SYNTHESIS OF 6-AMINOALKYLDIQUINO-1,4-THIAZINES AND THEIR ACYL AND SULFONYL DERIVATIVES

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Abstract – Syntheses of various 6-dialkylaminoalkyldiquino-1,4-thiazines (5-8) and 6-aminoalkyldiquino-1,4-thiazines (11-13) were elaborated in the reactions of diquino-1,4-dithiin (2) and 2,2’-dichloro-3,3’-diquinolinyl sulfide (3) with primary amines, and 6H-diquino-1,4-thiazine (4) with dialkylaminoalkyl chlorides and phthalimidoalkyl bromides followed by hydrolysis. 6-Aminoalkyldiquinothiazines (11-13) were transformed into acyl and sulfonyl derivatives (15-26). Some of the obtained compounds showed significant anticancer activity.

INTRODUCTION
Phenothiazines are known for varied chemical properties and very interesting biological activities (anti-psychotic, antihistaminic, antitussive and antiemet). Recent reports have focused interests on anticancer, antiplasmid and antibacterial activities, reversal of multidrug resistance and potential treatment in Alzheimer’s and Creutzfeldt-Jakob diseases. The most significant and perspective 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. In continuation of our search for pharmacoactive pyridine and quinoline derivatives 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 dibenzodiaziphenothiazines. On the other hand, pentacyclic carbocycles and heterocycles (pentacenes and pentaphenes) are considered as a new type of electron donors and show the significant conductive and photoelectric properties and constitute the active layer in a field-effect transistor device.

In our previous papers we found isomeric diquino-1,4-dithiins (1) and (2) (5,12-diaza-6,13-dithiapentacene and 5,7-diaza-6,13-dithiapentacene) to be effective starting materials to synthesis of 2,2’-dichloro-3,3’-diquinolinyl sulfide (3) in two or three steps (in total yield of 69% or 79% from compound...
The annulation reactions of this sulfide with selected divalent reagents gave new heteropentacenes. Reactions of sulfide (3) with acetamide, primary alkyl, aryl and heteroaryl amines led to 6H-diquino-1,4-thiazine (4) and their 6-alkyl-, aryl- and heteroaryl derivatives (Scheme 1).

As the most bioactive phenothiazines possess the aminoalkyl substituent attaching to the thiazine nitrogen atom, it prompted us to elaborate a synthesis of diquinothiazines with various aminoalkyl groups. In this paper, we describe the synthesis of anticancer 6-dialkylaminoalkydiquinothiazines, 6-aminoalkydiquinothiazines and their selected acyl and sulfonyl derivatives.

RESULTS AND DISCUSSION

Synthesis

6-Alkyl- and aryldiquinothiazines were obtained via annulation reactions of sulfide (3) with amines or via N-alkylation and N-arylation of 6H-diquinothiazine (4). Herein we would like to discuss the synthesis of 6H-diquinothiazine (4) and various 6-aminoalkydiquinothiazines directly from diquino-1,4-dithiin (2) via the 1,4-dithiin ring opening and the 1,4-thiazine ring closure reactions. Diquino-1,4-dithiin (2) reacted with boiling acetamide (221 °C) in the presence of potassium carbonate giving 6H-diquinothiazine (4) in 60% yield (Scheme 2). An evolution of hydrogen sulfide was observed.

Since classical neuroleptic and antihistaminic phenothiazines contain the dialkylaminopropyl and dialkylaminoethyl chain, we transformed 6H-diquinothiazine (4) into selected 6-dialkylaminoalkydiquinothiazines (5-8) in 54-63% yield in the reactions with the appropriate pharmacoactive hydrochlorides of dialkylaminoalkyl chlorides [2-diethylaminoethyl, 3-dimethylaminopropyl, 3-dimethylamino-2-methylpropyl, and 2-1’-methyl-2’-piperidinyl)ethyl] in refluxing dioxane in the presence of sodium hydroxide (Scheme 2). We also checked the annulation reactions of sulfide (3) with selected dialkylaminoalkylamines [2-(diethylamino)ethylamine and 3-(dimethylamino)propylamine] in boiling monomethyl ether of diethylene glycol (MEDG, 197 °C) to give 6-dialkylaminoalkydiquinothiazines (5) and (6) in 52% yield. Motohashi and co-workers described synthesis of 10-phthalimidoalkylphenothiazines (alkyl = propyl and...
butyl) from 10H-phenothiazine and their hydrolysis to 10-aminoalkylphenothiazines. The last compounds were transformed into selected acyl and sulfonyl derivatives. Most of them exhibited very promising anticancer and antimicrobial activity.\textsuperscript{2-6} Analogous reactions of 6H-diquinothiazine (4) with the same phthalimidoalkyl bromides in toluene in the presence of sodium hydride gave 6-phthalimidoalkyldiquinothiazines (9) and (10) in 72% and 82% yield. Hydrolysis of compounds (9) and (10) using hydrazine led to 6-aminoalkyl(diquinothiazines (12) and (13) in 89% and 70% yield (Scheme 2). Total yield of this two-step synthesis of 6-aminoalkyl(diquinothiazines (12) and (13) is 64% and 57%, respectively.

