Article

A Synthetic Method to Access Symmetric and Non-Symmetric 2-(*N*,*N*′-disubstituted)guanidinebenzothiazoles

Alejandro Cruz *, Itzia I. Padilla-Martínez and Efrén V. García-Báez

Departamento de Ciencias Básicas de la Unidad Profesional Interdisciplinaria de Biotecnología del IPN, Av. Acueducto s/n, Barrio la Laguna Ticomán, México, D.F., 07340, Mexico

* Author to whom correspondence should be addressed; E-Mail: alecruz@ipn.mx; Tel.: +5-557-296-000 (ext. 56324); Fax: +5-557-296-000 (ext. 563054).

Abstract: Symmetric and non-symmetric 2-(*N*-H, *N*-methyl, *N*-ethylenyl and *N*-aryl)guanidinebenzothiazoles were synthesized from the reaction of ammonia, methylamine, pyrrolidine and aniline with dimethyl benzo[*d*]thiazol-2-yl-carbono-dithioimidate (**5**) as intermediate. The products were characterized by ^{1}H-, ^{13}C-NMR spectroscopy and three of them by X-ray diffraction analysis. H*N*-phenyl protons formed intramolecular hydrogen bonds that assist the stereochemistry of the second substituent, whereas the H*N*-alkyl protons were involved in intermolecular hydrogen bonding.

Keywords: 2-aminobenzothiazole; dithiomethylcarboimidate; isothiourea; benzothiazole; guanidine

1. Introduction

The guanidine group has attracted considerable attention since it is found in a wide array of natural and synthetic biologically active compounds [1–3]. The guanidine groups are categorized as organosuperbases whose basicity is magnified because of the resonance stabilization of the corresponding conjugated acids. These molecules are basic enough (pKa of their conjugated acids is around 12.5) to form intermolecular contacts mediated by H-bonding interactions [4]. Its positive charge, resulting from protonation in a wide range of pH values, plays an important role in forming specific intermolecular interactions, comprising key-steps of many biological reactions including enzyme-mediated processes and interaction of hormones with their receptors [5]. The guanidinium

moiety interacts with functional groups present in enzymes or receptors on the basis of hydrogen bonds and electrostatic interactions to form intermolecular associations. Thus, they are useful pharmacophores in medicinal chemistry [6]. Moreover, synthetic guanidines have found wide applications in the engineering of advanced synthetic molecular recognition devices, sensors, organic materials and phase-transfer catalysts [7,8]. Recently, it has been demonstrated that by introduction of chirality in one of the guanidinyl nitrogen atoms [9–11], the resulting chiral guanidines were effective in catalytic [12–15] and stoichiometric asymmetric synthesis [16,17]. Due to this, continued interest has been shown in the transformation of amines into the corresponding guanidines, because the guanidine group, instead of an existing amino group, can significantly increase the potency and/or selectivity of biologically active compounds [18–20].

Typically, the synthesis of guanidine-containing compounds involves the treatment of an amine with an electrophilic amidine species. The most commonly used reagents include cyanamide (**1**) [21], *O*-methylisourea hydrogen sulfate (**2a**) [22], *S*-methyl isothiouronium salts (**2b**) [23–25], pyrazole-1-carboxamidine (**2c**) [26], *N*-protected thiourea (**3a**) [27–29], (*S*-methyl or -aryl)isothiourea (**3b**) [30–33] or pyrazole-1-carboxamidine (**3c**) derivatives [34,35] (Figure 1). To increase yields, new reagents with electron-withdrawing substituents have been developed in the recent years [36,37].

Figure 1. Electrophilic amidine species used to generate guanidines from amines, LG = leaving group.

LG (**1**, **2**) = OMe, **a**; SMe, **b**; Pyrazolyl, **c**   LG (**3**) = SMe, **b**; Pyrazolyl, **c**
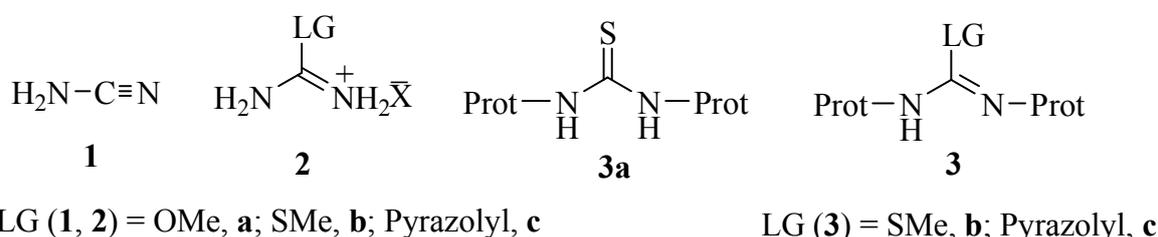
The synthesis of guanidines from thioureas and isothioureas are the most commons strategies used for the construction of the guanidine functionality. In the case of thioureas, they are activated through the reaction with DIC, EDCI, Hg^{2+} (most popular but toxic), 2-chloro-1-methylpyridinium iodide, 2,4-dinitrofluorobenzene, *etc*. Recently, a bismuth catalyst has been found to afford high yields (70%–97%) [38]. The attachment of thiourea groups to a solid phase has been used as precursor of guanidinium groups [39]. Recently, it has been demonstrated that guanylilation of an amine from a thiourea, involves the attack of the amine on what is generally accepted to be a carbodiimide intermediate [40–46].

