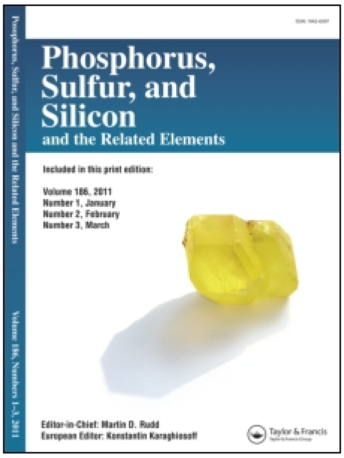

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Substituted Quinolinones, Part 10: Synthesis of Angular Tetracyclic Thieno and Thiopyrano[3,2-<i>c</i>]benzo[<i>h</i>]quinolinones Under PTC Conditions as Novel Enzymatic Enhancers

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Substituted Quinolinones, Part 10: Synthesis of Angular Tetracyclic Thieno and Thiopyrano[3,2-*c*]benzo[*h*]quinolinones Under PTC Conditions as Novel Enzymatic Enhancers

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*4-Chlorobenzo[h]quinolin-2(1H)-one (**4**) and its 4-sulfanyl derivative **6** were smoothly obtained via chlorination, hydrolysis, and sulfurization starting with 4-hydroxybenzo-[h]quinolin-2(1H)-one (**1**). Heterocyclization reaction of compound **6** with chloroacetaldehyde diethylacetal, phenacylbromide, chloroacetonitrile, ethyl chloroacetate, and bromomalononitrile under phase transfer catalysis (PTC) conditions was described affording benzo[h]thieno[3,2-c]quinolinones **7–9**, **11**, **12**, and **14**. The PTC-nucleophilic substitution of compound **4** with malononitrile gave quinolinylmalononitrile **15**, which subsequently cyclized with sulfur/triethylamine (TEA) to afford benzo[h]thieno[2,3-c]quinolinone **16**. The PTC reaction of compound 6 with CS_2 and malononitrile gave benzo[h]thiopyrano[3,2-c]quinolinone **18**. Similarly, cyclization of compound **4** with thiosalicylic acid furnished benzo[h]thiochromeno[3,2-c]quinolinedione **20**. Thermal condensation of compound **6** with ethyl 2-cyano-3-ethoxyacrylate or ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate afforded benzo[h]thiopyrano[3,2-c]quinolinones **22** and **24**, respectively. The effect of new 14 products on α-amylase activity was examined. Thienoquinolinones **9**, **11**, **14**, and **16** were the most potent enhancers in which these compounds multiplicate the activity of the enzyme to produce α-D-glucose up to eightfold.*

Keywords Benzo[*h*]quinolinone; enzymatic activity; phase transfer catalysis; thieno[3,2-*c*]quinolinone; thiopyrano[3,2-*c*]quinolinone

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This work is dedicated to Prof. Dr. Ali L. Ibrahim with best wishes of his recovery soon.

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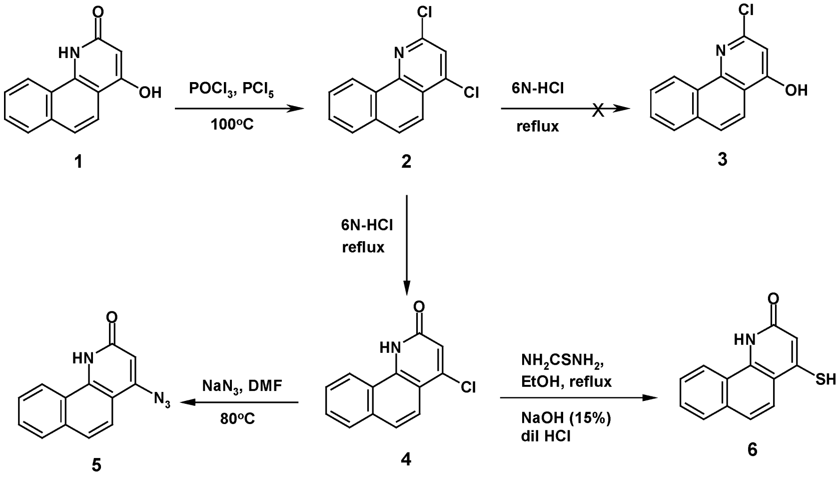
INTRODUCTION

Recently we reviewed the literature of azoloquinolines, including thienoquinolines,[1] and noticed that although this category of fused heterocyclic compounds is associated with important biological properties,[2–5] limited synthetic research work has been directed to these compounds.[6–10] Similarly, thiopyranoquinolines rarely appeare in literature.[1] On the other side, even 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one is readily available via facile high yield condensation of 1-aminonaphthalene with diethyl malonate in the presence of polyphosphoric acid (PPA),[11] barely very few cyclization reactions have been reported with this compound.[12] This encouraged us to continue our previous work on fused quinolinones.[13–15] In the present work we describe convenient methodology to obtain the hitherto unreported angular sulfur-containing S-shaped tetracyclic heteroaromatic compounds, e.g., thieno- and benzo[*h*]thiopyrano[3,2-c]quinolinones, which are of expected biological activity. The reported studies on enzymatic effect of quinolinones revealed their importance in the economical production of glucose via stimulation of α-amylase enzyme,[16] so that the effect of new compounds on activity of α-amylase was examined.

