ν=3333m, 3001w, 2950m, 2836w, 1686s, 1604s, 1578m, 1519s, 1454s, 1437s, 1415m, 1249s, 1209s, 1188m, 1159s, 1129m, 1084s, 1035m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.46). MS (ESI, MeOH): m/z=288.4 (100%, $(M+H)^+$). HRMS for $C_{16}H_{17}NO_4$: calcd: 287.1158; found: 287.1155.

3.5.31. Methyl 2-(2,5-dimethoxyanilino)benzoate (7q).[78] Compound **7q** (1.6 g, 73%) was obtained as an oil from methyl 2-iodobenzoate (2.0 g, 7.6 mmol) and 2,5-dimethoxyaniline (1.4 g, 9.1 mmol) following GP2. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.75 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.51 (dd, 1H, J=9.1, 2.9 Hz, H_{arom}), 6.74 (ddd, 1H, J=7.1, 7.1, 1.3 Hz, H_{arom}), 6.83 (d, 1H, J=8.7 Hz, H_{arom}), 7.03 (d, 1H, J=2.9 Hz, H_{arom}), 7.32 (ddd, 1H, J=7.1, 6.6, 1.7 Hz, H_{arom}), 7.38 (dd, 1H, J=8.7, 1.3 Hz, H_{arom}), 7.95 (dd, 1H, J=7.9, 1.7 Hz, H_{arom}), 9.45 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=51.8, 55.8, 56.5, 106.5, 106.7, 112.0, 113.2, 114.7, 117.4, 131.1, 131.5, 133.8, 145.5, 146.5, 153.6, 168.4. IR (film): ν=3328m, 3078w, 2999m, 2950m, 2834m, 1732m, 1690s, 1597s, 1579s, 1526s, 1455s, 1436s, 1314s, 1288s, 1260s, 1217s, 1200s, 1180s, 1164m, 1132s, 1085s, 1046s, 1026m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=233 nm (4.50). MS (ESI, MeOH): m/z=288.1 (100%, $(M+H)^+$). HRMS for $C_{16}H_{17}NO_4$: calcd: 287.1158; found: 287.1159.

3.5.32. Methyl 4-chloro-2-[4-(trifluoromethoxy)anilino]-benzoate (7r). Compound **7r** (2.1 g, 90%) was obtained from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 4-trifluoromethoxyaniline (1.5 g, 8.5 mmol) following GP2. Mp 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.70 (dd, 1H, J=8.3, 1.7 Hz, H_{arom}), 7.1 (d, 1H, J=2.1 Hz, H_{arom}), 7.16–7.24 (m, 4H, H_{arom}), 7.88 (d, 1H, J=8.3 Hz, H_{arom}), 9.53 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 110.4, 113.2, 117.8, 120.5 (q, J=256.6 Hz), 122.3, 124.1, 132.9, 138.6, 140.6, 145.5, 148.6, 168.2. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.7 (s, OCF_3).IR (KBr): ν=3321m, 2957m, 1697s, 1599s, 1576s, 1516s, 1439m, 1425s, 1406m, 1321m, 1257s, 1226s, 1200s, 1153s, 1100s, 1080w, 1014w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=243 nm (4.40). MS (ESI, MeOH): m/z=344.2 (100%, $(M-H)^-$). HRMS for $C_{15}H_{11}ClF_3NO_3$: calcd: 345.0380; found: 345.0381.

3.5.33. Methyl 4-chloro-2-(2,4-difluoroanilino)benzoate (7s). Compound **7s** (1.7 g, 86%) was obtained from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 2,4-difluoroaniline (1.1 g, 8.5 mmol) following GP2. Mp 89–91 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.89 (s, 3H, OCH_3), 6.69 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.78 (t, 1H, J=1.7 Hz, H_{arom}), 6.86–6.96 (m, 2H, H_{arom}), 7.28–7.34 (m, 1H, H_{arom}), 7.87 (d, 1H, J=8.7 Hz, H_{arom}), 9.30 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.0, 105.0 (dd, J=23.8, 23.8 Hz), 110.3, 111.4 (dd, J=21.5, 3.8 Hz), 112.8, 117.6, 123.7 (dd, J=12.3, 3.1 Hz), 126.9 (dd, J=10.0, 2.3 Hz), 132.7, 140.6, 149.0, 156.9 (dd, J=247.1, 10.7 Hz), 159.9 (dd, J=250.1, 12.3 Hz), 168.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−113.6 (m, F), −118.5 (m, F). IR (KBr): ν=3294w, 3070w, 2959w, 1693s, 1603m, 1579s, 1518s, 1435m, 1328m, 1287m, 1261s, 1245s, 1206m, 1186m, 1144m, 1101s, 1085m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=242 nm (4.50). MS (ESI, MeOH): m/z=296.3 (100%, $(M-H)^-$). HRMS for $C_{14}H_{10}ClF_2NO_2$: calcd: 297.0368; found: 297.0366.

3.5.34. Methyl 4-chloro-2-(2,3,4-trifluoroanilino)benzoate (7t). Compound **7t** (1.2 g, 54%) was prepared from methyl 4-chloro-2-iodobenzoate (2.0 g, 6.8 mmol) and 2,3,4-trifluoroaniline (1.2 g, 8.1 mmol) following GP2. Mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.90 (s, 3H, OCH_3), 6.74 (dd, 1H, J=8.7, 2.1 Hz, H_{arom}), 6.83 (t, 1H, J=1.6 Hz, H_{arom}), 6.94–7.02 (m, 1H, H_{arom}), 7.04–7.12 (m, 1H, H_{arom}), 7.89 (d, 1H, J=8.7 Hz, H_{arom}), 9.39 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.1, 110.7, 111.6 (dd, J=17.6, 3.8 Hz), 113.1, 118.2, 119.1 (dd, J=7.7, 3.8 Hz), 125.3 (dd, J=9.2, 3.1 Hz), 132.8, 140.6 (ddd, J=252.4, 14.6, 14.6 Hz), 140.6, 146.1 (ddd, J=249.4, 12.3, 3.8 Hz), 148.3 (ddd, J=247.8, 10.0, 2.3 Hz), 148.3, 168.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−138.1 (m, F), −142.3 (m, F), −157.8 (ddd, J=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=3244m, 2969w, 1696s, 1617s, 1594s, 1534s, 1515s, 1491s, 1441m, 1419m, 1328m, 1293m, 1257s, 1217m, 1190w, 1168w, 1151w, 1105m, 1082w, 1049s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=241 nm (4.42). MS (ESI, MeOH): m/z=300.3 (90%, $(M-H)^-$), 623.3 (100% $[(M-H)_2Na]^-$). HRMS for $C_{14}H_9ClF_3NO_2$: calcd: 315.0274; found: 315.0274.

