HETEROCYCLES, Vol. 55, No. 11, 2001, pp. 2085 - 2098, Received, 24th July, 2001

SYNTHESIS OF BIS-SUBSTITUTED AMIDINOBENZOTHIAZOLES AS POTENTIAL ANTI-HIV AGENTS

Livio Racanè[1], Vesna Tralić-Kulenović[2], Lelja Fišer-Jakić[2], David W. Boykin[3], and Grace Karminski-Zamola[1]*

[1]Faculty of Chemical Engineering and Technology, [2]Faculty of Textile Technology, University of Zagreb, 10 000 Zagreb, Croatia, and [3]Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, Atlanta, Georgia 30303-3083, USA

Abstract – In the multistep syntheses of the title compounds we obtained some new cyano-substituted heterocycles (**1a**, **1b**, **2a,** and **2b**) as intermediates. Starting from dinitriles (**2a** and **2b**) as well as from two formerly prepared dinitriles, substituted bisamidines (**3a, 3b, 5a, 5b, 7a,** and **7b**) and amidino dihydrochlorides (**4a, 4b, 6a, 6b, 8a, 8b, 9a**, and **9b**) have been synthesized.

In the recent time many authors pointed out their attention on the synthesis of bisamidines as new dicationic molecules which could serve as potential therapeutic agents against a number of microbial infections.[1-3] The amidine group at the termini of the molecules seemed to contribute significantly to the dications and the DNA[4,5] complex stability. A number of aromatic bisamidines have been shown to bind in minor groove on DNA at AT-rich sites and to be affective against many opportunistic organisms.[6,7] Several hypotheses have been proposed to explain the mode of action of these compounds. The important factors in minor groove binding are hydrogen-bonding, electrostatic interactions, van der Waals interactions, and the radius of curvature of the observed molecule.[8]

In connection with our studies on new bisamidines,[9] the preparation of the new bisamidine compounds containing benzothiazole and furan or thiophene nuclei (**3a, 3b**–**9a,** and **9b**) was achieved by using the multistep synthesis according to Scheme 1 and Scheme 2. As the key precursors of the bisamidino compounds the corresponding dinitriles were used.

According to the Scheme 1 the starting compound was *p*-aminobenzoic acid, which was diazotized and the obtained diazonium salt was used for arylation of 2-furancarbonitrile and 2-thiophenecarbonitrile. The

arylation of 2-furancarbonitrile takes place with better yield (24.7 %) than arylation of 2-thiophenecarbonitrile (12.4 %). Such difference between reactivities of furan and thiophene compounds was observed earlier.[10,11] The new compounds 5-(4-carboxyphenyl)-2-furancarbonitrile (**1a**) and 5-(4-carboxyphenyl)-2-thiophenecarbonitrile (**1b**) were condensed with 4-amino-3-mercaptobenzonitrile[11] yielding 2-[4-(6-cyanobenzothiazol-2-yl)phenyl]-5-furancarbonitrile (**2a**) and 2-[4-(6-cyanobenzothiazol-2-yl)phenyl]-5-thiophenecarbonitrile (**2b**), the key precursors for bisamidino compounds.

The classical Pinner method[12,13] was used to transform the cyano into amidino group. The imidate esters hydrochlorides generated as intermediate products were immediately converted, with the appropriate amine or bisamine, to the desired bisamidines (**3a, 3b, 5a**, and **5b**).

The conversion of the free bases into appropriate bishydrochlorides (**4a, 6a**, and **6b**) was achieved by treatment with gaseous hydrochloric acid, while the salt (**4b**) was obtained using concentrated hydrochloric acid.

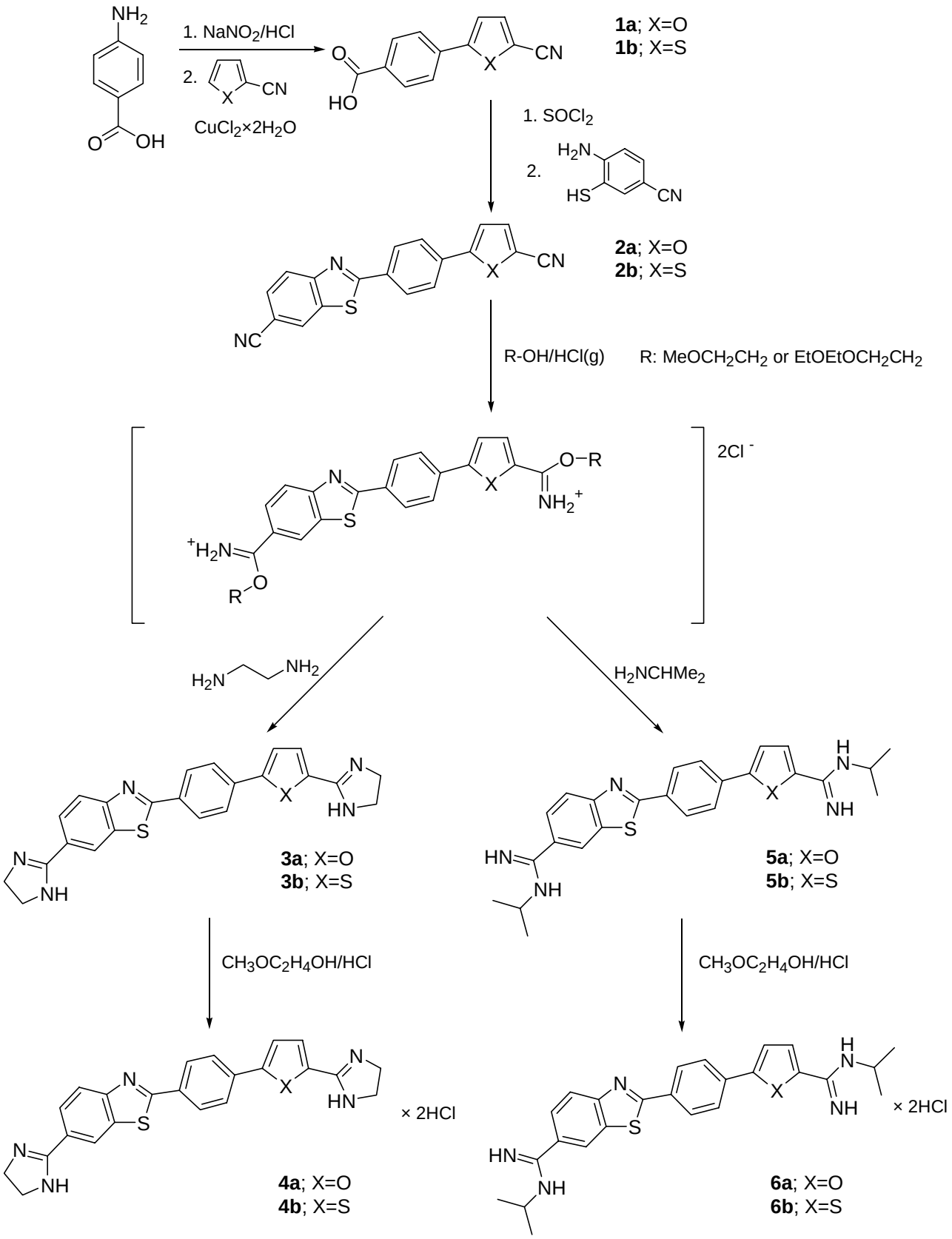
The synthetic steps for obtaining dicationic compounds (**8a, 8b, 9a** and **9b**) are outlined in Scheme 2. This bisamidines as hydrochloric salts were synthesized from appropriate bisnitriles[11] using also the classical Pinner-type approach for conversion of the cyano function into the amidino one. The attempt to employ fusion of the 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)furan with the hydrochloride salt of the ethylenediamine[14] gave very low yield of the 2-[4-(imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]furan (**7a**), while the 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene didn't react at all. From 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)furan and 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene[11], using Pinner method, free bases 2-[4-(imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]furan (**7a**) and 2-[4-(imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]thiophene (**7b**) are obtained. Treating the solution of free base (**7a**) in 2-methoxyethanol with gaseous hydrochloric acid, the corresponding bishydrochloride (**8a**) was obtained. From the free base (**7b**) the bishydrochloride (**8b**) was obtained with concentrated hydrochloric acid.