RESULTS AND DISCUSSION

Chemistry

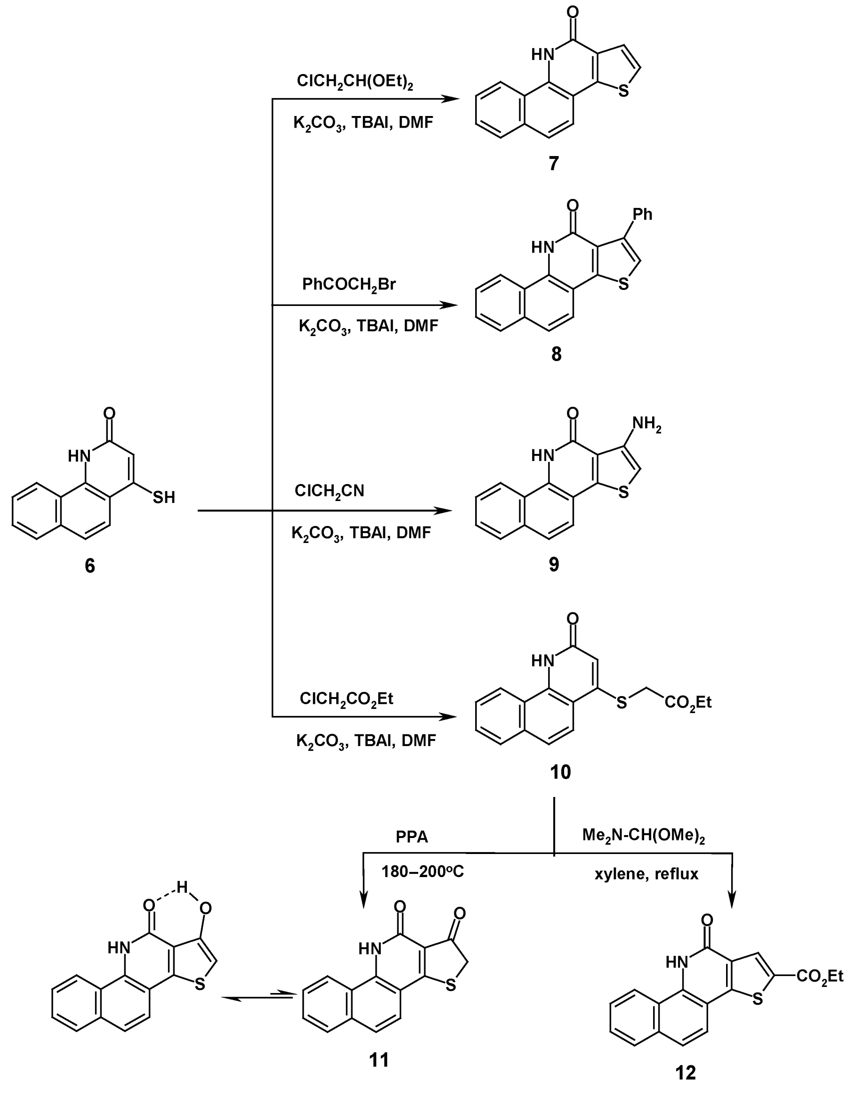
4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (**1**)[11] was chosen as starting material to obtain its isomeric 4-sulfanyl derivative **6**, using a facile unambiguous synthesis, as depicted in Scheme 1. The synthetic route includes



SCHEME 1

chlorination of the starting material **1**, using a mixture of phosphoryl chloride and phosphorus pentachloride to obtain the 2,4-dichloro derivative **2**[17] in a 68% yield. Hydrolysis of compound **2** was attempted in both acid and alkaline media. In an alkaline medium, tary material was obtained. Even after long-term work up, no definite product was isolated, as indicated by the very broad melting point and crowded ^{1}H NMR and IR spectra. Anyhow, only acid media was useful to hydrolyze compound **2** into the desired quinolinone **4**. The possibility of hydrolysis into either the hydroxybenzoquinolinone **1** and/or 2-chloro-4-hydroxybenzoquinoline **3** was excluded on the basis of the spectral and chemical properties of the product. Elemental analysis data showed that only one chlorine atom was replaced in this nucleophilic substitution. Since spectral data are not cut off to decide which is which, with respect to **3** and **4** possibilities, the reaction of the product with sodium azide was carried out, in which the substitution process took place with a chlorine atom. IR spectrum of the azido product **5** showed the characteristic band of N_3 group at ν 2115 cm^{-1}. The later reaction evidently proved the given structure **4** as the product of hydrolysis (Scheme 1). Sulfurization of compound **4** was achieved *via* the well-known methodology of formation of the corresponding isothiourea by nucleophilic substitution using thiourea followed by *in situ* alkaline hydrolysis to afford the desired 4-sulfanyl derivative **6** (Scheme 1).

