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

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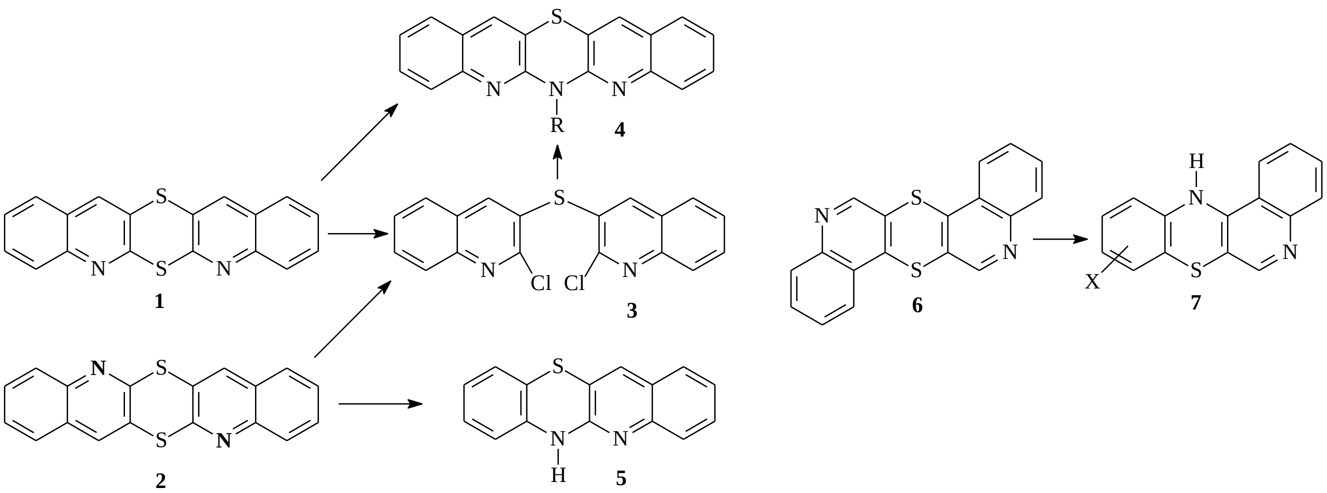
Abstract – Synthesis of new type of tetracyclic azaphenothiazines, 6-, 8-, 9- and 10-substituted quinobenzo-1,4-thiazines (benzo[b]-1-azaphenothiazines) (**5**) and (**10**), has been worked out from diquino-1,4-dithiin (5,12-diaza-6,13-dithiapenta-cene) (**2**) as fusion reactions with aniline hydrochlorides (**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 6*H*-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 (anti-psychotic, 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 papers[12-14] we found isomeric diquino-1,4-dithiins (**1**) and (**2**) (5,7-diaza-6,13-dithiapentacene and 5,12-diaza-6,13-dithia-pentacene)[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 = $CH_2CH_2NHCONHCH_2CH_2Cl$ showed 50% growth inhibition GI_{50} = 0.04 μg/mL against melanoma SK-MEL-5 line).[16] 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 12*H*-quino[3,4-b]benzo[1,4]-thiazines (**7**) (Scheme 1).[17]



