HETEROCYCLES, Vol. 81, No. 8, 2010, pp. 1799 - 1810. © The Japan Institute of Heterocyclic Chemistry
Received, 21st April, 2010, Accepted, 21st June, 2010, Published online, 21st June, 2010
DOI: 10.3987/COM-10-11963

2-METHYL- AND 2-DIMETYLAMINOQUINO[4,3-*e*]-1,2,4-THIADIAZINE 4,4-DIOXIDES – SYNTHESIS, STRUCTURE AND *N*-METHYLATION[#]

Elwira Chrobak,[a)] Michał Wlekliński,[a)] Andrzej Maślankiewicz,[a),*] Joachim Kusz,[b)] Maciej Zubko,[b)] and Andrzej Zięba[a)]

[a)] Department of Organic Chemistry, Medical University of Silesia, Jagiellońska 4, 41-200 Sosnowiec, Poland. [b)] Institute of Physics, University of Silesia, Uniwersytecka 4, 40-007 Katowice, Poland

E-mail: maslankiewicz@sum.edu.pl

Abstract – Reaction of 4-chloro-3-quinolinesulfonyl chloride (**1)** with acetamidine or with *N*,*N*-dimethyl- and *N*,*N*,*N*'-trimethylquanidine salts led directly or stepwise *via* 4-chloro-3-quinolinesulfonylguanidine (**6a**) to the title 2-substituted quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxides (**4**, **7a**, and **8**). X-Ray studies proved that 2-methyl derivative **4** exists as the 1H-tautomer while 2-dimethylamino derivative **7a** as the 6*H*-tautomer. Reaction of N-H derivatives **4** and **7a** and the pyrido-1,2,4-thiadiazine analog **11a** with CH_3I/CH_3OK/DMF system proceeded at the pyridine-ring nitrogen and led to 6-methylquino derivatives **5** and **7b** or the 7-methylpyrido derivative **11b**, respectively, as concluded from 2D ^1H - ^{13}C NMR data.

INTRODUCTION

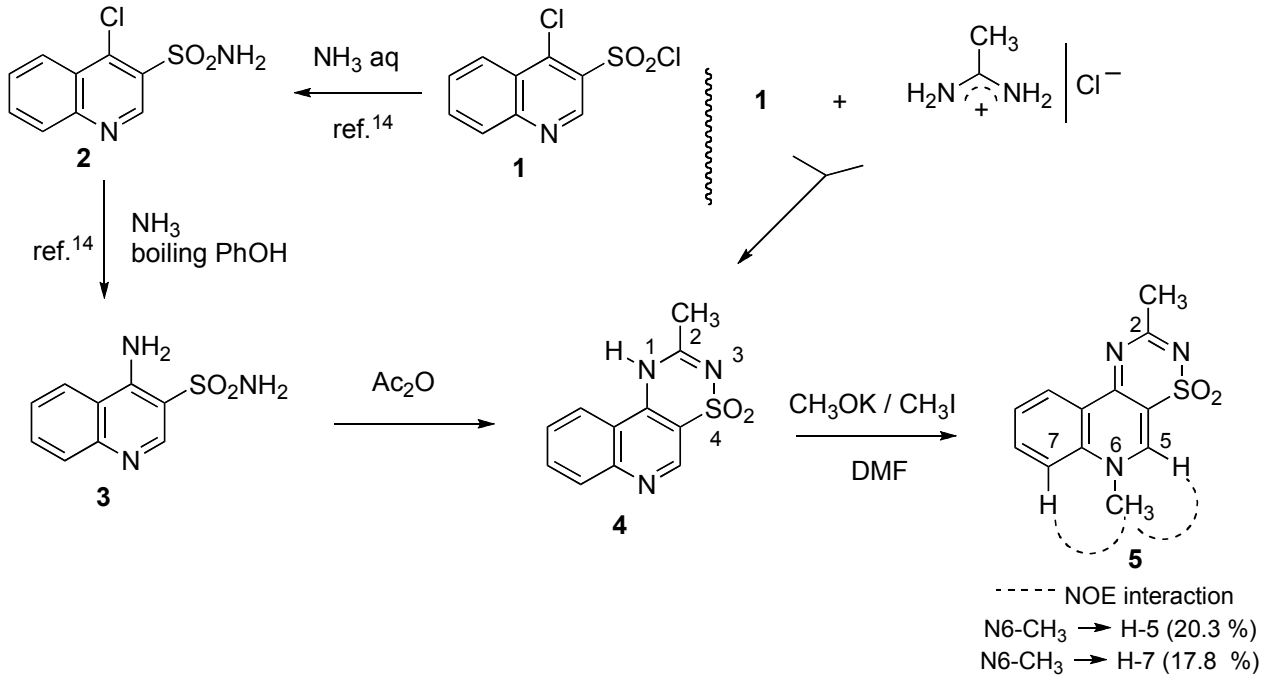
Significant biological activities of 1,2,4-benzo- and pyridothiadiazine 1,1-dioxides as potassium channel openers,[1-6] AMPA potentiators,[7] cytotoxic agents,[8] or anti-HIV agents[9] has turned medicinal chemists' attention to search for other areno- and heteroareno- fused 1,2,4-thiadiazine 1,1-dioxides as possible candidates for therapeutic application.

As far as heteroareno derivatives were concerned pyrido-1,2,4-thiadiazine derivatives[1,3,5,6,10] were the most studied but synthesis of pyrazo,[9] imidazo,[7,8] triazolo,[11] and thieno[9,12] derivatives was also reported. However, no literature data were found for the title quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxides **4**, **5**, **7a**,**b**, and **8**, which, as we describe in this paper, can be accessed from 4-chloro-3-quinolinesulfonyl chloride (**1**).

