Tetrahedron 64 (2008) 11594–11602

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new amidino-substituted 2-aminothiophenoles: mild basic ring opening of benzothiazole

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ARTICLE INFO

Article history:
Received 28 August 2008
Received in revised form
23 September 2008
Accepted 9 October 2008
Available online 15 October 2008

Keywords:
Benzothiazole
Amidine
Pinner reaction
Disulfide
Thiolate

ABSTRACT

The efficient synthesis of new amidino, *N*-isopropylamidino, 2-imidazolinyl substituted benzothiazoles and 2-aminothiophenoles by the Pinner reaction is described. The novel ring opening of benzothiazole with ammonia and ethylenediamine was found, and a plausible reaction mechanism proposed. The ring opening with ethylenediamine is selective and applicable to compounds bearing hydrolytically and amonolytically unstable substituents. Different amidino-substituted 2-aminothiophenoles were isolated in zwitterionic and disulfide form and their structures were determined by X-ray crystal structure analysis.

1. Introduction

Benzothiazole derivatives are of considerable interest due to their important biological and biophysical properties. Recently, 2-aryl or 2-heteroaryl substituted benzothiazoles have been associated with antitumour,[1] antimicrobial[2] and antifungal[3] activities, as well as used as β-amyloid imaging agents.[4] Also, the amidinic group is often a part of important medical and biochemical agents such as pentamidine and berenil, which have been commercialized as antimicrobial agents (Fig. 1) for treatment of human and animal infections caused by various species of trypanosome.[5,6]

Pentamidine is also a secondary drug for AIDS-related *Pneumocystis jirovecii* pneumonia. Therefore, related aromatic dicationic molecules have been extensively studied and a broad spectrum of antimicrobial activity reported. Binding in the minor groove of DNA at AT-rich sites is thought to be a key step in the mode of action of these types of aromatic diamidines and possibly leads to inhibition of DNA-dependent enzymes or transcription.[6] A new direction in the development of DNA sequence specific agents is modification of the structure of the diamidine by including a variety of nitrogen heterocycles into molecules of different shape.[7]

Consequently, a number of synthetic methods have been developed for the preparation of substituted benzothiazoles[8] and amidines.[9] Most of the methods for benzothiazole preparation involve the condensation of 2-aminobenzenethiol with the corresponding nitrile, aldehyde, acid, acid chloride or ester and by use of Jacobson's cyclization of thiobenzanilide.[8] The method mostly used for the preparation of amidines is nucleophilic addition of amines or ammonia to suitably activated carboxylate equivalents, such as imidates, thioimidates and imidoyl chlorides. Imidates can be prepared generally by either base-catalyzed or acid-catalyzed (Pinner synthesis) addition of an alcohol to a nitrile. The addition of dry hydrochloric acid to a mixture of a nitrile and an alcohol in the absence of water leads to the formation of the hydrochloride salt of an imino ester. This salt can further react with an excess of alcohol to form the *ortho*-ester, with ammonia or an amine to form an amidine or with water to form an ester.[9a] In the base-catalyzed addition of alcohol to nitrile, the formed imino ester requires an amine salt in the second reaction step for the formation of amidine.[10]

Recently, our investigation has been directed towards the synthesis of heterocyclic molecules substituted with different amidines, as well as towards studying their biological, especially

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doi:10.1016/j.tet.2008.10.026

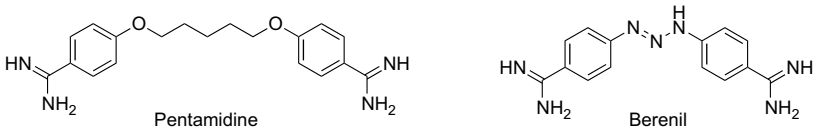
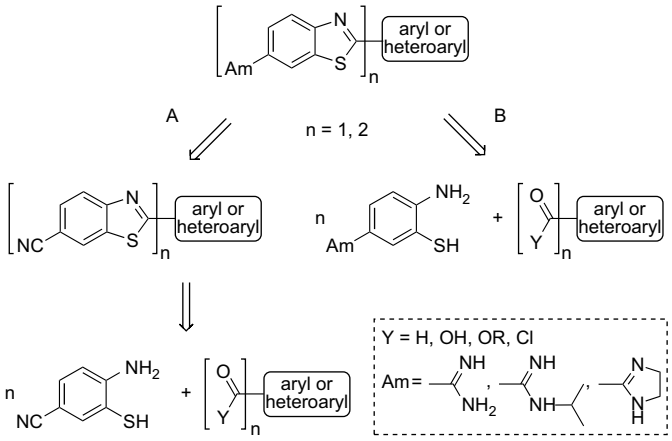


Figure 1. Antimicrobial agents.

antitumour, activity.[11] Our research shows that the antitumour activity strongly depends on the type and position of an amidino substituent on the 2-phenylbenzothiazole skeleton.[11c] Therefore, it was of importance to develop a synthetic method for the preparation of different amidino-substituted 2-aryl or 2-heteroarylbenzothiazoles. The synthetic strategy for the synthesis of unsubstituted, *N*-isopropyl substituted amidine, as well as 2-imidazolinyl derivatives of 2-phenyl or 2-heteroarylbenzothiazolyl molecules (Scheme 1) can be divided in two approaches.



Scheme 1.

Synthetic approach A involves two reaction steps: the condensation of 4-amino-3-mercaptobenzonitrile[12] with an aldehyde or acid chloride and the conversion of a nitrile into different amidines by the Pinner reaction.[11c] This approach has shown certain limitations and failed when 6-cyano-2-benzothiazolyl compounds of low solubility were employed in Pinner reaction, even by using solvents such as 2-methoxyethanol and 2-(2-ethoxyethoxy)ethanol.[11e]

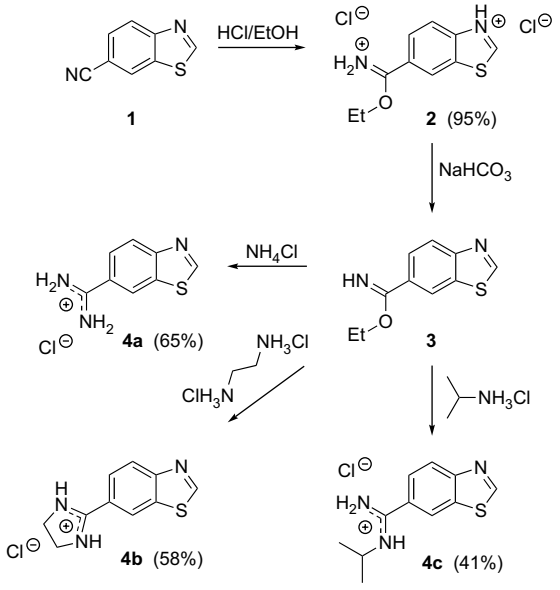
On the other hand, synthetic approach B includes the condensation of amidino-substituted 2-aminothiophenoles with aldehyde, acid, acid chlorides, or esters. In this report, we are following route B and present the preparation of different amidino-substituted 2-aminothiophenoles.

2. Results and discussion

2.1. Synthesis and X-ray crystal structure analysis

Hydrolysis of 6-cyanobenzothiazole to 4-amino-3-mercaptobenzonitrile[12] was easily accomplished by Claisen's alkali and using this methodology we tried to prepare different amidino-substituted 2-aminothiophenoles from amidino-substituted benzothiazoles (Scheme 2). The first step consists of acid-catalyzed addition of ethanol to 6-cyanobenzothiazole **1** and afforded ethyl-6-benzothiazole carboximidate dihydrochloride **2** in excellent yield of 95%. Due to its reactivity it was used without purification in second reaction step.

The imidate hydrochloride **2** was then converted into ethyl-6-benzothiazole carboximidate **3** with $NaHCO_3$ solution and extracted with chloroform. Evaporation of chloroform and subsequent



Scheme 2.

reaction of free base **3** with ammonium chloride, ethylenediamine dihydrochloride and isopropylamine hydrochloride, respectively, gave the corresponding amidines **4a–c** in moderate yields. We have previously reported[13] the synthesis and crystal structure of compound **4a**. Attempts to prepare crystals of **4b** and **4c** suitable for X-ray crystal structure analysis by slow evaporation of appropriate ethanolic solution were successful only for compound **4b** (Fig. 2).

