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ACYL AND SULFONYL DERIVATIVES OF 10-AMINOALKYL-2,7-DIAZAPHENOTHIAZINES[#]

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Abstract – Reaction of 3,3'-dinitro-4,4'-dipyridinyl disulfide (**1**) with sodium hydroxide in DMF led to 10*H*-2,7-diazaphenothiazine (**4**). *N*-Alkylation of (**4**) with phthalimidopropyl and phthalimidobutyl bromides gave phthalimidoalkyl derivatives (**5**) and (**6**) which were hydrolyzed to aminoalkyldiazaphenothiazines (**7**) and (**8**). *N*-Acylation with acetyl anhydride, benzoyl chloride, ethyl chloroformate and 2-chloroethyl isocyanate gave *N*-acyl derivatives (**9-16**). *N*-Sulfonylation with methanesulfonyl and *p*-toluenesulfonyl chlorides led to *N*-sulfonyl derivatives (**17-20**).

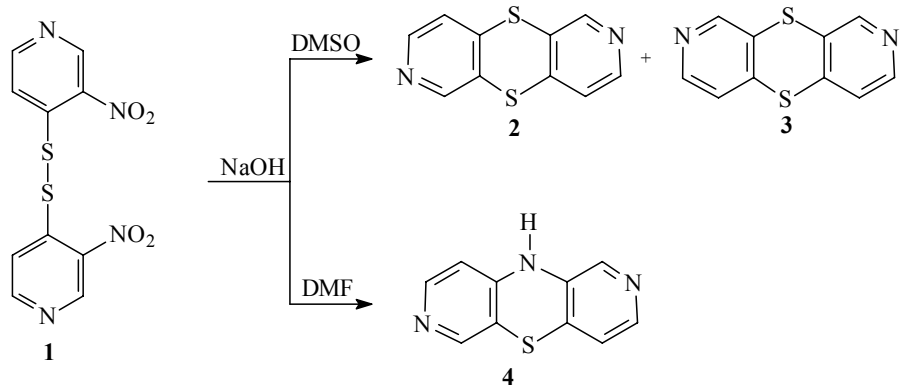
Phenothiazines form an important class of heterocyclic compounds because of significant biological activities such as antipsychotic, antihistaminic, antitussive and antiemetic, interesting chemical properties, wide and inexpensive availability.[1] Recent reports have focused interests on anticancer, antiplasmid and antibacterial activities, reversal of multidrug resistance (MDR) and potential treatment in Alzheimer's, Creutzfeldt-Jakob and AIDS diseases of classical and new synthesized phenothiazines.[2-10] New phenothiazines have been obtained by modifications of the parent phenothiazine structure by an introduction of a new substituent at the thiazine nitrogen atom (at position 10) or at the benzene ring (at positions 1-4 and 6-9) and by a substitution of one or two benzene rings with homoaromatic and heteroaromatic rings (most often azine rings). Motohashi and co-workers found that 10-aminopropyl- and 10-aminobutylphenothiazines (as maleates) and their selected *N*-acyl and *N*-sulfonyl derivatives exhibit promising anticancer and antibacterial activities.[7,10-12,]

In our previous paper[13,14] we described synthesis of new type of azaphenothiazine, 10*H*-dipyrido[3,4-*b*;-3',4'-*e*][1,4]thiazine, (named also as 10*H*-2,7-diazaphenothiazine (**4**)) and its 10-alkyl, aryl, heteroaryl and dialkylaminoalkyl derivatives. Since the syntheses of phenothiazines can proceed *via* the Smiles rearrangement of the S→N type, the 2,7-diazaphenothiazine structure was confirmed by X-ray analysis of 10-(3'-nitro-4'-pyridinyl) derivative.[14] In continuation of these studies we worked out an efficient

synthesis of 10*H*-2,7-diazaphenothiazine (**4**) from 3,3'-dinitro-4,4'-dipyridinyl sulfide (**1**) and transformed into aminoalkyl, acylaminoalkyl and sulfonylaminoalkyl derivatives (**5-20**).

Synthesis

In one of the previous papers,[15] we described reaction of 3,3'-dinitro-4,4'-dipyridinyl disulfide (**4**) (a side product in the synthesis of 4-mercapto-3-nitropyridine from the 4-chloro-3-nitropyridine) with sodium hydroxide in DMSO giving two isomeric dipyridodithiins (2,7-diazathianthrene (**2**) and 2,8-diazathianthrene (**3**), Scheme 1). As we found reductive properties of DMF in the presence of a base in relation to sodium 3-nitropyridine-4-thiolate and 4-chloro-3-nitropyridine (in the presence of sodium sulfide),[13,14] we carried out the reaction of disulfide (**1**) in those conditions for 24 h to give 10*H*-2,7-diazaphenothiazine (**4**) in 84% yield. In our opinion the reaction proceeded through the formation of sodium 3-nitropyridine-4-thiolate which underwent cyclization to compound (**4**) under reductive action of DMF, what we observed previously.[13]