RESULTS AND DISCUSSION

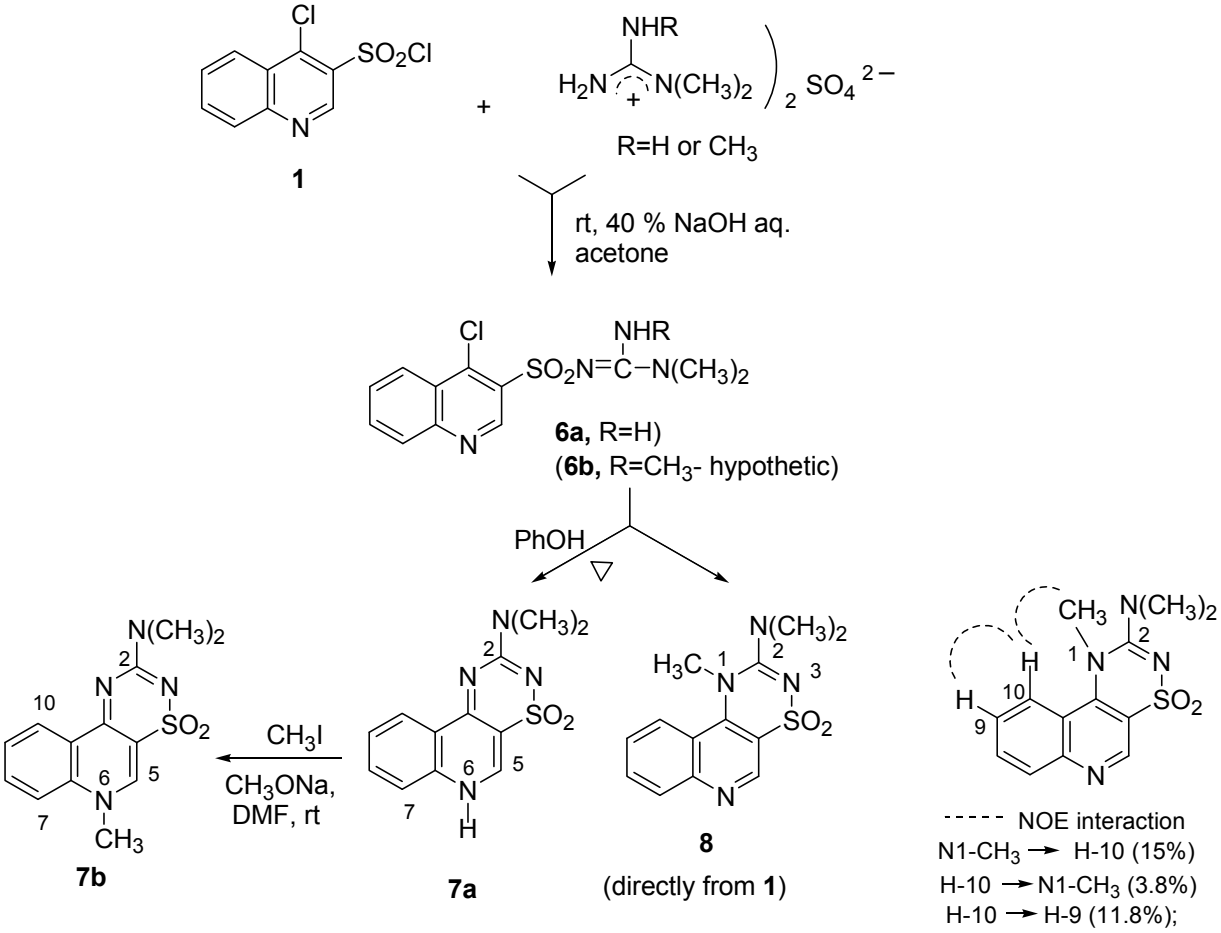
The 1,2,4-thiadiazine 1,1-dioxide ring system fused to a benzene or heteroarene moiety has usually been formed from *ortho*-amino-sulfonamide and appropriate cyclization agents. [1,2,3] This approach was preliminarily applied for the synthesis of the title quinothiadiazine (**4**). The required *ortho*-amino-sulfonamide, *i.e.* 4-amino-3-quinolinesulfonamide (**3**) could be prepared from easily available 4-chloro-3-quinolinesulfonyl chloride (**1**).[14] Cyclization of 4-amino-3-quinolinesulfonamide (**3**) with acetic anhydride afforded 2-methyl-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**). The structure of **4** as 1*H*-tautomer was deduced from X-ray data presented below.

Attempting to shorten the synthetic pathway leading from 4-chloro-3-quinolinesulfonyl chloride (**1**) to quinothiadiazine (**4**), 4-chloro-3-quinolinesulfonyl chloride (**1**) was directely subjected to reaction with acetamidine, or guanidine salts, applying the experimental procedure for sulfonylation of amidines and quanidines.[15] Indeed, the reaction with acetamidine hydrochloride led directly to quinothiadiazine **4** in 65 % yield.



Scheme 1

However, the reaction of sulfonyl chloride **1** with *N,N*-dimethylguanidine sulfate stopped at the sulfonylguanidine **6a** stage. The structure of **6a** as sulfonylimino tautomer was arbitrarily assigned based on literature data[15,16] concerning the sulfonylguanidines. Cyclization of *N*-(4-chloro-3-quinoline sulfonyl)-*N*',*N*'-dimethylguanidine (**6a**) to 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**) was performed in boiling phenol applying the *amino-de-chlorination* procedure for 4-chloroquinolines.[14] The structure of **7a** in the solid state was deduced from the X-ray study presented below.

