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## THE STRUCTURES OF 8- AND 10-TRIFLUOROMETHYLQUINO[3,2-*b*]-BENZO[1,4]THIAZINES AND THEIR BENZYL DERIVATIVES†

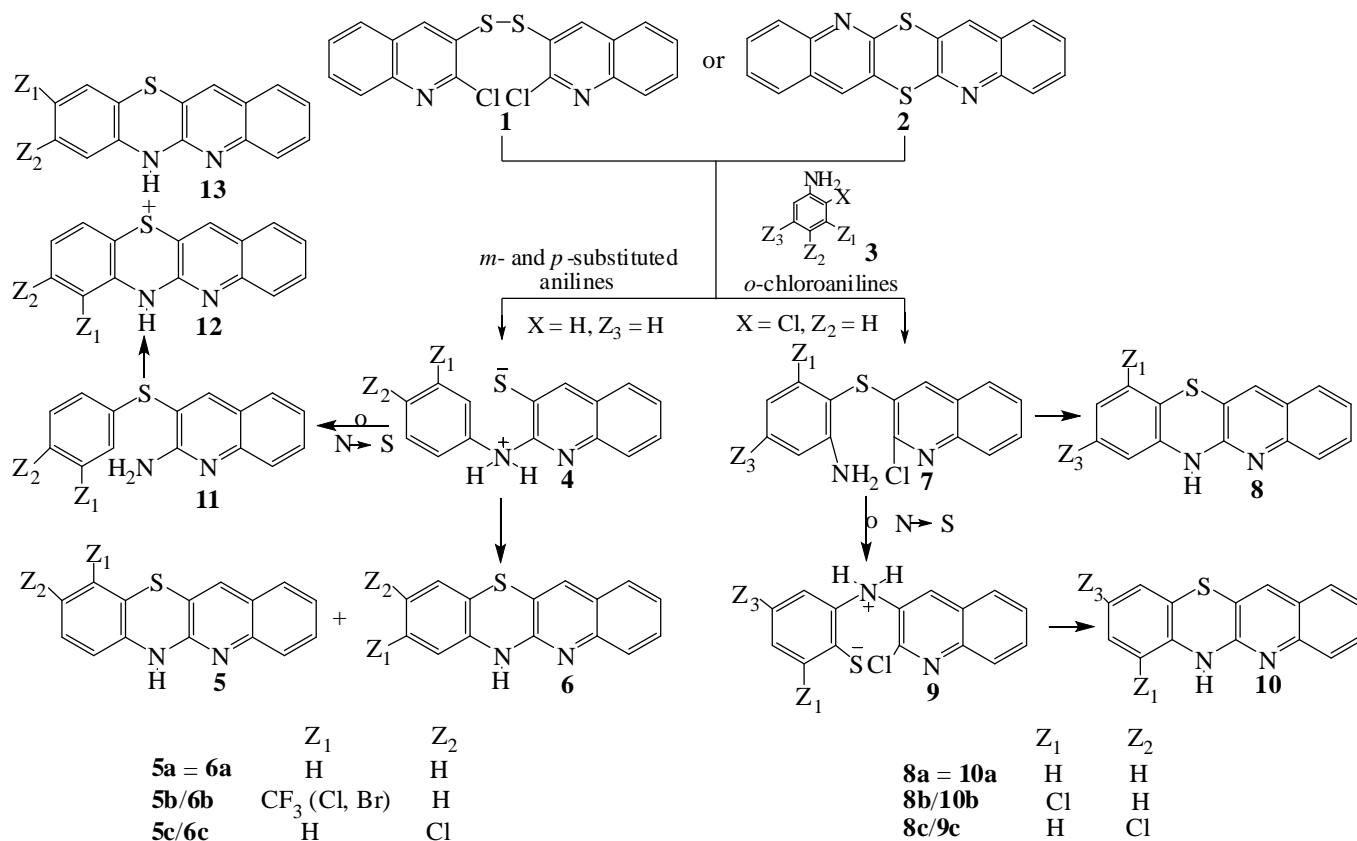
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**Abstract** – The modification of the phenothiazine structure *via* the substitution of the benzene ring with the quinoline ring may proceed through the Ullmann cyclization or the Smiles rearrangement of the appropriate sulfides followed by cyclization. Reactions of 2,2'-dichloro-3,3'-diquinolyl disulfide or pentacyclic diquinodithiin with *m*-trifluoromethylaniline led to two isomeric tetracyclic trifluoromethylquinobenzothiazines. The product structures as the appropriate 6*H*-X-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazines (X = 8, 10) were finally confirmed by X-ray analysis (one product was transformed into *N*-benzyl derivative). These results exclude the possibility of the reverse Smiles rearrangement and the existence of 5*H*-tautomers in these conditions. Although both compounds have the same quinobenzothiazine system, they differ in the spatial structures and geometric data. Molecule **6b** is unexpectedly almost planar that is the result of larger than usual the C–S–C and C–N–C angles in the thiazine ring. Molecule **14** is folded along the S–N axis with the thiazine ring in boat conformation and the benzyl group in equatorial position.

