Fused 1,2,4-Triazole Heterocycles. IV. Synthesis of Four New Heterocyclic Ring Systems of [1,2,4]Triazolo[1,3]thiazinoquinolines

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Syntheses of 5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,4-*c*]quinolines **8**, 5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,4-*c*]quinolines **9**, 5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,6-*c*]quinolines **14** and 5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,6-*c*]quinolines **15** are described starting from 4-chloro-3-chloromethylquinaldine (**4**) and 1,2,4-triazole-5-thiols **5** taking advantage of different reactivity of the chlorine atoms of **4** under different reaction conditions. The structures of products **8**, **9**, **14** and **15** and the intermediates leading to them were confirmed by desulfurization, unequivocal syntheses and nmr spectroscopy as well.

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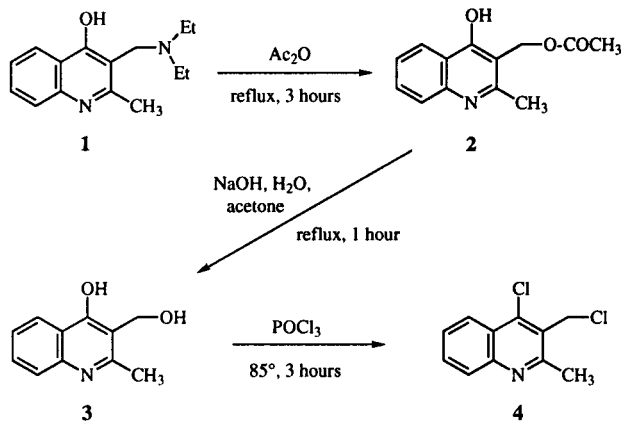
In the preceding paper of this series [1], we reported on the synthesis of the four possible regioisomers of [1,2,4]-triazolo[1,3]thiazinoquinolines accessible by the reaction of 1,2,4-triazole-5-thiols with 2-chloro-3-chloromethylquinoline. In the course of this work we found appropriate reaction conditions for selective substitution of two chlorine atoms of the latter compound and observed a new rearrangement of 3-chloromethyl-2-(1,2,4-triazol-5-yl)-thioquinoline.

With the aim of exploring the scope of our findings and in connection with our interest in the synthesis of new heterocyclic ring systems we here report on the reaction of 4-chloro-3-chloromethylquinaldine (**4**) with 1,2,4-triazole-5-thiols **5** affording derivatives of new heterocyclic ring systems.

The starting 4-chloro-3-chloromethylquinaldine (**4**) is a new compound which was synthesized from 3-diethylaminomethyl-4-hydroxyquinaldine [2] following the reaction sequence (Scheme 1) utilized for the preparation of its 6-methoxy derivative [3].