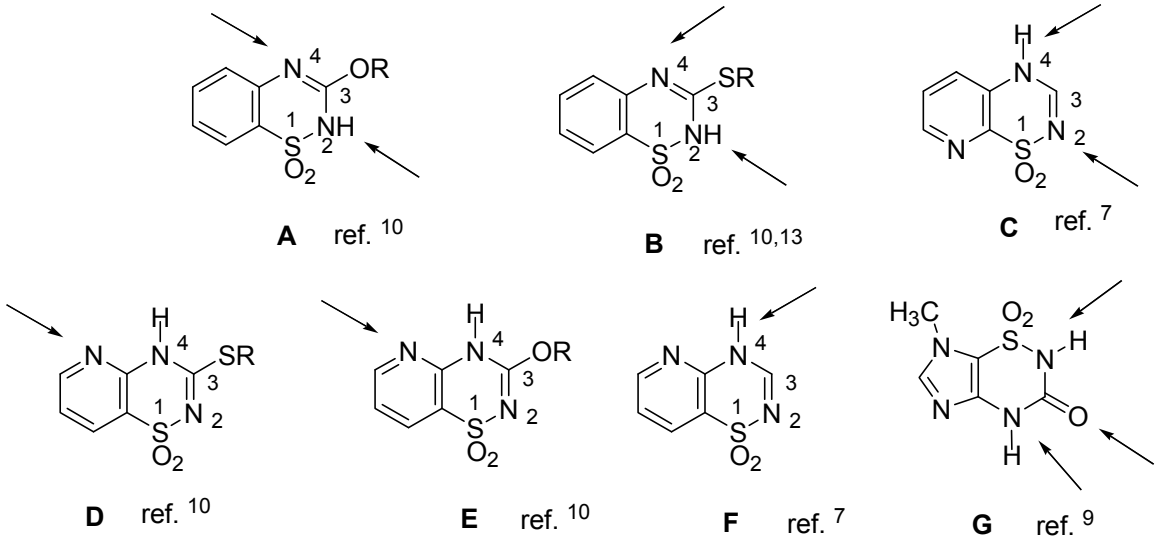


Scheme 2

The reaction between 4-chloro-3-quinolinesulfonyl chloride (**1)** and *N*,*N*,*N*'-trimethylguanidine did not proceed in a clean manner, but the major product (*ca.* 45%) was assigned as 1-methyl derivative **8** as presented below. This assignment was based on NOE experiments summarized in Scheme 2, indicating the spatial proximity of the 1-CH_3 group with to the H-10 proton because of irradiation of the *N*-methyl group protons (singlet, 3H, δ=3.69 ppm) led to enhancement of the H-10 proton signal (dd, δ=8.40 -8.42 ppm) by 15% but irradiation of the H-10 proton led to enhancement of both the N_1-CH_3 protons signal (δ=3.69 ppm, by 3.8%) and the H-9 signal (m, 1H, m, δ=7.76-7.80 ppm by 11.8%). As concluded from the structure of final product **8**, the reaction should start as sulfonylation at the less hindered NH_2 group, leaving the $NHCH_3$ group unaffected to produce intermediate compound **6b**. The latter was immediately consumed in the *amino de-chlorination* process to form final product **8.**

<u>*N*-Methylation.</u> In search of biologically active compounds, areno- and heteroareno-fused 1,2,4-thiadiazine 1,1-dioxides were modified by *N*-alkylation at N-H bonds.[3,7,9,10,13] 1,2,4-Thiadiazine 1,1-dioxides may exist in the form of N(2)-*H* and N(4)-*H* tautomers. However, only 4-alkylation products were isolated for pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxide **F**.[7] In the case of compounds **A**, **B**, **C** and **G** alkylation proceeded at both N(2) and N(4) nitrogens, but for pyrido[2,3-*e*]-1,2,4-thiadiazine 1,1-dioxides

D and **E**, it occurrred even outside the thiadiazine ring at the pyridine ring *endo*cyclic nitrogen atom.[10] (Scheme 3)



Scheme 3

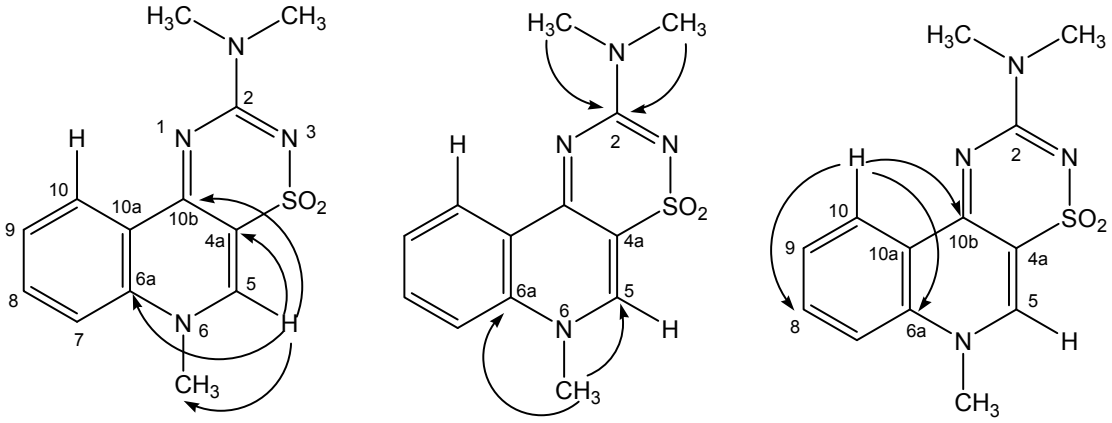
Orientation in the alkylation of 1,2,4-thiadiazine *S,S*-dioxide derivatives

Taking into consideration the above, both N-H quinothiadiazine 4,4-dioxides **4** and **7a** were subjected to methylation. The required potassium salts of **4** and **7a** were prepared *in situ* using potassium methoxide in DMF medium and then treated with methyl iodide at rt. Unexpectedly, the methylation of the potassium salt of quinothiadiazine **4a** proceeded at the pyridine-ring nitrogen atom and led to 2,6-dimethyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**5**) but not to the expected methylation products at the thiadiazine ring. The structure of **5** was deduced from the NOE study presented in Scheme 1 and also with HMBC experiments as shown in Scheme 4 for compound **7b**.

The same methylation approach performed on the potassium salt of **7a** also occurred at the pyridine ring to form 6-methyl derivative **7b**. The position of the newly-introduced N-CH_3 group was concluded from HSQC and HMBC experiments as presented in Scheme 4. The 400 MHz ^{1}H NMR spectrum of **7b** reveals three three-proton singlets of N-CH_3 groups, well separated multiplets of four benzene ring protons and a singlet of α-quinolinyl, *i.e.* H-5 proton. In the structure assignment of **7b** the key parts are played by the long range proton-carbon correlations between the H-5 proton (s, 1H, δ=9.05 ppm) and three quaternary carbon resonances of pyridine ring carbons accompanied by long range coupling with the N_6-methyl group carbon. A connectivity link between the benzene and pyridine parts of the quinothiadiazine molecule could be deduced from the long-range proton-carbon correlations of H-10 proton with C6a and C10b carbons.