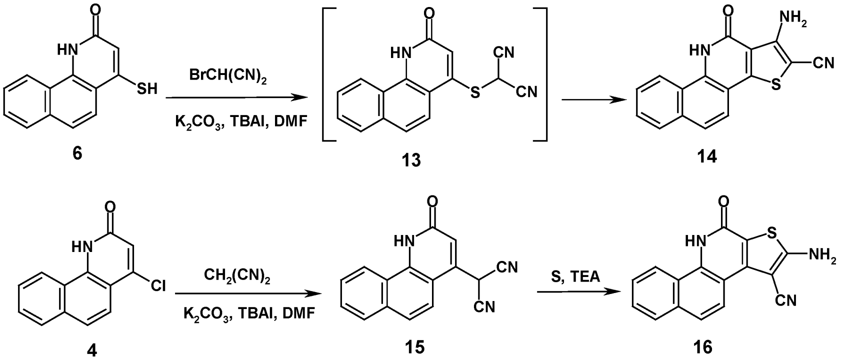
Compound **6** was subjected to react with some α-halo active methylene compounds viz. chloroacetaldehyde diethyl acetal, phenacyl bromide, chloroacetonitrile, ethyl chloroacetate, and 2-bromomalononitrile in the presence of potassium carbonate as the base. The reaction is conveniently carried out under solid-solution Phase Transfer Catalysis (PTC) conditions using Tetrabutylammonium Iodide (TBAI) as the PTC catalyst in dry dimethylformamide (DMF). Even the expected open chain *S*-alkylated products were not isolated in all cases except for ethyl chloroacetate, and it is obvious that alkylation took place selectively at the sulfur atom followed by cyclization in rest of the cases to afford the corresponding benzo[*h*]thieno[3,2-*c*]quinolinones **7–9** (Scheme 2). The formation of the acetate ester **10** was simply confirmed via the existence of the ethyl set of protons in its ^{1}H NMR spectrum (cf. the Experimental Section). Despite that there is no apparent reason for this dissimilar behavior of the later reagent under the same conditions for cyclization compared to previous ones, this highlights that the reaction may require an alternate condition that can be affected by ring closure. Hence, the acetate ester **10** was treated with PPA, a strong acidic catalyst, to give tetracyclic benzo[*h*]thieno[3,2-*c*]quinolinone **11**. The structure of compound **11** was confirmed with no doubt via its elemental and spectral analyses. The ^{1}HNMR spectrum did not show any indication for the



SCHEME 2

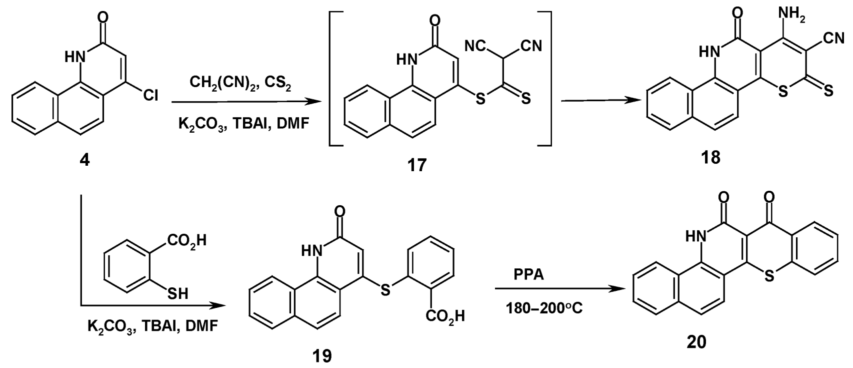
ethyl protons set. Moreover, as indicated by ^{1}H NMR, the ketonic form of compound **11** was not seen, and the compound assumed enolic structure, which may be explained by the stabilities gained by both intramolecular H-bonding with the neighboring carbonyl group and aromticity of thiophene in the enolic form. Thermal reaction of acetate ester **10** with Dimethylformamide Dimethylacetal (DMF-DMA) led smoothly to the formation of the tetracyclic benzothienoquinoline-2-carboxylate **12**, in a high yield (88%). The results emphasize again that the carboxylate group was not involved in the cyclization process (Scheme 2).

Similar to the previously discussed results, the reaction of compound **6** with 2-bromomalononitrile furnished directly 1-amino-11-oxo-10, 11-dihydrobenzo[*h*]thieno[3,2-*c*]quinoline-2-carbonitrile (**14**). Herein again, the *S*-alkylated intermediate **13** was non-isolable (Scheme 3). Interestingly, isomeric 2-amino-11-oxo-10,11-dihydrobenzo[*h*]thieno [2,3-*c*]quinoline-3-carbonitrile (**16**) was prepared in a two-step route starting with 4-chloro derivative **4**. Nucleophilic replacement of the chlorine atom using malononitrile, in the presence of potassium carbonate under the same previously described PTC conditions, gave the quinolinylmalononitrile **15**. The structure of compound **15** was verified from its ^{1}H NMR spectrum that revealed a singlet signal at δ 5.80 due to $CH(CN)_2$ and another singlet at δ 6.80 due to the proton at position 3. In addition, its IR spectrum revealed two sharp absorption bands at ν 2204 and 2175 cm^{-1} characteristic for a $CH(C{\equiv}N)_2$ system. A modified Gewald's method was followed to affect a thiophene ring closure by treating compound **15** with elemental sulfur and triethylamine as a base catalyst, affording the tetracyclic compound **16**, in a 78% yield (Scheme 3).