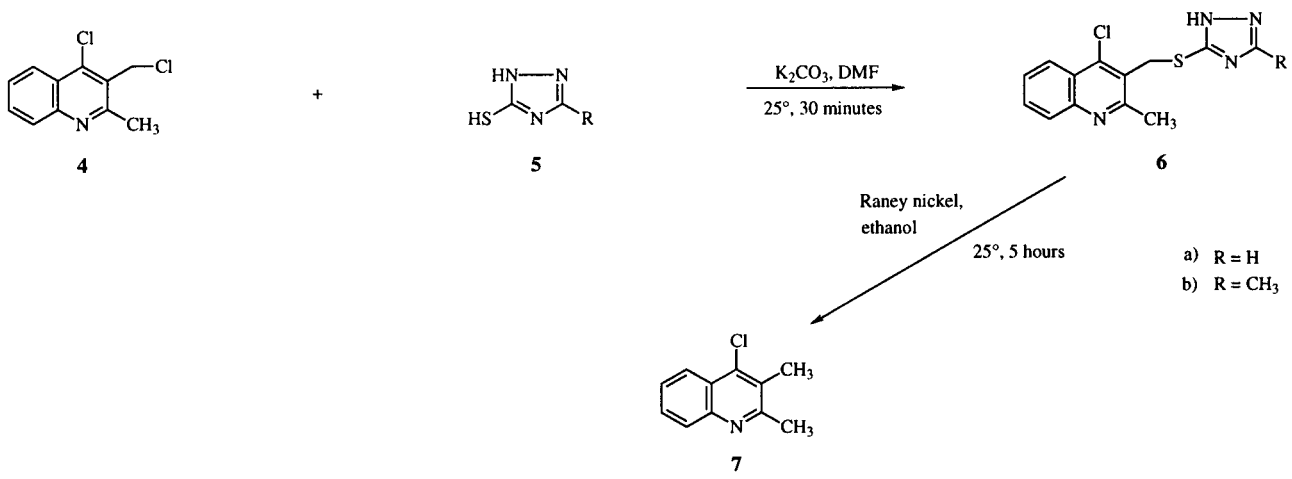
Scheme 1



In the first approach 4-chloro-3-chloromethylquinaldine (**4**) was treated with 1,2,4-triazole-5-thiols in dimethylformamide at room temperature in the presence of potassium carbonate affording 4-chloro-3-(1,2,4-triazol-5-yl)-thiomethylquinaldines **6** in excellent yields (Scheme 2). Under these conditions the substitution of the benzylic chlorine atom took only place but the 4-chlorine atom was found to remain unaffected in terms of both *S*-substitution and cyclization similarly to that was found in case of the reaction between 2-chloro-3-chloromethylquinoline and 1,2,4-triazolethiols [1]. The reason for this selectivity is that the presence of a strong base not only increases the nucleophilicity of the triazolethiol *via in situ* formation of thiolate anion but, at the same time, it prevents the activation of 4-chlorine atom by protonation of quinoline nitrogen atom. The position of the reacting chlorine atom was strongly indicated by an 0.4 ppm upfield shift of the methylene singlet in the ^{1}H-nmr spectra of compounds **6** in comparison with that of compond **4**. Nevertheless, the structure of **6** was unambiguously confirmed by desulfurization with Raney nickel in ethanol leading to 4-chloro-2,3-dimethylquinoline (**7**). Mass spectrometric investigations showed that compounds **6** lose hydrochloric acid in EI mode probably due to cyclocondensation, but thermospray technique was found to be suitable to detect MH^+ peaks.

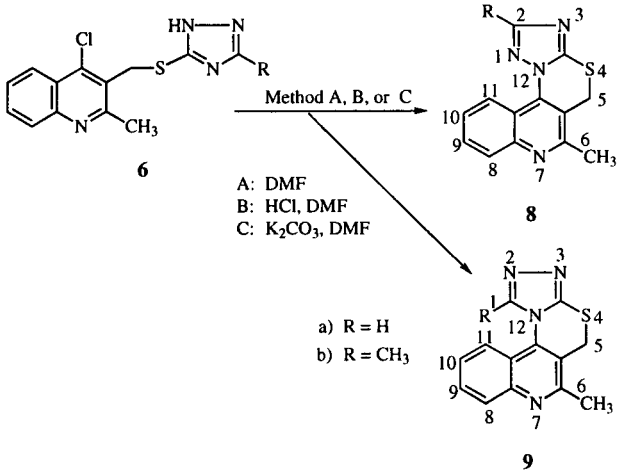
Cyclocondensation of **6** was investigated under different conditions. It was stirred at different temperatures in dimethylformamide without any additional reagent (method A), or in the presence of hydrochloric acid (method B), or potassium carbonate (method C). In case

Scheme 2



of R = H two products were formed (Scheme 3, Table 1) which were separated by column chromatography and were assigned as 6-methyl-5*H*-[1,2,4]triazolo[5',1':2,3]-[1,3]thiazino[5,4-*c*]quinoline (**8a**) and 6-methyl-5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,4-*c*]quinolines (**9a**) by elemental analysis, mass spectrometry and nmr spectroscopy. Elemental analysis and mass spectral data showed that the two compounds have the same composition, but on the basis of these data, it was not possible to distinguish between the regioisomers. However, ^{1}H- and ^{13}C-nmr spectroscopy were found to be suitable tools for structural differentiation. By detailed nmr study of different regioisomers of triazolothiazinoquinolines, we have established some general rules concerning the chemical shifts of triazole protons and carbons as well as one-bond triazole proton-carbon couplings which proved to be useful in establishing the anellation patterns of fused 1,2,4-triazoles [4]. Thus, for example, the triazole proton of the

Scheme 3



N-1-cyclized product **8a** resonates at higher field (δ 8.49 ppm) than the corresponding proton of the N-4-cyclized **9a** product (δ 9.62 ppm). This rule concerning the chemical shifts of triazole protons had been observed before us, and was successfully used for structural assignation of different other condensed triazoles [5-10]. Assignation based on these empirical rules was confirmed by homonuclear NOE difference spectroscopy [4].

The data in Table 1 clearly show that the cyclization of **6** is acid catalyzed due to the activation of 4-chlorine atom by protonation of the quinoline ring. The presence of potassium carbonate inhibits the cyclization reaction since it prevents the activation by protonation. In the latter case, the ratio of N-1-cyclized product **8a** is much higher than in the former. This fact can be explained considering that potassium carbonate deprotonates the triazole ring and the negative charge localizes mainly to N-1 rather than N-4, so N-1 has the greater nucleophilicity similarly to that was found in alkylation reactions of 1,2,4-triazole [11]. These observations were consistent with those reported on the cyclocondensation reaction of 2-chloro-3-(1,2,4-triazol-5-yl)thiomethylquinoline [1] with the exception that in the case of R = Me only one product **8b** was formed because of the steric compression between the methyl group and the closely spaced homoaromatic proton in the case of the assumed quasi-planar structure.