The molecular structure of compound **4b** in the crystalline state is not planar due to the presence of the ethylene part of the molecule and the single C5–C8 bond, which allow the twisting around it with the torsion angle C6–C5–C8–N2 of 10.6(2)°. In that way, the benzothiazole and imidazoline rings are mutually twisted. The S–C

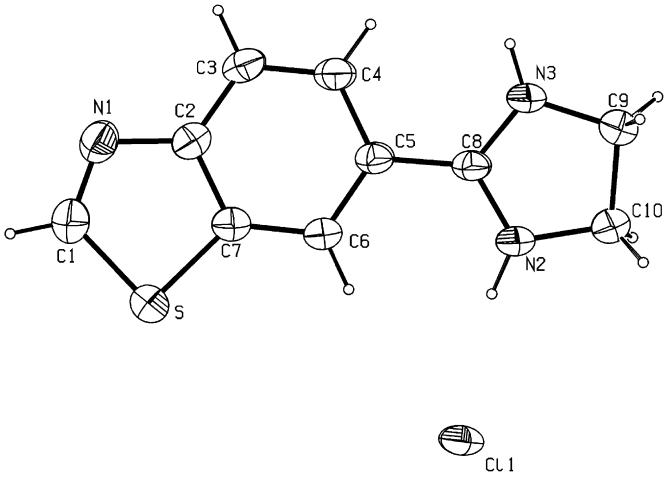


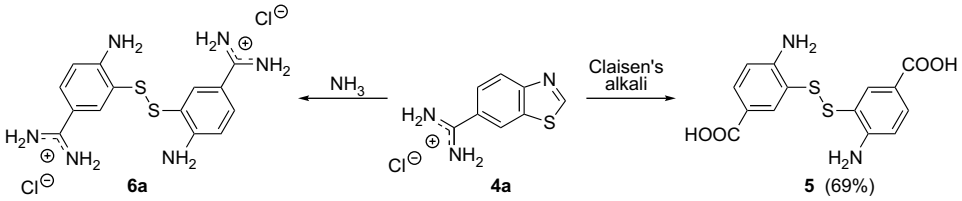
Figure 2. ORTEP drawing of **4b** with the atomic numbering scheme. The thermal ellipsoids are drawn at the 50% probability level at 293 K.

bond distances formed by the endocyclic sulfur atom are as expected slightly shorter than bonds in the C_{ar}–S–C_{ar} fragment being of average value 1.768(10) Å [S–C1 1.731(2) and S–C7 1.729(1) Å].[14] One C–N endocyclic bond within thiazole fragment is double in character [C1–N1 1.285(2) Å], while the other is significantly longer with a significant contribution of σ character [N1–C2 1.389(2) Å]. The C8–N2 and C8–N3 bonds in the imidazolinium ring are 1.315(2) Å and 1.316(2) Å indicating positive charge delocalization within N–C–N part of the imidazolinium ring. On the other hand, N3–C9 and N2–C10 bonds of 1.465(2) and 1.460(2) Å, respectively, are essentially σ in character.

Reaction of 6-amidinobenzothiazole **4a** with Claisen's alkali is shown in Scheme 3. The thiazole ring of **4a** cleaves in the presence of aqueous KOH as expected[16] but the amidine group also hydrolyses to a carboxylate. Subsequent acidification with acetic acid and crystallization affords 3,3′-disulfanediylbis(4-aminobenzoic acid) **5**. Interestingly, we obtained the same mp, ^{1}H and ^{13}C NMR spectroscopic data for compound **5** as it was reported for the hydrochloride salt,[15] which suggest that the previous authors did not isolate the hydrochloride salt.

structure (**6a** or **7a**), since both are characterized by very similar chemical shifts and the same ratio of the intensities of the signals in the ^{1}H NMR spectra. Fortunately, **6a** and **7a** could be crystallized from deoxygenated water as stable yellow crystals that were suitable for X-ray crystal structure analysis (Fig. 2). The yield of pure 3,3′-disulfanediylbis(4-aminobenzocarboxamidinium chloride) dihydrate **6a** and 5-amidinium-2-aminobenzothiolate **7a** were 31% and 51%, respectively. After separation of the main products, from the mother liquor, NH_4Cl and formamidinium chloride **8** were isolated as by products. The colourless crystal of **8** was extremely deliquescent and we were unable to determine the melting point.[18] However, the ^{1}H NMR spectrum in DMSO shows characteristic two broad signals of amidinium protons at 9.18 and 8.95 ppm, which disappear on addition of D_2O and a multiplet signal at 7.87 ppm, which corresponds to C–H proton. The ^{13}C NMR spectrum taken in DMSO shows only one doublet at 157.2 ppm.

The asymmetric unit of **6a** (Fig. 3) contains half of the disulfide molecule, one Cl^- ion and one water molecule. The two halves of the molecule are related by a twofold axis [S1–S1a (a=−x,y,1/2−z) disulfide single bond amounts 2.0859(8) Å]. The C–N bond dis-



Scheme 3.

To prevent the hydrolysis of the amidine we tried to perform the benzothiazole ring opening in mild basic conditions. In spite of the fact that the ring opening of benzothiazole in mild basic conditions is yet unknown, except with hydrazine,[16d] we carried out the reaction of compound **4a** with gaseous ammonia, hoping that the electron attracting nature of the amidino substituent (σ_p=0.65)[17] would facilitate the ring opening. After four days of stirring at room temperature, the reaction was complete and only benzothiazole ring opening occurred. Work-up of the reaction mixture afforded 5-amidino-2-aminothiophenol in disulfide form **6a** as the product of oxidative dimerization.

This result opened a possibility for formation of amidino function and benzothiazole ring opening in the Pinner reaction as a one-pot reaction. Thus, ethyl-6-benzothiazole carboximidate dihydrochloride **2** was treated with ethanol saturated with ammonia and reaction was carried out for five days at room temperature (Scheme 4).

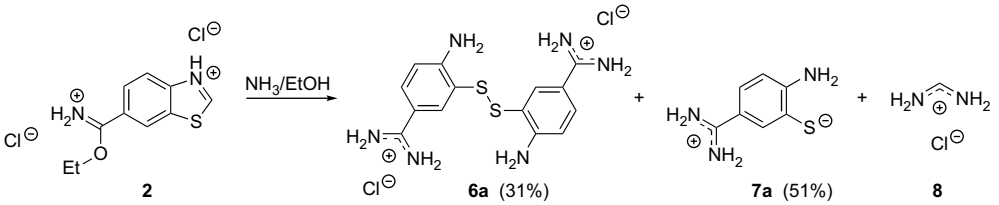
The resulting precipitate was a mixture of two products. In the ^{1}H NMR spectra taken in DMSO these two products were slowly interconverting. By treatment of this precipitate with deoxygenated methanol we were able to separate the insoluble zwitterion **7a**, from the methanol soluble disulfide **6a**, which precipitated on addition of diethyl ether. However, even from the NMR spectra of the isolated products it was impossible to assign

tances within the amidino group are 1.308(3) and 1.314(3) Å and the C–N bond distance of the amino group is 1.349(3) Å, while C1–S1 amounts 1.760(2) Å being predominantly σ in character.[19] The torsion angle S1–S1a–C1–C2 is −80.7(2)°. The molecule of **7a** is planar. The protonation of the amidino group along with the C1–S1 bond distance in **7a** [1.763(1) Å], which is dominantly σ in character, and the uniformity of C–N bond distances of the amidino group [1.316(2) and 1.323(2) Å], confirm the zwitterionic character of the molecule.

