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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

Abeer Ahmed,[a] Louise N. Dawe,[b] and Mohsen Daneshtalab[a]*

[a]School of Pharmacy, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada A1B 3V6. Fax: +1(709)-777-7044; E-mail: mohsen@mun.ca
[b]Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada A1B 3X7

Abstract – The first synthesis of a series of 4-oxo-1,4-dihydro-benzo[*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_2CO_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]

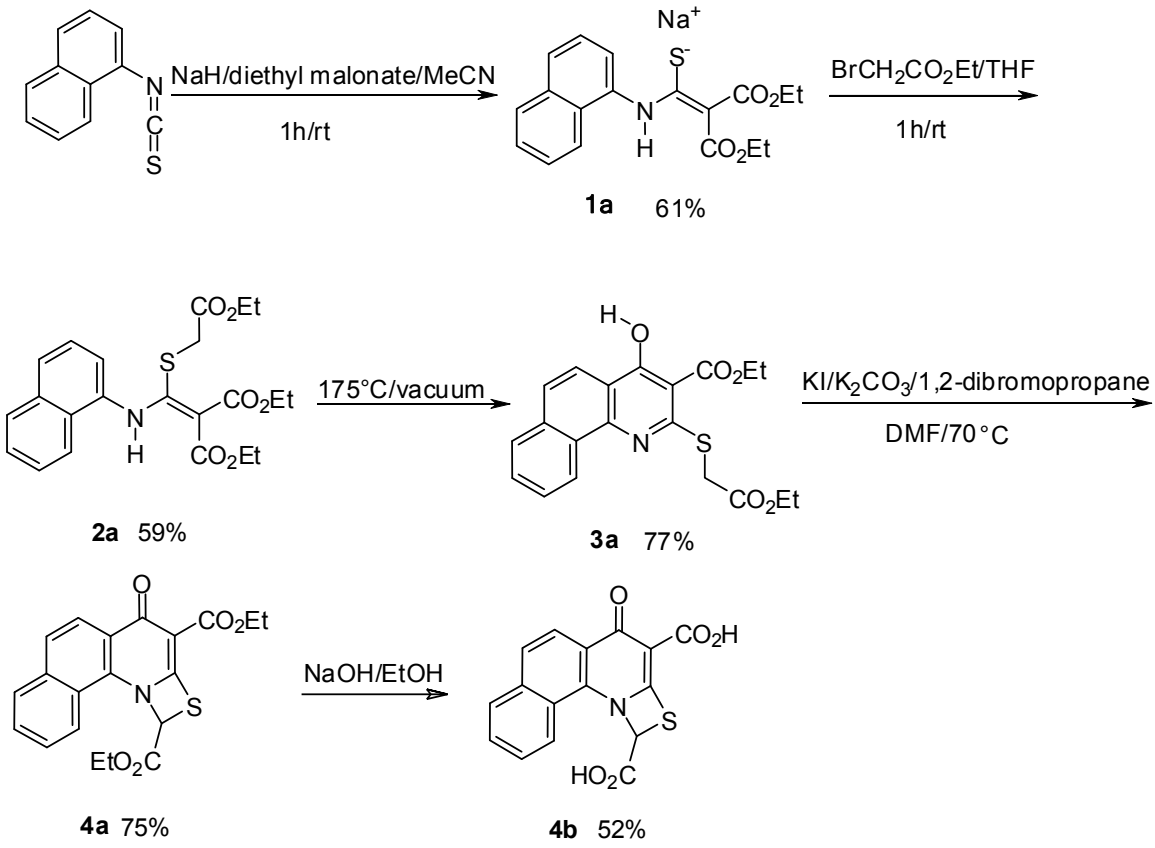
In continuation of our ongoing research towards the discovery of novel polycyclic quinoline-based antineoplastic agents using conventional synthetic procedures, we were able to isolate and identify, unexpectedly, a 4-oxo-benzo[*h*]thiazetoquinoline derivative (**4a**). The structure of this novel molecule 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,[4-9] there are limited reports on the synthesis of 4-oxo-thiazeto[3,2-*a*]quinolines[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 *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**.

