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DESIGN AND SYNTHESIS OF SOME NEW N-PHENYLANTHRANILIC ACIDS FROM HIGHLY STERICALLY HINDERED ANILINES

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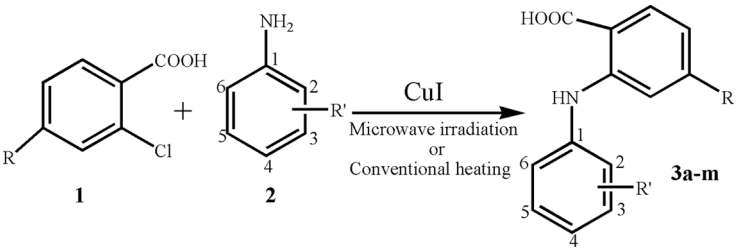
GRAPHICAL ABSTRACT



Abstract *Some new N-phenylanthranilic acids were designed and synthesized from highly sterically hindered anilines in an efficient and convenient method using CuI as catalyst with microwave irradiation and conventional heating.*

Keywords Copper(I) iodide; highly sterically hindered anilines; microwave irradiation; N-phenylanthranilic acids

INTRODUCTION

N-Phenylanthranilic acids, such as mefenamic acid, are important nonsteroidal anti-inflammatory drugs (NSAIDs)[1] and crucial intermediates for the synthesis of acridones and acridines, which possess bioactivity such as antimalarial and anticancer properties.[2–4] Ullmann first reported the synthesis of N-phenyanthranilic acids from 2-chlorobenzoic acid in 1903.[5] Since then, chemists have improved the efficiency of this reaction by use of various copper catalysts, such as copper powder,[6–9] copper acetate,[10] anhydrous copper sulfate,[11,12] copper/cuprous

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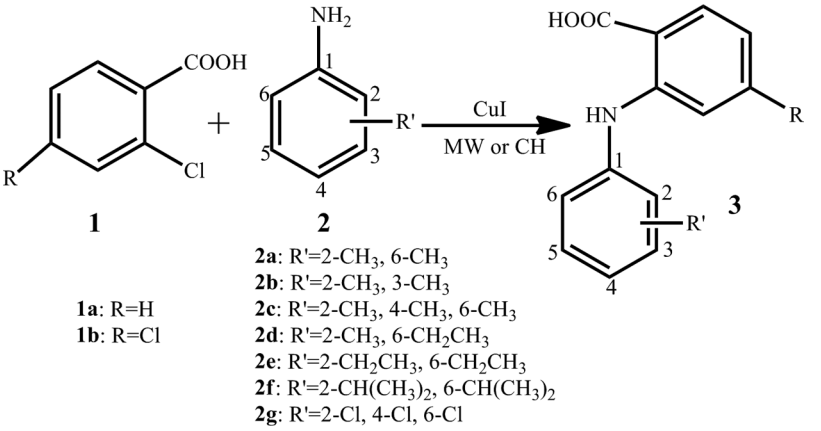


Scheme 1. Coupling reaction of *o*-chlorobenzoic acid with anilines using CuI as catalyst.

oxide,[13,14] and so on. Palladium-catalyzed C-N coupling reactions exhibiting free carboxylic acids groups in the *meta* or *para* position have been reported.[15] Moreover, besides conventional heating, ultrasound-assisted[8] or microwave-assisted[11,12] methods have been applied to enhance reaction rates for synthesis of N-phenylanthranilic acids.

Quantitative structure–activity relationship on NSAIDs indicated that the substituents at the 2′- and 3′-positions of mefenamic acid exert a steric effect to favor a nonplanar arrangement between the benzene ring and anthranilic acid, which is important in the effective interaction of mefenamic acid at its inhibitory site.[16,17] It is presumed that N-phenylanthranilic acids that have a nonplanar arrangement, such as mefenamic acid, would possess anti-inflammatory activity. However, to our knowledge, there are few relevant studies on the synthesis of N-phenylanthranilic acids from highly sterically hindered anilines at present, such as 2-((2,6-dimethylphenyl)amino)benzoic acid (**3a**)[13,14,18] and 2-((2,3-dimethylphenyl)amino) benzoic acid (**3b**).[7]

In this article, we report an efficient and convenient method for the synthesis of N-phenylanthranilic acids from highly sterically hindered anilines using CuI as catalyst under microwave irradiation and conventional heating, respectively (Scheme 1). Some of the target compounds are reported for the first time and expected to possess anti-inflammatory activity.

