Benzo-benzothiopyranoquinoline Derivatives of Possible Antiparasitic Activity

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For possible antiparasitic activity, benzo-benzothiopyranoquinoline-6-malonaldehyde was synthesized and condensed with hydrazine hydrate, phenylhydrazine and/or *o*-phenylenediamine. This afforded pyrazole, phenylpyrazole and diazepin derivatives respectively.

It has been found that a number of benzoquinolines possess antimalarial activity [1]. These type of compounds have the naphthalene moiety, which may undergo biological oxidation to the corresponding quinones [2, 3]. It was reported that some benzoquinones and naphthoquinones are potential bioreductive alkylating agents [4-6]. Also, naphthoquinones can highly reduce the rate of glycolysis in some parasites [7].

This led us to study the synthesis of benzo[h]-quinolines incorporating benzothiopyrano moiety, analogous to azamiracils [8-12], which are expected to possess biological activity.

Condensation of 1-naphthylamine with acetoacetic ester at room temperature, followed by cyclization in preheated mineral oil, gave 4-hydroxy-2-methylbenzo[h]quinoline (1). This upon treatment with phosphorus oxychloride, yielded the 4-chloro derivative (2). Reaction of 2 with thio-salicylic acid in presence of $C_2H_5O Na$ or alcoholic $NaOH$ soln. afforded 2-methyl-4-(benzo[h]quinolinoyl)-2-carboxyphenylsulphide (4). Compound 4 was also prepared by reaction of 2 with thiourea [13], followed by hydrolysis with $NaOH$ soln. to give 4-mercapto derivative (3), which was finally condensed with *o*-chlorobenzoic acid.

Cyclization of 4 was affected with polyphosphoric acid to give 6-methyl-7-*H*-benzo[h][1]benzothiopyrano[3,2,*C*]quinolin-7-one (5). The methyl group

in 5 was subjected to formylation reaction with $POCl_3$ -DMF, followed by alkaline hydrolysis with 5% KOH soln., which gave 7-oxo-7-*H*-benzo[h][1]benzothiopyrano[3,2,*C*]quinoline-6-malonaldehyde (6).

The chemotherapeutic interest of pyrazole, suggested its introduction. This was achieved by reaction of 6 with hydrazine hydrate and/or phenylhydrazine, to yield 6-(pyrazol-4-yl)-7-*H*-benzo[h][1]benzothiopyrano[3,2,*C*]quinolin-7-one (7a) and 6-[1-(phenyl)pyrazol-4-yl]-7-*H*-benzo[h][1]benzothiopyrano[3,2,*C*]quinolin-7-one (7b), respectively. While, the reaction of 6 with *o*-phenylenediamine, afforded 6-(3*H*-1,5-benzodiazepin-3-yl)-7-*H*-benzo[h][1]benzothiopyrano[3,2,*C*]quinolin-7-one (8) in 56% yield.

Experimental

Melting points are uncorrected, and were taken on Gallenkamp electric melting point apparatus and Boetius melting point microscope.

Infrared spectra were performed on a Carl Zeiss Infracord spectrophotometer model "UR 10" using KBr.

NMR spectra were obtained in CF_3COOH with a Varian Associates model "A-60" spectrometer.

Microanalysis were performed by the Micro-analytical Laboratory, National Research Centre, Cairo, Egypt.

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4-Hydroxy-2-methylbenzo[h]quinoline (1)

A mixture of 1-naphthylamine (14.3 g) and ethyl acetoacetate (13 g) containing 2 drops of conc. HCl was kept at room temperature overnight.

The thick, red oil was taken up in ether, and the ethereal extract was washed successively with water, dil. NaOH soln. and again with water. The solvent was distilled after drying over Na_2SO_4 anhydrous to leave the intermediate naphthylamino acrylate. This was poured gradually onto paraffin oil preheated to 270 °C. On cooling, **1** was obtained, m.p. > 300 °C [14].

4-Chloro-2-methylbenzo[h]quinoline (2)

Compound **1** (10 g) was refluxed with an excess of POCl_3 for 6 h. The reaction mixture was poured on crushed ice and filtered. The cold filtrate was basified with ammonia soln. to give **2** as white crystals, m.p. 91–92 °C (lit. [14], m.p. 93 °C).

4-Mercapto-2-methylbenzo[h]quinoline (3)

To a solution of thiourea (1 g) in absolute ethanol (15 ml) **2** was added (3 g) dissolved in least amount of ethanol. The reaction mixture was refluxed for 30 min. After cooling the thionium salt was precipitated, filtered off, and hydrolyzed by refluxing with 30% KOH (20 ml) for 5 h. The reaction mixture was filtered, and the cold filtrate was acidified with acetic acid to give **3**, m.p. 201–203 °C.

$\text{C}_{14}\text{H}_{11}\text{NS}$ (225.23)

Calcd	C 74.66	H 4.92	S 14.12,
Found	C 74.16	H 4.52	S 13.94.

