POLYCYCLIC QUINOLONES (PART 2) – SYNTHESIS OF NOVEL 4-OXO-1,4-DIHYDROBENZO[h][1,3]THIAZETO[3,2-a]QUINOLINE CARBOXYLIC ACIDS VIA OXIDATIVE CYCLIZATION OF THE CORRESPONDING 2-MERCAPTOQUINOLINE PRECURSORS

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Abstract – The first synthesis of a series of 4-oxo-1,4-dihydrobenzo[h][1,3]thiazeto[3,2-a]quinoline carboxylic acids and their esters via oxidative cyclization of ethyl 2-((2-ethoxy-2-oxoethyl)thio)-4-hydroxybenzo[h]quinoline-3-carboxylate derivatives in the presence of a vicinal dihaloalkane, KI, and K$_2$CO$_3$ is described. Structures of the synthesized compounds were characterized by spectrometric and X-ray crystallographic analyses.

INTRODUCTION

4-Oxo-1,4-dihydroquinoline-3-carboxylic acid derivatives (quinolones) have dominated the antibacterial market for decades. Quinolones have a unique mechanism of action, they inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase (main target in Gram-negative bacteria) and type IV topoisomerase (main target in Gram-positive bacteria), resulting in rapid bacterial death.1-3

Inhibitory activity of quinolones against human topoisomerase-2 has been reported by Kyowa-Hakko researchers via introduction of a series of tricyclic thiazoloquinolones that exhibited impressive anticancer activity.4

In continuation of our ongoing research towards the discovery of novel polycyclic quinoline-based antineoplastic agents using conventional synthetic procedures, we were able to isolate and identify, unexpectedly, a 4-oxo-benzo[h]thiazetoquinoline derivative (4a). The structure of this novel molecule was elucidated by $^1$H-NMR, $^{13}$C-NMR, HR-MS, and X-ray crystallography. Despite the availability of
several literatures on the syntheses and bioactivity of angular 4-oxo-thiazolo[3,2-a]quinoline-3-carboxylic acid derivatives,\textsuperscript{4-9} there are limited reports on the synthesis of 4-oxo-thiazeto[3,2-a]quinolines\textsuperscript{10-16} and there is no reported synthesis of 4-oxo-benzo[h]thiazeto[3,2-a]quinoline derivatives.

In our synthesis, the 4-oxo-thiazetoquinoline nucleus is formed via reaction of the carbanion at the alkylsulfide group of the C-2 position of the quinoline ring with a pseudohalogen (IBr), formed via reaction of iodide anion with the \textit{vic}-dihaloalkane, or a halogen (I$_2$), followed by nucleophilic attack of the N-1 on halogenated carbon and the departure of halogen. The role of the vicinal dihaloalkane in this process is the provision of a pseudohalogen (such as IBr) without direct interaction with the quinoline system. This synthetic procedure provides us with diverse 4-oxo-thiazetoquinoline-3-carboxylic acid derivatives possessing E-withdrawing groups at the C-1 position.

**CHEMISTRY**

The synthesis of 4-oxo-benzo[h]thiazetoquinoline carboxylic acid derivatives is outlined in **Scheme 1**.

\begin{align*}
\text{Namely, naphthylisothiocyanate was allowed to react with diethylmalonate in the presence of sodium hydride to yield the salt 1a which was further reacted with ethyl bromoacetate to afford 2a. Thermal}
\end{align*}
cyclization of 2a, under vacuum, yielded compound 3a. This compound was later reacted with 1,2-dibromopropane in the presence of KI and K$_2$CO$_3$ to obtain 4a, which was further saponified to afford 4b.

Synthesis of compound 4c was then carried out in an analogous manner to 4a using KI and K$_2$CO$_3$ in the presence of 1,2-dibromopropane starting from 3c, as depicted in Scheme 2.

![Scheme 2](image)

The most interesting step in the schemes was the cyclization using vicinal dihaloalkane instead of geminal, which were used in all previously reported procedures for the synthesis of 4-oxo-thiazeto[3,2-$\alpha$]quinolines.\textsuperscript{10-16} Also, the vicinal dihaloalkane did not appear in the final structure, which confirms the role of the vicinal dihaloalkane as a controlled source of the halogenating reagent which allows for cyclization to occur after it halogenates the carbon $\alpha$ to the thiol.