3.5.35. Methyl 5-nitro-2-[4-(trifluoromethoxy)anilino]-benzoate (7u). Compound **7u** (2.0 g, 87%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 4-trifluoromethoxyaniline (1.4 g, 7.9 mmol) following GP2. Mp 49–52 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.96 (s, 3H, OCH_3), 7.03 (d, 1H, J=9.5 Hz, H_{arom}), 7.24–7.30 (m, 4H, H_{arom}), 8.13 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 8.95 (d, 1H, J=2.5 Hz, H_{arom}), 10.13 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.5, 110.5, 112.9, 120.4 (q, J=275.4 Hz), 122.4, 125.8, 128.8, 129.4, 137.0, 137.8, 146.8, 152.4, 167.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.7 (s, OCF_3).

IR (KBr): ν=3254m, 2963m, 1702s, 1604s, 1586s, 1537m, 1509s, 1446m, 1348s, 1259s, 1209s, 1130s, 1109s, 1070m, 1014m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.33). MS (ESI, MeOH): *m*/*z*=355.4 (100%, (M−H)$^-$). HRMS for $C_{15}H_{11}F_3N_2O_4$: calcd: 356.0620; found: 356.0620.

3.5.36. Methyl 2-(2,4-difluoroanilino)-5-nitrobenzoate (7v). Compound **7v** (1.7 g, 85%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 2,4-difluoroaniline (1.0 g, 7.7 mmol) following GP2. Mp 178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=3.96 (s, 3H, OCH_3), 6.74 (dd, 1H, *J*=9.1, 1.7 Hz, H_{arom}), 6.90–7.00 (m, 2H, H_{arom}), 7.29–7.35 (m, 1H, H_{arom}), 8.13 (dd, 1H, *J*=9.5, 3.0 Hz, H_{arom}), 8.90 (d, 1H, *J*=2.5 Hz, H_{arom}), 9.89 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ=52.5, 105.3 (dd, *J*=26.1, 26.8 Hz), 110.5, 111.9 (dd, *J*=22.3, 3.8 Hz), 112.9, 122.2 (dd, *J*=12.6, 4.2 Hz), 128.1 (dd, *J*=10.0, 2.3 Hz), 128.6, 129.3, 137.9, 152.7, 157.2 (dd, *J*=251.7, 12.3 Hz), 160.9 (dd, *J*=249.4, 11.5 Hz), 167.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.0 (m, F), −116.7 (m, F). IR (KBr): ν=2926w, 1702s, 1612s, 1589s, 1542m, 1511s, 1439m, 1361m, 1331s, 1292m, 1266s, 1231m, 1198m, 1144m, 1095m, 1076m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=230 nm (4.37). MS (ESI, MeOH): *m*/*z*=307.3 (100%, (M−H)$^-$). HRMS for $C_{14}H_{10}F_2N_2O_4$: calcd: 308.0609; found: 308.0610.

3.5.37. Methyl 2-(2,3,4-trifluoroanilino)5-nitro-benzoate (7w). Compound **7w** (1.3 g, 60%) was prepared from methyl 2-iodo-5-nitrobenzoate (2.0 g, 6.5 mmol) and 2,3,4-trifluoroaniline (1.1 g, 7.5 mmol) according to GP2 followed by column chromatography (silica gel, $CHCl_3$). Mp 216–217 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 3.98 (s, 3H, OCH_3), 6.80 (dd, 1H, *J*=9.1, 1.7 Hz, H_{arom}), 6.99–7.13 (m, 2H, H_{arom}), 8.15 (dd, 1H, *J*=9.1, 2.5 Hz, H_{arom}), 8.92 (d, 1H, *J*=2.5 Hz, H_{arom}), 9.96 (s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6, 50 °C): δ=52.5, 110.8, 112.4 (dd, *J*=17.5, 3.7 Hz), 114.0, 122.2 (d, *J*=8.3 Hz), 123.9 (dd, *J*=10.1, 3.7 Hz), 127.5, 129.2, 137.5, 139.7 (ddd, *J*=249.5, 16.5, 13.8 Hz), 146.0 (ddd, *J*=249.5, 9.2, 3.7 Hz), 148.5 (ddd, *J*=249.5, 10.1, 3.7 Hz), 151.6, 166.3. ^{19}F NMR (200 MHz, $CDCl_3$): δ=−136.2 (m, F), −141.3 (dd, *J*=18.4, 6.2 Hz, F), −158.1 (ddd, *J*=23.1, 23.1, 8.4 Hz, F). IR (KBr): ν=2925w, 1705m, 1616s, 1595s, 1545m, 1508s, 1486m, 1444m, 1332s, 1304m, 1272s, 1224m, 1138w, 1077w, 1049m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=367 nm (4.38). MS (ESI, MeOH): *m*/*z*=325.4 (100%, (M−H)$^-$). HRMS for $C_{14}H_9F_3N_2O_4$: calcd: 326.0514; found: 326.0516.

3.5.38. 9-Chloro-2-methoxy-6-nitroacridine (8a). Compound **8a** (1.6 g, 80%) was prepared from **6a** (2.0 g, 6.9 mmol) following GP4. Mp 223–226 °C (Lit.: 229–230 °C;[79] 213–214 °C[80]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.05 (s, 3H OCH_3), 7.48 (d, 1H, *J*=2.9 Hz, H_{arom}), 7.54 (dd, 1H, *J*=9.5, 2.9 Hz, H_{arom}), 8.12 (d, 1H, *J*=9.5 Hz, H_{arom}), 8.29 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.47 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.08 (d, 1H, *J*=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0, 99.7, 107.7, 119.8, 126.2, 126.3, 126.6, 126.8, 127.3, 132.0, 138.1, 145.1, 147.7, 159.7. IR (KBr): ν=1634m, 1613s, 1558m, 1538m, 1511m, 1477m, 1426m, 1404m, 1344s, 1271w, 1223s, 1076w, 1024w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (4.44). HRMS for $C_{14}H_9ClN_2O_3$: calcd: 288.0302, found: 288.0293.

