CONVENIENT SYNTHESIS OF SOME 3-PHENYL-1-BENZOFURAN-2-CARBOXYLIC ACID DERIVATIVES AS NEW POTENTIAL INHIBITORS OF CLC-Kb CHANNELS

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Abstract – Improved experimental conditions were carried out for the preparation in high yields of some 3-phenyl-1-benzofuran-2-carboxylic acids, potent inhibitors of ClC-K chloride channels. A one-pot condensation-cyclization was set up starting from different 2-hydroxybenzophenones whose reactivity was significantly affected from the electronic properties of their substituents.

ClC-Ka and ClC-Kb chloride channels are pivotal for renal salt reabsorption and water balance.\(^1\) Therefore, there is growing interest in identifying ligands that allow pharmacological interventions aimed to modulate their activity. Recently, the 3-phenyl-1-benzofuran-2-carboxylic acids 1-6 (Figure 1) have been reported as potent inhibitors of these channels proposing themselves as leads for the development of agents capable of regulating diuresis.\(^2\)

![Figure 1](image-url)
This promising activity prompted us to investigate the possibility to improve the synthesis of these compounds which need to be available in great amount for in vivo studies. Differently from literature, in fact, the procedure for the preparation of the ethyl ester of derivative 1, in our hands occurred in two steps and very low yield. Herein we report improved experimental conditions for the preparation of ethyl 3-phenyl-1-benzofuran-2-carboxylates 1a-6a shown in Table 1. The cyclization reaction occurs in a single step and with high yields providing, therefore, a simple and fast way to obtain the desired compounds. Esters 7a-9a were also prepared to evaluate the importance of the benzene ring in position 3 of the benzofuran nucleus in affecting the reactivity of the reagents. Finally, the alkaline hydrolysis of all the above esters allowed the achievement of the target 1-benzofuran-2-carboxylic acids 1-6 as well as 7-9.

The synthesis of ethyl 5-chloro-3-phenyl-1-benzofuran-2-carboxylate 1a was reported to occur by direct condensation of 5-chloro-2-hydroxybenzophenone with ethyl 2-bromoacetate in dry toluene in the presence of NaH. In our hands, instead, this reaction led to an intermediates mixture of ethyl (2-benzoyl-4-chloro)phenoxyacetate 10 and ethyl 5-chloro-3-hydroxy-3-phenyl-2,3-dihydro-1-benzofuran-2-carboxylate 11 with poor yield. The treatment of this mixture with \( p \)-toluenesulfonic acid in boiling toluene afforded only small amounts of the ethyl ester 1a after separation on silica gel column from the unreacted ester 10. Quantitative yields, however, were obtained by using sodium ethoxide in refluxing absolute ethanol. The basic condition, in fact, allowed, both the cyclization of 10 and the dehydration of 11 (Scheme 1).

Scheme 1. i) NaH (powder, 95%), dry toluene, reflux; ii) \( p \)-toluenesulfonic acid, toluene, reflux; iii) EtONa, abs EtOH, 70 °C; iv) 2N NaOH, THF
Searching in the literature for an alternative procedure allowing a direct and high yield synthesis of 1a, we found that some furochromenes could be prepared by cyclization with diethyl bromomalonate in the presence of K$_2$CO$_3$ in dry acetone.$^4$ When we applied this procedure to the synthesis of 1a starting from 5-chloro-2-hydroxybenzophenone, the desired compound was obtained in one-pot reaction and in 99% yield (Scheme 2).

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\begin{align*}
\text{R}_1 \text{OH} & \quad \text{O} & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{O} & \quad \text{Br} & \quad \text{vi} & \quad \text{1a-9a} \\
\text{Br} & \quad \text{O} & \quad \text{O} & \quad \text{vii} & \quad \text{1-9}
\end{align*}
\]

**Scheme 2.** vi) anhydrous K$_2$CO$_3$, acetone, reflux; vii) 2N NaOH, THF

The preparation of the other ethyl 3-phenyl-1-benzofuran-2-carboxylates we were interested in, occurred with similar results even though the reactivity of the starting ketone was influenced from the electronic properties of its substituents.