In the second approach the reaction of **4** and **5** was performed in dimethylformamide at room temperature in the absence of any additional reagent (Scheme 4). After a while, the reaction mixture became acidic and a crystalline product began to separate which was removed by filtration. It was assumed that 3-chloromethyl-4-(1,2,4-triazol-5-yl)thioquinoline hydrochloride (**10**) was formed in the autocatalytic *S*-substitution of 4-chlorine atom of **4**. The supposed structure of **10** was consistent with the ele-

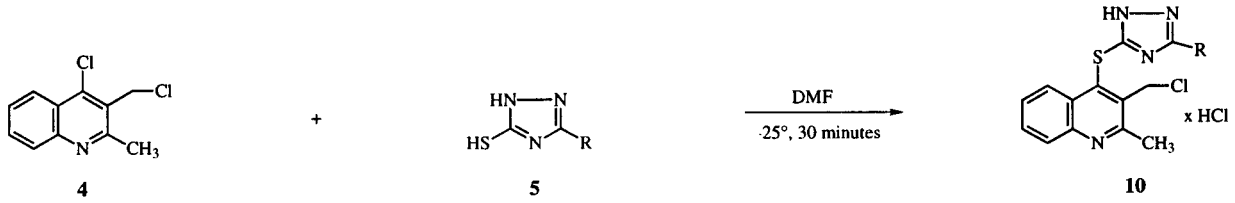
Table 1

Cyclization of 4-Chloro-3-1,2,4-triazol-5-yl)thioquinolines **6**

R	Method	Temperature (°C)	Time (hours)	Yield [a] %	Ratio of the products (%) [b] **8**	**9**
H	A	25	72	96	61	39
H	A	60	1	96	61	39
H	B	25	9	94	63	37
H	C	80	4	96	90	10
Me	A	60	6	92	100	0
Me	B	60	3	90	100	0

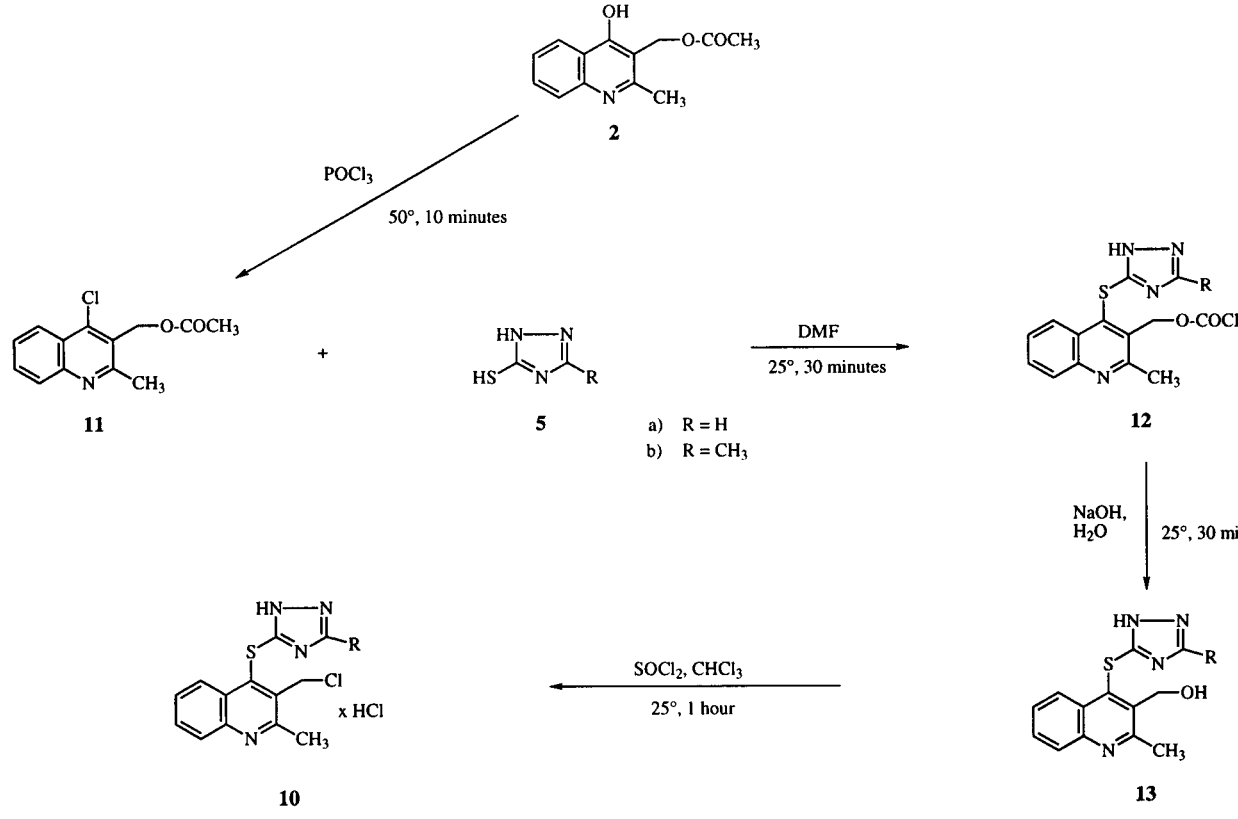
[a] Yield of the crude product containing only the two regioisomers; [b] The ratio was determined by ^{1}H-nmr spectroscopy.