Scheme 1

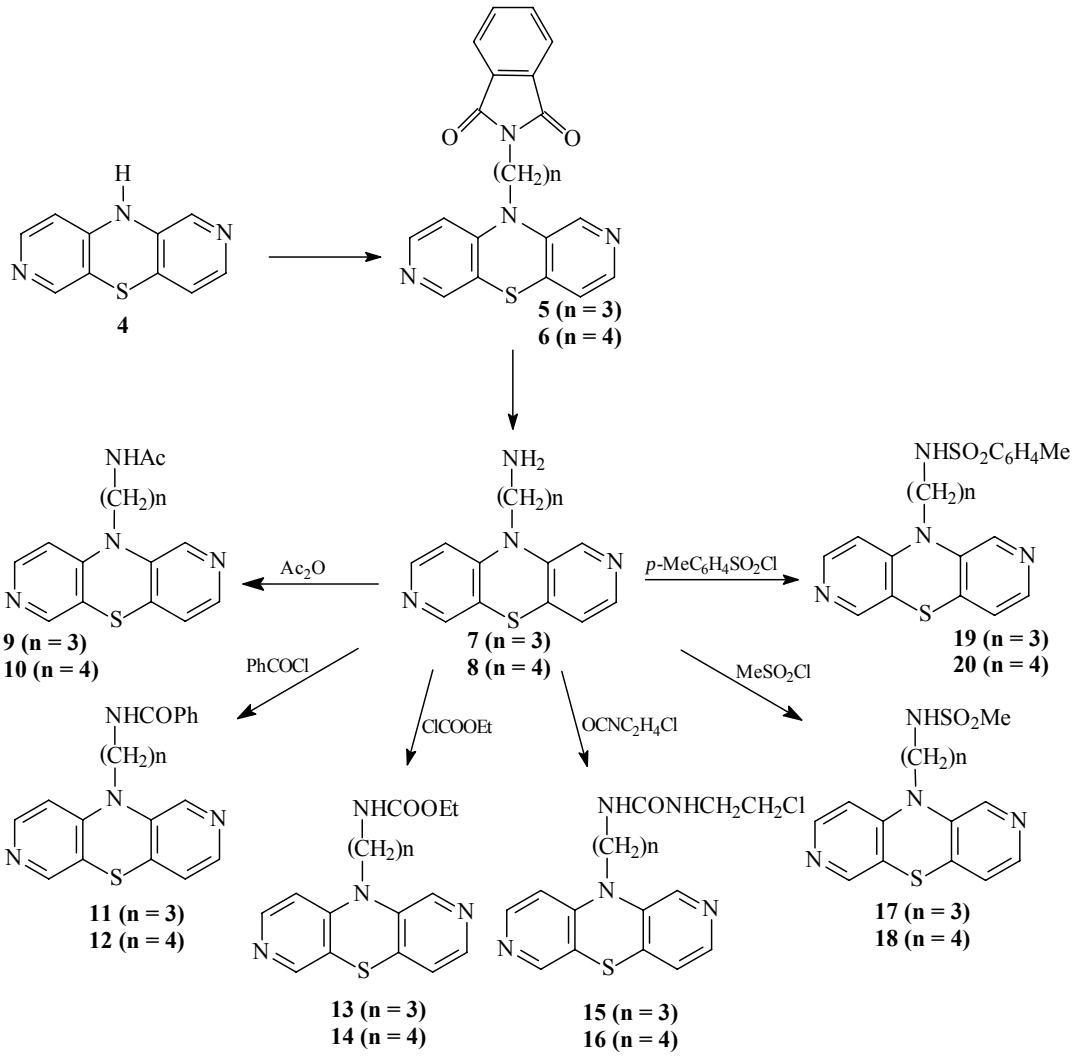
Reactions of 10*H*-2,7-diazaphenothiazine (**4**) with phthalimidopropyl and phthalimidobutyl bromides in toluene in the presence of sodium hydride gave 10-phthalimidoalkyl-2,7-diazaphenothiazines (**5**) and (**6**) (alkyl = propyl, butyl) in 70% and 76% yield, respectively (Scheme 2). Hydrolysis of compounds (**5**) and (**6**) using hydrazine led to 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) in 72% and 77% yield.

The obtained (**7**) and (**8**) were transformed into amide and sulfonami-de derivatives (Scheme 2). The acetylation and benzoylation with acetyl anhydride and benzoyl chloride gave 10-acetyl- and 10-benzoylaminoalkyldiazaphenothiazines (**9-12**) in 69-80% yield. Reactions with ethyl chloroformate led to 10-ethoxycarbonyaminolalkyldiazaphenothiazines (**13**) and (**14**) in 82% and 80% yield. Reactions with 2-chloroethyl isocyanate led to the urea derivatives (**15**) and (**16**) in 68% and 71% yield. The sulfonamide derivatives were obtained in the reactions with methanesulfonyl and *p*-toluenesulfonyl chlorides giving 10-methane- and 10-*p*-toluenesulfonylaminoalkyldiazaphenothiazines (**17-20**) in 68-80% yield.