Diphenylcarbodiimide has been used for the synthesis of diphenylguanidinobenzothiazole [47] and dicyandiamide for the synthesis of 2-guanidinobenzothiazole [48]. However, to the best of our knowledge, there is no reports about non-symmetrical guanidines derived from 2-aminobenzothiazole.

We have reported [49] a detailed study and characterization of the intermediates involved in the synthesis of dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate (**5**), from the reaction of 2-aminobenzothiazole (**4**) with carbon disulfide in basic media, using DMF as solvent [50]. Two molecules of HSMe are displaced when **5** reacts with *o*-XH substituted anilines in refluxing DMF to get NH-bisbenzazoles **7** [51–53] (Scheme 1). We found that the reaction proceeds through the

intermediacy of isothiourea derivatives **6a–c** when *o*-XH anilines are refluxed 16 h in ethanol. Under these conditions, isothiourea **6c** could be isolated and the reaction was extended to *m*- and *p*-phenylenediamines [54]. In the same work, we reported the synthesis of S-methyl-*N*-alkylbenzothiazolyl-isothioureas **8a–d** when ammonia, methylamine, pyrrolidine, aniline and 1,4-piperazine were used (Scheme 2).

Scheme 1. NH-bisbenzazoles from dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate (**5**).
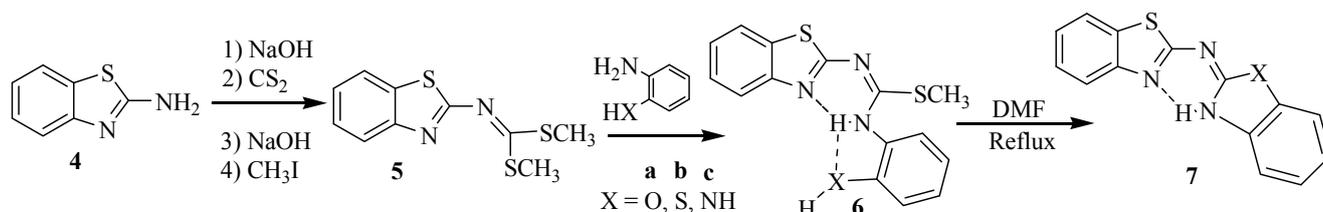
Scheme 2. *S*-methylisothioureas **8**, cyanamides **9** and guanidines **10** derived from 2-aminobenzothiazole **4**, through dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate **5**.
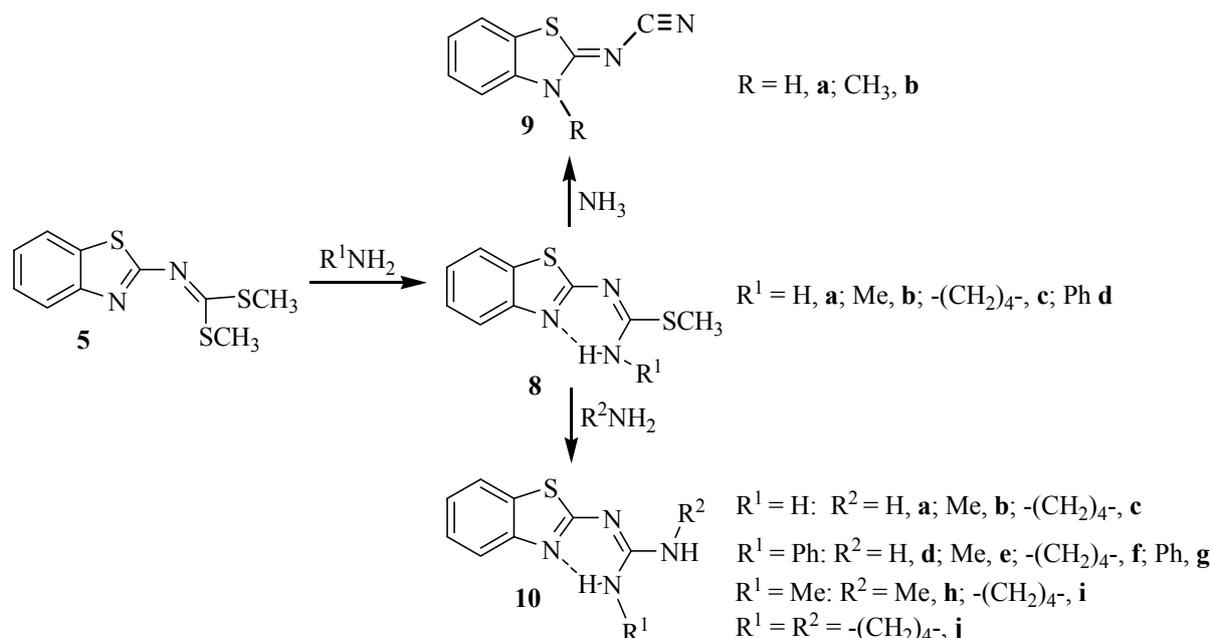
In continuation of this work, we were interested in extending the routes of synthesis of guanidine compounds, in this sense, we generalized this reaction to prepare symmetrical **10g,h,j** and nonsymmetrical **10b–f,i** guanidine derivatives obtained from 2-aminobenzothiazole (**4**, Scheme 2). Herein we report the preparation and ^{1}H and ^{13}C-NMR structural study of a series of guanidines **10b–j**. The isolation of *S*-methylisothiourea intermediates **8** is important since their remaining reactive *S*-methyl group was subsequently substituted by amines to form the guanidine group.