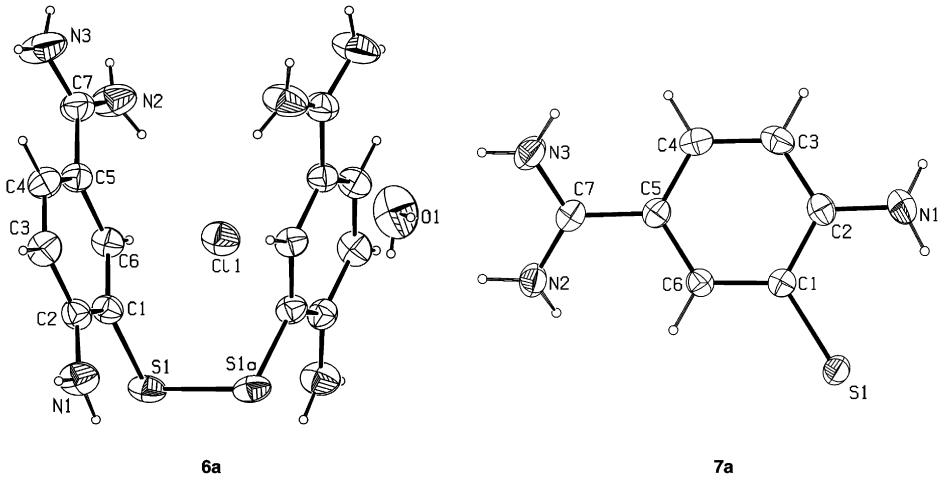
Reaction of imino ester hydrochloride **2** with ethylenediamine in abs ethanol (Scheme 5) was carried out at reflux temperature for 4 h.

The resulting precipitate, after second crystallization from deoxygenated water gave 5-(imidazolinium-2-yl)-2-aminobenzothiolate hydrate **7b** in a yield of 55%. To the ethanolic mother liquor, diethyl ether was added and the precipitate crystallized from deoxygenated water yielding 18% of 3,3′-disulfanediylbis[4-aminobenzo(imidazolinium-2-yl-chloride)] dihydrate **6b**.The structure of disulfide **6b** and zwitterion **7b** were confirmed by X-ray crystal structure analyses (Fig. 4).

As in **6a**, the asymmetric unit of **6b** (Fig. 3) contains half of the disulfide molecule, one Cl^- ion and one water molecule. The two halves of the molecule are related by the twofold axis [S1–S1a (a=1−x,y,1/2−z) disulfide single bond amounts 2.0851(1) Å]. The

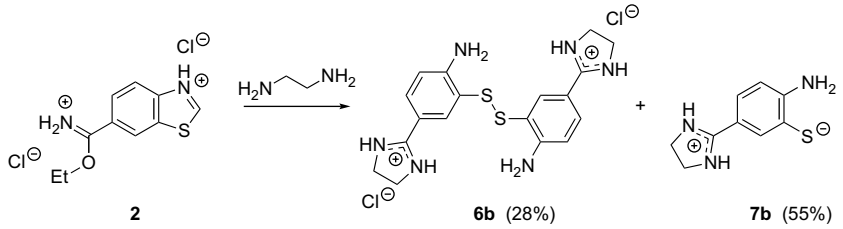


Scheme 4.



6a **7a**

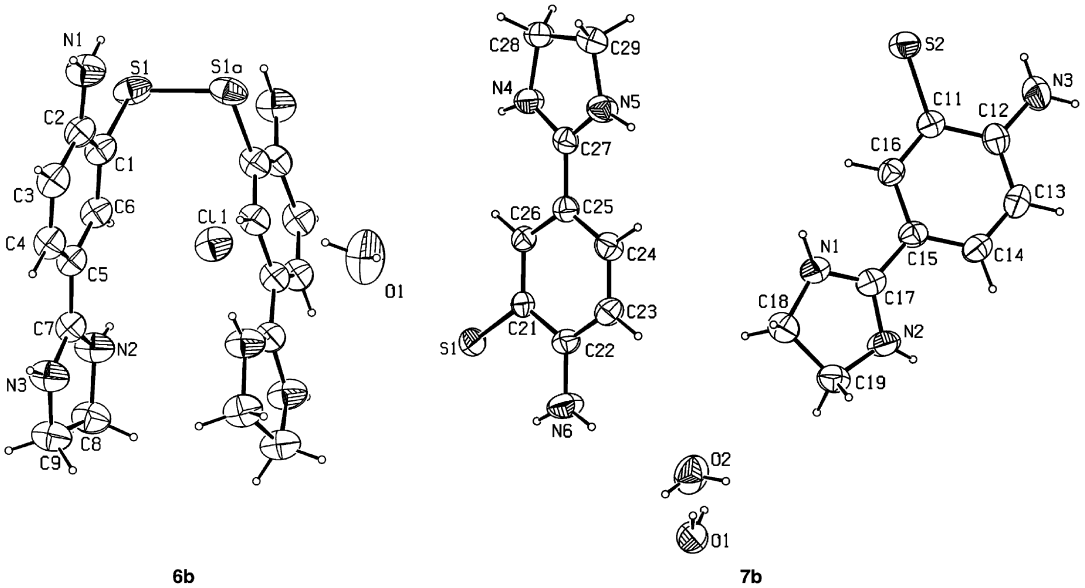
Figure 3. ORTEP drawing of compounds **6a** and **7a** with the atomic numbering scheme. The thermal ellipsoids are drawn at the 50% probability level at 293 K for both structures.



2 **6b** (28%) **7b** (55%)

Scheme 5.

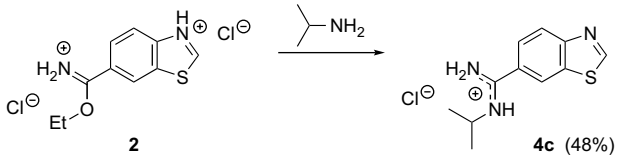
bond distance values in **6b** correspond with those in **6a**. For example, the S1–C1 bond in **6b** is 1.767(2) Å and 1.760(2) Å in **6a**. The C–N bond distances within the imidazolinium cation are N2–C7 1.326(3) Å and N3–C7 1.322(3) Å. The bonds N2–C8 and N3–C9 of 1.456(3) and 1.460(3) Å are essentially single carbon-to-nitrogen bond. The torsion angle C6–C5–C7–N3 of 179.2(2)° indicates planarity of half of the molecule. The torsion angle S1–S1a–C1–C2 is 85.6(2)°. Two crystallographically independent molecules are found in the crystal structure of **7b**, which crystallize with two water molecules. They are two conformers, which differ in twisting around single C15–C17 and C25–C27 bonds (C16–C15–C17–N1 and C26–C25–C27–N4 amount −12.7(3)° and 2.5(3)°, respectively). The equality of bond distances in the N–C–N fragment of imidazolinium cations along with C11–S2 and C21–S1 bond distances (1.764(2) and 1.758(2) Å, respectively) exhibit zwitterionic character of the molecules of **7b** as it is found for **7a**.



6b **7b**

Figure 4. ORTEP drawing of compounds **6b** and **7b** with the atomic numbering scheme. The thermal ellipsoids are drawn at the 50% probability level at 293 K for both structures.

Reaction conditions used for preparation of compounds **6a**, **6b** and **7a**, **7b** were applied to the reactions of **2** with excess of isopropylamine instead of ammonia or ethylenediamine (Scheme 6). The reactions were carried out at room temperature or at refluxing ethanol for a maximum of five days. Although we expected *N*-isopropylamidino-substituted 2-aminothiophenol as main product, only compound **4c** was isolated. The ring opening of benzothiazole did not occur. We tried to prepare *N*-isopropylamidino-substituted 2-aminothiophenol from compound **4c** in reaction with an ethanolic solution of ammonia (Scheme 7) at room temperature.



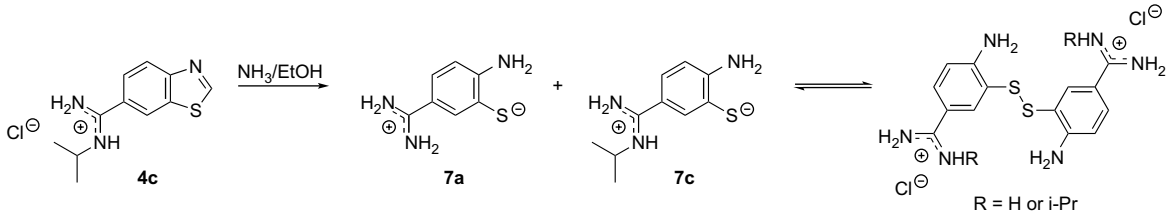
Scheme 6.