Scheme 1

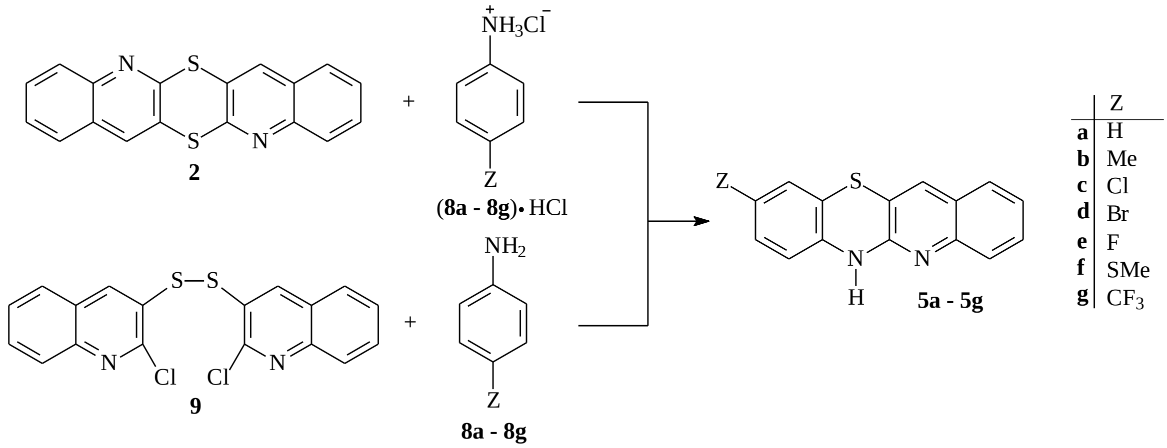
RESULTS AND DISCUSSION

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 6*H*-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 ^{o}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 ^{o}C for 4 h and led to 9-substituted 6*H*-quinobenzothiazines (**5b-5g**) in 28-50% yield (Scheme 2).

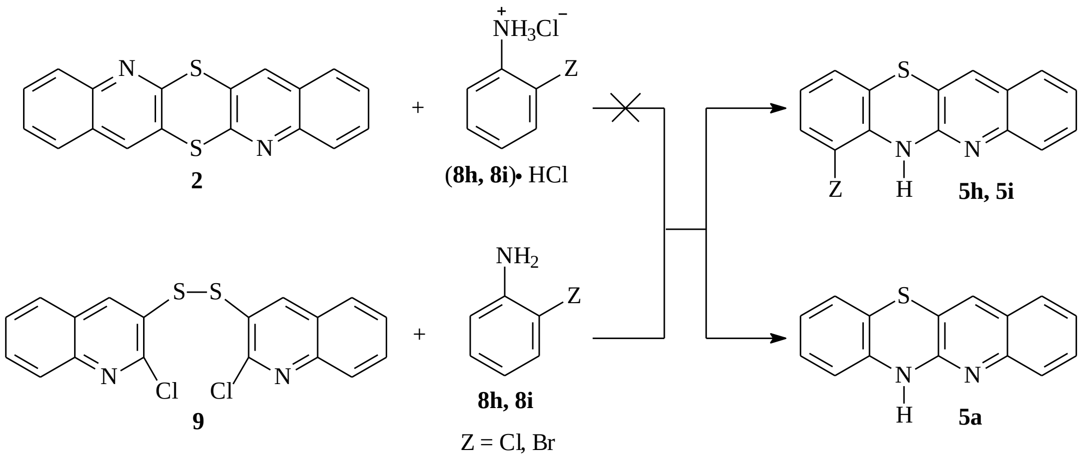
As the yields were unsatisfactory, we used other 2,3-disubstituted quinoline, 2,2'-dichloro-3,3'-diquinolinyl disulfide (**9**), which can be obtained from the reaction of 3,4-dihydro-2(1*H*)-quinolone with thionyl chloride (diquino-1,4-dithiins (**1**) and (**2**) as well as).[12,18] Reaction of disulfide (**9**) with aniline (**8a**) were carried out initially in DMF at 153 ^{o}C, in DMSO at 130 ^{o}C and in refluxing MEDG at 194 ^{o}C (the best solvent in the synthesis of diquinothiazines (**4**) from sulfide (**3**)[13,14]) giving 6*H*-quinobenzothiazine (**5a**) in

36%, 24% and 52% yields, respectively. Further reactions with *p*-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]



