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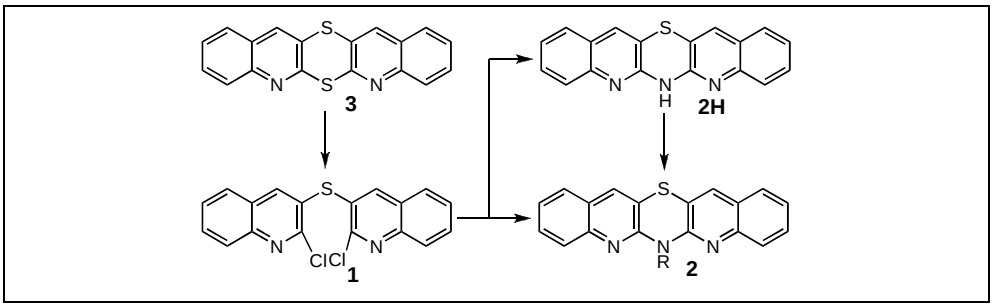

Reactions of 2,2'-dichloro-3,3'-diquinolinyl sulfide **1** with ammonia derivatives and various primary alkylamines and arylamines proceeded as a thiazine ring closure to form linear annulated pentacyclic 6*H*-diquinothiazine **2H** and 6-substituted derivatives **2** with alkyl, alkylaryl, aryl and heteroaryl substituents in moderate to good yields. Reaction with 2-chloroethylamine did not stop at the formation of half-mustard derivative **2k** but ran to ethylenediquinothiazinium salt **11**. 6*H*-Diquinothiazine **2H** was *N*-alkylated and *N*-arylated to give 6-substituted derivatives **2**. The crucial substrate **1** was obtained from other heteropentacenes **3** and **4** *via* 1,4-dithiin ring opening and further transformations. X-ray analysis of *p*-nitrophenyldiquinothiazine **2i** revealed unexpected planar thiazine ring.

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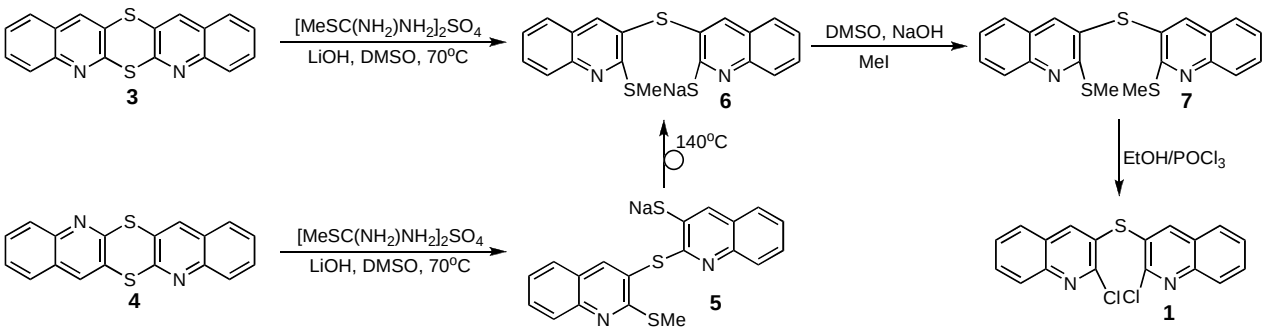
INTRODUCTION

Phenothiazines attract attention because of their wide chemical properties and very interesting biological activities (antipsychotic and anticancer). Some modifications of the phenothiazine structures were directed into azaphenothiazines, where the benzene ring was substituted with an azine ring [2]. In continuation of our search for pharmacoactive quinoline derivatives we modified the phenothiazine structure with the quinoline ring to obtain diquino-1,4-thiazines being pentacyclic dibenzodiazaphenothiazines [3,4]. It is worth noting that pentacyclic carbocycles and heterocycles (pentacenes and pentaphenes) are considered as a new types of electron donors [5-9] and show the significant conductivity [10] and photoelectric properties [11] and are the active layer in a FET device [12]. In the search of biologically active and semiconductive heterocycles a series of triazathiapentacenes being linear condensed pentacyclic diquino-1,4-thiazines has been synthesized.

RESULTS AND DISCUSSION

Synthesis. In our previous paper [13] we found 2,2'-dichloro-3,3'-diquinolinyl sulfide **1** to be very promising substrate to obtain various types of heteropentacenes in the heterocyclic ring (1,4-dithiin, 1,4-oxathiin, 1,4-thiaselenin, thiopyran and 1,4-thiazine) closure reactions with various reagents. The reaction of sulfide **1** with methylamine in hot phenol and with aniline in boiling monomethyl ether of diethylene glycol (MEDG) led to 6-methyl- and 6-phenyldiquino[3,2-*b*;2',3'-*e*][1,4]thiazines **2a** and **2b**. In this paper



Scheme 1

we describe the synthesis of 6*H*-diquinothiazine **2H** and various 6-substituted diquinothiazines **2** with alkyl, alkylaryl, aryl and heteroaryl substituents.

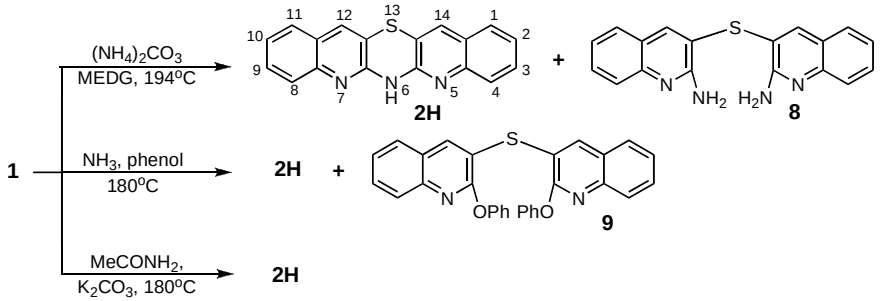
The crucial substrate **1** was obtained in the reaction of 1,4-dithiin ring opening in isomeric heteropentacenes (diquino-1,4-dithiins) **3** and **4** with *S*-methylisothiouronium sulfate in the presence of sodium hydroxide in DMSO at 70°C or 140°C followed by methylation with methyl iodide to give sulfide **7** which next was chlorinated with phosphoryl chloride in ethanol solution (Scheme 1). The use of *S*-methylisothiouronium sulfate made it possible to avoid working with very odorous sodium methanethiolate. In case of the reaction of heteropentacene **4** the dithiin ring opening was accompanied by the Smiles rearrangement of unusual type (S→S, the quinoline moiety migrated from one sulfur atom to another) of the resulting sulfide **5** to sulfide **6**.