SCHEME 3

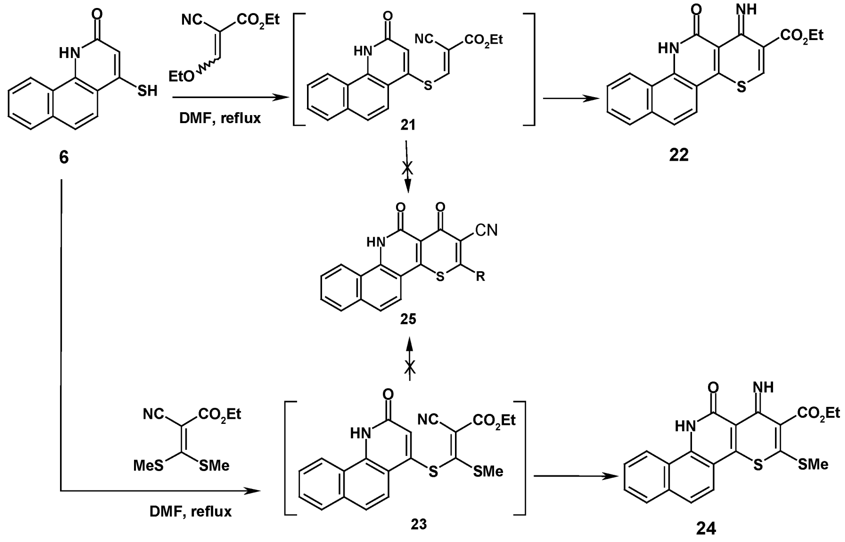
Under the same PTC condition as previously cited (K_2CO_3, TBAI, DMF), the one-pot synthesis of tetracyclic benzothiopyranoquinoline **18** was accomplished. Thus, the chloro derivative **4** was treated with a mixture of carbon disulfide and malononitrile. The intermediacy of dithioate **17** was expected in such reactions via the first formation of dicyanodithioacetate anion, which consequently substituted a chlorine atom in compound **4**. The process was completed by an intramolecular *exo-dig* nucleophilic addition affording compound **18** (Scheme 4). The PTC reaction of thiosalicylic acid with the chloro derivative **4**



SCHEME 4

furnished the thio-ether **19**, in an 82% yield. Cyclization of compound **19** was affected using PPA to afford the hitherto unreported pentacyclic benzothiochromenoquinolinedione **20** (Scheme 4).

The condensation of 4-sulfanyl derivative **6** with ethyl 2-cyano-3-ethoxyacrylate led to the formation of tetracyclic imino-ester **22** (Scheme 5). The possibility of the formation the corresponding oxo-carbonitrile **25**, as a product for the expected thio-ether intermediate **21**, was absolutely excluded, whereas the IR spectrum of the product lacked the $C\equiv N$ specific bands. Additionally, the ^{1}H NMR spectrum



SCHEME 5

indicated the presence of the ethyl ester set of protons and the imino proton, exchangeable on addition of D_2O (cf. Experimental Section).

Similarly, in the reaction of the compound **6** with ethyl 2-cyano-3,3-di(methylsulfanyl)-acrylate, the possible conversion of the intermediate **23** to either the ester **24** or its competitor carbonitrile **25** was considered. However, herein again the only product afforded was the ester **24** as evidenced by elemental microanalysis and IR and ^{1}H NMR spectral data (Scheme 5).

Enzymatic Results

The effect of fourteen new compounds, **4–9**, **11**, **12**, **14**, **16**, **18**, **20**, **22**, and **24**, on the activity of α-amylase in the hydrolysis of starch was indicated by monitoring production of α-D-glucose. Screening of the new compounds showed that compounds **14**, **16**, **9**, and **11** are the most potent enzyme enhancer candidates as these compounds multiplicate the activity of the enzyme to 8, 7.4, 6.3, Sixfold, respectively (Table I). It is noted that all the tested compounds have a stimulation effect on α-amylase except for compound **8**, which revealed an inhibition effect and reduced the activity to half. The remark on the structure of compound **8** is that it possesses a phenyl group, which increases its hydrophobicity. This hypothesis is confirmed by replacing this phenyl group with more polar groups, such as amino and hydroxyl functions in compounds **9** and **11**, respectively, where we received high stimulation effect as previously cited. Likewise, the results supported this finding as compounds **14** and **16**, which have neighboring two-polar functions in positions 2 and 3, showed the highest stimulation in this series.