Next step was a trial of the synthesis of 6-aminoalkyl(diquinothiazines (11-13) (alkyl = ethyl, propyl and butyl) in one step in the reaction of diquino-1,4-dithiin (2) with primary amine. Although a model reaction with selected amine, boiling aniline, was unsuccessful, the fusion reaction with its hydrochloride at 210 °C (without a solvent) gave 6-phenyl(diquinothiazine (14) in 84% yield. Analogous fusion reaction with dihydrochloride of 1,2-diaminoethane was failed. Only reaction with a mixture of 1,2-diaminoethane and its dihydrochloride (1:1) in boiling MEDG led to 6-aminoethyl(diquinothiazine (11) in 70% yield. Repeating reactions with the mixtures of other diaminoalkanes and their dihydrochlorides (1,3-diaminopropane and 1,4-diaminobutane) gave 6-aminopropyl- and 6-aminobutyldiquinothiazines (12) and (13) in 44% and 54% yields.

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
\text{Structure} & \text{-CH}_2\text{NH}_2 & \% \\
\hline
5 & \text{-CH}_2\text{NEt}_2 & 60 \\
6 & \text{-CH}_2\text{CH}_2\text{NH}_2 & 63 \\
7 & \text{-CH}_2\text{CH}_2\text{NMe}_2 & 62 \\
8 & \text{-CH}_2\text{CH}(\text{Me})\text{CH}_2\text{NMe}_2 & 54 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
\text{Structure} & \text{NH}_2\text{NH}_2 & n & \% \\
\hline
9 & \text{H}_2\text{N(CH}_2\text{)}_3\text{NH}_2 & 3 & 72 \\
10 & \text{H}_2\text{N(CH}_2\text{)}_4\text{NH}_2 & 4 & 82 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
\text{Structure} & \text{NH}_2\text{NH}_2 & n & \% \\
\hline
11 & \text{H}_2\text{N(CH}_2\text{)}_2\text{NH}_2 & 2 & 76 \\
12 & \text{H}_2\text{N(CH}_2\text{)}_3\text{NH}_2 & 3 & 75 \\
13 & \text{H}_2\text{N(CH}_2\text{)}_4\text{NH}_2 & 4 & 73 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{|c|c|}
\hline
\text{Structure} & \text{-CH}_2\text{NR}_2 \\
\hline
5 & \text{-CH}_2\text{CH}_2\text{NEt}_2 & 52 \\
6 & \text{-CH}_2\text{CH}_2\text{NMe}_2 & 52 \\
\hline
\end{tabular}
\end{center}

\begin{center}
\text{Scheme 2}
\end{center}
We also checked the annulation route using sulfide (3) and diaminoalkanes. Reactions with 1,2-diaminoethane, 1,3-diaminopropane and 1,4-diaminobutane in boiling MEDG gave 6-aminoalkyldiquinothiazines (11-13) in 73-76% yield (Scheme 2). Although this process is more efficient, total efficiency of the synthesis is lesser since sulfide (3) is obtained from diquino-1,4-dithiin (2) in two or three steps.

The obtained 6-aminoalkyldiquinothiazines (11-13) were transformed into amide and sulfonamide derivatives. The acetylation with acetyl anhydride gave 6-acetylaminoalkyldiquinothiazines (15-17) in 78-90% yield. Reactions with ethyl chloroformate led to 6-ethoxycarbonylalkyldiquinothiazines (18-20) in 74-83% yield. Reactions with 2-chloroethyl isocyanate led to the urea derivatives possessing half-mustard unit - 6-chloroethylureidoalkyldiquinothiazines (21-23) in 69-75% yield. The sulfonamide derivatives were obtained in the reactions with p-toluenesulfonyl chloride giving 6-p-toluenesulfonylaminoalkyldiquinothiazines (24-26) in 68-85% yield (Scheme 3).

Properties of 6-aminoalkyldiquinothiazines (5-26)
Syntheses of 6-aminoalkyldiquinothiazines were followed by TLC analysis as the chromatograms of the products, unlike to the chromatograms of substrates (2) and (3), showed colour changing during irradiation with UV lamp from blue to yellow. Similar yellow colour was observed when the diquinothiazine chromatograms were sprayed with a mixture detecting the phenothiazine system (sulfuric acid-water-ethanol 1:1:8). The 1H NMR spectra of compound (5-26) showed the spectral equivalency of the left and right parts of diquinothiazine system (the C2v symmetry) which is evidence that the 1,4-thiazine ring formation proceeded without the Smiles rearrangement of the S→S and S→N types. The diquinothiazine ring protons showed one singlet and four multiplets: two doublet-shaped with one ortho-coupling and triplet-shaped

![Scheme 3](image-url)
with two ortho-couplings. These protons were assigned according to the methyl and phenyl (14) derivatives determined previously using the $^1$H-$^1$H correlations and NOE experiments.\textsuperscript{11} The structure of the pentacyclic ring system as 5,6,7-triaza-13-thiapentacene was confirmed by X-ray analysis of the phenyl (14) and $p$-nitrophenyl derivatives. The pentacene system and the thiazine ring turned out to be planar or non-planar depending on the nature of the substituent at the position 6.\textsuperscript{12,23} Since EI MS spectra of 6-aminoalkyldiquinothiazines (5-26) showed labile aminoalkyl chains, FAB MS spectra were used to determine the molecular ions. The diquinothiazine system turned out to be more lipophilic than classical phenothiazine one.\textsuperscript{24}