RESULTS AND DISCUSSION

At first, the synthesis of N-phenylanthranilic acids from the coupling reaction of *o*-chlorobenzoic acid (**1a**) and 2,6-dimethylaniline (**2a**) was studied to optimize the reaction conditions under microwave irradiation. In the solvents tested for this reaction, it was found that the best result was obtained in dimethylformanide (DMF). Later, the effect of catalyst amount was examined, and the optimal yield of product was obtained when 8 mol% of CuI was used. To study the effect of temperature, the model reactions were performed at three different temperatures (110, 140, and

Table 1. Optimization of the reaction conditions[a]

Entry	CuI (mol%)	Solvent	T (°C)	Time (min)	Yield (%)[b]
1	8	Water	100	90	25
2	8	Water	120	30	32
3	8	Water	140	30	40
4	8	DMF	140	10	63
5	12	DMF	140	10	55
6	4	DMF	140	10	46
7	8	DMF	110	30	22
8	8	DMF	150	10	61

[a]All the reactions were carried out with *o*-chlorobenzoic acid (4 mmol), 2,6-dimethylaniline (8 mmol), potassium carbonate (2 mmol), and solvent (3 mL) under microwave irradiation.
[b]Yields refer to the isolated pure prouducts.

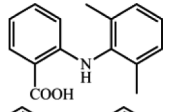
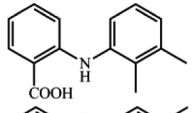
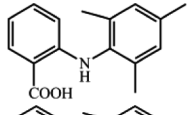
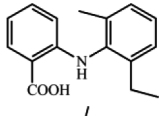
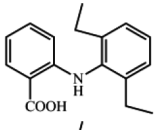
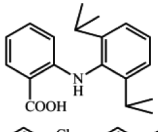
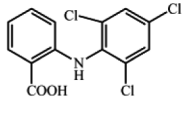
150 °C). The best yield has been obtained at 140 °C. The results are summarized in Table 1.

Under the optimized conditions, the reactions of *o*-chlorobenzoic acids with a variety of highly sterically hindered anilines were performed to produce a series of N-phenylanthranilic acids, and the results are listed in Table 2. Incorporation of the *ortho* substituents to aniline has impeded effective amination, so only moderate yield was obtained in all the reactions. It was found the presence of more bulky *ortho* substituents for anilines causes lower yields. For example, 2,6-dimethylaniline, **2a**, and 2,6-diisopropylaniline, **2f**, gave 2-((2,6-dimethylphenyl)amino)benzoic acid, **3a**, in 63% yield and 2-((2,6-diisopropylphenyl)amino)benzoic acid, **3f**, in 48% yield (Table 2, entries 1 and 6). It is noteworthy that Dokorou et al.[18] reported the formation of **3a** in only 24% yield by copper(II) acetate–promoted amination of 2-bromobenzoic acid (145 °C, 3 h), and Mei et al.[13] also reported the formation of **3a** in 65% yield by copper/cuprous oxide–promoted amination of 2-chlorobenzoic acid (130 °C, 24 h). It is thus clear that copper(I) iodide is a good catalyst for amination of *o*-chlorobenzoic acids with highly sterically hindered anilines with moderate yields in a short reaction time.

The high regio- and chemoselectivity was found in the reactions of 2,4-dichlorobenzoic acid (**1a**) with different anilines (Table 2, entries 8–13). Amination only occurred when the halide was located in the *ortho* position of the carboxylic acid moiety, which suggested the carboxylic acid moiety may direct the amination through coordination with the Cu catalyst.[19] The same phenomena had been reported by Mei.[13] Moreover, it was found that the presence of chlorine atoms at the *para* position of **1b** could improve amination. For example, coupling of 2,4,6-trimethylaniline with 2-chlorobenzoic acid or 2,4-dichlorobenzoic acid gave the corresponding products **3c** and **3j** in 64% and 79% yield (Table 2, entries 3 and 10).