Long-range proton-carbon couplings with N_6-methyl group protons (s, 3H, δ=4.16 ppm) and C5 and C6a carbons were also observed. Additionally, couplings of protons from dimethylamino group with C2

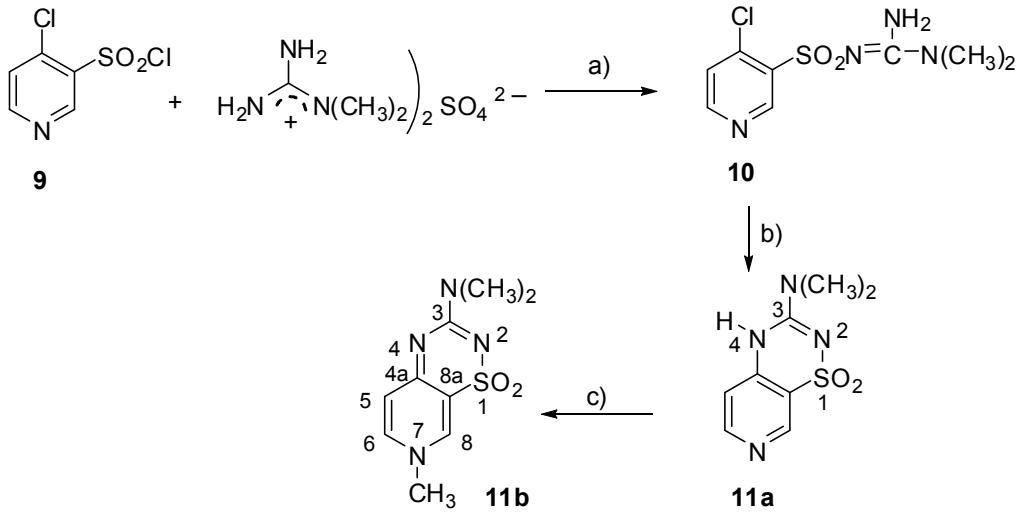
carbon allowed a complete assignment of the ^{1}H and ^{13}C NMR spectra of **7b** and therefore proved the structure of **7b**.



Scheme 4

Set of long-range proton-carbon correlations used in the NMR assignment of 6-methylquinothiadiazine dioxide **7b**

To evaluate the unexpected orientation in the methylation of quinothiadiazine 4,4-dioxides **4** and **7a**, we returned to 3-dimethylaminopyrido[4,3-*e*]-1,2,4-thiadiazine 1,1-dioxide (**11a)** as *des-benzo* analog of **7a**. For this purpose compound **11a** was prepared as presented in Scheme 5. Treatment of **11a** with potassium methoxide in DMF solution followed by reaction with methyl iodide at rt also proceeded at the pyridine ring N_7-nitrogen and led to the 7-methylderivative **11b**.



a) 40 % NaOH aq., acetone, rt; b) Cs_2CO_3, 1-butanol, boiling temp., 72 h, according to ref.[12]; c) CH_3OK, DMF, CH_3I, rt.

Scheme 5

X-Ray study.

X-Ray data for 2-methyl- and 2-dimethylaminoquinothiadiazine 4,4-dioxides **4** and **7a** were presented

graphically in the form of ORTEP drawings in figs. 1 and 2. The positions of N-H hydrogen atoms prove the tautomeric preferences for quinothiadiazine dioxide **4** as the 1H-tautomer but for **7a** as the 6H-tautomer.

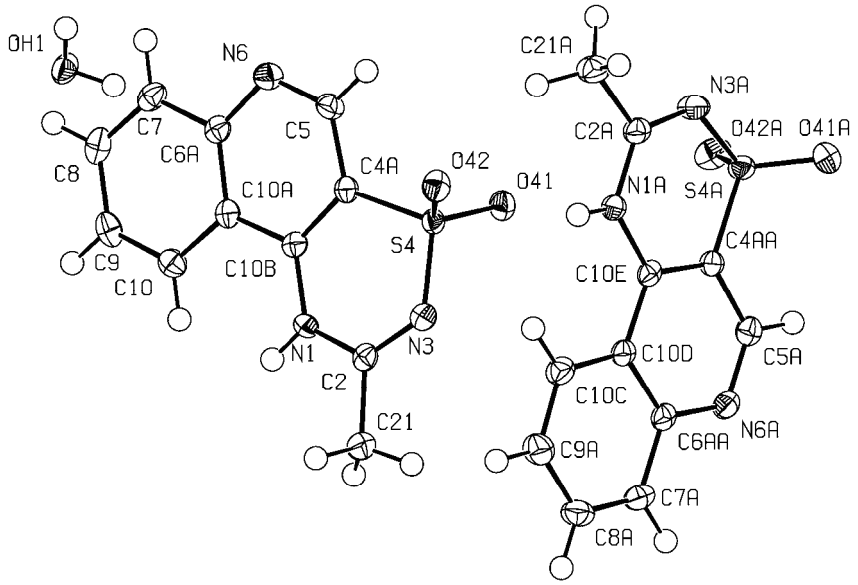


Figure 1. ORTEP drawing of 2-methyl-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**) semihydrate with the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

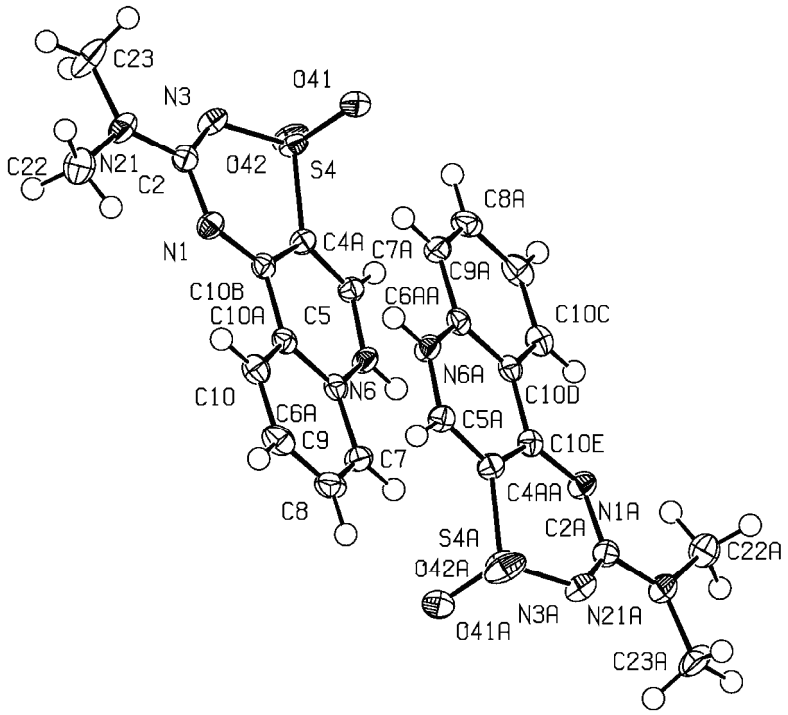


Figure 2. ORTEP drawing of 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**) with the atom labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