Scheme 2

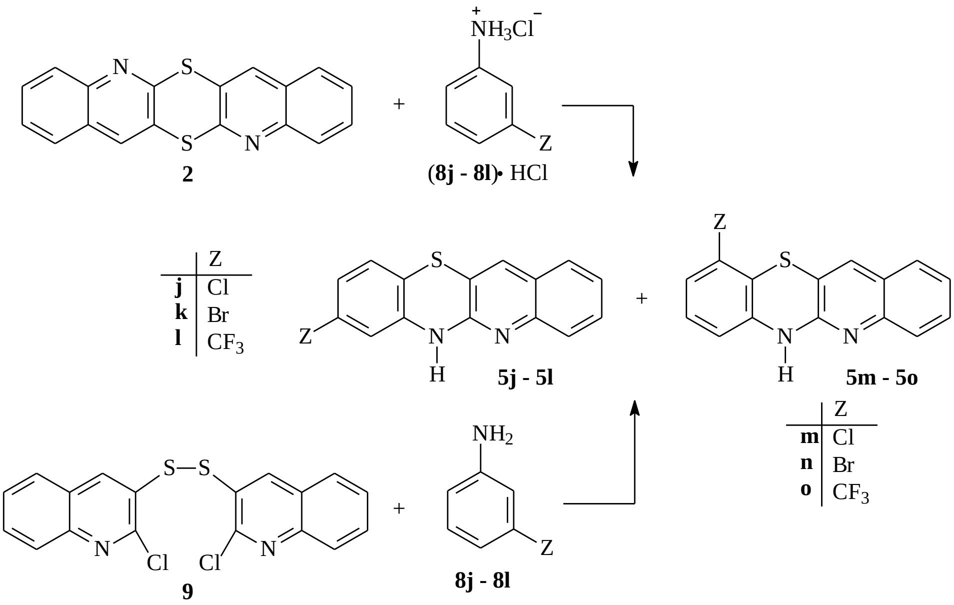
The next step was to perform reactions of dithiin (**2**) with *o*-chloroaniline and *o*-bromoaniline hydrochlorides (**8h, 8i**)·HCl to form 7-chloro- and 7-bromo-6*H*-quinobenzothiazines (**5h, 5i**) but instead of it unexpectedly 6*H*-quinobenzothiazine (**5a**) was formed in 32% yield. The same compound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



Scheme 3

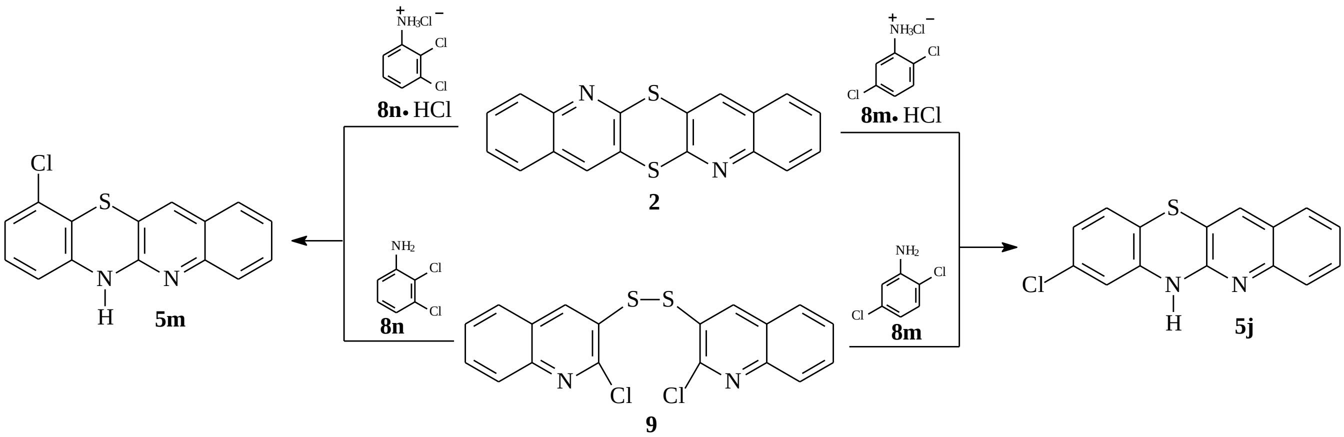
These results showed the chlorine atom to be more susceptible to substitution than the hydrogen atom and the thiazine ring closure proceeded as aromatic nucleophilic substitution mechanism.