In order to obtain 6*H*-diquinothiazine **2H** we examined reactions of sulfide **1** with various ammonia derivatives. First of all we carried reactions in the conditions found for the annulation reactions of the isomeric sulfide – 4,4'-dichloro-3,3'-diquinolinyl [3]. In the reaction of sulfide **1** with ammonium carbonate in MEDG at 194°C we obtained the annulated product – diquinothiazine **2H** in only 10% yield and the main product was the disubstituted compound – 2,2'-diamino-3,3'-diquinolinyl **8** in 44% yield. Similar result was obtained when sulfide **1** was reacted with gaseous ammonia in hot phenol (180°C) giving diquinothiazine **2H** in 13% yield and 2,2'-diphenoxy-3,3'-diquinolinyl **9** in 39% yield. Only the reaction of sulfide **1** with potassium carbonate in acetamide at 180°C gave the annulated product **2H** in moderate yield (57%) (Scheme 2).

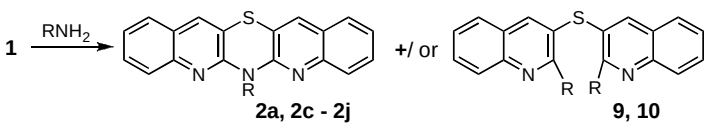
In order to obtain 6-substituted diquinothiazines **2** annulation reactions with alkyl and aryl amines were carried out in MEDG. The reaction of sulfide **1** with methylamine hydrochloride (5 equivalents) in MEDG gave diquinothiazine **2a** in higher yield (76%) than in phenol (51%) and without by-product **9** [13]. Reaction with butylamine gave 6-butyldiquinotiazines **2c** in low yield (17%) but repeated in an autoclave gave better yield (59%). Reactions with benzylamine led to benzyldiquinothiazine **2d** and open ring product – sulfide **10** depending on the reaction conditions and amounts of amine (Table 1).

The reactions with 3 equivalents of aromatic amines, being *para*-substituted anilines, (*p*-toluidine, 4-chloroaniline, 4-bromoaniline, 4-aminobenzoic acid) gave 6-aryldiquinothiazines **2e-2h** in moderate to good yield (61-82%, Table 1). The reaction with 4-nitroaniline gave (4'-nitrophenyl)diquinothiazine **2i** in very low yield (10%) but better yield was achieved in an autoclave (56%). The reaction with heteroaromatic amine, 2-aminopyridine, in MEDG gave no product but in phenol at 180°C gave (2'-pyridyl)diquinothiazine **2j** in very low yield (11%) and sulfide **9** as the main product (63%). Repeating the reaction in boiling 1-methyl-2-pyrrolidinone (MP, 202°C) did not bring better yield (Scheme 3).

Reaction of sulfide **1** with 2-chloroethylamine to give nitrogen half-mustard derivative **2k** led to compound possessing different properties from diquinothiazines **2a-2j**. This product first of all was soluble in water and the Beilstein test and the reaction with silver nitrate showed the chlorine atom in the molecule of anionic nature. The ^{1}H NMR spectrum revealed unsymmetrical structure since both quinoline proton signals were nonequivalent. All these data suggest the product structure as 5,6-ethylenediquinothiazinium chloride **11** formed from diquinothiazine **2k** by *N*-alkylation of one of the quinoline nitrogen atoms with reactive 2-chloroethyl group (Scheme 4).



Scheme 2

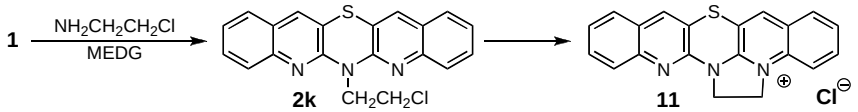


9 R = OPh
10 R = $NHCH_2Ph$

Scheme 3

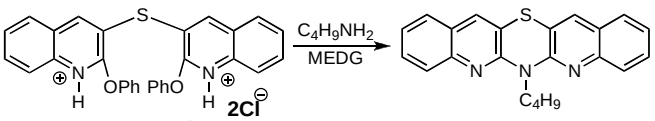
Table 1. Reactions of 2,2'-dichloro-3,3'-diquinolinyl sulfide **1** with aliphatic and aromatic amines

No	Amine (mmol)	Solvent, temp. (°C)/ time (hours)	Products: diquinothiazines **2**, **11**, sulfides **9, 10,** R, (yield, %)
1	methylamine x·HCl (5)	MEDG, reflux/3	**2a** R = CH_3 (76)
2	butylamine (5)	MEDG, reflux/3	**2c** R = $CH_2CH_2CH_2CH_3$ (17)
3	butylamine (3)	MEDG, 180/3, autoclave	**2c** R = $CH_2CH_2CH_2CH_3$ (59)
4	benzylamine (5)	MEDG, reflux/3	**2d** R = $CH_2C_6H_5$ (33), **10** (40)
5	benzylamine (3)	MEDG, 180/3, autoclave	**2d** R = $CH_2C_6H_5$ (45), **10** (23)
6	benzylamine (10)	MEDG, 180/3, autoclave	**10** R = $NHCH_2C_6H_5$ (84)
7	*p*-toluidine (3)	MEDG, reflux/4	**2e** R = p-$C_6H_4CH_3$ (61)
8	4-chloroaniline (3)	MEDG, reflux/4	**2f** R = p-C_6H_4Cl (70)
9	4-bromoaniline (3)	MEDG, reflux/4	**2g** R = p-C_6H_4Br (82)
10	4-aminobenzoic acid (3)	MEDG, reflux/4	**2h** R = p-C_6H_4COOH (76)
11	4-nitroaniline (3)	MEDG, reflux/4	**2i** R = p-$C_6H_4NO_2$ (10)
12	4-nitroaniline (3)	MEDG, 180/4, autoclave	**2i** R = p-$C_6H_4NO_2$ (56)
13	2-aminopyridine (3)	MP, reflux/4	**2j** R = 2-C_5H_4N (11)
14	2-aminopyridine (3)	phenol, 180/1	**2j** R = 2-C_5H_4N (11), **9** R = OC_6H_5 (63)
15	$NH_2CH_2CH_2Cl$ (5)	MEDG, reflux/4	**11** R = CH_2CH_2/Cl (44)
16	$NH_2CH_2CH_2Cl$ (5)	MEDG, 180/4, autoclave	**11** R = CH_2CH_2/Cl (53)