CONCLUSIONS

The title quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxides **4**, **5**, **7a**,**b** are easily available from reactions of

4-chloro-3-quinolinesulfonyl chloride (**1**) with acetamidine or *N*,*N*-dimethylguanidine salts. Although the 2-methyl derivative **4** exists in the form of a 1*H*-tautomer and 2-dimethylamino derivative **7a** as a 6H-tautomer, the potassium salts of **4** and **7a** were methylated outside the thiadiazine ring at the pyridine ring nitrogen, which led to 6-methyl derivatives **5** or **7b**, respectively. The same methylation of pyrido-1,2,4-thiadiazine dioxide **11b**, reported as NH tautomer at γ-pyridine-ring position,[17] also proceeded at the pyridine-ring *endo*cyclic nitrogen to form 7-methyl derivative **11b**.

EXPERIMENTAL

Melting points were taken in open capillary tubes and are uncorrected. All NMR spectra were recorded on a Bruker AVANCE 400 spectrometer operating at 400.22 MHz and 100.64 MHz for ^{1}H and ^{13}C nuclei, respectively, in deuterochloroform or in hexadeuterodimethyl sulfoxide solutions with tetramethylsilane (δ 0.0 ppm) as internal standard. NOE experiments were performed for DMSO-d_6 solutions of compounds **5** and **8**. Two-dimensional ^{1}H-^{13}C HSQC and HMBC experiments were performed using standard Bruker software HSQCGP and HMBCGP, respectively, and the following parameters: the spectral widths in F_2 and F_1 were *ca* 5 kHz for ^{1}H and 16.7 kHz for ^{13}C, the relaxation delay was 1.5 s, the refocusing in the HSQC experiment was 1.7 ms and the delay for long-range evolutions was 50 ms in ^{1}H / ^{13}C HMBC. 2D spectra were acquired as 2048 x 1024 hypercomplex files, with 1-4 transients. EI MS spectra were determined on a Finnigan MAT 95 spectrometer at 70 eV.TLC analyses were performed employing Merck's aluminium oxide 60 F_{254} neutral (type E) plates and using chloroform as an eluent.
Acetamidine hydrochloride and *N,N*-dimethylguanidine sulfate were commercial products, *N*,*N*,*N*'-trimethylguanidine sulfate was prepared from *N*,*S*-dimethylisothiouronium sulfate and dimethylamine according to the reported method.[18] 4-Chloro-3-pyridinesulfonyl chloride (**9**)[19] and 4-chloro-3-quinolinesulfonyl chloride (**1**) were prepared as described previously.[14]

Synthesis of 2-methyl-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**) from 4-amino-3-quinolinesulfonamide (**3**) and acetic anhydride

4-Amino-3-quinolinesulfonamide (**3**)[14] (446 mg, 2 mM) and acetic anhydride (4 mL) was refluxed for 4 h and cooled down to rt. The solid was filtered off and washed with ethanol. It was recrystallized from EtOH to give 374 mg (73%) of **4** semihydrate.

2-Methyl-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**)

mp 295-297 ºC (ethanol). EI MS (70 eV): m/z(%) = 247 (90.7, M^+), 206 (100), 142 (99.8). ^{1}H NMR (DMSO-d_6), δ: 2.52 (s, 3H, CH_3), 7.84-7.88 (m, 1H, $\mathbf{H}_{arom}$), 7.97-8.01 (m, 1H, $\mathbf{H}_{arom}$), 8.12-8.14 (m, 1H, $\mathbf{H}_{arom}$), 8.73 -8.76 (m, 1H, $\mathbf{H}_{arom}$), 9.11 (s, 1H, **H**-5), 12.02 (bs, 1H, NH). *Anal.* Calcd for $C_{11}H_9N_3O_2S$ x ½ H_2O: C 51.62, H 3.93, N 16.41. Found: C 51.16, H 3.87, N 16.28.

Reactions of 4-chloro-3-quinolinesulfonyl chloride (**1**) with acetamidine hydrochloride or with *N*,*N*-dimethyl- and *N*,*N*,*N*'-trimethylguanidine sulfates

Solution of 4-chloro-3-quinolinesulfonyl chloride (**1**) (524 mg, 2 mMol) in 14 mL of acetone was added dropwise within 30 min upon stirring to a mixture of acetamidine hydrochloride (200 mg, ca. 2.1 mMol), 50 % aqueous NaOH (0.4 mL) and acetone (2 mL) at rt. The mixture was stirred for 2 h at rt.

In the same manner were performed reactions with *N*,*N*-dimethyl- and *N*,*N*,*N*'-trimethylguanidine sulfates (*ca.* 1.05 mMol).

The solid was filtered off. In order to isolate chloro derivative **6a**, the solid was treated with warm water, cooled down to rt, and crude **6a** was filtered off.

Since quinothiadiazines **4** and **8** remained in the acetone filtrates, the filtrates were evaporated to dryness at vacuum with a rotatory evaporator. The semisolid residue was dissolved in 5% aqueous NaOH (2.5 mL) and then neutralized to pH 5-6 with 10% hydrochloric acid. The solid was filtered off, washed with water and dried on air.