<table>
<thead>
<tr>
<th>compound</th>
<th>R$_1$</th>
<th>R$_2$</th>
<th>Yield</th>
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<tbody>
<tr>
<td>1a</td>
<td>Cl</td>
<td></td>
<td>99%</td>
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<tr>
<td>2a</td>
<td>Cl</td>
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<tr>
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<td></td>
<td>80%</td>
</tr>
<tr>
<td>4a</td>
<td>Br</td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>5a</td>
<td>Me</td>
<td></td>
<td>64%</td>
</tr>
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</table>
The presence, in fact, of an electron-withdrawing group in R_1 increased the reactivity of the carbonylic function. The chlorine atom turned out to be better than the bromine atom as shown from the 99% yield for the preparation of 1a compared to 3a (80%). The presence of an additional chlorine atom on the phenyl of R_2 group showed a remarkable additive effect as demonstrated by the increased yield of 4a (98%) compared to 3a. By contrast, as expected, the presence in R_1 of an electron-donor group like a methyl or the lacking of substituents decreased the electrophilic properties of ketone affording lower yields for the corresponding benzofurans 5a and 6a. The influence on the reactivity of the carbonylic group by the R_2 group was even greater. Starting, in fact, from acetophenone (R_2 = methyl) or benzaldehyde (R_2 = H), the corresponding benzofurans 7a-9a were obtained in low yields (17-20%). Finally, all the above esters were easily hydrolyzed to the target acids by treatment with a 2N NaOH/THF mixture. Yields as high as 77-94% were obtained with the exception of acid 7 (52%).

In conclusion, a simple, fast and high yield synthesis of the 3-phenyl-1-benzofuran-2-carboxylic acids 1-6 was carried out by significantly modifying a previously reported procedure. The reactivity of the starting benzophenone was significantly affected by the electronic properties of its substituents with electron-withdrawing groups affording the best yields. The reactivity of the starting carbonylic compound was even more greatly reduced by substitution of benzophenone with acetophenone or benzaldehyde. Importantly, this improved procedure for the preparation of acids 1-6 allows the availability of gram scale of these potent CIC-K chloride channel inhibitors for in vivo studies.

**EXPERIMENTAL**

**General.** All commercial reagents and solvents were used without further purification. Reactions were monitored by TLC analysis using silica-coated TLC plates (Merck F 60254) and visualized under UV light. Column chromatography was performed on ICN silica gel 60 J (63–200 mm) as a stationary phase. Melting points were determined in open capillaries on a Gallenkamp electrothermal apparatus and are uncorrected. Mass spectra were recorded with an HP GC–MS 6890–5973 MSD spectrometer, electron impact 70 eV, equipped with HP chemstation. \(^1\)H-NMR spectra were recorded in CDCl₃ or DMSO-d₆ on a Varian-Mercury 300 (300 MHz) spectrometer at room temperature (20 °C). Chemical shifts are expressed as parts per million (δ).
Ethyl (2-benzoyl-4-chloro)phenoxyacetate and ethyl 5-chloro-3-hydroxy-3-phenyl-2,3-dihydro-1-benzofuran-2-carboxylate. (Scheme 1, step i) NaH powder (95%, 190 mg, 7.9 mmol) was carefully added, under nitrogen atmosphere, to a solution of 5-chloro-2-hydroxybenzophenone (1.5 g, 5.3 mmol) in 20 mL of anhydrous toluene. The resulting mixture was stirred and was refluxed for 15 minutes. Then a solution of ethyl 2-bromoacetate (1.5 g, 9.0 mmol) in 10 mL of anhydrous toluene was slowly dropped and the mixture was refluxed 11 h. After cooling at room temperature it was treated with water. The organic solution was separated and evaporated and the residue oil was taken up with Et2O; the organic phase was washed with brine and dried over Na2SO4. The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel using petroleum ether-EtOAc as eluent (95:5) to give the mixture (94.5:5.5, as determined by GC-MS and 1H-NMR) as a white solid (890 mg).

Ethyl (2-benzoyl-4-chloro)phenoxyacetate (10). 1H-NMR (300 MHz, CDCl3): 1.21 (t, 3H, CH3; \( J = 7.2 \) Hz), 4.16 (q, 2H, CH3-CH2-O; \( J = 7.2 \) Hz), 4.51 (s, 2H, O-CH2-CO), 6.77-6.82, 7.36-7.60 and 7.83-7.87 (m, 8H, aromatics); GC-MS (tR: 13.22 min): m/z 320 (M+ +2) (9), 318 (M+) (27), 244 (M+ – C3H6O2) (100), 105 (M+ – C9H6ClO4+ ) (66), 91 (M+ - C10H8ClO4+) (98).

Ethyl 5-chloro-3-hydroxy-3-phenyl-2,3-dihydro-1-benzofuran-2-carboxylate (11). 1H-NMR (300 MHz, CDCl3): 1.23 (t, 3H, CH3; \( J = 7.2 \) Hz), 2.03 (s, 1H, OH), 4.17 (q, 2H, CH3-CH2-O; \( J = 7.2 \) Hz), 5.16 (s, 1H, CH), 6.52-6.58 and 6.95-7.09 (m, 8H, aromatics); GC-MS (tR: 12.91 min): m/z 320 (M+ +2) (17), 318 (M+) (42), 244 (M+ – C3H6O2) (100).