Physical and spectroscopic properties of 2,7-diazaphenothiazines

The described reactions were monitored by TLC analysis. All chromatograms of 2,7-diazaphenothiazines

showed colour changing [from yellowish to celadon (**9-14**, **17-20)**, light-greenish (**7**, **8**) and intensive yellow (**5**, **6**, **15**, **16**)] during irradiation with UV lamp unlike to chromatograms of other compounds used and formed. Similar effect color [light-yellow (**5**, **6**), yellow (**9-14**, **17-20)**, canary (**15**, **16**) and orange-yellow (**5**, **6**)] was observed when chromatograms of diazaphenothiazines were sprayed with a phenothiazine detection mixture (sulfuric acid-water-ethanol 1:1:8).[16] In contrast to 10-diethylaminoethyl- and 10-dimethylaminopropyl-2,7-diazaphenothiazines,[13] 10-aminopropyl and 10-aminobutyl derivatives (**7**) and (**8**) turn out to be less stable.



Scheme 2

The ^{1}H NMR spectra of the obtained azaphenothiazines (**5-20**) were recorded in deuteriochloroform and revealed two singlet signals and four doublet signals showing unsymmetrical structure of the diazaphenothiazine system.[13] Since EI MS spectra showed labile the aminoalkyl chains in compounds (**5-20**), FAB MS spectra were used to determine the molecular ions.

All diazaphenothiazines (**5-20**) are diaza-analogs of the anticancer and antibacterial compounds obtained by Motohashi[7,10-12] and show promising potential anti-inflammatory, anticancer, antihistaminic, antiviral, cardiotonic and immunomodulating activities[17] and relatively low lipophilic character in comparison with

neuroleptic phenothiazines (logP = 3.5-5.9[18]). Basic compound, 10*H*-2,7-diazaphenothiazine (**4**), was tested against 57 human cancer lines in National Cancer Institute in Bethesda showing promising activity against lung, colon and renal cancers, and leukemia.[13,19]

We report here an efficient synthesis of 10*H*-2,7-diazaphenothiazine (**4**) from 3,3'-dinitro-4,4'-dipyridinyl disulfide (**1**) in reductive conditions of DMF and its transformation into aminopropyl and aminobutyl compounds (**7**) and (**8**), and further to their *N*-acyl and *N*-sulfonyl derivatives (**9-20**).

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 and a Bruker DRX spectrometers at 300 and 500 MHz in deuteriochloroform with tetramethylsilane as the internal standard. Fast Atom Bombardment mass spectra (FAB MS) were run in glycerol 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 $CHCl_3$-EtOH (5:1 and 10:1 v/v) and on aluminum oxide 60 F_{254} neutral (type E) (Merck 1.05581) with $CHCl_3$-EtOH (10:1 v/v) as eluents.

Synthesis of 10*H*-2,7-diazaphenothiazine (4)

A mixture of 3,3'-dinitro-4,4'-dipyridinyl disulfide (**1**) (0.31 g; 1 mmol) and sodium hydroxide (0.12 g; 3 mmol) in dry DMF (5 mL) was refluxed for 24 h under argon atmosphere. After cooling the solvent was evaporated *in vaccuo* and water (10 mL) was added and neutralized with diluted hydrochloric acid to pH = 7. The resulted solid was filtered off and the filtrate was extracted with $CHCl_3$ (3 x 5 mL). the extracts were washed with water, dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The obtained residue and solid were purified by column chromatography (aluminum oxide, $CHCl_3$-EtOH 10:1) to give 10*H*-2,7-diazaphenothiazine (**4**) (0.17 g, 84%); mp 169-170 ^{o}C (EtOH), (lit.,[13] mp 169-170 ^{o}C).

Synthesis of 10-phthalimidoalkyl-2,7-diazaphenothiazines (5) and (6)

To a stirred solution of 10*H*-2,7-diazaphenothiazine (**4**) (0.100 g, 0.5 mmol) in dry toluene (10 mL) NaH (0.12 g, 5 mmol, washed out with hexane) was added. The mixture was stirred for 10 min at rt, then refluxed for 1 h and a solution of *N*-(bromoalkyl)phthalimide [1.5 mmol, *N*-(3-bromopropyl)phthalimide – 0.405 g, *N*-(4-bromobutyl)phthalimide – 0.420 g] in toluene (5 mL) was added. The mixture was refluxed for 24 h. After cooling the resulted solid was filtered off, toluene was evaporated *in vaccuo* and the residue was purified by column chromatography (aluminum oxide, $CHCl_3$) to give:

1. 10-(3'-phthalimidopropyl)-2,7-diazaphenothiazine (IUPAC name: N-[3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)propyl]phthalamide) (**5**) (0.124 g, 70%); mp 87-88 ^{o}C (EtOH). ^{1}H NMR (DMSO-d_6) δ:

1.78 (m, 2H, CH_2), 3.58 (t, J = 6.1 Hz, 2H, NCH_2), 3.65 (t, J = 6.0 Hz, 2H, NCH_2), 5.73 (d, J = 6.8 Hz, 1H, H-9), 6.60 (d, J = 4.6 Hz, 1H, H-4), 7.08 (s, 1H, H-1), 7.25 (d, J = 6.8 Hz, 1H, H-8), 7.48 (s, 1H, H-6), 7.68 (d, J = 4.6 Hz, 1H, H-3), 7.84 (m, $4H_{phthalimide}$). FAB MS m/z: 389 (M+H, 95), 185 (2gly+H, 100). Anal. Calcd for $C_{21}H_{16}N_4O_2S$: C 64.93, H 4.15, N 14.42. Found C 64.78, H 4.21, N 14.20.

2. 10-(4'-phthalimidobutyl)-2,7-diazaphenothiazine (IUPAC name: *N*-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)butyl]phthalamide) (**6**) (0.153 g, 76%); mp 43-44 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.71 (m, 4H, $2CH_2$), 3.46 (t, J = 6.3 Hz, 2H, NCH_2), 3.72 (t, J = 6.3 Hz, 2H, NCH_2), 5.69 (d, J = 7.2 Hz, 1H, H-9), 6.17 (s, 1H, H-1), 6.36 (s, 1H, H-6), 6.57 (d, J = 7.2 Hz 1H, H-4), 7.74 (m $4H_{phthalimide}$), 7.87 (m, 2H, H-3 and H-8). FAB MS m/z: 403 (M+1, 70), 185 (2gly+H, 100). Anal. Calcd for $C_{22}H_{18}N_4O_2S$: C 65.65, H 4.51, N 13.92. Found C 65.38, H 4.55, N 13.69.

Synthesis of 10-aminoalkyl-2,7-diazaphenothiazines (7) and (8)

To a solution of 10-phthalimidoalkyl-2,7-diazaphenothiazines (**5**) and (**6**) [1 mmol, 0.388 g of (**5**), 0.402 g of (**6**)] in EtOH (20 mL) 80% aqueous solution of hydrazine (0.2 mL, 5 mmol) was sdded. The mixture was refluxed for 2 h. After cooling the reaction mixture was acidified with conc. hydrochloric acid to pH = 2. The solution was concentrated and the resulted solid was filtered off. The filtrate was alkalized with 10% aqueous solution of sodium hydroxide and extracted with $CHCl_3$ (3 x 10 mL). The extracts were washed with water, dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The obtained residue was purified by column chromatography (aluminum oxide, $CHCl_3$) to give:

1. 10-(3'-aminopropyl)-2,7-diazaphenothiazine (IUPAC name: 3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)propan-1-amine) (**7**), (0.186 g, 72%), an oil. ^1H NMR ($CDCl_3$) δ: 1.93 (m, 2H, CH_2), 2.34 (broad s, 2H, NH_2), 2.90 (m, 2H, $C\underline{H}_2NH_2$), 3.95 (t, J = 6.9 Hz, 2H, NCH_2), 6.75 (d, J = 5.4 Hz, 1H, H-9), 7.08 (d, J = 4.8 Hz, 1H, H-4), 8.06 (s, 1H, H-1), 8.11 (d, J = 4.8 Hz, 1H, H-3), 8.13 (s, 1H, H-6), 8.25 (d, J = 5.4 Hz, 1H, H-8). FAB MS m/z: 259 (M+1, 18), 202 (M-$C_3H_5NH_2$, 19), 185 (2gly+H, 100). Anal. Calcd for: $C_{13}H_{14}N_4S$: C 60.44, H 5.46, N 21.69. Found: C 60.21, H 5.58, N 21.58.

2. 10-(4'-aminobutyl)-2,7-diazaphenothiazine (IUPAC name: 4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)butan-1-amine) (**8**), (0.209 g, 77%), an oil. ^1H NMR ($CDCl_3$) δ: 1.89 (m, 2H, CH_2), 1.96 (m, 2H, CH_2), 2.42 (broad s, 2H, NH_2), 3.12 (m, 2H, $C\underline{H}_2NH_2$), 3.67 (t, J = 6.3 Hz, 2H, NCH_2), 6.67 (d, J = 6.0 Hz, 1H, H-9), 6.97 (d, J = 6.0 Hz, 1H, H-4), 8.04-8.23 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 273 (M+1, 20), 202 (M-$C_4H_7NH_2$, 100). Anal. Calcd for $C_{14}H_{16}N_4S$: C 61.74, H 5.92, N 20.57. Found C 61.52, H 5.90, N 20.29.

