SYNTHESIS OF QUINOBENZO-1,4-THIAZINES FROM DIQUINO-1,4-DITHIIN AND 2,2’-DICHLORO-3,3’-DIQUINOLINYL DISULFIDE

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Abstract – Synthesis of new type of tetracyclic azaphenothiazines, 6-, 8-, 9- and 10-substituted quinobenzo-1,4-thiazines (benzo[b]-1-azaphenothiazines) (5) and (10), has been worked out from diquino-1,4-dithiin (5,12-diaza-6,13-dithiapentacene) (2) as fusion reactions with aniline hydrochlorides (8)·HCl via the 1,4-dithiin ring opening and the 1,4-thiazine ring closure. The better results were obtained when 2,2’-dichloro-3,3’-diquinolinyl disulfide (9) reacted with anilines (8) in MEDG. Selected 6H-quinobenzo-1,4-thiazines (5a) (5c) and (5g) were transformed into 6-alkyl derivatives (10a-10n) by N-alkylation with alkyl halides. Homonuclear NOE experiment for the 6-methyl derivative (10a) confirmed the product structure as quino[3,2-b]benzo[1,4]thiazine.

INTRODUCTION

Phenothiazines are known for varied chemical properties and very interesting biological activities (antipsychotic, antihistaminic, antitussive and antiemetic).1 Furthermore, recent reports deals with very promising anticancer and antibacterial activities, reversal of multidrug resistance and potential treatment in Alzheimer’s and Creutzfeldt-Jakob diseases.2-9 The most significant modifications of the phenothiazine structures were made by introduction of new pharmacophoric substituents at the thiazine nitrogen atom and by substitution of the benzene ring with an azine ring (to form azaphenothiazines). We modified the phenothiazine structure with the quinoline ring to form new type of the linear and angular fused diquino-1,4-thiazines, being pentacyclic dibenzodiazaphenothiazines.10-14 In our previous papers12-14 we found isomeric diquino-1,4-dithiins (1) and (2) (5,7-diaza-6,13-dithiapentacene and 5,12-diaza-6,13-dithiapentacene)15 to be effective starting materials to synthesis of 2,2’-dichloro-3,3’-diquinolinyl sulfide (3) which formed diquino-1,4-thiazines (4) in the annulation reactions with acetamide and primary alkyl, aryl and heteroaryl amines. Some diquino-1,4-thiazines (4) were obtained directly from diquino-1,4-dithiin (1) via the 1,4-dithiin ring opening and the 1,4-thiazine ring closure. (Scheme 1).14 Selected 6-substituted
diquino-1,4-thiazines were tested against 57 human cancer lines in National Cancer Institute in Bethesda (USA) showing significant anticancer activities against lung, colon, breast, renal and CNS cancers, melanoma and leukemia (for example, (4) R = CH₂CH₂NHCONHCH₂CH₂Cl showed 50% growth inhibition GI₅₀ = 0.04 µg/mL against melanoma SK-MEL-5 line). Herein we would like to describe synthesis of novel tetracyclic azaphenothiazines, quino[3,2-b]benzo[1,4]thiazines (5) of potential anticancer activity, in the reactions of diquino-1,4-dithiin (2) with substituted aniline hydrochlorides via the dithiin ring opening and the thiazine ring closure. The idea came from the reactions of angular condensed diquino-1,4-dithiin (6) with aniline hydrochlorides giving 12H-quino[3,4-b]benzo[1,4]-thiazines (7) (Scheme 1).

RESULTS AND DISCUSSION

Synthesis

Reactions of diquino-1,4-dithiin (2) with anilines were initially carried out using boiling aniline (8a) but without expected results. Only when aniline hydrochloride (8a)·HCl was used the product was 6H-quinobenzothiazine (5a). That reaction was carried out in various solvents (aniline, diphenyl ether, MEDG – monomethyl ether of diethylene glycol) in 16-28% yield but the best result (52% yield) was obtained when that reaction was performed as a fusion (without a solvent) at 200-205 °C for 4 h. An evolution of hydrogen sulfide was observed during the reaction. Reactions of diquino-1,4-dithiin (2) with p-substituted aniline hydrochlorides (8b-8g)·HCl were also carried out as a fusion at 200-205 °C for 4 h and led to 9-substituted 6H-quinobenzothiazines (5b-5g) in 28-50% yield (Scheme 2).

As the yields were unsatisfactory, we used other 2,3-disubstituted quinoline, 2,2’-dichloro-3,3’-diquinolinyl disulfide (9), which can be obtained from the reaction of 3,4-dihydro-2(1H)-quinolone with thionyl chloride (diquino-1,4-dithiins (1) and (2) as well as). Reaction of disulfide (9) with aniline (8a) were carried out initially in DMF at 153 °C, in DMSO at 130 °C and in refluxing MEDG at 194 °C (the best solvent in the synthesis of diquinothiazines (4) from sulfide (3)13,14) giving 6H-quinobenzothiazine (5a) in
36%, 24% and 52% yields, respectively. Further reactions with \( \rho \)-substituted anilines (8b-8g) were carried out in refluxing MEDG for 3 h giving 9-substituted 6\( H \)-quinobenzothiazines (5b-5g) in 56-67% yield. Diquino-1,4-dithiin (2) was obtained in those reactions as a side-product (in 15-30% yield), what is not unexpected result as disulfide (9) was previously transformed into dithiin (2) in reductive conditions (sodium borohydride, butanol) in 91% yield.\(^{18}\)