It should be noted that all amidino-substituted 2-aminothiophenoles **6a–c** and **7a**, **7b** in solution show interconversion from zwitterionic to disulfide form and vice versa. Raman spectroscopy has proved to be very useful in detecting disulfides. Two narrow and intense bands was observed in the region of 430–480 cm^{-1} for all isolated disulfide compounds **5** and **6a–c** corresponding to S–S stretching vibration and in accordance with the literature.[20]

2.2. Mechanism

On the basis of the product analysis and the results of preliminary DFT calculations, both in the gas phase and in ethanol, we propose the following mechanism for benzothiazole ring opening (Scheme 9).

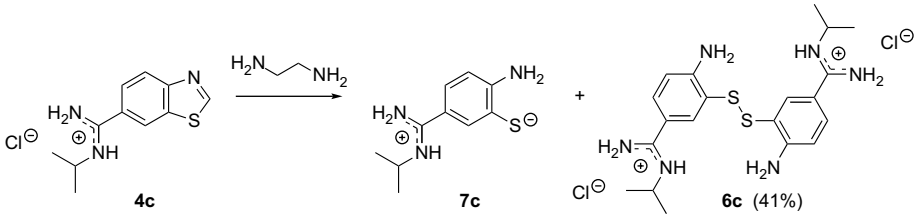
Without getting into any details, which will be published elsewhere, it is necessary to point out that thiazole ring opening and final zwitterion producing fragmentation proceeds much faster with imidate group already converted into amidino group (Scheme 9a). Due to the stereoelectronic reasons, the ring



Scheme 7.

The LC–MS analysis showed that a mixture of products was formed, due to the competition between reaction of benzothiazole ring opening, amonolysis of *N*-substituted amidine and dimerization of thiophenoles. Selective ring opening of benzothiazole without reaction of the *N*-isopropylamidino functional group was achieved in the reaction of **4c** with excess of ethylenediamine in ethanol at reflux temperature for 2 h (Scheme 8).

opening goes smoothly with ammonia (Scheme 9b) and ethylenediamine (Scheme 9c), but not with isopropylamine. The only difference between ammonia and ethylenediamine is that, prior to fragmentation, the attack of second amino group of ethylenediamine produces the entropically favoured imidazolidine ring (Scheme 9c).



Scheme 8.

The LC–MS analysis of crude precipitate showed only zwitterion **7c** and disulfide **6c** molecular ion signals. However, we were able to isolate by crystallization from water only 3,3′-disulfanediylbis[4-aminobenzo(*N*-isopropylamidinium chloride)] dihydrate **6c** in a yield of 41%. The crystals of **6c** suitable for X-ray crystal structure analysis (Fig. 5) were prepared by slow evaporation of its solution from water.

The asymmetric unit contains half of the disulfide molecule, one Cl^- ion and one water molecule. The S–Sa ($a=-x,-y+1/2,z$) bond amounts 2.0825(10) Å. The torsion angle Sa–S–C1–C2 value of 78.2(2)° exhibits the twisting around the single S–C1. The *N*-isopropylamidinium fragment is rotated around C5–C7 bond by 135.8(2)° (torsion angle C4–C5–C7–N2).

3. Conclusion

In summary, we have found a novel, simple and efficient method for the synthesis of amidino, *N*-isopropylamidino and 2-imidazolinyl substituted 2-aminothiophenoles in zwitterionic and disulfide form in high yield. The products **6a–c** and **7a**, **7b** are the key precursors for the more versatile synthesis of amidino-substituted benzothiazoles and other medicinally interesting N,S-heterocycles. The ring opening of benzothiazole with ethylenediamine is selective and applicable to compounds bearing hydrolytically and amonolytically unstable substituents.

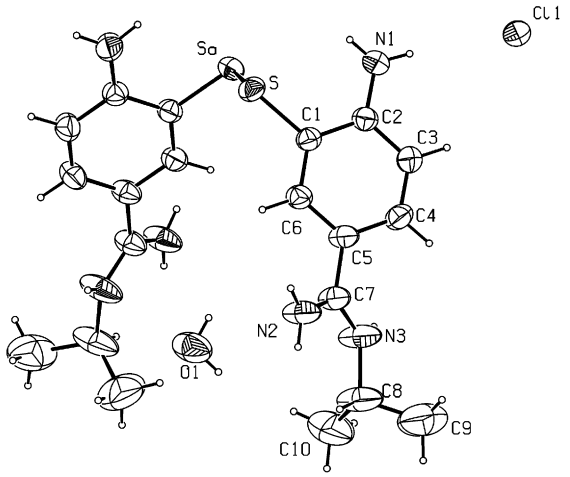


Figure 5. ORTEP drawing of **6c** with the atomic numbering scheme. The thermal ellipsoids are drawn at the 50% probability level at 293 K.

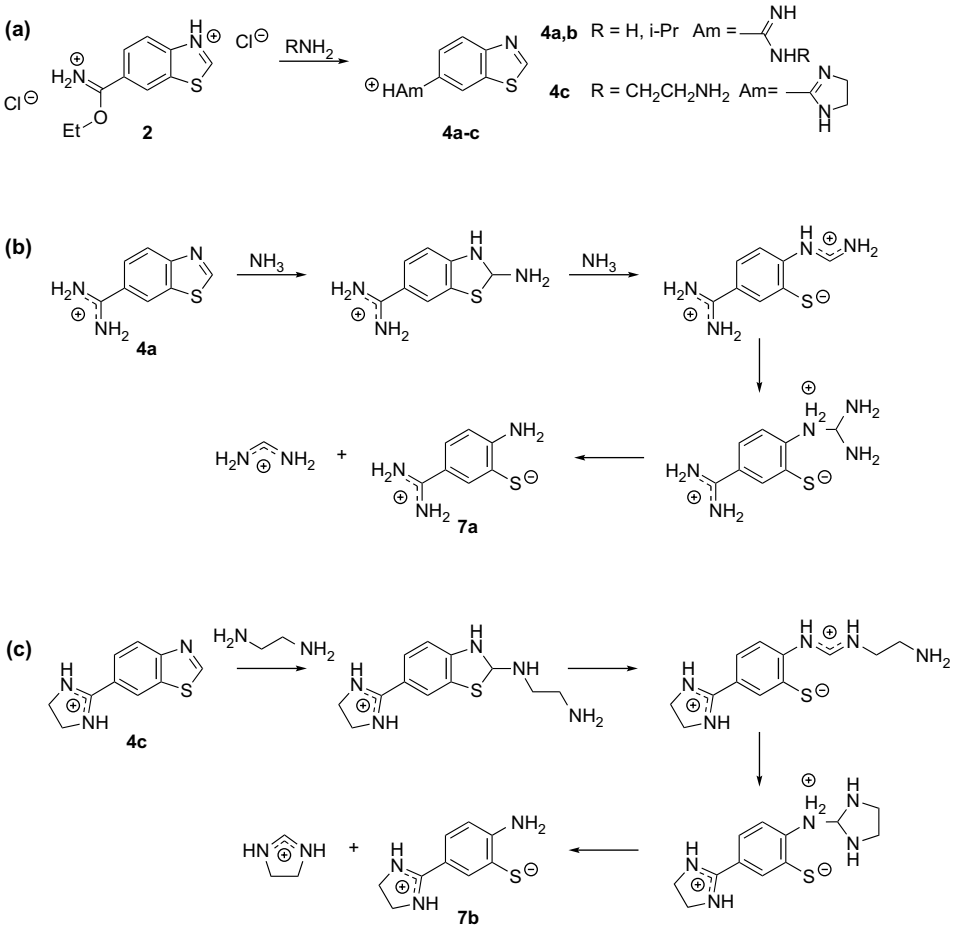
4. Experimental

4.1. General

All solvents and reagents were dried and purified by standard methods. 6-Cyanobenzothiazole **1** was prepared as described in the literature.[21] Claisen's alkali was prepared dissolving 35 g 85% KOH in 25 mL of water and 100 mL of methanol. The ^{1}H NMR and the ^{13}C NMR spectra were recorded with a Brucker Avance DPX-300 (300 MHz and 75.5 MHz, for ^{1}H and ^{13}C, respectively), the deuterated solvents indicated were used. Chemical shifts are reported in parts per million relative to TMS as an internal standard. IR spectra were recorded with Nicolet Magna 760 spectrophotometer. Raman spectra were recorded with a Brucker FT-IR interferometer Equinox 55 with a FT-Raman FRA 106/S with a Nd:YAG laser source 1064 nm and a liquid nitrogen cooled Ge detector. Mass spectra were recorded with an Agilent 1100 Series LC/MSD Trap SL spectrometer using electrospray ionization (ESI). Elemental analyses were performed at the microanalytical laboratories of the 'Ruđer Bošković' Institute. Melting points were determined on a Kofler block apparatus.