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

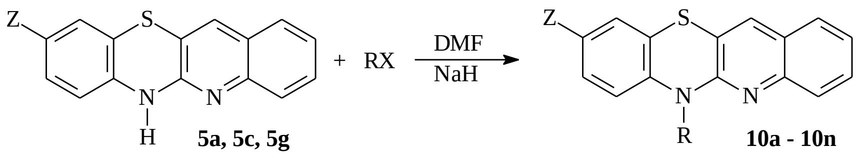
The problem of identification of these pairs of products was solved using ^{1}H NMR spectra and confirmed by independent syntheses exploiting higher reactivity of the chlorine atom than the hydrogen atom in position 2 in substituted anilines. Dithiin (**2**) and disulfide (**9**) reacted with 2,5-dichloroaniline (**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

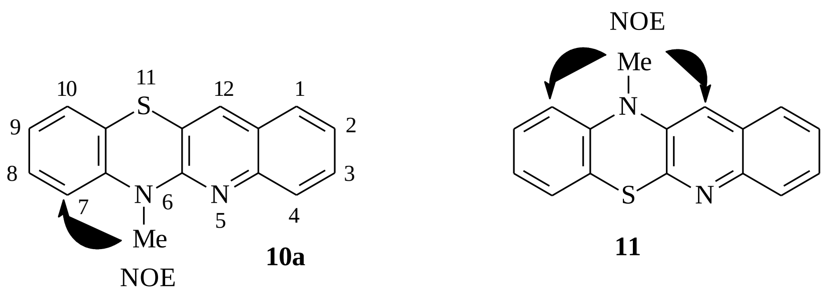
The selected 6*H*-quinobenzothiazines (**5a**), (**5c**) and (**5g**) were transformed into 6-alkyl derivatives (**10a-10n**) in 79-92% yield by *N*-alkylation with alkyl halides in DMF in the presence of sodium hydride (Scheme 6).

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-azapheno-thiazines as the phenothiazine derivatives).



	Z	R		Z	R		Z	R
a	H	Me	**g**	Cl	Me	**k**	CF_3	Me
b	H	Et	**h**	Cl	Bu	**l**	CF_3	Bu
c	H	*i*-Pr	**i**	Cl	$CH_2CH=CH_2$	**m**	CF_3	$CH_2CH=CH_2$
d	H	Bu	**j**	Cl	CH_2Ph	**n**	CF_3	CH_2Ph
e	H	$CH_2CH=CH_2$						
f	H	CH_2Ph						

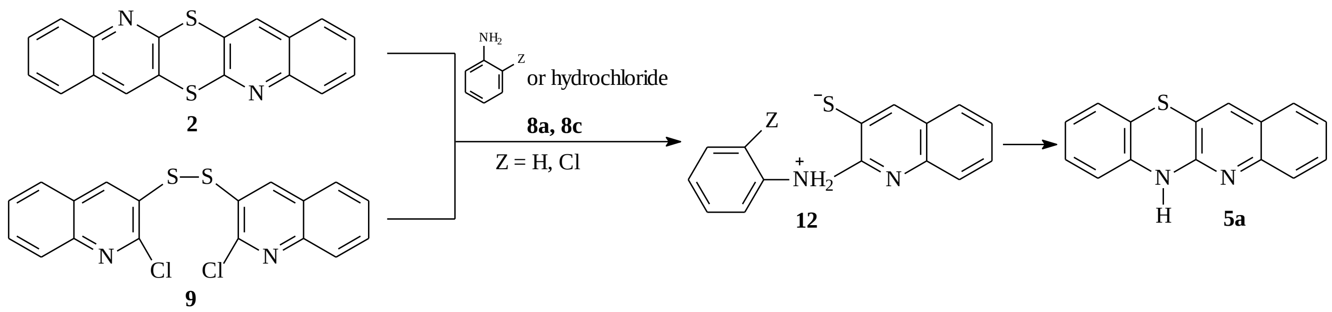
Scheme 6



Scheme 7

The [1]H 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**).[13] 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

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).[19] Quinobenzothiazines (**5**) and (**10**) exhibit promising potential antiinflammatory, antiparkinsonic, antirheumatic, anticancer, antiallergic, antidiabetic and immunosuppressive activities.[20]

CONCLUSION

We report here synthesis of novel tetracyclic 6*H*-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 6*H*-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 F_{254} neutral (type E) (Merck 1.05581) with CH_2Cl_2 and on silica gel 60 F_{254} (Merck 1.05735) with $CHCl_3$-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, $CHCl_3$) to give 6*H*-quinobenzothiazine **5a** (0.06 g, 24%), mp 169-170 °C (EtOH). ^{1}H NMR ($CDCl_3$) 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 $C_{15}H_{10}N_2S$: 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, $CHCl_3$) to give 6*H*-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, $CHCl_3$) to give 6*H*-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, $CHCl_3$) to give quinobenzothiazines (**5a-5o**).