The next step was to perform reactions of dithiin (2) with \( \omega \)-chloroaniline and \( \omega \)-bromoaniline hydrochlorides (8h, 8i)·HCl to form 7-chloro- and 7-bromo-6\( H \)-quinobenzothiazines (5h, 5i) but instead of it unexpectedly 6\( H \)-quinobenzothiazine (5a) was formed in 32% yield. The same compound (in 64% and 56% yield) was obtained also from reaction of disulfide (9) with \( \omega \)-chloroaniline (8h) and \( \omega \)-bromoaniline (8i) (Scheme 3).

These results showed the chlorine atom to be more susceptible to substitution than the hydrogen atom and the thiazine ring closure proceeded as aromatic nucleophilic substitution mechanism.
Reactions of dithiin (2) with \( m \)-substituted aniline hydrochlorides (8j-8l)-HCl led to two products, 8-substituted 6\( H \)-quinobenzothiazines (5j-5l) and 10-substituted 6\( H \)-quinobenzothiazines (5m-5o) in 14-22% and 18-28% yields, respectively. Analogous reactions of disulfide (9) gave these products in 28-33% and 32-36% yields (Scheme 4).

Scheme 4

The problem of identification of these pairs of products was solved using \( ^1 \)H NMR spectra and confirmed by independent syntheses exploiting higher reactivity of the chlorine atom than the hydrogen atom in position 2 in substituted anilines. Dithiin (2) and disulfide (9) reacted with 2,5-dichloroaniline (8m) and its hydrochloride (8m)-HCl to give 8-chloro-6\( H \)-quinobenzothiazine (5j) in 18% and 64% yield, respectively. In similar way, reactions with 2,3-dichloroaniline (8n) and its hydrochloride (8n)-HCl led to 10-chloro-6\( H \)-quinobenzothiazine (5m) in 21% and 57% yield (Scheme 5).

Scheme 5

The selected 6\( H \)-quinobenzothiazines (5a), (5c) and (5g) were transformed into 6-alkyl derivatives (10a-10n) in 79-92% yield by \( N \)-alkylation with alkyl halides in DMF in the presence of sodium hydride (Scheme 6).
In order to identify unequivocally the structure of novel quinobenzothiazines (5) and (10) we carried out homonuclear NOE experiment for product (10a). Irradiation of the methyl protons at 3.61 ppm gave an enhancement of the only one proton signal, i.e. the H7 proton at 6.93 ppm by 8.51% what excludes structure (11) (in this case the enhancement would involve two protons: the H10 and H12 ones, Scheme 7). Therefore, the products were identified as quino[3,2-b]benzo[1,4]thiazines (and benzo[b]-1-azaphenothiazines as the phenothiazine derivatives).

The 1H NMR spectra were very useful for identification of the products as 8-, 9- and 10-substituted quinobenzothiazines (5) and (10). The proton signals of the quinoline part were found at low field (over 7.2 ppm) as a singlet (proton H12), two doublet-shaped multiplet signals with one ortho-coupling and two triplet-shaped multiplet signals with two ortho-couplings. These signals were identical to those found in the spectra of diquinothiazines (4). The proton signals of the benzene ring were found most often at high field (below 7.2 ppm). Substituted benzene ring signals were considered as the signals of 1,2,4-trisubstituted benzenes in 8- and 9-substituted quinobenzothiazines (5j-5l) and (5b-5g), and 1,2,3-trisubstituted benzenes in 10-substituted quinobenzothiazines (5m-5o). A discrimination of the isomeric products of the reactions with m-substituted anilines (5j-5l versus 5m-5o) was based on the coupling constants $J_{ortho}$ and $J_{meta}$ in the former compounds (giving two doublet signals of the H7 and H10 protons and one multiplet as a double doublet signal of the H8 proton) and two $J_{ortho}$, and $J_{meta}$ in the latter compounds (giving two multiplets as double doublet signals of the H7 and H9 protons, and one multiplet.
as a triplet-shaped signal of the H8 proton). As the coupling constant $J_{meta}$ is very small the signal of the H7 proton in 8-substituted quinobenzothiazines (5m-5o) is observed as a narrow doublet.
In our opinion, the formation of quinobenzothiazines (5) from dithiin (2) and disulfide (9) proceeded through anilinoquinoline (12) which further underwent cyclization to form the 1,4-thiazine ring (Scheme 8).

![Scheme 8](image)

**Properties of quinobenzothiazines (5) and (10)**

Syntheses of substituted quinobenzothiazines (5) and (10) were followed by TLC analysis as the chromatograms of the products, unlike to the chromatograms of substrates (2) and (9), showed colour changing during irradiation with UV lamp from blue or green to yellow and orange. Yellow colour was observed when the quinobenzothiazine chromatograms were sprayed with a mixture detecting the phenothiazine system (sulfuric acid-water-ethanol 1:1:8). Quinobenzothiazines (5) and (10) exhibit promising potential antiinflammatory, antiparkinsonic, antirheumatic, anticancer, antiallergic, antidiabetic and immunosuppressive activities.