Scheme 4



a) R = H
b) R = CH_3

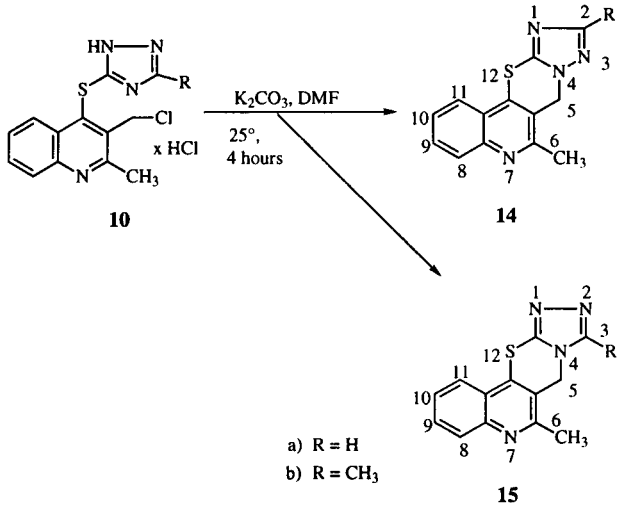
Scheme 5



mental analysis and ^{1}H-nmr data, but in this case nmr data could not give much of help in confirmation of this structure since the proton signal of the methylene group may *a priori* have a downfield shift because of the protonation of the quinoline ring. Our effort for preparation of free base from **10** failed because ring-closured products were formed upon neutralization, so we confirmed the structure of **10** by unequivocal synthesis. Starting from **2**, following the reaction sequence outlined on Scheme 5, *via* compounds **11**, **12** and **13** we got through to compounds **10** which were identical (^{1}H-nmr, mp) with those prepared by the reaction of **4** and **5**.

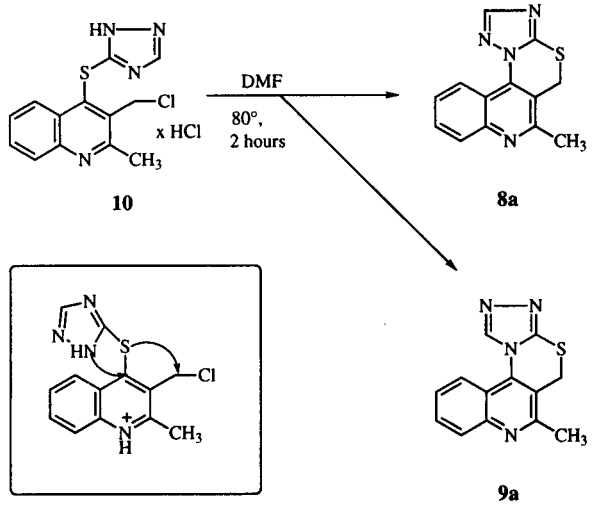
Cyclocondensation of compounds **10** was studied under different reaction conditions. When they were treated with two molar equivalents of potassium carbonate in dimethylformamide at room temperature formation of two products was observed (Scheme 6), but neither of them was identical (tlc) with compounds **8** or **9**. They were separated by column chromatography and were subjected to analytical, mass spectrometric and nmr spectroscopic investigations. Microanalysis and mass spectral data showed that the separated products are regioisomers, furthermore they have the same compositions as compounds **8** and **9**. Finally, they were assigned as 5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,6-*c*]quinoline (**14**) and 5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,6-*c*]quinoline (**15**) derivatives by homonuclear NOE difference spectroscopy in agreement with the characteristic nmr data of different regioisomers of [1,2,4]triazolo[1,3]thiazinoquinolines [4].

Scheme 6



When **10a** was heated in dimethylformamide at 80° (Scheme 7) formation of the mixture of **8a** and **9a** was observed. Compounds **14** and **15** could not be detected in

Scheme 7



the crude product by tlc and nmr spectroscopy. This observation can be explained by assuming an acid catalyzed rearrangement *via* a four membered cyclic system (Scheme 7) at the transition state similarly to that was found in the case of 3-chloromethyl-2-(1,2,4-triazol-5-yl)-thioquinoline [1] This rearrangement is supposed to consist of two quasi-simultaneous nucleophilic steps: the acid catalyzed nucleophilic attack of the triazole ring nitrogen atom to the C-4 atom of the quinoline ring and the nucleophilic attack of the sulfur atom to the benzylic carbon atom. This type of rearrangements was first observed by us [1] however, some similarities can be found with the mechanism of the Newman-Kwart rearrangement of thionocarbamates to thiolcarbamates [12].

We can summarize the results of our work presented in this paper by the following:

(1) We have found that the two chlorine atoms of 4-chloro-3-chloromethylquinaldine can be substituted selectively by 1,2,4-triazole-5-thiols. Under acid catalytic or autocatalytic reaction conditions the 4-chlorine atom, whereas in the presence of a strong base or toward anionic form of the nucleophile, the benzylic chlorine atom of **4** has greater reactivity.