2. Results and Discussion

When dithiocarboimidate **5** reacts with one molar equivalent of ammonia, alkylamine or aniline in ethanol, one molar equivalent of thiomethanol was evolved to afford the corresponding S-methylbenzothiazolyl-isothiourea **8a–d** as isolable intermediates (Scheme 2). Ammonia required

72 h and alkylamine 48 h on stirring at room temperature, to be completed, whereas aniline required 24 h in refluxing ethanol.

The reaction of isothiourea intermediates **8a–d** with a second equivalent of several amines (ammonia, methylamine, aniline and pyrrolidine) was then carried out. When the reaction of isothiourea intermediate **8a** was performed with excess ammonia in refluxing ethanol, 2-cyanamido-benzothiazole **9a** crystallized as the only product in a 62% yield. The X-ray diffraction structure of **9a** is shown in Figure 2, along with a summary of representative distances and angles. The N12-C11 bond length is the shortest N–C bond, its value of 1.155(3) Å is in the characteristic range of a triple bond [55], confirming the presence of the cyano group. In addition, N10-C11 [1.337(3) Å] and N3-C2 [1.338(3) Å] are in agreement with a single bond whereas the shorter N10-C2 [1.311(3) Å] bond length is more appropriate for a double bond character. On the other hand, the X-ray diffraction structure of **9a** shows that the mobile hydrogen atom prefers to stay on the benzothiazole nitrogen because of two intermolecular interactions, N3-H3···N10, stabilize the molecule as a dimer [H3···N10 = 2.01 Å, N3···N10 = 2.866(2) Å, N3-H3···N10 = 174°; symmetry code: –x, –y, 1–z]. In this arrangement, the nitrile group is *cis* positioned to the sulfur atom, thus the electronic conjugation is extended from the benzothiazole system to the nitrile group. The torsion angles S1-C2-N10-C11 [−1.0°(3)] and C11-N10-C2-N3 [178.3°(2)] are in agreement with a planar molecule. The nitrile is a polarized functional group whose interaction with sulfur atom, as Lewis acid, is favored by *cis* configuration [N12···S1 = 3.160(3) Å] and C7-H7···N12 interaction [H7···N12 = 2.677 Å, C7-N12 = 3.343(4) Å, C7-H7···N12 = 138°; symmetry code: 1−x, 1−y, 1−z].