**CONCLUSION**

We report here synthesis of novel tetracyclic 6H-quinobenzothiazines (5a-5o) in the fusion reactions of diquinodithiin (2) with substituted aniline hydrochlorides via the 1,4-dithiin ring opening and the 1,4-thiazine ring closure, and with better yields in the reactions of diquinolinyl disulfide (3) with substituted anilines in MEDG. N-Alkylation reactions of selected 6H-quinobenzothiazines led to 6-substituted quinobenzothiazines (10a-10n) of potential biological activities. The structure of the products as quino[3,2-b]benzo[1,4]thiazines was determined using homonuclear NOE experiment for the 6-methyl derivative.

**EXPERIMENTAL**

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and were uncorrected. The $^{1}$H NMR spectra were recorded on a Varian Unity-Inova-300 and a Bruker DRX spectrometers at 300 and 500 MHz in deuteriochloroform with tetramethylsilane as the internal standard. Electron impact (EI MS) mass spectra were run on a Finnigan MAT 95 spectrometer at 70 eV. The thin
layer chromatography was performed on aluminum oxide 60 F254 neutral (type E) (Merck 1.05581) with CH2Cl2 and on silica gel 60 F254 (Merck 1.05735) with CHCl3-EtOH (10:1 v/v) as eluents. Diquino-1,4-dithiin (2) and 2,2’-dichloro-3,3’-diquinolinyl disulfide (9) were obtained according to the described procedures.12,15,18

Reactions of diquino-1,4-dithiin (2) with aniline and aniline hydrochloride (8a) HCl in solvents
A. A mixture of diquino-1,4-dithiin (2) (0.16 g, 0.5 mmol) and aniline hydrochloride (8a)-HCl (0.32 g, 2.5 mmol) was stirred in aniline (5 mL) and then refluxed for 8 h. After cooling water was added (10 mL) and aniline was distilled off. After cooling the resulting solid was filtered off, washed with water and purified by column chromatography (silica gel, CHCl3) to give 6H-quinobenzothiazine 5a (0.06 g, 24%), mp 169-170 °C (EtOH).1H NMR (CDCl3) δ: 6.58 (m, 1H, H7), 6.85 (m, 1H, H9), 6.99 (m, 2H, H8, H10), 7.23 (m, 1H, H2), 7.38 (broad s, 1H, NH), 7.46 (m, 2H, H1, H3), 7.55 (s, 1H, H12), 7.56 (m, 1H, H4). EI MS m/z: 250 (M, 100), 218 (M-S, 41). Anal. Calcd for C15H10N2S: C 71.97, H 4.03, N 11.19. Found: C 71.82, H 4.00, N 11.01.

B. A mixture of diquino-1,4-dithiin (2) (0.16 g, 0.5 mmol) and aniline hydrochloride (8a)-HCl (0.32 g, 2.5 mmol) was stirred in melted diphenyl ether (5 mL) and heated on an oil bath at 200-205 °C for 4 h. After cooling the resulting solid was filtered off, washed with water and ethanol, and purified by column chromatography (silica gel, CHCl3) to give 6H-quinobenzothiazine 5a (0.04 g, 16%).

C. A mixture of diquino-1,4-dithiin (2) (0.16 g, 0.5 mmol) and aniline hydrochloride (8a)-HCl (0.32 g, 2.5 mmol) was stirred in MEDG (5 mL) and refluxed for 8 h. After cooling the solution was poured into water (20 mL) and the resulting solid was filtered off, washed with water and purified by column chromatography (silica gel, CHCl3) to give 6H-quinobenzothiazine 5a (0.07 g, 28%).

Fusion reactions of diquino-1,4-dithiin (2) with aniline hydrochlorides (8a-8n) HCl – general procedure
A mixture of diquino-1,4-dithiin (2) (0.16 g, 0.5 mmol) and substituted aniline hydrochloride (8a-8n) HCl (2.5 mmol) was finely powdered together and then heated on an oil bath at 200-205 °C for 4 h. After cooling water was added (10 mL) and the insoluble solid was filtered off. The filtrate was alkalized with 5% aqueous sodium hydroxide to pH = 10 and the resulting solid was filtered off and washed with water. The combined solids were purified by column chromatography (silica gel, CHCl3) to give quinobenzothiazines (5a-5o).