(2) Taking advantage of this finding we have managed to synthesize derivatives **8**, **9**, **14** and **15** all the four possible new heterocyclic ring systems accessible starting from 4-chloro-3-chloromethylquinaldine (**4**) and 1,2,4-triazole-5-thiols **5**.

(3) We have found another example for the rearrangement reported recently [1] for 3-chloromethyl-2-(1,2,4-triazol-5-yl)thioquinoline. Investigation of the scope of this rearrangement is a part of our ongoing project.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Nmr spectra were recorded on a Varian Gemini-200 instrument at 200 MHz in DMSO-d_6 solution using trimethylsilane as internal standard and chemical shifts are expressed in ppm. The NOE experiments along with the total ^{1}H- and ^{13}C-nmr assignation of compounds **8**, **9**, **14** and **15** have already been published [4]. Mass spectra were scanned on a VG TRIO-2 spectrometer in EI mode at 70 eV, or using TSP technique. The purification and separation of some products was performed by column chromatography using Kieselgel 60 (0.063-0.2 mm) packing and chloroform-ethanol (95:5, v/v) eluent.

4-Hydroxy-3-acetoxymethylquinaldine (**2**).

The mixture of 4-hydroxy-3-diethylaminomethylquinaldine (**1**) and 150 ml of acetic anhydride was heated at reflux temperature until all the solid material went into the solution (3 hours). The solution was evaporated to dryness under reduced pressure and the residue was crystallized from ethanol to yield **2**, 18.45 g (40%), mp >300°; ^{1}H-nmr: δ 1.97 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.04 (s, 2H, CH_2), 7.29 (m, 1H, 6-H), 7.50 (m, 1H, 5-H), 7.63 (m, 1H, 7-H), 8.06 (m, 1H, 8-H), 11.70 (br, 1H, OH); ms (TSP): m/e (%) 232 (MH^+, 20), 172 (100).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.49; H, 5.71; N, 6.08.

4-Hydroxy-3-hydroxymethylquinaldine (**3**).

Compound **2** (11.5 g, 50 mmoles) was refluxed in the mixture of 2 *M* aqueous sodium hydroxide solution (50 ml) and acetone (50 ml) for 1 hour. The solution was neutralized with 10% aqueous hydrochloric acid solution and the precipitated material was collected and washed with water to give **3**, 9.34 g (99%), mp >300°; ^{1}H-nmr: δ 2.48 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 7.23 (m, 1H, 6-H), 7.45 (m, 1H, 5-H), 7.55 (m, 1H, 7-H), 8.06 (m, 1H, 8-H), 11.40 (br, 1H, OH); ms: (EI) m/z (%) 189 (M^+, 40), 171 (100).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.65; H, 5.89; N, 7.32.

4-Chloro-3-chloromethylquinaldine (**4**).

The mixture of compound **3** (14.1 g, 75 mmoles) and phosphorus oxychloride (115 g, 750 mmoles) was heated at 85° for 3 hours. The mixture was then poured onto crushed ice (1 kg), the mixture was neutralized with concentrated aqueous ammonia solution, the precipitated material was collected, washed with water and purified by column chromatography (silica gel packing, chloroform-ethanol (9:1, v/v) eluent) to afford **4**, 5.96 g (35%), mp 91-93° (hexane); ^{1}H-nmr: δ 2.83 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 7.72 (m, 1H, 6-H), 7.87 (m, 1H, 7-H), 8.00 (m, 1H, 5-H), 8.17 (m, 1H, 8-H); ms: (EI) m/z (%) 225 (M^+, 31), 190 (100).

Anal. Calcd. for $C_{11}H_9Cl_2N$: C, 58.43; H, 4.01; N, 6.19. Found: C, 58.51; H, 4.03; N, 6.17.

General Procedure for the Preparation of 4-Chloro-3-(1,2,4-triazol-5-yl)thiomethylquinaldines **6**.

The mixture of the corresponding 1,2,4-triazole-5-thiol **5** (12 mmoles) and potassium carbonate (1.66 g, 12 mmoles) was stirred in dimethylformamide (10 ml) at 25° for 15 minutes. Compound **4** (2.26 g, 10 mmoles) was then added to the mixture, and it was stirred at the same temperature for 30 minutes, then was poured into ice-water (50 ml). The precipitated product was collected, washed with water and ethanol, and dried at room temperature.

4-Chloro-3-(1,2,4-triazol-5-yl)thiomethylquinaldine (**6a**).

This compound was obtained in a yield of 97% (2.82 g), mp 111-113° dec; ^{1}H-nmr: δ 2.78 (s, 3H, CH_3), 4.71 (s, 2H, CH_2), 7.70 (m, 1H, 6-H), 7.82 (m, 1H, 7-H), 8.00 (m, 1H, 5-H), 8.12 (m, 1H, 8-H), 8.56 (s, 1H, Tr-H), 14.15 (br, 1H, NH); ms: (TSP) m/z (%) 291 (MH^+, 100).

Anal. Calcd. for $C_{13}H_{11}ClN_4S$: C, 53.70; H, 3.81; N, 19.27. Found: C, 53.59; H, 3.80; N, 19.12.