Figure 2. Molecular structure of 2-cyanamidabenzothiazole **9a** (**left**) and hydrogen bonding scheme (**right**). Selected bond lengths (Å) and angles (°): S(1)-C(2) = 1.744(2), N(3)-C(2) = 1.338(3), N(10)-C(2) = 1.311(3), N(10)-C(11) = 1.337(3), N(12)-C(11) = 1.155(3), C(2)-N(10)-C(11) = 118.90(19), S(1)-C(2)-N(3) = 112.59(16), S(1)-C(2)-N(10) = 126.44(18), N(3)-C(2)-N(10) = 121.0(2), S(1)-C(8)-C(9) = 111.40(16), N(3)-C(9)-C(8) = 111.69(19), N(10)-C(11)-N(12) = 174.3(3), C(8)-S(1)-C(2)-N(3) = 0.40(17), C(8)-S(1)-C(2)-N(10) = 179.7(2), S1-C2-N10-C11 = −1.0°(3), C(11)-N(10)-C(2)-N(3) = 178.3(2).
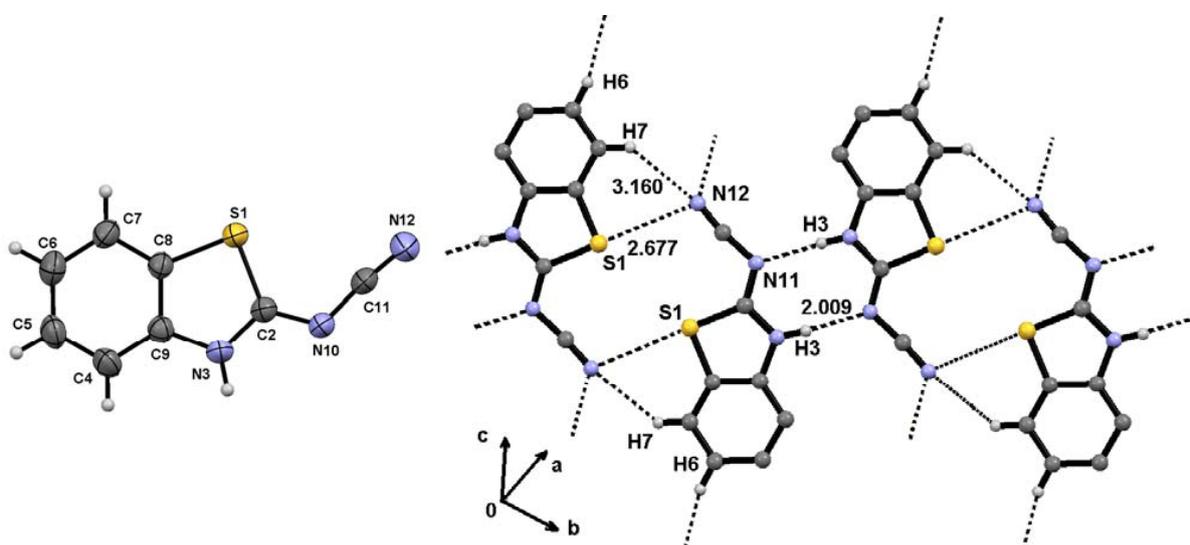
Compound **9a** is formed when *S*-methylisothiourea **8a** suffers HSMe group elimination promoted by the basic media (Scheme 3). The proposed mechanistic pathway involves the participation of NH_4OH to remove one NH hydrogen atom from **8a** to *in situ* form the ammonium intermediate **I**, which is stabilized as the tautomer intermediate **II**. A second molecule of NH_4OH promotes the elimination of the HSMe group to generate the nitrile **9a**. The intermediate **II** was transformed to **8-NMe**, ($\delta = 3.80$ NMe, 2.66 SMe) by reaction with one molar equivalent of NaOH and CH_3I, which is readily transformed into 2-cyanamide-*N*-methylbenzothiazole compound **9b** by a second molar equivalent of NaOH (Scheme 3).

Scheme 3. Thioamidines **II** and **8-NMe** as intermediates in the formation of 2-cyanoimino-benzothiazoles **9a** and **9b**.
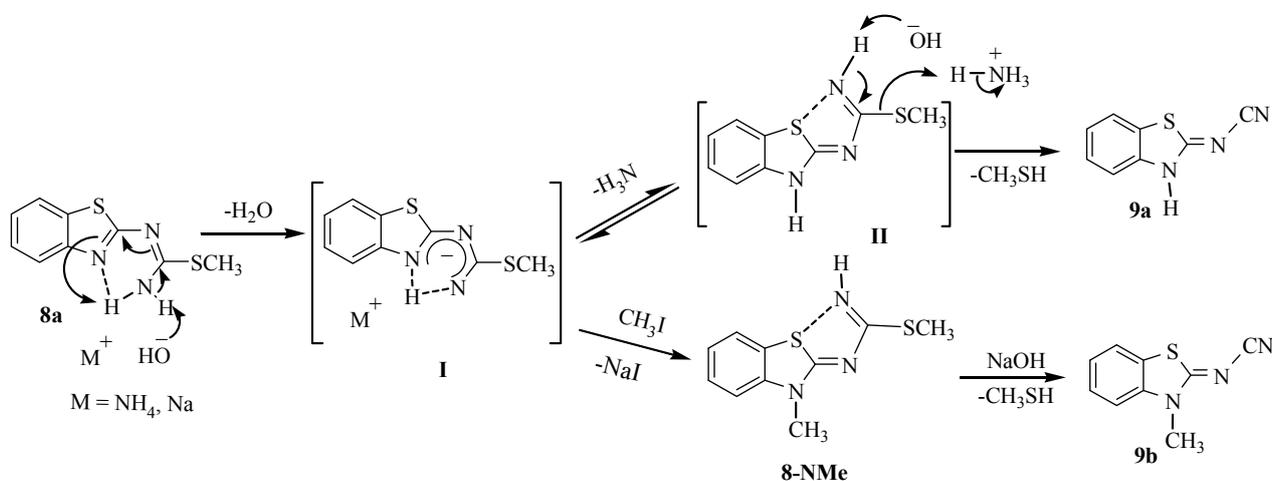
Compound **9a** was characterized in solution by NMR. The nitrile carbon atom appears as a small signal at 117.7 ppm, very similar to the observed value of 118.7 ppm in benzonitrile [56]. The mass spectrometry [M^+ = 175 *m/z* (100%)] and elemental analysis, are in agreement with the proposed structure. Under the same conditions already described for **8a**, isothioureas **8b** and **8c** failed to react with an excess of ammonia to give nonsymmetrical guanidines **10b** and **10c** respectively, and the starting materials were recovered, however, the reaction of isothiourea **8d** with an excess of ammonia, affords the nonsymmetrical guanidine **10d** as the only product. In this case, the acidic aniline hydrogen is intramolecularly engaged with the benzothiazole nitrogen atom. This hydrogen bonding interaction is strong enough to polarize the imine carbon and favors the substitution of the SMe group by ammonia.