A. with aniline and p-substituted aniline hydrochlorides (8a-8g) HCl
1. 6H-Quinobenzothiazine (5a) (0.013 g, 52%).
2. 6H-9-Methylquinobenzothiazine (5b) (0.08 g, 30%), mp 197-198 °C (EtOH).1H NMR (CDCl3) δ: 2.24 (s, 3H, CH3), 6.57 (d, 1H, H7), 6.81 (d, 1H, H10), 6.84 (m, 1H, H8), 7.25 (m, 1H, H2), 7.46 (m, 1H, H1), 7.48 (m, 1H, H3), 7.55 (s, 1H, H12), 7.56 (m, 1H, H4). EI MS m/z: 264 (M, 100), 233 (M-SH, 21). Anal. Calcd for C16H12N2S: C 72.70, H 4.58, N 10.60. Found: C 72.58, H 4.49, N 10.35.
3. 6H-9-Chloroquinobenzothiazine 5c (0.08 g, 28%), mp 224-225 °C (EtOH).1H NMR (CDCl3) δ: 6.91 (d, 1H, H7), 6.95 (d, 1H, H10), 7.07 (m, 1H, H8), 7.39 (m, 1H, H2), 7.51 (m, 1H, H1), 7.62 (s+m, 3H, H3,
H4, H12). EI MS m/z: 284 (M, Cl<sup>35</sup>, 100), 286 (M+2, Cl<sup>37</sup>, 34), 249 (M-Cl, 30). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>ClN<sub>2</sub>S: C 63.27, H 3.19, N 9.84. Found: C 63.02, H 3.17, N 9.63.

4. 6H-9-Bromoquinobenzothiazine 5d (0.12 g, 36%), mp 212-213 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.45 (d, 1H, H7), 7.11 (m, 2H, H8, H10), 7.25 (m, 1H, H2), 7.48 (m, 2H, H1, H3), 7.56 (m, 1H, H4), 7.57 (s, 1H, H12). EI MS m/z: 328 (M, Br<sup>79</sup>, 98), 330 (M+2, Br<sup>81</sup>, 100), 249 (M-Br, 55). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>BrN<sub>2</sub>S: C 54.73, H 2.76, N 8.51. Found: C 54.42, H 2.72, N 8.29.

5. 6H-9-Fluoroquinobenzothiazine 5e (0.13 g, 49%), mp 158-159 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.58 (d, 1H, H7), 6.75 (m, 2H, H8, H10), 7.26 (m, 1H, H2), 7.49 (m, 2H, H1, H3), 7.56 (m, 1H, H4), 7.57 (s, 1H, H12). EI MS m/z: 268 (M, 100), 236 (M-S, 60). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>FN<sub>2</sub>S: C 67.15, H 3.38, N 10.44. Found: C 67.01, H 3.39, N 10.21.

6. 6H-Methylthioquinobenzothiazine 5f (0.16 g, 54%), mp 204-205 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 2.43 (s, 3H, CH<sub>3</sub>), 6.58 (d, 1H, H7), 6.93 (d, 1H, H10), 6.98 (m, 1H, H8), 7.25 (m, 1H, H2), 7.48 (m, 2H, H1, H3), 7.58 (s+m, 2H, H4, H12). EI MS m/z: 268 (M, 100), 236 (M-S, 60). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>S<sub>2</sub> C 64.84, H 4.08, N 9.45. Found: C 64.71, H 4.05, N 9.22.

7. 6H-Trifluoromethylquinobenzothiazine 5g (0.16 g, 50%), mp 236-237 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.62 (d, 1H, H7), 7.23 (m, 2H, H8, H10), 7.29 (m, 1H, H2), 7.50 (m, 2H, H1, H3), 7.57 (m, 1H, H4), 7.59 (s, 1H, H12). EI MS m/z: 318 (M, 100), 286 (M-S, 22), 249 (M-CF<sub>3</sub>, 3). Anal. Calcd for C<sub>16</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>S: C 60.37, H 2.85, N 8.80. Found: C 60.22, H 2.71, N 8.59.

B. with o-substituted aniline hydrochlorides

1a. 6H-Quinobenzothiazine 5a (0.08 g, 32%), mp 169-170 °C (EtOH).

C. with m-substituted aniline hydrochlorides

1b. 6H-8-Chloroquinobenzothiazine 5j (0.06 g, 21%), mp 230-231 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.59 (d, 1H, H7), 6.83 (m, 1H, H9), 6.90 (d, 1H, H10), 7.04 (broad s, 1H, NH), 7.26 (m, 1H, H2), 7.49 (m, 2H, H1, H3), 7.58 (s+m, 2H, H4, H12). EI MS m/z: 284 (M, Cl<sup>35</sup>, 100), 286 (M+2, Cl<sup>37</sup>, 37), 252 (M-S, 20), 249 (M-Cl, 18). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>ClN<sub>2</sub>S: C 63.27, H 3.19, N 9.84. Found: C 63.09, H 3.15, N 9.56.

1b. 6H-10-Chloroquinobenzothiazine 5m (0.04 g, 14%), mp 242-243 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.44 (m, 1H, H7), 6.88 (m, 1H, H9), 6.92 (m, 1H, H8), 7.04 (broad s, 1H, NH), 7.25 (m, 1H, H2), 7.47 (m, 2H, H1, H3), 7.54 (m, 1H, H4), 7.58 (s, 1H, H12). EI MS m/z: 284 (M, Cl<sup>35</sup>, 100), 286 (M+2, Cl<sup>37</sup>, 39), 252 (M-S, 22), 249 (M-Cl, 17). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>ClN<sub>2</sub>S: C 63.27, H 3.19, N 9.84. Found: C 63.12, H 3.12, N 9.65.