In order to investigate the details of the cyclization process, the following reactions were attempted:

- 3a + KI + 1,2-dibromopropane;
- 3a + K$_2$CO$_3$ + 1,2-dibromopropane;
- 3a + KI + K$_2$CO$_3$;
- 3a + KI + K$_2$CO$_3$ + 1, 2-dibromopropane.

No cyclised product was separated in the first 3 experiments and only the 4$^{th}$ procedure yielded the title compound 4a.

Based on the above information, the following pathway is suggested as a plausible mechanism for the formation of 4a from 3a. Namely, nucleophilic reaction of iodide anion with 1,2-dibromopropane would
result in the formation of propene, bromide ion, and iodobromide (pseudohalide). Nucleophilic attack of the carbanion form of \(3a\) on iodobromide would afford the iodo intermediate \(3a-a\), which upon nucleophilic cyclization yields \(4a\), as depicted in Scheme 3.

![Scheme 3](image)

In order to prove the critical role of 1,2-dihaloalkanes in the formation of the above 4-oxo-thiazetoquinolines, we attempted the same reaction using 1,2-dibromobutane and 1,2-dibromohexane instead of 1,2-dibromopropane. In all trials, compound \(4a\) was obtained in a very good yield. On the other hand, when compound \(3a\) was allowed to react with 1,3-dibromopropane and 1,2-dibromoethane, the corresponding \(O\)-alkylated products (5 and 6) were obtained as shown in Scheme 4.

![Scheme 4](image)
In order to confirm the involvement of the pseudohalide (iodobromide), formed by the reaction of 1,2-dibromopropane and KI, in the oxidative cyclization of compound 3a to 4a, we attempted the reaction of 3a with either iodobromide (IBr) or iodine (I$_2$) in the presence of K$_2$CO$_3$. In both attempts, we were able to obtain compound 4a in moderate yields.

The x-ray crystallographic structures of compound 4a and its carboxylic acid derivative (4b)$^{17}$ are shown in Figure 1. Experimental and refinement details can be found in the supplementary data.

Figure 1. ORTEP representations of the X-ray structures of thiazetoquinoline derivatives 4a and 4b, with 50% probability ellipsoids
We also attempted the decarboxylation of 4b using conventional decarboxylation procedures with no success. Unexpectedly, when 4b was allowed to react with ethyl chloroformate followed by hydroxylamine hydrochloride, compound 4d was afforded. Formation of 4d can be explained via the reaction of ethyl chloroformate with the carboxylate anions (formed in the presence of Et₃N) to afford a mix-anhydride intermediate 4b-b, which upon reaction with hydroxylamine hydrochloride lead to decarboxylation of the conjugated anhydride, while the unconjugated anhydride transforms into a carboxylic acid, as depicted in Scheme 5.

![Scheme 5](image)

**CONCLUSION**

We have presented herein a novel and effective method for a facile synthesis of the 4-oxo-thiazetoquinoline nucleus via a homo- or heterohalide catalyzed oxidative cyclization of 2-((2-ethoxy-2-oxoethyl)thio) or 2-((cyano-methyl)thio)-4-hydroxybenzo[h]quinoline-3-carboxylate, the designed structures did not show cytotoxicity as shown in the MTT cytotoxicity bioassay on the Hela cell line.