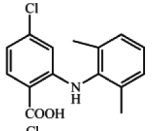
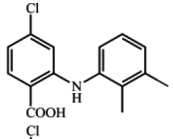
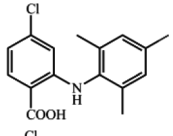
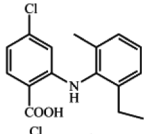
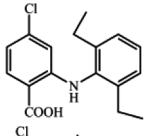
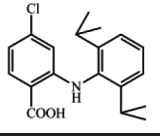
To investigate the difference between the microwave irradiation and conventional heating, all the reactions were processed at the same conditions under conventional heating. The results are shown in Table 2. There was shorter reaction time and fewer by-products under microwave irradiation than with conventional heating, which indicated the actual temperature on the catalyst should be greater than the bulk solution.[20]

Table 2. CuI-catalyzed reaction of *o*-chlorobenzoic acids with highly sterically hindered anilines in DMF

Entry	*o*-Chlorobenzoic acids	Anilines	Products	Microwave irradiation		Conventional heating	
				Conditions	Yield[a] (%)	Conditions	Yield[a] (%)
1	**1a**	**2a**	 **3a**	10 min, 140 °C	63	30 min, 140 °C	57
2	**1a**	**2b**	 **3b**	10 min, 140 °C	66	30 min, 140 °C	60
3	**1a**	**2c**	 **3c**	10 min, 140 °C	64	30 min, 140 °C	62
4	**1a**	**2d**	 **3d**	10 min, 140 °C	52	30 min, 140 °C	46
5	**1a**	**2e**	 **3e**	10 min, 140 °C	50	30 min, 140 °C	48
6	**1a**	**2f**	 **3f**	10 min, 140 °C	48	30 min, 140 °C	45
7	**1a**	**2g**	 **3g**	40 min, 160 °C	30	2.5 h, reflux	25

(*Continued*)

Table 2. Continued

Entry	*o*-Chlorobenzoic acids	Anilines	Products	Microwave irradiation		Conventional heating	
				Conditions	Yield[a] (%)	Conditions	Yield[a] (%)
8	**1b**	**2a**	 **3h**	10 min, 140 °C	71	40 min, 140 °C	69
9	**1b**	**2b**	 **3i**	10 min, 140 °C	83	30 min, 140 °C	80
10	**1b**	**2c**	 **3j**	10 min, 140 °C	79	30 min, 140 °C	75
11	**1b**	**2d**	 **3k**	10 min, 140 °C	74	50 min, 140 °C	68
12	**1b**	**2e**	 **3l**	10 min, 140 °C	67	60 min, 140 °C	63
13	**1b**	**2f**	 **3m**	10 min, 140 °C	65	60 min, 140 °C	60

[a]Yields refer to the isolated pure products.

CONCLUSION

In conclusion, some new N-phenylanthranilic acids were synthesized from highly sterically hindered anilines in an efficient and convenient method using CuI as catalyst under microwave irradiation and conventional heating. Preliminary investigations on the anti-inflammatory activity of the new N-phenylanthranilic acids **3** will be reported elsewhere.

EXPERIMENTAL

Staring materials were purchased from commercial sources and used without further purification. Microwave experiments were carried out in the CEM reactor. The course of the reactions was monitored by thin-layer chromatography (TLC) on GF254 silica-gel chromatoplates using a mixture of chloroform and methanol as developing solvent system and visualization with ultraviolet (UV) irradiation at 254 nm. Melting points were measured using a micro-melting-point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR Affinity-1 spectrometer. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 500-MHz spectrometer with dimethylsulfoxide (DMSO-d_6) as the solvent. Chemicals shifts were reported in values (ppm) relative to internal tetramethylsilane (TMS). High-resolution mass spectra (HRMS) were recorded on a Micromass GCT-MS spectrometer with the electron ionization (EI) mode.

General Procedure

N-phenylanthranic acids were synthesized from highly sterically hindered anilines under microwave irradiation and conventional heating.

A mixture of 2-chlorbenzoic acid (4 mmol), aniline derivatives (8 mmol), anhydrous potassium carbonate (2 mmol), 8 mol% copper (I) iodide, and dimethylformamide (DMF) (3 mL) was placed into a 10-mL reaction vessel. After the vessel was sealed, the sample was irradiated for the time at the temperature measured by the IR radiation thermometer indicated in Table 2. The reaction mixture was subsequently cooled to 50 °C by compressed air, the vessel was opened, and the TLC was used to monitor the progress of the reaction until the starting material disappeared. The mixture was acidified with aqueous HCl solution upon the careful pH adjustment and then left to stand overnight in cold storage. The solid was filtered off and dried under vacuum conditions. The crude product was purified by flash columm chromatography on silica gel (eluent: gradient $CHCl_3/CH_3OH$, 100:0 to 20:1) to provide the desired product. The yields are listed in Table 2. All the reactions were processed at the same conditions under conventional heating.