4-Chloro-3-(3-methyl-1,2,4-triazol-5-yl)thiomethylquinaldine (**6b**).

This compound was obtained in a yield of 95% (2.90 g), mp 137-140° dec; ^{1}H-nmr: δ 2.36 (s, 3H, CH_3) 2.78 (s, 3H, CH_3), 4.67 (s, 2H, CH_2), 7.70 (m, 1H, 6-H), 7.83 (m, 1H, 7-H), 8.00 (m, 1H, 5-H), 8.14 (m, 1H, 8-H), 14.12 (br, 1H, NH); ms: (TSP) m/z (%) 305 (MH^+, 100).

Anal. Calcd. for $C_{14}H_{13}ClN_4S$: C, 55.17; H, 4.30; N, 18.38. Found: C, 55.01; H, 4.30; N, 18.29.

Desulfurization of Compound **6b**.

Compound **6b** (0.61 g, 2 mmoles) and Raney nickel (5 g wet paste washed with ethanol) were stirred in ethanol (20 ml) at 25° for 6 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness and was purified by column chromatography (silica gel packing, chloroform eluent) to yield 4-chloro-2,3-dimethylquinoline (**7**), 0.26 g (68%), mp 75-76° (ethanol); ^{1}H-nmr: δ 2.51 (s, 3H, CH_3) 2.67 (s, 3H, CH_3), 7.66 (m, 1H, 6-H), 7.76 (m, 1H, 7-H), 7.97 (m, 1H, 5-H), 8.12 (m, 1H, 8-H); ms: (EI) m/z (%) 191 (M^+, 100)

Anal. Calcd. for $C_{11}H_{10}ClN$: C, 68.94; H, 5.26; N, 7.31. Found: C, 68.99; H, 5.24; N, 7.29.

Cyclization of Compounds **6**. General Procedures for the Preparation of 6-Methyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino-[5,4-*c*]quinolines **8** and 6-Methyl-5*H*-[1,2,4]triazolo[3',4':2,3]-[1,3]thiazino[5,4-*c*]quinoline (**9**).

The corresponding compound **6** (10 mmoles) was stirred in dimethylformamide (10 ml) without any additional reagent (method A); in the presence of hydrochloric acid (10 mmoles) (method B); or potassium carbonate (10 mmoles) (method C) at the temperature indicated in Table 1 until all the starting material had been consumed (tlc). The reaction mixture was then diluted with water (50 ml), neutralized with concentrated aqueous ammonia solution (methods A and B), the solid material was collected, washed with water and dried. The yield of crude products and the ratio of isomers **8**, **9** determined by ^{1}H-nmr spectroscopy are indicated in Table 1.

6-Methyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,4-*c*]quinoline (**8a**).

The crude product obtained from the cyclization reaction of **6a** using method A at 25° was subjected to column chromatography (silica gel packing, chloroform:ethanol (9:1, v/v) eluent). The first crop from the column was **8a**, 1.41 g (55%), mp 172-174°; ms: (EI) m/z (%) 254 (M^+, 100).

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.53; H, 3.95; N, 22.11.

6-Methyl-5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,4-*c*]quinoline (**9a**).

Compound **9a** was obtained as a second crop from the column described above in a yield of 36% (0.91 g), mp 252-253°; ms: (EI) m/z (%) 254 (M^+, 100).

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.37; H, 3.93; N, 22.07.

2,6-Dimethyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[4,5-*c*]-quinoline (**8b**).

The crude product obtained from the cyclization reaction of **6b** using method A at 60° was recrystallized from chloroform-ethanol (1:1, v/v) mixture afforded **8b**, 1.86 g (69%), mp 170-172°, ms: (EI) m/z (%) 268 (M^+, 100).

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.70; H, 4.57; N, 20.89.

General Procedure for the Preparation of Hydrochloric Acid Salts of 3-Chloromethyl-4-(1,2,4-triazol-5-yl)thioquinaldines **10** by the Reaction of **4** and **5**.

The solution of compound **4** (2.26 g, 10 mmoles) and the corresponding compound **5** (12 mmoles) in dimethylformamide (10 ml) was stirred at 25°. After 10 minutes a crystalline material began to separate; after 30 minutes all the starting **4** was consumed (tlc). The crystalline product was removed by filtration, washed with acetone and dried.

3-Chloromethyl-4-(1,2,4-triazol-5-yl)thioquinaldine Hydrochloride (**10a**).

This compound was obtained in a yield of 90% (2.94 g), mp 246-248°; ^{1}H-nmr: δ 3.00 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 7.73 (m, 1H, 6-H), 7.93 (m, 1H, 7-H), 8.22 (m, 1H, 5-H), 8.37 (m, 1H, 8-H), 8.50 (s, 1H, Tr-H).

Anal. Calcd. for $C_{13}H_{12}Cl_2N_4S$: C, 47.72; H, 3.70; N, 17.12. Found: C, 47.55; H, 3.78; N, 17.29.

3-Chloromethyl-4-(3-methyl-1,2,4-triazol-5-yl)thioquinaldine Hydrochloride (**10b**).