Synthesis of 10-acetylaminoalkyl-2,7-diazaphenothiazines (9) and (10)

To a suspension of 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) [0.5 mmol, 0.129 g of (**7**); 0.136 g

of (**8**)] in pyridine (5 mL) acetic anhydride (1.48 mL, 1.5 mmol) was added and the mixture was stirred at rt for 2 h. After evaporation of pyridine *in vaccuo* the residue was dissolved in $CHCl_3$ (10 mL). The solution was washed with water, dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The residue was purified by column chromatography (aluminum oxide, $CHCl_3$) to give:

1. 10-(3'-acetylaminopropyl)-2,7-diazaphenothiazine (IUPAC name: *N*-[3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)propyl]acetamide) (**9**), (0.108 g, 72%) mp 117-118 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 2.03 (s, 3H, CH_3), 2.05 (m, 2H, CH_2), 3.40 (m, 2H, NHC$\underline{H}_2$), 3.92 (t, *J* = 6.6 Hz, 2H, NCH_2), 6.09 (broad s, 1H, NH), 6.70 (d, *J* = 4.8 Hz, 1H, H-9), 7.01 (d, *J* = 4.4 Hz, 1H, H-4), 8.01-8.27 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 301 (M+H, 100), 202 (M+1-$C_3H_5NHCOCH_3$, 20). Anal. Calcd for $C_{15}H_{16}N_4OS$: C 59.98, H 5.37, N 18.65. Found C 59.69, H 5.31, N 18.32.

2. 10-(4'-acetylaminobutyl)-2,7-diazaphenothiazine (IUPAC name: *N*-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)butyl]acetamide) (**10**), (0.126 g, 80%. mp 119-120 ^oC (EtOH). ^1H NMR ($CDCl_3$) δ: 1.66 (m, 2H, CH_2), 1.84 (m, 2H, CH_2), 1.97 (s, 3H, CH_3), 3.29 (m, 2H, NHC$\underline{H}_2$), 3.84 (t, *J* = 7.2 Hz, 2H, NCH_2), 5.62 (broad s, 1H, NH), 6.67 (d, 1H, *J* = 5.7 Hz, H-9), 7.00 (d, *J* = 4.8 Hz, 1H, H-4), 8.04-8.29 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 315 (M+1, 89), 202 (M+1-$C_4H_7NHCOCH_3$, 100). Anal. Calcd for $C_{16}H_{18}N_4OS$: C 61.12, H 5.77, N 17.82. Found C 60.83, H 5.71, N 17.57.

Synthesis of 10-benzoylaminoalkyl-2,7-diazaphenothiazines (11) and (12)

To a stirred solution of 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) (0.5 mmol) in a mixture of CH_2Cl_2 (5 mL) and 10% aqueous Na_2CO_3 solution (5 mL), benzoyl chloride ((0.12 mL, 1.5 mmol) was added. The solutions were stirred at rt for 12 h. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with water (10 mL) and dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The residue was purified by column chromatography (aluminum oxide, CH_2Cl_2) to give:

1. 10-(3'-benzoylaminopropyl-2,7-diazaphenothiazine (IUPAC name: *N*-[3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)propyl]benzamide) (**11**), (0.128 g, 71%), an oil. ^1H NMR ($CDCl_3$) δ: 2.09 (m, 2H, CH_2), 3.62 (m, 2H, NHC$\underline{H}_2$), 4.03 (t, *J* = 6.6 Hz, 2H, NCH_2), 6.38 (broad s, 1H, NH), 6.73 (d, *J* = 5.7 Hz, 1H, H-9), 6.99 (d, *J* = 4.8 Hz, 1 H, H-4), 7.41 (m 2H, *m*-C_6H_5), 7.49 (m 1H, *p*-C_6H_5), 7.68 (m 2H, *o*-C_6H_5), 8.10-8.26 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 363 (M+1, 10), 202 (M+1-$C_3H_5NHCOC_6H_5$, 8), 162 ($C_3H_5NHCOC_6H_5$, 49), 105 (C_6H_5CO, 100). Anal. Calcd for $C_{20}H_{18}N_4OS$: C 66.28, H 5.01, N 15.46. Found C 66.01, H 4.97, N 15.19.

2. 10-(4'-benzoylaminobutyl-2,7-diazaphenothiazine (IUPAC name: *N*-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)butyl]benzamide) (**12**), (0.130 g, 69%), an oil. ^1H NMR ($CDCl_3$) δ: 1.78 (m, 2H, CH_2), 1.98 (m, 2H, CH_2), 3.52 (m, 2H, NHC$\underline{H}_2$), 3.95 (t, *J* = 7.2 Hz, 2H, NCH_2), 6.31 (broad s, 1H, NH), 6.78

(d, J = 5.7 Hz, 1H, H-9), 6.95 (d, J = 4.8 Hz, 1H, H-4), 7.41 (m, 2H, *m*-C_6H_5), 7.51 (m, 1H, *p*-C_6H_5), 7.68 (m, 2H, *o*-C_6H_5), 8.01-8.24 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 377 (M+1, 57), 202 (M+1-$C_4H_7NHCOC_6H_5$, 9), 176 ($C_4H_7NHCOC_6H_5$, 10), 105 (C_6H_5CO, 100). Anal. Calcd for $C_{21}H_{20}N_4OS$: C 67.00, H 5.35, N 14.88. Found C 66.81, H 5.29, N 14.61.