Scheme 4

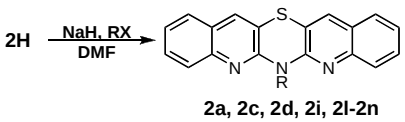
Since substituted 4-aminoquinolines can be easily obtained in reactions of chloroquinolines with alkylamines in hot phenol *via* phenoxy derivative [14], we tried to use the by-product, sulfide **9**, in synthesis of diquinothiazines **2**. Although sulfide **9** was unreactive towards selected alkyl-amine, butylamine, in MEDG, its dihydrochloride (**9 x 2HCl**) gave 6-butyldiquinothiazine **2c** in good yield, 73% (Scheme 5).



9 * 2HCl **2c**

Scheme 5

6-Substituted diquinothiazines were also obtained in the thiazine hydrogen substitution in 6*H*-diquinothiazine **2H**. *N*-Alkylation reactions were carried out in DMF in the presence of sodium hydride at room temperature with selected alkyl halides (methyl, ethyl, butyl, allyl, benzyl and phenacyl) to give diquinothiazines **2a**, **2c**, **2d** and **2l-2n** with relatively good yield (59-83%, Scheme 6, Table 2). *N*-Arylation to give nitrophenyldiquinothiazine **2i** was succeeded in 86% in the case of phenylation with 4-fluoronitrobenzene. 4-Chloro- and 4-bromonitrobenzene were ineffective under these reaction conditions. In the case of benzylation and nitrophenylation synthesis of diquinothiazines **2d** and **2i** was more effective than using the annulation reactions.



2a, 2c, 2d, 2i, 2l-2n

Scheme 6

Table 2. *N*-Alkylation and *N*-arylation reactions of 6*H*-diquinothiazine **2H** in DMF (20 °C/24 h)

No	Alkylating or arylating agent	Diquinothiazine **2** (yield, %)
1	methyl iodide	**2a** R = CH_3 (64)
2	butyl iodide	**2c** R = $CH_2CH_2CH_2CH_3$ (59)
3	benzyl chloride	**2d** R = $CH_2C_6H_5$ (83)
4	4-fluoronitrobenzene	**2i** R = $C_6H_4NO_2$ (86)
5	ethyl iodide	**2l** R = CH_2CH_3, (61)
6	allyl bromide	**2m** R = $CH_2CH{=}CH_2$ (68)
7	phenacyl bromide	**2n** R = $CH_2COC_6H_5$ (79)

Physical and spectroscopic properties of diquinothiazines 2. The annulation rections of sulfide **1** and *N*-alkylation reactions of diquinothiazine **2H** were followed by TLC analysis. All chromatograms of diquinothiazines **2** showed colour changes (from blue to yellow) during irradiation with UV lamp unlike to chromatograms of sulfides **1** and **8-10**. Similar effect (orange colour for diquinothiazine **2H** and yellow colour for diquinothiazines **2a-2n**) was observed when chromatograms of diquinothiazines **2** were sprayed with a phenothiazine detection mixture (sulfuric acid-water-ethanol 1:1:8) [15]. Only diquinothiazinium salt **11** gave a spot of intensive yellow colour at once.

The ^{1}H NMR spectra of the obtained diquinothiazines **2** recorded in deuteriochloroform showed four multiplets (two doublet-shaped with one *ortho*-coupling and two triplet-shaped multiplets with two *ortho*-coupling, J = 7-8.5 Hz) of an ABCD system of benzene ring protons and a singlet of the pyridine ring protons (H12/H14). Unquestionable assignment of the benzene protons (H1/H11, H2/H10, H3/H9 and H4/H8) was based on homonuclear NOE experiment and homonuclear ^{1}H-^{1}H correlation (COSY) as described in reference [13] for compounds **2a** and **2b**. All the ^{1}H NMR spectra for diquinothiazines **2** showed the spectral equivalency of the left and right parts of the molecule. This result is evidence that all these reactions ran without a cleavage of the C-S bond and the Smiles rearrangement as we found for other diquinolinyl sulfides [16-18]. Only diquinothiazinium salt **11** showed the spectral nonequivalency of both parts of the molecule. Mass spectra of diquinothiazines **2** revealed relatively high intensity of the molecular ions and some fragmentary ions. In the case of compound **11** the molecular ion was equal with diquinothiazinium cation (m/z = 328).

All diquinothiazines **2** show promising potential anti-psychotic, antidepressant, antihistaminic, antiasthmatic, anticancer and sedative activity [19] and very lipophilic character (logP = 4.13-6.85) [20].