Ethyl 5-chloro-3-phenyl-1-benzofuran-2-carboxylate (Scheme 1, step ii). p-Toluensulfonic acid (1 g, 5.7 mmol) was added to a solution in toluene (30 mL) of the mixture obtained in step (i). The mixture was refluxed for 13 h. Then the solvent was distilled off and the oily residue was dissolved in Et2O; the organic phase was washed with brine and dried over Na2SO4. The solvent was removed under reduced pressure to give the crude oil, which was purified by column chromatography on silica gel using petroleum ether/EtOAc as eluent (95:5) to give the desired product as a white solid (60 mg).

Ethyl 5-chloro-3-phenyl-1-benzofuran-2-carboxylate (Scheme 1, step iii). A solution of the mixture obtained in step (i) (200 mg) in absolute EtOH (2mL) was dropped to a solution of sodium ethoxide (0.55 mmol) in absolute EtOH (5 mL). After reflux for 1 h, the mixture was cooled at room temperature. The solvent was removed under reduced pressure to afford the desired product in quantitative yield.

General procedure for the synthesis of ethyl 1-benzofuran-2-carboxylate derivates 1a-9a (Scheme 2, step vi). To a suspension of 16.2 g of anhydrous K2CO3 (0.012 mol) in 195 mL of acetone was added, under
nitr

Ethyl 5-chloro-3-phenyl-1-benzofuran-2-carboxylate (1a). Yield: 99%; mp 105-106 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 1.27 (t, 3H, CH$_3$; $J = 7.2$ Hz), 4.35 (q, 2H, CH$_2$; $J = 7.2$ Hz), 7.41–7.58 (m, 8H, aromatics); GC-MS: $m/z$ (302, M$^+$ + 2) (35), 300 (M$^+$) (100). Anal. Calcd for C$_{17}$H$_{13}$ClO$_3$: C, 67.89; H, 4.36. Found: C, 68.12; H, 4.31.

Ethyl 5-chloro-3-(2-chlorophenyl)-1-benzofuran-2-carboxylate (2a). Yield: 99%; mp 60-63 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.18 (t, 3H, CH$_3$; $J = 7.2$ Hz), 4.17–4.36 (m, 2H, CH$_2$; $J = 7.2$ Hz), 7.32–8.32 (m, 7H, aromatics); GC-MS: $m/z$ 338 (M$^+$ + 4) (1), 336 (M$^+$ + 2) (2), 334 (M$^+$) (3), 271 (M$^+$ - C$_3$H$_5$O$_2$) (100). Anal. Calcd for C$_{17}$H$_{12}$Cl$_2$O$_3$: C, 60.92; H, 3.61. Found: C, 60.70; H, 3.70.

Ethyl 5-bromo-3-phenyl-1-benzofuran-2-carboxylate (3a). Yield: 80%; mp 128-130 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.27 (t, 3H, CH$_3$; $J = 7.2$ Hz), 4.33 (q, 2H, CH$_2$; $J = 7.2$ Hz), 7.25–7.71 (m, 8H, aromatics); GC-MS: $m/z$ 346 (M$^+$ + 2) (97), 344 (M$^+$) (100). Anal. Calcd for C$_{17}$H$_{13}$BrO$_3$: C, 59.15; H, 3.80. Found: C, 58.86; H, 3.97.

Ethyl 5-bromo-3-(2-chlorophenyl)-1-benzofuran-2-carboxylate (4a). Yield: 98%; mp 82-84 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.28 (t, 3H, CH$_3$-CH$_2$; $J = 7.2$ Hz), 4.28 (q, 2H, CH$_2$; $J = 7.2$ Hz), 7.26-7.59 (m, 7H, aromatics); GC-MS: $m/z$ 382 (M$^+$ + 4) (3), 380 (M$^+$ + 2) (4), 378 (M$^+$) (1), 343 (M$^+$ - Cl) (60), 315 (M$^+$ - COCl) (100). Anal. Calcd for C$_{17}$H$_{12}$BrClO$_3$: C, 53.78; H 3.19. Found: C, 53.88; H, 3.16.

