On the Reaction Products of 4-Substituted 3-Pyridinesulfonamides with Some Benzenesulfonyl Chloride Derivatives

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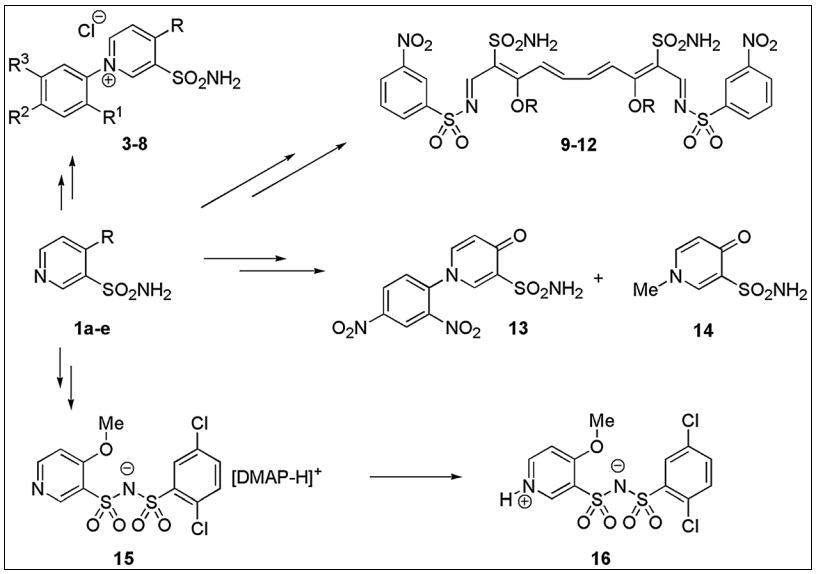

The reactions of 4-substituted 3-pyridinesulfonamides **1a–e** with benzenesulfonyl chlorides **2a–f** in acetonitrile were investigated. Depending on the structure of arylsulfonyl chlorides and the reaction conditions the following four types of products were obtained in good yields: 3-sulfamoyl-4-*R*-1-arylpyridinium chlorides **3–8**; 1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamides **9–12**; 1-substituted 1,4-dihydro-4-oxo-3-pyridinesulfonamides **13–14**; and 4-methoxy-3-[*N*-(2,5-dichlorophenyl)sulfonyl] sulfonamidates **15** and **16**. The mechanisms of these reactions were discussed.

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INTRODUCTION

The aryl/heteroaryl sulfonamide constitutes an important class of compounds with several types of biological activities and well-established safety profiles [1]. Currently, there is significant interest in the discovery and development of novel sulfonamides for the treatment of cancer and HIV infection [2–5]. As part of extensive research program on the synthesis of compound containing 2-thiobenzenesulfonamide scaffold, several series of novel sulfonamides with remarkable anticancer activity [6–20], anti-HIV activity [14], [20–29], or carbonic anhydrase inhibitors [30–32] were discovered in our laboratories. In the course of study on the synthesis of heterocyclic compounds bearing sulfonamide moiety, we developed new methods for preparation of novel series of 3-pyridinesulfonamides [33–36] and found that numerous sulfonamides of type **I** [35] and **II** [36] (Fig. 1) showed excellent inhibitory efficacy against carbonic anhydrase isozyme hCA IX (cancer-associated) with inhibition constants of 4.6–12.0 n*M*, being much more effective in comparison to the clinically used sulfonamides **AAZ**, **MZA**, **EZA**, **DCP**, and **IND** (K_Is = 24–50 n*M*). In this work, a possibility of using reactions of 4-substituted 3-pyridinesulfonamides with arylsulfonyl chlorides for the synthesis of novel sulfonamides with expected activity as potential carbonic anhydrase inhibitors has been surveyed. It was expected that these reactions may provide either 1-(arylsulfonyl)pyridinium chlorides of type **III** and/or typical *N*-(arylsulfonyl)pyridine-3-sulfonamide derivatives of type **IV** (Fig. 1).

RESULTS AND DISCUSSION

First, we found that the reaction of 3-pyridinesulfonamide **1a** with one molar equivalent of 2,5-dichlorobenzenesylfonyl chloride **2a** carried out in boiling acetonitrile (6–12 h) led to the formation of a mixture of brown pithy products. However, treatment of **1a** with **2a** in acetonitrile initially at room temperature for 32 h, and further heating at reflux for 40 h, led to 4-chloro-3-sulfamoyl-1-(2,5-dichlorophenyl)pyridinium chloride **3** in 85% yield (Scheme 1). An analogous reaction of 3-pyridinesulfonamides **1a** or **1b** with benzenesulfonyl

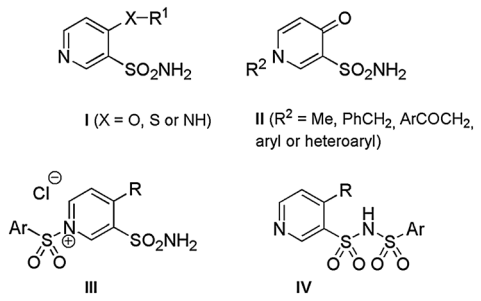


Figure 1. General structures of effective hCA IX inhibitors **I**, **II**, and structures of novel pyridine-3-sulfonamide derivatives **III** and **IV**.

chlorides **2a–d** (bearing substituents in the benzene ring with a relatively weak electron-withdrawing effect) afforded the corresponding 3-sulfamoyl-4-*R*-1-arylpyridinium chlorides **4–8** in 50–90% yields (Scheme 1).