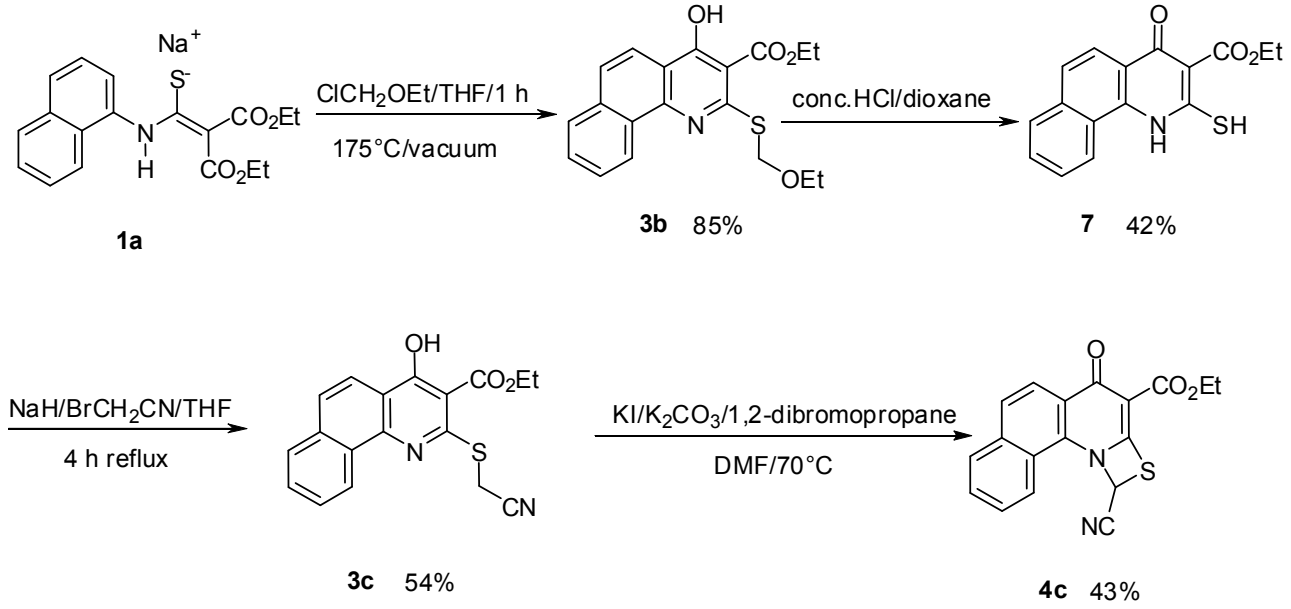


Scheme 1

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

cyclization of **2a**, under vacuum, yielded compound **3a**. This compound was later reacted with 1,2-dibromopropane in the presence of KI and K_2CO_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_2CO_3 in the presence of 1,2-dibromopropane starting from **3c**, as depicted in **Scheme 2**.



1a **3b** 85% **7** 42%

3c 54% **4c** 43%

Scheme 2

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-*a*]quinolines.[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 α to the thiol.

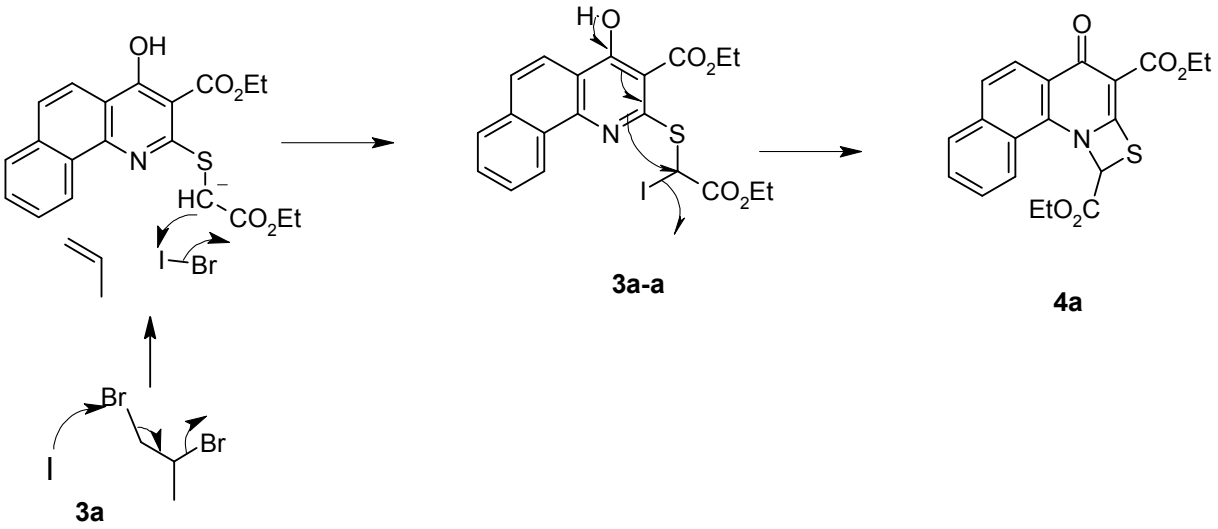
In order to investigate the details of the cyclization process, the following reactions were attempted:

- **3a** + KI + 1,2-dibromopropane;
- **3a** + K_2CO_3 + 1,2-dibromopropane;
- **3a** + KI + K_2CO_3;
- **3a** + KI + K_2CO_3 + 1, 2-dibromopropane.

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

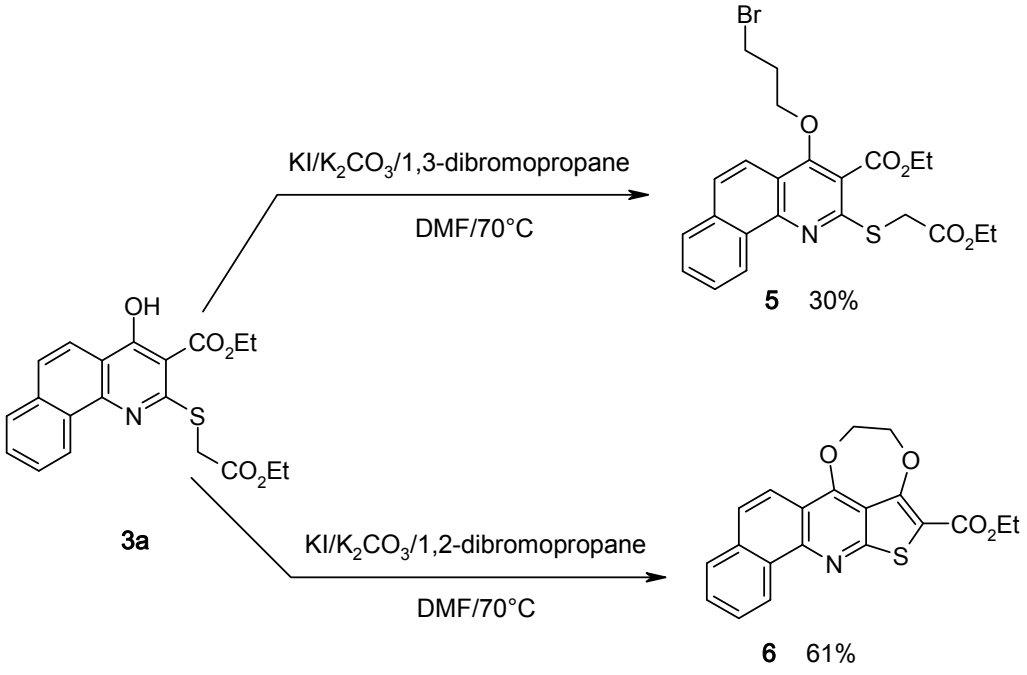
Based on the above information, the following pathway is suggested as a plausible mechanism for the formation of **4a** from **3a**. Namely, nucleophilic reaction of iodide anion with 1,2-dibromoprapane would

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

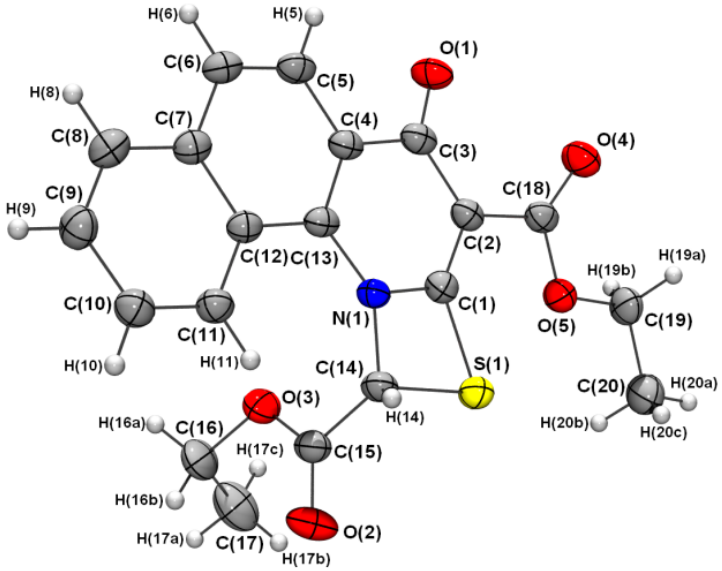
In order to prove the critical role of 1,2-dihaloalkanes in the formation of the above 4-oxo-thiazetoquinolines, we attempted the same reaction using 1,2-dibromobutane and 1,2-dibromohexane instead of 1,2-dibromopropane. In all trials, compound **4a** was obtained in a very good yield. On the other hand, 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**.