X-ray study. There are only a few reports on the crystal structure of heteropentacenes [12,13,18,21]. The X-ray study of compounds **2b** [21] and **2i** confirmed their triazathiapentacene structure and the C_{2v} symmetry. In the search of biologically active heterocycles, a series of 10-arylphenothiazines were synthesized and X-ray structure studied. The most interesting structural aspects (boat conformation of the thiazine ring, a butterfly folding around the N...S axis, location and rotation of the aryl substituent and the N-aryl bond length) were concerned with aryl substituents, especially substituted phenyls with electron-donating and electron-accepting groups. These studies indicated that the phenyl substituent can be in the equatorial or axial location and the phenyl ring plane is coplanar or perpendicular to the plane bisecting the dihedral angle of the phenothiazine ring system depending on steric and electronic interactions [2,22-25]. Whereas X-ray analysis of phenyldiquinothiazine **2b** showed folding ring system with the central thiazine ring in boat conformation [21], the analysis of *p*-nitrophenyl-diquinothiazine **2i** revealed planar thiazine ring. The folding angle between the planes of the two halves of the thiazine ring (*i.e*. C2/C3/S1/N3 and C12/C13/S1/N3) is 178.4(2)°. The displacements of S1 and N3 atoms from the central C2/C3/C12/C13 was very small in comparison with compound **2b** (Table 3). The pentacyclic ring system is a little twisted (Figure 1) with the angle between the quinoline ring planes of 164.8(1)°. The nitrogen atom N3 is perfectly planar in configuration (the sum of the C-N3-C bond angles is 360(4)°) and the C21-N3...S1 angle is 178.3(3)° which suggests the sp^2 hybridization of the nitrogen atom. The planar thiazine ring permits an increase of the C2-N3-C12 and C3-S1-C13 bond angles in comparison with the appropriate angles in diquinothiazine **2b**. The phenyl ring plane bisects the pentacene ring system with the angle between the phenyl ring plane and the C2/C3/-C12/C13 plane of 78.3(1)°. The bisecting conformation of the nitrophenyl group is also shown by the torsion angles about the N(3)-C(21) bond: C(2)-N(3)-C(21)-C(22) and C(2)-N(3)-C(21)-C(26) of -79.9(6)° and 97.9(6)°. The nitro group plane is tilted from the phenyl ring plane by 3.5(5)°. It is worth noting that the phenyl group plane in 10-(*p*-nitrophenyl)phenothiazine is perpendicular to the bisecting plane of tricyclic ring system as a result of resonance interactions between the thiazine nitrogen atom and the phenyl carbon atom. As a consequence of these interactions, the nitrophenyl substituent is situated in an axial location and the C_{phenyl}-N bond is shorter than usual (1.389 Å) [24]. The analogous bond in diquinothiazine **2b** (C21-N3) is significantly longer, 1.443(6) Å. It seems that the electron-accepting N1 and N2 nitrogen atoms in *p*-nitrophenyldiquino-thiazine **2i** prevents overlapping of the N3 lone pair and the π-deficient *p*-nitrophenyl ring.

Table 3. Comparison of geometrical features of diquinothiazines **2b** and **2i**

Geometrical feature	**2b** [21]	**2i**
C3/C13-S1 bond length/Å	1.750(3), 1.761(4)	1.752(5), 1.743(6)
C2/C12-N3 bond length/Å	1.395(40, 1.410(4)	1.412(7), 1.408(7)
C21-N3 bond length/Å	1.451(4)	1.443(6)
C3-S1-C13 angle/°	100.1(2)	102.6(3)
C2-N3-C12 angle/°	123.8(2)	125.7(4)
Angle between the halves of the thiazine ring/°	149.4(1)	178.4(2)
Dihedral angle between the quinoline moieties/°	159.5(1)	164.8(1)
Dihedral angle between the phenyl ring and C2/C3/C12/C13 planes/°	73.4(1)	78.3(1)
Displacement of the S1 atom from C2/C3/C12/C13 plane/ Å	0.481(1)	-0.028(2)
Displacement of the N3 atom from C2/C3/C12/C13 plane/ Å	0.247(4)	- 0.007(4)

In the crystal the parallel stacking of pentacene rings is observed (Figure 2). The distance between the r.m.s. planes of the pentacene rings of two neighbouring molecules in the stack is 3.777(8) Å. The nitrophenyl substituents of the stacking molecules are also parallel and the distance between the r.m.s. planes of nitrophenyl is 2.739(7) Å. This is the first example of the *N*-substituted diareno-1,4-thiazines, excluding some

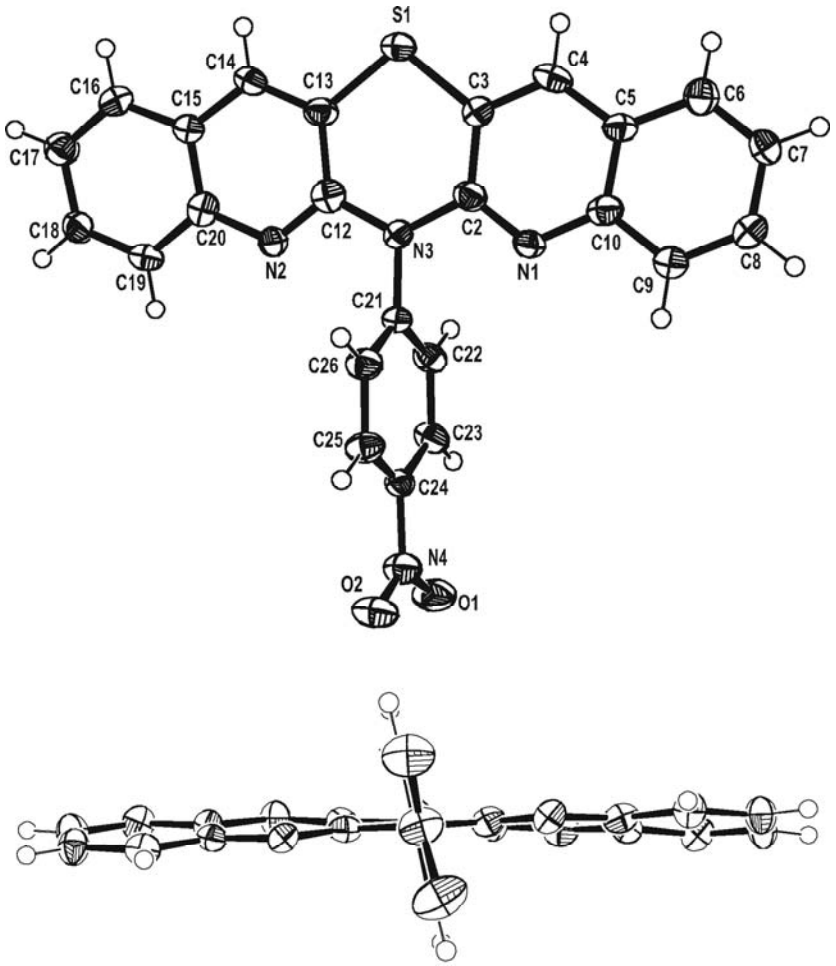


Figure. 1. A view of compound **2i** with atom numbering. Displacement ellipsoids are drawn at the 50% probability level.