3.5.39. 9-Chloro-5-methoxy-2-nitroacridine (8b). Compound **8b** (1.5 g, 75%) was prepared from **6b** (2.0 g, 6.9 mmol) following GP4. Mp 360 °C (Lit.: 265–267 °C[54]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.17 (s, 3H OCH_3), 7.17 (d, 1H, *J*=8.3 Hz, H_{arom}), 7.63 (dd, 1H, *J*=9.1, 7.9 Hz, H_{arom}), 8.00 (dd, 1H, *J*=8.7, 1.2 Hz, H_{arom}), 8.47 (m, 2H, H_{arom}), 9.37 (d, 1H, *J*=1.2 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.6, 108.8, 116.4, 122.3, 122.9, 122.9, 125.9, 128.5, 132.7, 144.0, 145.8, 148.2, 155.3, 158.4. IR (KBr): ν=1628m, 1609m, 1582m, 1542s, 1509m, 1468m, 1457m, 1401s, 1346s, 1337s, 1305w, 1278m, 1267m, 1219w, 1177w, 1135w, 1107m, 1069w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=255 nm (3.76). MS (ESI, MeOH+TFA): *m*/*z*=289.2 (100%, (M+H)$^+$).

3.5.40. 9-Chloro-2,4-dimethoxy-6-nitroacridine (8c).[27,81] Compound **8c** (1.4 g, 70%) was prepared from **6c** (2.0 g, 6.3 mmol) following GP4. Mp 250–252 °C (Lit.: 225–227 °C[27]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.03 (s, 3H OCH_3), 4.14 (s, 3H OCH_3), 6.80 (d, 1H, *J*=2.5 Hz, H_{arom}), 7.12 (d, 1H, *J*=2.5 Hz, H_{arom}), 8.32 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.46 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.27 (d, 1H, *J*=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.0, 56.8, 92.4, 103.7, 120.2, 125.9, 127.0, 127.3, 127.6, 138.0, 141.7, 143.9, 147.8, 156.6, 160.4. IR (KBr): ν=2945w, 1631m, 1614m, 1570w, 1515s, 1421m, 1402m, 1346s, 1330s, 1244s, 1045w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=273 nm (4.44). HRMS for $C_{15}H_{11}ClN_2O_3$: calcd: 318.0407, found: 318.0399.

3.5.41. 9-Chloro-5-methoxy-3-nitroacridine (8f). Compound **8f** (1.6 g, 79%) was prepared from **6f** (2.0 g, 6.9 mmol) following GP4. Mp 230–235 °C (Lit.: 204–205 °C[79]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.18 (s, 3H OCH_3), 7.14 (d, 1H, *J*=7.1 Hz, H_{arom}), 7.65 (dd, 1H, *J*=8.7, 7.5 Hz, H_{arom}), 7.99 (dd, 1H, *J*=8.7, 0.8 Hz, H_{arom}), 8.32 (dd, 1H, *J*=9.5, 2.5 Hz, H_{arom}), 8.52 (d, 1H, *J*=9.5 Hz, H_{arom}), 9.31 (d, 1H, *J*=2.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.6, 108.0, 116.3, 120.0, 126.3, 126.5, 126.6, 127.2, 129.2, 141.3, 143.6, 145.8, 148.4, 155.5. IR (KBr): ν=2924w, 1625w, 1566w, 1512s, 1455m, 1398s, 1347m, 1310m, 1270w, 1155w, 1069w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.49). HRMS for $C_{14}H_9ClN_2O_3$: calcd: 288.0302, found: 288.0303.

3.5.42. 9-Chloro-2,4-dimethoxy-7-nitroacridine (8g). Compound **8g** (1.7 g, 85%) was prepared from **6g** (2.0 g, 6.3 mmol) following GP4. Mp 258–261 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 4.04 (s, 3H OCH_3), 4.14 (s, 3H OCH_3), 6.85 (d, 1H, *J*=2.1 Hz, H_{arom}), 7.14 (d, 1H, *J*=2.5 Hz, H_{arom}), 8.40–8.46 (m, 2H, H_{arom}), 9.34 (dd, 1H, *J*=2.1, 0.8 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.9, 56.7, 92.3, 104.5, 121.7, 123.4, 126.8, 132.6, 140.7, 141.9, 146.0, 146.6, 156.4, 159.7. IR (KBr): ν=1633s, 1560m, 1542s, 1509s, 1466s, 1420s, 1406s, 1343s, 1310m, 1246m, 1209s, 1169m, 1148m, 1115w, 1048m, 1012w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=264 nm (4.28). MS (ESI, MeOH): *m*/*z*=319.2 (100%, (M+H)$^+$). HRMS for $C_{15}H_{11}ClN_2O_4$: calcd: 318.0407; found: 318.0435.

3.5.43. 9-Chloro-2-methoxyacridine (8h).[82–87] Compound **8h** (1.8 g, 91%) was prepared from **6h** (2.0 g, 8.2 mmol) following GP4. Mp 162–163 °C (Lit.: 154 °C;[82] 152 °C;[83] 153 °C;[84] 148–149 °C[85]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.02 (s, 3H OCH_3), 7.47 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 7.51 (d, 1H, J=2.5 Hz, H_{arom}), 7.61 (ddd, 1H, J=7.5, 6.6, 0.8 Hz, H_{arom}), 7.73 (ddd, 1H, J=7.9, 6.6, 1.2 Hz, H_{arom}), 8.09 (d, 1H, J=9.1 Hz, H_{arom}), 8.18 (dd, 1H, J=8.7, 0.8 Hz, H_{arom}), 8.37 (ddd, 1H, J=8.7, 1.2, 0.8 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.7, 99.9, 102.2, 124.1, 124.5, 125.3, 125.9, 127.0, 129.3, 129.8, 131.5, 146.2, 147.3, 158.2. IR (KBr): ν=3012w, 2976w, 1636s, 1560m, 1552s, 1524w, 1479s, 1445m, 1426m, 1398m, 1350w, 1307w, 1280w, 1265s, 1223s, 1219w, 1203s, 1135w, 1182s, 1139m, 1116w, 1014m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=271 nm (5.07). HRMS for $C_{14}H_{10}ClNO$: calcd: 243.0451, found: 243.0458.