Phenothiazines are known mainly as recognized antipsychotic, antihistaminic, antitussive and antiemetic drugs.<sup>1</sup> Recent reports deal with very promising anticancer and antibacterial activities, reversal of

multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases not only for classical but also for newly synthesized phenothiazines.<sup>2-6</sup> The phenothiazine structures were modified by the introduction of new pharmacophoric substituents at the thiazine nitrogen atom and the substitution of the benzene ring with an azine ring. In continuation of our search for new anticancer and immunosuppressive azaphenothiazines containing azine rings (pyridine and quinoline)<sup>7-12</sup> we synthesized tetracyclic quinobenzothiazines in original way from 2,2'-dichloro-3,3'-diquinolyl disulfide **1** or pentacyclic diquinodithiin **2** in the reactions with various substituted anilines **3** (Scheme 1).<sup>13</sup> The reaction ran through the formation of anilinium quinolinethiolate **4** which underwent the thiazine ring formation to quino[3,2-*b*]benzo[1,4]thiazines **5**, the only product in the reaction with *p*-substituted anilines ( $Z_1 = Z_3 = X = H$ ). In the case of the reaction with *m*-substituted anilines (*m*-chloroaniline, *m*-bromoaniline, *m*-trifluoromethylaniline,  $Z_1 = \text{Cl, Br, CF}_3, Z_2 = Z_3 = X = \text{H}$ ) additional quinobenzothiazines **6** were also observed as the result of two ways of the thiazine ring formation. Anilinium quinolinethiolate **4** can undergo the Smiles rearrangement to sulfide **11** which can give quinobenzothiazines **12** and **13**. When *o*-chloroanilines **3** ( $X = \text{Cl}$ ) were used, the reaction ran through the formation of sulfide **7** which could give quinobenzothiazines **8** or could undergo the Smiles rearrangement to amine **9** and further to quinobenzothiazines **10**.



Scheme 1

We found the products with *m*-chloroaniline to be the same as those with 2,3- and 2,5-dichloroanilines, and therefore we assigned them as 8-chloro- and 10-chloroquino[3,2-*b*]benzo[1,4]thiazines **5b** and **6b**, respectively. The kind of fusion of the thiazine ring with the quinoline ring [3,2-*b*] in obtained quinobenzothiazines was confirmed by homonuclear NOE experiment for the 6-methyl derivative. A discrimination of 8-substituted and 10-substituted quinobenzothiazines was based on the <sup>1</sup>H NMR analysis of the benzene ring proton signals (as 1,2,4- and 1,2,3-trisubstituted benzenes, respectively) and their coupling constants  $J_{ortho}$  and  $J_{meta}$ .<sup>13</sup>