Bishydrochlorides (**9a**, and **9b**) were obtained from corresponding imidate esters hydrochloride in the reaction with isopropylamine. Inspite of the excess of isopropylamine the hydrochloric salts (**9a**, and **9b**) were isolated from reaction mixture. It seems that the reason for it is the difference in the basicity of the isopropylamine and corresponding amidine.

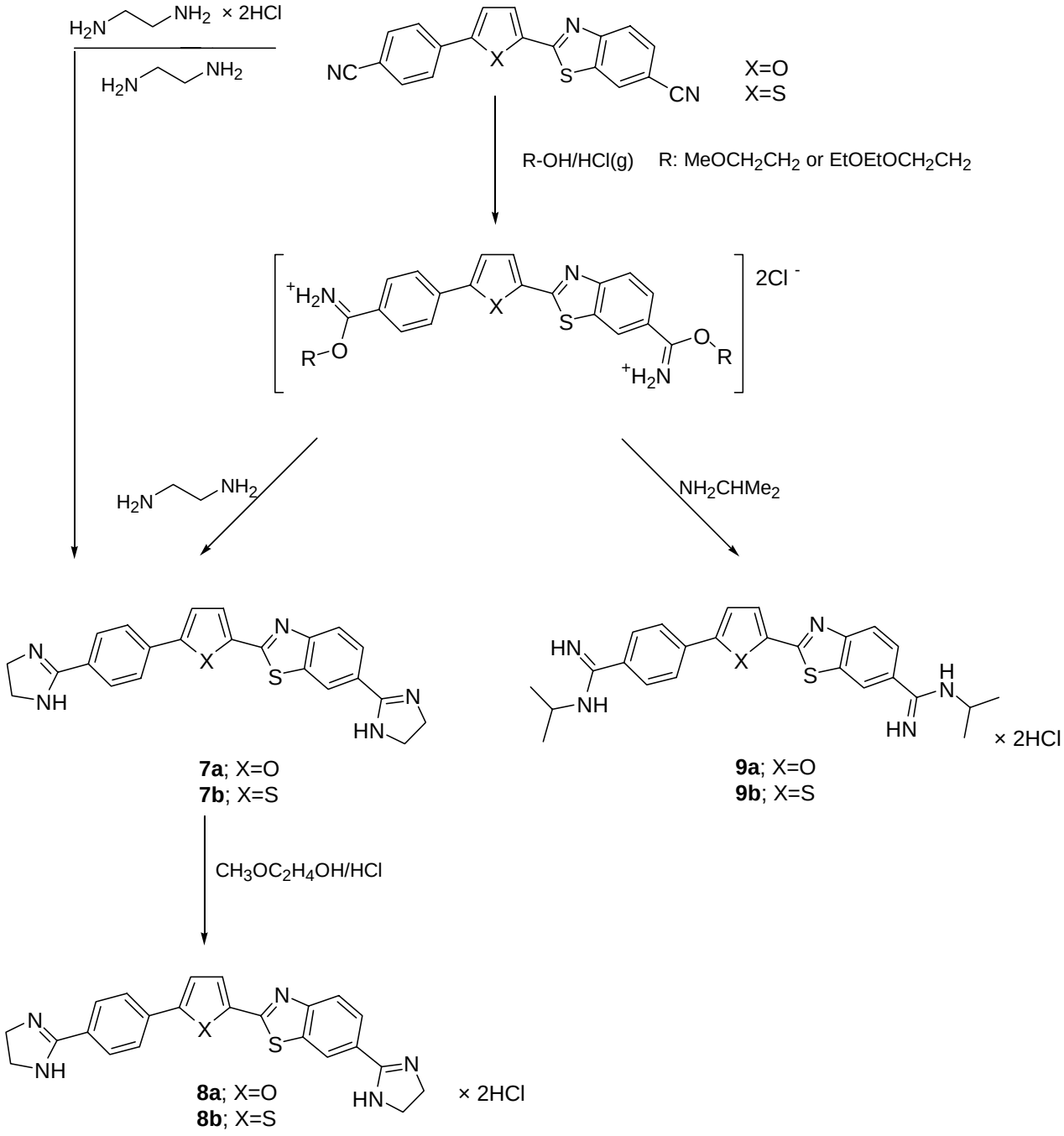
The structure of the new compounds was confirmed by elemental analysis, IR, ^{1}H NMR and in some cases ^{13}C NMR spectra. Due to a very low solubility of most compounds in appropiate solvent it was impossible to record some of the ^{13}C NMR spectra.

The examination of biological activity of the compounds (**4a**, **4b**, **6a**, **6b**, **8a**, **8b**, **9a**, and **9b**) are in course.

Scheme 1


1. NaNO2/HCl
2.
CuCl2×2H2O
1a; X=O
1b; X=S
1. SOCl2
2.
2a; X=O
2b; X=S
R-OH/HCl(g)
R: MeOCH2CH2 or EtOEtOCH2CH2
2Cl -
H2NCHMe2
3a; X=O
3b; X=S
5a; X=O
5b; X=S
CH3OC2H4OH/HCl
CH3OC2H4OH/HCl
× 2HCl
× 2HCl
4a; X=O
4b; X=S
6a; X=O
6b; X=S

Scheme 2



EXPERIMENTAL

Melting points were determined on a Kofler block apparatus and are uncorrected. IR spectra were determined with a Nicolet Magna 760 infrared spectrophotometer in KBr pellets. ^{1}H NMR spectral data were determined with a Brucker Avance DPX 300 MHz NMR spectrometer with tetramethylsilane as an internal standard. Elemental analyses were carried out in the Microanalitical laboratory at the Rugjer Boskovic Institute.