Spectroscopic Data and Melting Points for Compounds in Table 2

2-((2,6-Dimethylphenyl)amino)benzoic acid (3a). Mp 205–206 °C (lit.[18] 209–210 °C); FT-IR (KBr): $\nu_{N\text{-}H}$ 3346, $\nu_{C=O}$ 1654, 1577 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): $\delta = 2.12$ (s, 6H, CH_3), 6.08 (d, $J = 8.00$ Hz, 1H, ArH), 6.64 (t, $J = 7.50$ Hz, 1H, Ar-H), 7.13–7.19 (m, 3H, Ar-H), 7.25 (t, $J = 7.50$ Hz, 1H, Ar-H),

8.75 (d, $J = 7.50$ Hz, 1H, Ar-H), 9.17 (s, 1H, NH), 12.94 (1H, COOH) ppm. HRMS: found 241.1102; calcd. 241.1103 for $C_{15}H_{15}NO_2$.

2-((2,3-Dimethylphenyl)amino)benzoic acid (3b). Mp 226–228 °C (lit.[7] 228–230 °C); FT-IR (KBr): $\nu_{N\text{-}H}$ 3314, $\nu_{C=O}$ 1653, 1577 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 2.10$ (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 6.70 (t, $J = 8.00$ Hz, 2H, Ar-H), 7.02–7.13 (m, 3H, Ar-H), 7.30 (t, $J = 8.00$ Hz, 1H, Ar-H), 7.80 (dd, $J = 8.00$ Hz, 1.50 Hz, 1H, Ar-H), 9.46 (s, 1H, NH), 13.01 (s, 1H, COOH) ppm. HRMS: found 241.1106; calcd. 241.1103 for $C_{15}H_{15}NO_2$.

2-(Mesitylamino)benzoic acid (3c). Mp 229–230 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3350, $\nu_{C=O}$ 1653, 1573 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 2.07$ (s, 6H, CH_3), 2.27 (s, 3H, CH_3), 6.06 (d, $J = 8.00$ Hz, 1H, Ar-H), 6.62 (t, $J = 7.50$ Hz, 1H, Ar-H), 6.99 (s, 2H, Ar-H), 7.23 (t, $J = 8.00$ Hz, 1H, Ar-H), 7.86 (dd, $J = 8.00$ Hz, 1.50 Hz, 1H, Ar-H), 9.07 (s, 1H, NH), 12.87 (s, 1H, COOH) ppm. HRMS: found 255.1265; calcd. 255.1259 for $C_{16}H_{17}NO_2$.

2-((2-Ethyl-6-methylphenyl)amino)benzoic acid (3d). Mp 153–155 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3343, $\nu_{C=O}$ 1653, 1573 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 1.06$ (t, $J = 7.50$ Hz, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.47 (t, $J = 7.50$ Hz, 2H, CH_2), 6.08 (d, $J = 8.50$ Hz, 1H, Ar-H), 6.63 (t, $J = 7.50$ Hz, 1H, Ar-H), 7.18–7.21 (m, 3H, Ar-H), 7.25 (t, $J = 8.00$ Hz, 1H, Ar-H), 7.87 (dd, $J = 8.00$ Hz, 1.50 Hz, 1H, Ar-H), 9.22 (s, 1H, NH), 12.92 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ170.43, 149.88, 141.99, 136.41, 136.36, 134.57, 131.83, 128.67, 127.10, 127.00, 115.73, 112.07, 110.35, 24.61, 18.02, 15.09. HRMS: found 255.1262; calcd. 255.1259 for $C_{16}H_{17}NO_2$.

2-((2,6-Diethylphenyl)amino)benzoic acid (3e). Mp 177–178 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3350, $\nu_{C=O}$ 1657, 1577 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 1.06$ (t, $J = 7.50$ Hz, 6H, CH_3), 2.43–2.48 (m, 4H, CH_2), 6.09 (d, $J = 8.50$ Hz, 1H, Ar-H), 6.62 (t, $J = 7.50$ Hz, 1H, Ar-H), 7.20–7.26 (m, 4H, Ar-H), 7.86 (dd, $J = 8.00$ Hz, 1.50 Hz, 1H, Ar-H), 9.24 (s, 1H, NH), 12.92 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 170.30, 150.16, 142.08, 135.58, 134.32, 131.61, 127.15, 126.88, 115.45, 111.95, 110.07, 24.34, 14.81. HRMS: found 269.1418; calcd. 269.1416 for $C_{17}H_{19}NO_2$.