Synthesis of 10-ethoxycarbonylaminoalkyl-2,7-diazaphenothiazines (13) and (14)

To a stirred solution of 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) (0.5 mmol) in a mixture of CH_2Cl_2 (5 mL) and 10% aqueous Na_2CO_3 solution (5 mL) a solution of ethyl chloroformate (0.14 mL, 1.5 mmol) in CH_2Cl_2 (3 mL) was added. The solutions were stirred at rt for 12 h. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with water (10 mL) and dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The residue was purified by column chromatography (aluminum oxide, CH_2Cl_2) to give:

1. 10-(3'-ethoxycarbonylaminopropyl-2,7-diazaphenothiazine (IUPAC name: ethyl 3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)propylcarbamate) (**13**), (0.135 g, 82%), an oil. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J = 6.6 Hz, 3H, CH_3), 2.05 (m, 2H, CH_2), 3.34 (m, 2H, NHC<u>H</u>$_2$), 3.95 (t, J = 7.2 Hz, 2H, NCH_2), 4.11 (q, J = 6.6 Hz, 2H, OCH_2), 4.92 (broad s, 1H, NH), 6.70 (d, J = 5.7 Hz, 1H, H-9), 6.98 (d, J = 4.8 Hz, 1H, H-4), 8.08-8.28 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 331 (M+1, 100), 202 (M+1-$C_3H_6NHCOOC_2H_5$, 25). Anal. Calcd for $C_{16}H_{18}N_4O_2S$: C 58.16, H 5.49, N 16.96. Found C 58.01, H 5.44, N 16.65.

2. 10-(4'-ethoxycarbonylaminobutyl-2,7-diazaphenothiazine (IUPAC name: ethyl 4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)butylcarbamate) (**14**), (0.138 g, 80%), an oil. ^{1}H NMR ($CDCl_3$) δ: 1.23 (t, J = 6.7 Hz, 3H, CH_3), 1.78 (m, 2H, CH_2), 1.95 (m, 2H, CH_2), 3.24 (m, 2H, NHC<u>H</u>$_2$), 3.86 (t, J = 7.1 Hz, 2H, NCH_2), 4.10 (q, J = 6.7 Hz, 2H, OCH_2), 4.95 (broad s, 1H, NH), 6.70 (d, J = 5,7 Hz, 1 H, H-9), 6.98 (d, J = 4.8 Hz, 1 H, H- 4), 8.00-8.19 (m, 4 H, H-1, H-3, H-6 and H-8). FAB MS m/z: 345 (M+1, 40), 201 (M-$C_4H_7NHCOOC_2H_5$, 15), 202 (M+1-$C_4H_7NHCOOC_2H_5$, 100). Anal. Calcd for $C_{17}H_{20}N_4O_2S$: C 59.28, H 5.85, N 16.27. Found C 59.21, H 5.80, N 16.02.

Synthesis of 10-chloroethylureidoalkyl-2,7-diazaphenothiazines (15) and (16)

To a stirred solution of 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) (0.5 mmol) in dry EtOH (10 mL) at 0 ^{o}C 2-chloroethyl isocyanate (0.87 mL, 1 mmol) was added. The mixture was stirred at 0 ^{o}C for 0.5 h and at rt for 24 h. After evaporation of EtOH *in vaccuo* the residue was purified by column chromatography (aluminum oxide, CH_2Cl_2) to give:

1. 10-chloroethylureidopropyl-2,7-diazaphenothiazine (IUPAC name: 1-[3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)propyl]-3-(2-chloroethyl)urea) (**15**), 0.124 g, 68%), mp 101-102 ^{o}C (EtOH). ^{1}H NMR

(DMSO-d_6) δ: 1.95 (m, 2H, CH_2), 3.36 (m, 6H, $3CH_2$), 3.90 (broad s, 1H, NH), 3.96 (m, 2H, CH_2), 4.22 (broad s, 1H, NH), 6.98 (d, J = 5.4 Hz, 1H, H-9), 7.14 (d, J = 4.8 Hz, 1H, H-4), 8.03-8.27 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 365 (M+2, 4), 367 (M+4, 2) 328 (M-Cl, 2), 202 (M+H-$C_3H_6NHCONHCH_2CH_2Cl$, 10), 185 (2gly+H, 100). Anal. Calcd for $C_{16}H_{18}ClN_5OS$: C 52.82, H 4.99, N 19.25. Found: C 52.51, H 5.17, N 18.87.