Results :	Substrate	Product (yield%)
	Acetamidine hydrochloride	quinothiadiazine **4** (65%)
	N,*N*-dimethylguanidine sulfate	quinolinesulfonylguanidine **6a** (72%)
	N,*N*,*N*'-trimethylguanidine sulfate	quinothiadiazine **8** (45%)

Reaction of 4-chloro-3-pyridinesulfonyl chloride (**9**) with *N*,*N*-dimethylguanidine sulfate was carried out in the same way as for treatment of **1** to give *N*-(4-chloro-3-pyridinesulfonyl)-*N*',*N*'-dimethylguanidine (**10**) with 71% yield.

2-Methyl-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**)

mp and analytical data – the same as that prepared from **3** and acetic anhydride.

N-(4-Chloro-3-quinolinesulfonyl)-*N*',*N*'-dimethylguanidine (**6a**):

mp 205-207 ºC (EtOH). EIMS (70 eV): m/z(%) = 312 (48.6, M^+), 313 [20.3, (M+1)] 314 [19.6, (M+2)], 268 (100). ^{1}H NMR (DMSO-d_6), δ: 2.91[s, 6H, $N(CH_3)_2$], 7.64-7.68 (bs, 2H, NH_2), 7.85-7.88 (m, 1H, $\mathbf{H}_{arom}$), 7.97-8.01 (m, 1H, $\mathbf{H}_{arom}$), 8.15-8.17 (m, 1H, $\mathbf{H}_{arom}$), 8.39-8.41 (m, 1H, $\mathbf{H}_{arom}$), 9.34 (s, 1H, **H**-2). *Anal.* Calcd for $C_{12}H_{13}ClN_4O_2S$: C 46.08, H 4.19, N 17.91. Found: C 46.09, H 4.27, N 17.42.

N-(4-Chloro-3-pyridinesulfonyl)-*N*',*N*'-dimethylguanidine (**10**):

mp 169-171 ºC (EtOH). EIMS (70 eV): m/z(%) = 262 (75, M^+), 264 [(24, $(M + 2)^+$]. ^{1}H NMR (DMSO-d_6), δ: 2.87 [s, 6H, $N(CH_3)_2$], 7.09 (s, 2H, NH_2), 7.64 (d, ^3J = 5.6Hz, 1H, H5), 8.61 (d, ^3J = 5.6Hz, 1H, H6), 8.99 (s, 1H, H2). *Anal.* Calcd for $C_8H_{11}ClN_4O_2S$: C 36.57, H 4.22, N 21.33. Found: C 36.48, H 4.16, N 21.17.

2-Dimethylamino-1-methyl-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**8**):

mp 217-219 ºC (EtOH). EIMS (70 eV): m/z(%) = 290 (85, M^+), 155 (100). ^{1}H NMR (DMSO-d_6), δ: 3.15-3.30 [bs, 6H, $N(CH_3)_2$], 3.69 [(s, 3H, $CH_3N(1)$], 7.77-7.80 (m, 1H, H-9), 7.93-7.96 (m, 1H, H-8), 8.14-8.16 (dd, 1H, *J*=8.4 Hz, *J*=0.6 Hz, H-7), 8.40-8.42 (dd, 1H, *J*=8.45 Hz, *J*=0.7 Hz, H-10), 9.08 (s, 1H, H-5). ^{1}H NMR ($CDCl_3$), δ: 3.28 [bs, 6H, $N(CH_3)_2$], 3.69 [(s, 3H, $CH_3N(1)$], 7.68-7.72 (m, 1H, $\mathbf{H}_{arom}$), 7.83-7.88 (m, 1H, $\mathbf{H}_{arom}$), 7.99-8.01 (m, 1H, $\mathbf{H}_{arom}$), 8.22 -8.24 (m, 1H, $\mathbf{H}_{arom}$), 9.30 (s, 1H, **H**-5). *Anal.* Calcd for $C_{13}H_{14}N_4O_2S$: C 53.78, H 4.86, N 19.30, S 11.04. Found: C 53.61, H 4.82, N 19.10.

Cyclization of *N*-(4-chloro-3-quinolinesulfonyl)-*N*',*N*'-dimethylguanidine (**6a**) to 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**)

A mixture of quinolinesulfonylguanidine **6a** (313 mg, 1 mM), NH_4Cl (15 mg) and phenol (2 g) was kept in an oil-bath at 190-195 ºC for 2 h. The mixture was cooled down and phenol was removed by steam distillation. The residue was cooled down to rt and filtered off to give crude product **7a**. It was dried on air, and recrystallized from EtOH to give quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**) (313 mg, 73%).

2-Dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**):

mp 313-316 ºC (EtOH). EIMS (70 eV): m/z(%) = 276 (100). ^{1}H NMR (DMSO-d_6), δ: 3.31 [s, 6H, $N(CH_3)_2$], 7.64-7.68 (m, 1H, $\mathbf{H}_{arom}$), 7.83-7.84 (m, 1H, $\mathbf{H}_{arom}$), 7.87-7.91(m, 1H, $\mathbf{H}_{arom}$), 8.60 -8.63 (m, 1H, $\mathbf{H}_{arom}$), 8.93 (s, 1H, **H**-5), 13.70 (bs, 1H, NH). *Anal.* Calcd for $C_{12}H_{12}N_4O_2S$: C 52.16, H 4.38, N 20.28. Found: C 51.91, H 4.41, N 19.98.

Cyclization of *N*-(4-chloro-3-pyridinesulfonyl)-*N*',*N*'-dimethylguanidine (**10**) to 3-dimethylamino-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**11a**)

Cyclization was performed in the same way as for thienothiadiazines, ref.[12]

A mixture of pyridinesulfonylguanidine **10** (520 mg, 2 mM), cesium carbonate (1 g) and 30 mL of dry butanol was kept in an oil-bath at 110 ºC for 72 h and then concentrated to dryness under vaccum. The residue was dissolved in water (ca. 20 mL) and acidified with formic acid up to pH = 6. The solid was filtered off, dried over anhydrous $CaCl_2$ and boiled with EtOH. Hot solution was decanted off to leave pyrido[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**11a**) (320 mg, 71%).