The reaction sequence involved the initial formation of 1-arylsulfonylpyridinium chloride **A** (Scheme 1), followed by elimination of SO_2 process which gave rise to the formation of final products **3–8**. On the other hand, an analogous reaction of 3-pyridinesulfonamides **1b–e** with benzenesulfonyl chloride **2e** (having an strong electron-withdrawing NO_2 group in the benzene ring) furnished 1,10-bis-(3-nitrobenzenesulfonylimino)-deca-2,4,6,8-tetraene-2,9-disulfonamides **9–12**, which have been isolated in 69–83% yields. We propose a reaction sequence for these transformations as shown in Scheme 2. The initial step is believed to be the formation of 1-(3-nitrobenzenesulfonyl) pyridinium chloride intermediate **B**, and then 6-chloro-1-(3-nitrobenzenesulfonyl)-3-pyridinesulfonamide intermediate **C** which undergoes ring opening with the formation of intermediate **D**. In the final stage of the reaction, the non-isolable intermediate **D** was, under these reaction conditions, converted into a free radical **E**, which was stabilized by dimerization to give the corresponding disulfonamide derivatives **9–12**.

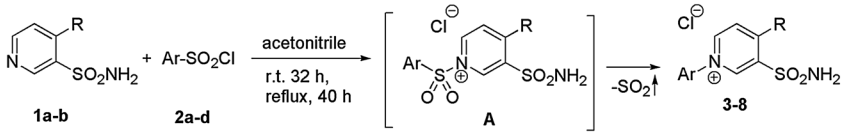
The proposed mechanism of the reaction of 4-methoxy-3-pyridinesulfonamide (**1b**) with 2,4-dinitrobenzenesulfonyl chloride (**2f**) (with a relatively stronger electron-withdrawing substituents effect) leading to the pyridones **13** and **14** is outlined in Scheme 3. Similar to the reaction sequence presented in Scheme 1 (for **1b** with benzenesulfonyl chloride **2a–d**), the initial formation of intermediate **F** was stabilized in the two main routes. In the route ***A***, *via* two-step addition–elimination process led to the intermediate **G** and unstable 6-chloro-4-methoxy-1-(2,4-dinitrophenyl)-3-pyridinesulfonamide **H**, which by elimination of 1-chloro-2,4-dinitrobenzene **I** gave starting sulfonamide **J**. Then, the reaction of intermediates **I** with **J** gave the 1-(2,4-dinitrophenyl)-4-methoxy-3-sulfamoylpyridinium chloride intermediate **K**, which undergoes a S_N2 substitution on the methyl by chloride to form 1,4-dihydro-1-(2,4-dinitrophenyl)-4-oxo-3-pyridinesulfonamide **13** as final product.

In the route ***B*** however, the intermediate **F** by migration process of CH_3 group to nitrogen atom of pyridine ring led to the 1,4-dihydro-1-methyl-4-oxo-1-(2,4-dinitrophenylsulfonyl)-3-pyridinium chloride, intermediate **L**, which by elimination of starting 2,4-dinitrobenzenesulfonyl chloride **2f** gave 1,4-dihydro-1-methyl-4-oxo-3-pyridinesulfonamide **14** as a second final product.

However, an analogous reaction of 4-methoxy-3-pyridinesulfonamide **1b** with 2,5-dichlorobenzenesulfonyl chloride **2a** carried out in the presence of 4-dimethylaminopyridine (DMAP) led to the formation of expected 1H^+-pyridinium-4-methoxy-3-[*N*-(2,5-dichlorophenyl)sulfonyl]sulfonamidate **16** and its dimethylaminopyridinium salt **15** in 94 and 91% yields, respectively. According to the mechanism proposed (Scheme 4), the initial step is believed to be the formation of a mixture of intermediates **M** and **N**, followed by nucleophilic attack of sulfonamidate anion of **M** at the sulfonyl group of **N** led to the pyridinesulfonamide salt **15.** Then, upon acidification of the salt **15** with hydrochloric acid, the corresponding free sulfonamide intermediate **O** was produced, and finally tautomerized to a stable betaine of type **16**.

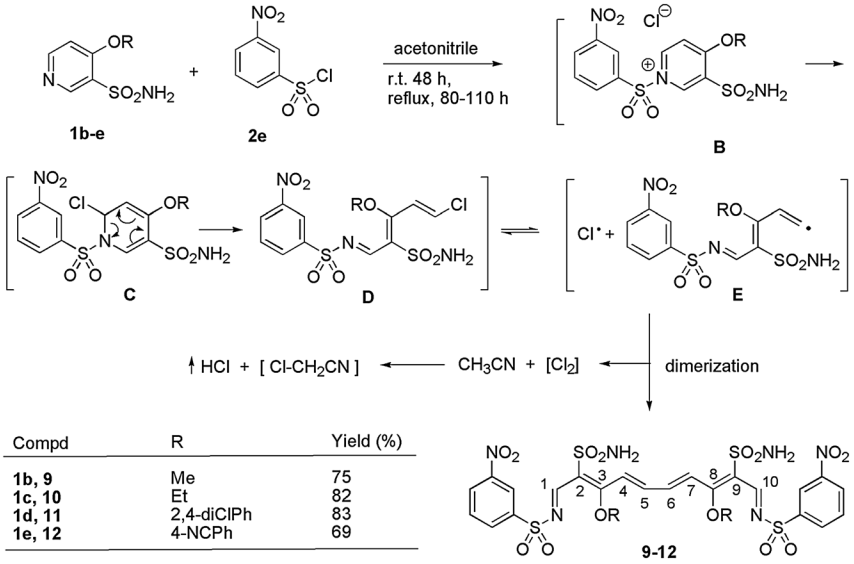
The ^{1}H-NMR spectra of the 1-arylpyridinium chlorides **3–8** and betaine **16** revealed the characteristic three signals of pyridine protons, two doublet signals with coupling

Scheme 1. Synthesis of 3-sulfamoyl-4-R-1-arylpyridinium chlorides **3-8** in the reaction of 3-pyridinesulfonamide **1a** and **1b** with some arylsulfonyl chlorides **2a-d**.



Compd	R	Ar	Yield (%)
1a, 2a, 3	Cl	2,5-diClPh	85
1a, 2b, 4	Cl	2,4-diCl-5-MePh	90
1b, 2c, 5	MeO	4-ClPh	68
1b, 2d, 6	MeO	4-BrPh	50
1b, 2a, 7	MeO	2,5-diClPh	89
1b, 2b, 8	MeO	2,4-diCl-5-MePh	86

Scheme 2. Synthesis and plausible mechanism of the formation of 1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamides **9-12** in the reaction of 3-pyridinesulfonamides **1b-d** with 3-nitrobenzenesulfonyl chloride **2e**.