All 6-aminoalkyldiquinothiazines and their amide and sulfonamide derivatives (5-26) show promising potential antipsychotic, antidepressant, antihistaminic, antiasthmatic, anticancer and sedative activity\textsuperscript{25} and some selected compounds (5, 6, 15, 16, 19, 21, 24 and 25) 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.\textsuperscript{26}

Conclusion

We report here synthesis of novel 6-dialkylaminoalkyldiquinothiazines, 6-aminoalkyldiquinothiazines and their amide and sulfonamide derivatives (5-26) via the annulation reactions of diquinolinyl sulfide (3), the dithiin ring opening - thiazine ring closure reactions of diquinodithiin (2) and $N$-dialkylaminoalkylation reactions of $6H$-diquinothiazine (4). Some compounds show significant anticancer activities.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and are uncorrected. The $^1$H NMR spectra were recorded on a Varian Unity-Inova-300 spectrometer at 300 MHz in deuteriochloroform with tetramethylsilane as the internal standard. Electron impact (EI MS) and Fast Atom Bombardment [FAB MS, in the $m$-nitrobenzyl alcohol (nba) and glycerol (gly) matrixes] mass spectra were run on a Finnigan MAT 95 spectrometer at 70 eV. The thin layer chromatography were performed on aluminum oxide 60 F254 neutral (type E) (Merck 1.05581) with CH2Cl2 on silica gel 60 F254 (Merck 1.05735) with CHCl3-EtOH (10:1 v/v) and as eluents.

Diquino-1,4-dithiins (1) and (2) were obtained from the reaction of 2-chloro-3-bromoquinoline with sodium sulfide according to described procedure.\textsuperscript{21} Diquino-1,4-dithiin (2) was also obtained from diquino-1,4-dithiin (1) through the Smiles rearrangement.\textsuperscript{21} 2,2’-Dichloro-3,3’-diquinolinyl sulfide (3) was obtained in the reaction of 2,2’-dimethyl-3,3’-diquinolinyl sulfide with phosphoryl chloride.\textsuperscript{12}
Synthesis of 6H-diquinothiazine (4)

A mixture of diquinodithiin (2) (0.32 g, 1 mmole) and K₂CO₃ (0.54 g, 4 mmol) was added portionally to a boiling acetamide (7.40 g, 125 mmol). Reaction was carried out for 2 h adding portionally from time to time another amount of K₂CO₃ (1.12 g, 8 mmol). After cooling water (20 mL) was added to the reaction mixture and the resulting solid was filtered off, washed with water, air-dried and crystallized from DMF to give 6H-diquinothiazine (4) (0.32 g, 60% yield); mp > 300 oC (DMF), lit., mp > 300 oC.

Synthesis of 6-dialkylaminoalkyldiquinothiazines (5-8)

A. from 6H-diquinothiazine (4)

A mixture of 6H-diquinothiazine (4) (0.30 g, 1 mmol), sodium hydroxide (0.60 g, 15 mmol) and hydrochloride of dialkylaminoalkyl chloride (3 mmol, 2-diethylaminoethyl – 0.52 g, 3-dimethylaminopropyl – 0.47 g, 3-dimethylamino-2-methylpropyl – 0.52 g, 2-(1’-methyl-2’-piperidinyl)ethyl – 0.59 g) in dry dioxane (5 mL) was refluxed for 3 h. After cooling the reaction mixture was poured into water (50 mL) and the resulted solid was filtered off washed with water, air-dried and purified by column chromatography (silica gel, CHCl₃-EtOH 10:1) to give:

1. 6-(2’-Diethylaminoethyl)diquinothiazine (5) (0.24 g, 60%); mp 144-145 oC (EtOH). ¹H NMR (CDCl₃) δ: 1.76 (t, J = 7.2 Hz, 6H, 2CH₃), 3.42 (q, J = 7.2 Hz, 4H, 2CH₂), 3.74 (t, J = 7.6 Hz, 2H, CH₂), 4.99 (t, J = 7.6 Hz, 2H, NCH₂), 7.36 (m, 2H, H-2, H-10), 7.56 (m, 2H, H-3, H-9), 7.57 (m, 2H, H-1, H-11), 7.74 (m, 2H, H-4, H-8), 7.75 (s, 2H, H-12, H-14). FAB MS m/z: 401 (M+1, 100), 328 (M-N(C₂H₅)₂, 52), 301 (M+1-CH₂CH₂N(C₂H₅)₂, 2). Anal. Calcd for C₂₄H₂₄N₄S: C 71.97, H 6.04, N 13.99. Found C 71.68, H 6.01, N 13.62.