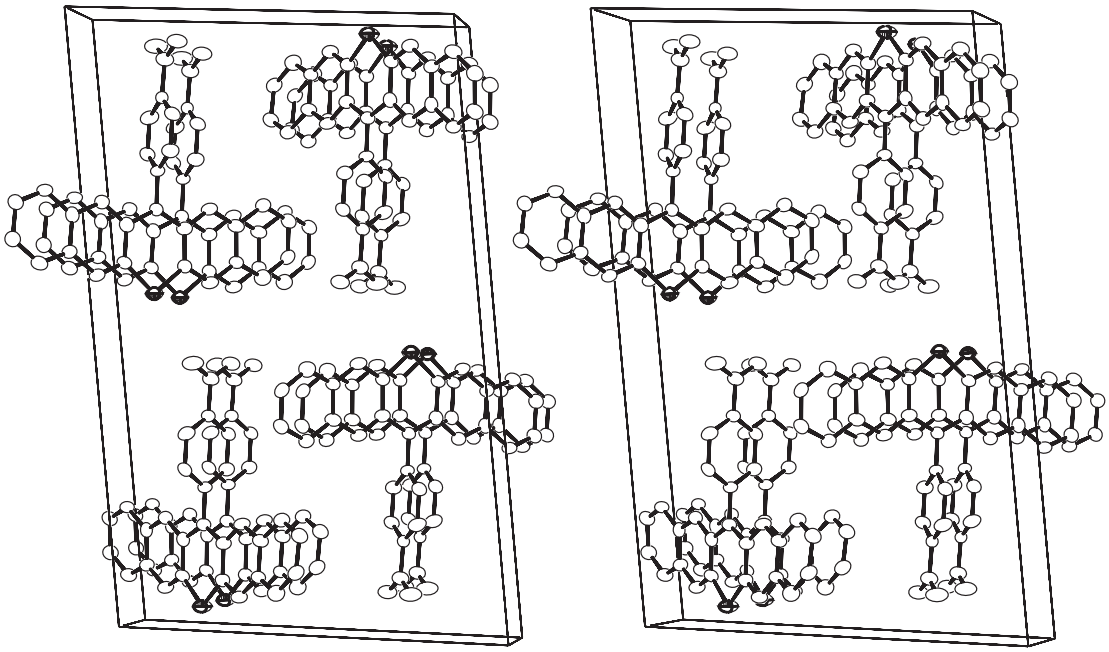


Figure 2. A Stereoview of the unit cell along b direction. Hydrogen atoms are omitted for clearity.

complexes with inorganic salts and organic compounds [26], with the thiazine ring to be planar.

CONCLUSION

We report an efficient synthesis of novel triazathiapentacenes being diquinothiazines **2** in the annulation reaction as a thiazine ring closure of 2,2'-dichloro-3,3'-diquinolinyl sulfide **1** with ammonia derivatives and primary alkyl, alkylaryl, aryl and heteroaryl amines. 6*H*-Diquinothiazine **2H** was transformed into 6-substituted diquinothiazines **2** *via* *N*-alkylation and *N*-arylation. The crucial substrate **1** was obtained from other diazadithiapentacenes **3** and **4** *via* 1,4-dithiin ring opening and further transformations. X-ray analysis of *p*-nitrophenyldiquinothiazine **2i** revealed unexpected planar thiazine ring.

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. Mass spectra (EI MS and FAB MS in the *m*-nitrobenzyl alcohol matrix) were run on a Finnigan MAT 95 spectrometer at 70 eV. The thin layer chromatography were performed on silica gel 60 F_{254} (Merck 1.05735) with chloroform-ethanol (10:1 v/v) and on aluminum oxide 60 F_{254} neutral (type E) (Merck 1.05581) with methylene chloride as eluent.

Synthesis. Diquinodithiins **3** and **4** were obtained from 3-bromo-2(1*H*)-quinolinethione or 2-chloro-3-bromoquinoline according to described procedure [18].

2,2'-Dimethyl-3,3'-diquinolinyl sulfide (**7**)**.**

A. from diquinodithiin (3). To a suspension of diquinodithiin (**3**) (0.32 g, 1 mmole) in dry DMSO (10 ml) at 70 °C was added *S*-methylisothiouronium sulfate (0.21 g, 1.5 mmoles) and lithium hydroxide (LiOH × H_2O, 0.13 g, 3 mmoles). The mixture was stirred for 30 min. After cooling the reaction mixture was poured into 15% aqueous sodium hydroxide (30 ml). Possibly unreacted substrates were filtered off and the filtrate was stirred with methyl iodide (0.1 ml, 1.6 mmoles). The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, methylene chloride) to give sulfide **7** (0.31 g, 82%); mp 188-189 °C (lit [18] 188-189 °C).

B. from diquinodithiin 4. To a suspension of diquinodithiin **4** (0.32 g, 1 mmole) in dry DMSO (10 ml) at 140 °C was added *S*-methylisothiouronium sulfate (0.21 g, 1.5 mmoles) and lithium hydroxide (LiOH × H_2O, 0.13 g, 3 mmoles). The mixture was stirred for 30 min. After cooling the reaction mixture was poured into 15% aqueous sodium hydroxide (30 ml). Possibly unreacted substrates were filtered off and the filtrate was stirred with methyl iodide (0.1 ml, 1.6 mmoles). The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, methylene chloride) to give sulfide **7** (0.21 g, 55%); mp 188-189 °C (lit [18] 188-189 °C).

2,2'-Dichloro-3,3'-diquinolinyl sulfide (1). To a solution of sulfide **7** (0.38 g, 1 mmole) in ethanol (10 ml) phosphoryl chloride (10 ml) was added very carefully drop by drop through a condenser. The mixture was refluxed for 10 hours and the progress of the reaction was monitored by TLC. After cooling, the reaction was stirred with ice (20 g) and alkalized with concentrated ammonia to pH~10. The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, methylene chloride) to give sulfide **1** (0.28 g, 78%); mp 198-199 °C (lit [27] 198-200 °C).

6*H*-Diquinothiazine (2H).