Compd	R	Yield (%)
1b, 9	Me	75
1c, 10	Et	82
1d, 11	2,4-diClPh	83
1e, 12	4-NCPh	69

constants J = 5.2–7.8 Hz of H-5 and H-6 protons in the regions δ 7.76–7.84 and 8.74–8.93 ppm, respectively, and sharp singlet of H-2 at downfield region of δ 8.29–9.04 ppm. Moreover, the sulfonamide NH_2 protons (**3**–**8**) are found as a singlet signal at δ 7.41–7.93 ppm that integrated for two protons. As could be expected, the resonance signals of H-5 and H-6 protons of pyridone ring in **13** and **14** are shifted upfield to the region δ 6.35–6.52 and 7.76–8.04 ppm, respectively. The same upfield shift concerns the signal of H-2 proton (δ 8.29–8.52 ppm). Is worth emphasizing that signals of pyridine protons in dimethylaminopyridinium salt **15** are found in the different region as compared in 1-arylpyridinium chlorides **3**–**8** or betaine **16**, for instance, doublet signal of H-5 proton (J = 5.8 Hz) at δ = 6.90 ppm, and doublet of H-6 (J = 5.8 Hz) at δ = 8.40 ppm, in the absence of the sulfonamide NH proton signal.

The ^{1}H-NMR spectra of compounds **9**–**12** showed two doublet signals corresponding to magnetically equivalent pairs H-5 and H-6 (J = 6.2–6.6 Hz) δ 7.09–7.71 ppm, as well as H-4 and H-7 protons (J = 6.2–6.6 Hz) δ 8.76–8.99 ppm, and singlet signal of magnetically equivalent pairs H-1 and H-10 in the region δ = 8.95–9.06 ppm, that integrated for two protons, whereas singlet signal of sulfonamide NH_2 protons was observed at δ = 7.30–7.80.

Furthermore, the ^{13}C-NMR and IR spectroscopic data are in accordance with the proposed structures which were confirmed also by elemental analyses (C, H, N) (see Experimental section).

CONCLUSION

We have demonstrated that the reactions of 4-substituted 3-pyridinesulfonamides **1a**–**e** with X-benzenesulfonyl chloride **2a**–**e** in acetonitrile, depending on the nature of electron-withdrawing substituent X at benzene ring led to the formation of three types of novel sulfonamides: **3**–**8** (X = 4-Cl; 4-Br; 2,5-diCl or 2,4diCl-5-Me); **9**–**12** (X = 3-NO_2) and **13**–**14** (X = 2,4-diNO_2). An analogous reaction of 4-methoxy-3-pyridinesulfonamide (**1b**) with 2,5-dichlorobenzenesulfonyl chloride (**2c**) carried out in the presence of DMAP afforded the expected 1H^+-pyridinium-4-methoxy-3-[*N*-(2,5-dichlorophenyl)sulfonyl]sulfonamidate (**16**) and its dimethylaminopyridinium salt **15**.

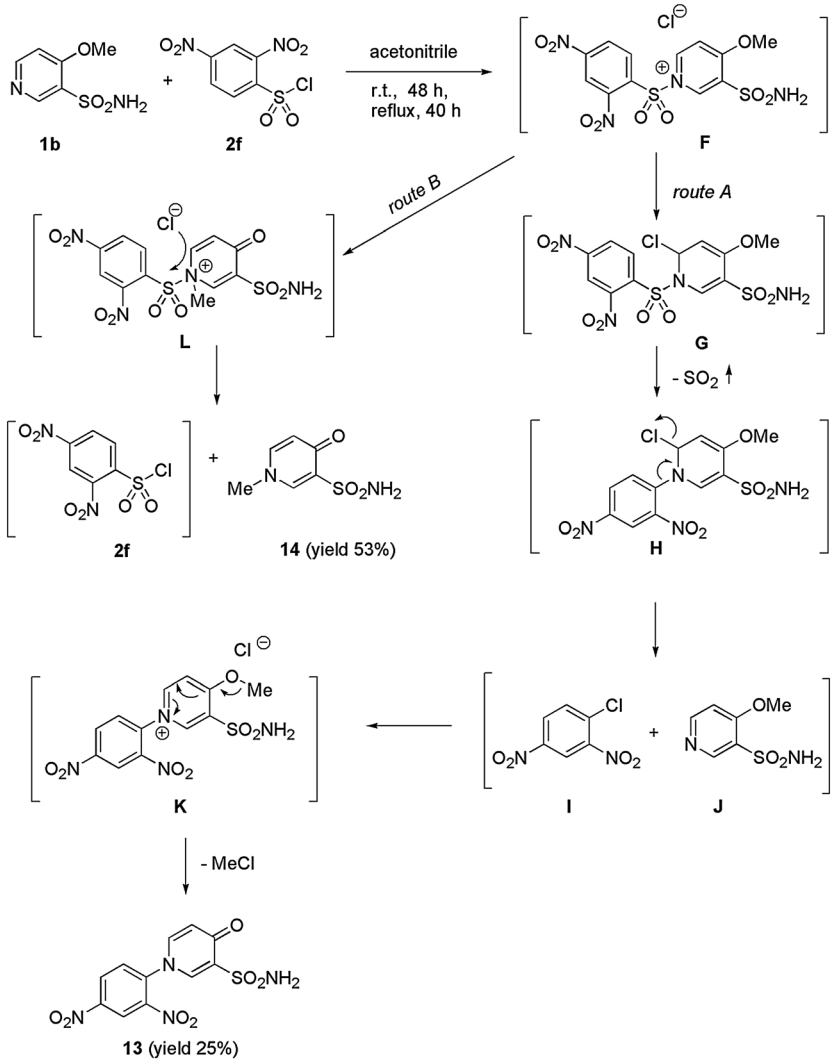
Further structural modifications and biological evolution of these compounds are in progress and will be described elsewhere.