On the basis of this result, the reaction of isothiourea **8a** with methylamine and pyrrolidine were carried out to get nonsymmetrical guanidines **10b** and **10c**, after refluxing in ethanol for 4 and 2 days, respectively. The reaction of **8a** with aniline failed to give the corresponding guanidine compound **10d**, even after 4 days in refluxing ethanol. Under these conditions, aniline is not nucleophilic enough to add to the carbodiimide intermediate **II**. The reaction of isothiourea **8b** or **8c** with one molar equivalent of methylamine or pyrrolidine in refluxing ethanol for 8 h afforded the corresponding guanidines **10h,i** or guanidines **10i,j**, respectively. Symmetric guanidines **10h,j** can also be obtained when dithiocarboimidate **5** is reacted with two molar equivalents of the corresponding amine in refluxing ethanol for 8 h.

The reaction of isothiourea **8d** with one molar equivalent of methylamine, pyrrolidine and aniline was tested. After 3 days in refluxing ethanol, the corresponding nonsymmetrical guanidines **10e** and **10f**, were obtained. The reaction with aniline required harsh conditions: refluxing DMF or solventless heating. In the ^{1}H-NMR spectrum of **10g**, only aromatic protons and a broad signal at 12.4 ppm, assigned to the N-H protons, were observed. Moreover, sixteen signals in the ^{13}C-NMR spectrum are indicative of the presence of the 2-*N,N*-diphenyl guanidinebenzothiazole **10g** (Tables 1 and 2). The mass spectrometry data [$M^+ = 344$ *m/z* (19%)] is in agreement with the proposed structure.

Table 1. ^{1}H-NMR chemical shifts of compounds **9a–b**, **10b–j**.
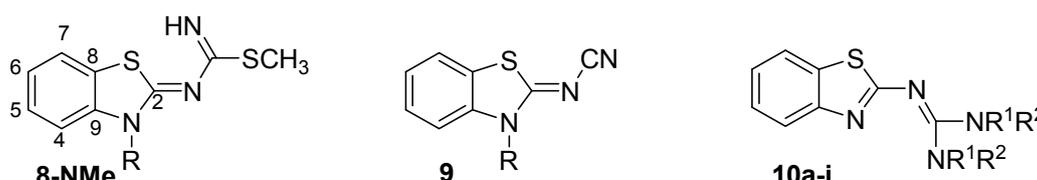
Comp.	H4	H5	H6	H7	NH	NCH$_3$, SCH$_3$	NPh	N(CH$_2$CH$_2$)$_2$
8-NMe [a]	8.00	7.76	7.61	7.46	9.8	3.80, 2.66		
9a [a]	7.75	7.27	7.24	7.39				
9b [b]	7.58	7.46	7.31	7.24		3.62		
10b [a]	7.62	7.21	7.03	7.42	7.7	2.75		
10c [a]	7.63	7.21	7.04	7.44	8.2			3.4, 1.8
10d [b]	7.61	7.30	7.14	7.59			7.4–7.3	
10e [b]	7.69	7.30	7.17	7.63	11.2	2.97	7.5–7.3	
10f [b]	7.66	7.32	7.18	7.63	11.6		7.3–7.1	3.4, 1.8
10g [a]	7.73			7.31	11.9		7.4–7.3	
10h [b]	7.61	7.24	7.10	7.55	9.6	2.92		
10i [b]	7.60	7.26	7.08	7.57	8.9	3.53		3.0, 1.9
10j [b]	7.51	7.20	7.00	7.49				3.4, 1.8

[a] DMSO-d_6; [b] CDCl$_3$.