TABLE I Effect of the New Compounds, at a Concentration of 100 μg/mL, on the Activity of α-Amylase at 40°C as Indicated by then Amount of Produced Glucose

Compound no.	Produced α-D-Glucose (mg/L)	Compound no.	Produced α-D-Glucose (mg/L)
4	860	**14**	2880
5	1370	**15**	—
6	1300	**16**	2680
7	910	**18**	1540
8	180	**19**	—
9	2270	**20**	1010
10	—	**22**	2030
11	2150	**24**	2100
12	1830	Control	360

EXPERIMENTAL

Melting points are uncorrected and were determined on a digital Gallen-kamp MFB-595. IR spectra were taken on Perkin-Elmer FT-IR 1650 or Nicolet FT-IR 710 spectrophotometers, using samples in KBr disks. ^{1}H NMR spectra were recorded on Varian Gemini 200 (200 MHz) spectrometer, using DMSO-d_6 as the solvent and TMS as an internal reference. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer, at the Cairo University Microanalytical Centre (Cairo, Egypt). 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (**1**) was prepared according to the reported methods.[11]

2,4-Dichlorobenzo[*h*]quinoline (2)

Phosphoryl chloride (93 mL, 1 mol) was added to a mixture of phosphorus pentachloride (32 g, 0.15 mol) and compound **1** (10.55 g, 0.05 mol) and then heated under reflux for 2 h. The excess phosphoryl chloride was removed in a vacuum, and the residue was poured onto crushed ice (200 g). The solution that was obtained was neutralized using cold 2N sodium hydroxide solution to give solid deposits, which were filtered and crystallized from acetone to yield 8.43 g (68%); m.p. 136–138°C, lit.[17] m.p. 134–135°C (52%).

4-Chlorobenzo[*h*]quinolin-2(1*H*)-one (4)

A suspension of dichloroquinoline **2** (2.48 g, 10 mmol) in hydrochloric acid (50 mL, 6N) was heated under reflux for 4 h. Afterward, the solution that was obtained was diluted with cold water to give white precipitate, which was filtered and crystallized from acetone to yield 1.95 g (85%); m.p. 229–231°C. IR (KBr):ν_{max} 3216 (N–H), 3120, 1668 (C=O), 772 cm^{-1} (C–Cl); ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.94 (s, 1H, 3-H), 7.18–8.09 (m, 6H, H$_{arom}$), 11.24 (b, 1H, N–H). Anal. calcd. for $C_{13}H_8ClNO$ (229.67): C, 67.99; H, 3.51; N, 6.10. Found C, 67.84; H, 3.30; N, 5.96.

4-Azidobenzo[*h*]quinolin-2(1*H*)-one (5)

A mixture of chloroquinolinone **4** (1.15 g, 0.005 mol) and sodium azide (0.65 g, 0.01 mol), in DMF (25 mL), was stirred at 80°C for 6 h. Then the mixture was poured onto cold water, and the precipitate material that was formed was collected by filtration and crystallized from dioxane to yield 1.04 g (88%); m.p. 253–254°C (decomp.). IR, ν: 3047, 2115 (N_3), 1667 (C=O), 1613, 1566, 1528 and 1488 cm^{-1}. ^{1}H NMR, δ: 5.74 (s, 1H, 3-H), 7.12–8.05 (m, 6H, H$_{arom}$) and 10.85 (b, 1H, N–H). Anal. calcd. for

$C_{13}H_8N_4O$ (236.23): C, 66.10; H, 3.41; N, 23.72. Found: C, 65.94; H, 3.15; N, 23.60.

4-Sulfanylbenzo[*h*]quinolin-2(1*H*)-one (6)

A mixture of 4-chloroquinolinone **4** (2.30 g, 10 mmol) and thiourea (1.52 g, 20 mmol) was heated in an oil-bath at 170–190°C for 1 h. The reaction mixture was then treated with ethanol (50 mL) and refluxed for 2 h. After that, the mixture was left to cool and treated with an aqueous solution of sodium hydroxide (50 mL, 2N), and the solution that was obtained was filtered off. The clear filtrate was then acidified by hydrochloric acid (100 mL, 2N) to give a yellow precipitate that filtered and crystallized from DMF to yield 1.45 g (64%); m.p. >300°C. IR, ν: 3165 (N-H), 2510 (br S-H), 1666 (C=O), 1613 cm^{-1}. ^{1}H NMR, δ: 1.72 (s, 1H, S—H), 6.78 (s, 1H, 3—H), 7.21–8.12 (m, 6H, H$_{\text{arom}}$) and 11.12 (b, 1H, N–H). Anal. calcd. for $C_{13}H_9NOS$ (227.29): C, 68.70; H, 3.99; N, 6.16; S, 14.11. Found C, 68.62; H, 4.02; N, 6.05; S, 13.94.

General Method for a PTC Reaction of Thiol Derivative 6 With Halo Compounds

A mixture of anhydrous potassium carbonate (5 g), dry DMF (25 mL), compound **6** (5 mmol), the appropriate halo reagent (6 mmol), and TBAI (0.6 g) was stirred in a boiling water bath for 4–6 h. The reaction mixture was filtered off, and the filtrate was evaporated in vacuum. The solid residue that was obtained was washed thoroughly with water, dried, and crystallized from the proper solvent to give compounds **7**, **8**, **9**, **10**, and **14**.

Benzo[*h*]thieno[3,2-*c*]quinolin-11(10*H*)-one (7) was obtained according to the previously discussed general method from compound **6** (1.14 g) and chloroacetaldehyde diethyl acetal (1.0 mL) and crystallized from DMF. Yield 0.9 g (72%); m.p. 288–290°C. IR (KBr):$\nu_{\max}$ 3245 (N–H), 3120, 1644 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.12–8.04 (m, 8H, H$_{\text{arom}}$), 11.83 (b, 1H, N–H). Anal. calcd. for $C_{15}H_9NOS$ (251.31): C, 71.69; H, 3.61; N, 5.57; S, 12.76. Found C, 71.56; H, 3.49; N, 5.32; S, 12.50.