5-(4-Carboxyphenyl)-2-furancarbonitrile (1a). The solution of 14.7 g (107 mmol) of *p*-aminobenzoic acid in 35 mL of water and 65 mL of concd HCl was cooled to 5 °C and diazotated with the solution of 8.28 g (120 mmol) of $NaNO_2$. After 20 min to the stirred reaction mixture the solution of 9.4 g (107 mmol) of 2-furancarbonitrile in 140 mL of acetone and the solution of 2.55 g (15 mmol) of $CuCl_2 \times 2H_2O$ in 30 mL of water were added. The obtained reaction mixture was left to stand at rt for two days by occasional shaking. After dilution with 500 mL of water the precipitated crystals were filtered off and washed with a lot of water. Crystallization from diluted ethanol yielded 5.64 g (24.7 %) of product, mp 263–267 °C. IR (KBr, cm^{-1}): 2972 (OH), 2231 (CN), 1682 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 13.18 (br s, 1H, H-COOH), 8.05 (d, 2H, *J*=8.2 Hz, H-arom.), 7.96 (d, 2H, *J*=8.2 Hz, H-arom.), 7.78 (d, 1H, *J*=3.6 Hz, H-fur.), 7.45 (d, 1H, *J*=3.6 Hz, H-fur.). Anal. Calcd for $C_{12}H_7NO_3$: C, 67.61; H, 3.31; N, 6.57. Found: C, 67.73; H, 3.24; N, 6.43.

5-(4-Carboxyphenyl)-2-thiophenecarbonitrile (1b). The solution of 10.3 g (76 mmol) of *p*-aminobenzoic acid in 120 mL of water and 40 mL of concd HCl was cooled to 5 °C and diazotated with the solution of 6.30 g (92 mmol) of $NaNO_2$. After 20 min to the stirred reaction mixture the solution of 8.30 g (76 mmol) of 2-thiophenecarbonitrile in 100 mL of acetone and the solution of 1.45 g (9 mmol) of $CuCl_2 \times 2H_2O$ in 10 mL of water were added. The obtained reaction mixture was left to stand at rt for five days by occasional shaking. After dilution with 500 mL of water the precipitated crystals were filtered off and washed with lot of water. Crystallization from diluted ethanol yielded 2.14 g (12.4 %) of product, mp>300 °C. IR (KBr, cm^{-1}): 2970 (OH), 2221 (CN), 1680 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 13.18 (br s, 1H, H-COOH), 8.02 (d, 1H, *J*=4.0 Hz, H-thioph.), 7.99 (d, 2H, *J*=8.6 Hz, H-arom.), 7.87 (d, 2H, *J*=8.3 Hz, H-arom.), 7.81 (d, 1H, *J*=4.0 Hz, H-thioph.). Anal. Calcd for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11. Found: C, 62.59; H, 3.21; N, 6.01.

2-[4-(6-Cyanobenzothiazol-2-yl)phenyl]-5-furancarbonitrile (2a). Heating a mixture of 5.50 g (26 mmol) of 5-(4-carboxyphenyl)-2-furancarbonitrile (**1a**) with 25 mL (344 mmol) of thionyl chloride yielded 3.88 g (64.5 %) of 2-(4-chlorocarbonylphenyl)-5-furancarbonitrile, mp 131–132 °C. To a mechanically stirred hot solution of 2.0 g (8.6 mmol) of 2-(4-chlorocarbonylphenyl)-5-furancarbonitrile dissolved in 40 mL of chlorobenzene 1.36 g (9.0 mmol) of 4-amino-3-mercaptobenzonitrile was added. The reaction mixture was refluxed for 80 h in a stream of nitrogen. After cooling the mixture was filtered, the crude product was washed with ethanol and crystallized from DMF. Yield was 1.85 g (65.6 %) of yellow crystals, mp 285-287 °C. IR (KBr, cm^{-1}): 2227 (CN). ^1H NMR (300 MHz, DMSO-d_6) δ: 8.75 (s, 1H, H-arom), 8.22-8.19 (m, 3H, H-arom.), 8.01 (d, 2H, *J*=8.4 Hz, H-arom.), 7.93 (d, 1H, *J*=8.7 Hz, H-arom.), 7.76 (d, 1H, *J*=3.7 Hz, H-fur.), 7.43 (d, 1H, *J*=3.7 Hz, H-fur.). Anal. Calcd for $C_{19}H_9N_3OS$: C, 69.71; H, 2.77; N, 12.85. Found: C, 69.50; H, 2.85; N, 12.93.

2-[4-(6-Cyanobenzothiazol-2-yl)phenyl]-5-thiophenecarbonitrile (2b). Heating a mixture of 1.85 g (8 mmol) of 5-(4-carboxyphenyl)-2-thiophenecarbonitrile (**1b**) with 10 mL (137 mmol) of thionyl chloride yielded 1.63 g (82.3 %) of 2-(4-chlorocarbonylphenyl)-5-thiophenecarbonitrile, mp 182–184 °C. To a mechanically stirred hot solution of 1.00 g (4.0 mmol) of 2-(4-chlorocarbonylphenyl)-5-thiophenecarbonitrile in 60 mL of chlorobenzene 0.61 g (4.0 mmol) 4-amino-3-mercaptobenzonitrile was added. The reaction mixture was refluxed for 70 h in a stream of nitrogen. After cooling the mixture was filtered, the crude product was washed with ethanol and crystallized from DMF. Yield was 1.00 g (73.2 %) of yellow crystals, mp>300 °C. IR (KBr, cm^{-1}): 2225 (CN). ^{1}H NMR (300 MHz, TFA) δ: 8.43 (s, 1H, H-arom.), 8.12 (d, 1H, *J*=8.7, H-arom.), 8.03 (d, 2H, *J*=8.1 Hz, H-arom.), 7.95 (d, 1H, *J*=8.7 Hz, H-arom.), 7.81 (d, 2H, *J*=8.1 Hz, H-arom.), 7.57 (d, 1H, *J*=3.3 Hz, H-thioph.), 7.42 (d, 1H, *J*=3.3 Hz, H-thioph.). Anal. Calcd for $C_{19}H_9N_3S_2$: C, 66.47; H, 2.64; N, 12.25. Found: C, 66.62; H, 2.58; N, 12.13.