Ethyl 5-methyl-3-phenyl-1-benzofuran-2-carboxylate (5a). Yield: 64%; mp 80-82 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.28 (t, 3H, CH$_3$-CH$_2$; $J = 7.3$ Hz), 2.43 (s, 3H, CH$_3$-Ph), 4.33 (q, 2H, CH$_2$; $J = 7.3$ Hz), 7.25–7.59 (m, 8H, aromatics); GC-MS: $m/z$ 280 (M$^+$) (100), 208 (M$^+$ - C$_3$H$_4$O$_2$) (64). Anal. Calcd for C$_{18}$H$_{16}$O$_3$: C, 77.12; H 5.75. Found: C, 77.22; H, 5.71.

Ethyl 3-phenyl-1-benzofuran-2-carboxylate (6a). Yield: 72%; mp 63-65 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.29 (t, 3H, CH$_3$; $J = 7.2$ Hz), 4.35 (q, 2H, CH$_2$; $J = 7.2$ Hz), 7.25-7.65 (m, 9H, aromatics); GC-MS: $m/z$ 266 (M$^+$) (100), 194 (M$^+$ - C$_3$H$_4$O$_2$) (62). Anal. Calcd for C$_{17}$H$_{14}$O$_3$: C, 76.68; H, 5.30. Found: C, 76.91; H, 5.22.

Ethyl 5-chloro-3-methyl-1-benzofuran-2-carboxylate (7a). Yield: 17%; mp 65-67 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 1.44 (t, 3H, CH$_3$-CH$_2$; $J = 7.2$ Hz), 2.55 (s, 3H, CH$_3$), 4.45 (q, 2H, CH$_2$; $J = 7.2$ Hz), 7.37 (m, 2H, aromatics), 7.60 (m, 1H, aromatic); GC-MS: $m/z$ 240 (M$^+$ + 2) (37), 238 (M$^+$) (100). Anal. Calcd for C$_{12}$H$_{11}$ClO$_3$: C, 60.39; H, 4.65. Found: C, 60.44; H, 4.55.
Ethyl 5-chloro-1-benzofuran-2-carboxylate (8a). Yield: 20%; mp 56-58 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.43 (t, 3H, CH$_3$; $J$ = 7.2 Hz), 4.44 (q, 2H, CH$_2$; $J$ = 7.2 Hz), 7.38-7.66 (m, 4H, aromatics); GC-MS: $m/z$ 226 (M$^+$+2) (30), 224 (M$^+$) (85), 198 ((M$^+$+2) – C$_2$H$_4$) (36), 196 (M$^+$ – C$_2$H$_4$) (100), 181 (M$^+$ + 2– C$_2$H$_5$O) (37), 179 (M$^+$ – C$_2$H$_5$O) (99). Anal. Calcd for C$_{11}$H$_9$ClO$_3$: C, 58.81; H, 4.04. Found: C, 58.88; H 3.93.

Ethyl 5-bromo-3-methyl-1-benzofuran-2-carboxylate (9a). Yield: 17%; mp 90-92 °C; $^1$H-NMR (300 MHz, CDCl$_3$) δ (ppm): 1.44 (t, 3H, CH$_3$; $J$ = 7.2 Hz), 2.55 (s, 3H, CH$_3$), 4.45 (q, 2H, CH$_2$; $J$ = 7.2 Hz), 7.26-7.83 (m, 3H, aromatics); GC-MS: $m/z$ 284 (M$^+$+2) (98), 282 (M$^+$) (100), 256 ((M$^+$+2) – C$_2$H$_4$) (70), 254 (M$^+$ – C$_2$H$_4$) (100), 239((M$^+$+2) – OC$_2$H$_4$) (73), 237 (M$^+$ – OC$_2$H$_4$) (100). Anal. Calcd for C$_{12}$H$_{11}$BrO$_3$: C, 50.91; H 3.91. Found: C, 50.73; H, 3.96.

General procedure for the synthesis of acids 1-9. (Scheme 1, step iv and Scheme 2, step vii) The ethyl 1-benzofuran-2-carboxylate(10 mmol), obtained from the reaction described above, was stirred at room temperature with 2N NaOH (175 mL) in THF (175 mL) for 4–6 h. The organic solvent was distilled off under reduced pressure and the aqueous phase was washed with Et$_2$O, acidified to pH 1 with 6N HCl, and extracted with Et$_2$O (3x35 mL). The combined organic extracts were dried over Na$_2$SO$_4$, and the solvent was removed under reduced pressure to afford the desired acids as solids, which were purified by crystallization from CHCl$_3$/n-hexane.

5-Chloro-3-phenyl-1-benzofuran-2-carboxylic acid (1). Yield: 77%; mp 254-255 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 7.41–7.82 (m, 8H, aromatics), 13.62 (bs, 1H, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 288 (M$^+$+2) (35), 286 (M$^+$) (100). Anal. Calcd for C$_{15}$H$_9$ClO$_3$: C, 66.07; H, 3.33. Found: C, 66.31; H, 3.30.