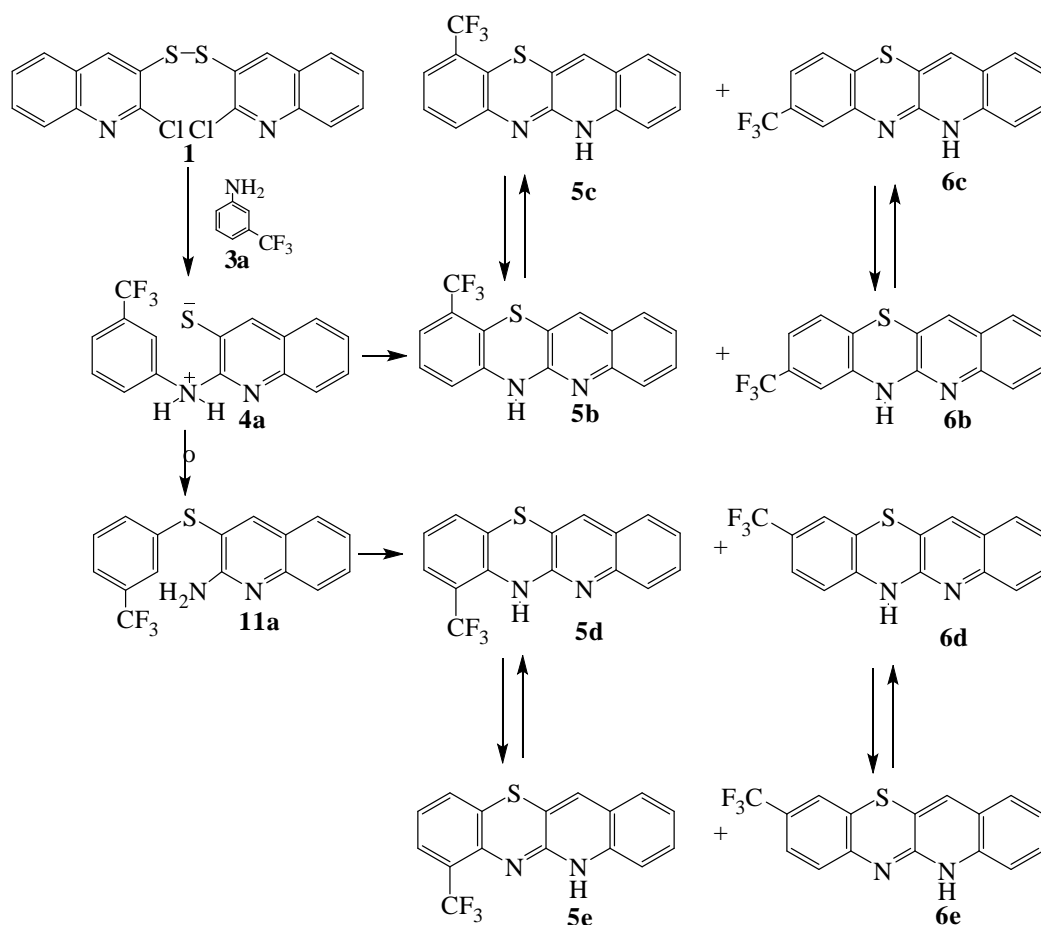
Phenothiazines with biological activities are obtained most often from *N*-unsubstituted phenothiazines in *N*-alkylation reactions. Such alkylations mainly occurred at the thiazine nitrogen atom but there are some evidences that the azine nitrogen atom, sulfur atom or even carbon atom were also alkylated, even in basic conditions.<sup>14-16</sup> A ring contraction was also observed during alkylation.<sup>17</sup> As biological activities of phenothiazines depend on their structures, configurations and conformations, especially on the nature of the substituent at the thiazine nitrogen atom, the place of additional substituents, and on the nature of the phenothiazine and azaphenothiazine ring system, it is obvious the structures of phenothiazines should be determined without any doubts. The proper determination of the phenothiazine products is difficult as the Smiles rearrangement, which is widespread during synthesis *via* appropriate sulfide, is not always easy to observe.<sup>15-17</sup> The aim of this paper is to confirm unequivocally the kind of fusion of the quinoline ring with thiazine ring and proper discrimination of the two isomeric trifluoromethylquinobenzothiazines, to verify the place of the hydrogen atom ( $N_{thiazine}\text{-H}$  or  $N_{quinoline}\text{-H}$ ) and an alkyl substituent at the nitrogen atom, and finally to find out about planar or folded tetracyclic quinobenzothiazine ring system.

### Synthesis and the product structures

The reaction of disulfide **1** or diquinodithiin **2** with *m*-trifluoromethylaniline **3a** (or its hydrochloride) in boiling monomethyl ether of diethylene glycol (MEDG) at 194 °C or without solvent at 200–205 °C, respectively, led to two products with melting points of 225–226 °C and 219–220 °C assigned as trifluoromethylquinobenzothiazines **5b** and **6b**<sup>13</sup> but other tautomeric structures **5c** and **6c** should be also taken into consideration. On the other hand intermediate **4a** can undergo the reverse Smiles rearrangement to sulfide **10** and further to trifluoromethylquinobenzothiazines **5d** and **6d** or their tautomers **5e** and **6e** (Scheme 2).

The direct reaction products were changed into *N*-benzyl derivatives in 81% and 86% yield in the model alkylation reaction with benzyl chloride in DMF in the presence of sodium hydride. As we found that *N*-substituted quinobenzothiazines with pharmacophoric aminoalkyl groups exhibited very promising antiproliferative and anticancer activities,<sup>18</sup> this model benzylation showed which nitrogen atom underwent alkylation.

For X-ray study, we obtained proper quality monocrystals of the direct product of higher melting point. The monocrystal quality of the second product (of lower melting point) was insufficient, therefore this compound was transformed into *N*-benzyl derivative. X-Ray study confirmed the correctness of the assumed structures of 6*H*-8-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine **6b** and 6-benzyl-10-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine **14** and proved that the model *N*-benzyl reactions occurred at the thiazine nitrogen atom (giving compounds **14** and **15**). These results exclude the possibility of the reverse Smiles rearrangement and the existence of 5*H*-tautomers in these conditions.