1-Phenylbenzo[*h*]thieno[3,2-*c*]quinolin-11(10*H*)-one (8) was obtained according to the previously discussed general method from compound **6** (1.14 g) and phenacyl bromide (1.22 g), and crystallized from DMSO. Yield 1.23 g (75%); m.p. >300°C. IR (KBr):$\nu_{\max}$ 3245 (N–H), 3120, 1644 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.79 (s, 1H, 2-H), 7.20–8.05 (m, 11H, H$_{\text{arom}}$), 11.24 (b, 1H, N–H). Anal. calcd.

for $C_{21}H_{13}NOS$ (327.41): C, 77.04; H, 4.00; N, 4.28; S, 9.79. Found C, 76.83; H, 3.93; N, 4.32; S, 9.66.

1-Aminobenzo[*h*]thieno[3,2-*c*]quinolin-11(10*H*)-one (9) was obtained according to the previously discussed general method from compound **6** (1.14 g) and chloroacetonitrile (0.4 mL) and crystallized from dioxane. Yield 0.9 g (68%); m.p. >300°C. IR (KBr):ν_{max} 3224 (N–H), 3145, 1654 cm^{-1} (C=O); ^1H NMR (200 MHz, DMSO-d_6): δ 6.04 (b, 2H, NH_2), 6.55 (s, 1H, 2-H), 7.18–7.99 (m, 6H, H_{arom}), 10.88 (b, 1H, N–H). Anal. calcd. for $C_{15}H_{10}N_2OS$ (266.32): C, 67.65; H, 3.78; N, 10.52; S, 12.04. Found C, 67.40; H, 3.64; N, 10.31; S, 11.84.

Ethyl [(2-Oxo-1,2-dihydrobenzo[*h*]quinolin-4-yl)sulfanyl] acetate (10) was obtained according to the previously discussed general method from compound **6** (1.14 g) and ethyl chloroacetate (0.7 mL), and crystallized from ethanol. Yield 1.31 g (84%); m.p. 208–210°C. IR (KBr):ν_{max} 3228 (N–H), 3142, 2940, 2885, 1725 (C=O), 1643 cm^{-1} (C=O); ^1H NMR (200 MHz, DMSO-d_6): δ 1.38 (t, 3H, OCH_2CH_3), 3.65 (s, 2H, S-CH_2-CO), 4.21 (q, 2H, OCH_2CH_3), 6.68 (s, 1H, 3-H), 7.15–8.06 (m, 6H, H_{arom}), 10.90 (b, 1H, N–H). Anal. calcd. for $C_{17}H_{15}NO_3S$ (313.38): C, 65.16; H, 4.82; N, 4.47; S, 10.23. Found C, 65.03; H, 4.76; N, 4.59; S, 10.15.

1-Hydroxybenzo[*h*]thieno[3,2-*c*]quinolin-11(10*H*)-one (11)

A mixture of the acetate ester **10** (1.57 g, 5 mmol) and PPA (5.0 g) was heated at 180°C for 1 h; after that the temperature was raised gradually to 200°C for 1 h. The reaction mixture was left to cool to r.t. and was poured onto crushed ice. The precipitate that was obtained was filtered off and dissolved in excess aqueous sodium hydroxide (50 mL, 2N). The alkaline solution was filtered off, and 2N hydrochloric acid was added until the solution became acidic to litmus and then was left to settle down for 2 h. The precipitate that was formed was filtered and crystallized from anisole to yield 0.84 g (63%); m.p. >300°C. IR (KBr):ν_{max} 3324–2665 (N–H, O–H), 1643 cm^{-1} (C=O); ^1H NMR (200 MHz, DMSO-d_6): δ 6.43 (s, 1H, 2-H), 7.09–8.12 (m, 6H, H_{arom}), 11.24 (b, 1H, N–H). Anal. calcd. for $C_{15}H_9NO_2S$ (267.31): C, 67.40; H, 3.39; N, 5.24; S, 12.00. Found C, 67.22; H, 3.41; N, 5.01; S, 11.75.

Ethyl 11-Oxo-10,11-dihydrobenzo[*h*]thieno[3,2-*c*]quinoline-2-carboxylate (12)

A mixture of the acetate ester **10** (1.57 g, 5 mmol) and DMF-DMA (0.8 mL, 6 mmol), in *o*-xylene (50 mL) was heated under reflux for 4 h. The reaction mixture was left to cool to r.t., and the precipitate that was obtained was filtered off and recrystallized from DMF. Yield 1.42 g (88%); m.p. 245–246°C. IR (KBr):ν_{max} 3242 (N–H), 3045, 2992, 2934, 1727 (C=O), 1649 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.44 (t, 3H, OCH_2CH_3), 4.28 (q, 2H, OCH_2CH_3), 6.98 (s, 1H, 3-H), 7.22-8.02 (m, 6H, H$_{arom}$), 11.40 (b, 1H, N–H). Anal. calcd. for $C_{18}H_{13}NO_3S$ (323.37): C, 66.86; H, 4.05; N, 4.33; S, 9.92. Found C, 66.64; H, 3.97; N, 4.42; S, 9.74.