This compound was obtained in a yield of 92% (3.14 g), mp 290-292°; ^{1}H-nmr: δ 2.22 (s, 3H, CH_3) 3.05 (s, 3H, CH_3), 5.34 (s, 2H, CH_2), 7.80 (m, 1H, 6-H), 7.98 (m, 1H, 7-H), 8.33 (m, 1H, 5-H), 8.42 (m, 1H, 8-H).

Anal. Calcd. for $C_{14}H_{14}Cl_2N_4S$: C, 49.27; H, 4.14; N, 16.42. Found: C, 49.22; H, 4.21; N, 16.57.

3-Acetoxymethyl-4-chloroquinaldine (**11**).

Compound **2** (4.62 g, 20 mmoles) was added to phosphoryl chloride (15.35 g, 100 mmoles) during the period of 5 minutes while the temperature of the mixture went up to 50°. In an additional 5 minutes the reaction went to completion. The mixture was poured onto crushed ice (100 g), then was neutralized with concentrated aqueous ammonia solution, the precipitated product was collected, dried and recrystallized from ethanol-hexane (1:1, v/v) to give **11**, 3.53 g (72%), mp 66-68°; ^{1}H-nmr: δ 2.12 (s, 3H, CH_3) 2.82 (s, 3H, CH_3), 5.50 (s, 2H, CH_2), 7.60 (m, 1H, 6-H), 7.76 (m, 1H, 7-H), 8.03 (m, 1H, 5-H), 8.23 (m, 1H, 8-H); ms: (EI) m/z (%) 249 (M^+, 10), 189 (100).

Anal. Calcd. for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.62; H, 4.83; N, 5.59

General Procedure for the Preparation of 3-Acetoxymethyl-4-(1,2,4-triazol-5-yl)thioquinaldines (**12**).

A solution of compound **11** (2.5 g, 10 mmoles) and the corresponding compound **5** (12 mmoles) in dimethylformamide (10 ml) was stirred at 25° for 1 hour. After the consumption of the starting compound **11**, the reaction mixture was diluted with water, neutralized with concentrated aqueous ammonia solution, the precipitated material was collected, washed with water and ethanol, and dried.

3-Acetoxymethyl-4-(1,2,4-triazol-5-yl)thioquinaldine (**12a**).

This compound was obtained in a yield of 92% (2.89 g), mp 191-193° (dimethyl sulfoxide-ethanol); ^{1}H-nmr: δ 2.00 (s, 3H, CH_3) 2.78 (s, 3H, CH_3), 5.63 (s, 2H, CH_2), 7.61 (m, 1H, 6-H), 7.78 (m, 1H, 7-H), 8.01 (m, 1H, 5-H), 8.34 (m, 1H, 8-H), 8.50 (s, 1H, Tr-H), 14.17 (br, 1H, NH); ms: (EI) m/z (%) 314 (M^+, 8), 254 (100).

Anal. Calcd. for $C_{15}H_{14}N_4O_2S$: C, 57.31; H, 4.49; N, 17.82. Found: C, 57.24; H, 4.54; N, 17.76.

3-Acetoxymethyl-4-(3-methyl-1,2,4-triazol-5-yl)thioquinaldine (**12b**).

This compound was obtained in a yield of 90% (2.95 g), mp 224-226° (dimethyl sulfoxide-ethanol); ^{1}H-nmr: δ 2.00 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.80 (s, 3H, CH_3), 5.61 (s, 2H, CH_2), 7.60 (m, 1H, 6-H), 7.77 (m, 1H, 7-H), 8.01 (m, 1H, 5-H), 8.36 (m, 1H, 8-H), 13.74 (br, 1H, NH); ms: (EI) m/z (%) 328 (M^+, 8), 268 (100).

Anal. Calcd. for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06. Found: C, 58.69; H, 4.88; N, 17.05.

General Procedure for the Preparation of 3-Hydroxymethyl-4-(1,2,4-triazol-5-yl)thioquinaldines (**13**).

The mixture of the corresponding compound **12** (10 mmoles) and 2 *M* aqueous sodium hydroxide solution (10 ml) was stirred at 25° for 1 hour. After the completion of the reaction, the solution was neutralized with 2 *M* aqueous hydrochloric acid solution, the precipitated product was collected, washed with water and ethanol and dried.

3-Hydroxymethyl-4-(1,2,4-triazol-5-yl)thioquinaldine (**13a**).

This compound was obtained in a yield of 96% (2.62 g), mp 212-213° (dimethyl sulfoxide-ethanol); ^{1}H-nmr: δ 2.85 (s, 3H, CH_3), 5.05 (s, 2H, CH_2), 7.56 (m, 1H, 6-H), 7.72 (m, 1H, 7-H), 7.97 (m, 1H, 5-H), 8.30 (m, 1H, 8-H), 8.42 (s, 1H, Tr-H), 13.74 (br, 1H, NH); ms: (EI) m/z (%) 272 (M^+, 33), 241 (100).

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.36; H, 4.40; N, 20.45.