2-{4-[6-(Imidazolin-2-yl)benzothiazol-2-yl]phenyl}-5-(imidazolin-2-yl)furan (3a). A suspension of 1.20 g (3.6 mmol) of 2-[4-(6-cyanobenzothiazol-2-yl)phenyl]-5-furancarbonitrile (**2a**) in 120 mL of dry 2-methoxyethanol was cooled to 5 °C and saturated with HCl. The flask was then stoppered, and the content stirred at rt for 5 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was poured in 400 mL of dry ether and the obtained crystals of imidoyl ether dihydrochloride were filtered off, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 1.83 g (92.0 %). To the suspension of crude imidoyl ether dihydrochloride (1.83 g, 34 mmol) in 50 mL of dry ethanol 5.0 mL (7.5 mmol) of freshly distilled ethylenediamine in 10 mL of dry ethanol was added. The reaction mixture was refluxed for 20 h. After cooling the obtained crystals were filtered and washed with dry ether. After drying the product was suspended in 100 mL of water, made alkaline with 15 mL of 2M NaOH, heated to boil and cooled to rt. The crystalline product was filtered off, washed with dry ethanol and dry ether and crystallized from the solvent mixture 2-methoxyethanol/water. Yield was 0.750 g (50.4 %) of yellow crystals, mp 279-282 °C. IR (KBr, cm^{-1}): 3250, 3127 (NH), 2927, 2861 (CH_2), 1632 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.55 (s, 1H, H-arom.), 8.04 (d, 1H, *J*=8.3 Hz, H-arom.), 7.98 (d, 1H, *J*=8.6 Hz, H-arom.), 7.93 (d, 2H, *J*=8.9 Hz, H-arom.), 7.90 (d, 2H, *J*=8.6 Hz, H-arom.), 7.54 (d, 1H, *J*=3.7 Hz, H-fur.), 7.38 (d, 1H, *J*=3.7 Hz, H-fur.), 7.02 (br s, 2H, H-NH, disappeared on addition of D_2O), 3.62 (s, 4H, H-CH_2), 3.60 (s, 4H, H-CH_2). Anal. Calcd for $C_{23}H_{19}N_5OS$: C, 66.81; H, 4.63; N, 16.94. Found: C, 66.53; H, 4.72; N, 16.63.

2-{4-[6-(Imidazolin-2-yl)benzothiazol-2-yl]phenyl}-5-(imidazolin-2-yl)thiophene (3b). A suspension of 0.600 g (1.74 mmol) of 2-[4(-6-cyanobenzothiazol-2-yl)phenyl]-5-thiophenecarbonitrile (**2b**) in 110 mL of 2-(2-ethoxyethoxy)ethanol was heated to boil. After cooling to 150 °C the solution was saturated with HCl and cooled to 5 °C. The flask was stoppered, and the content was stirred at rt for five days (until

IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was then poured into 500 mL of dry ether and the obtained crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 0.970 g (82.0 %). To the suspension of 0.970 g (1.4 mmol) of dry imidoyl ether dihydrochloride in 20 mL of dry ethanol 2.0 mL (30 mmol) of freshly distilled ethylenediamine in 5 mL of dry ethanol was added. The reaction mixture was refluxed for 24 h. After cooling the obtained crystals were filtered off and washed with dry ether. The product was suspended in 150 mL of water, made alkaline with 10 mL of 2M NaOH, heated to boil and cooled to rt. The crystalline product was filtered, washed with ethanol and crystallized from 2-methoxyethanol/ether. Yield was 0.23 g (37.9 %) of yellow crystals, mp>300 °C. IR (KBr, cm^{-1}): 3413, 3175 (NH), 2926, 2853 (CH_2), 1634 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.56 (s, 1H, H-arom.), 8.29-8.26 (m, 3H, H-arom.), 8.10 (d, 1H, *J*=8.7 Hz, H-arom.), 7.89 (d, 2H, *J*=8.6 Hz, H-arom.), 7.68 (d, 1H, *J*=3.9 Hz, H-thioph.), 7.51 (d, 1H, *J*=4.0 Hz, H-thioph.), 7.18 (br s, 2H, H-NH, disappeared on addition of D_2O), 3.65 (s, 4H, H-CH_2), 3.59 (s, 4H, H-CH_2). Anal. Calcd for $C_{23}H_{19}N_5S_2$: C, 64.31; H, 4.46; N, 16.30. Found: C, 64.02; H, 4.53; N, 16.42.

2-{4-[6-(Imidazolin-2-yl)benzothiazol-2-yl]phenyl}-5-(imidazolin-2-yl)furan dihydrochloride dihydrate (4a). Free base (**3a**) (0.615g, 1.5 mmol) was dissolved in 50 mL of hot 2-methoxyethanol and the solution was saturated with HCl. The flask was then stoppered, and the content was stirred at 5 °C for 12 h. The excess of HCl was removed by a stream of nitrogen. The crystals obtained after filtration were washed with dry ether, and dried in vacuum at 85 °C for 4 h. Yield was 0.650 g (89.9 %) of yellow crystals, mp>300 °C. IR (KBr, cm^{-1}): 3411, 3105 (NH), 1638 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.83 (s, 4H, H-NH_2^+, disappeared on addition of D_2O), 8.88 (s, 1H, H-arom.), 8.33-8.28 (m, 3H, H-arom.), 8.19 (d, 2H, *J*=8.3 Hz, H-arom.), 8.11 (d, 1H, *J*=8.6 Hz, H-arom.), 7.87 (d, 1H, *J*=3.7 Hz, H-fur.), 7.54 (d, 1H, *J*=3.7 Hz, H-fur.), 4.03 (s, 4H, H-CH_2), 3.99 (s, 4H, H-CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.8 (s), 164.0 (s), 157.2 (s), 156.2 (s), 154.0 (s), 136.6 (s), 134.8 (s), 131.6 (s), 130.3 (s), 127.8 (d), 125.8 (d), 125.2 (d), 123.2 (d), 122.9 (d), 122.0 (d), 117.7 (s), 110.2 (d), 44.4 (t). Anal. Calcd for $C_{23}H_{21}N_5OCl_2S\times2H_2O$: C, 52.87; H, 4.82; N, 13.41; Cl, 13.57. Found: C, 52.94; H, 4.73; N, 13.57; Cl, 13.56.