EXPERIMENTAL

The following instruments and parameters were used: melting points Buchi 535 apparatus; IR spectra: KBr pellets, 400–4000 cm^{-1} Perkin Elmer 1600 FTIR spectrometer; ^{1}H and ^{13}C-NMR: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; chemical shifts are expressed at δ values relative to Me_4Si as standard. Thin-layer chromatography was performed on Merck TLC Silica gel 60 F_{254} plates using benzene/ethanol (4:1) or chloroform/hexane/acetone (1:1:1) as mobile phases, and visualized with UV light or with iodine vapour. The starting 4-substituted 3-pyridinesulfonamide **1a**–**e** were prepared according to the method described previously [[35]].

Procedure for the preparation of 3-sulfamoyl-4-*R*-1-arylpyridinium chlorides (3–8). A mixture of the corresponding 3-pyridinesulfonamides **1a** or **1b** (0.01 mol) and the appropriate arylsulfonyl chloride **2a**–**d** (0.0106 mol) in dry acetonitrile (35 mL) was stirred at room temperature for 32 h, followed at reflux for 40 h. After cooling to room temperature and standing overnight, the precipitate of the adequate 1-aryl-6-chloro-1,6-dihydro-3-pyridinesulfonamide was filtered off, washed with acetonitrile, and dried.

Scheme 3. Synthesis and plausible mechanism of the formation of 1,4-dihydro-4-oxo-3-pyridinesulfonamides **13** and **14** in the reaction of 4-methoxy-3-pyridinesulfonamide **1b** with 2,4-dinitrobenzenesulfonyl chloride.



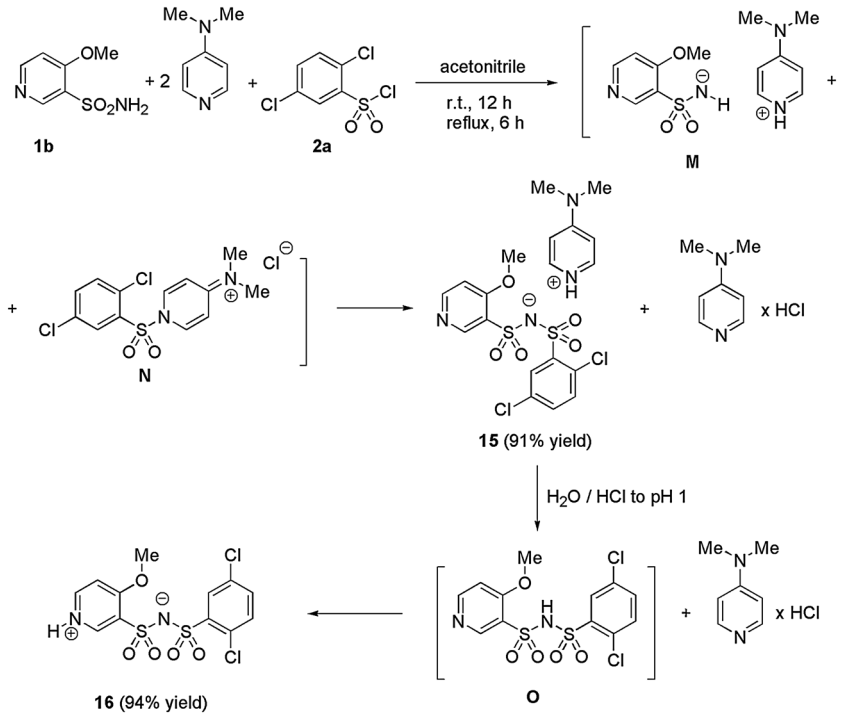
4-Chloro-3-sulfamoyl-1-(2,5-dichlorophenyl)pyridinium chloride (3). Starting from 4-chloro-3-pyridinesulfonamide **1a** (1.93 g) and 2,5-dichlorobenzenesulfonyl chloride **2a** (2.6 g), the title compound **3** was obtained (3.2 g, 85%): m.p. 197–198°C; IR (KBr) 3320, 3200, 3105 (SO_2NH_2), 1365, 1175 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 7.40 (d, J = 2.2 Hz, 1H, H-6, 2,5-diClPh), 7.80 (d, J = 5.3 Hz, 1H, H-5, pyrid.), 7.90–8.10 (m, 2H, H-3 and H-4, 2,5-diClPh), 8.74 (d, J = 5.3 Hz, 1H, H-6, pyrid.), 9.04 (s, 1H, H-2, pyrid.), 9.96 (br.s, 2H, SO_2NH_2) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 126.68, 128.76, 130.05, 131,00, 132.47, 137.50, 141.47, 142.96, 146.90, 148.72, 153.65 ppm. Analysis calculated for $C_{11}H_8Cl_4N_2O_2S$ (374.06): C, 35.32; H, 2.15; N, 7.49. Found: C, 35.30; H, 2.19; N, 7.55.

4-Chloro-3-sulfamoyl-1-(2,5-dichloro-5-methylphenyl)pyridinium chloride (4). Starting from 4-chloro-3-pyridinesulfonamide **1a** (1.93 g) and 2,4-dichloro-5-methylbenzenesulfonyl chloride **2b** (2.75 g), the title compound **4** was obtained (3.5 g, 90%): m.p. 204–206°C; IR (KBr) 3330, 3190 (SO_2NH_2), 1365, 1175 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 2.29 (s, 3H, CH_3), 7.46 (s, 1H, H-6, Ph), 7.80 (d, J = 5.2 Hz, 1H, H-5, pyrid.), 7.93 (br.s, 3H, SO_2NH_2 and H-3, Ph), 8.74 (d, J = 5.2 Hz, 1H, H-6, pyrid.), 9.03 (s, 1H, H-2, pyrid.) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 19.23, 126.68, 129.07, 130.09, 131.36, 133.85, 133.91, 137.49, 141.44, 144.13, 148.75, 153.69 ppm. Analysis calculated for $C_{12}H_{10}Cl_4N_2O_2S$ (388.09): C, 37.38; H, 2.59; N, 7.22. Found: C, 37.33; H, 2.64; N, 7.33.