2a. 6H-8-Bromoquinobenzothiazine 5k (0.06 g, 18%), mp 217-218 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.77 (d, 1H, H7), 6.85 (d, 1H, H10), 6.88 (broad s, 1H, NH), 6.96 (m, 1H, H9), 7.26 (m, 1H, H2), 7.49 (m, 2H, H1, H3), 7.58 (s+m, 2H, H4, H12). EI MS m/z: 328 (M, Br<sup>79</sup>, 98), 330 (M+2, Br<sup>81</sup>, 100), 296 (M-S, 7), 249 (M-Br, 40). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>BrN<sub>2</sub>S: C 54.73, H 2.76, N 8.51. Found: C 54.48, H 2.69, N 8.32.

2b. 6H-10-Bromoquinobenzothiazine 5n (0.07 g, 21%), mp 231-232 °C (EtOH). 1H NMR (CDCl<sub>3</sub>) δ: 6.48 (m, 1H, H7), 6.85 (m, 1H, H8), 6.92 (broad s, 1H, NH), 7.05 (m, 1H, H9), 7.26 (m, 1H, H2), 7.47 (m, 2H, H1, H3), 7.50 (m, 1H, H4), 7.58 (s, 1H, H12). EI MS m/z: 328 (M, Br<sup>79</sup>, 96), 330 (M+2, Br<sup>81</sup>, 100),
296 (M-S, 7), 249 (M-Br, 37). Anal. Caled for C_{15}H_9BrN_2S: C 54.73, H 2.76, N 8.51. Found: C 54.45, H 2.64, N 8.35.

3a. 6H-8-Trifluoromethylquinobenzothiazine 5l (0.09 g, 28%), mp 219-220 °C (EtOH). 1H NMR (CDCl_3) δ: 8.61 (d, 1H, H7), 7.07 (d, 1H, H10), 7.09 (m, 1H, H9), 7.28 (m, 1H, H2), 7.52 (m, 2H, H1, H3), 7.59 (s, 1H, H12), 7.60 (m, 1H, H4). EI MS m/z: 318 (M, 100), 298 (M-HF, 19), 286 (M-S, 38), 249. Anal. Caled for C_{16}H_9F_3N_2S: C 60.37, H 2.85, N 8.80. Found: C 60.20, H 2.88, N 8.58.

3b. 6H-10-Trifluoromethylquinobenzothiazine 5n (0.07 g, 22%), mp 225-226 °C (EtOH). 1H NMR (CDCl_3) δ: 6.84 (m, 1H, H7), 7.14 (m, 1H, H8), 7.24 (m, 1H, H9), 7.31 (m, 1H, H2), 7.54 (m, 2H, H1, H3), 7.62 (m, 1H, H4), 7.71 (s, 1H, H12), 7.92 (broad s, 1H, NH). EI MS m/z: 318 (M, 100), 298 (M-HF, 5), 286 (M-S, 30). Anal. Caled for C_{16}H_9F_3N_2S: C 60.37, H 2.85, N 8.80. Found: C 60.18, H 2.80, N 8.53.

D. with disubstituted aniline hydrochlorides (8m, 8n) · HCl

1. 6H-Quinobenzothiazine 5a (0.09 g, 36% or 0.06 g, 24%, respectively).

Reactions of 2,2’-dichloro-3,3’-diquinolinyl disulfide (9) with aniline in DMF and DMSO
A solution of disulfide (9) (0.20g, 0.5 mmol) and aniline (8a) (0.18 mL, 2 mmol) in DMF (5 mL) was refluxed for 3 h or in DMSO (5 mL) was heated at 130 °C for 3 h. After cooling the solution was poured into water (20 mL) and alkalized with 5% aqueous sodium hydroxide to pH = 10. The resulting solid was filtered off, washed with water and purified by column chromatography (silica gel, CHCl_3) to give 6H-quinobenzothiazines 5a (0.09 g, 36% or 0.06 g, 24%, respectively).

Reactions of 2,2’-dichloro-3,3’-diquinolinyl disulfide (9) with aniline and substituted anilines in MEDG – general procedure
A solution of disulfide (9) (0.20g, 0.5 mmol) and aniline (8a-8n) (2 mmol) in MEDG (5 mL) was refluxed for 3 h. After cooling the solution was poured into water (20 mL) and alkalized with 5% aqueous sodium hydroxide to pH = 10. The resulting solid was filtered off, washed with water and purified by column chromatography (silica gel, CHCl_3) to give quinobenzothiazines 5a-5o.

A. with aniline and p-substituted anilines (8a-8g)
1. 6H-Quinobenzothiazine 5a (0.013 g, 52%); 2. 6H-9-Methylquinobenzothiazine 5b (0.16 g, 59%); 3. 6H-9-Chloroquinobenzothiazine 5c (0.19 g, 67%); 4. 6H-9-Bromoquinobenzothiazine 5d (0.19 g, 57%); 5. 6H-9-Fluoroquinobenzothiazine 5e (0.15 g, 56%); 6. 6H-9-Methylthioquinobenzothiazine 5f (0.18 g, 60%); 7. 6H-9-Trifluoromethylquinobenzothiazine 5g (0.18 g, 56%).