A. with aniline and *p*-substituted aniline hydrochlorides **(8a-8g)**·HCl

1. 6*H*-Quinobenzothiazine (**5a**) (0.013 g, 52%).

2. 6*H*-9-Methylquinobenzothiazine (**5b**) (0.08 g, 30%), mp 197-198 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 2.24 (s, 3H, CH_3), 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 $C_{16}H_{12}N_2S$: C 72.70, H 4.58, N 10.60. Found: C 72.58, H 4.49, N 10.35.

3. 6*H*-9-Chloroquinobenzothiazine **5c** (0.08 g, 28%), mp 224-225 °C (EtOH). ^{1}H NMR ($CDCl_3$) 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^{35}, 100), 286 (M+2, Cl^{37}, 34), 249 (M-Cl, 30). Anal. Calcd for $C_{15}H_9ClN_2S$: C 63.27, H 3.19, N 9.84. Found: C 63.02, H 3.17, N 9.63.

4. 6*H*-9-Bromoquinobenzothiazine **5d** (0.12 g, 36%), mp 212-213 °C (EtOH). ^1H NMR ($CDCl_3$) 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^{79}, 98), 330 (M+2, Br^{81}, 100), 249 (M-Br, 55). Anal. Calcd for $C_{15}H_9BrN_2S$: C 54.73, H 2.76, N 8.51. Found: C 54.42, H 2.72, N 8.29.

5. 6*H*-9-Fluoroquinobenzothiazine **5e** (0.13 g, 49%), mp 158-159 °C (EtOH). ^1H NMR ($CDCl_3$) 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 $C_{15}H_9FN_2S$: C 67.15, H 3.38, N 10.44. Found: C 67.01, H 3.39, N 10.21.

6. 6*H*-9-Methylthioquinobenzothiazine **5f** (0.16 g, 54%), mp 204-205 °C (EtOH). ^1H NMR ($CDCl_3$) δ: 2.43 (s, 3H, CH_3), 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 $C_{16}H_{12}N_2S_2$ C 64.84, H 4.08, N 9.45. Found: C 64.71, H 4.05, N 9.22.

7. 6*H*-9-Trifluoromethylquinobenzothiazine **5g** (0.16 g, 50%), mp 236-237 °C (EtOH). ^1H NMR ($CDCl_3$) 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_3, 3). Anal. Calcd for $C_{16}H_9F_3N_2S$: 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 **(8h, 8i)**·HCl

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

C. with *m*-substituted aniline hydrochlorides **(8j-8l)**·HCl

1a. 6*H*-8-Chloroquinobenzothiazine **5j** (0.06 g, 21%), mp 230-231 °C (EtOH). ^1H NMR ($CDCl_3$) 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^{35}, 100), 286 (M+2, Cl^{37}, 37), 252 (M-S, 20), 249 (M-Cl, 18). Anal. Calcd for $C_{15}H_9ClN_2S$: C 63.27, H 3.19, N 9.84. Found: C 63.09, H 3.15, N 9.56.

1b. 6*H*-10-Chloroquinobenzothiazine **5m** (0.04 g, 14%), mp 242-243 °C (EtOH). ^1H NMR ($CDCl_3$) 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^{35}, 100), 286 (M+2, Cl^{37}, 39), 252 (M-S, 22), 249 (M-Cl, 17). Anal. Calcd for $C_{15}H_9ClN_2S$: C 63.27, H 3.19, N 9.84. Found: C 63.12, H 3.12, N 9.65.

2a. 6*H*-8-Bromoquinobenzothiazine **5k** (0.06 g, 18%), mp 217-218 °C (EtOH). ^1H NMR ($CDCl_3$) 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^{79}, 98), 330 (M+2, Br^{81}, 100), 296 (M-S, 7), 249 (M-Br, 40). Anal. Calcd for $C_{15}H_9BrN_2S$: C 54.73, H 2.76, N 8.51. Found: C 54.48, H 2.69, N 8.32.