Table 2. ^{13}C-NMR chemical shift of compounds **9a–b**, **10b–j**, in DMSO-d_6.

Comp.	C2	C4	C5	C6	C7	C8	C9	C11	NCH$_3$, SCH$_3$	Ph
8-NMe [a]	166.0	114.6	124.1	124.6	128.7	126.2	138.5	175.1	33.6, 15.7	
9a [a]	174.0	114.0	123.7	124.4	128.2	125.0	139.4	117.7		
9b [b]	171.5	112.2	122.9	124.8	127.9	123.3	139.4	116.9	31.3	
10b [a]	158.4	125.9	122.3	121.4	118.9	130.9	152.5	174.3	28.3	
10c [a]	155.4	125.9	122.2	121.4	119.0	130.9	152.6	174.4		
10d [b]	156.0	125.7	122.7	122.1	119.6	131.3	151.8	173.7		136.8, 130.2, 125.7, 127.0
10e [b]	154.6	125.6	122.5	121.2	119.5	131.7	151.9	174.5	28.6	137.0, 130.2, 126.9, 126.0
10f [b]	154.4	125.6	122.4	121.1	119.6	132.0	151.9	173.8		139.9, 129.5, 125.6, 123.3
10g [a]	151.5	125.8	121.5	121.3	119.9	132.0	151.0	173.6		137.3, 129.8, 123.6, 123.0
10h [b]	157.2	125.5	122.2	121.0	119.1	131.6	152.2	174.7	28.2	
10i [b]	159.2	125.4	122.0	121.0	119.1	132.1	152.2	173.6	31.5	
10j [b]	158.0	125.2	121.2	121.8	119.1	133.4	153.3	171.3		

N(CH$_2$CH$_2$): 46.9, 25.5 (**10c**); 49.3, 25.6 (**10f**); 49.2, 25.7 (**10i**); 49.6, 25.6 (**10j**). [a] DMSO-d_6; [b] CDCl$_3$.

Comparison of ^{13}C-NMR chemical shifts of guanidine compounds **10** to those of dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate **5**, shows that C2 and C11 are shifted to low frequencies by approximately 10 and 2 ppm, respectively (Table 2). This effect is explained by the extended conjugation of N12 and N13 electron pairs to the benzothiazole ring, increasing the electronic protection of C2 atom. This effect also shifts C7 and C8 to low frequencies by 6 and 3 ppm, respectively. In contrast, C2 is shifted by 6.5 ppm to higher frequencies in 2-aminonitrilebenzothiazole **9a**.

Nonsymmetrical guanidines **10f** and **10i** were crystallized from ethanol; their molecular structures are shown in Figures 3 and 4, respectively. The aniline N-H proton in **10f** is intramolecularly bridged with benzothiazole nitrogen [H17···N3 = 2.13 Å, N17···N3 = 2.697(3) Å, N17-H17···N3 = 123°], forcing the guanidine group to be in the same plane of the benzothiazole ring [N17-C11-N10-C2 = −1.7(3)°] and [N12-C11-N10-C2 = −179.62(17°)]. In addition, two phenyl hydrogen atoms make intermolecular CH···π contacts: H19 with guanidine carbon atom [H19···C11 = 2.792 Å, C19···C11 = 3.684(3) Å, C19-H19···C11 = 160.9°; symmetry code: 1−x, −y, 1−z], and H20 with the π electrons of the benzothiazole aromatic ring [H20···π = 3.130 Å, C20···π = 3.898(3) Å, C20-H20···π = 141.2°, symmetry code: 1−x, −1/2+y, 1/2−z].