2. 10-chloroethylureidobutyl-2,7-diazaphenothiazine (IUPAC name: 1-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*]-[1,4]thiazin-10-yl)butyl]-3-(2-chloroethyl)urea) (**16**), 0.134 g, 71%), mp 104-105 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 1.69 (m, 2H, CH_2), 1.86 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 3.52 (m, 2H, CH_2), 3.62 (t, J = 5.5 Hz, 2H, CH_2Cl), 3.88 (t, J = 7.4 Hz, 2H, NCH_2), 4.35 (broad s, 1H, NH), 4.65 (broad s, 1H, NH), 6.68 (d, J = 2.9 Hz, 1H, H-9), 6.92 (d, J = 5.6 Hz, 1H, H-4), 8.05-8.24 (m, 4 H, H-1, H-3, H-6 and H-8). FAB MS m/z: 378 (M+1, 90), 201 (M-$C_4H_7NHCONH$-CH_2CH_2Cl, 50), 202 (M+1-$C_4H_7NHCONHCH_2CH_2Cl$, 100). Anal. Calcd for $C_{17}H_{20}ClN_5OS$: C 54.03, H 5.33, N 18.53. Found C 54.03, H 5.33, N 18.31.

Synthesis of 10-sulfonylaminoalkyl-2,7-diazaphenothiazines (17-20)

To a stirred solution of 10-aminoalkyl-2,7-diazaphenothiazines (**7**) and (**8**) (0.5 mmol) in a mixture of CH_2Cl_2 (5 mL) and 10% aqueous Na_2CO_3 solution (5 mL) a solution of methanesulfonyl chloride (0.12 mL, 1.5 mmol) or *p*-toluenesulfonyl chloride (0.286 g, 1.5 mmol) in CH_2Cl_2 (3 mL) was added. The solutions were stirred at rt for 12 h and 24 h, respectively. The organic phase was separated and aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with water (10 mL) and dried with anhydrous sodium sulfate and evaporated *in vaccuo*. The residue was purified by column chromato-graphy (aluminum oxide, CH_2Cl_2) to give:

1. 10-(3'-methanesulfonylaminopropyl-2,7-diazaphenothiazine (IUPAC name: *N*-[3-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)propyl]methanesulfonamide) (**17**), (0.133 g, 79%), an oil. ^{1}H NMR ($CDCl_3$) δ: 2.09 (m, 2H, CH_2), 2.92 (s, 3H, CH_3), 3.31 (m, 2H, $NHC\underline{H}_2$), 4.02 (t, J = 6.9 Hz, 2H, NCH_2), 5.50 (broad s, 1H, NH), 6.73 (d, J = 5.7 Hz, 1H, H-9), 7.03 (d, J = 5.1 Hz, 1H, H-4), 8.09-8.26 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 337 (M+1, 100), 202 (M+1-$C_3H_5NHSO_2CH_3$,30). Anal. Calcd for $C_{14}H_{16}N_4O_2S_2$: C 49.98, H 4.79, N 16.65. Found C 49.71, H 4.71, N 16.42.

2. 10-(4'-methanesulfonylaminobutyl-2,7-diazaphenothiazine (IUPAC name: *N*-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)butyl]methanesulfonamide) (**18**), (0.140 g, 80%), an oil. ^{1}H NMR ($CDCl_3$) δ: 1.75 (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.93 (s, 3H, CH_3), 3.18 (m, 2H, $NHC\underline{H}_2$), 3.86 (t, J = 7.2 Hz, 2H, NCH_2), 5.02 (broad s, 1H, NH), 6.68 (d, J = 5.7 Hz, 1H, H-9), 6.99 (d, J = 4.8 Hz, 1H, H-4), 8.05-8.26 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 351 (M+1, 100), 202 (M+1-$C_4H_7NHSO_2CH_3$, 58). Anal. Calcd for $C_{15}H_{18}N_4O_2S_2$: C 51.41, H 5.18, N 15.99. Found C 51.33, H 5.11, N 15.78.

3. 10-(3'-*p*-toluenesulfonylaminopropyl-2,7-diazaphenothiazine (IUPAC name: *N*-[3-(10*H*-dipyrido[3,4-

b;3',4'-*e*][1,4]thiazin-10-yl)propyl]-4-methylbenzenesulfonamide) (**19**), (0.140 g, 68%), an oil. ^{1}H NMR ($CDCl_3$) δ: 2.08 (m, 2H, CH_2), 2.44 (s, 3H, CH_3), 3.32 (m, 2H, NHC$\underline{H_2}$), 4.01 (t, J = 6.8 Hz, 2H, NCH_2), 4.78 (broad s, 1H, NH), 6.66 (d, J = 5.7 Hz, 1H, H-9), 6.96 (d, J = 4.9 Hz, 1H, H-4), 7.72 (m, 4H, C_6H_4), 8.03-8.12 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 413 (M+1, 30), 202 (M+1-$C_3H_5NHSO_2C_6H_4CH_3$, 30), 155 ($SO_2C_6H_4CH_3$, 100). Anal. Calcd for $C_{20}H_{20}N_4O_2S_2$: C. 58.23, H 4.89, N 13.58. Found C. 58.05, H 4.83, N 13.39.