2-Methyl-4-(benzo[h]quinolinoyl)-2-carboxyphenylsulfide (4)**Method A**

A mixture of **2** (4.69 g; 0.02 mole) and thio-salicylic acid (3.12 g; 0.02 mole) was added to an alcoholic soln. of $\text{C}_2\text{H}_5\text{O Na}$, that prepared from Na (1 g) and absolute ethanol (40 ml). The reaction mixture was refluxed for 12 h, then the alcohol was concentrated and acidified with dil. acetic acid. The precipitated product was isolated, washed with water and dried. Recrystallization from aqueous ethanol gave 66% yield of **4**, m.p. 212–213 °C. IR: 1690 (–COOH) and 700 cm^{-1} (–S–).

$\text{C}_{21}\text{H}_{14}\text{NS}_2\text{O}$ (344.34)

Calcd	C 73.25	H 4.09	N 4.07	S 9.30,
Found	C 73.65	H 4.49	N 3.99	S 9.70.

Method B

A mixture of **2** (5 g) and thio-salicylic acid (3.5 g) in ethanol (100 ml) was refluxed, whereby 40% NaOH soln. (5 ml) was added dropwise. Refluxing was continued for 8 h. The product was isolated as previously described to give **4** in 71% yield, m.p. 213–214 °C.

Method C

To a soln. of $\text{C}_2\text{H}_5\text{O Na}$ (0.4 g of Na in 20 ml absolute ethanol) was added a mixture of **3** (1.5 g; 0.003 mole) and *o*-chlorobenzoic acid (1.04 g; 0.003 mole). The reaction mixture was refluxed for 10 h and the product was worked up as mentioned above, 68% yield. The three methods gave the same product (m.p. and admixed m.p.).

6-Methyl-7H-benzo[h][l]benzothiopyrano[3,2,C]-quinolin-7-one (5)

Polyphosphoric acid (20 g) was heated to 170 °C, then **4** (3 g) was added portionwise by gentle shaking. After 4 h the mixture was cooled and poured onto ice-water. The obtained precipitate was collected, washed thoroughly with boiling ammonium hydroxide soln., then with water and dried. It gave 72% yield of **5**, m.p. 248–250 °C (chloroform).

IR: 1640 (–C=O); 1590 (–C=N) and 750 cm^{-1} (–S–).

$\text{C}_{21}\text{H}_{13}\text{NSO}$ (327.39)

Calcd	C 77.04	H 4.00	N 4.28	S 9.80,
Found	C 77.13	H 4.05	N 4.52	S 10.30.

7-Oxo-7H-benzo[h][l]benzothiopyrano[3,2,C]-quinoline-6-malonaldehyde (6)

Freshly distilled POCl_3 (1 ml) was added dropwise with stirring to dimethylformamide (3 ml) at 0–5 °C. A soln. of **5** (1.2 g; 0.003 mole) in dimethylformamide (2 ml) was added dropwise at 5–10 °C, and the reaction mixture was allowed to stand at room temperature for 30 min. It was then heated at 70 °C for about 6 h, and poured onto crushed ice. The aqueous soln. was treated with 5% KOH soln., which furnished 1 g (72% yield) of **6**, it showed m.p. 305–306 °C from chloroform.

IR: 1660 cm^{-1} (–CHO).

NMR (CF_3COOH): τ 8.65 (methine protons, triplet); τ 7.10 and τ 6.52 aldehydic protons, doublet) and τ 2.2 (aromatic protons, complex pattern).

$\text{C}_{23}\text{H}_{13}\text{NO}_3\text{S}$ (383.35)

Calcd	C 72.06	H 3.40	N 3.60	S 8.30,
Found	C 72.45	H 3.75	N 3.54	S 8.76.

6-(Pyrazol-4-yl)-7H-benzo[h][l]benzothiopyrano[3,2,C]quinolin-7-one (7a)

A mixture of **6** (0.8 g) and hydrazine hydrate (0.17 ml) in ethanol (20 ml) was refluxed for 10 h. The reaction mixture was cooled, and the separated solid was isolated, crystallized from dimethylformamide, m.p. 345–348 °C (81% yield).

IR: 3160 cm^{-1} (–NH Stretching).

$\text{C}_{23}\text{H}_{13}\text{N}_3\text{OS}$ (279.37)

Calcd	C 72.82	H 3.43	N 11.08,
Found	C 72.32	H 3.69	N 10.90.

6-[1-(Phenyl)pyrazol-4-yl]-7H-benzo[h][l]benzothiopyrano[3,2,C]quinolin-7-one (7b)

Compound **6** (0.8 g) in ethanol (15 ml) was heated under reflux for 8 h, with phenylhydrazine (0.25 ml). After cooling the obtained precipitate was crystallized from chloroform to furnish 83% yield of **7b**, m.p. 274–276 °C.

$C_{29}H_{17}N_3OS$ (455.46)

Calcd	C 76.48	H 3.70	N 9.20	S 7.03,
Found	C 76.60	H 4.03	N 9.09	S 7.46.

6-(3H-1,5-Benzodiazepin-3-yl)-7H-benzo[h][l]benzothiopyrano[3,2,C]quinolin-7-one (8)

A mixture of **6** (0.8 g) and *o*-phenylenediamine (0.23 g) in ethanol (20 ml) was heated under reflux for 8 h working up as described above produced **8** in 56% yield, m.p. > 350 °C from dimethylformamide.

$C_{29}H_{16}N_3SO$ (454.45)

Calcd	C 76.65	H 3.52	N 9.40	S 7.04,
Found	C 76.30	H 3.62	N 9.00	S 7.54.

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