2-((2,6-Diisopropylphenyl)amino)benzoic acid (3f). Mp 217–219 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3340, $\nu_{C=O}$ 1661, 1574 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 1.07$ (d, $J = 7.00$ Hz, 6H, CH_3), 1.10 (d, $J = 6.50$ Hz, 6H, CH_3), 2.97–3.03 (m, 2H, CH), 6.07 (d, $J = 8.50$ Hz, 1H, Ar-H), 6.61 (t, $J = 7.50$ Hz, 1H, Ar-H), 7.23–7.27 (m, 3H, Ar-H), 7.33 (t, $J = 8.00$ Hz, 1H, Ar-H), 7.85 (dd, $J = 8.00$ Hz, 1.50 Hz, 1H, ArH), 9.12 (s, 1H, NH), 12.92 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 170.30, 150.86, 146.78, 134.29, 133.96, 131.61, 127.68, 123.82, 115.37, 112.10, 109.85, 27.98, 24.33, 22.67. HRMS: found 297.1736; calcd. 297.1729 for $C_{19}H_{23}NO_2$.

2-((2,4,6-Trichlorophenyl)amino)benzoic acid (3g). Mp 238–240 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3300, $\nu_{C=O}$ 1662, 1580 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): $\delta = 6.24$ (d, $J = 8.50$ Hz, 1H, ArH), 6.80 (t, $J = 7.50$ Hz, 1H, ArH), 7.32 (t, $J = 8.00$ Hz, 1H, ArH), 7.88 (s, 1H, ArH), 7.90 (dd, $J = 8.00$ Hz, 1.50 Hz, 2H,

ArH), 9.50 (s, 1H, NH), 13.23 (s, 1H, COOH)ppm.^{13}C NMR (DMSO-d_6, 500 MHz): δ 170.36, 147.03, 134.55, 131.90, 131.72, 129.19, 118.21, 113.39, 112.50. HRMS: found 314.9615; calcd. 314.9621 for $C_{13}H_8NO_2Cl_3$.

4-Chloro-2-((2,6-dimethylphenyl)amino)benzoic acid (3h). Mp 245–246 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3337, $\nu_{C=O}$ 1659, 1562 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.12 (s, 6H, CH_3), 5.97 (d, J = 1.50 Hz, 1H, Ar-H), 6.69 (dd, J = 8.50 Hz, 2.00 Hz, 1H, Ar-H), 7.19–7.23 (m, 3H, Ar-H), 7.87 (d, J = 8.50 Hz, 1H, ArH), 9.30 (s, 1H, NH), 13.21 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 169.43, 150.22, 139.18, 136.13, 135.93, 133.65, 128.61, 127.00, 115.60, 110.74, 109.46, 17.71. HRMS: found 275.0714; calcd. 275.0713 for $C_{15}H_{14}NO_2Cl$.

4-Chloro-2-((2,3-dimethylphenyl)amino)benzoic acid (3i). Mp 239–240 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3345, $\nu_{C=O}$ 1661, 1564 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.09 (s, 3H, CH_3), 2.30 (s, 3H, CH_3), 6.50 (d, J = 2.50 Hz, 1H, Ar-H), 6.71 (dd, J = 8.50 Hz, 2.00 Hz, 1H, Ar-H), 7.10–7.19 (m, 3H, Ar-H), 7.88 (d, J = 8.50 Hz, 1H, A-rH), 9.55 (s, 1H, NH), 13.26 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 169.50, 150.00, 138.98, 138.18, 137.38, 133.59, 132.09, 127.37, 126.28, 123.23, 115.97, 111.73, 109.88, 20.15, 13.62. HRMS: found 275.0715; calcd. 275.0713 for $C_{15}H_{14}NO_2Cl$.