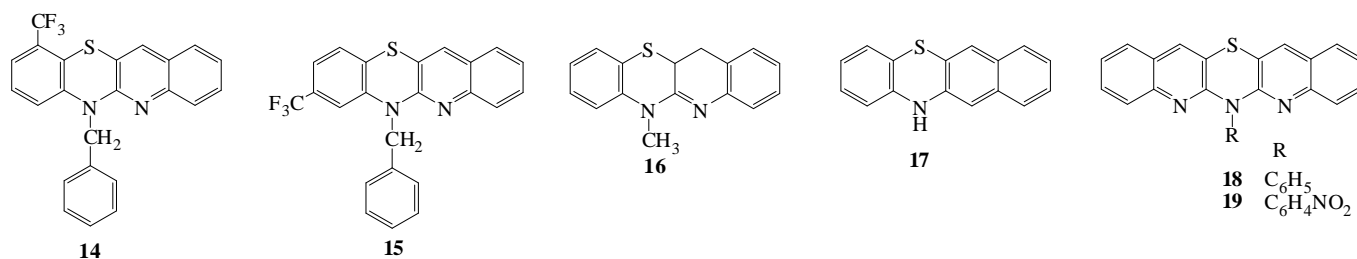
Scheme 2

### X-Ray analysis

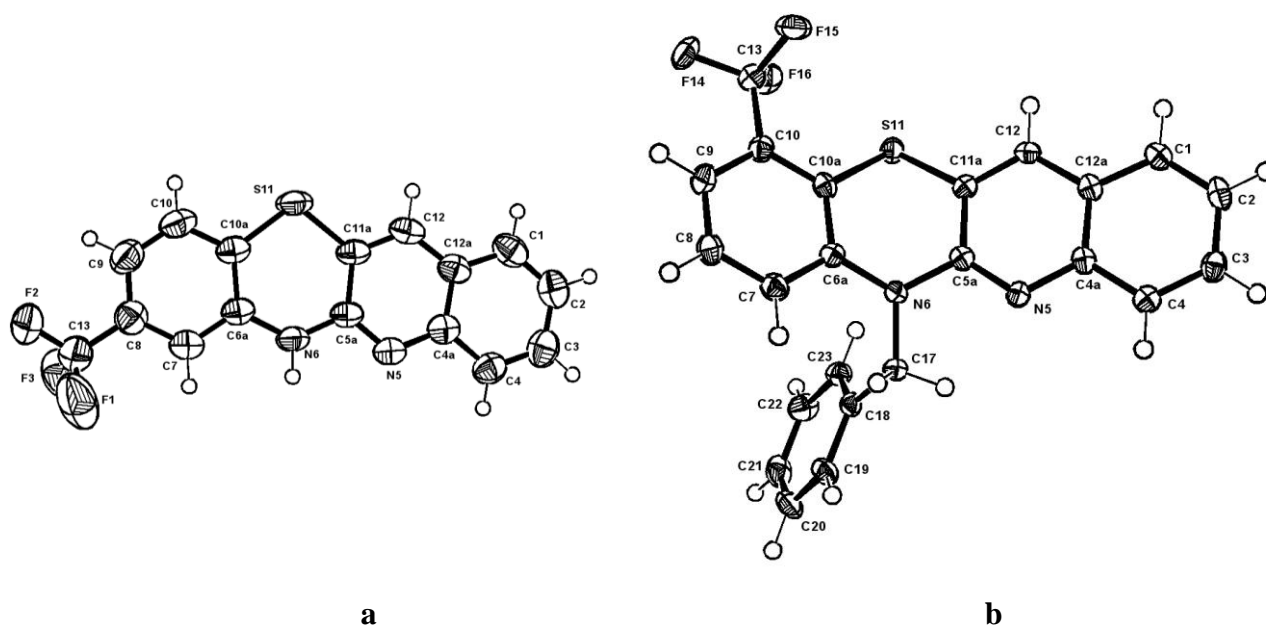
The isomeric trifluoromethylquinobenzothiazine systems have different spatial structures. Contrary to all known structures of tricyclic phenothiazins, molecule **14** and other tetracyclic compounds i.e. dihydroquinobenzothiazine **16**<sup>19</sup> and naphthobenzothiazine **17**<sup>20</sup> (Scheme 3), molecule **6b** is unexpectedly almost planar (Figure 1). The dihedral angle between the halves of the thiazine ring (N6/C5a/C11a/S11 vs. N6/C6a/C10a/S11) and between the benzene ring and quinoline ring (C6a/C7/C8/C9/C10/C10a vs.