3-Dimethylamino-(4*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**11a**)

mp > 320 ºC, lit.,[3] mp > 320 ºC. EIMS (70 eV): m/z (%) = 226 (100). ^{1}H NMR spectrum in DMSO-d_6 was identical with the reported data.[3]

N-Methylation of 2-methyl-(1*H*)-quino-[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**4**) or 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7a**)

Potassium methoxide (0.150 g, *ca.* 2.1 mM) was added on stirring to the suspension of quinothiadiazine

dioxide (2 mMol) in dry DMF (8 mL). The mixture was stirred for 5-10 min until the mixture became clear. Then, a solution of methyl iodide (0.8 mL, *ca.* 2 mMol) in DMF (2.5 mL) was added dropwise for 15 min and the mixture was stirred at rt for 20 h.

2-Dimethylamino-6-methyl derivative **7b** was filtered off and recrystallized from EtOH to give pure **7b** (510 mg, 88%). For isolation of compound **5**, the mixture was diluted with 60 mL of water. The solid was filtered off, washed with warm water and dried on air. It was recrystallized from EtOH to give 2,6-dimethyl derivative **5** (360 mg, 69%).

Methylation of 3-dimethylaminopyridothiadiazine 4,4-dioxide **1a** was performed in the same way as above for **7b** to give 3-dimethylamino-7-methyl-(7*H*)-pyridothiadiazine 4,4-dioxide (**11b**) with 63% yield.

2,6-Dimethyl-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**5**):

mp 286-289 ºC (EtOH). EIMS (70 eV): m/z(%) = 261 (100). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 2.37 [(s, 3H, CH_3C); 27.9 (C2)], 4.31 [(s, 3H, CH_3N); 42.9 (CH_3N) / 138.5 (C6a), 146.0 (C5)], 7.81 [(m, 1H, H9); 128.0 (C9) / 118.5 (C7), 124.1 (C10a)], 8.08 [(m, 1H, H8); 133.9 (C8) / 125.5 (C10), 138.5 (C6a)], 8.13 [(m, 1H, H7); 118.5 (C7) / 124.1 (C10a), 128.0 (C9)], 8.83 [(m, 1H, H10); 125.5 (C10) / 133.9 (C8), 138.5 (C6a), 155.5 (C10b)], 9.47 [(s, 1H, H5); 146.0 (C5) / 42.9 (CH_3N), 111.4 (C4a), 138.5 (C6a), 155.5 (C10b)]. *Anal.* Calcd for $C_{12}H_{11}N_3O_2S$: C 55.16, H 4.24, N 16.08. Found: C 55.07, H 4.31, N 16.12.

2-Dimethylamino-6-methyl-(*6H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**7b**):

mp 283-286 ºC (EtOH). EIMS (70 eV): m/z(%) = 290 (35.7, M+), 183 (100). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.10 [(s, 3H, CH_3N); 36.62 (CH_3N) / 158.6 (C-2)], 3.32 [(s, 3H, CH_3N); 36.72 (CH_3N / 158.6 (C2)], 4.16 [(s, 3H, N_6-CH_3); 41.8 (CH_3-N_6) / 138.6 (C-6a), 143.2 (C-5)], 7.72 [(m, 1H, H-9); 126.9 (C-9) / 118 (C-7), 123.8 (C-10a)], 7.91 [(m, 1H, m, H-8); 133.4 (C-8) / 125.4 (C-10), 138.6 (C-6a)], 7.92 [(m, 1H, m, H-7); 118.0 (C-7) / 123.8 (C-10a), 126.9 (C-9)], 8.71 [(m, 1H, H-10); 125.4 (C-10) / 133.4 (C8), 138.6 (C-6a), 155.7 (C-10b)], 9.05 [(s, 1H, H-5); 143.2 (C-5) / 41.8 (CH_3-N_6), 111.7 (C-4a), 138.6 (C-6a), 155.7 (C-10b)]. *Anal.* Calcd for $C_{13}H_{14}N_4O_2S$ x 2 H_2O: C 47.84, H 5.56, N 17.07. Found: C 47.58, H 5.29, N 17.06.

3-Dimethylamino-7-methyl-(7*H*)-pyrido[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide (**11b**)

mp 261-263 ºC (EtOH). EIMS (70 eV): m/z(%) = 240 (74.1, M+). ^{1}H NMR (DMSO-d_6), δ [δ_C for carbons from single bond and / long range proton-carbon correlations]: 3.08 [(s, 3H, CH_3N); 36.6 (CH_3N) / 159.5 (C-3)], 3.22 [(s, 3H, CH_3N); 36.5 (CH_3N / 159.5 (C-3)], 3.99 [(s, 3H, N_7-CH_3); 44.6 (CH_3-N_7) / 140.1 (C-8), 142.2 (C-6)], 7.64 [(d, 1H, ^3J=7.5 Hz, H-5); 118.7 (C-5) / 119.2 (C-8a), 128.0 (C9), 142.2 (C-6)], 7.79 [(d, 1H, ^4J=1.8 Hz, H-8); 140.1 (C-8) / 44.6 (CH_3-N_7), 142.2 (C-6), 157.0 (C-4a, 8.09 [(dd,

1H, ^{3}J=7.5 Hz, ^{4}J=1.8 Hz, H-6); 142.2 (C-6) / 140.1 (C-8), 157.0 (C-4a)]. *Anal.* Calcd for $C_9H_{12}N_4O_2S$: C 44.99, H 5.03, N 23.32. Found: C 44.75, H 4.95, N 23.22.

X-Ray structure analysis

The diffraction data were collected with a four – circle Xcalibur diffractometer with Sapphire3 CCD detector using graphite monochromated Mo Kα radiation. The intensity data were collected and processed using Oxford Diffraction CrysAlis Software.[20] The crystal structures were solved by direct methods with the program SHELXS-97[21] and refined by full-matrix least-squares method on F^2 with SHELXL-97.[21]

Crystals of 2-methyl-(1*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide semihydrate $C_{11}H_9N_3O_2S \cdot ½ H_2O$ **(4)** were obtained by slow evaporation of 2-butanone solution at room temperature. Crystal data for **4**: monoclinic, space group $P2_1/c$, a = 15.6102(2) Å , b = 9.0947(1) Å, c = 16.3347(2) Å, α = 90º, β = 113.469(2)º , γ = 90º, V = 2127.20(4) Å^3, Z = 4, d_x = 1,600 Mg m^{-3}, T = 100(1) K. Data were collected for a crystal of dimensions 0.40 x 0.38 x 0.13 mm^3. Final R indices for 3424 reflections with $I > 2\sigma(I)$ and 338 refined parameters are R_1= 0.0271, wR_2= 0.0748, (R_1= 0.0297 and wR_2= 0.0758, for all 3772 data).