**EXPERIMENTAL**

¹H and ¹³C NMR spectra, HSQC, and COSY spectra were recorded on a Bruker 500 MHz NMR spectrometer using TMS as an internal standard. LC-MS and HR-MS were conducted using a GCT Premier Micromass spectrometer. X-Ray structures were measured with on Rigaku Saturn 70 instrument, equipped with a CCD area detector and a SHINE optic, using Mo Kα radiation. Silicycle Ultrapure silica gel (0–20 μm) G and F-254 was used for the preparative-layer TLC, and Silicycle Silia-P Ultrapure Flash silica gel (40–63 μm) was used for flash column chromatography. TLC was conducted on Polygram SIL G/UV254 precoated plastic sheets. Solvents were purified using standard conditions before use.
Sodium 3-ethoxy-2-(ethoxycarbonyl)-1-(naphthalen-1-ylamino)-3-oxoprop-1-ene-1-thiolate (1a). To a suspension of sodium hydride (0.6 g, 25 mmol) in MeCN (50 mL) at 5–10 °C was added dropwise diethyl malonate (4 mL, 26.34 mmol) over a period of 15 min. The mixture was stirred at 5-10 °C for additional 30 min., then 1-naphthylisothiocyanate (5 g, 26.99 mmol) was added portionwise at the same temperature and stirring was continued for another 30 min. Evaporation of MeCN yielded a yellowish solid which was washed with Et₂O; mp 118–120 °C; 1H-NMR: (500 MHz, DMSO-d₆): δ = 12.33 (s, NH), 8.57 (d, J = 7.1 Hz, 1H), 8.16 (t, J = 7.7 Hz, 1H), 7.91–7.86 (m, 1H), 7.52 (ddd, J = 4.7, 11.1, 8.8 Hz, 3H), 7.46–7.38 (m, 1H), 4.02 (q, J = 7.0 Hz, 4H), 1.16 (t, J = 7.0 Hz, 6H); 13C NMR (175 MHz, DMSO-d₆): δ = 181.65, 166.45, 136.18, 132.58, 127.07, 126.67, 124.36, 124.27, 123.99, 121.21, 120.66, 119.49, 116.89, 95.27, 56.88 (2CH₂), 13.37 (2CH₃); APCI-MS: 368.4 (M⁺+1, 100).

Ethyl 2-((2-ethoxy-2-oxoethyl)thio)-4-hydroxybenzo[h]quinoline-3-carboxylate (3a). To the above yellow solid (1a, 2 g, 5.44 mmol) in THF (50 mL) was added BrCH₂CO₂Et (0.6 mL, 5.44 mmol) dropwise at 0 °C and the mixture was stirred for 1 h at room temperature. The solvent was then evaporated, extracted with CHCl₃ and dried over Na₂SO₄. The organic layer was evaporated by rotary evaporator to give a yellow oil (2a). The obtained oil was heated at 170–180 °C in an oil bath under vacuum for 10 min. The resulting oil was solidified, then washed with ether to afford (3a) as white needles; mp 136–138 °C; 1H-NMR: (500 MHz, CDCl₃): δ = 13.11 (s, 1H, OH), 9.22–9.15 (m, 1H), 8.10 (d, J = 8.9 Hz, 1H), 7.89 (dd, J = 3.1, 6.0 Hz, 1H), 7.76–7.68 (m, 3H), 4.61 (q, J = 7.0, 6.9 Hz, 2H), 4.22 (q, J = 7.0, 6.9 Hz, 2H), 4.13 (s, 2H), 1.60 (t, J = 7.0 Hz, 3H), 1.29 (t, J = 7.0 Hz, 3H); 13C NMR (175 MHz, CDCl₃): δ = 170.99, 170.46, 168.29, 158.14, 147.62, 135.89, 130.69, 129.47, 128.19, 127.33, 126.27, 125.97, 119.97, 115.10, 104.00, 63.29, 61.91, 34.65, 14.66, 14.62; HR-MS (TOFEI) calcd for C₂₀H₁₉NO₅S: (385.0984); found (385.0991).

Ethyl 2-[(ethoxymethyl)thio]-4-hydroxybenzo[h]quinoline-3-carboxylate (3b). This compound was prepared according to the same procedure as that applied for 3a using chloromethyl ethyl ether; yellow crystals; mp 120–122 °C; 1H-NMR: (500 MHz, CDCl₃): δ = 13.11 (s, 1H, OH), 9.26–9.19 (m, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.91 (d, J = 3.3 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H), 7.72 (dd, J = 3.2, 6.1 Hz, 2H), 5.76 (s, 2H), 4.60 (q, J = 7.1 Hz, 2H), 3.76 (q, J = 7.0 Hz, 2H), 1.59 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H); 13C NMR (175 MHz, CDCl₃): δ = 171.17, 168.31, 158.23, 147.41, 135.89, 130.69, 129.47, 128.19, 127.15, 126.27, 125.97, 119.97, 115.10, 104.00, 63.29, 61.91, 34.65, 14.66, 14.62; HR-MS (TOFEI) calcd for C₁₉H₁₉NO₄S: (357.0984); found (357.0991).