C1/C2/C3/C4/C4a/N5/C5a/C11a/C12/C12a) are  $171.86(10)^\circ$  and  $174.02(8)^\circ$ , respectively. We found only one case in literature when the phothiazine structure was planar, despite some complexes with inorganic and organic compounds. Out from two reported structures of related linear fused azaphenothiazines possessing two quinoline rings instead of the benzene rings, pentacyclic 6-phenyldiquinothiazine **18** was folded but 6-(*p*-nitrophenyl)diquinothiazine **19** was unexpected planar due to the interaction of the thiazine nitrogen atom with electron-withdrawing *p*-nitrophenyl group.<sup>21,22</sup>

The similar dihedral angles in molecule **14** are  $139.20(9)^\circ$  and  $145.97(6)^\circ$ , respectively. The thiazine ring is in boat conformation and the benzyl group is located in equatorial position with the S11...N6-C17 angle of  $163.8(2)^\circ$  and torsion angles C10a-C6a-N6-C17 and C11a-C5a-N6-C17 of  $-164.4(2)^\circ$  and  $168.1(2)^\circ$ . The benzyl group is turned around the N6-C17 bond (the torsion angles C5a-N6-C17-C18 and



Scheme 3

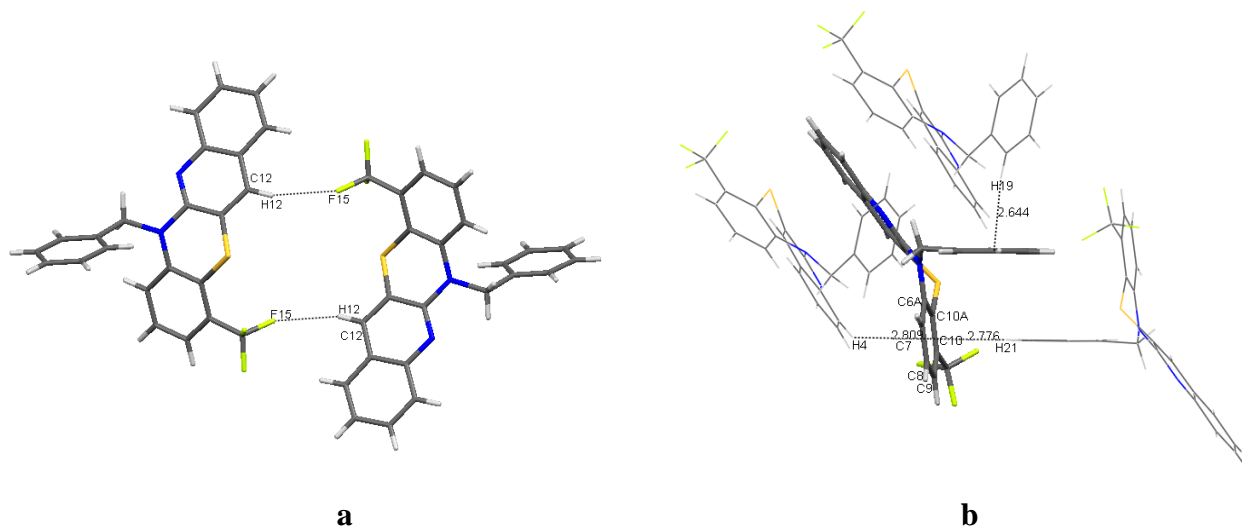


**Figure 1.** ORTEP drawings: (a) 6*H*-8-trifluoromethylquino[3,2-*b*]benzothiazine **6b**; (b) 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine **14**