4.2. X-ray crystal structure analysis of compound 4b, 6a–c and 7a, 7b

Crystallographic data were recorded on an Xcalibur diffractometer, equipped with a CCD area detector, using Mo Kα radiation (λ=0.71073 Å) at T=293 K. Lorentz and polarization correction (CryAlis RED)[22a] was applied. Structure was solved by direct methods (SHELXS97)[22b] and refined by full-matrix least squares against F^2 using all data (SHELXL97).[22b] All non-H atoms were refined anisotropically. The H atoms were positioned geometrically with C_{ar}–H, $C_{methylene}$–H, C_{methyl}–H=0.93, 0.97 and 0.96 Å, respectively, and were constrained to ride on their parent atoms, with U_{iso}(H)=1.2 U_{eq}(C) for C_{ar}–H and $C_{methylene}$–H and 1.5 U_{eq}(C) for C_{methyl}–H. Hydrogen atoms of amine in **6a**–**c**, **7a**, **7b**, amidinium groups in **6a** and **7a** and of water molecules in hydrates **6a**, **6b**, **7b**



Scheme 9.

and **6c** were located in difference Fourier syntheses and refined freely. The molecular diagrams were drawn by PLATON98.[22c]

*4.2.1. Compound **4b***

X-ray crystal structure determination of **4b** (CCDC No. 694988): molecular formula: $C_{10}H_{10}ClN_3S$, M_r=239.72, colourless prism, triclinic, space group: *P*1, crystal dimensions: 0.24×0.17×0.10 mm^3, unit cell parameters: *a*=7.223(1), *b*=8.340(1), *c*=10.347(1) Å, *α*=72.782(11), *β*=70.830(12), *γ*=71.064(12)°, *V*=544.16(12) Å^3, *Z*=2, D_c=1.463 g cm^{-3}, *μ*=0.51 mm^{-1}, *F*(000)=248, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.5–27.0°, *h*,*k*,*l* range: −9:9; −10:10; −13:13, scan type: *ω*, no. measured reflections: 5334, no. independent reflections (R_{int}=0.021): 2275, no. refined parameters: 144, no. observed reflections *I*≥2*σ*(*I*): 2161, *R*[*I*≥2*σ*(*I*)]=0.0333, *wR*[*I*≥2*σ*(*I*)]=0.1057, *R*[all data]=0.0347, *wR*[all data]=0.1034, *S*=1.03, max., min. electron density=−0.20, 0.25 e Å^{-3}, maximum Δ/*σ*=0.001.

*4.2.2. Compound **6a***

X-ray crystal structure determination of **6a** (CCDC No. 676831): molecular formula: $C_{14}H_{22}Cl_2N_6O_2S_2$, M_r=441.42, regular yellow prism, monoclinic, space group: *C*2/*c*, crystal dimensions 0.42×0.37×0.30 mm^3, *a*=12.2670(10), *b*=12.1319(10), *c*=14.4643(13) Å, *β*=109.731(8)°, *V*=2026.2(3) Å^3, *Z*=4, D_c=1.447 g cm^{-3}, *μ*=0.55 mm^{-1}, *F*(000)=920, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.3–27.0°, *h*,*k*,*l* range: −15:15; −15:15; −18:18, scan type: *ω*, no. measured reflections: 8850, no. independent reflections (R_{int}=0.035)=2187, no. refined parameters=150, no. observed reflections *I*≥2*σ*(*I*)=2014, *R*[*I*≥2*σ*(*I*)]=0.0396, *wR*[*I*≥2*σ*(*I*)]=0.0907, *R*[all data]=0.0432, *wR*[all data]=0.0939, *S*=1.09, max., min. electron density=−0.28, 0.43 e Å^{-3}, maximum Δ/*σ*=0.001.

*4.2.3. Compound **6b***

X-ray crystal structure determination of **6b** (CCDC No. 694989): molecular formula: $C_{18}H_{26}Cl_2N_6O_2S_2$, M_r=493.46, regular pale yellow prism, monoclinic, space group: *C*2/*c*, crystal dimensions: 0.37×0.26×0.18 mm^3, *a*=12.1938(12), *b*=13.6974(13), *c*=14.1414(17) Å, *β*=108.746(10)°, *V*=2236.6(4) Å^3, *Z*=4, D_c=1.465 g cm^{-3}, *μ*=0.51 mm^{-1}, *F*(000)=1032, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.5–27.0°, *h*,*k*,*l* range: −15:15; −17:12; −18:17, scan type: *ω*, no. measured reflections: 8413, no. independent reflections (R_{int}=0.025)=2439, no. refined parameters=160, no. observed reflections *I*≥2*σ*(*I*)=2003, *R*[*I*≥2*σ*(*I*)]=0.0441, *wR*[*I*≥2*σ*(*I*)]=0.1466, *R*[all data]=0.0542, *wR*[all data]=0.1344, *S*=1.03, max., min. electron density=−0.27, 0.46 e Å^{-3}, maximum Δ/*σ*<0.001.

*4.2.4. Compound **6c***

X-ray crystal structure determination of **6c** (CCDC No. 694991): molecular formula: $C_{20}H_{34}Cl_2N_6O_2S_2$, M_r=525.56, irregular dark yellow prism, tetragonal, space group: *I*4$_1$/*a*, crystal dimensions: 0.51×0.47×0.39 mm^3, *a*=17.2448(7), *b*=17.2448(8), *c*=18.7091(9) Å, *V*=5563.8(4) Å^3, *Z*=8, D_c=1.255 g cm^{-3}, *μ*=0.41 mm^{-1}, *F*(000)=2224, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.3–27.0°, *h*,*k*,*l* range: −22:22; −22:22; −23:23, scan type: *ω*, no. measured reflections: 44,846, no. independent reflections (R_{int}=0.044)=3014, no. refined parameters=175, no. observed reflections *I*≥2*σ*(*I*)=3000, *R*[*I*≥2*σ*(*I*)]=0.0476, *wR*[*I*≥2*σ*(*I*)]=0.1204, *R*[all data]=0.0479, *wR*[all data]=0.1207, *S*=1.14, max., min. electron density=−0.33, 0.23 e Å^{-3}, maximum Δ/*σ*<0.001.

*4.2.5. Compound **7a***

X-ray crystal structure determination of **7a** (CCDC No. 676832): molecular formula: $C_7H_9N_3S$, M_r=167.23, irregular yellow prism, orthorhombic, space group: *Pbca*, crystal dimensions: 0.39×0.36×0.30 mm^3, unit cell parameters: *a*=8.2797(6), *b*=0.8575(7), *c*=17.1949(11) Å, *V*=1545.77(18) Å^3, *Z*=8, D_c=1.437 g cm^{-3}, *μ*=0.4 mm^{-1}, *F*(000)=704, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.4–27.0°, *h*,*k*,*l* range: −10:10; −12:13; −21:21, scan type: *ω*, no. measured reflections: 13,057, no. independent reflections (R_{int}=0.024): 1671, no. refined parameters: 124, no. observed reflections *I*≥2*σ*(*I*): 1671, *R*[*I*≥2*σ*(*I*)]=0.0294, *wR*[*I*≥2*σ*(*I*)]=0.0794, *R*[all data]=0.0299, *wR*[all data]=0.0789, *S*=1.09, max., min. electron density=−0.22, 0.24 e Å^{-3}, maximum Δ/*σ*=0.001.