Figure 3. Molecular structure of guanidine **10f** (**left**) and intermolecular interactions (**right**). Selected bond lengths (Å) and angles (°): S(1)-C(2) = 1.774(2), N(3)-C(2) = 1.310(3), N(10)-C(2) = 1.354(3), N(10)-C(11) = 1.332(3), N(12)-C(11) = 1.343(3), N(17-C(11) = 1.360 (3), C(2)-N(10)-C(11) = 121.06(17), S(1)-C(2)-N(3) = 114.34(15), S(1)-C(2)-N(10) = 114.72(14), N(3)-C(2)-N(10) = 130.94(18), S(1)-C(8)-C(9) = 109.07(15), N(3)-C(9)-C(8) = 115.67(18), N(10)-C(11)-N(12) = 116.97(17), C(8)-S(1)-C(2)-N(3) = −0.82(16), C(8)-S(1)-C(2)-N(10) = 179.46(15), S1-C2-N10-C11 = −172.69°(15), C(11)-N(10)-C(2)-N(3) = 7.7(3), N(12)-C(11)-N(10)-C(2) = −179.62(17), N(17)-C(11)-N(10)-C(2) = −1.7(3), N(10)-C(11)-N(12)-C(13) = −4.0(3), N(10)-C(11)-N(12)-C(16) = 155.66(19), N(17)-C(11)-N(12)-C(13) = 177.99(19), N(17)-C(11)-N(12)-C(16) = −22.4(3).
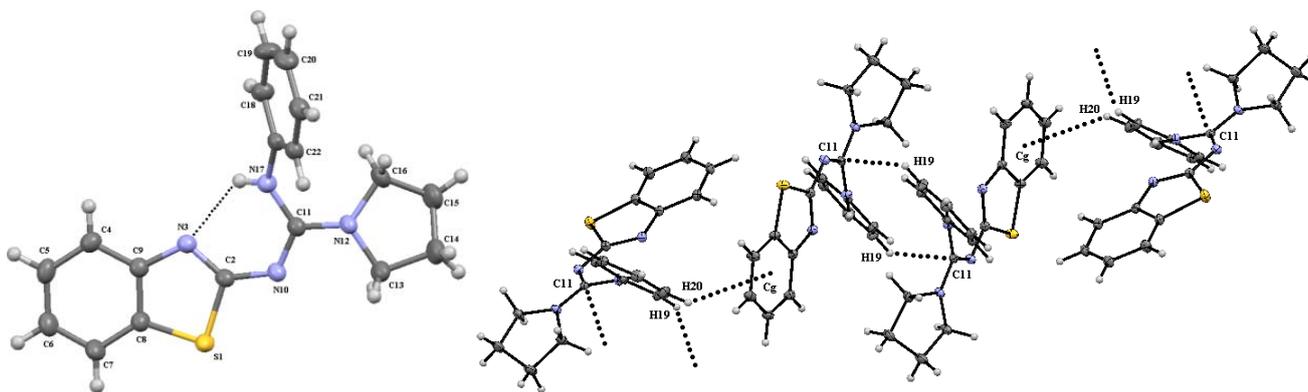
Figure 4. Molecular structure of guanidine **10i** (**left**) and intermolecular interactions (**right**). Selected bond lengths (Å) and angles (°): S(1)-C(2) = 1.779(7), N(3)-C(2) = 1.310(8), N(10)-C(2) = 1.329(9), N(10)-C(11) = 1.332(8), N(12)-C(11) = 1.340(8), N(17)-C(11) = 1.330(7), C(2)-N(10)-C(11) = 122.0(5), S(1)-C(2)-N(3) = 113.4(5), S(1)-C(2)-N(10) = 117.3(5), N(3)-C(2)-N(10) = 129.1(6), S(1)-C(8)-C(9) = 109.9(5), N(3)-C(9)-C(8) = 114.8(5), N(10)-C(11)-N(12) = 123.5(5), C(8)-S(1)-C(2)-N(3) = −1.0(5), C(8)-S(1)-C(2)-N(10) = −176.8(5), S1-C2-N10-C11 = −149.3°(5), C(11)-N(10)-C(2)-N(3) = 35.8(10), N(12)-C(11)-N(10)-C(2) = 39.2(9), N(17)-C(11)-N(10)-C(2) = −144.6(6), N(10)-C(11)-N(12)-C(13) = 13.2(9), N(10)-C(11)-N(12)-C(16) = 177.3(6), N(17)-C(11)-N(12)-C(13) = −163.0(6), N(17)-C(11)-N(12)-C(16) = 1.0(9).
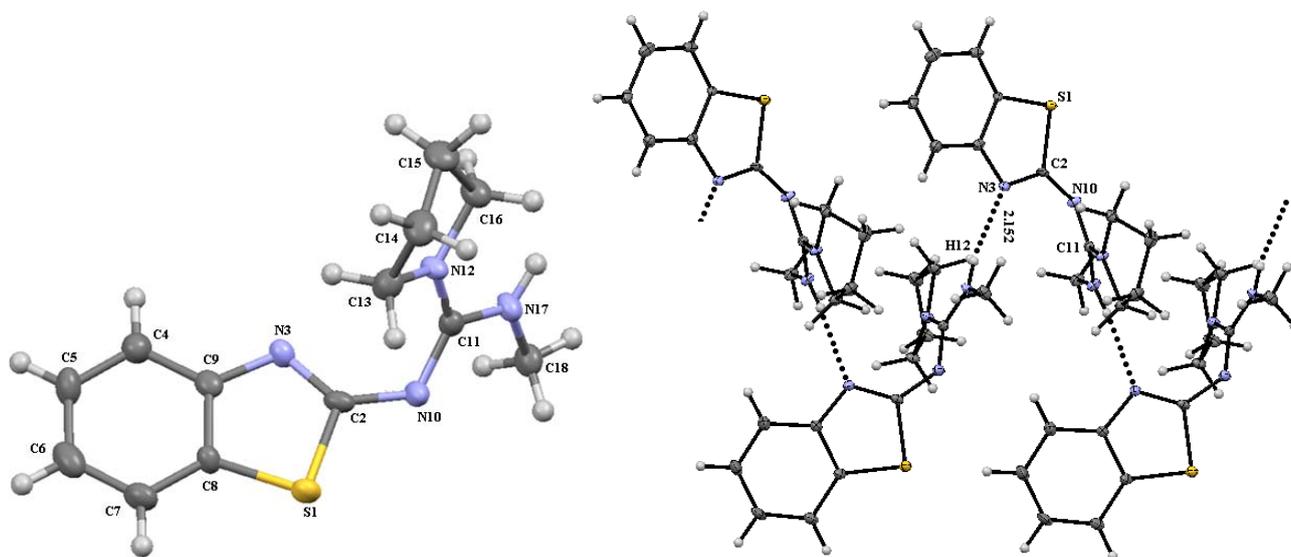
Moreover, in the case of guanidine **10i**, derived from two alkylamines, the conformation is not fixed by intramolecular hydrogen bonding as in **10f**, the methylamine N-H proton is intermolecularly hydrogen bonded with benzothiazole nitrogen of a second molecule and so on to get an helix-like polymer [H17···N23 = 2.16Å, N17···N23 = 2.973(6), N17-H17···N23 =158°; symmetry code: x, y ,z and H37···O3 = 2.19 Å, N37···O3 = 2.997(7) Å, N37-H37···O3 =157°; symmetry code: x, 1−y, z], this forces the plane of the guanidine system approximately 35° out of the benzothiazole mean plane [N17-C11-N10-C2 = −144.6(6)°, N12-C11-N10-C2 = 39.2 (9)°] in agreement with the steric demand of the pyrrolidine moiety.