B. with o-substituted anilines (8h, 8i)
1. 6H-Quinobenzothiazine 5a (0.016 g, 64% and 0.14 g, 56%, respectively).

C. with m-substituted anilines (8j-8l)
1. 6H-8-Chloroquinobenzothiazine 5j (0.09 g, 31%) and 6H-10-chloroquinobenzothiazine 5m (0.08 g, 28%); 2. 6H-8-Bromoquinobenzothiazine 5k (0.12 g, 36%) and 6H-10-bromoquinobenzothiazine 5n (0.11 g, 33%); 3. 6H-8-Trifluoromethylquinobenzothiazine 5l (0.11 g, 34%) and 6H-10-trifluoromethylquinobenzothiazine 5n (0.09 g, 28%).
D. with disubstituted anilines (8m, 8n)

1. 6H-8-Chloroquinobenzothiazine 5j (0.18 g, 64%); 2. 6H-10-Chloroquinobenzothiazine 5m (0.16 g, 57%).

**N-Alkylation of selected 6H-quinobenzothiazines**

To a solution of 6H-quinobenzothiazines (5a), (5c) and (5g) (0.5 mmol) in dry DMF (5 mL) NaH (0.12 g, 5 mmol, 60% NaH in mineral oil was washed out with hexane) was added. The reaction mixture was stirred at room temperature for 1 h, alkyl halide (methyl iodide, ethyl iodide, isopropyl iodide, butyl iodide, allyl bromide, benzyl chloride, 1.5 mmol) was added and the stirring was continued for 24 h. The reaction mixture was poured into water (25 mL). The resulting solid was filtered off, washed with water and purified by column chromatography (aluminum oxide, CHCl₃) to give 6-substituted quinobenzothiazines (10a-10n):

1. 6-Methylquinobenzothiazine (10a) (0.12 g, 92%), mp 88-89 °C (EtOH). ¹H NMR (CDCl₃) δ: 3.61 (s, 3H, CH₃), 6.93 (m, 1H, H7), 6.94 (m, 1H, H9), 7.13 (m, 1H, H10), 7.19 (m, 1H, H8), 7.26 (m, 1H, H2), 7.50 (m, 1H, H3), 7.52 (m, 1H, H1), 7.66 (s, 1H, H12), 7.75 (m, 1H, H4). EI MS m/z: 264 (M, 100), 249 (M-CH₃, 13). Anal. Calcd for C₁₆H₁₂N₂S: C 72.70, H 4.58, N 10.60. Found: C 72.43, H 4.42, N 10.32.

2. 6-Ethylquinobenzothiazine (10b) (0.11 g, 85%), an oil. ¹H NMR (CDCl₃) δ: 1.48 (t, J = 6.9 Hz, 3H, CH₃), 4.31 (q, J = 6.9 Hz, 2H, CH₂), 6.90 (m, 1H, H9), 6.96 (m, 1H, H7), 7.07 (m, 1H, H10), 7.16 (m, 1H, H8), 7.25 (m, 1H, H2), 7.48 (m, 1H, H3), 7.49 (m, 1H, H1), 7.59 (s, 1H, H12), 7.71 (m, 1H, H4). EI MS m/z: 278 (M, 100), 263 (M-CH₃, 44), 250 (M-C₂H₄, 72). Anal. Calcd for C₁₇H₁₄N₂S: C 73.35, H 5.07, N 10.06. Found: C 73.02, H 5.00, N 9.78.

3. 6-Isopropylquinobenzothiazine (10c) (0.11 g, 79%), an oil. ¹H NMR (CDCl₃) δ: 1.83 (d, J = 6.8 Hz, 6H, 2CH₃), 4.63 (m, 1H, CH), 6.94 (m, 1H, H9), 7.15 (m, 1H, H7), 7.17 (m, 1H, H10), 7.19 (m, 1H, H8), 7.26 (m, 1H, H2), 7.50 (m, 1H, H3), 7.53 (m, 1H, H1), 7.67 (s, 1H, H12), 7.75 (m, 1H, H4). EI MS m/z: 292 (M, 100), 277 (M-CH₃, 9), 250 (M-C₃H₆, 100). Anal. Calcd for C₁₈H₁₆N₂S: C 73.94, H 5.52, N 9.58. Found: C 73.62, H 5.45, N 9.33.

4. 6-Butylquinobenzothiazine (10d) (0.12 g, 80%), an oil. ¹H NMR (CDCl₃) δ: 1.01 (t, J = 7.5 Hz, 3H, CH₃), 1.52 (m, 2H, CH₂), 1.86 (m, 2H, CH₂), 4.26 (t, J = 7.4 Hz, 2H, NCH₂), 6.91 (m, 1H, H9), 6.93 (m, 1H, H7), 7.08 (m, 1H, H10), 7.16 (m, 1H, H8), 7.25 (m, 1H, H2), 7.48 (m, 1H, H3), 7.49 (m, 1H, H1), 7.60 (s, 1H, H12), 7.71 (m, 1H, H4). EI MS m/z: 306 (M, 74), 277 (M-C₂H₅, 21), 263 (M-C₃H₇, 52), 250 (M-C₄H₈, 100). Anal. Calcd for C₁₉H₁₈N₂S: C 74.47, H 5.52, N 9.14. Found: C 74.19, H 5.45, N 8.89.