4-Methoxy-3-sulfamoyl-1-(4-chlorophenyl)pyridinium chloride (5). Starting from 4-methoxy-3-pyridinesulfonamide **1b** (1.88 g) and 4-chlorobenzenesulfonyl chloride **2c** (2.24 g), the title compound **5** was obtained (2.3 g, 68%): m.p. 190–191°C; IR (KBr) 3330, 3165 (SO_2NH_2), 1350, 1170 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 4.19 (s, 3H, CH_3O), 7.38 (d, J = 8.3 Hz, 2H, 4-ClPh), 7.59 (d, J = 8.3 Hz, 2H, 4-ClPh), 7.84 (d, J = 6.6 Hz, 1H, H-5, pyrid.), 7.88 (s, 2H, SO_2NH_2), 8.92 (d, J = 6.6 Hz, 1H, H-6, pyrid.), 8.97 (s, 1H, H-2, pyrid.) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 58.99, 111.34, 127.73, 128.01, 129.87, 133.31, 142.45, 147.34, 148.54, 167.32 ppm. Analysis calculated for $C_{12}H_{12}Cl_2N_2O_3S$ (335.21): C, 42.99; H, 3.61; N, 8.35. Found: C, 42.97; H, 3.73; N, 8.43.

4-Methoxy-3-sulfamoyl-1-(4-bromophenyl)pyridinium chloride (6). Starting from sulfonamide **1b** (1.88 g) and 4-bromobenzenesulfonyl chloride **2d** (2.7 g), the title compound **6** was

Scheme 4. Proposed mechanisms of the formation 4-dimethylaminopyridinium-3-pyrimidinesulfonamidate **15** and 1*H*+-pyridinium-3-sulfonamidate **16** in the reaction of 4-methoxy-3-pyridinesulfonamide **1b** with DMAP and 2,5-dichlorobenzenesulfonyl chloride **2a**.



obtained (1.9 g, 50%): m.p. 186–188°C; IR (KBr) 3345, 3170 (SO_2NH_2), 1350, 1170 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 4.20 (s, 3H, CH_3O), 7.52 (s, 4H, 4-BrPh), 7.77 (d, J = 6.7 Hz, 1H, H-5, pyrid.), 7.87 (s, 2H, SO_2NH_2), 8.93 (d, J = 6.7 Hz, 1H, H-6, pyrid.), 8.98 (s, 1H, H-2, pyrid.) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 59.03, 111.39, 121.99, 128.02, 129.90, 130.94, 142.34, 147.73, 148.42, 167.41 ppm. Analysis calculated for $C_{12}H_{12}BrClN_2O_3S$ (379.65): C, 37.96; H, 3.18; N, 7.37. Found: C, 38.03; H, 3.20; N, 7.41.

4-Methoxy-3-sulfamoyl-1-(2,5-dichlorophenyl)pyridinium chloride (7). Starting from sulfonamide **1b** (1.88 g) and 2,5-dichlorobenzenesulfonyl chloride **2a** (2.6 g), the title compound **7** was obtained (3.3 g, 89%): m.p. 207–208°C; IR (KBr) 3320, 3220 (SO_2NH_2), 1355, 1175 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 4.20 (s, 3H, CH_3O), 7.41 (s, 2H, SO_2NH_2), 7.76 (d, J = 6.8 Hz, 1H, H-5, pyrid.), 7.83–7.92 (m, 3H, 2,5-diClPh), 8.92 (d, J = 6.8 Hz, 1H, H-6, pyrid.), 8.98 (s, 1H, H-2, pyrid.) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 50.06, 111.42, 128.76, 129.94, 130.05, 131.01, 132.47, 142.26, 148.32, 148.94, 153.93, 167.48 ppm. Analysis calculated for $C_{12}H_{11}Cl_3N_2O_3S$ (369.65): C, 38.99; H, 3.00; N, 7.57. Found: C, 38.97; H, 3.07; N, 7.58.

4-Methoxy-3-sulfamoyl-1-(2,4-dichloro-5-methylphenyl) pyridinium chloride (8). Starting from sulfonamide **1b** (1.88 g) and 2,4-dichloro-5-methylbenzenesulfonyl chloride **2b** (2.75 g), the title compound **8** was obtained (3.3 g, 86%): m.p. 189–190° C; IR (KBr) 3205, 3180 (SO_2NH_2), 1350, 1170 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 2.29 (s, 3H, CH_3), 4.20 (s, 3H, CH_3O), 7.46 (s, 1H, H-6, 2,4-diCl-5-MePh) 7.76 (d, J = 6.8 Hz, 1H, H-5, pyrid.), 7.81(s, 1H, H-3, 2,4-diCl-5-MePh), 7.86 (s, 2H, SO_2NH_2), 8.93 (d, J = 6.8 Hz, 1H, H-6, pyrid.), 8.98 (s, 1H, H-2, pyrid.), ppm. Analysis calculated for $C_{13}H_{13}Cl_3N_2O_3S$ (383.67): C, 40.69; H, 3.41; N, 7.30. Found: C, 40.72; H, 3.40; N, 7.29.

Procedure for the preparation of 1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamide derivatives (9–12). A mixture of 3-nitrobenzenesulfonyl chloride **2e** (1.2 g, 0.0054 mol) and the appropriate 3-pyridinesulfonamide **1b, 1c, 1d,** or **1e** (0.005 mol) in dry acetonitrile (25 mL) was stirred at room temperature for 48 h, followed at reflux until the evolution of HCl had ceased (80–110 h). After cooling to room temperature and standing overnight the precipitate was filtered off, washed with acetonitrile (4× 1.5 mL) and dried. In this manner, the following products were obtained.