3.5.44. 6,9-Dichloro-2-methoxyacridine (8i).[60,88–90] Compound **8i** (1.5 g, 77%) was prepared from **6i** (2.0 g, 7.2 mmol) following GP4. Mp 169–172 °C (Lit.: 164 °C;[88] 160–161 °C[60]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.01 (s, 3H OCH_3), 7.44–7.49 (m, 2H, H_{arom}), 7.52 (dd, 1H, J=9.1, 2.1 Hz, H_{arom}), 8.05 (d, 1H, J=9.1 Hz, H_{arom}), 8.16 (d, 1H, J=2.1 Hz, H_{arom}), 8.28 (d, 1H, J=9.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.3, 99.9, 122.8, 125.3, 125.6, 126.4, 128.2, 128.2, 131.5, 135.3, 138.3, 146.7, 147.1, 158.4. IR (KBr): ν=2925w, 1633s, 1554w, 1517w, 1476s, 1420s, 1262s, 1062w, 1027w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=276 nm (4.07). HRMS for $C_{14}H_9Cl_2NO$: calcd: 277.0061, found: 277.0032. HRMS for $C_{14}H_9Cl_2NO$: calcd: 277.0061; found: 277.0032.

3.5.45. 9-Chloro-2-(trifluoromethoxy)acridine (8j). Following GP4 from **6j** (2.0 g, 6.7 mmol) **8j** (1.8 g, 90%) as a brown solid. Mp 250 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): 7.63 (m, 2H, H_{arom}), 7.84 (ddd, 1H, J=6.6, 6.6, 1.3 Hz, H_{arom}), 8.20–8.28 (m, 3H, H_{arom}), 8.44 (dd, 1H, J=8.3, 0.9 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=114.1, 120.5 (q, J=258.4 Hz), 124.1, 124.4, 124.5, 125.2, 127.7, 130.0, 130.9, 132.5, 140.9, 146.9, 147.2, 149.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.3 (s, OCF_3). IR (KBr): ν=3041w, 2926w, 1636m, 1559m, 1522m, 1507m, 1476m, 1460m, 1439m, 1401m, 1267s, 1215s, 1170s, 1012w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=269 nm (5.05). MS (ESI, MeOH): m/z=298.0 (100%, $(M+H)^+$).

3.5.46. 9-Chloro-3-fluoro-acridine (8m1) and 9-chloro-1-fluoro-acridine (8m2).[72,73,91] Following GP4 from **7m** (1.2 g, 5.2 mmol) **8m1** (0.64 g, 53%) and **8m2** (0.31 g, 26%) were obtained; the products were separated by chromatography (silica gel, $CHCl_3$).

Data for **8m1**: Mp 158–159 °C (Lit.: 151 °C;[72] 150–152 °C[73]). ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.16–7.30 (m, 1H, H_{arom}), 7.60–7.75 (m, 2H, H_{arom}), 7.82 (ddd, 1H, J=6.6, 6.6, 1.7 Hz, H_{arom}), 8.02 (d, 1H, J=8.3 Hz, H_{arom}), 8.18 (d, 1H, J=9.1 Hz, H_{arom}), 8.52 (d, 1H, J=9.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=110.8 (d, J=23.1 Hz), 116.2 (d, J=8.8 Hz), 124.6, 125.1, 126.3 (d, J=5.6 Hz), 127.4, 129.2 (d, J=9.6 Hz), 129.6, 131.1, 138.5 (d, J=4.0 Hz), 148.9, 149.9, 157.4 (d, J=262.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−111.1 (dd, J=12.2, 4.7 Hz, F). IR (KBr): ν=2923m, 1636s, 1553s, 1525m, 1466m, 1426s, 1393m, 1349m, 1316s, 1278m, 1256m, 1220m, 1140m, 1034m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (5.15). MS (ESI, MeOH+TFA): m/z=232.2 (100%, $(M+H)^+$).

Data for **8m2**: Mp 131–133 °C (Lit.: 130–131 °C[73]). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.45 (ddd, 1H, J=7.9, 7.9, 2.5 Hz, H_{arom}), 7.63 (ddd, 1H, J=6.6, 6.6, 1.2 Hz, H_{arom}), 7.79–7.85 (m, 2H, H_{arom}), 8.18 (d, 1H, J=8.7 Hz, H_{arom}), 8.40–8.48 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=111.9 (d, J=20.0 Hz), 118.7 (d, J=27.1 Hz), 121.6, 123.7, 124.6, 126.7, 127.2 (d, J=10.4 Hz), 129.4, 131.0, 141.4, 149.4, 149.5, 163.5 (d, J=254.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−107.5 (m, F). IR (KBr): ν=3060w, 2924w 1634m, 1616m, 1552m, 1522m, 1480m, 1458m, 1437m, 1400m, 1311w, 1278s, 1261m, 1178m, 1150m, 1136m, 1113w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=262 nm (5.12). MS (ESI, MeOH+TFA): m/z=232.2 (100%, $(M+H)^+$).