2b. 6*H*-10-Bromoquinobenzothiazine **5n (**0.07 g, 21%), mp 231-232 °C (EtOH). ^1H NMR ($CDCl_3$) 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^{79}, 96), 330 (M+2, Br^{81}, 100), 296 (M-S, 7), 249 (M-Br, 37). Anal. Calcd 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. 6*H*-8-Trifluoromethylquinobenzothiazine **5l** (0.09 g, 28%), mp 219-220 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 6.81 (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. Calcd 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. 6*H*-10-Trifluoromethylquinobenzothiazine **5n** (0.07 g, 22%), mp 225-226 °C (EtOH). ^{1}H 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. Calcd 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. 6*H*-8-Chloroquinobenzothiazine **5j** (0.05 g, 18%), mp 230-231 °C (EtOH).

2. 6*H*-10-Chloroquinobenzothiazine **5m** (0.06 g, 21%), mp 242-243 °C (EtOH).

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 6*H*-quinobenzothiazine **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. 6*H*-Quinobenzothiazine **5a** (0.013 g, 52%); 2. 6*H*-9-Methylquinobenzothiazine **5b** (0.16 g, 59%); 3. 6*H*-9-Chloroquinobenzothiazine **5c** (0.19 g, 67%); 4. 6*H*-9-Bromoquinobenzothiazine **5d** (0.19 g, 57%); 5. 6*H*-9-Fluoroquinobenzothiazine **5e** (0.15 g, 56%); 6. 6*H*-9-Methylthioquinobenzothiazine **5f** (0.18 g, 60%); 7. 6*H*-9-Trifluoromethylquinobenzothiazine **5g** (0.18 g, 56%).

B. with *o*-substituted anilines **(8h, 8i)**

1. 6*H*-Quinobenzothiazine **5a** (0.016 g, 64% and 0.14 g, 56%, respectively).

C. with *m*-substituted anilines **(8j-8l)**

1. 6*H*-8-Chloroquinobenzothiazine **5j** (0.09 g, 31%) and 6*H*-10-chloroquinobenzothiazine **5m** (0.08 g, 28%); 2. 6*H*-8-Bromoquinobenzothiazine **5k** (0.12 g, 36%) and 6*H*-10-bromoquinobenzothiazine **5n** (0.11 g, 33%); 3. 6*H*-8-Trifluoromethylquinobenzothiazine **5l** (0.11 g, 34%) and 6*H*-10-trifluoromethyl-quinobenzothiazine **5n** (0.09 g, 28%).

D. with disubstituted anilines **(8m, 8n)**

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

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

To a solution of 6*H*-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, $CHCl_3$) to give 6-substituted quinobenzothiazines (**10a-10n**):

1. 6-Methylquinobenzothiazine (**10a**) (0.12 g, 92%), mp 88-89 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 3.61 (s, 3H, CH_3), 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-CH_3, 13). Anal. Calcd for $C_{16}H_{12}N_2S$: 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. ^{1}H NMR ($CDCl_3$) δ: 1.48 (t, *J* = 6.9 Hz, 3H, CH_3), 4.31 (q, *J* = 6.9 Hz, 2H, CH_2), 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-CH_3, 44), 250 (M-C_2H_4, 72). Anal. Calcd for $C_{17}H_{14}N_2S$: 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. ^{1}H NMR ($CDCl_3$) δ: 1.83 (d, *J* = 6.8 Hz, 6H, 2CH_3), 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-CH_3, 9), 250 (M-C_3H_6, 100). Anal. Calcd for $C_{18}H_{16}N_2S$: 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. ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, *J* = 7.5 Hz, 3H, CH_3), 1.52 (m, 2H, CH_2), 1.86 (m, 2H, CH_2), 4.26 (t, *J* = 7.4 Hz, 2H, NCH_2), 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-C_2H_5, 21), 263 (M-C_3H_7, 52), 250 (M-C_4H_8, 100). Anal. Calcd for $C_{19}H_{18}N_2S$: C 74.47, H 5.92, N 9.14. Found: C 74.19, H 5.88, N 8.89.