3,8-Dimethoxy-1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamide (9). Starting from 4-methoxy-3-pyridinesulfonamide **1b** (0.94 g), the title compound **9** was obtained (1.4 g, 75%): m.p. 180–181°C; IR (KBr) 3310, 3215 (SO_2NH_2), 2920, 2850 (CH_3O), 1635, 1175, (NO_2), 1350, 1155 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 4.18 (s, 6H, 3,8-diCH_3O), 7.65 (t, J = 7.8 Hz, 2H, H-5 and H-5′, benzene rings), 7.71 (d, J = 6.3 Hz, 2H, H-5 and H-6), 7.80 (s, 4H, 2,9-di-SO_2NH_2), 8.02 (d, J = 7.8 Hz, 2H, H-6 and H-6′, benzene rings), 8.19 (d, J = 7.8 Hz, 2H, H-4 and H-4′, benzene rings), 8.34 (s, 2H, H-2 and H-2′, benzene rings), 8.89 (d, J = 6.3 Hz, 2H, H-4 and H-7), 8.95 (s, 2H, H-1 and H-10) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 58.66, 110.95, 119.08, 120.33, 123.64, 130.05, 132.24, 138.88, 140.05, 143.25, 149.48, 166.61 ppm. Analysis calculated for $C_{24}H_{24}N_6O_{14}S_4$ (748.76): C, 34.49; H, 3.23; N, 11.22. Found: C, 34.55; H, 3.30; N, 11.11.

3,8-Diethoxy-1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamide (10). Starting from 4-ethoxy-3-pyridinesulfonamide **1c** (1.01 g), the title compound **10** was obtained (1.6 g, 82%): m.p. 175–176°C; IR (KBr) 3300, 3200 (SO_2NH_2), 2925, 2850 (EtO), 1635, 1190 (NO_2), 1355, 1145 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 1.44 (t, J = 7.0 Hz, 6H, 3,8-di CH_3CH_2O), 4.55 (q, J = 7.0 Hz, 4H, 3,8-di CH_3CH_2O), 7.61 (t, J = 7.7 Hz, 2H, H-5, and H-5′, benzene rings), 7.71 (d, J = 6.6 Hz, 2H, H-5 and H-6), 7.79 (s, 4H, 2,9-di-SO_2NH_2), 8.04 (d, J = 7.7 Hz, 2H, H-6 and H-6′, benzene rings), 8.19 (d, J = 7.8 Hz, 2H, H-4 and H-4′, benzene rings), 8.33 (s, 2H, H-2, and H-2′, benzene rings), 8.87 (d, J = 6.6 Hz, 2H, H-4 and H-7), 8.96 (s, 2H, H-1 and H-10) ppm. Analysis calculated for $C_{26}H_{28}N_6O_{14}S_4$ (776.81): C, 40.20; H, 3.63; N, 10.81. Found: C, 40.22; H, 3.65; N, 10.92.

3,8-Di(2,4-dichlorophenoxy)-1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamide (11). Starting from 4-(2,4-dichlorophenoxy)-3-pyridinesulfonamide **3d** (1.6 g), the title compound **11** was obtained (2.1 g, 83%): m.p. 175–176° C; IR (KBr) 3230, 3165 (SO_2NH_2), 1630, 1180 (NO_2), 1355, 1145 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 7.09 (d, J = 6.3 Hz, 2H, H-5 and H-6), 7.30 (s, 4H, 2,9-di-SO_2NH_2), 7.49 (d, J = 8.7 Hz, 2H, H-6 and H-6′, 2,4-diClPh), 7.62 (d, J_{meta} = 2.0 Hz, 2H, H-3 and H-3′, 2,4-diClPh), 7.68 (d, J = 7.6 Hz, 2H, H-5 and H-5′, 3-O_2NPh), 7.93 (dd, J_{ortho} = 8.7 Hz, 2H, H-5 and H-5′, 2,4-diClPh), 8.03 (d, J = 7.6 Hz, 2H, H-6 and H-6′, 3-O_2NPh), 8.19 (dd, J_{ortho} = 7.6 Hz, J_{meta} = 1.1 Hz, 2H, H-4 and H-4′, 3-O_2NPh), 8,32 (s, 2H, H-2 and H-2′, 3-O_2NPh), 8.74 (d, J = 6.3 Hz, 2H, H-4 and H-7), 9.06 (s, 2H, H-1 and H-10) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 112.06, 120.33, 123.69, 125.45, 127.30, 129.56, 129.86, 130.07, 130.97, 132.22, 132.29, 146.30, 147.31, 147.49, 150.14, 151.84, 152.87 ppm. Analysis calculated for $C_{34}H_{24}Cl_4N_6O_{14}S_4$ (1010.68): C, 40.40; H, 2.39; N, 8.31. Found: C, 40.40; H, 2.41; N, 8.32.

3,8-Di(4-cyanophenoxy)-1,10-bis(3-nitrobenzenesulfonylimino)deca-2,4,6,8-tetraene-2,9-disulfonamide (12). Starting from 4-(4-cyanophenoxy)-3-pyridinesulfonamide **1e** (1.4 g), the title compound **12** was obtained (1.6 g, 69%): m.p. 274–275°C; IR (KBr) 3350, 3250 (SO_2NH_2), 2235 (C N), 1690, 1175 (NO_2), 1350, 1150 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 7.22 (d, J = 8.0 Hz, 4H, H-3,3′ and H-5,5′, PhC N), 7.45 (d, J = 8.0 Hz, 4H, H-2,2′ and H-6,6′, PhC N), 7.56 (s, 4H, 2,9-di-SO_2NH_2), 7.15 (d, J = 6.2 Hz, 2H, H-5 and H-6), 7.96 (d, J = 7.6 Hz, 2H, H-5,5′, 3-O_2NPh), 8.02 (d, J = 7.6 Hz, 2H, H-6,6′, 3-O_2NPh), 8.17 (d, J = 7.6 Hz, 2H, H-4,4′, 3-O_2NPh), 8.30 (s, 2H, H-2,2′, 3-O_2NPh), 8.76 (d, J = 6.2 Hz, 2H, H-4 and H-7), 9.06 (s, 2H, H-1 and H-10) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 109.00, 113.58, 118.24, 120.06, 121.89, 123.42, 129.81, 130.47, 131.96, 135.09, 146.58, 146.75, 149.90, 152.12, 156.54, 162.14 ppm. Analysis calculated for $C_{36}H_{26}N_8O_{14}S_4$ (922.93): C, 46.85; H, 2.84; N, 12.14. Found: C, 46.81; H, 2.30; N, 12.12.