5. 6-Allylquinobenzothiazine (10e) (0.12 g, 85%), an oil. ¹H NMR (CDCl₃) δ: 4.91 (d, J = 5.4 Hz, 2H, NCH₂), 5.28 (d, J = 14.7 Hz, 1H, CH=), 5.33 (d, J = 21.6 Hz, 1H, CH=), 6.13 (m, 1H, CH=), 6.90 (m, 1H, H9), 6.98 (m, 1H, H7), 7.07 (m, 1H, H10), 7.11 (m, 1H, H8), 7.25 (m, 1H, H2), 7.48 (m, 1H, H3), 7.49 (m, 1H, H1), 7.61 (s, 1H, H12), 7.70 (m, 1H, H4). EI MS m/z: 290 (M, 34), 275 (M-C₃H₅, 100), 249 (M-C₃H₅, 60). Anal. Calcd for C₁₉H₁₄N₂S: C 74.45, H 4.86, N 9.65. Found: C 74.20, H 4.78, N 9.37.

6. 6-Benzylquinobenzothiazine (10f) (0.14 g, 82%), mp 127-128 °C (EtOH). ¹H NMR (CDCl₃) δ: 5.60 (s, 2H, CH₂), 6.77 (m, 1H, H7), 6.87 (m, 1H, H9), 6.92 (m, 1H, H8), 7.08 (m, 1H, H10), 7.24 (m, 1H, H2),
7.29 (m, 3H, C₆H₃), 7.38 (m, 2H, C₆H₂), 7.45 (m, 1H, H₃), 7.52 (m, 1H, H₁), 7.68 (s, 1H, H₁₂), 7.69 (m, 1H, H₄). El MS m/z: 340 (M, 60), 249 (M-CH₂C₆H₅, 100). Anal. Calcd for C₂₂H₁₆N₂S: C 77.62, H 4.74, N 8.23. Found: C 77.51, H 4.70, N 8.04.

7. 6-Methyl-9-chloroquinobenzothiazine (10g) (0.12 g, 82%), mp 150-151 °C (EtOH). ¹H NMR (CDCl₃) δ: 3.58 (s, 3H, CH₃), 6.82 (d, 1H, H₇), 7.11 (d, 1H, H₁₀), 7.13 (m, 1H, H₈), 7.29 (m, 1H, H₂), 7.52 (m, 1H, H₃), 7.54 (m, 1H, H₁), 7.67 (s, 1H, H₁₂), 7.75 (m, 1H, H₄). El MS m/z: 298 (M, Cl₃⁵, 100), 300 (M+2, Cl₃⁷, 35), 283 (M-CH₃, 13). Anal. Calcd for C₁₆H₇ClN₂S: C 64.32, H 3.71, N 9.38. Found: C 64.19, H 3.73, N 9.18.

8. 6-Butyl-9-chloroquinobenzothiazine (10h) (0.15 g, 88%), mp 71-72 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.00 (t, J = 7.3 Hz, 3H, CH₃), 1.53 (m, 2H, CH₂), 1.81 (m, 2H, CH₂), 4.23 (t, J = 6.5 Hz, 2H, NCH₂), 6.82 (d, 1H, H₇), 7.06 (d, 1H, H₁₀), 7.09 (m, 1H, H₈), 7.27 (m, 1H, H₂), 7.51 (m, 1H, H₃), 7.56 (m, 1H, H₁), 7.61 (s, 1H, H₁₂), 7.70 (m, 1H, H₄). El MS m/z: 340 (M, Cl₃⁵, 80), 300 (M+2, Cl₃⁷, 31), 297 (M-CH₃, 44), 284 (M-C₄H₈, 100). Anal. Calcd for C₁₉H₁₇ClN₂S: C 66.95, H 5.03, N 8.22. Found: C 66.85, H 4.94, N 8.03.

9. 6-Allyl-9-chloroquinobenzothiazine (10i) (0.13 g, 81%), mp 93-94 °C (EtOH). ¹H NMR (CDCl₃) δ: 4.87 (d, J = 3.2 Hz, 2H, NCH₂), 5.28 (d, J = 16.5 Hz, 1H, CH=), 5.31 (d, J = 24.0 Hz, 1H, CH=), 6.08 (m, 1H, CH=), 6.87 (d, 1H, H₇), 7.05 (d, 1H, H₁₀), 7.06 (m, 1H, H₈), 7.27 (m, 1H, H₂), 7.49 (m, 1H, H₃), 7.50 (m, 1H, H₁), 7.62 (s, 1H, H₁₂), 7.69 (m, 1H, H₄). El MS m/z: 324 (M, Cl₃⁵, 39), 326 (M+2, Cl₃⁷, 15), 309 (M-C₃H₅, 100), 283 (M-C₃H₅, 62). Anal. Calcd for C₁₈H₁₃ClN₂S: C 66.56, H 4.03, N 8.62. Found: C 66.47, H 3.93, N 8.39.