2. 6-(3’-Dimethylaminopropyl)diquinothiazine (6) (0.24 g, 63%); mp 110-111 oC (EtOH). ¹H NMR (CDCl₃) δ: 2.40 (m, J = 6.9 Hz, 2H, CH₂), 2.65 (s, 6H, 2CH₃), 3.02 (t, J = 6.9 Hz, 2H, CH₂), 4.72 (t, J = 6.9 Hz, 2H, NCH₂), 7.31 (m, 2H, H-2, H-10), 7.53 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 387 (M+1, 100), 342 (M+1-(CH₃)₂NH, 68), 301 (M+1-C₅H₆N(CH₃)₂, 20). Anal. Calcd for C₂₃H₂₂N₄S: C 71.47, H 5.74, N 14.50. Found C 71.28, H 5.68, N 14.21.

3. 6-(3’-Dimethylamino-2’-methylpropyl)diquinothiazine (7) (0.25 g, 62%); mp 136-137 oC (EtOH). ¹H NMR (CDCl₃) δ: 1.00 (d, J = 6.8 Hz, 3H, CCH₃), 2.31 (s, 6H, 2CH₃), 2.27-2.45 (m, 2H, CCH₂), 2.52 (m, 1H, CH), 4.76 (m, 1H, NCH), 4.90 (m, 1H, NCH), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 2H, H-3, H-9), 7.53 (m, 2H, H-1, H-11), 7.69 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 401 (M+1, 100), 356 (M-N(CH₃)₂, 53), 301 (M+1-C₄H₆N(CH₃)₂, 38). Anal. Calcd for C₂₄H₂₄N₄S: C 71.97, H 6.04, N 13.99. Found C 71.62, H 6.09, N 13.69.

4. 6-(1’-Methyl-2’-piperidinylethyl)diquinothiazine (8) (0.23 g, 54%); mp 160-161 oC (EtOH). ¹H NMR (CDCl₃) δ: 1.20-2.24 (m, 10H, 5CH₂), 2.64 (s, 3H, CH₃), 2.99 (m, 1H, CH), 4.67 (m, 2H, NCH₂), 7.28 (m,
2H, H-2, H-10), 7.50 (m, 4H, H-1, H-3, H-9, H-11), 7.63 (s, 2H, H-12, H-14), 7.71 (m, 2H, H-4, H-8).

FAB MS m/z: 427 (M+1, 56), 301 (M-C7H11NCH3, 44), 154 (nba, 100). Anal. Calcd for C26H26N4S: C 73.21, H 6.14, N 13.13. Found C 72.82, H 6.16, N 12.78.

B. from 2,2'-dichloro-3,3'-diquinolinyl sulfide (3)

A mixture of sulfide (3) (0.36 g, 1 mmol) and dialkylminoalkylamine [5 mmol, 2-(diethylamino)ethylamine – 0.70 mL, 3-(dimethylamino)propylamine – 0.64 mL] in MEDG (5 mL) was refluxed for 4 h. After cooling the reaction mixture was poured into water (50 mL) and the resulted solid was filtered off washed with water, air-dried and purified by column chromatography (silica gel, CHCl3-EtOH 10:1) to give:

1. 6-(2'-Diethylaminoethyl)diquinothiazine (5) (0.21 g, 52%); mp 144-145 °C.
2. 6-(3'-Dimethylaminopropyl)diquinothiazine (6) (0.20 g, 52%); mp 110-111 °C.

Synthesis of 6-aminoalkyldiquinothiazines (11-13)

A. from 6-phthalimidoalkyldiquinothiazines (9-10)

To a stirred solution of 6H-diquinothiazine (4) (0.30 g, 1 mmol) in dry toluene (10 mL) NaH (0.24 g, 10 mmol, washed out with hexane) was added. The mixture was stirred for 15 min at rt, then refluxed for 15 min and a solution of N-(bromoalkyl)phthalimide [2 mmol, N-(3-bromopropyl)phthalimide – 0.54 g, N-(4-bromobutyl)phthalimide – 0.56 g] in toluene (5 mL) was added. The mixture was refluxed for 24 h. Next toluene was evaporated in vacuo and the residue was extracted with CHCl3 (2 x 5 mL). The extract was concentrated and purified by column chromatography (silica gel, CHCl3) to give:

1. 6-(3'-Phthalimidopropyl)diquinothiazines (9) (0.35 g, 72%); mp 210-211 °C (EtOH). \(^1\)H NMR (CDCl3) \(\delta\): 2.43 (m, 2H, CH2), 3.98 (t, \(J = 6.9\) Hz, 2H, NCH2), 4.83 (t, \(J = 6.9\) Hz, 2H, NCH2), 7.30 (m, 2H, H-2, H-10), 7.47 (m, 2H, H-3, H-9), 7.53 (m, 2H, H-1, H-11), 7.68 (s, 2H, H-12, H-14), 7.69 (m, 4H, H-4, H-8, 2Hphthalimide), 7.78 (m, 2Hphthalimide). FAB MS m/z: 489 (M+1, 29), 488 (M\(^+\), 11), 301 (M+1-C11H10O2N, 7), 154 (nba, 100). Anal. Calcd for C29H20N4O2S: C 71.29, H 4.13, N 11.47. Found C 70.94, H 4.12, N 11.09.
2. 6-(4'-Phthalimidobutyl)diquinothiazines (10) (0.41 g, 82%); mp 215-216 °C (EtOH). \(^1\)H NMR (CDCl3) \(\delta\): 1.98 (m, 4H, 2CH2), 3.86 (t, \(J = 7.3\) Hz, 2H, NCH2), 4.71 (t, \(J = 7.3\) Hz, 2H, NCH2), 7.27 (m, 2H, H-2, H-10), 7.49 (m, 2H, H-3, H-9), 7.51 (m, 2H, H-1, H-11), 7.65 (s, 2H, H-12, H-14), 7.69 (m, 4H, H-4, H-8, 2Hphthalimide), 7.83 (m, 2Hphthalimide). FAB MS m/z: 503 (M+1, 8), 461 (M+1-C6H8, 32), 301 (M+1-C12H12O2N, 2), 185 (gly, 100). Anal. Calcd for C30H22N4O2S: C 71.69, H 4.41, N 11.15. Found C 71.44, H 4.24, N 10.91.