2-{4-[6-(Imidazolin-2-yl)benzothiazol-2-yl]phenyl}-5-(imidazolin-2-yl)thiophene dihydrochloride dihydrate (4b). Free base (**3b**) (0.090g, 0.21 mmol) was dissolved in 90 mL of hot 2-methoxyethanol and to the hot solution 0.5 mL concd hydrochloric acid was added by stirring. The stirring was continued for 12 h at room temperature. The obtained solid was collected by filtration, washed with dry ether, and dried in vacuum at 80 °C for 4 h. Yield was 0.085 g (75.2 %) of pure yellow crystals wich were not further recrystallised, mp>300 °C. IR (KBr, cm^{-1}): 3418, 3077 (NH), 2964 (CH_2), 1639 (C=N). ^{1}H NMR (300

MHz, DMSO-d_6) δ: 10.77 (br s, 4H, H-NH_2^+, disappeared on addition of D_2O), 8.89 (s, 1H, H-arom.), 8.35 (d, 1H, *J*=8.7 Hz, H-arom.), 8.31 (d, 2H, *J*=8.6 Hz, H-arom.), 8.24 (d, 1H, *J*=4.1 Hz, H-thioph.), 8.13 (d, 1H, *J*=8.6 Hz, H-arom.), 8.02 (d, 2H, *J*=8.4 Hz, H-arom.), 7.99 (d, 1H, *J*=4.0 Hz, H-thioph.), 4.07 (s, 4H, H-CH_2), 4.01 (s, 4H, H-CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 172.1 (s), 165.3 (s), 159.4 (s), 157.5 (s), 151.5 (s), 136.9 (d), 135.8 (s), 135.5 (s), 133.2 (s), 129.0 (d), 127.4 (d), 126.9 (d), 126.8 (d), 124.1 (d), 123.9 (d), 123.0 (s), 119.3 (s), 45.1 (t). Anal. Calcd for $C_{23}H_{21}N_5Cl_2S_2\times2H_2O$: C, 51.30; H, 4.68; N, 13.01; Cl, 13.17. Found: C, 51.52; H, 4.60; N, 12.98; Cl, 13.08.

2-{4-[6-(*N*-Isopropylamidino)benzothiazol-2-yl]phenyl}-5-(*N*-isopropylamidino)furan (5a). A suspension of 1.2 g (3.6 mmol) of 2-[4-(-6-cyanobenzothiazol-2-yl)phenyl]-5-furancarbonitrile (**2a**) in 120 mL of dry 2-methoxyethanol was cooled to 5 °C and saturated with HCl. The flask was then stoppered, and the content was stirred at rt for 5 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was poured in 400 mL of dry ether and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 1.86 g (93.5%). To the suspension of crude imidoyl ether dihydrochloride (1.80 g, 3.26 mmol) in 60 mL of dry ethanol 3.5 mL (41 mmol) of freshly distilled isopropylamine in 20 mL dry ethanol was added. The reaction mixture was refluxed for 50 h. The solvent was evaporated and the crystals were dissolved in 150 mL of hot water. After cooling the solution was made alkaline with 2M NaOH and the crystals were filtered and washed with water. After crystallization from 2-methoxyethanol the yield of pale yellow crystals was 0.82 g (51.2 %), mp 235-242 °C. IR (KBr, cm^{-1}): 3444, 3235, 3054 (NH), 2971, 2930 (CH, CH_3), 1608 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.42 (s, 1H, H-arom.), 8.14 (d, 2H, *J*=8.3 Hz, H-arom.), 8.03-8.00 (m, 3H, H-arom.), 7.87 (d, 1H, *J*=7.6 Hz, H-arom.), 7.19 (d, 1H, *J*=3.8 Hz, H-fur.), 7.06 (d, 1H, *J*=3.8 Hz, H-fur.), 6.48 (br s, 4H, H-NH, disappeared on addition of D_2O), 3.79 (m, 2H, H-CH), 1.12 (d, 12H, *J*=6.0 Hz, H-CH_3). Anal. Calcd for $C_{25}H_{27}N_5OS$: C, 67.34; H, 6.10; N, 15.78. Found: C, 67.57; H, 6.10; N, 15.61.

2-{4-[6-(*N*-Isopropylamidino)benzothiazol-2-yl]phenyl}-5-(*N*-isopropylamidino)thiophene (5b). A suspension of 0.300 g (0.87 mmol) of 2-[4(-6-cyanobenzothiazol-2-yl)phenyl]-5-thiophenecarbonitrile (**2b**) in 50 mL of 2-(2-ethoxyethoxy)ethanol was heated to boil. After cooling to 150 °C the solution was saturated with HCl and cooled to 5 °C. The flask was then stoppered, and the content was stirred at rt for 5 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was poured in 300 mL of dry ether and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 0.485 g (83.9 %). To the suspension of 0.485 g (0.7 mmol) of dry imidoyl ether dihydrochloride in 15 mL of dry ethanol 1.2 mL (14 mmol) of freshly

distilled isopropylamine in 5 mL of dry ethanol was added. The reaction mixture was refluxed for 24 h. The solvent was evaporated and the crystals were dissolved in 100 mL of hot water. After cooling the solution was made alkaline with 2M NaOH and the crystals were filtered and washed with water. After crystallization from 2-methoxyethanol/ether the yield of yellow crystals was 0.11 g (34 %), mp 233-238 °C. IR (KBr, cm^{-1}): 3463, 3218, 3062 (NH), 2968, 2924 (CH, CH_3), 1615 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.45 (s, 1H, H-arom.), 8.14 (d, 2H, *J*=8.6 Hz, H-arom.), 8.04 (d, 1H, *J*=8.4 Hz, H-arom.), 7.89 (m, 3H, H-arom.), 7.60 (d, 1H, *J*=3.6 Hz, H-thioph.), 7.56 (d, 1H, *J*=3.6 Hz, H-thioph.), 6.38 (br s, 4H, H-NH, disappeared on addition of D_2O), 3.81 (m, 1H, H-CH), 3.63 (m, 1H, H-CH), 1.15 (d, 6H, *J*=6.3 Hz, H-CH_3), 1.08 (d, 6H, *J*=6.2 Hz, H-CH_3). Anal. Calcd for $C_{25}H_{27}N_5S_2$: C, 65.04; H, 5.90; N, 15.17. Found: C, 64.91; H, 5.98; N, 15.25.

2-{4-[6-(*N*-Isopropylamidino)benzothiazol-2-yl]phenyl}-5-(*N*-isopropylamidino)furan dihydrochloride dihydrate (6a). Free base (**5a**) (0.400g, 0.89 mmol) was dissolved in 25 mL of hot 2-methoxyethanol and the solution was saturated with HCl. The flask was then stoppered, and the content was stirred at rt overnight. The excess of HCl was removed by a stream of nitrogen. The crystals after filtration were washed with dry ether, and dried in vacuum at 90 °C for 4 h. Yield was 0.390 g (74.2 %) of pure yellow crystals wich were not further recrystallised, mp>300 °C. IR (KBr, cm^{-1}): 3390, 3063 (NH), 2977, 2928 (CH, CH_3), 1667 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.80-9.70 (m, 4H, H-NH_2^+, disappeared on addition of D_2O), 9.27 (s, 2H, H-NH_2^+, disappeared on addition of D_2O), 8.65 (s, 1H, H-arom.), 8.29-8.27 (m, 5H, H-arom.), 8.03 (d, 1H, *J*=3.8 Hz, H-fur.), 7.88 (d, 1H, *J*=8.6 Hz, H-arom.), 7.52 (d, 1H, *J*=3.8 Hz, H-fur.), 4.16 (m, 2H, H-CH), 1.34 (d, 6H, *J*=6.1 Hz, H-CH_3), 1.31 (d, 6H, *J*=6.0 Hz, H-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.2 (s), 161.3 (s), 156.2 (s), 156.1 (s), 149.8 (s), 141.2 (s), 134.5 (s), 132.6 (s), 131.4 (s), 127.9 (d), 126.8 (d), 126.1 (s), 125.9 (d), 123.5 (d), 122.7 (d), 120.4 (d), 110.2 (d), 45.3 (d), 44.9 (d), 21.4 (q), 21.3 (q). Anal. Calcd for $C_{25}H_{29}N_5OCl_2S\times2H_2O$: C, 54.15; H, 6.00; N, 12.63; Cl, 12.79. Found: C, 53.99; H, 6.04; N, 12.80; Cl, 12.92.