10. 6-Benzyl-9-chloroquinobenzothiazine (10j) (0.15 g, 80%), mp 157-158 °C (EtOH). ¹H NMR (CDCl₃) δ: 5.53 (s, 2H, CH₂), 6.63 (d, 1H, H₇), 6.89 (m, 1H, H₈), 7.06 (d, 1H, H₁₀), 7.22 (m, 1H, H₂), 7.30 (m, 3H, C₆H₃), 7.33 (m, 2H, C₆H₂), 7.46 (m, 1H, H₃), 7.52 (m, 1H, H₁), 7.62 (m, 1H, H₄), 7.67 (s, 1H, H₁₂). El MS m/z: 374 (M, Cl₃⁵, 54), 376 (M+2, Cl₃⁷, 21), 283 (M-C₃H₅, 100). Anal. Calcd for C₂₂H₁₅ClN₂S: C 70.49, H 4.03, N 9.46. Found: C 70.23, H 4.00, N 9.31.

11. 6-Methyl-9-trifluoromethylquinobenzothiazine (10k) (0.14 g, 82%), mp 90-91 °C (EtOH). ¹H NMR (CDCl₃) δ: 3.63 (s, 3H, CH₃), 6.92 (d, 1H, H₇), 7.31 (m, 1H, H₁₀), 7.36 (m, 1H, H₁), 7.42 (m, 1H, H₈), 7.54 (m, 1H, H₃), 7.55 (m, 1H, H₁), 7.69 (s, 1H, H₁₂), 7.77 (m, 1H, H₄). El MS m/z: 332 (M, Cl₃⁵, 39), 326 (M+2, Cl₃⁷, 31), 284 (M-C₃H₅, 44), 283 (M-C₃H₅, 100). Anal. Calcd for C₁₇H₁₁F₃N₂S: C 61.44, H 3.34, N 8.43. Found: C 61.23, H 3.34, N 8.39.

12. 6-Butyl-9-trifluoromethylquinobenzothiazine (10l) (0.16 g, 84%), mp 95-96 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.02 (t, J = 6.8 Hz, 3H, CH₃), 1.53 (m, 2H, CH₂), 1.84 (m, 2H, CH₂), 4.27 (t, J = 7.0 Hz, 2H, NCH₂), 6.95 (d, 1H, H₇), 7.28 (m, 1H, H₂), 7.30 (d, 1H, H₁₀), 7.38 (m, 1H, H₈), 7.51 (m, 1H, H₃), 7.52 (m, 1H, H₁), 7.61 (s, 1H, H₁₂), 7.72 (m, 1H, H₄). El MS m/z: 374 (M, Cl₃⁵, 37, 359 (M-C₃H₃, 13), 331 (M-C₃H₃, 33), 318 (M-C₄H₈, 100). Anal. Calcd for C₂₀H₁₇F₃N₂S: C 64.16, H 4.58, N 7.48. Found: C 64.01, H 4.52, N 7.31.

13. 6-Allyl-9-trifluoromethylquinobenzothiazine (10m) (0.15 g, 83%), mp 62-63 °C (EtOH). ¹H NMR (CDCl₃) δ: 4.92 (d, J = 3.4 Hz, 1H, NCH₂), 5.29 (d, J = 11.5 Hz, 1H, CH=), 5.32 (d, J = 19.0 Hz, 1H, CH=), 6.09 (m, 1H, CH=), 7.01 (d, 1H, H₇), 7.28 (m, 1H, H₂), 7.29 (d, 1H, H₁₀), 7.33 (m, 1H, H₈), 7.51
(m, 2H, H1, H3), 7.63 (s, 1H, H12), 7.71 (m, 1H, H4). EI MS m/z: 358 (M, 42), 343 (M-CH3, 100), 317 (M-C3H5, 46). Anal. Calcd for C19H13F3N2S: C 63.68, H 3.66 , N 7.82. Found: C 63.39, H 3.60 , N 7.59.

14. 6-Benzyl-9-trifluoromethylquinobenzothiazine (10n) (0.16 g, 80%), mp 142-143 °C (EtOH). 1H NMR (CDCl3) δ: 5.58 (s, 2H, CH2), 6.78 (d, 1H, H7), 7.19 (m, 1H, H8), 7.24 (m, 1H, H2), 7.29 (m, 2H, C6H2), 7.33 (d, 1H, H10), 7.36 (m, 3H, C6H3), 7.47 (m, 1H, H3), 7.54 (m, 1H, H1), 7.62 (m, 1H, H4), 7.69 (s, 1H, H12). EI MS m/z: 408 (M, 62), 317 (M-CH2C6H5, 100). Anal. Calcd for C17H11F3N2S: C 61.44, H 3.34 , N 8.43. Found: C 67.64, H 3.70 , N 6.86. Found: C 67.37, H 3.65 , N 6.63.

REFERENCES

#Part CXVII in the series of Azinyl Sulfides.
16. National Cancer Institute Developmental Therapeutics Program, In-Vitro Testing Results, Bethesda, USA.
20. PASS (Prediction of Activity Spectra for Substance) http://ibmc.msk.ru/PASS.