1-Amino-11-oxo-10,11-dihydrobenzo[*h*]thieno[3,2-*c*]quinoline-2-carbonitrile (14)

According to the previously discussed PTC general method, this compound was obtained from compound **6** (1.14 g, 5 mmol) and 2-bromomalononitrile (0.87 g, 6 mmol), and the product was crystallized from DMF. Yield 1.15 g (79%); m.p. 290–291°C. IR (KBr):ν_{max} 3424, 3325 (NH$_2$), 3145, 2224 (C≡N), 1646 (C=O), 1628, 1612 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.15 (b, 2H, NH$_2$), 7.32–8.09 (m, 6H, H$_{arom}$), 11.23 (b, 1H, N–H). Anal. calcd. for $C_{16}H_9N_3OS$ (291.33): C, 65.97; H, 3.11; N, 14.42; S, 11.01. Found C, 65.62; H, 3.05; N, 14.30; S, 10.88.

2-(2-Oxo-1,2-dihydrobenzo[*h*]quinolin-4-yl)malononitrile (15)

To equimolar amounts (5 mmol) of chloroquinolinone **4** (1.15 g) and malononitrile (0.35 g) in DMF (25 mL), anhydrous potassium carbonate (4.18 g, 30 mmol) and TBAI (0.6 g) were added. The reaction mixture was stirred in a boiling water bath for 6 h and then filtered off, and the filtrate was evaporated in vacuum. The solid residue that was obtained was washed thoroughly with cold water, dried, and crystallized from dioxane to yield 0.91 g (70%); m.p. 266–267°C. IR (KBr):ν_{max} 3267 (N–H), 3111, 2204, 2175 (C≡N), 1644 (C=O), 1605 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.80 (s, 1H, $CH(CN)_2$), 6.80 (s, 1H, 3-H), 7.04–7.70 (m, 6H, H$_{arom}$), 11.25 (b, 1H, N–H). Anal. calcd. for $C_{16}H_9N_3O$ (259.27): C, 74.12; H, 3.50; N, 16.21. Found C, 74.11; H, 3.42; N, 16.09.

2-Amino-11-oxo-10,11-dihydrobenzo[*h*]thieno[2,3-*c*]quinoline-3-carbonitrile (16)

To a solution of compound **15** (1.30 g, 5 mmol) in DMF (50 mL), containing triethyamine (0.3 mL, 2.1 mmol), elemental sulfur (0.16 g, 5 mmol) was added. The reaction mixture was heated under reflux for 3 h. The solid deposits that formed after cooling to r. t. were filtered, washed with ethanol, dried, and crystallized from acetonitrile to yield 1.14 g (78%); m.p. 287–288°C. IR (KBr):ν_{max} 3384, 3335 (NH$_2$), 3145, 2218 (C≡N), 1652 (C=O), 1620, 1604 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.92 (b, 2H, NH$_2$), 7.22–8.02 (m, 6H, H$_{arom}$), 11.45 (b, 1H, N–H). Anal. calcd. for $C_{16}H_9N_3OS$ (291.33): C, 65.97; H, 3.11; N, 14.42; S, 11.01. Found C, 65.90; H, 2.96; N, 14.23; S, 10.84.

1-Amino-12-oxo-3-thioxo-11,12-dihydro-3*H*-benzo[*h*]thiopyrano[3,2-*c*]quinoline-2-carbonitrile (18)

To equimolar amounts (5 mmol) of the chloroquinolinone **4** (1.15 g), malononitrile (0.35 g) in DMF (25 mL), carbon disulfide (0.3 mL), anhydrous potassium carbonate (4.18 g, 30 mmol), and TBAI iodide (0.6 g) were added. The reaction mixture was stirred in a boiling water bath for 4 h and then filtered off, and the filtrate was evaporated in vacuum. The solid residue that was obtained was washed thoroughly with cold water, dried, and crystallized from acetonitrile to yield 1.11 g (66%); m.p. >300°C. IR (KBr):ν_{max} 3412, 3297 (NH$_2$), 3121, 2225 (C≡N), 1638 (C=O), 1618, 1604 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 5.80 (s, 2H, NH$_2$), 7.14–7.95 (m, 6H, H$_{arom}$), 11.03 (b, 1H, N–H). Anal. calcd. for $C_{17}H_9N_3OS_2$ (335.41): C, 60.88; H, 2.70; N, 12.53; S, 19.12. Found C, 60.54; H, 2.61; N, 12.44; S, 19.05.

2-[(2-Oxo-1,2-dihydrobenzo[*h*]quinolin-4-yl)sulfanyl]benzoic Acid (19)

To equimolar amounts (5 mmol) of the chloroquinolinone **4** (1.15 g) and thiosalicylic acid (0.79 g), anhydrous potassium carbonate (4.18 g, 30 mmol) and TBAI (0.6 g) were added. The reaction mixture was stirred in a boiling water bath for 4 h and then filtered, and the solid residue that separated was dissolved in hot water (100 mL). The solution that was obtained was acidified with diluted acetic acid tile for complete precipitation. The precipitate was filtered, washed with cold water, dried, and crystallized from DMSO to yield 1.42 g (82%); m.p. >300°C. IR (KBr):ν_{max} 3435-2550 (br, COOH), 1712 (C=O), 1648 (C=O), 1606 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6): δ 6.80 (s, 1H, 3-H), 7.14–7.95 (m, 10H, H$_{arom}$), 10.23 (b, 1H, N–H). Anal. calcd. for $C_{20}H_{13}NO_3S$ (347.40): C, 69.15; H, 3.77; N, 4.03; S, 9.23. Found C, 68.96; H, 3.65; N, 3.90; S, 9.05.