2-{4-[6-(*N*-Isopropylamidino)benzothiazol-2-yl]phenyl}-5-(*N*-isopropylamidino)thiophene dihydrochloride dihydrate (6b). Free base (**5b**) (0.080g, 0.17 mmol) was dissolved in 20 mL of 2-methoxyethanol and the solution was saturated with HCl. The flask was then stoppered, and the content was stirred at rt overnight. The excess of HCl was removed by a stream of nitrogen. The reaction mixture was poured into 100 mL of dry ether and the crystals were filtered, washed with dry ether, and dried in vacuum at 80 °C for 4 h. Yield was 0.082 g (84.5 %) of pure yellow crystals wich were not further recrystallised, mp>300 °C. IR (KBr, cm^{-1}): 3417, 3215, 3053 (NH), 2969 (CH, CH_3), 1667 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.81-9.74 (m, 2H, H-NH_2^+, disappeared on addition of D_2O), 9.64 (br s, 2H, H-NH_2^+, disappeared on addition of D_2O), 9.27 (br s, 2H, H-NH_2^+, disappeared on addition of D_2O), 8.66 (s, 1H, H-arom.), 8.30-8.21 (m, 3H, H-arom.), 8.07 (d, 1H, *J*=3.7 Hz, H-thioph.), 8.02 (d, 2H, *J*=8.0

Hz, H-arom.), 7.93 (d, 1H, *J*=3.7 Hz, H-thioph.), 7.89 (d, 1H, *J*=8.6 Hz, H-arom.), 4.13 (m, 2H, H-CH), 1.33 (d, 6H, *J*=6.0 Hz, H-CH_3), 1.30 (d, 6H, *J*=5.9 Hz, H-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 170.1 (s), 161.4 (s), 156.1 (s), 154.7 (s), 148.0 (s), 135.2 (s), 134.7 (d), 134.5 (s), 132.6 (s), 129.1 (s), 128.5 (d), 128.3 (d), 126.7 (d), 126.2 (s), 125.9 (d), 123.5 (d), 122.8 (d), 45.3 (d), 45.2 (d), 21.2 (q), 21.1 (q). Anal. Calcd for $C_{25}H_{29}N_5Cl_2S_2\times2H_2O$: C, 52.62; H, 5.83; N, 12.27; Cl, 12.43. Found: C, 52.50; H, 5.98; N, 12.45; Cl, 12.61.

2-[4-(Imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]furan (7a).

Method a) A suspension of 1.50 g (4.6 mmol) of 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)furan in 150 mL of dry 2-methoxyethanol was heated to boil and saturated with HCl by cooling to 5 °C. The flask was stoppered, and the content was stirred at rt for 15 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 2.25 g (88.6 %). To the suspension of crude imidoyl ether dihydrochloride (2.25 g, 4.1 mmol) in 100 mL of dry ethanol 6.4 g (95 mmol) of freshly distilled ethylenediamine in 20 mL of dry ethanol was added under nitrogen. The reaction mixture was refluxed for 70 h. After cooling the crystals were collected by filtration washed with ethanol and dry ether. The dried product was suspended in 100 mL of water, made alkaline with 15 mL of 2M NaOH and heated to boil. After cooling the separated crystals were washed with cold water, dry ethanol and finally with dry ether and dried at 80 °C under reduced pressure. Recrystallization from *N*,*N*'-dimethylacetamide yielded 1.15g (60.5 %) of yellow crystals, mp>300 °C.

Method b) A mixture of 1.24 g (3.8 mmol) of 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)furan and 9.8 g (75 mmol) of ethylenediamine dihydrochloride was pulverised in an agate mortar, 5 mL (75 mmol) of ethylenediamine was added and the reaction was effected in a sand bath at 300-320 °C for 40 min. The crude product was dissolved in 200 mL of boiling water, the solution was filtered through celite 545 and made alkaline with 2M NaOH. The crystals of the crude base were collected by filtration, washed with water and recrystallized firstly from ethanol and then from *N*,*N*'-dimethylacetamide, yield 0.11g (7.0 %) of yellow crystals, mp>300 °C. IR (KBr, cm^{-1}): 3439, 3201 (NH), 2936, 2861 (CH_2), 1610 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.58 (s, 1H, H-arom.), 8.07 (d, 1H, *J*=8.8 Hz, H-arom.), 8.01 (d, 1H, *J*=8.8 Hz, H-arom.), 7.96 (d, 2H, *J*=8.3 Hz, H-arom.), 7.93 (d, 2H, *J*=8.5 Hz, H-arom.), 7.56 (d, 1H, *J*=3.6 Hz, H-fur.), 7.40 (d, 1H, *J*=3.6 Hz, H-fur.), 7.04 (br s, 2H, H-NH, disappeared on addition of D_2O), 3.82 (s, 4H, H-CH_2), 3.65 (s, 4H, H-CH_2). Anal. Calcd for $C_{23}H_{19}N_5OS$: C, 66.81; H, 4.63; N, 16.94. Found: C, 67.07; H, 4.70; N, 16.75.