Synthesis of 1,4-dihydro-1-(2,4-dinitrophenyl)-4-oxo-3-pyridinesulfonamide (13) and 1,4-dihydro-1-methyl-4-oxo-3-pyridinesulfonamide (14) in the reaction of 4-metoxy-3-pyridinesulfonamide (1b) with 2,4-dinitrobenzenesulfonyl chloride. A mixture of pyridinesulfonamide **1b** (1.89 g, 0.01 mol) and 2,4-dinitrobenzenesulfonyl chloride **2f** (2.72 g, 0.0102 mol) in dry acetonitrile (35 mL) was stirred at room temperature for 48 h, followed at reflux for 40 h, and then left to stand overnight. The title compound **13** thus obtained was collected by filtration, washed with acetonitrile (3× 1.5 mL), (filtrates was left for further work-up), and dried. Yield: 0.85 g (25%): m.p. 250–251°C; IR (KBr) 3370, 3270 (SO_2NH_2), 1645 (C O), 1610, 1600 (NO_2), 1345, 1160 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 6.52 (d, J = 7.8 Hz, 1H, H-5, pyrid.), 7.02 (s, 2H, SO_2NH_2), 8.02 (dd, J_{ortho} = 7.8 Hz, J_{meta} = 2.3 Hz, 1H, H-6 pyrid.), 8.18 (d, J = 8.7 Hz, 1H, H-6, 2,4-diO_2NPh), 8.52 (d, J_{meta} = 2.3 Hz, 1H, H-2, pyrid.), 8.74 (dd, J_{ortho} = 8.7 Hz, J_{meta} = 2.6 Hz, 1H, H-5 di-O_2NPh), 8.98 (d, J_{meta} = 2.6 Hz, 1H, H-3, 2,4-di O_2NPh) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 119.98, 121.70, 129.82, 130.99, 132.24, 139.88, 141.30, 142.13, 144.35, 147.87, 172.86 ppm. Analysis calculated for $C_{11}H_8N_4O_7S$ (340.27): C, 38.82; H, 2.37; N, 16.45. Found: C, 38.83; H, 2.41; N, 16.47.

The acetonitrile filtrate was evaporated to 1/3 volume at normal pressure and left to stand at room temperature for three days. The precipitate of title compound **14** was filtrated off, washed with acetonitrile (1.5 mL) and recrystallized from acetonitrile. Yield: 1.0 g (53%): m.p. 246–247°C; IR (KBr) 3350, 3150 (SO_2NH_2), 1650 (C O), 1330, 1160 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 3.73 (s, 3H, CH_3), 6.35 (d, J = 7.5 Hz, 1H, H-5), 6.79 (s, 2H, SO_2NH_2), 7.76 (dd, J_{ortho} = 7.5 Hz, J_{meta} = 2.2 Hz, 1H, H-6), 8.29 (d, J_{meta} = 2.2 Hz, 1H, H-2) ppm; ^{13}C-NMR (dimethyl sulfoxide-d_6) δ 43.65, 120.04, 129.93, 142.19, 143.45, 172.34 ppm. Analysis calculated for $C_6H_8N_2O_3S$ (188.20): C, 38.29; H, 4.28; N, 14.88. Found: C, 38.34; H, 4.30; N, 14.90.

Synthesis of 4-dimethylaminopyridinium 4-methoxy-*N*-(2,5-dichlorophenylsulfonyl)-3-pyridinesulfonamidate (15) and 1*H*$^+$-pyridinium-4-methoxy-3-[*N*-(2,5-dichlorophenyl) sulfonyl]sulfonamidate (16). To a stirred suspension of 4-methoxy-3-pyridinesulfonamide **1b** (1.5 g, 8 mmol) and 4-dimethyaminopyridine (2.1 g, 17 mmol) in acetonitrile (25 mL), the 2,5-dichlorobenzenesulfonyl chloride **2a** (2.0 g, 8.1 mmol) was added portion wise. The reaction mixture was stirred at room temp. for 12 h, followed at reflux for 6 h. The solution obtained was cooled to room temperature and the resulting suspension was left overnight. The precipitate of title compound **15** was filtered off, washed successively with water (4× 2 mL) and tetrahydrofuran (3× 2 mL) and dried. Yield: 3.8 g (91%); m.p. 185–186°C; IR (KBr) 3225 (NH), 2925 (CH_3), 2850, 2805, 2690 (NH^+), 1645 (C N), 1580, 1555 (C C), 1315, 1160 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 3.17 (s, 6H, CH_3- N-CH_3), 3.35 (s, 1H, NH), 3.71 (s, 3H, CH_3O), 6.90 (d, J = 5.8 Hz, 1H, H-5, Py-SO_2N), 6.98 (d, J = 7.1 Hz, 2H, DMAP), 7.41 (s, 2H, H-3 and H-4, 2,5-diClPh), 7.49 (s, 1H, H-6, 2,5-diClPh), 8.21 (d, J = 7.1 Hz, 2H, DMAP), 8.40 (d, J = 5.8 Hz, 1H, H-6, Py-SO_2N), 8.49 (s, 1H, H-2, Py-SO_2N) ppm. Analysis calculated for $C_{19}H_{20}Cl_2N_4O_5S_2$ (519.44): C, 43.93; H, 3.88; N, 10.78. Found: C, 43.90; H, 3.92; N, 10.80.