3.5.47. 9-Chloro-2,4-difluoroacridine (8n). Compound **8n** (1.3 g, 96%) was prepared from **6n** (1.4 g, 5.6 mmol) following GP4. Mp 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.34 (ddd, 1H, J=10.0, 10.0, 2.9 Hz, H_{arom}), 7.68 (ddd, 1H, J=6.6, 6.6, 1.2 Hz, H_{arom}), 7.80–7.86 (m, 2H, H_{arom}), 8.30 (dd, 1H, J=8.7, 1.0 Hz, H_{arom}), 8.38 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=103.0 (dd, J=24.6, 5.5 Hz), 106.3 (dd, J=22.7, 22.3 Hz), 124.1, 125.0, 128.2, 130.4, 130.4, 130.8, 137.5 (d, J=13.0 Hz), 140.3 (dd, J=8.4, 5.4 Hz), 148.0, 158.4 (dd, J=262.8, 13.0 Hz), 159.0 (dd, J=151.0, 11.5 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−107.8 (dd, J=15.3, 9.2 Hz, F), −117.7 (t, J=9.2 Hz, F). IR (KBr): ν=1646s, 1559m, 1526m, 1508m, 1473s, 1432s, 1402s, 1330s, 1277m, 1249m, 1207m, 1158m, 1129s, 1080w cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=269 nm (5.13). MS (ESI, MeOH): m/z=250.0 (100%, $(M+H)^+$). HRMS for $C_{13}H_6ClF_2N$: calcd: 249.0157; found: 249.0154.

3.5.48. 9-Chloro-2,3,4-trifluoroacridine (8o). Compound **8o** (1.2 g, 85%) was prepared from **6o** (1.4 g, 5.18 mmol) following GP4. Mp 327–333 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.70 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.86 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.96 (ddd, 1H, J=2.5, 7.9, 10.7 Hz, H_{arom}), 8.30 (dd, 1H, J=7.8, 1.1 Hz, H_{arom}), 8.38 (dd, 1H, J=7.8, 1.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=104.0 (dd, J=20.3, 5.4 Hz), 120.2 (d, J=9.2 Hz), 124.2, 124.5, 128.1, 130.0, 131.3, 137.7 (d, J=10.4 Hz), 141.2 (ddd, J=259.7, 20.3, 19.5 Hz), 140.7, 145.0 (ddd, J=260.9, 10.4, 4.2 Hz), 148.6, 150.4 (dd, J=255.2, 15.0 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−129.7 (m, F), −144.2 (dd, J=15.2, 6.2 Hz, F), −152.4 (m, F). IR (KBr): ν=3259m, 3179m, 3009m, 1660w, 1629s, 1599s, 1585s, 1542w, 1506s, 1474s, 1454s, 1399w, 1359w, 1321m, 1321m, 1294m, 1254w, 1199w, 1160w, 1131m, 1106m, 1047m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=268 nm (4.72). MS (ESI, MeOH): m/z=268.2 (100%, $(M+H)^+$). HRMS for $C_{13}H_5ClF_3N$: calcd: 267.0063; found: 267.0090.

3.5.49. 9-Chloro-2,4-dimethoxyacridine (8p). Compound

8p (1.3 g, 95%) was prepared from **6p** (1.4 g, 5.1 mmol) following GP4. Mp 220–222 °C (Lit.: 170–172 °C[25]). ^{1}H NMR (400 MHz, $CDCl_3$): 4.00 (s, 3H OCH_3), 4.11 (s, 3H OCH_3), 6.74 (d, 1H, J=2.5 Hz, H_{arom}), 7.12 (d, 1H, J=2.5 Hz, H_{arom}), 7.61 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.71 (ddd, 1H, J=9.1, 6.6, 1.7 Hz, H_{arom}), 8.30–8.36 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=55.6, 56.5, 92.2, 102.4, 123.8, 124.9, 125.8, 127.3, 128.8, 130.5, 137.9, 139.7, 146.1, 156.2, 158.5. IR (KBr): ν=3136m, 1635s, 1564m, 1528s, 1468s, 1445s, 1419s, 1396s, 1327s, 1282w, 1245s, 1230m, 1201s, 1163s, 1152s, 1110m, 1043s, 1008m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=284 nm (4.93). HRMS for $C_{15}H_{12}ClNO_2$: calcd: 273.0556, found: 273.0577.

3.5.50. 9-Chloro-1,4-dimethoxyacridine (8q).[25,92] Compound **8q** (1.2 g, 83%) was prepared from **6q** (1.4 g, 5.1 mmol) following GP4. Mp 152–154 °C (Lit.: 148–149 °C;[92] 107 °C[25]). ^{1}H NMR (400 MHz, $CDCl_3$): 3.08 (s, 3H OCH_3), 4.09 (s, 3H OCH_3), 6.80 (d, 1H, J=8.3 Hz, H_{arom}), 6.93 (d, 1H, J=8.3 Hz, H_{arom}), 7.62 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 7.77 (ddd, 1H, J=8.7, 6.6, 1.2 Hz, H_{arom}), 8.32 (d, 1H, J=8.7 Hz, H_{arom}), 8.57 (d, 1H, J=8.7 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=56.3, 56.6, 105.2, 106.1, 118.6, 124.8, 125.5, 127.1, 130.2, 130.3, 140.0, 142.9, 147.4, 149.4, 149.5. IR (KBr): ν=2934m, 2836m, 1625s, 1611m, 1534w, 1470s, 1409m, 1376m, 1329m, 1314s, 1266s, 1233m, 1169m, 1156w, 1116s, 1080m, 1043s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.60). HRMS for $C_{15}H_{12}ClNO_2$: calcd: 273.0556, found: 273.0562.

3.5.51. 6,9-Dichloro-2-(trifluoromethoxy)acridine (8r). Compound **8r** (1.2 g, 82%) was prepared from **6r** (1.5 g, 4.5 mmol) following GP4. Mp 250 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.87 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 8.00 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 8.36 (s, 1H, H_{arom}), 8.56 (d, 1H, J=9.5 Hz, H_{arom}), 9.13 (s, 1H, H_{arom}), 9.27 (d, 1H, J=9.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=114.1, 118.9, 120.6, 121.5, 123.7 (q, J=234.5 Hz), 124.8, 126.6, 131.4, 131.7, 138.5, 140.2, 141.3, 145.0, 151.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.5 (s, OCF_3). IR (KBr): ν=2925m, 1628m, 1489m, 1460m, 1421m, 1260s, 1212s, 1081m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=273 nm (4.58). MS (ESI, MeOH+TFA): m/z=332.2 (100%, $(M+H)^+$). HRMS for $C_{14}H_6Cl_2F_3NO$: calcd: 330.9778; found: 330.9758.