A. Reaction with ammonium carbonate in MEDG. To a solution of sulfide 1 (0.36 g, 1 mmole) in boiling MEDG (10 ml) ammonium carbonate (0.48 g, 5 mmoles) was added portionally during 4 hours. After cooling the reaction mixture was poured into water (25 ml). The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, chloroform-ethanol 10:1) to give:

6*H*-diquinothiazine (2H). This compound was obtained as orange powder (0.03 g, 10%); mp > 300 °C; ^{1}H NMR: δ ($CDCl_3$) 7.38 (m, 2H, 2-H, 10-H), 7.54 (m, 2H, 1-H, 11-H), 7.59 (m, 2H, 3-H, 9-H), 7.71 (s, 2H, 12-H, 14-H), 7.82 (m, 2H, 4-H, 8-H); MS: m/z (EI) 301 (M^+, 100), 269 (17.9, M-S), 257 (8.2, M-CS). *Anal*. Calcd for $C_{18}H_{11}N_3S$: C, 71.74; H, 3.68; N, 13.94. Found: C, 71.57; H, 3.72; N, 13.68.

2,2'-diamino-3,3'-diquinolinyl sulfide (7). This compound was obtained as yellow crystals (0.14 g, 44%); mp 218-220 °C; ^{1}H NMR: δ ($CDCl_3$) 7.53 (m, 2H, 2 × 6-H), 7.70 (m, 2H, 2 × 7-H), 7.76 (m, 2H, 2× 5-H), 8.03 (m, 2H, 2 × 8-H), 8.19 (s, 2H, 2 × 4-H); MS: m/z (EI) 318 (M^+, 100), 301 (29.7, M-NH_3). *Anal*. Calcd for $C_{18}H_{14}N_4S$: C, 67.90; H, 4.43; N, 17.60. Found: C, 67.58; H, 4.75; N, 17.27.

B. Reaction with ammonia in phenol. To a solution of sulfide 1 (0.36 g, 1 mmole) in phenol (2 g) at 180 °C gaseous ammonia was portionally during 1 hour. After cooling, water was added and the phenol was removed by distillation. The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, chloroform-ethanol 10:1) to give: 6*H*-diquinothiazine (**2H**) (0.04 g, 13%); mp > 300 °C.

2,2'-diphenoxy-3,3'-diquinolinyl sulfide (9). This compound was obtained as white crystals (0.18 g, 39%); mp 129-130 °C; ^{1}H NMR: δ ($CDCl_3$) 7.19 (m, 4H, 2 × C_6H_2), 7.44 (m, 8H, 2 × 6-H, 2 × C_6H_3), 7.60 (m, 2H, 2 × 7-H), 7.67 (m, 2H, 2 × 5-H), 7.75 (m, 2H, 2 × 8-H), 8.10 (s, 2H, 2 × 4-H); MS: m/z (EI) 472 (M^+, 88.5), 379 (100, M-OPh). *Anal*. Calcd for $C_{30}H_{20}N_2O_2S$: C, 76.25; H, 4.27; N, 5.93. Found: C, 75.91; H, 4.43; N, 5.79.

C. Reaction with potassium carbonate in acetamide. To acetamide (3.70 g, 60 mmoles) at 180 °C a mixture of sulfide **1** (0.36 g, 1 mmole) and potassium carbonate (0.56 g, 4 mmoles) was added portionally during 10 minutes. The mixture was stirred for 20 minutes. After cooling water (10 ml) was added and the resulting solid was collected by filtration, washed with water, air-dried and crystallized from DMF to give 6*H*-diquinothiazine (**2H**) (0.17 g, 57%); mp > 300 °C.

6-Substituted diquinothiazines (2)

A. in the annulation reactions of sulfide 1 - general procedure. To a solution of sulfide **1** (0.36 g, 1 mmole) in MEDG (5 ml), boiling or at 180 °C in an autoclave or in phenol (2 g, at 180 °C), or in boiling 1-methyl-2-pyrrolidinone (5 ml) amine (3, 5 or 10 mmoles, Table 1) was added. The reaction mixture was heated for 3 or 4 hours. After cooling the mixture

was poured into water (25 ml). In the case of the phenol procedure phenol was removed by steam distillation. The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, chloroform) to give diquinothiazines **2a**, **2c**-**2j** and sulfides **8-10** (Table 1).

6-Methyldiquinothiazine (2a). This compound had mp 200-201 °C (lit [13] 200-201 °C).

6-Butyldiquinothiazine (2c). This compound was obtained as yellow crystals; mp 136-137 °C; ^{1}H NMR: δ ($CDCl_3$) 1.07 (t, 3H, J = 8.6 Hz, CH_3), 1.57 (m, 2H, J = 8.6 Hz, CH_2), 1.85 (m, 2H, J = 8.6 Hz, CH_2), 4.67 (t, 2H, J = 8.6 Hz, CH_2),7.28 (m, 2H, 2-H, 10-H), 7.51 (m, 4H, 1-H, 3-H, 9-H, 11-H), 7.66 (s, 2H, 12-H, 14-H), 7.76 (m, 2H, 4-H, 8-H); MS: m/z (EI) 357 (M^+, 48.9), 328 (13.2, M-C_2H_5), 301 (100, M-C_4H_8). *Anal*. Calcd for $C_{22}H_{19}N_3S$: C, 73.92; H, 5.36; N, 11.75. Found: C, 73.64; H, 5.46; N, 11.47.

6-Benzyldiquinothiazine (2d). This compound was obtained as yellow crystals; mp 144-145 °C; ^{1}H NMR: δ ($CDCl_3$) 6.04 (S, 2H, CH_2), 7.18 (m, 2H, *o*-Ph), 7.25 (m, 3H, 2-H, 10-H, *p*-Ph), 7.49 (m, 2H, 3-H, 9-H), 7.51 (m, 2H, 1-H, 11-H), 7.63 (m, 2H, *m*-Ph), 7.66 (s, 2H, 12-H, 14-H), 7.73 (m, 2H, 4-H, 8-H); MS: m/z (EI) 391 (M^+, 100), 300 (44.3, M-Ph). *Anal*. Calcd for $C_{25}H_{17}N_3S$: C, 76.70; H, 4.38; N, 10.73. Found: C, 76.32; H, 4.29; N, 10.35.