4-Chloro-2-(mesitylamino)benzoic acid (3j). Mp 263–264 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3342, $\nu_{C=O}$ 1666, 1564 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 2.07 (s, 6H, CH_3), 2.28 (s, 3H, CH_3), 5.97 (s, 1H, Ar-H), 6.61–6.68 (m, 1H, Ar-H), 7.01 (s, 2H, Ar-H), 7.86 (d, J = 7.50 Hz, 1H, Ar-H), 9.20 (s, 1H, NH), 12.65 (s, 1H, COOH) ppm. HRMS: found 289.0878; calcd. 289.0870 for $C_{16}H_{16}NO_2Cl$.

4-Chloro-2-((2-ethyl-6-methylphenyl)amino)benzoic acid (3k). Mp 193–195 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3339, $\nu_{C=O}$ 1670, 1564 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.07 (t, J = 7.00 Hz, 3H, CH_3), 2.11 (s, 3H, CH_3), 2.50 (s, 2H, CH_2), 5.97 (s, 1H, Ar-H), 6.75 (d, J = 8.00 Hz, 1H, Ar-H), 7.23 (s, 3H, Ar-H), 7.87 (d, J = 8.50 Hz, 1H, Ar-H), 9.34 (s, 1H, NH), 13.20 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 169.69, 150.77, 141.98, 139.35, 136.27, 135.57, 133.81, 128.86, 127.53, 127.29, 115.73, 110.98, 109.45, 24.51, 17.90, 15.03. HRMS: found 289.0874; calcd. 289.0870 for $C_{16}H_{16}NO_2Cl$.

4-Chloro-2-((2,6-diethylphenyl)amino)benzoic acid (3l). Mp 212–214 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3314, $\nu_{C=O}$ 1653, 1568 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.07 (t, J = 7.50, 6H, CH_3), 2.45–2.49 (m, 4H, CH_2), 5.98 (s, 1H, Ar-H), 6.72 (d, J = 8.00 Hz, 1H, Ar-H), 7.24–7.31 (m, 3H, Ar-H), 7.87 (d, J = 8.50 Hz, 1H, Ar-H), 9.36 (s, 1H, NH), 12.96 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 169.57, 151.04, 141.98, 139.10, 134.75, 133.60, 127.67, 127.10, 115.49, 110.91, 109.18, 24.28, 14.77. HRMS: found 303.1022; calcd. 303.1026 for $C_{17}H_{18}NO_2Cl$.

4-Chloro-2-((2,6-diisopropylphenyl)amino)benzoic acid (3m). Mp 249–251 °C; FT-IR (KBr): $\nu_{N\text{-}H}$ 3333, $\nu_{C=O}$ 1663, 1566 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.08–1.15 (m, 12H, CH_3), 2.94–2.99 (m, 2H, CH), 6.00 (s, 1H, Ar-H), 6.67 (d, J = 8.50 Hz, 1H, Ar-H), 7.29–7.39 (m, 3H, Ar-H), 7.87 (d,

$J = 8.50$ Hz, 1H, Ar-H), 9.17 (s, 1H, NH), 12.94 (s, 1H, COOH) ppm. ^{13}C NMR (DMSO-d_6, 500 MHz): δ 169.57, 151.60, 146.52, 139.00, 133.59, 133.10, 128.15, 124.10, 115.41, 111.18, 109.04, 28.06, 24.24, 22.69. HRMS: found 331.1342; calcd. 331.1339 for $C_{19}H_{22}NO_2Cl$.