4. 10-(4'-*p*-toluenesulfonylaminobutyl-2,7-diazaphenothiazine (IUPAC name: *N*-[4-(10*H*-dipyrido[3,4-*b*;3',4'-*e*][1,4]thiazin-10-yl)butyl]-4-methylbenzenesulfonamide) (**20**), (0.152 g, 71%), an oil. ^{1}H NMR ($CDCl_3$) δ: 1.62 (m, 2H, CH_2), 1.87 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 3.10 (m, 2H, NHC$\underline{H_2}$), 3.79 (t, J = 7.3 Hz, 2H, NCH_2), 4.72 (broad s, 1H, NH), 6.64 (d, J = 5.7 Hz, 1H, H-9), 6.96 (d, J = 4.8 Hz, 1H, H-4), 7.70 (m, 4 H, C_6H_4), 8.01-8.10 (m, 4H, H-1, H-3, H-6 and H-8). FAB MS m/z: 427 (M+1, 100), 202 (M+1-$C_4H_7NHSO_2C_6H_4CH_3$, 30). Anal. Calcd for $C_{21}H_{22}N_4O_2S_2$: C 59.13, H 5.20, N 13.13. Found C 58.88, H 5.15, N 12.88.

REFERENCES

#Part CXIV in the series of Azinyl Sulfides.

1. R. R. Gupta and M. Kumar, M. in Phenothiazines and 1,4-Benzothiazines – Chemical and Biological Aspects, ed. by R. R. Gupta, Elsevier, Amsterdam, 1988, pp. 1-161.
2. L. Amaral, M. Vivieros, and J. E. Kristiansen, *Trop. Med. Int. Health*, 2001, **6**, 1016.
3. L. Amaral and J. E. Kristiansen, *Int. J. Antimicrob. Agents,* 2001, **18**, 411.
4. D. Ordway, M. Viveiros, C. Leandro, R. Bettencourt, J. Almeida, M. Martins, J. E. Kristiansen, J. Molnar, and L. Amaral, *Antimicrob. Agents Chemother*., 2003, **47**, 917.
5. M. Viveiros, M. Martins, I. Couto, J. E. Kristiansen, J. Molnar, and L. Amaral, *In vivo*, 2005, **19**, 733.
6. L. Amaral, M. Martins, and M. Viveiros, *J. Antimicrob. Chemother*., 2007, **59**, 1237.
7. N. Motohashi, M. Kawase, T. Kurihara, A. Hever, S. Nagy, I. Ocsocvszki, M. Tanaka, and J. Molnar, *Anticancer Res*., 1996, **16**, 2525.
8. N. Motohashi, T. Kurihara, H. Sakagami, D. Szabo, K. Csuri, and J. Molnar, *Anticancer Res.,* 1999, **19**, 1859.
9. N. Motohashi, M. Kawase, S. Saito, and H. Sakagami, *Curr. Drug Targets*, 2000, **1**, 237.
10. N. Motohashi, M. Kawase, K. Satoh, and H. Sakagami, *Curr. Drug Targets*, 2006, **7**, 1055.
11. N. Motohashi, M. Kawase, S. Saito, T. Kurihara, K. Satoh, H. Nakashima, M. Premanathan, R. Arakaki, H. Sakagami, and J. Molnar, *Int. J. Antimicrob. Agents,* 2000, **14**, 203.
12. N. Motohashi, M. Kawase, J. Molnar L. Ferenczy, O. Wesolowska, A. B. Hendrich, M. Bobrowska-

Hägerstrand, H. Hägerstrand, and K. Michalak, *Arzneim.-Forsch./Drug Res*., 2003, **53**, 590.

13. B. Morak-Młodawska and K. Pluta, *Heterocycles,* 2007, **71**, 1347.
14. B. Morak, K. Pluta, and K. Suwińska, *Heterocyclic Commun.,* 2002, **8**, 331.
15. B. Morak, K. Pluta, K. Suwińska, M. Grymel, C. Bernard, M. Schiltz, C. Kloc, and T. Siegrist, *Heterocycles*, 2005, **65**, 2619.
16. E. Stahl, Thin-layer chromatography, Springer-Verlag, Berlin, 1969, p. 508.
17. Prediction of Activity Spectra for Substance, http://ibmc.msk.ru/PASS/.
18. U. Franke, A. Munk, and M. Wiese, *J. Pharm. Sci.,* 1999, **88**, 89.
19. National Cancer Institute Developmental Therapeutics Program, In-Vitro Testing Results, Bethesda, USA.