5,6-Dihydro-7*H*-benzo[*h*]thiochromeno[3,2-*c*]quinoline-6,7-dione (20)

A mixture of acid **19** (1.74 g, 5 mmol) and PPA (5.0 g) was heated at 180°C for 1 h; after that the temperature was raised gradually to 200°C for 1 h. The reaction mixture was left to cool to r.t. and poured onto crushed ice. The precipitate that was formed was filtered and crystallized from DMSO to yield 1.07 g (65%); m.p. 275–278°C. IR (KBr):ν_{max} 3224 (N–H), 3125, 1688 (C=O), 1642 cm^{-1} (C=O); ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.09–8.02 (m, 9H, H$_{arom}$), 8.15 (d, 1H, 8-H$_{arom}$) 11.41 (b, 1H, N–H). Anal. calcd. for $C_{20}H_{11}NO_2S$ (329.38): C, 72.93; H, 3.37; N, 4.25; S, 9.73. Found C, 73.02; H, 3.29; N, 4.22; S, 9.62.

Ethyl 3-Imino-12-oxo-11,12-dihydro-3*H*-benzo[*h*]thiopyrano[3,2-*c*]quinoline-2-carboxylate (22)

A mixture of the compound **6** (1.14 g, 5 mmol) and ethyl 2-cyano-3-ethoxyacrylate (1.0 g, 6 mmol), in dry DMF (25 mL), was heated under reflux for 4 h. The reaction mixture was poured onto crushed ice, and the precipitate that formed was filtered, dried, and crystallized from absolute ethanol to yield 1.5 g (86%); m.p 268–287°C. IR (KBr):ν_{max} 3320 (N–H), 3225, 1719 (C=O), 1645 (C=O), 1622 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.23 (t, 3H, OCH$_2$CH_3), 4.19 (q, 2H, OCH_2CH$_3$), 7.09–8.14 (m, 7H, H$_{arom}$), 8.78 (s, 1H, NH$_{imine}$), 10.56 (b, 1H, NH$_{lactam}$). Anal. calcd. for $C_{19}H_{14}N_2O_3S$ (350.40): C, 65.13; H, 4.03; N, 7.99; S, 9.15. Found C, 64.97; H, 4.10; N, 7.86; S, 9.04.

Ethyl 3-Imino-2-methylsulfanyl-12-oxo-11,12-dihydro-3*H*-benzo[*h*]thiopyrano[3,2-*c*]quinoline-2-carboxylate (24)

A mixture of the compound **6** (1.14 g, 5 mmol) and ethyl 2-cyano-3,3-di(methylsulfanyl)acrylate (1.3 g, 6 mmol), in dry DMF (25 mL), was heated under reflux for 4 h. The reaction mixture was left to cool overnight, and the precipitate that formed was filtered, dried, and recrystallized from DMF/EtOH to yield 1.65 g (83%); m.p 291–293°C. IR (KBr):ν_{max} 3287 (N–H), 3204, 1722 (C=O), 1639 (C=O), 1621 cm^{-1} (C=N); ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.24 (t, 3H, OCH$_2$CH_3), 2.63 (s, 3H, SCH$_3$), 4.18 (q, 2H, OCH_2CH$_3$), 7.11–8.05 (m, 6H, H$_{arom}$), 8.62 (s, 1H, NH$_{imine}$), 10.84 (b, 1H, NH$_{lactam}$). Anal. calcd. for $C_{20}H_{16}N_2O_3S_2$ (396.49): C, 60.59; H, 4.07; N, 7.07; S, 16.17. Found C, 60.40; H, 3.88; N, 6.95; S, 15.88.

Examination of the Effect on α-Amylase

The procedure of determination of the effect of the tested compounds on α-amylase activity was based on measuring of the amount of α-D-glucose (mg/L) that librated from enzymatic hydrolysis of starch using the standard enzymatic glucose-oxidase method.[18,19] The tests were carried out on α-amylase enzyme produced by *Thermomyces lanuginosus*, a thermophilic fungus which is grown on starch-containing substances. The tested samples were added as a DMF solution (0.1 mL, 100 μg/mL) to an assay mixture consisting of enzyme solution (0.5 mL), citrate phosphate buffer (4.5 mL, $p\text{H} = 5.0$), containing 1% starch. Then it was incubated at 40°C for 30 min, and the released α-D-glucose was determined on a Spekol-k colorimeter at $\lambda = 505$ nm. Tests were carried out in triplicates, and the mean reading was recorded. A blank test was prepared using distilled water instead of the enzyme, and it was used for zero-setting of the colorimeter. A control test was prepared using DMF without the addition of the candidate compounds.

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