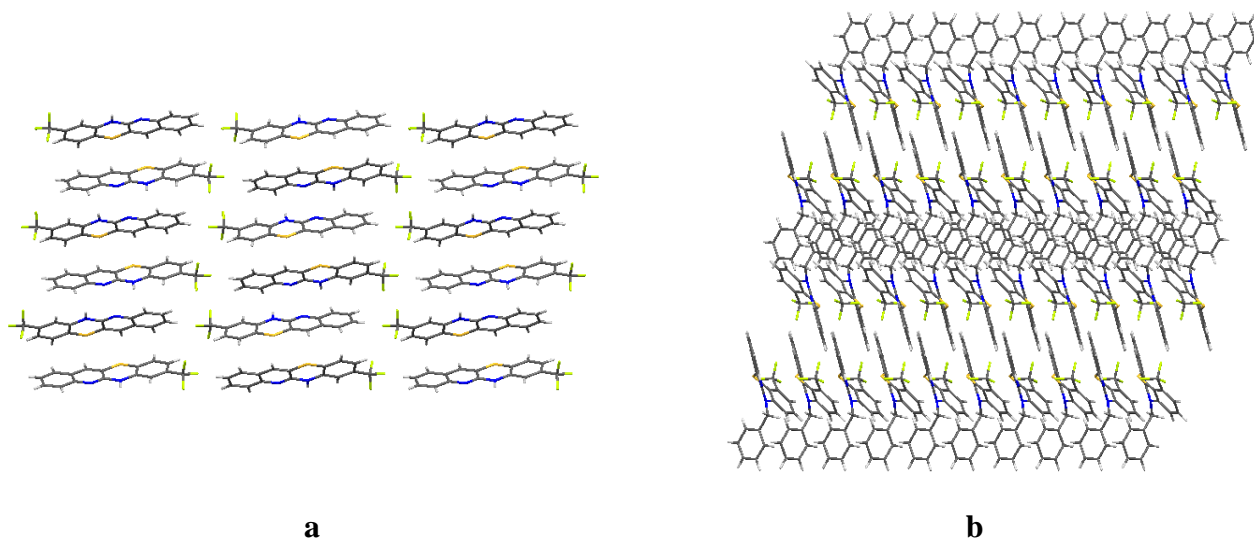
C6a-N6-C17-C18 of  $-133.4(2)^\circ$  and  $68.2(3)^\circ$ ) and less turned around the C17-C18 bond (the torsion angles N6-C17-C18-C19 and N6-C17-C18-C23 of  $-164.4(2)^\circ$  and  $26.1(3)^\circ$ ). The phenyl group plane

(C18/C19/C20/C21/–C22/C23) is rather perpendicular to the C5a/C6a/C10a/C11a plane with the angle of  $112.89(9)^\circ$ .

Whereas the thiazine ring is symmetrical with similar S–C (1.753(2) and 1.754(2) Å) and N–C bond lengths (1.388(2) and 1.377(2) Å), the pyridine ring is distorted with different C–C (1.355(3) vs. 1.432(2) Å) and



**Figure 2.** Intermolecular interactions in 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine **14** crystal structure: (a) dimer formation; (b) C–H··· $\pi$  interactions.



**Figure 3.** Crystal packing shown along the *b* axis in: (a) 6*H*-8-trifluoromethylquino[3,2-*b*]benzothiazine **6b**; (b) 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine **14**

N–C bond lengths (1.303(2) Å vs. 1.373(2) Å). The C–N–C and C–S–C angles in the thiazine ring are significantly large ( $128.22(15)^\circ$  and  $103.31(9)^\circ$ ) in molecule **6b** in comparison with appropriate angles in molecule **14** ( $120.9(2)^\circ$  and  $98.78(12)^\circ$ ), what enables the thiazine ring to be almost planar. It is worth noting that the same angles in planar similar structure **19** are also large ( $125.7(4)^\circ$  and  $102.6(3)^\circ$ ) but in folded

structure **18** are smaller ( $123.8(2)^\circ$  and  $100.1(2)^\circ$ , respectively).<sup>21,22</sup> Similarly to compound **6b**, the thiazine ring in compound **14** is quite symmetrical (with the S–C bond lengths of 1.759(3) and 1.768(3) Å, and with the N–C bond lengths of 1.408(3) and 1.411(3) Å), but the pyridine ring is distorted with different the C–C (1.360(4) vs 1.429(4) Å) and N–C bond lengths (1.306(4) Å vs. 1.377(3) Å).

The electron-withdrawing trifluoromethyl group in compounds **6b** and **14**, similarly to the *p*-nitrophenyl group in compound **19**, reduces the electron density at the thiazine nitrogen atom what makes possible to take a planar conformation of the thiazine ring and thereby the whole molecule **6b**. In case of molecule **14**, the electron-withdrawing action of the trifluoromethyl group is compensated by the electron-donating action of the benzyl group. The sum of three C–N6–C angles is  $356.21^\circ$  indicating nearly pyramidal configuration of the bonds around the central nitrogen atom.

Two molecules **14** related by crystallographic center of symmetry are arranged in dimers *via* two C–H...F hydrogen bonds [ $d_{\text{H}\cdots\text{F}} = 2.56$  Å,  $d_{\text{C}\cdots\text{F}} = 3.394$  Å,  $\angle_{\text{C-H}\cdots\text{F}} = 146.8^\circ$ ] (Figure 2a). Each molecule interacts with neighboring three molecules with C–H... $\pi$  interactions (Figure 2b). Additionally, in the crystal structure,  $\pi$ – $\pi$  interactions between the quinoline moieties of the adjacent molecules are observed. The  $\pi$ – $\pi$  stacking propagates along *c* crystallographic axis.