Ethyl 2-[(cyanomethyl)thio]-4-hydroxybenzo[h]quinoline-3-carboxylate (3c). To a stirring solution of 4 (0.8 g, 2.67 mmol) in THF (10 mL) and H₂O (40 mL) was added NaHCO₃ (1 g, 7.23 mmol), and stirred
for 15 min, then bromoacetonitrile (0.5 g, 4.16 mmol) was added to the resulting solution and stirred for 4 h at room temperature. After completion of the reaction, the solution was acidified by acetic acid, extracted with chloroform, dried over Na$_2$SO$_4$, filtered to give 3c as a white powder; mp 208–210 °C; $^1$H-NMR: (500 MHz, DMSO-$d_6$): $\delta$ = 12.42 (s, 1H, OH), 9.26–9.21 (m, 1H), 8.12 (d, $J$ = 8.8 Hz, 1H), 8.10–8.07 (m, 1H), 7.97 (d, $J$ = 9.1 Hz, 1H), 7.82 (m, 2H), 4.53 (q, $J$ = 7.09, 7.08 Hz, 2H), 4.43 (s, 2H), 1.45 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (175 MHz, DMSO-$d_6$): $\delta$ = 169.97, 168.07, 155.09, 147.23, 135.59, 130.17, 129.48, 127.97, 127.41, 126.65, 125.31, 119.37, 117.49, 115.02, 103.45, 63.17, 17.27, 14.28; HR-MS (TOFEI) calcd. for C$_{18}$H$_{14}$N$_2$O$_3$S (338.0725); found (338.0722).

Diethyl 4-oxo-1,4-dihydrobenzo[h][1,3]thiazeto[3,2-a]quinoline-1,3-dicarboxylate (4a).

i) Oxidative Cyclization using KI and 1,2-dibromopropane

To a mixture of 3a (0.385 g, 1 mmol) and K$_2$CO$_3$ (0.386 g, 2.8 mmol) in dry DMF (25 mL) under nitrogen atmosphere was added 1,2-dibromopropane (0.56g, 2.8 mmol) along with KI (0.464 g, 2.8 mmol). The reaction mixture was heated at 70 °C for 24 h, and then poured into ice-H$_2$O. The resulting thiazetoquinoline derivative was collected by filtration and recrystallized from hexane: CHCl$_3$ (1:3) to afford yellowish crystals; yield = 75%.

ii) Oxidative Cyclization using iodobromide and/or iodine

To a mixture of 3a (0.385 g, 1 mmol) and K$_2$CO$_3$ (0.386 g, 2.8 mmol) in dry DMF (25 mL) under nitrogen atmosphere was added iodobromide and/or iodine (2.8 mmol). The reaction mixture in case of iodobromide was stirred at room temperature for 24 h (in case of iodine the reaction mixture was heated at 70 °C for 24 h). After cooling, both reaction mixtures were poured into ice-H$_2$O. The resulting thiazetoquinoline derivative was collected by filtration and recrystallized from hexane: CHCl$_3$ (1:3) to afford yellowish crystals; yield (IBr) = 40%, yield (I$_2$) = 49%. mp 223–225 °C; $^1$H-NMR: (500 MHz, CDCl$_3$): $\delta$ = 8.42 (d, $J$ = 8.6 Hz, 1H), 7.91 (d, $J$ = 8.3 Hz, 1H), 7.82 (d, $J$ = 8.5 Hz, 1H), 7.68 (d, $J$ = 8.7 Hz, 1H), 7.61 (t, $J$ = 7.4 Hz, 1H), 7.56–7.52 (m, 1H), 6.67 (s, 1H), 4.38 (q, $J$ = 6.7, 6.2 Hz, 2H), 4.23 (q, $J$ = 7.2 Hz, 2H), 1.41 (t, $J$ = 7.3 Hz, 3H), 1.08 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (175 MHz, CDCl$_3$): $\delta$ = 173.28, 165.74, 165.41, 136.16, 135.16, 134.80, 129.94, 129.09, 127.55, 123.91, 122.47, 122.43, 121.73, 121.67, 106.92, 67.75, 64.11, 61.75, 31.31, 14.75, 14.14; HR-MS (TOFEI) calcd. for C$_{20}$H$_{17}$NO$_5$S (383.0827); found (383.0826).