Hydrolysis of 6-phthalimidoalkyldiquinothiazines (9) and (10)

To a solution of 6-phthalimidoalkyldiquinothiazines (9) and (10) (0.5 mmol) in EtOH (25 mL) 40% aqueous solution of hydrazine (0.67 mL, 6 mmol) was added. The mixture was stirred at rt for 24 h. EtOH was evaporated in vacuo and the residue was extracted with CHCl3 (5 mL). The extract was washed with
10% ammonium hydroxide and water, and dried over Na₂SO₄. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, CHCl₃-EtOH 10:1) to give:

1. 6-(3'-Aminopropyl)diquinothiazine (12) (0.16 g, 89% yield); mp 152-153 °C (EtOH). ¹H NMR (CDCl₃) δ: 2.12 (m, 2H, CH₂), 2.82 (t, J = 6.6 Hz, 2H, NCH₂), 4.79 (t, J = 6.6 Hz, 2H, NCH₂), 7.29 (m, 2H, H-2, H-10), 7.56 (m, 4H, H-1, H-3, H-9, H-11), 7.65 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 359 (M+1, 14), 342 (M+1-NH₃, 11), 301 (M+1-C₃H₆NH₂, 6), 154 (nba, 100). Anal. Calcd for C₂₁H₁₈N₄S: C 70.37, H 5.06, N 15.63. Found C 70.09, H 4.98, N 15.27.

2. 6-(4'-Aminobutyl)diquinothiazine (13) (0.13 g, 70% yield); mp 184-185 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.71 (m, 2H, CH₂), 1.96 (m, 2H, CH₂), 2.89 (t, J = 7.0 Hz, 2H, NCH₂), 4.66 (t, J = 7.6 Hz, 2H, NCH₂), 7.29 (m, 2H, H-2, H-10), 7.51 (m, 4H, H-1, H-3, H-9, H-11), 7.65 (s, 2H, H-12, H-14), 7.66 (m, 2H, H-4, H-8). FAB MS m/z: 373 (M+1, 72), 356 ((M+1-NH₃, 12), 301 (M+1-C₄H₈NH₂, 100). Anal. Calcd for C₂₂H₂₀N₄S: C 70.94, H 5.41, N 15.04. Found C 70.70, H 5.49, N 14.79.

B. from 2,2'-dichloro-3,3'-diquinolinyl sulfide (3)

A mixture of sulfide (3) (0.36 g, 1 mmol) and diaminoalkane (5 mmol, 1,2-diaminoethane – 0.33 mL, 1,3-diaminopropane – 0.42 mL, 1,4-diaminobutane – 0.50 mL) in boiling MEDG (5 mL) was refluxed for 5 h. After cooling water (50 mL) was added and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel, CHCl₃-EtOH 10:1) to give:

1. 6-Aminoethyldiquinothiazine (11) (0.26 g, 76% yield); mp 134-135 °C.
2. 6-Aminopropyldiquinothiazine (12) (0.27 g, 75% yield); mp 152-153 °C.
3. 6-Aminobutyldiquinothiazine (13) (0.27 g, 73% yield); mp 184-185 °C.

C. from diquinodithiin (2)

A mixture of diquinodithiin (2) (0.32 g, 1 mmol), diaminoalkane (2 mmol, 1,2-diaminoethane – 0.13 mL, 1,3-diaminopropane – 0.16 mL, 1,4-diaminobutane – 0.20 mL) and diaminoalkane dihydrochlorides (2 mmol, 1,2-diaminoethane dihydrochloride – 0.26 g, 1,3-diaminopropane dihydrochloride – 0.29 g, 1,4-diaminobutane dihydrochloride – 0.32 g) in MEDG (5 mL) was refluxed for 5 h. After cooling water (50 mL) was added and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (SiO₂, CHCl₃-EtOH 10:1) to give:

1. 6-Aminoethyldiquinothiazine (11) (0.24 g, 70% yield); mp 134-135 °C. ¹H NMR (CDCl₃) δ: 3.31 (t, J = 6.3 Hz, 2H, NCH₂), 4.76 (t, J = 6.3 Hz, 2H, NCH₂), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 2H, H-3, H-9), 7.55 (m, 2H, H-1, H-11), 7.68 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 345 (M+1, 7), 328 (M+1-NH₃, 11), 301 (M+1-C₃H₆NH₂, 4), 154 (nba, 100). Anal. Calcd for C₂₀H₁₆N₄S: C 69.74, H 4.68, N 16.27. Found C 69.48, H 4.72, N 15.93.