Figure 3 shows crystal packing along the *b* axis for both crystal structures.

The trifluoromethyl group rotates very fast in molecule **6b** and is coplanar with the benzene ring as the torsion angles C13/C8/C9/C10 and C6a/C7/C8/C13 are  $-179.5(2)^\circ$  and  $179.76(18)^\circ$ , respectively.

The CF<sub>3</sub> group is disordered in molecule and was modelled using two components, whose geometry was restrained to be the same. Restraints were also applied on anisotropic displacement parameters.

X-Ray study confirmed the right structures of 6*H*-8-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine **6b** and 6*H*-10-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine **5b** (concluded from the <sup>1</sup>H NMR study) as the direct reaction products which exist as the 6*H*-tautomers. The structure of 6-benzyl-10-trifluoromethylquino[3,2-*b*]benzothiazine **14** proved that the model *N*-benzyl reaction occurred at the thiazine nitrogen atom. These results exclude the possibility of the reverse Smiles rearrangement and the existence of the 5*H*-tautomers in these conditions. Although both compounds have the same quinobenzothiazine system, they differ in geometric data and molecule **6b** is unexpectedly almost planar. The thiazine ring in molecule **14** is in boat conformation with the benzyl group in equatorial position. The planarity of the thiazine ring in molecule **6b** is the result of larger than usual the C–S–C and C–N–C angles.

## EXPERIMENTAL

Melting points were determined in open capillary tubes on a Boetius melting point apparatus and were uncorrected. The <sup>1</sup>H NMR spectra were recorded on a Bruker AV III spectrometers at 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 IR spectra were recorded on a Shimadzu IR-Affinity-1 FT-IR spectrophotometer.

**General synthesis of 6*H*-8-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine 6b and 6*H*-10-trifluoromethylquino[3,2-*b*]benzo[1,4]thiazine 5b**

The reaction of disulfide **2** (0.20 g, 0.5 mmol) with *m*-trifluoromethylaniline **3a** (2 mmol) in boiling monomethyl ether of diethylene glycol (5 mL) was carried out as described previously.<sup>13</sup> The column chromatography separation (silica gel, CHCl<sub>3</sub>) gave two products:

- 6*H*-8-Trifluoromethylquinobenzothiazine **6b** (0.11 g, 34%), mp 225–226 °C, R<sub>f</sub> = 0.65 (Al<sub>2</sub>O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>),
- 6*H*-10-trifluoromethylquinobenzothiazine **5b** (0.09 g, 28%), mp 219–220 °C, R<sub>f</sub> = 0.58 (Al<sub>2</sub>O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>).

The same products were obtained in 28% and 22% yield in the reaction of diquinodithiin **1** with hydrochloride of *m*-trifluoromethylaniline **3a** in an oil bath at 200–205 °C.<sup>13</sup>

**Synthesis of 6-benzyl-10-trifluoromethylquino[3,2-*b*]benzothiazine 14 and 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine 15**

To a solution of 10-trifluoromethylquinobenzothiazine **5b** or 8-trifluoromethylquinobenzothiazine **6b** (0.32 g, 1 mmol) in dry DMF (10 mL) sodium hydride (0.24 g, 10 mmol, washed out from mineral oil with hexane) was added. The reaction mixture was stirred for 1 h in room temperature. Then benzyl chloride (0.35 mL, 3 mmol) was added and the stirring was continued for 24 h. The reaction mixture was poured into water (40 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water, dried with anhydrous sodium sulfate. The drying agent was filtered off and the solution was evaporated *in vacuo*. The residue was purified by column chromatography (Al<sub>2</sub>O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>) to give 6-benzyl-10-trifluoromethylquino[3,2-*b*]benzothiazine **14** (0.18 g, 86%), mp 127–128 °C (EtOH) or 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine **15** (0.17 g, 81%), mp 115–116 °C (EtOH).

6-benzyl-10-trifluoromethylquinobenzothiazine **14** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.60 (s, 2H, CH<sub>2</sub>), 6.97 (d, 1H, H7), 7.07 (t, 1H, H8), 7.23 (m, 1H, H2), 7.24 (d, 1H, H9), 7.31 (m, 3H, C<sub>6</sub>H<sub>3</sub>), 7.38 (m, 2H, C<sub>6</sub>H<sub>2</sub>), 7.51 (m, 2H, H3), 7.58 (m, 1H, H1), 7.69 (m, 1H, H4), 7.83 (s, 1H, H12). EI MS *m/z*: 408 (M, 63), 317 (M-CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 100). Ir (KBr): 1130.33, 1309.72, 1399.42 cm<sup>-1</sup>. Anal. Calcd for C<sub>23</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>S: C 67.64, H 3.70, N 6.86. Found: C 67.44, H 3.83, N 6.76.