5-Chloro-3-(2-chlorophenyl)-1-benzofuran-2-carboxylic acid (2). Yield: 88%; mp 215-218 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 7.36-7.62 (m, 6H, aromatics), 13.57 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 324 (M$^+$+4) (0.1), 322 (M$^+$+2) (1), 320 (M$^+$) (3), 285 ((M$^+$+2)– Cl) (35), 285 (M$^+$ – Cl) (100). Anal. Calcd for C$_{15}$H$_8$Cl$_2$O$_3$: C, 58.66; H, 2.63. Found: C, 58.20; H, 2.73.

5-Bromo-3-phenyl-1-benzofuran-2-carboxylic acid (3). Yield: 85%; mp 248-251 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 7.42-7.76 (m, 7H, aromatics), 13.51 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 332 (M$^+$+2) (98), 330 (M$^+$) (100), 299 (M$^+$ – CH$_3$O) (50), 301 ((M$^+$+2) – CH$_3$O) (49). Anal. Calcd for C$_{15}$H$_9$BrO$_3$: C, 56.81; H, 2.86. Found: C, 56.92; H, 3.03.

5-Bromo-3-(2-chlorophenyl)-1-benzofuran-2-carboxylic acid (4). Yield: 89%; mp 218-219 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) δ (ppm): 7.36-7.62 (m, 6H, aromatics), 13.46 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 366 (M$^+$+2) (26), 364 (M$^+$) (27), 335 ((M$^+$+2) – CH$_3$O) (98), 333 (M$^+$ – CH$_3$O) (100). Anal. Calcd for C$_{15}$H$_9$BrClO$_3$: C, 51.24; H 2.29. Found: C, 51.20; H, 2.34.
5-Methyl-3-phenyl-1-benzofuran-2-carboxylic acid (5). Yield: 94%; mp 233-234 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 2.38 (s, 3H, CH$_3$-Ph), 7.31- 7.62 (m, 8H, aromatics), 13.23 (bs, 1H, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 266 (M$^+$) (100), 235 (M$^+$ - CH$_3$O) (53). Anal. Calcd for C$_{16}$H$_{12}$O$_3$: C, 76.18; H 4.79. Found: C, 76.12; H, 4.74.

3-Phenyl-1-benzofuran-2-carboxylic acid (6). Yield: 93%; mp 236-238 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 7.32- 7.75 (m, 8H, aromatics), 13.42 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 252 (M$^+$) (100), 221 (M$^+$ - CH$_3$O) (52). Anal. Calcd for C$_{15}$H$_{10}$O$_3$: C, 75.62; H, 4.23. Found: C, 75.96; H, 4.22.

5-Chloro-3-methyl-1-benzofuran-2-carboxylic acid (7). Yield: 52%; mp 268-269 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 3.50 (s, 3H, CH$_3$), 7.50 (m, 1H, aromatic), 7.70 (m, 1H, aromatic), 7.90 (m, 1H, aromatic), 13.50 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 226 (M$^+$+2) (28), 224 (M$^+$) (100), 193 (M$^+$ - CH$_3$O) (87). Anal. Calcd for C$_{10}$H$_7$ClO$_3$: C, 57.03; H, 3.35. Found: C, 57.34; H, 3.53.

5-Chloro-1-benzofuran-2-carboxylic acid (8). Yield: 94%; mp 215-217 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 7.30- 7.51 (m, 4H, aromatics), 13.66 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 212 (M$^+$+2) (34), 210 (M$^+$) (88), 181 ((M$^+$+2) – CH$_3$O) (42), 179 (M$^+$ - CH$_3$O) (100). Anal. Calcd for C$_9$H$_5$ClO$_3$: C, 54.99; H, 2.56. Found: C, 54.87; H, 2.73.

5-Bromo-3-methyl-1-benzofuran-2-carboxylic acid (9). Yield: 77%; mp 263-264 °C; $^1$H-NMR (300 MHz, DMSO-d$_6$) $\delta$ (ppm): 2.49 (s, 3H, CH$_3$), 7.61 (m, 2H, aromatics), 8.01 (m, 1H, aromatic), 13.52 (bs, COOH, D$_2$O exchangeable); GC-MS: $m/z$ (methyl ester) 270 (M$^+$+2) (97), 268 (M$^+$) (100), 239 ((M$^+$+2) – CH$_3$O) (59), 237 (M$^+$ - CH$_3$O) (56). Anal. Calcd for C$_{10}$H$_7$BrO$_3$: C, 47.09; H 2.77. Found: C, 46.93; H, 2.86.

REFERENCES