*4.2.6. Compound **7b***

X-ray crystal structure determination of **7b** (CCDC No. 694990): molecular formula: $C_9H_{13}N_3OS$, M_r=211.29, pale yellow prism, monoclinic, space group: $P2_1/c$ (No. 14), crystal dimensions: 0.44×0.31×0.20 mm^3, unit cell parameters: *a*=7.2604(14), *b*=15.3734(18), *c*=18.115(2) Å, *β*=96.435(13)°, *V*=2009.1(5) Å^3, *Z*=8, D_c=1.397 g cm^{-3}, *μ*=0.3 mm^{-1}, *F*(000)=896, Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD, Mo K*α* radiation (*λ*=0.71073 Å), *T*=293(2) K, *θ* range for data collection=4.3–27.0°, *h*,*k*,*l* range: −9:9; −19:19; −23:23, scan type: *ω*, no. measured reflections: 23,102, no. independent reflections (R_{int}=0.043): 4349, no. refined parameters: 301, no. observed reflections *I*≥2*σ*(*I*): 3686, *R*[*I*≥2*σ*(*I*)]=0.0529, *wR*[*I*≥2*σ*(*I*)]=0.1210, *R*[all data]=0.0696, *wR*[all data]=0.1119, *S*=1.16, max., min. electron density=−0.21, 0.20 e Å^{-3}, maximum Δ/*σ*=0.001.

4.3. Ethyl-6-benzothiazole carboximidate dihydrochloride 2

A suspension of 6-cyanobenzothiazole (**1**, 4.0 g, 25 mmol) in 50 mL of abs ethanol was cooled to 5 °C and saturated with dry gaseous HCl. The flask was stoppered and stirred at room temperature for 72 h (until IR spectra indicate the disappearance of the nitrile peak). Excess HCl was removed from the suspension with a stream of N_2. The reaction mixture was poured into abs Et_2O (250 mL), and the resulting crystals filtered off, washed with abs Et_2O and dried under reduced pressure over KOH to afford the compound **2** as white hygroscopic crystalline solid. It is unstable and decomposes on heating. The synthesis of **2** has been preformed prior to use without purification. Yield: 6.60 g (95%). IR (KBr): *ν*=3072, 2983, 2855, 1911, 1811, 1697, 1631, 1610, 1398, 1085, 852, 793 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): *δ*=1.53 (t, 3H, ^3J=7.0 Hz, –OCH$_2$C*H*$_3$), 4.73 (q, 2H, ^3J=7.0 Hz, –OC*H*$_2$CH$_3$), 6.20 (br s, 1H, H-3), 8.32 (m, 2H, H-4, H-5), 9.13 (s, 1H, H-7), 9.75 (s, 1H, H-2), 11.71 (br s, 1H, =N*H*$_2^+$), 12.52 (br s, 1H, –C=N*H*$_2^+$). Anal. Calcd for $C_{10}H_{12}Cl_2N_2OS$: C, 43.02; H, 4.33; Cl, 25.40; N, 10.03. Found: C, 43.18; H, 4.15; N, 9.71; Cl, 25.43%.

4.4. General procedure for preparation of the 6-amidino-substituted benzothiazoles 4a–c

The imidoyl ether dihydrochloride (**2**, 2.0 g, 7.2 mmol) was poured into cold water (50 mL) and neutralized with 5% $NaHCO_3$. The free base **3** was extracted with chloroform, and combined chloroform extract washed with water and dried over $CaCl_2$. The solvent was removed under reduced pressure to give colourless oil of ethyl-6-benzothiazole carboximidate **3**, which was dissolved in

ethanol (25 mL). A solution of hydrochloride salts of amine (8.0 mmol) in water (5 mL) was added and the mixture was heated under reflux for 5 h. The hot mixture was filtered (charcoal), and solvents were then removed under reduced pressure and the residues were crystallized as follows.

4.4.1. 6-Amidinobenzothiazole hydrochloride dihydrate **4a**[13]

Using **3** and ammonium chloride as starting material and crystallization from 75% ethanol gave colourless crystals. Yield: 1.17 g (65%). Mp 274–275 °C (lit.[13] 275 °C). IR (KBr): ν=3265, 3080, 1679, 1607, 1544, 1297, 908, 650 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=7.95 (dd, 1H, ^3J=8.6 Hz, ^4J=1.8 Hz, H-5), 8.31 (d, 1H, ^3J=8.6 Hz, H-4), 8.74 (d, 1H, ^4J=1.7 Hz, H-7), 9.41 (br s, 4H, –(C=NH_2)NH_2^+), 9.67 (s, 1H, H-2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=123.8, 124.2, 125.7, 126.4, 134.5, 156.5, 161.3, 166.2. Anal. Calcd for $C_8H_8ClN_3S\cdot 2H_2O$: C, 38.48; H, 4.84; N, 16.83. Found: C, 38.52; H, 4.67; N, 17.01%.

4.4.2. 6-(Imidazolin-2-yl)benzothiazole hydrochloride hydrate **4b**

Using **3** and ethylenediamine dihydrochloride as starting material and crystallization from 75% ethanol gave white crystals. Yield: 1.20 g (58%). Mp >300 °C. IR (KBr): ν=3055, 2947, 1656, 1595, 1367, 1279, 874, 692 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=4.04 (s, 4H, –(CH_2)$_2$–), 8.23 (d, 1H, ^3J=8.5 Hz, H-5), 8.32 (d, 1H, ^3J=8.6 Hz, H-4), 9.07 (s, 1H, H-7), 9.72 (s, 1H, H-2), 11.1 (br s, 2H, –NHC=NH^+–). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=44.9 (2C), 119.7, 124.1, 124.8, 126.7, 134.6, 154.4, 156.7, 164.9. Anal. Calcd for $C_{10}H_{10}ClN_3S\cdot H_2O$: C, 46.60; H, 4.69; N, 16.30. Found: C, 46.80; H, 4.53; N, 16.18%.

4.4.3. 6-(N-Isopropylamidino)benzothiazole hydrochloride **4c**

Method A. Using **3** and isopropylamine hydrochloride as starting material and crystallization from abs ethanol gave white crystals. Yield: 0.84 g (41%). Mp 278 °C. IR (KBr): ν=3193, 3046, 2970, 1688, 1614, 1127, 907, 887, 702 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.31 (d, 6H, ^3J=6.4 Hz, (CH_3)$_2$CH–), 4.18 (m, 1H, (CH_3)$_2$CH–), 7.87 (dd, 1H, ^3J=8.6 Hz, ^4J=1.8 Hz, H-5), 8.27 (d, 1H, ^3J=8.6 Hz, H-4), 8.67 (d, 1H, ^4J=1.6 Hz, H-7), 9.66 (s, 1H, H-2), 9.42 (br s, 1H, –(C=NH_2)NH^+–), 9.66 (br s, 1H, –(C=NH_2)NH^+–), 9.83 (br s, 1H, –(C=NH_2)NH^+–). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=21.7 (2C), 45.7, 123.5, 124.3, 126.6, 126.7, 134.2, 156.0, 162.0. Anal. Calcd for $C_{11}H_{14}ClN_3S$: C, 51.67; H, 5.51; N, 16.42. Found: C, 51.57; H, 5.35; N, 16.39%.

Method B. Using (**2**, 2.8 g, 10 mmol) and isopropylamine (4.25 mL, 50 mmol) as starting material in reaction in abs ethanol (40 mL) at reflux temperature for 24 h, and crystallization of residue from abs ethanol gave 1.22 g (48%) of compound **4c**.

4.5. 3,3′-Disulfanediylbis(4-aminobenzoic acid) 5

The mixture of 6-amidinobenzothiazole (**4a**, 1.25 g, 5 mmol) and Claisen's alkali (25 mL) was stirred at reflux temperature for 15 min. After cooling the mixture was poured in water (100 mL) and acidified with acetic acid. The resulting precipitate, after standing for a week in refrigerator, was filtered off and crystallized from ethanol to give yellowish crystals of **5**. Yield: 0.68 g (69%). Mp 282–285 °C. IR (KBr): ν=3488, 3377, 2925, 2647, 1678, 1609, 1587, 1289, 1151, 766 cm^{-1}. Raman: ν=3070, 1588, 1451, 1283, 1258, 1140, 882, 704, 478, 438 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.31 (s, 4H, –NH_2), 6.76 (d, 2H, ^3J=8.6 Hz, H-5, H-5′), 7.48 (d, 2H, ^4J=1.8 Hz, H-7, H-7′), 7.64 (dd, 2H, ^4J=1.8 Hz, ^3J=8.5 Hz, H-6, H-6′), 12.08 (br s, 1H, –COOH). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=113.8, 114.9, 117.6, 132.7, 138.0, 153.5, 166.5. Anal. Calcd for $C_{14}H_{12}N_2O_4S_2$: C, 49.99; H, 3.60; N, 8.33; S, 19.06. Found: C, 49.81; H, 3.67; N, 8.45; S, 19.01%.