Crystals of 2-dimethylamino-(6*H*)-quino[4,3-*e*]-1,2,4-thiadiazine 4,4-dioxide $C_{12}H_{12}N_4O_2S$ (**7a**) were grown by slow evaporation from acetone – DMF (10 : 1, v/v) solution at room temperature. Crystal data for (**7a**): monoclinic, space group $P2_1/c$, a = 12.4887(2) Å, b = 14.9486(2) Å, c = 14.2984(2) Å, α = 90º, β = 115.359(2)º, γ = 90º, V = 2412.14(7) Å^3, Z = 8, d_x = 1,522 Mg m^{-3}, T= 100(1) K. Data were collected for a crystal of dimensions 0.42x 0.23 x 0.14 mm^3. Final R indices for 3396 reflections with $I > 2\sigma(I)$ and 353 refined parameters are R_1= 0.0272, wR_2= 0.0843, (R_1= 0.0352 and wR_2= 0.0872, for all 4267 data).

Crystallographic data for compounds **4** and **7a** have been deposited with Cambridge Crystallographic Data Centre (CCDC deposition numbers 761849 and 772826, respectively) Copies of the data can be obtained upon request from CCDC, 12 Union road, Cambridge CB2 1EZ, UK).

REFERENCES AND NOTES

Part CXX in the series of Azinyl Sulfides

1. B. Pirotte, P. de Tullio, P. Lebrun, M. H. Antoine, J. Fontaine, B. Masereel, M. Schynts, L. Dupont, A. Herchuelz, and J. Delarge, *J. Med. Chem*., 1993, **36**, 3211.
2. S. Boverie, M. H. Antoine, F. Somers, B. Becker, S. Sebille, R. Ouedraogo, S. Counerotte, B. Pirotte, P. Lebrun, and P. de Tullio, *J. Med. Chem*., 2005, **48**, 3492.
3. P. de Tullio, B. Pirotte, L. Dupont, B. Masereel, D. Laeckmann, T. Podona, O. Diouf, P. Lebrun, and J. Delarge, *Tetrahedron,* 1995, **51**, 3221.

4. A. Jahangir and A. Terzic, *J. Mol. Cell. Card.,* 2005, **39**, 99.
5. B. Pirotte, P. de Tullio, Q.-A. Nguyen, F. Somers, P. Fraikin, X. Florence, P. Wahl, J. B. Hansen, and P. Lebrun, *J. Med. Chem*., 2010, **53**, 147.
6. P. Lebrun, B. Becker, N. Morel, P. Ghisdal, M.-H. Antoine, P. de Tullio, and B. Pirotte, *Biochem. Pharmacol.*, 2008, **75**, 468.
7. P. Francotte, P. de Tullio, T. Podona, O. Diouf, P. Fraikin, P. Lestage, L. Danober, J. Y. Thomas, D. H. Caignard, and B. Pirotte*, Bioorg. Med. Chem*., 2008, **16**, 9948.
8. A. Kamal, M. Naseer, A. Khan, K. S. Reddy, S. K. Ahmed, M. S. Kumar, A. Juvekar, S. Sen, and S. Zingde, *Bioorg. Med. Chem. Lett.,* 2007, **17**, 5345.
9. a) X. Y. Liu, R. Z. Yan, N. G. Chen, and W. F. Xu, *Chin. Chem. Lett.,* 2007, **18**, 137; b) X. Y. Liu, R. Z. Yan, N. G. Chen, W. F. Xu, M. T. Molina, and S. Vega, *Molecules*, 2006, **11**, 827.
10. H. N. Weller, A. V. Miller, R. V. Moquin, K. E. J. Dickinson, S. A. Hedberg, S. Moreland, R. B. Cohen, C. L. Delaney, S. Skwish, and S. Williams, *Bioorg. Med. Chem. Lett.,* 1992, **2**, 1115.
11. A. Kamal, M. Naseer, A. Khan, K. S. Reddy, K. Rohini, G. N. Sastry, B. Sateesh, and B. Sridhar, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5400.
12. F. E. Nielsen, S. Ebdrup, A. Frost Jensen, L. Ynddal, T. B. Bodvarsdottir, C. Stidsen, A. Worsaae, H. C. M. Boonen, P. O. G. Arkhammar, T. Fremming, P. Wahl, H. T. Kornø, and J. B. Hansen. *J. Med. Chem.,* 2006, **49**, 4127.
13. P. de Tullio, B. Becker, S. Boverie, M. Dabrowski, P. Wahl, M. H. Antoine, F. Somers, S. Sebille, R. Ouedraogo, J. B. Hansen, P. Lebrun, and B. Pirotte, *J. Med. Chem*., 2003, **46**, 3342.
14. A. Maślankiewicz and L. Skrzypek, *Heterocycles*, 1994, **38**, 1317.
15. S.-O. Chua, M. J. Cook, and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. II*, 1973, 546.
16. G. Albers-Schonberg, H. Joshua, M. B. Lopez, O. D. Hensens, J. P. Springer, J. Chen, S. Ostrove, C. H. Hoffman, A. W. Alberts, and A. A. Patchett, *J. Antibiot.,* 1981, **34**, 507.
17. P. de Tullio, R. Ouedraogo, L. Dupont, F. Somers, S. Boverie, J. M. Dogne, J. Delarge, and B. Pirotte, *Tetrahedron*, 1999, **55**, 5419.
18. R. Pant, *Hoppe Seylers' Z. Physiol. Chem.,* 1964, **335**, 272.
19. J. Delarge, *Ann. Pharm. Franç*., 1973, **31**, 467.
20. Oxford Diffraction (2006) CrysAlis CCD and CrysAlis RED. Versions 1.171.32.29. Oxford Diffraction Ltd, Wrocław, Poland.
21. G. M. Sheldrick, *Acta Cryst.*, 2008, **A 64**, 112.