3.5.52. 6,9-Dichloro-2,4-difluoroacridine (8s). Compound **8s** (0.87 g, 87%) was prepared from **6s** (1.0 g, 3.5 mmol) following GP4. Mp 171–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.39 (ddd, 1H, J=9.5, 8.3, 2.5 Hz, H_{arom}), 7.63 (dd, 1H, J=9.5, 2.1 Hz, H_{arom}), 7.83 (ddd, 1H, J=9.5, 2.5, 1.7 Hz, H_{arom}), 8.33 (d, 1H, J=9.1 Hz, H_{arom}), 8.40 (d, 1H, J=2.1 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=103.4 (dd, J=24.5, 5.4 Hz), 107.3 (dd, J=31.5, 22.3 Hz), 123.4, 124.9 (dd, J=11.5, 2.5 Hz), 125.6, 128.2, 129.7, 137.5 (d, J=13 Hz), 137.7, 141.4, 147.3, 158.0 (dd, J=252.4, 10.7 Hz), 159.4 (dd, J=264.7, 13.4 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−106.7 (dd, J=16.8, 9.2 Hz, F), −116.9 (t, J=9.2 Hz, F). IR (KBr): ν=1630s, 1591s, 1535m, 1485m, 1438m, 1284m, 1248m, 1130m, 1082m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=274 nm (5.39). MS (ESI, MeOH+TFA): m/z=284.2 (100%, $(M+H)^+$). HRMS for $C_{13}H_5Cl_2F_2N$: calcd: 282.9767; found: 282.9757.

3.5.53. 6,9-Dichloro-2,3,4-trifluoroacridine (8t). Compound **8t** (0.51 g, 65%) was prepared from **6t** (0.8 g, 2.6 mmol) following GP4. Mp 173–176 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 7.61 (dd, 1H, J=9.5, 2.1, H_{arom}), 7.94 (ddd, 1H, J=10.7, 8.7, 2.5 Hz, H_{arom}), 8.28–8.34 (m, 2H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=104.2 (dd, J=20.7, 5.4 Hz), 120.2 (d, J=9.2 Hz), 122.8, 125.6, 128.3, 129.4, 137.9, 138.1 (d, J=10.7 Hz), 141.0, 141.3 (ddd, J=260.9, 20.0, 13.8 Hz), 144.8 (ddd, J=261.6, 9.2, 4.6 Hz), 148.3, 150.6 (dd, J=257.8, 13.8 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−128.9 (m, F), −143.8 (dd, J=15.3, 6.1 Hz, F), −151.4 (m, F). IR (KBr): ν=1658m, 1609m, 1573w, 1521s, 1496s, 1455s, 1444s, 1402s, 1336s, 1311m, 1288w, 1239w, 1216m, 1190m, 1147w, 1080m, 1064m, 1002s cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=272 nm (5.18). MS (ESI, MeOH): m/z=302.21 (100%, $(M+H)^+$). HRMS for $C_{13}H_4Cl_2F_3N$: calcd: 300.9672; found: 300.9698.

3.5.54. 9-Chloro-2-nitro-7-(trifluoromethoxy)acridine (8u). Compound **8u** (1.3 g, 84%) was prepared from **6u** (1.5 g, 4.4 mmol) following GP4. Mp 315 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): 7.77 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 8.30 (s, 1H, H_{arom}), 8.31 (d, 1H, J=9.5 Hz, H_{arom}), 8.35 (d, 1H, J=9.5 Hz, H_{arom}), 8.53 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 9.40 (d, 1H, J=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ=113.8, 120.4 (q, J=259.0 Hz), 122.3, 122.9, 123.7, 124.8, 127.2, 132.3, 132.9, 144.1, 146.1, 148.1, 148.8, 149.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ=−58.4 (s, OCF_3). IR (KBr): ν=3133m, 1636s, 1610s, 1579s, 1543m, 1517s, 1492s, 1404s, 1340s, 1266s, 1215s, 1150s, 1073m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=255 nm (4.27). HRMS for $C_{14}H_6ClF_3N_2O_3$: calcd: 342.0019, found: 342.0007.

3.5.55. 9-Chloro-2,3,4-trifluoro-7-nitroacridine (8w). Compound **8w** (0.67 g, 84%) was prepared from **6w** (0.8 g, 2.6 mmol) following GP4. Mp 263–266 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.03 (ddd, 1H, J=10.4, 7.5, 2.1 Hz, H_{arom}), 8.45 (d, 1H, J=10.4 Hz, H_{arom}), 8.58 (dd, 1H, J=9.5, 2.5 Hz, H_{arom}), 9.39 (dd, 1H, J=2.5 Hz, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): 104.6 (dd, J=20.7, 5.4 Hz), 121.1 (d, J=9.2 Hz), 122.1, 123.2, 124.2, 132.4, 140.0 (dd, J=10.2, 3.2 Hz), 142.3 (ddd, J=263.2, 22.25, 13.5 Hz), 144.1, 145.2 (ddd, J=263.2, 10.0, 4.5 Hz), 146.3, 149.1, 151.3 (ddd, J=258.6, 14.2, 1.9 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ=−126.3 (m, F), −142.6 (m, F), −148.3 (m, F). IR (KBr): ν=3166w, 1687m, 1625s, 1491s, 1408s, 1296s, 1140m, 1052m cm^{-1}. UV–vis (methanol): λ_{max} (log ε)=259 nm (4.19). MS (ESI, MeOH+TFA): m/z=313.1 (100%, $(M+H)^+$). HRMS for $C_{13}H_4ClF_3N_2O_2$: calcd: 311.9913; found: 300.9917.

References and notes

1. Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemière, P.; Debreu, M.; Davioud-Charvet, E.; Sergheraert, C. *J. Med. Chem.* **2000**, *43*, 2646–2654.

2. Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Des.* **2001**, *7*, 1703–1724.
3. Brana, M.; Cacho, M.; de Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745–1780.
4. El-Subbagh, H.; Abadi, A. H.; Al-Khames, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277–284.
5. Cholody, W.; Horowska, B.; Paradziej-Lukowicz, J.; Martelli, S.; Konopa, J. *J. Med. Chem.* **1996**, *39*, 1028–1032.
6. Chen, T.; Fico, R.; Canellakis, E. S. *J. Med. Chem.* **1978**, *21*, 868–874.
7. Denny, W.; Atwell, G. J.; Baguley, B. C.; Wakelin, L. P. G. *J. Med. Chem.* **1985**, *28*, 1568–1574.
8. Rewcastle, G.; Atwell, G. J.; Chambers, D.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1986**, *29*, 472–477.
9. Aguzzi, A.; Heikenwalder, M. *Nature* **2003**, *423*, 127–129.
10. Korth, C.; May, B. C.; Cohen, F. E.; Prusiner, S. B. *Proc. Natl. Acad. Sci.* **2001**, *98*, 9836–9841.
11. Ryou, C.; Legname, G.; Peretz, D.; Craig, J. C.; Baldwin, M. A.; Prusiner, S. B. *Lab. Invest.* **2003**, *83*, 837–843.
12. Turnbull, S.; Tabner, B.; Brown, D. R.; Allsop, D. *Neuroreport* **2003**, *14*, 1743–1745.
13. Kocisko, D.; Baron, G. S.; Rubenstein, R.; Chen, J.; Kuizon, S.; Caughey, B. *J. Virol.* **2003**, *77*, 10288–10294.
14. May, B. C.; Fafarman, A. T.; Hong, S. B.; Rogers, M.; Deady, L. W.; Prusiner, S. B.; Cohen, F. E. *Proc. Natl. Acad. Sci.* **2003**, *100*, 3416–3421.
15. Vogtherr, M.; Grimme, S.; Elshorst, B.; Jacobs, D.; Fiebig, K.; Griesinger, C.; Zahn, R. *J. Med. Chem.* **2003**, *46*, 3563–3564.
16. Folette, P. *Science* **2003**, *299*, 191–192.
17. Barret, A.; Tagliavini, F.; Forloni, G.; Bate, C.; Salmona, M.; Colombo, L.; De Luigi, A.; Limido, L.; Suardi, S.; Rossi, G.; Auvré, F.; Adjou, K.; Salès, N.; Williams, A.; Lasmézas, C.; Deslys, J. P. *J. Virol.* **2003**, *77*, 8462–8469.
18. Scoazec, J.; Krolak-Salmon, E.; Casez, O.; Besson, G.; Thobois, S.; Kopp, N.; Perret-Liaudet, A.; Streichenberger, N. *Ann. Neurol.* **2003**, *53*, 546–547.
19. El-Subbagh, H.; Abadi, A. H.; Al-Khames, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277.
20. Mueller, D.; Hudson, R. A.; Lee, C. *J. Am. Chem. Soc.* **1981**, *103*, 1860–1862.
21. Oza, V.; Petrassi, H. M.; Purkey, H. E.; Kelly, J. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1–6.
22. Green, N.; Palaninathan, S. K.; Sacchettini, J. C.; Kelly, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 13404–13414.
23. Oza, V.; Smith, C.; Raman, B.; Koepf, E. K.; Lashuel, H. A.; Petrassi, H. M.; Chiang, K. P.; Powers, E. T.; Sachettinni, J.; Kelly, J. W. *J. Med. Chem.* **2002**, *45*, 321–332.
24. Baures, P.; Oza, V. B.; Peterson, A.; Kelly, J. W. *Bioorg. Med. Chem.* **1999**, *7*, 1339–1347.
25. Monge, A.; Martínez-Crespo, F.; Santamaría, L.; Narro, S.; López de Ceráin, A. *J. Heterocyclic Chem.* **1994**, *31*, 1455–1460.
26. Reisch, J.; Probst, W. *Arch. Pharm.* **1987**, *320*, 1065–1072.
27. Ionescu, M.; Hopartean, I. *Stud. Univ. Babes-Bolyai Chem.* **1972**, *17*, 105–109.
28. SanFilippo, L. *J. Org. Prep. Proc. Int.* **1991**, *23*, 130–132.
29. Finet, J.; Fedorov, A.; Combes, S.; Boyer, G. *Curr. Org. Chem.* **2002**, *6*, 597–626.
30. Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455.
31. Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583–2586.
32. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805.
33. Kwong, F.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.
34. Gamage, S. A.; Spicer, J. A.; Rewcastle, G. W.; Milton, J.; Sohal, S.; Dangerfield, W.; Mistry, P.; Vicker, N.; Charlton, P. A.; Denny, W. A. *J. Med. Chem.* **2002**, *45*, 740–743.
35. Ali, M. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2560–2565.
36. Pellón, R.; Mamposo, T.; Carrasco, R.; Rodés, L. *Synth. Commun.* **1996**, *26*, 3877–3883.
37. Pellón, R.; Carrasco, R.; Rodés, L. *Synth. Commun.* **1993**, *23*, 1447–1453.
38. Razavi, Z.; McCapra, F. *Luminescence* **2000**, *15*, 239–244.
39. Saphier, M.; Masarwa, A.; Cohen, H.; Meyerstein, D. *Eur. J. Inorg. Chem.* **2002**, *5*, 1226–1234.
40. Kondratov, S.; Litvak, V. V.; Shein, S. M. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1112–1117.
41. Van Dort, M.; Robins, D. M.; Wayburn, B. *J. Med. Chem.* **2000**, *43*, 3344–3347.
42. Hosangadi, B.; Dave, R. H. *Tetrahedron Lett.* **1996**, *37*, 6375–6378.
43. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
44. Kranenburg, M.; van der Burgt, Y. E.; Kramer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089.
45. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
46. Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694–3703.
47. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
48. Zhang, X.; Harris, M. C.; Sadighi, J. P.; Buchwald, S. L. *Can. J. Chem.* **2001**, *79*, 1799–1805.
49. Ozawa, F.; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, *11*, 2177–2180.
50. El-Subbagh, H. I.; Abadi, A. H.; Al-Khamees, A. H. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 277–284.
51. Mueller, D. M.; Hudson, R. A.; Lee, C. *J. Am. Chem. Soc.* **1981**, *103*, 1860–1862.
52. Mietzsch, F.; Mauss, A. *Fortschr. Teerfarbenfabr. Verw. Industriezweige* **1932**, *19*, 1167.
53. Ionescu, M.; Hopartean, I. *Stud. Univ. Babes-Bolyai Chem.* **1970**, *15*, 77–80.
54. Kikhteva, V. I.; Dykhanov, N. N. *Metody Poluch Khim. Reakt. Prep.* **1964**, *10*, 78–80.
55. Reisch, J.; Probst, W. *Arch. Pharm.* **1987**, *320*, 1065–1072.
56. Krishnegowda, G.; Thimmaiah, P.; Hegde, R.; Dass, C.; Houghton, P. J.; Thimmaiah, K. N. *Biorg. Med. Chem.* **2002**, *10*, 2367–2380.
57. Lormier, A. T.; Boyer, G.; Faure, R.; Galy, J. P. *Heterocycles* **2002**, *57*, 449–463.
58. Chatterjee, A.; Raychaudhuri, R. J. *Org. Chem.* **1968**, *33*, 2546–2547.
59. Chen, M. H.; Beylin, V. G.; Iakovleva, E.; Kesten, S. J.; Magano, J.; Vrieze, D. *Synth. Commun.* **2002**, *32*, 411–418.
60. Mauss, A. *Fortschr. Teerfarbenfabr. Verw. Industriezweige* **1932**, *19*, 1176–1178.
61. Giral, F.; Calderon, L. *Ciencia (Mexico City)* **1945**, *6*, 369–370.
62. Ledochowski, Z.; Ledochowski, A.; Borowski, E.; Wysocka, B.; Kikmunter, A.; Morawski, B.; Gawle, K.; Wypych, H. *Rocz. Chem.* **1960**, *34*, 63–70.