2-[4-(Imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]thiophene (7b). A suspension of 1.00 g (2.9 mmol) of 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene in 150 mL of 2-(2-

ethoxyethoxy)ethanol was heated to boil. After cooling to 150 °C the solution was saturated with HCl and cooled. The reaction mixture was saturated with HCl at 5 °C, the flask stoppered, and the contents stirred at rt for 4 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was then poured into 400 mL of dry ether and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 1.72 g (84.7 %). To the suspension of 1.7 g (2.43 mmol) of dry imidoyl ether dihydrochloride in 100 mL of dry ethanol 4.0 g (60 mmol) of freshly distilled ethylenediamine in 20 mL of dry ethanol was added under nitrogen. The reaction mixture was refluxed for 20 h. After cooling the crystals were collected by filtration and washed with ethanol and dry ether. The dried product was suspended in 150 mL of water, made alkaline with 15 mL of 2M NaOH and heated to boiling point. After cooling the separated crystals were washed with cold water, dry ethanol and finally with dry ether. Yield was 0.960 g (77.6 %) of pure yellow crystals wich were not further recrystallised, mp>300 °C. IR (KBr, cm^{-1}): 3409, 3238 (NH), 2925, 2857 (CH_2), 1611 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.54 (s, 1H, H-arom.), 8.03 (d, 1H, *J*=8.6 Hz, H-arom.), 7.99 (d, 1H, *J*=8.7 Hz, H-arom.), 7.95 (d, 1H, *J*=3.7 Hz, H-thioph.), 7.91 (d, 2H, *J*=8.0 Hz, H-arom.), 7.87 (d, 2H, *J*=8.1 Hz, H-arom.), 7.78 (d, 1H, *J*=3.7 Hz, H-thioph.), 7.25 (br s, 2H, H-NH, disappeared on addition of D_2O), 3.66 (s, 8H, H-CH_2). Anal. Calcd for $C_{23}H_{19}N_5S_2$: C, 64.31; H, 4.46; N, 16.30. Found: C, 64.48; H, 4.52; N, 16.18.

2-[4-(Imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]furan dihydrochloride dihydrate (8a). Free base (**7a**) (0.780 g, 1.9 mmol) was dissolved in 100 mL of hot 2-methoxyethanol and saturated with HCl at 50 °C. The flask was stoppered, and the content was stirred for 12 h at rt. The excess of HCl was removed from the suspension by a stream of nitrogen. The solid was collected by filtration, washed with dry ether, and dried in high vacuum at 80 °C for 2 h. Yield was 0.926 g (93.5 %) of pure yellow crystals wich were not further recrystallised, mp>300°C. IR (KBr, cm^{-1}): 3416, 3111 (NH), 2967 (CH_2), 1611 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.87 (s, 2H, H-NH_2^+, disappeared on addition of D_2O), 10.83 (s, 2H, H-NH_2^+, disappeared on addition of D_2O), 8.92 (s, 1H, H-arom.), 8.30 (d, 1H, *J*=8.8 Hz, H-arom.), 8.20 (m, 4H, H-arom.), 8.16 (d, 1H, *J*=8.8 Hz, H-arom.), 7.76 (d, 1H, *J*=3.8 Hz, H-fur.), 7.67 (d, 1H, *J*=3.8 Hz, H-fur.), 4.08 (s, 4H, H-CH_2), 4.05 (s, 4H, H-CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.3 (s), 163.9 (s), 160.3 (s), 156.8 (s), 154.6 (s), 148.1 (s), 134.3 (s), 133.7 (s), 129.7 (d), 127.0(d), 124.6 (d), 124.0 (d), 123.1 (d), 121.7 (s), 118.9 (s), 116.5 (d), 112.7 (d), 44.5 (t). Anal. Calcd for $C_{23}H_{21}N_5OCl_2S\times2H_2O$: C, 52.87; H, 4.82; N, 13.41; Cl, 13.57. Found: C, 52.92; H, 4.96; N, 13.29; Cl, 13.60.

2-[4-(Imidazolin-2-yl)phenyl]-5-[6-(imidazolin-2-yl)benzothiazol-2-yl]thiophene dihydrochloride dihydrate (8b). Free base (**7b**) (0.100 g, 0.233 mmol) was dissolved in 40 mL of 2-methoxyethanol and to

the hot solution 0.90 mL of concd HCl was added by stirring. The stirring was continued for 20 h at rt. The solid was collected by filtration, washed with dry ethanol and dry ether, and dried in vacuum at 90 °C for 2 h. Yield was 0.087 g (69.6 %) of pure yellow for crystals wich were not further recrystallised, mp>300 °C. IR (KBr, cm^{-1}): 3417, 3113 (NH), 2966, 2933 (CH_2), 1610(C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.69 (br s, 4H, H-NH_2^+, disappeared on addition of D_2O), 8.79 (s, 1H, H-arom.), 8.27 (d, 1H, *J*=8.9 Hz, H-arom.), 8.16-8.06 (m, 6H, 5H-arom.+1H-thioph.), 7.99 (d, 1H, *J*=4.0 Hz, H-thioph.), 4.06 (s, 4H, H-CH_2), 4.04 (s, 4H, H-CH_2). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 166.1 (s), 165.2 (s), 165.1 (s), 157.2 (s), 147.1 (s), 138.7 (s), 136.9 (s), 135.9 (s), 133.5 (d), 130.1 (d), 128.5 (d), 127.4 (d), 126.9 (d), 123.9 (d), 123.8 (d), 122.0 (s), 119.1 (s), 45.4 (t). Anal. Calcd for $C_{23}H_{21}N_5Cl_2S_2\times2H_2O$: C, 51.30; H, 4.68; N, 13.01; Cl, 13.17. Found: C, 51.50; H, 4.76; N, 13.09; Cl, 13.21.

2-[4-(*N*-Isopropylamidino)phenyl]-5-[6-(*N*-isopropylamidino)benzothiazol-2-yl]furan dihydrochloride dihydrate (9a). A suspension of 1.50 g (4.6 mmol) of 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)furan (**8a**) in 150 mL of dry 2-methoxyethanol was heated to boil and saturated with HCl by cooling to 5 °C. The flask was stoppered, and the content was stirred at rt for 15 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 2.06 g (81.1 %). To the suspension of crude imidoyl ether dihydrochloride (2.00 g, 3.62 mmol) in 80 mL of dry ethanol 3.90 g (46 mmol) of freshly distilled isopropylamin in 20 mL of dry ethanol was added under nitrogen. The reaction mixture was refluxed for 70 h, the solvent was evaporated and the obtained crude oily product was washed twice with 50 mL of dry ether. The crystals obtained after evaporation of ether were dried and purified by crystallization from water. After drying at 80 °C under reduced pressure the yield of yellow crystals was 1.05 g (41.2 %), mp>300 °C. IR (KBr, cm^{-1}): 3390, 3201, 3052 (NH), 2977, 2930 (CH, CH_3), 1672 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.75 (br s, 2H, H-NH_2^+, disappeared on addition of D_2O), 9.55 (br s, 2H, H-NH_2^+, disappeared on addition of D_2O), 9.20 (s, 2H, H-NH_2^+, disappeared on addition of D_2O), 8.62 (s, 1H, H-arom.), 8.23 (d, 1H, *J*=8.6 Hz, H-arom.), 8.08 (d, 2H, *J*=8.5 Hz, H-arom.), 7.89-7.84 (m, 3H, H-arom.), 7.69 (d, 1H, *J*=3.8 Hz, H-fur.), 7.59 (d, 1H, *J*=3.7 Hz, H-fur.), 4.08 (m, 2H, H-CH), 1.29 (d, 12H, *J*=6.0 Hz, H-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 161.3 (s), 161.0 (s), 159.2 (s), 156.2 (s), 154.7 (s), 148.0 (s), 133.9 (s), 132.9 (s), 129.6 (d), 128.8 (s), 127.2 (d), 126.0 (s), 124.2 (d), 123.8 (d), 122.6 (d), 116.2 (d), 112.0 (d), 45.5 (d), 45.4 (d), 21.5 (q). Anal. Calcd for $C_{25}H_{29}N_5OCl_2S\times2H_2O$: C, 54.15; H, 6.00; N, 12.63; Cl, 12.79. Found: C, 54.07; H, 5.73; N, 12.62; Cl, 12.62.