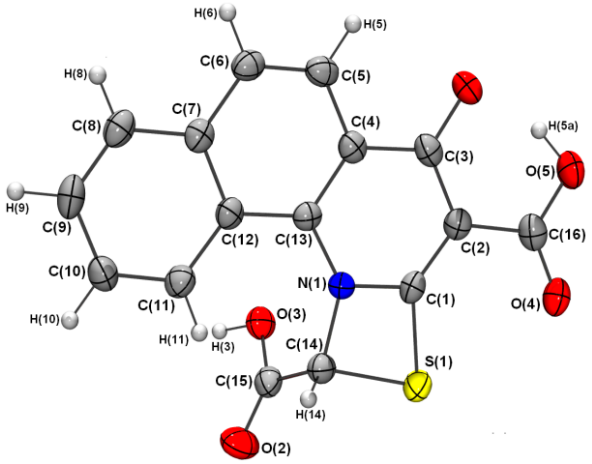
Scheme 4

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_2CO_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.



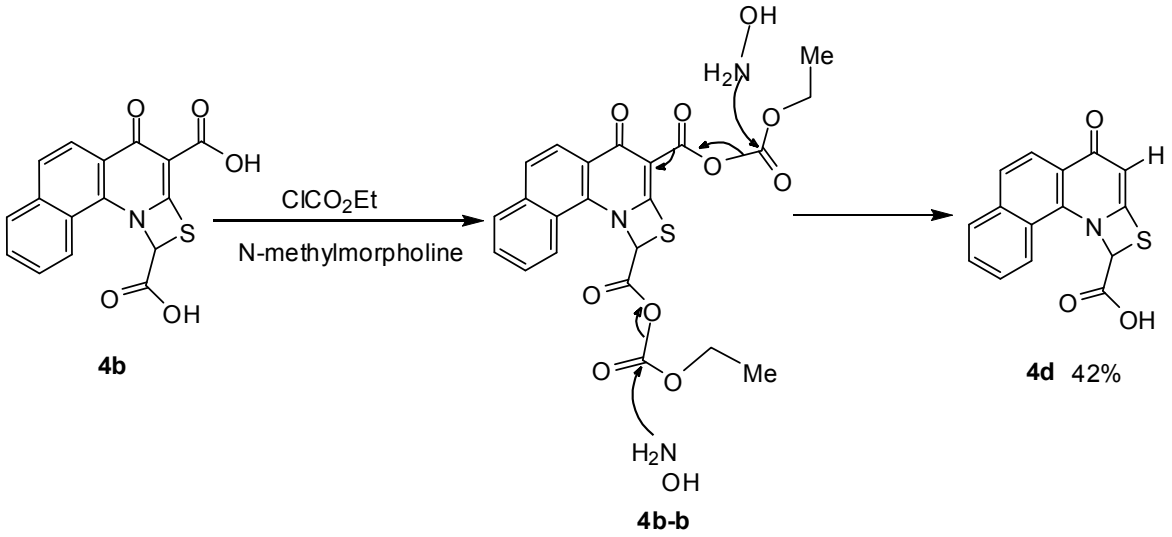
4a



4b

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 Et_3N) 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