4.6. Procedure for preparation of 5-amidino-substituted 2-aminothiophenoles 6a and 7a

4.6.1. 5-Amidinium-2-aminobenzothiolate **7a**

A suspension of ethyl-6-benzothiazole carboximidate dihydrochloride (**2**, 6.0 g, 21 mmol) in abs ethanol (125 ml) was cooled to 10 °C and saturated with ammonia. The flask was stoppered and content was stirred at room temperature for five days. After cooling to 5 °C the obtained solid was filtered off and washed with dry ether. The solid mixture was suspended and heated to boiling in hot deoxygenated abs methanol (150 ml), filtered hot and obtained crystals purified by crystallization from water to afford zwitterion **7a** as yellow crystals. Yield: 1.78 g (50.7%). Mp 235–240 °C (dec). IR (KBr): ν=3401, 3363, 2996, 1663, 1623, 1588, 1565, 1517, 1473 cm^{-1}. Raman: ν=1584, 1570, 1518, 1461, 1184, 871, 671, 562 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.08 (s, 2H, –NH_2), 6.44 (d, 1H, ^3J=8.1 Hz, H-3), 6.99 (d, 1H, ^3J=8.3 Hz, H-4), 7.57 (d, 1H, ^4J=2.3 Hz, H-6), 8.19 (br s, 4H, –(C=NH_2)NH_2^+). LC–MS (ESI), m/z: 168 (MH$^+$). Anal. Calcd for $C_7H_9N_3S$: C, 50.27; H, 5.42; N, 25.13. Found C, 49.99; H, 5.24; N, 24.89%.

4.6.2. 3,3′-Disulfanediylbis(4-aminobenzocarboxamidinium chloride) dihydrate **6a**

To methanolic filtrate (150 mL) remaining after separation of zwitterion **7a** abs Et_2O was added. The resulting precipitate was filtered, washed with Et_2O and crystallized from water to give yellowish crystals of disulfide **6a**. Yield: 1.43 g (30.9%). Mp >300 °C. IR (KBr): ν=3482, 3318, 3195, 1654, 1595, 1545, 1472, 1189 cm^{-1}. Raman: ν=1590, 1558, 1473, 1174, 1089, 878, 475, 445 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.70 (s, 4H, –NH_2), 6.85 (d, 2H, ^3J=8.7 Hz, H-5), 7.57 (d, 2H, ^4J=2.0 Hz, H-2), 7.66 (dd, 1H, ^4J=2.0 Hz, ^3J=8.7 Hz, H-6), 8.60 (br s, 4H, –(C=NH_2)NH_2^+), 8.84 (br s, 4H, –(C=NH_2)NH_2^+). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=112.7, 114.1, 115.4, 131.2, 136.7, 154.7, 163.6. LC–MS (ESI), m/z: 333 (MH$^+$−2HCl). Anal. Calcd for $C_{14}H_{20}Cl_2N_6S_2\cdot 2H_2O$: C, 38.10; H, 5.44; N, 19.03. Found: C, 37.89; H, 5.15; N, 18.87%.

4.7. Procedure for preparation of 5-(imidazolinium-2-yl)-substituted 2-aminothiophenoles 6b and 7b

4.7.1. 5-(Imidazolinium-2-yl)-2-aminobenzothiolate hydrate **7b**

To a suspension of ethyl-6-benzothiazole carboximidate dihydrochloride (**2**, 6.0 g, 21 mmol) in abs ethanol (100 ml) freshly distilled ethylenediamine (8.4 mL, 0.125 mol) was added in nitrogen atmosphere. The flask was refluxed for 5 h under nitrogen, cooled to 5 °C and the obtained solid was filtered off and washed with dry ether. The solid mixture was suspended and heated to boiling in hot deoxygenated abs methanol (150 ml), filtered hot and obtained crystals purified by crystallization from water to afford compound **7b** as yellow crystals. Yield: 2.46 g (55.3%). Mp 202–205 °C (dec). IR (KBr): ν=3457, 3405, 3328, 3127, 1580, 1536, 1493, 1356, 1325, 1286 cm^{-1}. Raman: ν=1595, 1570, 1518, 1354, 1279, 963, 926, 845, 717, 634 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.80 (s, 4H, –NH(CH_2)$_2$NH–), 6.24 (s, 2H, NH_2), 6.43 (d, 1H, ^3J=8.4 Hz, H-3), 7.04 (dd, 1H, ^3J=8.4 Hz, ^4J=2.4 Hz, H-4), 7.66 (d, 1H, ^4J=2.4 Hz, H-6), 9.55 (br s, 2H, –NHC=NH^+–). LC–MS (ESI), m/z: 194 (MH$^+$). Anal. Calcd for $C_9H_{11}N_3S\cdot H_2O$: C, 51.16; H, 6.16; N, 19.88. Found C, 50.88; H, 6.03; N, 19.58%.

4.7.2. 3,3′-Disulfanediylbis[4-aminobenzo(imidazolinium-2-yl-chloride)] dihydrate **6b**

To methanolic filtrate (150 mL) remaining after separation of zwitterion **7b** abs Et_2O was added. The resulting precipitate was filtered, washed with Et_2O and crystallized from water to give yellowish crystals of disulfide **6b**. Yield: 2.86 g (27.6%). Mp >300 °C. IR (KBr): ν=3308, 3189, 2963, 1590, 1498, 1361, 817 cm^{-1}. Raman: ν=1589, 1477, 1357, 1290, 930, 473, 431 cm^{-1}. ^{1}H NMR (300 MHz,

DMSO-d_6): δ=3.86 (s, 8H, –NH(CH_2)$_2$NH–), 6.89 (d, 2H, ^3J=8.7 Hz, H-5, H-5′), 6.94 (s, 2H, –NH_2), 7.38 (d, 2H, ^4J=2.2 Hz, H-2, H-2′), 7.79 (dd, 2H, ^3J=8.8 Hz, ^4J=2.0 Hz, H-6, H-6′), 9.96 (br s, 4H, –N*H*C=N*H*$^+$–). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=44.3 (4C), 107.8, 114.9, 115.5, 132.3, 138.7, 155.7, 163.8. LC–MS (ESI), *m*/*z*: 385 (MH$^+$−2HCl). Anal. Calcd for $C_{18}H_{22}Cl_2N_6S_2\cdot 2H_2O$: C, 43.81; H, 5.31; N, 17.03. Found: C, 43.77; H, 5.42; N, 16.98%.

4.8. 3,3′-Disulfanediylbis[4-aminobenzo(*N*-isopropylamidinium-chloride)] dihydrate 6c

To a suspension of 6-(*N*-isopropylamidino)benzothiazole hydrochloride (**4c**, 0.65 g, 2.5 mmol) in abs ethanol (15 ml) freshly distilled ethylenediamine (0.84 mL, 12.5 mmol) was added in nitrogen atmosphere. The flask was refluxed for 2 h under nitrogen (TLC-control), cooled to 5 °C and dry ether (5 mL) added. The obtained solid was filtered off and washed with dry ether. Crystallization from deoxygenated water afforded only disulfide **6c** as yellow crystals. Yield: 0.55 g (41.0%). Mp 232–235 °C. IR (KBr): ν=3430, 3306, 3145, 2978, 1671, 1618, 1501, 1403, 1130, 834, 682 cm^{-1}. Raman: ν=1593, 1392, 1172, 881, 479, 429 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.21 (d, 12H, ^3J=6.1 Hz, –CH(CH_3)$_2$), 4.04 (m, 2H, –C*H*(CH_3)$_2$), 6.51 (s, 4H, –NH_2), 6.85 (d, 2H, ^3J=9.0 Hz, H-5, H-5′), 7.59 (m, 4H, H-2, H-2′, H-6, H-6′), 8.99 (br s, 6H, –(C=NH_2)N*H*$^+$–). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ=21.9 (4C), 45.1, 114.5, 115.2, 116.2, 131.8, 136.7, 154.7, 160.6. LC–MS (ESI), *m*/*z*: 417 (MH$^+$−2HCl). Anal. Calcd for $C_{20}H_{30}Cl_2N_6S_2\cdot 2H_2O$: C, 45.71; H, 6.52; N, 15.99. Found: C, 45.60; H, 6.42; N, 16.19%.