2-[4-(*N*-Isopropylamidino)phenyl]-5-[6-(*N*-isopropylamidino)benzothiazol-2-yl]thiophene dihydrochloride dihydrate (9b). A suspension of 1.00 g (2.9 mmol) of 2-(4-cyanophenyl)-5-(6-cyanobenzothiazol-2-yl)thiophene (**8b**) in 100 mL of dry 2-(2-ethoxyethoxy)ethanol was heated to boil,

the obtained solution was cooled to 150 °C and saturated with HCl. After cooling to 5 °C the flask was stoppered, and the content was stirred at rt for 5 days (until IR spectra indicated the disappearance of the cyano peak). The excess of HCl was removed from the suspension by a stream of nitrogen. The reaction mixture was poured into 400 mL of dry ether and the crystals of imidoyl ether dihydrochloride were filtered, washed with dry ether, and dried under reduced pressure over KOH. Yield of crude product was 1.56 g (76.8 %). To the suspension of crude imidoyl ether dihydrochloride (1.56 g, 2.2 mmol) in 80 mL of dry ethanol 2.55 mL (30 mmol) of freshly distiled isopropylamine in 20 mL of dry ethanol was added under nitrogen. The reaction mixture was refluxed for 42 h. After cooling the solvent was evaporated and the obtained crude crystals were dissolved in water and precipitated with acetone. Pure crystals were obtained by dissolving the product in ethanol and precipitating with ether. After drying at 85 °C under reduced pressure the yield of yellow crystals was 0.73 g (44.12 %), mp>300 °C. IR (KBr, cm^{-1}): 3399, 3213, 3052 (NH), 2927 (CH, CH_3), 1671 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.56 (br s, 6H, H-NH_2^+, disappeared on addition of D_2O), 8.61 (s, 1H, H-arom.), 8.19 (d, 1H, *J*=8.5 Hz, H-arom.), 8.10 (d, 1H, *J*=3.9 Hz, H-thioph.), 8.05 (d, 2H, *J*=8.3 Hz, H-arom.), 7.93 (d, 1H, *J*=3.9 Hz, H-thioph.), 7.87-7.84 (m, 3H, H-arom.), 4.11 (m, 2H, H-CH), 1.30 (d, 12H, *J*=6.0 Hz, H-CH_3). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.2 (s), 161.6 (s), 161.2 (s), 155.8 (s), 146.5 (s), 136.9 (s), 136.2 (s), 134.6 (s), 132.5 (d), 129.6 (d), 129.1 (s), 127.5 (d), 127.1 (d), 126.3 (s), 125.9 (d), 123.6 (d), 122.5 (d), 45.3 (d), 45.2 (d), 21.7 (q). Anal. Calcd for $C_{25}H_{29}N_5Cl_2S_2\times2H_2O$: C, 52.62; H, 5.83; N, 12.27; Cl, 12.43. Found: C, 52.72; H, 5.82; N, 12.43; Cl, 12.28.

ACKNOWLEDGMENT

This study was financially supported by the Ministry of Science of the Republic of Croatia within project No. 107039, and US-Croatian Scientific and Technogical Cooperation Award No. JF 146.

REFERENCES

1. R. R. Tidwell, S. K. Jones, J. D. Geratz, K. A. Ohemeng, M. Cory, and J. E. Hall, *J. Med. Chem.*,1990, **33**, 1252.
2. M. Cory, R. R. Tidwell, and T. A. Fairley, *J. Med. Chem.*, 1992, **35**, 431.
3. A. Kumar, D. W. Boykin, W. D. Wilson, S. K. Jones, B. K. Bender,C. C. Dykstra, J. E. Hall, and R. R. Tidwell, *Eur. J. Med. Chem.*, 1996, **31**, 767.
4. S. Neidle, L. R. Kelland, J. O. Trent, I. J. Simpson, D. W. Boykin, A. Kumar, and W. D. Wilson, *Bioorg. Med. Chem. Lett.*,1997, **7**, 1403.

5. I. Francesconi, W. D. Wilson, F. A. Tanious, J. E. Hall, B. C. Bender, R. R. Tidwell, D. McCurdy, and D. W. Boykin, *J. Med. Chem.*, 1999, **42**, 2260.
6. R. L. Lombardy, F. A. Tanious, K. Ramachandran, R. R. Tidwell, and W. D. Wilson, *J. Med. Chem.*, 1996, **39**, 1452.
7. D. W. Boykin, A. Kumar, G. Xiao, W. D. Wilson, B. C. Bender, D. R. McCurdy, J. E. Hall, and R. R. Tidwell, *J. Med. Chem.*, 1998, **41**, 124.
8. A. Czarny, D. W. Boykin, A. A. Wood, C. M. Nunn, S. Neidle, M. Zhao, and W. D.Wilson, *J. Am. Chem. Soc.*, 1995, **117**, 4716.
9. D. Pavličić, and G. Karminski-Zamola, *Syn. Commun.*, 2001, **31**, 111.
10. L. Racanè, V. Tralić-Kulenović, G. Karminski-Zamola, and L. Fišer-Jakić, *Monatsh. Chem.*, 1995, **126,** 1375.
11. V. Tralić-Kulenović, G. Karminski-Zamola, L. Racanè, and L. Fišer-Jakić, *Heterocyclic Comm.*, 1998, **4**, 423.
12. G. V. Boyd, "*Recent Advances in the Synthesis of Amidines*" in *"The Chemistry of Amidines and Imidates"*, Vol. **2**, ed. by S. Patai, John Wiley & Sons, New York, 1991, pp. 339-366.
13. O. Dann, E. Heike, H. Hahn, H. H. Miserre, G. Lürding, and R. Rösler, *Liebigs Ann. Chem.,*1970, **734**, 23.
14. D. A. Patrick, D. W. Boykin, W. D. Wilson, F. A. Tanious, J. Spychala, B. C. Bender, J. E. Hall, C. C. Dykstra, K. A. Ohemeng, and R. R. Tidwell, *Eur. J. Med. Chem.*, 1997, **32**, 781.