6-(*p*-Tolyl)diquinothiazine (2e). This compound was obtained as yellow crystals; mp 236-237 °C; ^{1}H NMR: δ ($CDCl_3$) 2.52 (s, 3H, CH_3) 7.25 (m, 2H, 2-H, 10-H), 7.31 (m, 2H, *o*-C_6H_4), 7.38 (m, 2H, *m*-C_6H_4), 7.39 (m, 2H, 3-H, 9-H), 7.48 (m, 2H, 1-H, 11-H), 7.51 (m, 2H, 4-H, 8-H), 7.75 (s, 2H, 12-H, 14-H); MS: m/z (EI) 391 (M^+, 60.4), 390 (100, M-1). *Anal*. Calcd for $C_{25}H_{17}N_3S$: C, 76.70; H, 4.38; N, 10.73. Found: C, 76.48; H, 4.42; N, 10.42.

6-(4'-Chlorophenyl)diquinothiazine (2f). This compound was obtained as yellow crystals; mp 256-257 °C; ^{1}H NMR: δ ($CDCl_3$) 7.27 (m, 2H, 2-H, 10-H), 7.38 (m, 2H, *o*-C_6H_4), 7.43 (m, 2H, 3-H, 9-H), 7.48 (m, 2H, 1-H, 11-H), 7.53 (m, 2H, 4-H, 8-H), 7.54 (m, 2H, *m*-C_6H_4), 7.77 (s, 2H, 12-H, 14-H); MS: m/z (EI) 411 (M^+, 69.5), 413 (27.3, M+2), 410 (100, M-1). *Anal*. Calcd for $C_{24}H_{14}ClN_3S$: C, 69.98; H, 3.43; N, 10.20. Found: C, 69.63; H, 3.32; N, 10.02.

6-(4'-Bromophenyl)diquinothiazine (2g). This compound was obtained as yellow crystals; mp 265-266 °C; ^{1}H NMR: δ ($CDCl_3$) 7.30 (m, 2H, 2-H, 10-H), 7.32 (m, 2H, *o*-C_6H_4), 7.43 (m, 2H, 3-H, 9-H), 7.49 (m, 2H, 1-H, 11-H), 7.53 (m, 2H, 4-H, 8-H), 7.54 (m, 2H, *m*-C_6H_4), 7.70 (s, 2H, 12-H, 14-H); MS: m/z (EI) 455 (M^+, 57.8), 457 (63.5, M+2), 456 (100, M+1). *Anal*. Calcd for $C_{24}H_{14}BrN_3S$: C, 63.17; H, 3.09; N, 9.21. Found: C, 62.92; H, 3.18; N, 8.90.

6-(4'-Carboxyphenyl)diquinothiazine (2h). This compound was obtained as yellow crystals; mp 212-214 °C; ^{1}H NMR: δ ($CDCl_3$) 7.42 (m, 6H, 2-H, 10-H, C_6H_4), 7.51 (m, 4H, 1-H, 3-H, 9-H, 11-H), 7.59 (m, 2H, 4-H, 8-H), 7.77 (s, 2H, 12-H, 14-H); MS: m/z (EI) 421 (M^+, 1), 377 (61.1, M-CO_2), 376 (100, M-COOH). *Anal*. Calcd for $C_{25}H_{15}N_3O_2S$: C, 71.24; H, 3.59; N, 9.97. Found: C, 71.11; H, 3.70; N, 9.76.

6-(4'-Nitrophenyl)diquinothiazine (2i). This compound was obtained as yellow crystals; mp > 300 °C; ^{1}H NMR: δ ($CDCl_3$) 7.31 (m, 2H, 2-H, 10-H), 7.45 (m, 4H, 3-H, 4-H, 8-H, 9-H), 7.57 (m, 2H, 1-H, 11-H), 7.66 (m, 2H, *o*-C_6H_4), 7.82 (s, 2H, 12-H, 14-H) 8.45 (m, 2H, *m*-C_6H_4); MS: m/z (EI) 422 (M^+, 100), 421 (90.3, M-1), 410 (100, M-1). *Anal*. Calcd for $C_{24}H_{14}N_4O_2S$: C, 68.23; H, 3.34; N, 13.26. Found: C, 68.01; H, 3.38; N, 12.94.

6-(2'-Pyridyl)diquinothiazine (2j). This compound was obtained as orange crystals; mp 194-195 °C; ^{1}H NMR: δ ($CDCl_3$) 7.26 (m, 2H, 2-H, 10-H), 7.39 (m, 4H, 3-H, 4-H, 8-H, 9-H), 7.49 (m, 4H, 1-H, 11-H, 3-$H_{pyridynyl}$, 5-$H_{pyridynyl}$), 7.74 (s, 2H, 12-H, 14-H) 7.99 (m, 1H, 4-$H_{pyridynyl}$), 8.79 (m, 1H, 6-$H_{pyridynyl}$); MS: m/z (EI) 378 (M^+, 85.0), 377 (100, M-1). *Anal*. Calcd for $C_{23}H_{14}N_4S$: C, 73.00; H, 3.73; N 14.80. Found: C, 72.85; H, 3.78; N, 14.42.

2,2'-Dibenzylamino-3,3'-diquinolinyl sulfide (10). This compound was obtained as yellow crystals; mp 193-194 °C; ^{1}H NMR: δ ($CDCl_3$) 4.73 (d, 4H, J = 5.4 Hz, 2 × CH_2), 5.70 (t, 2H, J = 5.4 Hz, 2 × NH), 7.21 (m, 12H, 2 × 6-H, 2 × Ph), 7.48 (m, 2H, 2 × 5-H), 7.56 (m, 2H, 2 × 7-H), 7.73 (m, 2H, 2 × 8-H), 7.91 (s, 2H, 2 × H-4); MS: m/z (EI) 498 (M^+, 55.3), 408 (48.7, M-CH_2Ph). *Anal*. Calcd for $C_{32}H_{26}N_4S$: C, 77.08; H, 5.26; N, 11.24. Found: C, 76.89; H, 5.47; N, 10.92.