2. 6-Aminopropyldiquinothiazine (12) (0.16 g, 44% yield); mp 152-153 °C.
3. 6-Aminobutyldiquinothiazine (13) (0.20 g, 54% yield); mp 184-185 °C.
Synthesis of 6-phenyldiquinothiazine (14)
Diquinodithiin (2) (0.32 g, 1 mmole) was mixed with aniline hydrochloride (0.26 g, 2 mmol) and the mixture was heated at 210 °C for 3 h. After cooling water (10 mL) was added to the reaction mixture and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (Al₂O₃, CH₂Cl₂) to give: 6-phenyldiquinothiazine (14) (0.32 g, 84% yield); mp 262-263 °C (EtOH), lit., mp 262-263 °C.

Synthesis of 6-aminoalkyldiquinothiazines (15-17)
To a suspension of aminoalkyldiquinothiazines (11-13) (0.5 mmol) in pyridine (3 mL) acetic anhydride (3 mL, 32 mmol) was added and the mixture was stirred at rt for 24 h. The reaction mixture was poured into water (10 mL) and the resulting solid was filtered off, washed with water, air-dried and purified by column chromatography (silica gel, CHCl₃) to give:
1. 6-(2'-Acetylaminoethyl)diquinothiazine (15) (0.16 g, 84% yield); mp 246-247 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.39 (s, 3H, CH₃), 3.98 (m, 2H, NCH₂), 4.81 (t, J = 6.3 Hz, 2H, NCH₂), 7.34 (m, 2H, H-2, H-10), 7.59 (m, 4H, H-1, H-3, H-9, H-11), 7.71 (s, 2H, H-12, H-14), 7.75 (m, 2H, H-4, H-8). FAB MS m/z: 387 (M+1, 100), 328 (M+1-CH₃CONH₂, 46), 301 (M+1-C₄H₄NHCOCH₃, 11). Anal. Calcd for C₂₂H₁₈N₄OS: C 68.37, H 4.69, N 14.50. Found C 68.22, H 4.60 N 14.23.
2. 6-(3'-Acetylaminopropyl)diquinothiazine (16) (0.18 g, 90% yield); mp 285-286 °C (EtOH). ¹H NMR (CDCl₃) δ: 2.08 (s, 3H, CH₃), 2.18 (m, 2H, CH₂), 3.43 (m, 2H, NCH₂), 4.80 (t, J = 6.6 Hz, 2H, NCH₂), 7.32 (m, 2H, H-2, H-10), 7.54 (m, 4H, H-1, H-3, H-9, H-11), 7.68 (s, 2H, H-12, H-14), 7.74 (m, 2H, H-4, H-8). FAB MS m/z: 401 (M+1, 78), 369 (M+1-CH₃OH, 26), 301 (M+1-C₄H₈NHCOOC₂H₅, 2), 154 (nba, 100). Anal Calcd. for C₂₃H₂₀N₄OS: C 68.98, H 5.03, N 13.99. Found C 68.79, H 5.09, N 13.75.
3. 6-(4'-Acetylaminobutyl)diquinothiazine (17) (0.16 g, 78% yield); mp 210-211 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.77 (m, 2H, CH₂), 1.95 (s, 3H, CH₃), 2.00 (m, 2H, CH₂), 3.50 (m, 2H, NCH₂), 4.68 (t, J = 7.2 Hz, 2H, NCH₂), 7.31 (m, 2H, H-2, H-10), 7.53 (m, 4H, H-1, H-3, H-9, H-11), 7.68 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 415 (M+1, 100), 356 (M+1-CH₃CONH₂, 17), 301 (M+1-C₄H₈NHCOCH₃, 36). Anal. Calcd for C₂₄H₂₂N₄OS: C 69.54, H 5.35, N 13.52. Found C 69.29, H 5.37, N 13.37.

Synthesis of 6-(ethoxycarbonylaminoalkyldiquinothiazines (18-20)
To a stirred solution of aminoalkyldiquinothiazines (11-13) (0.5 mmol) in a mixture of CH₂Cl₂ (3 mL) and 10% Na₂CO₃ solution (3 mL), a solution of ethyl chloroformate (0.64 mL, 0.67 mmol) in CH₂Cl₂ (3 mL) was added. The mixture was stirred at rt for 24 h. The organic phase was separated and aqueous phase was extracted with CH₂Cl₂ (2 x 3 mL). The combined extracts were washed with water (2 x 5 mL)
and dried over Na₂SO₄. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, CHCl₃) to give:

1. 6-(2’-Ethoxycarbonylethyl)diquinothiazine (18) (0.17 g, 83% yield); mp 200-201 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.93 (t, J = 6.8 Hz, 3H, CH₃), 3.88 (m, 2H, NCH₂), 4.09 (q, J = 6.8 Hz, 2H, CH₂), 4.78 (t, J = 6.3 Hz, 2H, CH₂), 7.32 (m, 2H, H-2, H-10), 7.54 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 7.80 (m, 2H, H-4, H-8). FAB MS m/z: 417 (M+1, 100), 328 (M+1-NH₂COOC₂H₅, 90), 301 (M+1-C₂H₄NHCOC₂H₅, 63). Anal. Calcd for C₂₃H₂₀N₄O₂S: C 66.33, H 4.84, N 13.45. Found C 66.21, H 4.85, N 13.30.