To a stirred suspension of dimethylamino pyridinium-3-pyridinesulfonamidate **15** (2.08 g, 4 mmol) in water (25 mL) was slowly acidified to pH 1 with 1% hydrochloric acid. After 2 h of stirring, the title compound **16** was filtered off, washed with water (4× 5 mL) and methanol (3× 1.5 mL), and dried. Yield: 1.5 g (94%); m.p. 269–270°C; IR (KBr) 3090 (CH-arom) 2920 (CH_3O), 2785, 2610 (NH^+), 1635 (C N), 1555, 1495 (C C), 1330, 1145 (SO_2) cm^{-1}; ^{1}H-NMR (dimethyl sulfoxide-d_6) δ 4.00 (s, 3H, CH_3O), 7.42 (d, J = 7.4 Hz, 1H, H-5, Py-SO_2N), 7.50 (s, 2H, H-3 and H-4, 2,5-diClPh), 7.61 (s, 1H, H-6, 2,5-diClPh), 8.21 (br.s, 1H, NH^+), 8.70 (d, J = 7.4 Hz, 1H, H-6, Py-SO_2N), 8.76 (s, 1H, H-2, Py-SO_2N) ppm. Analysis calculated for $C_{12}H_{10}Cl_2N_2O_5S_2$ (397.26): C, 36.28; H, 2.53; N, 7.05. Found: C, 36.30; H, 2.64; N, 7.10.

REFERENCES AND NOTES

[1] Negwer, M. Organic-Chemical Drugs and Their Synonyms; Akademie Verlag: Berlin, 1994; pp215, 375, 630, 2972.

[2] Casini, A.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. Curr Cancer Drug Targets 2002, 2, 55.

[3] Scozzafava, A.; Casini, A.; Supuran, C. T. Curr Med Chem 2002, 9, 1167.

[4] Supuran, C. T. Casini, A.; Scozzafava, A. Med Res Rev 2003, 5, 535.

[5] Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. Curr Med Chem 2003, 10, 925.

[6] Brzozowski, Z.; Sączewski, F.; Gdaniec, M. Eur J Med Chem 2002, 37, 285.

[7] Brzozowski, Z.; Sączewski, F. J Med Chem 2002, 45, 430.

[8] Brzozowski, Z.; Sączewski, F.; Gdaniec, M. Bioorg Med Chem 2003, 11, 3673.

[9] Brzozowski, Z.; Sączewski, F.; Gdaniec, M. Eur J Med Chem 2003, 38, 991.

[10] Pomarnacka, E.; Gdaniec, M. Bioorg Med Chem 2003, 11, 1259.

[11] Sławiński, J.; Gdaniec, M. Eur J Med Chem 2003, 40, 377.

[12] Brzozowski, Z.; Sączewski, F. J Heterocycl Chem 2005, 42, 1297.

[13] Sławiński, J.; Brzozowski, Z. Eur J Med Chem 2006, 1, 1180.

[14] Brzozowski, Z.; Sączewski, F.; Neamati, N. Bioorg Med Chem 2006, 14, 2985.

[15] Brzozowski, Z.; Sławiński, J. Pol J Chem 2007, 81, 1419.

[16] Brzozowski, Z.; Sławiński, J. Pol J Chem 2007, 81, 1433.

[17] Brzozowski, Z.; Sączewski, F.; Sławiński, J. Pol J Chem 2007, 81, 2133.

[18] Brzozowski, Z.; Sączewski, F.; Sławiński, J. Eur J Med Chem 2007, 42, 1218.

[19] Brzozowski, Z.; Sączewski, F.; Sławiński, J.; Bednarski, P. J.; Grünert, R.; Gdaniec, M. Bioorg Med Chem 2007, 15, 2560.

[20] Brzozowski, Z.; Sławiński, J.; Sączewski, F.; Sanchez, T.; Neamati, N. Eur J Med Chem 2008, 43, 1188.

[21] Brzozowski, Z. Acta Polon Pharm Drug Res 1998, 55, 473.

[22] Kuo, Ch.L.; Assefa, H.; Brzozowski, Z.; Sławiński, J.; Sączewski, F.; Buolamwini, I.K.; Neamati, N. J Med Chem 2004, 47, 385.

[23] Brzozowski, Z.; Sączewski, F.; Sanchez, T.; Kuo, Ch. L.; Gdaniec, M.; Neamati, N. Bioorg Med Chem 2004, 12, 3663.

[24] Brzozowski, Z.; Sławiński, J. Pol J Chem 2006, 80, 1807.

[25] Brzozowski, Z.; Sączewski, F.; Sanchez, T.; Kuo, Ch. L.; Gdaniec, M.; Neamati, N. Bioorg Med Chem 2006, 16, 5298.

[26] Brzozowski, Z.; Sączewski, F. J Heterocycl Chem 2007, 44, 261.

[27] Brzozowski, Z.; Sławiński, J. Pol J Chem 2007, 81, 1419.

[28] Brzozowski, Z.; Sławiński, J.; Sączewski, F.; Sanchez, T.; Neamati, N. Eur J Med Chem 2008, 43, 1188.

[29] Brzozowski, Z.; Sączewski, F.; Sanchez, T.; Neamati, N. Eur J Med Chem 2009, 44, 190.

[30] Sławiński, F.; Innocenti, A.; Brzozowski, Z.; Sławiński, J.; Pomarnacka, E.; Kornicka, A.; Scozzafava, A.; Supuran, C. T. J Enzyme Inhib Med Chem 2006, 21, 563.

[31] Sączewski, F.; Sławiński, J.; Kornicka, A.; Brzozowski, Z.; Pomarnacka, E.; Innocenti, A.; Scozzafava, A.; Supuran, C. T. Bioorg Med Chem Lett 2006, 16, 4846.

[32] Sączewski, F.; Innocenti, A.; Sławiński, J.; Brzozowski, Z.; Pomarnacka, E.; Scozzafava, A.; Temperini, C; Supuran, C. T. Bioorg Med Chem 2008, 16, 3933.

[33] Brzozowski, Z.; Sączewski, F.; Sławiński, J. J Heterocycl Chem 2008, 45, 1407.

[34] Brzozowski, Z.; Sławiński, J.; Kędzia, A.; Kwapisz, E.; Gdaniec, M. J Heterocycl Chem 2009, 46, 1396.

[35] Brzozowski, Z.; Sławiński, J.; Sączewski, F.; Innocenti, A.; Supuran, C. T. Eur J Med Chem 2010, 45, 2396.

[36] Brzozowski, Z.; Sławiński, J.; Innocenti, A.; Supuran, C. T. Eur J Med Chem 2010, 45, 3656.