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 ^{13}C 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 Et_2O; mp 118–120 °C; ^{1}H-NMR: (500 MHz, DMSO-d_6): 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);^{13}C NMR (175 MHz, DMSO-d_6): 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 ($2CH_2$), 13.37 ($2CH_3$); 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 $BrCH_2CO_2Et$ (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 $CHCl_3$ and dried over Na_2SO_4. 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; ^{1}H-NMR: (500 MHz, $CDCl_3$): 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); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 170.99, 170.46, 168.29, 158.14, 147.62, 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 $C_{20}H_{19}NO_5S$: (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; ^{1}H-NMR: (500 MHz, $CDCl_3$): 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); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 171.17, 168.31, 158.23, 147.41, 135.88, 129.49, 128.24, 127.33, 126.21, 125.73, 120.02, 115.14, 104.38, 71.49, 65.78, 63.14, 31.29, 15.47, 14.61; HR-MS (TOFEI): calcd for $C_{19}H_{19}NO_4S$ (357.1035); found: (357.1031).

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 H_2O (40 mL) was added $NaHCO_3$ (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_2SO_4, filtered to give **3c** as a white powder; mp 208–210 °C; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ = 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): δ = 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 $C_{18}H_{14}N_2O_3S$ (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_2CO_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_2O. 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_2CO_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_2O. 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, $CDCl_3$): δ = 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, $CDCl_3$): δ = 173.28, 165.74, 165.41, 136.16, 135.80, 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 $C_{20}H_{17}NO_5S$ (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_2Cl_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; ^{1}H-NMR: (500 MHz, DMSO-d_6): δ = 8.27 (d, J = 8.8 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 11.0, 4.0 Hz, 1H), 7.81–7.76 (m,1H), 7.73 (s, 1H); ^{13}C NMR (175 MHz, DMSO-d_6): δ = 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 $C_{15}H_9NO_3S$ (283.0303); found (283.0313).[20]

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, K_2CO_3 and 1,2-dibromopropane starting from **3c**; white powder; mp 220–222 °C; ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 9.35 (dd, J = 5.3, 3.1 Hz, 1H), 8.17-8.02 (m,1H), 7.90 (dd, J = 5.5, 3.4 Hz, 1H), 7.86–7.81 (m, 1H), 7.79–7.72 (m, 2H), 4.59 (q, J = 7.11, 7.08 Hz, 2H), 4.17 (1H, s), 1.56 (t, J = 7.13 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ= 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, 63.82, 30.98, 14.24; HR-MS (TOFEI) calcd for $C_{18}H_{12}N_2O_3S$ (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 K_2CO_3 (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-H_2O. The resulting product was collected by filtration and recrystallized from hexane: $CHCl_3$ (1:3) to yield a white powder; mp 162–164 °C; ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 9.21–9.14 (m, 1H), 7.95 (d, J = 8.9 Hz, 1H), 7.91–7.85 (m, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.70 (m, 2H), 4.53 (q, J = 7.1Hz, 2H), 4.35 (t, J = 5.8 Hz, 2H), 4.22 (q, J = 7.1Hz, 2H), 4.15 (s, 2H), 3.70 (t, CH_2Br, J = 6.4 Hz, 2H), 2.42 (q, $CH_2CH_2CH_2$, J = 6.1 Hz, 2H), 1.49 (t, J = 7.1 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 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; ^{1}H-NMR: (500 MHz, $CDCl_3$): δ = 9.35–9.28 (m, 1H), 8.14 (d, J = 9.1 Hz, 1H), 7.93-7.87 (m, 1H), 7.74 (dt, J = 5.9, 9.7 Hz, 3H), 4.96–4.92 (m, 2H), 4.84–4.79 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 162.14, 159.55, 158.21, 152.80, 148.32, 134.34, 130.16, 129.10, 127.63, 127.08, 125.82, 125.48, 119.48, 113.87, 111.47, 104.81, 73.66, 72.21, 61.15, 14.42; HR-MS (TOFEI) calcd for $C_{20}H_{15}NO_4S$ (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,[21] 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 ^{o}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 Et_3N (1.3 g, 12.9 mmol) in DMF (20 mL) for 10 min. The reaction mixture was stirred for 30 min at 25 ^{o}C. DMF was evaporated *in vacuo*. The residue was extracted with EtOAC (80 mL) and washed with water. The solvent was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by silica gel column chromatography using EtOAC: hexane (1 : 1); yellow powder; mp 250–252 $^{\circ}$C; ^{1}H-NMR: (500 MHz, DMSO-d_6): 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). ^{13}C NMR (175 MHz, DMSO-d_6): 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 $C_{15}H_9NO_3S$ (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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