4.9. Computational methods

Geometries of all of the structures involved in all of the more or less plausible reaction paths leading to experimentally observed products were fully optimized at B3LYP/6-311G(d,p) level of theory, both in the gas phase and in ethanol, and identified as minima or transition structures by vibrational analysis. Solvent effects were introduced via polarizable continuum model using IEF-PCM method as implemented in Gaussian 03.[23] Based on the calculation results, paths involving nonexistent or higher-lying transition structures were eliminated, and the resulting stepwise minimum-energy mechanism is proposed in Scheme 9.

4.10. Supplementary data

Supplementary publication numbers CCDC 676831, 676832 and 694988–694991 for compounds **4b**, **6a**–**c**, **7a**, **7b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (0) 1223 336033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

This work is supported by Ministry of Science, Education and Sports of the Republic of Croatia (projects no. 125-0982464-1356, 117-0000000-3283 and 119-1191342-1339).

References and notes

1. Leong, C. O.; Suggitt, M.; Swaine, D. J.; Bibby, M. C.; Stevens, M. F. G.; Bradshaw, T. D. *Mol. Cancer Ther.* **2004**, *3*, 1565–1575.
2. Yldiz-Oren, I.; Yalcin, I.; Aki-Sener, E.; Ucarturk, N. *Eur. J. Med. Chem.* **2004**, *39*, 291–298.
3. Sheng, C.; Zhu, J.; Zhang, W.; Zhang, M.; Ji, H.; Song, Y.; Xu, H.; Yao, J.; Miao, Z.; Zhou, Y.; Zhu, J.; Lu, J. *Eur. J. Med. Chem.* **2007**, *42*, 477–486.
4. Lochart, A.; Ye, L.; Judd, D. B.; Merritt, A. T.; Lowe, P. N.; Morgenstern, J. L.; Hong, G.; Gee, A. D.; Brown, J. *J. Biol. Chem.* **2005**, *280*, 7677–7684.
5. (a) Grout, R. J. In *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley & Sons: New York, NY, 1975; Vol. 1, p 255–281.
6. Tidwell, R. R.; Boykin, D. W. In *Small Molecule DNA and RNA Binders*; Demeunynck, M., Bailly, C., Wilson, W. D., Eds.; Wiley-VCH: Weinheim, 2003; Vol. 2, p 414–501.
7. (a) Munde, M.; Ismail, M. A.; Arafa, R.; Peixoto, P.; Collar, C. J.; Liu, Y.; Hu, L.; David-Cordonnier, M.-H.; Lansiaux, A.; Bailly, C.; Boykin, D. W.; Wilson, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 13732–13743; (b) Arafa, R. K.; Brun, R.; Wenzler, T.; Tanious, F. A.; Wilson, W. D.; Stephens, C. E.; Boykin, D. W. *J. Med. Chem.* **2005**, *48*, 5480–5488.
8. (a) Metzger, J.; Plank, H. *Chim. Ind.* **1956**, *75*, 929–939; (b) Metzger, J.; Plank, H. *Chim. Ind.* **1956**, *75*, 1290–1303; (c) Jacobson, P. *Chem. Ber.* **1886**, *19*, 1067–1078; (d) Spitulnik, M. J. *Synthesis* **1976**, 730–731; (e) Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119–10128; (f) Jayanthi, G.; Muthusamy, S.; Paramasivam, R.; Ramakrishnan, V. T.; Ramasamy, N. K.; Ramamurthy, P. *J. Org. Chem.* **1997**, *62*, 5766–5770; (g) Stanetty, P.; Krumpak, B. *J. Org. Chem.* **1996**, *61*, 5130–5133; (h) Spyros, M.; Gatos, D.; Barlos, K. *Tetrahedron Lett.* **2001**, *42*, 2201–2204; (i) Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802–1808; (j) Bose, D. S.; Idrees, M. *Tetrahedron Lett.* **2007**, *48*, 669–672; (k) Batista, R. M. F.; Costa, S. P. G.; Malheiro, E. L.; Belsley, M.; Raposo, M. M. M. *Tetrahedron* **2007**, *63*, 4258–4265; (l) Downer-Riley, N. K.; Jackson, Y. A. *Tetrahedron* **2008**, 7741–7744.
9. (a) Boyd, G. V. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, NY, 1991; Vol. 2, p 339–365; (b) Cai, L.; Han, Y.; Ren, S.; Huang, L. *Tetrahedron* **2000**, *56*, 8253–8262; (c) Yin, Z.; Zhang, Z.; Zhu, J.; Wong, H.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *Tetrahedron Lett.* **2005**, *46*, 4919–4923; (d) Gargipati, S. R. *Tetrahedron Lett.* **1990**, *31*, 1969–1972; (e) Rousselt, G.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1993**, *34*, 6395–6398; (f) Gielen, H.; Alonso-Alija, C.; Hendrix, M.; Niewohner, U.; Schauss, D. *Tetrahedron Lett.* **2002**, *43*, 419–421.
10. Schaefer, F. C.; Peters, G. A. *J. Org. Chem.* **1961**, *26*, 412–418.
11. (a) Hranjec, M.; Kralj, M.; Piantanida, I.; Sedić, M.; Šuman, L.; Pavelić, K.; Karminski-Zamola, G. *J. Med. Chem.* **2007**, *50*, 5696–5711; (b) Starčević, K.; Kralj, M.; Ester, K.; Sabol, I.; Grce, M.; Pavelić, K.; Karminski-Zamola, G. *Bioorg. Med. Chem.* **2007**, *15*, 4419–4426; (c) Racanè, L.; Tralić-Kulenović, V.; Kitson, R. P.; Karminski-Zamola, G. *Monatsh. Chem.* **2006**, *137*, 1571–1577; (d) Racanè, L.; Tralić-Kulenović, V.; Fišer-Jakić, L.; Boykin, W. D.; Karminski-Zamola, G. *Heterocycles* **2001**, *55*, 2085–2098; (e) Racanè, L.; Tralić-Kulenović, V.; Boykin, W. D.; Karminski-Zamola, G. *Molecules* **2003**, *8*, 342–349.
12. Tralić-Kulenović, V.; Karminski-Zamola, G.; Racanè, L.; Fišer-Jakić, L. *Heterocycl. Commun.* **1998**, *4*, 423–428.
13. Matković-Čalogović, D.; Popović, Z.; Tralić-Kulenović, V.; Racanè, L.; Karminski-Zamola, G. *Acta Crystallogr.* **2003**, *C59*, o190–o191.
14. Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.
15. Lang, R. C.; Williams, C. M.; Garson, M. J. *Org. Prep. Proced. Int.* **2003**, *35*, 520–524.
16. (a) Metzger, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 6, p 235–231; (b) Bartoli, G.; Ciminale, F.; Todesco, P. E. *Tetrahedron Lett.* **1975**, *16*, 1785–1786; (c) Bartoli, G.; Lelli, M.; Ciminale, F.; Attanasi, O. *J. Chem. Soc., Perkin Trans. 2* **1977**, 20–24; (d) Chedekel, M. R.; Sharp, D. E.; Jeffery, G. A. *Synth. Commun.* **1980**, 167–173.
17. Shorter, J. In *The Chemistry of Amidines and Imidates*; Patai, S., Rappoport, Z., Eds.; Wiley & Sons: New York, NY, 1991; Vol. 2, p 689–705.
18. Taylor, E. C.; Ehrhart, W. A. *J. Am. Chem. Soc.* **1960**, *82*, 3138–3141.
19. Trinajstić, N. *Tetrahedron Lett.* **1968**, *12*, 1529–1532.
20. Field, L. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, NY, 1977; pp 303–382.
21. Boggust, W. A.; Cocker, W. *J. Chem. Soc.* **1949**, 355–361.
22. (a) *Oxford Diffraction. Xcalibur CCD System, CrysAlis Software System, Version 171.23*; Oxford Diffraction: Abingdon, UK, 2004; (b) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122; (c) Spek, A. L. *Acta Crystallogr.* **1990**, *A46*, 34.
23. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision D02*; Gaussian: Wallingford, CT, 2004.