4-Oxo-1,4-dihydrobenzo[h][1,3]thiazeto[3,2-a]quinoline-1,3-dicarboxylic acid (4b). Following a reported procedure,$^{19}$ a mixture of ester (4a) (0.385 g, 1 mmol) and sodium hydroxide (0.08g, 2.2 mmol) in water (20 mL) was stirred and heated at 100 °C for 3–4 h. After cooling, the reaction mixture was neutralized with hydrochloric acid (1 mol/L), extracted with CH$_2$Cl$_2$, dried over MgSO$_4$, then evaporated. The solid obtained was purified by recrystallization from EtOH to afford compound 4b as yellowish
white powder; mp 233–235 °C; 1H-NMR: (500 MHz, DMSO-d6): \( \delta = 8.27 \text{ (d, } J = 8.8 \text{ Hz, 1H)} \), 8.25 (d, \( J = 8.4 \text{ Hz, 1H}) \), 8.17 (d, \( J = 7.5 \text{ Hz, 1H}) \), 8.02 (d, \( J = 8.8 \text{ Hz, 1H}) \), 7.83 (dd, \( J = 11.0, 4.0 \text{ Hz, 1H}) \), 7.81–7.76 (m, 1H), 7.73 (s, 1H); 13C NMR (175 MHz, DMSO-d6): \( \delta = 175.76, 165.64, 165.25, 164.26, 136.09, 135.26, 129.58, 128.97, 127.58, 126.05, 122.67, 122.33, 121.53, 121.15, 103.64, 70.43 \); HR-MS (TOFEI) calcd for C15H9NO3S (283.0303); found (283.0313).

**Ethyl 1-cyano-4-oxo-1,4-dihydrobenzo[h][1,3]thiazeto[3,2-a]quinoline-3-carboxylate (4c).** This compound was prepared using the same procedure as that used for the synthesis of 4a using KI, K2CO3 and 1,2-dibromopropane starting from 3c; white powder; mp 220–222 °C; 1H-NMR: (500 MHz, CDCl3): \( \delta = 9.35 \text{ (dd, } J = 5.3, 3.1 \text{ Hz, 1H)}, 8.17-8.02 \text{ (m, 1H)}, 7.90 \text{ (dd, } J = 5.5, 3.4 \text{ Hz, 1H)}, 7.86–7.81 \text{ (m, 1H)}, 7.79–7.72 \text{ (m, 2H)}, 4.59 \text{ (q, } J = 7.1, 7.08 \text{ Hz, 2H)}, 4.17 \text{ (1H, s)}, 1.56 \text{ (t, } J = 7.13 \text{ Hz, 3H}); 13C NMR (175 MHz, CDCl3): \( \delta = 168.35, 167.93, 149.37, 147.90, 135.51, 130.23, 130.06, 128.01, 127.89, 127.75, 126.16, 118.91, 115.89, 109.39, 103.21, 14.24 \); HR-MS (TOFEI) calcd for C18H12N2O3S (336.0568); found (336.0561).

**Ethyl 4-(3-bromopropoxy)-2-((2-ethoxy-2-oxoethyl)thio)benzo[h]quinoline-3-carboxylate (5).** To a mixture of 3a (0.385 g, 1 mmol) and K2CO3 (0.386 g, 2.8 mmol) in dry DMF (25 mL) under nitrogen atmosphere was added 1,3-dibromopropane (0.56 g, 2.8 mmol) along with KI (0.464 g, 2.8 mmol). The reaction mixture was heated at 70 °C for 24 h, and then poured into ice-H2O. The resulting product was collected by filtration and recrystallized from hexane: CHCl3 (1:3) to yield a white powder; mp 162–164 °C; 1H-NMR: (500 MHz, CDCl3): \( \delta = 9.21–9.14 \text{ (m, 1H)}, 7.95 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 7.91–7.85 \text{ (m, 1H)}, 7.76 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 7.70 \text{ (m, 2H)}, 4.53 \text{ (q, } J = 7.1, 7.08 \text{ Hz, 2H)}, 4.35 \text{ (t, } J = 5.8 \text{ Hz, 2H)}, 4.22 \text{ (q, } J = 7.1, 7.08 \text{ Hz, 2H)}, 4.15 \text{ (s, 2H)}, 3.70 \text{ (t, CH2Br, } J = 6.4 \text{ Hz, 2H)}, 2.42 \text{ (q, CH2CH2CH2J = 6.1 Hz, 2H)}, 1.49 \text{ (t, } J = 7.1, 7.08 \text{ Hz, 2H)}, 1.27 \text{ (t, } J = 7.1, 7.08 \text{ Hz, 3H}); 13C NMR (175 MHz, CDCl3): \( \delta = 162.11, 160.69, 160.25, 153.77, 148.08, 134.29, 130.22, 129.08, 127.61, 127.07, 125.94, 125.47, 119.97, 115.82, 113.80, 70.98, 70.01, 61.21, 33.81, 29.86, 25.01, 14.43, 14.31 \); APCI-MS: 506.40 (M+1, 100).