5. 6-Allylquinobenzothiazine (**10e**) (0.12 g, 85%), an oil. ^{1}H NMR ($CDCl_3$) δ: 4.91 (d, *J* = 5.4 Hz, 2H, NCH_2), 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-CH_3, 100), 249 (M-C_3H_5, 60). Anal. Calcd for $C_{18}H_{14}N_2S$: 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 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 5.60 (s, 2H, CH_2), 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, C_6H_3), 7.38 (m, 2H, C_6H_2), 7.45 (m, 1H, H3), 7.52 (m, 1H, H1), 7.68 (s, 1H, H12), 7.69 (m, 1H, H4). EI MS m/z: 340 (M, 60), 249 (M-$CH_2C_6H_5$, 100). Anal. Calcd for $C_{22}H_{16}N_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 3.58 (s, 3H, CH_3), 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). EI MS m/z: 298 (M, Cl^{35}, 100), 300 (M+2, Cl^{37}, 35), 283 (M-CH_3, 13). Anal. Calcd for $C_{16}H_{11}ClN_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.00 (t, *J* = 7.3 Hz, 3H, CH_3), 1.53 (m, 2H, CH_2), 1.81 (m, 2H, CH_2), 4.23 (t, *J* = 6.5 Hz, 2H, NCH_2), 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). EI MS m/z: 340 (M, Cl^{35}, 80), 300 (M+2, Cl^{37}, 31), 297 (M-C_3H_7, 44), 284 (M-C_4H_8, 100). Anal. Calcd for $C_{19}H_{17}ClN_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 4.87 (d, *J* = 3.2 Hz, 2H, NCH_2), 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). EI MS m/z: 324 (M, Cl^{35}, 39), 326 (M+2, Cl^{37}, 15), 309 (M-CH_3, 100), 283 (M-C_3H_5, 62). Anal. Calcd for $C_{18}H_{13}ClN_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 5.53 (s, 2H, CH_2), 6.63 (d, 1H, H7), 6.89 (m, 1H, H8), 7.06 (d, 1H, H10), 7.22 (m, 1H, H2), 7.30 (m, 3H, C_6H_3), 7.33 (m, 2H, C_6H_2), 7.46 (m, 1H, H3), 7.52 (m, 1H, H1), 7.62 (m, 1H, H4), 7.67 (s, 1H, H12). EI MS m/z: 374 (M, Cl^{35}, 54), 376 (M+2, Cl^{37}, 21), 283 (M-$CH_2C_6H_5$, 100). Anal. Calcd for $C_{22}H_{15}ClN_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 3.63 (s, 3H, CH_3), 6.92 (d, 1H, H7), 7.31 (m, 1H, H2), 7.36 (d, 1H, H10), 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). EI MS m/z: 332 (M, 100), 317 (M-CH_3, 11). Anal. Calcd for $C_{17}H_{11}F_3N_2S$: C 61.44, H 3.34 , N 8.43. Found: C 61.23, H 3.30 , N 8.21.

12. 6-Butyl-9-trifluoromethylquinobenzothiazine (**10l**) (0.16 g, 84%), mp 95-96 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.02 (t, *J* = 6.8 Hz, 3H, CH_3), 1.53 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 4.27 (t, *J* = 7.0 Hz, 2H, NCH_2), 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). EI MS m/z: 374 (M, 37), 359 (M-CH_3, 13), 331 (M-C_3H_7, 33), 318 (M-C_4H_8, 100). Anal. Calcd for $C_{20}H_{17}F_3N_2S$: 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 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 4.92 (d, *J* = 3.4 Hz, 1H, NCH_2), 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-CH_3, 100), 317 (M-C_3H_5, 46). Anal. Calcd for $C_{19}H_{13}F_3N_2S$: 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 ^{o}C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 5.58 (s, 2H, CH_2), 6.78 (d, 1H, H7), 7.19 (m, 1H, H8), 7.24 (m, 1H, H2), 7.29 (m, 2H, C_6H_2), 7.33 (d, 1H, H10), 7.36 (m, 3H, C_6H_3), 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-$CH_2C_6H_5$, 100). Anal. Calcd for $C_{17}H_{11}F_3N_2S$: C 61.44, H 3.34 , N 8.43. Found $C_{23}H_{15}F_3N_2S$: C 67.64, H 3.70 , N 6.86. Found: C 67.37, H 3.65 , N 6.63.

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