6-benzyl-8-trifluoromethylquinobenzothiazine **15** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ: 5.60 (s, 2H, CH<sub>2</sub>), 6.98 (d, 1H, H7), 7.09 (dd, 1H, H9), 7.15 (d, 1H, H10), 7.23 (m, 1H, H2), 7.31 (m, 3H, C<sub>6</sub>H<sub>3</sub>), 7.39 (m, 2H, C<sub>6</sub>H<sub>2</sub>), 7.50 (m, 2H, H3), 7.54 (m, 1H, H1), 7.70 (s, 1H, H12), 7.72 (m, 1H, H4). EI MS *m/z*: 408 (M, 55), 317 (M-CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 100). Ir (KBr): 1119.73, 1324.19, 1406.70 cm<sup>-1</sup>. Anal. Calcd for C<sub>23</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>S: C 67.64,

H 3.70, N 6.86. Found: C 67.41, H 3.85, N 6.69.

### X-Ray analysis of 6H-8-trifluoromethylquino[3,2-*b*]benzothiazine **6b** and 6-benzyl-8-trifluoromethylquino[3,2-*b*]benzothiazine **14**

A. A yellow crystal of compound **6b** (dimensions: 0.40 × 0.30 × 0.04 mm) was grown from ethanol-chloroform solution at room temperature. Crystallographic data were collected at 260 K on a Stoe IPDS diffractometer with graphite monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å). The structure was solved by direct methods (SHELXS-86)<sup>23</sup> and refined by full-matrix least-squares minimization based on all unique  $F^2$  (SHELXL).<sup>24</sup> Crystal data: C<sub>16</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>S,  $M_r = 318.32$ , monoclinic,  $a = 7.6423$  (9),  $b = 6.0471$  (4),  $c = 28.940$  (3) Å,  $\beta = 97.60$  (1)°, space group  $P2_1/c$ ,  $V = 1325.7$  (2) Å<sup>3</sup>,  $Z = 4$ ,  $\mu = 0.28$  mm<sup>-1</sup>. The crystal system is monoclinic but the system could be indexed using an orthorhombic unit-cell with parameters  $a = 7.665$ ,  $b = 57.331$ ,  $c = 6.054$  Å. This cell is the result of a perfect superposition of two monoclinic twins with twin law [1 0 0, 0 -1 0, -1 0 -1]. The twin law was included in the refinement and the twin fraction refined to 0.53 / 0.47. 7878 reflections were collected of which 2593 were independent and 2337 reflections with  $I > 2\sigma(I)$  ( $R_{\text{int}} = 0.039$ ). The structure was refined to  $R[F^2 > 2\sigma(F^2)] = 0.031$  and  $wR(F^2) = 0.077$ . H-atoms were included in geometric positions and refined as 'riding' atoms with isotropic thermal parameters based upon the corresponding bonding carbon atom [ $U_{\text{iso}} = 1.2U_{\text{eq}}$ ].

B. A yellow crystal of compound **14** (dimensions: 0.15 × 0.20 × 0.30 mm) was grown from ethanol-chloroform solution at room temperature. Crystallographic data were collected at 100 K on a Kappa ApexII diffractometer with graphite monochromated MoK $\alpha$  radiation ( $\lambda = 0.71073$  Å). The structure was solved by direct methods (SHELXS-97)<sup>25</sup> and refined by full-matrix least-squares minimization based on all unique  $F^2$  (SHELXL-97).<sup>26</sup> Crystal data: C<sub>23</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>S,  $M_r = 3408.44$ , monoclinic,  $a = 16.7752$  (6),  $b = 16.2145$  (7),  $c = 7.0434$ (2) Å,  $\beta = 99.971$ (2)°, space group  $P2_1/c$ ,  $V = 1884.3$  (2) Å<sup>3</sup>,  $Z = 4$ ,  $\mu = 0.212$  mm<sup>-1</sup>. 24702 reflections were collected of which 3208 were independent and 2503 reflections with  $I > 2\sigma(I)$  ( $R_{\text{int}} = 0.042$ ). The structure was refined to  $R[F^2 > 2\sigma(F^2)] = 0.049$  and  $wR(F^2) = 0.100$ . H-atoms were included in geometric positions and refined as 'riding' atoms with isotropic thermal parameters based upon the corresponding bonding carbon atom [ $U_{\text{iso}} = 1.2U_{\text{eq}}$ ].

### ACKNOWLEDGEMENTS

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