2. 6-(3’-Ethoxycarbonylpropyl)diquinothiazine (19) (0.18 g, 83% yield); mp 183-184 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.33 (t, J = 6.8 Hz, 3H, CH₃), 2.21 (m, 2H, CH₂), 3.36 (m, 2H, NCH₂), 4.20 (q, J = 7.2 Hz, 2H, CH₂), 4.71 (t, J = 6.8 Hz, 2H, NCH₂), 7.31 (m, 2H, H-2, H-10), 7.52 (m, 4H, H-1, H-3, H-9, H-11), 7.67 (s, 2H, H-12, H-14), 7.86 (m, 2H, H-4, H-8). FAB MS m/z: 431 (M+1, 80), 369 (M+1-C₂H₅OOH, 16), 301 (M+1-C₃H₆NHCOOC₂H₅, 10), 154 (nba, 100). Anal. Calcd for C₂₄H₂₂N₄O₂S: C 66.96, H 5.15, N 13.01. Found C 66.77, H 5.11, N 12.91.

3. 6-(4’-Ethoxycarbonylbutyl)diquinothiazine (20) (0.17 g, 74% yield); mp 187-188 °C (EtOH). ¹H NMR (CDCl₃) δ: 1.24 (t, J = 6.6 Hz, 3H, CH₃), 1.76 (m, 2H, CH₂), 2.00 (m, 2H, CH₂), 3.41 (m, 2H, NCH₂), 4.12 (q, J = 6.6 Hz, 2H, CH₂), 4.66 (t, J = 7.6 Hz, 2H, NCH₂), 7.30 (m, 2H, H-2, H-10), 7.51 (m, 4H, H-1, H-3, H-9, H-11), 7.67 (s, 2H, H-12, H-14), 7.79 (m, 2H, H-4, H-8). FAB MS m/z: 445 (M+1, 52), 416 (M+1-C₂H₅, 100), 301 (M+1-C₄H₈NHCOOC₂H₅, 2). Anal. Calcd for C₂₅H₂₄N₄O₂S: C 67.55, H 5.44, N 12.60. Found C 67.41, H 5.49, N 12.49.

Synthesis of 6-(chloroethylureidoalkyl)diquinothiazines (21-23)

To a stirred solution of 6-aminoalkyldiquinothiazines (11-13) (0.5 mmol) in ethanol (25 mL) at 0 °C 2-chloroethyl isocyanate (0.08 mL, 1 mmol) was added. The mixture was stirred at 0 °C for 1h and at rt for 24 h. After evaporation of EtOH in vacuo the residue was purified by column chromatography (silica gel, CHCl₃) to give:

1. 6-(2’-Chloroethylureidoethyl)diquinothiazine (21) (0.16 g, 72% yield); mp 204-205 °C (EtOH). ¹H NMR (CDCl₃) δ: 3.64 (m, 4H, 2CH₂), 3.85 (m, 2H, CH₂), 4.77 (t, J = 6.3 Hz, 2H, NCH₂), 7.34 (m, 2H, H-2, H-10), 7.56 (m, 4H, H-1, H-3, H-9, H-11), 7.70 (s, 2H, H-12, H-14), 7.76 (m, 2H, H-4, H-8). FAB MS m/z: 452 (M+3, 33), 451 (M+2, 25), 450 (M+1, 100), 387 (M-CH₂CH₂Cl, 11), 301 (M+1-C₂H₂NHCONHCH₂Cl, 35). Anal. Calcd for C₂₃H₂₀ClN₅OS: C 61.40, H 4.48, N 15.56. Found C 61.29, H 4.53, N 15.39.

2. 6-(3’-Chloroethylureidopropyl)diquinothiazine (22) (0.16 g, 69% yield); mp 217-218 °C (EtOH). ¹H NMR (CDCl₃) δ: 2.26 (m, 2H, CH₂), 3.59 (m, 6H, 3CH₂), 5.20 (m, 2H, CH₂), 7.53 (m, 2H, H-2, H-10), 7.65 (m, 2H, H-1, H-11), 7.73 (m, 2H, H-3, H-9), 7.92 (s, 2H, H-12, H-14), 7.96 (m, 2H, H-4, H-8).
MS m/z: 466 (M+3, 13), 465 (M+2, 15), 464 (M+1, 37), 421 (M-HCNO, 17), 154 (nba, 100). Anal. Calcd for C_{24}H_{22}ClN_{5}OS: C 62.13, H 4.78, N 15.09. Found C 61.98, H 4.79, N 14.72.