3-Hydroxymethyl-4-(3-methyl-1,2,4-triazol-5-yl)thioquinaldine (**13b**).

This compound was obtained in a yield of 96% (2.75 g), mp 237-238° (dimethyl sulfoxide-ethanol); ^{1}H-nmr: δ 2.22 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 5.04 (s, 2H, CH_2), 7.57 (m, 1H, 6-H), 7.71 (m, 1H, 7-H), 7.96 (m, 1H, 5-H), 8.35 (m, 1H, 8-H), 13.80 (br, 1H, NH); ms: (EI) m/z (%) 286 (M^+, 33), 268 (100).

Anal. Calcd. for $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57. Found: C, 58.71; H, 4.90; N, 19.62.

General Procedure for the Preparation of the Hydrochloric Acid Salt of 3-Chloromethyl-4-(1,2,4-triazol-5-yl)thioquinaldines **10** from compounds **13**.

The mixture of the corresponding compound **13** (5 mmoles) and thionyl chloride (10 ml) was stirred at 25°. After 10 minutes crystalline material began to separate, and in 1 hour the reaction went to completion. Chloroform (10 ml) was then added to the reaction mixture, the product was removed by filtration, washed with chloroform and dried.

3-Chloromethyl-4-(1,2,4-triazol-5-yl)thioquinaldine Hydrochloride (**10a**).

This compound was obtained in a yield of 93% (1.52 g), mp 247-249°; ^{1}H-nmr: δ 3.00 (s, 3H, CH_3), 5.33 (s, 2H, CH_2), 7.75 (m, 1H, 6-H), 7.93 (m, 1H, 7-H), 8.22 (m, 1H, 5-H), 8.37 (m, 1H, 8-H), 8.50 (s, 1H, Tr-H).

3-Chloromethyl-4-(3-methyl-1,2,4-triazol-5-yl)thioquinaldine Hydrochloride (**10b**).

This compound was obtained in a yield of 96% (1.64 g), mp 291-293°; ^{1}H-nmr: δ 2.23 (s, 3H, CH_3) 3.05 (s, 3H, CH_3), 5.35 (s, 2H, CH_2), 7.80 (m, 1H, 6-H), 7.98 (m, 1H, 7-H), 8.32 (m, 1H, 5-H), 8.42 (m, 1H, 8-H).

Cyclization of Compounds **10**. General Procedure for the Preparation of 6-Methyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,6-*c*]quinolines **14** and 6-Methyl-5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,6-*c*]quinolines **15**.

The mixture of the corresponding compound **10** (5 mmoles) and potassium carbonate (1.38 g, 10 mmoles) was stirred in dimethylformamide at 25° for 4 hours. The mixture was then diluted with water (25 ml) and the precipitated material was collected by filtration, washed with water and dried.

6-Methyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,6-*c*]quinoline (**14a**).

The crude product (1.19 g, 94%) obtained from the cyclization reaction of **10a** was subjected to column chromatography (silica gel packing, chloroform-ethanol (9:1, v/v) eluent). The first crop from the column was **14a**, 0.70 g (55%), mp 238-240°; ms: (EI) m/z (%) 254 (M^+, 100).

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.42; H, 3.95; N, 22.05.

6-Methyl-5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,6-*c*]quinoline (**15a**).

The second crop from the column described above was **15a**, 0.39 g (31%), mp 244-245°; ms: (EI) m/z (%) 254 (M^+, 100).

Anal. Calcd. for $C_{13}H_{10}N_4S$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.39; H, 3.98; N, 22.14.

2,6-Dimethyl-5*H*-[1,2,4]triazolo[5',1':2,3][1,3]thiazino[5,6-*c*]-quinoline (**14b**).

The crude product (1.18 g, 88%) obtained from the cyclization reaction of **10b**, was subjected to column chromatography (silica gel packing, chloroform-ethanol (9:1, v/v) eluent). The first crop from the column was **14b**, 0.73 g (54%), mp 198-199°; ms: (EI) m/z (%) 268 (M^+, 100).

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.59; H, 4.50; N, 20.88.

3,6-Dimethyl-5*H*-[1,2,4]triazolo[3',4':2,3][1,3]thiazino[5,6-*c*]-quinoline (**15b**).

The second crop from the column described above was **15b**, 0.37 g (28%), mp 262-264°; ms: m/z (%) 268 (M^+, 100).

Anal. Calcd. for $C_{14}H_{12}N_4S$: C, 62.67; H, 4.51; N, 20.88. Found: C, 62.62; H, 4.51; N, 20.85.

Transformation of **10a** to the Mixture of **8a** and **9a**.

Compound **10a** (0.65 g, 2 mmoles) was heated with stirring in dimethylformamide (4 ml) at 80° for 2 hours. The reaction mixture was then diluted with water and neutralized with concentrated aqueous ammonia solution. The precipitated material was collected, washed with water and dried. The crude product obtained was 0.42 g (83%); consisted of **8a** (76%) and **9a** (24%) according to the ^{1}H-nmr spectrum of the mixture.

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