5,6-Ethylenediquinothiazinium chloride (11). This compound was obtained as yellow powder; mp > 300 °C; ^{1}H NMR: δ ($CDCl_3$) 4.26 (t, 2H, J = 9.9 Hz, CH_2), 4.95 (t, 2H, J = 9.9 Hz, CH_2), 7.51-7.94 (m, 8H, 1-H, 2-H, 3-H, 4-H, 8-H, 9-H, 10-H, 11-H), 8.38 and 8.57 (2s, 2H, 12-H, 14-H); MS: m/z (FAB) 328 (M-Cl, 21.3), 145 (100, m-nitrobenzyl alcohol). *Anal*. Calcd for $C_{20}H_{14}ClN_3S$: C, 66.02; H, 3.88; N, 11.55. Found: C, 65.79; H, 3.91; N, 11.21.

B. In the annulation reaction of sulfide 9 × 2HCl. A solution of sulfide **9 × 2HCl** (0.54 g, 1 mmole, obtained from sulfide **9** and hydrochloric acid) and butylamine (0.30 ml, 3 mmoles) in MEDG (5 ml) was refluxed for 4 hours. Another portion of butylamine (0.20 ml, 2 mmoles) was added and the reaction mixture was refluxed for 2 hours. After cooling the mixture was poured into water (25 ml). In the case of the phenol procedure phenol was removed by steam distillation. The resulting solid was collected by filtratino, washed with water, air-dried and purified by column chromatography (silica gel, chloroform) to give 6-butyldiquinothiazine (**2c**) (0.26 g, 73%).

C. In *N*-alkylation and *N*-arylation reactions - general procedure. To a solution of 6*H*-diquinothiazine (**2H**) (0.30 g, 1 mmole) in dry DMF (10 ml) sodium hydride (0.24 g, 10 mmoles) was added. The reaction mixture was stirred for 1.5 hours at room temperature and then alkyl or aryl halide (3 mmoles, Table 2). The stirring was continued for 24 hours and the mixture was poured into water (40 ml). The resulting solid was collected by filtration, washed with water, air-dried and purified by column chromatography (silica gel, chloroform) to give 6-substituted diquinothiazines **2a, 2c, 2d, 2i** and **2l-2n** as pale yellow crystals (Table 2):

6-Ethyldiquinothiazine (2l). This compound was obtained as yellow crystals; mp 180-181 °C; ^{1}H NMR: δ ($CDCl_3$) 1.50 (t, 3H, J = 6.8 Hz, CH_3), 4.47 (q, 2H, J = 6.8 Hz, CH_2),7.29 (m, 2H, 2-H, 10-H), 7.52 (m, 4H, 1-H, 3-H, 9-H, 11-H), 7.66 (s, 2H, 12-H, 14-H), 7.77 (m, 2H, 4-H, 8-H); MS: m/z (EI) 329 (M^+, 47.4), 314 (22.2, M-CH_3), 301 (100, M-C_2H_4), 300 (14.2, M-C_2H_5). *Anal*. Calcd for $C_{20}H_{15}N_3S$: C, 72.92; H, 4.59; N, 12.76. Found: C, 72.68; H, 4.61; N, 12.67.

6-Allyldiquinothiazine (2m). This compound was obtained as yellow crystals; mp 149-150 °C; ^{1}H NMR: δ ($CDCl_3$) 5.22 (d, 1H, J = 10.2 Hz, CH_2=), 5.37 (d, 2H, J = 5.7 Hz, CH_2), 5.55 (d, 1H, J = 18.6 Hz, CH_2=), 6.23 (m, 1H, J = 5.7 Hz, CH=), 7.29 (m, 2H, 2-H, 10-H), 7.51 (m, 4H, 1-H, 3-H, 9-H, 11-H), 7.67 (s, 2H, 12-H, 14-H), 7.76 (m, 2H, 4-H, 8-H); MS: m/z (EI) 341 (M^+, 35.0), 326 (100, M-CH_3), 300 (12.3, M-C_3H_5). *Anal*. Calcd for $C_{21}H_{15}N_3S$: C, 73.87; H, 4.43; N, 12.31. Found: C, 73.50; H, 4.46; N, 11.99.

6-Phenacyldiquinothiazine (2n). This compound was obtained as yellow crystals; mp 82-83 °C; ^{1}H NMR: δ ($CDCl_3$) 5.59 (s, 2H, CH_2), 7.48 (s, 2H, 12-H, 14-H), 7.58 (m, 6H, 1-H, 2-H, 3-H, 9-H, 10-H, 11-H), 7.60 (m, 3H, 4-H, 8-H, *p*-Ph), 7.98 (m, 2H, C_6H_2), 8.15 (m, 2H, C_6H_2); MS: m/z (EI) 419 (M^+, 31.2), 314 (42.2, M-COPh), 105 (100, $PhCO^+$). *Anal.* Calcd for $C_{26}H_{17}N_3OS$: C, 74.44; H, 4.08; N, 10.02. Found C, 74.19; H, 4.32; N, 9.84.

X-Ray analysis. Single crystals of 6-(4'-nitrophenyl)diquinothiazine **2i** were obtain by recrystallization from DMF. The intensity data were collected on a Bruker KappaApexII diffractometer with graphite-monochromated CuKα radiation (λ = 1.54178 Å). The structures were solved by direct methods (SHELXS-97) [28] and refined on F^2 by full-matrix least-squares (SHELXL-97) [29]. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were 'riding' on their carbon atoms ($d_{C–H}$ = 0.93 Å, U_{iso} = 1.2U_{eq} of the attached C atom.

Crystal data for **2i**: $C_{24}H_{14}N_4O_2S$, M = 422.45, translucent needle, 0.25 × 0.08 × 0.04 mm, monoclinic, space group $P2_1/c$ (No. 14), a = 14.997(1), b = 5.1898(4), c = 23.951(2) Å, β = 97.194(6)°, V = 1849.5(2) Å^3, Z = 4, D_c = 1.517 g/cm^3, F_{000} = 872, T = 100(2)K, μ(CuKα) = 1.825 mm^{-1}.

16659 reflections collected ($2\theta_{max}$ = 117.6°), 2537 unique (R_{int} = 0.125). Final *GooF* = 1.01, R = 0.089, wR = 0.212, R indices based on 1564 reflections with $I > 2\sigma(I)$, 281 parameters. Lp and absorption corrections applied but no correction for absorption.

CIF file deposited with Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (No 292797).

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