3. 6-(4’-Chloroethylureidobutyl)diquinothiazine (23) (0.18 g, 75% yield); mp 155-156 °C (EtOH). H NMR (CDCl₃) δ: 2.05 (m, 4H, 2CH₂), 3.46 (m, 2H, CH₂), 3.71 (m, 4H, 2CH₂), 5.05 (m, 2H, CH₂), 7.56 (m, 2H, H-2, H-10), 7.59 (m, 2H, H-1, H-11), 7.68 (m, 2H, H-3, H-9), 7.76 (m, 2H, H-4, H-8), 7.98 (s, 2H, H-12, H-14). FAB MS m/z: 480 (M+3, 35), 479 (M+2, 42), 478 (M+1, 100), 415 (M-C₂H₄Cl, 12), 301 (M+1-C₄H₈NHCONHC₂H₄Cl, 40). Anal. Calcd for C_{25}H_{24}ClN_{5}OS: C 62.82, H 5.06, N 14.65 Found C 62.61, H 5.01, N 14.38.

**Synthesis of 6-p-toluenesulfonaminoalkyldiquinothiazines (24-26)**

To a stirred solution of aminoalkyldiquinothiazines (11-13) (0.5 mmol) in a mixture of CH₂Cl₂ (3 mL) and 10% Na₂CO₃ solution (3 mL), a solution of p-toluenesulfonyl chloride (0.14 g, 0.76 mmol) in CH₂Cl₂ (3 mL) was added. The mixture was stirred at rt for 24 h. The organic phase was separated and aqueous phase was extracted with CH₂Cl₂ (2 x 3 mL). The combined extracts were washed with water (2 x 5 mL) and dried over Na₂SO₄. The drying agent was filtered off and filtrate was evaporated. The resulting residue was purified by column chromatography (silica gel, CHCl₃) to give:

1. 6-(2’-p-Toluenesulfonylaminoethyl)diquinothiazine (24) (0.17 g, 68% yield); mp 228-229 °C (EtOH). H NMR (CDCl₃) δ: 2.11 (s, 3H, CH₃), 3.88 (t, J = 6.3 Hz, 2H, NCH₂), 4.54 (t, J = 6.3 Hz, 2H, NCH₂), 6.56 (d, J = 7.7 Hz, 2H, C₆H₂), 7.16 (d, J = 7.7 Hz, 2H, C₆H₂), 7.37 (m, 2H, H-2, H-10), 7.60 (m, 4H, H-1, H-3, H-9, H-11), 7.64 (s, 2H, H-12, H-14), 7.78 (m, 2H, H-4, H-8). FAB MS m/z: 499 (M+1, 100), 328 (M+1-NH₂SO₂C₆H₄CH₃, 10), 301 (M+1-C₃H₆NHSO₂C₆H₄CH₃, 25). Anal. Calcd for C_{27}H_{22}N₄O₂S₂: C 65.04, H 4.45, N 11.24. Found C 64.84, H 4.49, N 11.02.

2. 6-(3’-p-Toluenesulfonaminopropyl)diquinothiazine (25) (0.18 g, 70% yield); mp 166-167 °C (EtOH). H NMR (CDCl₃) δ: 2.22 (m, 2H, CH₂), 2.34 (s, 3H, CH₃), 3.11 (t, J = 6.3 Hz, 2H, NCH₂), 4.72 (t, J = 7.2 Hz, 2H, NCH₂), 7.25 (d, J = 8.1 Hz, 2H, C₆H₂), 7.36 (m, 2H, H-2, H-10), 7.54 (d, J = 8.1 Hz, 2H, C₆H₂), 7.60 (m, 4H, H-1, H-3, H-9, H-11), 7.69 (s, 2H, H-12, H-14), 8.02 (m, 2H, H-4, H-8). FAB MS m/z: 513 (M+1, 100), 342 (M-NHSO₂C₆H₄CH₃, 10), 301 (M+1-C₆H₄NHSO₂C₆H₄CH₃, 25). Anal. Calcd for C_{28}H_{24}N₄O₂S₂: C 65.60, H 4.72, N 10.93. Found C 65.39, H 4.66, N 10.87.

3. 6-(4’-p-Toluenesulfonaminobutyl)diquinothiazine (26) (0.23 g, 85% yield); mp 165-166 °C (EtOH). H NMR (CDCl₃) δ: 1.71 (m, 2H, CH₂), 1.92 (m, 2H, CH₂), 2.39 (s, 3H, CH₃), 3.20 (t, J = 6.6 Hz, 2H, NCH₂), 4.55 (t, J = 7.2 Hz, 2H, NCH₂), 7.25 (d, J = 7.9 Hz, 2H, C₆H₂), 7.30 (m, 2H, H-2, H-10), 7.52 (m, 4H, H-1, H-3, H-9, H-11), 7.64 (s, 2H, H-12, H-14), 7.76 (m, 4H, H-4, H-8, C₆H₂). FAB MS m/z: 527 (M+1, 97), 391 (M+1-C₄H₈NHSO₂, 100), 301 (M+1-C₄H₈NHSO₂C₆H₄CH₃, 7). Anal. Calcd for C_{29}H_{26}N₄O₂S₂: C 66.14, H 4.98, N 10.64. Found C 66.01, H 4.96, N 10.55.
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