**Ethyl 8,9-dihydro-7,10-dioxa-12-thia-13-azaazuleno[8,1-ab]phenanthrene-11-carboxylate (6).** This compound was prepared using the same procedure as that used for the synthesis of 4a using 1,2-dibromoethane to afford a yellow crystalline product; mp 250–252 °C; 1H-NMR: (500 MHz, CDCl3): \( \delta = 9.35–9.28 \text{ (m, 1H)}, 7.95 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 7.91–7.85 \text{ (m, 1H)}, 7.76 \text{ (d, } J = 8.9 \text{ Hz, 1H)}, 7.70 \text{ (m, 2H)}, 4.53 \text{ (q, } J = 7.1, 7.08 \text{ Hz, 2H)}, 4.35 \text{ (t, } J = 5.8 \text{ Hz, 2H)}, 4.22 \text{ (q, } J = 7.1, 7.08 \text{ Hz, 2H)}, 4.15 \text{ (s, 2H)}, 3.70 \text{ (t, CH2Br, } J = 6.4 \text{ Hz, 2H)}, 2.42 \text{ (q, CH2CH2CH2J = 6.1 Hz, 2H)}, 1.49 \text{ (t, } J = 7.1, 7.08 \text{ Hz, 2H}), 1.27 \text{ (t, } J = 7.1, 7.08 \text{ Hz, 3H}); 13C NMR (175 MHz, CDCl3): \( \delta = 162.11, 160.69, 160.25, 153.77, 148.08, 134.29, 130.22, 129.08, 127.61, 127.07, 125.94, 125.47, 119.97, 115.82, 113.80, 70.98, 70.01, 61.21, 33.81, 29.86, 25.01, 14.43, 14.31 \); HR-MS (TOFEI) calcd for C20H13NO5S (365.0722); found (365.0727).
4-Oxo-1,4-dihydrobenzo[h][1,3]thiazeto[3,2-a]quinoline-1-carboxylic acid (4d). Following a reported procedure, to a solution of 4b (2.43 g, 8.6 mmol) and N-methylmorpholine (0.960 g, 9.5 mmol) in THF (15 mL) at 0 °C was added ethyl chloroformate (1.03 g, 9.5 mmol) dropwise and the mixture was stirred for 30 min. The solid was filtered off and the filtrate was added to the solution of hydroxylamine hydrochloride (0.896 g, 12.9 mmol) and Et₃N (1.3 g, 12.9 mmol) in DMF (20 mL) for 10 min. The reaction mixture was stirred for 30 min at 25 °C. DMF was evaporated in vacuo. The residue was extracted with EtOAC (80 mL) and washed with water. The solvent was dried over MgSO₄ and evaporated to dryness. The crude product was purified by silica gel column chromatography using EtOAC: hexane (1:1); yellow powder; mp 250–252 °C; ¹H-NMR: (500 MHz, DMSO-d₆): δ = 8.28 (t, J = 9.1 Hz, 2H), 7.98 (d, J = 7.9 Hz, 1H), 7.68 (m, 2H), 7.55 (t, J = 7.6 Hz, 1H), 6.43 (s, 1H), 5.68 (s, 1H). ¹³C NMR (175 MHz, DMSO-d₆): δ = 178.96, 173.54, 171.13, 170.55, 141.58, 139.85, 133.54, 133.34, 131.27, 129.56, 128.25, 128.20, 128.11, 116.77, 76.18; HR-MS (TOFEI) calcd for C₁₅H₉NO₃S (283.0303); found (283.0301).

SUPPLEMENTARY DATA
Experimental and refinement details of the X-ray crystallographic structure of compound 4a and 4b can be obtained free of charge from the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk), reference codes CCDC 811440 and 826518.

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REFERENCES
20. While X-ray, $^1$H- and $^{13}$C-NMR data confirmed the dicarboxylic acid structure for 4b, the HR-MS displayed a molecular peak that matched the mono-carboxylic acid product.