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REFERENCES

1. Baures, P. W.; Oza, V. B.; Peterson, S. A.; Kelly, J. K. Synthesis and evaluation of inhibitors of transthyretin amyloid formation based on the nonsteroidal anti-inflammatory drug, flufenamic acid. *Bioorg. Med. Chem.* **1999**, *7*, 1339–1347.
2. Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemière, P.; Debreu, M.-A.; Davioud-Charvet, E.; Sergheraert, C. Antimalarial, antitrypanosomal, and antileishmanial activities and cytotoxicity of bis(9-amino-6-chloro-2-methoxyacridines): Influence of the linker. *J. Med. Chem.* **2000**, *43*, 2646–2654.
3. Csuk, R.; Barthel, A.; Raschke, C. Convenient access to substituted acridines by a Buchwald–Hartwig amination. *Tetrahedron* **2004**, *60*, 5737–5750.
4. Barrett, S. D.; Bridges, A. J.; Dudley, D. T.; Saltiel, A. R.; Fergus, J. H. The discovery of the benzhydroxamate MEK inhibitors CI-1040 and PD0325901. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6501–6504.
5. Ullmann, F. Ueber eine neue bildungweise von diphenylaminderivaten. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382–2384.
6. Pellón, R. F.; Carrasco, R.; Rodés, L. Synthesis of N-phenylantranilicacids using water as solvent. *Synth. Commun.* **1993**, *23* (10), 1447–1453.
7. Pellón, R. F.; Carrasco, R.; Mfirquez, T.; Mamposo, T. Use of N,N-dimethylformamide as solvent in the synthesis of N-phenylanthranilic acids. *Tetrahedron Lett.* **1997**, *38*(29), 5107–5110.
8. Docampo, M. L.; Pellón, R. F.; Estevez-Braun, A.; Ravelo, A. G. Ultrasound-promoted reaction of 2-chlorobenzoic acids and aliphatic amines. *Eur. J. Org. Chem.* **2007**, 4111–4115.
9. Fascio, M. L.; D'Accorso, N. B.; Pellón, R. F.; Docampo, M. L. Synthesis of novel carbohydrate acridinone derivatives with potential biological activities using 1,3-dipolar cyclo addition. *Synth. Commun.* **2007**, *37*, 4209–4217.
10. Girisha, H. R.; Srinivasa, G. R.; Gowda, D. C. A simple and environmentally friendly method for the synthesis of N-phenylanthranilic acid derivatives. *J. Chem. Res.* **2006**, 342–344.
11. Martín, A.; Pellón, R. F.; Mesa, M.; Docampo, M. L.; Gómez, V. Microwave-assisted synthesis of N-phenylanthranilic acids in water. *J. Chem. Res.* **2005**, 561–563.
12. Martín, A.; Mesa, M.; Docampo, M. L.; Gómez, V.; Pellón, R. F. Fast synthesis of substituted N-phenylanthranilic acids using Ullmann condensation under microwave irradiation in dry media. *Synth. Commun.* **2006**, *36*, 271–277.
13. Mei, X. F.; August, A. T.; Wolf, C. Regioselective copper-catalyzed amination of chlorobenzoic acids: synthesis and solid-state structures of N-aryl anthranilic acid derivatives. *J. Org. Chem.* **2006**, *71*, 142–149.

14. Wolf, C.; Liu, S. L.; Mei, X. F.; August, A. T.; Casimir, M. D. Regioselective copper-catalyzed amination of bromobenzoic acids using aliphatic and aromatic amines. *J. Org. Chem.* **2006**, *71*, 3270–3273.
15. Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. Expanding Pd-catalyzed C-N bond-forming processes: The first amidation of aryl sulfonates, aqueous amination, and complementarity with Cu-catalyzed reactions. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.
16. Hadjipavlou-Litina, D. Quantitative structure–activity relationship (QSAR) studies on nonsteroidal anti-inflammatory drugs (NSAIDs). *Curr. Med. Chem.* **2000**, *7*, 375–388.
17. Zheng, H. *Medicinal Chemistry*; People's Medical Publishing House: Beijing, China, 2003.
18. Dokorou, V.; Demertzis, M. A.; Jasinski, J. P.; Kovala-Demertz, D. Synthesis and spectroscopic studies of diorganotin derivatives with 2-[(2,6-dimethylphenyl)amino]benzoic acid. Crystal and molecular structure of the first complexes of 2-[(2,6-dimethylphenyl) amino]benzoic acid. Crystal and molecular structures of 1,2:3,4-di-l2-2-[(2,6-dimethylphenyl) amino]-benzoato-O,O-1,3-bis-2-[(2,6-dimethylphenyl)amino]benzoato-O-1,2,4:2,3,4-di-l3-oxo-tetrakis[di-butyltin(IV)] and bis-2-[(2,6-dimethylphenyl)amino]benzoato-di-n-butyltin(IV). *J. Organomet. Chem.* **2004**, *689*, 317–325.
19. Saphier, M.; Masarwa, A.; Cohen, H.; Meyerstein, D. Copper(I) as a homogeneous catalyst for the Ullmann reactionin aqueous solutions—The transformation of 2-bromobenzoate into salicylate. *Eur. J. Inorg. Chem.* **2002**, *5*, 1226–1234.
20. Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. Microwaves in organic synthesis: Thermal and non-thermal microwave effects. *Chem. Soc. Rev.* **2005**, *34*, 164–178.