63. Samarin, A. S.; Shchurova, I. G. *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.* **1971**, *14*, 256–257.
64. Legrand, L.; Lozag'h, N. *Bull. Soc. Chim. Fr.* **1967**, 2067–2074.
65. Hörlein, U. *Arch. Pharmaz.* **1971**, *304*, 80–99.
66. Endel'man, E. S.; Danilenko, V. S.; Trinus, F. P.; Yufa, P. A.; Fadeicheva, A. G.; Muravov, I. I.; Fialkov, Yu. A.; Yagupol'skii, L. M. *Pharm. Chem. J. (Engl. Transl.)* **1973**, *7*, 755–759.
67. Banerji, A.; Cass, J. C.; Katritzky, A. R. *J. Chem. Soc. Perkin Trans. 1* **1977**, *10*, 1162–1166.
68. Ege, G.; Beisiegel, E.; Arnold, P. *Chem. Ber.* **1972**, *105*, 2898–2912.
69. Hannig, E.; Brummer, R. *Pharmazie* **1971**, *26*, 135–137.
70. Ullmann, F. *Justus Liebigs Ann. Chem.* **1907**, *355*, 352–354.
71. Ramana, D. V.; Srinivas, R.; Mahalakshni, P. *Org. Mass Spectrom.* **1991**, *26*, 305–310.
72. Wilkinson, J. H.; Finar, I. L. *J. Chem. Soc.,* **1947**, 759–762.
73. Horowska, B.; Ledochowski, A. *Rocz. Chem.* **1971**, *45*, 1447–1455.
74. Horiguchi, Y.; Sakuma, S.; Suzuki, H.; Sano, T. *Heterocycles* **2000**, *53*, 1305–1316.
75. Alvares, M.; Feliu, L.; Ajana, W.; Joule, J. A.; Fernandes-Puentes, J. L. *Eur. J. Org. Chem.* **2000**, *5*, 849–856.
76. Hellwinkel, D.; Melan, M. *Chem. Ber.* **1971**, *104*, 1001–1016.
77. Kondratov, S. A.; Litvak, V. V.; Shein, S. M. *J. Org. Chem. USSR (Engl. Transl.)* **1977**, *13*, 1112–1117.
78. Hangar, W. G.; Howell, W. C.; Johnson, A. W. *J. Chem. Soc.* **1958**, 496–504.
79. Sukhomlinov, A. K.; Maksimets, V. P. *Khim. Geterotsikl. Soedin.* **1966**, *3*, 416–419.
80. Ledochowski, A.; Zielinski, J.; Glowacki, A.; Maruszewski, J.; Irzykowska, A.; Stepnowska, K. *Rocz. Chem.* **1976**, *50*, 341–345.
81. Mager, S.; Hopartean, I.; Binisor, D. *Monatsh. Chem.* **1978**, *109*, 1393–1401.
82. Drosdow, N. S.; Lesnowa, N. S. *Zhurn. Obsch. Khim.* **1935**, *5*, 690–700.
83. Lormier, A. T.; Boyer, G.; Faure, R.; Galy, J. P. *Heterocycles* **2002**, *57*, 449–464.
84. SanFilippo, L. *J. Org. Prep. Proc. Int.* **1991**, *23*, 130–132.
85. Goodall, R. R.; Kermack, W. O. *J. Chem. Soc.* **1936**, 1163–1166.
86. Mazagova, D.; Sabolova, D.; Kristian, P.; Imrich, J.; Antalik, M.; Podhradsky, D. *Collect. Czech. Chem. Commun.* **1994**, *59*, 203–212.
87. Gaidukevich, A. N.; Sidom, M. B.; Bezuglyi, V. D. *J. Anal. Chem. USSR (Engl. Transl.)* **1977**, *32*, 1435–1439.
88. Hall, D. M.; Turner, E. E. *J. Chem. Soc.,* **1945**, 694–699.
89. Kimura, M.; Okabayashi, I.; Kato, A. *Chem. Pharm. Bull.* **1989**, *37*, 697–701.
90. Robidoux, S.; Guo, Y.; Damha, M. J. *Tetrahedron Lett.* **1995**, *36*, 6651–6654.
91. Faure, R.; Galzy, J.; Barbe, J.; Boukir, A. L.; Vincent, E. *Bull. Soc. Chim. Belg.* **1991**, *100*, 639–646.
92. Horowska, B.; Ledochowski, A. *Rocz. Chem.* **1968**, *42*, 1351–1355.