The proton NMR chemical shift of the NH protons of compounds **10f** and **10i** are in 11.5 and 8.9 ppm respectively. These results show that aniline N-H hydrogen atom of guanidine **10f** is involved in hydrogen bonding in solution whereas the NH of **10i** is not. This result is explained because of, in the case of compound **10f**, the electron pairs of the aniline nitrogen atom are conjugated with the aromatic ring making the NH more acid and thus able for hydrogen bonding. The same effect is observed in the ^{1}H-NMR spectra of the series of non-symmetric guanidines based on aniline derivatives. The NH protons are in 11.2 for **10e**, 11.6 for **10f** and 12.4 for **10g**. This intramolecular interaction, make the benzothiazole ring and the guanidine system to be in the same plane, increasing the electronic protection on C2 atom and, shifting the corresponding ^{13}C-NMR signals by approximately 3 ppm to lower frequencies, in comparison with guanidines without this group, Table 2.

3. Experimental

3.1. General Procedures

Melting points were measured on an Electrothermal IA apparatus and are uncorrected. IR spectra were recorded in a film on ZnSe using a Perkin-Elmer 16F PC IR spectrophotometer. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Mercury 300 MHz (^{1}H, 300.08; ^{13}C, 75.46 MHz). The spectra were measured with tetramethylsilane as internal reference following standard techniques. Physicochemical data is listed in Table 3. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC **10f** (820770), **10i** (820769), and **9a** (820768). A summary of collection and refinement X-ray data are listed in Table 4. For this compound, H atoms were treated as riding atoms, with C–H distances in the range of 0.93–0.96 Å and N-H distances of 0.82 Å. X-ray diffraction cell refinement and data collection: BRUKER SMART APEX Diffractometer and SAINT [57], programs used to solve structures: SHELXS-97 [58], software used to prepare material for publication: PLATON [59] and *WinGX* [60]. 2-Aminobenzothiazole **4** was a commercial product. Dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate **5** was prepared according to a literature procedure [7].

Table 3. Complementary data of the starting materials **4**, **5**, **9a** and guanidines**10b**–**j**.

Comp.	Yield (%)	Physical appearance	M.p. (°C)	υ (cm^{-1})	m/z (%M$^+$)	Elemental analysis Found (calculated)		
						C	H	N
4	SM	White solid	126–129					
5	82	Yellow powder	72–73	509, 1464	254(20)	47.05 (47.24)	3.95 (3.94)	11.13 (11.02)
9a	62	Colorless crystals	198–199	2186, 1600, 1580	175(100)	54.02 (54.85)	3.03 (2.85)	23.73 (24.00)
10b	88	White powder	158–160	3406, 3260, 1624	206(100)	52.14 (52.42)	4.88 (4.85)	27.20 (27.18)
10c	92	White powder	242–244	3395, 3161, 1609, 1547	246(100)	58.13 (58.53)	5.71 (5.69)	22.40 (22.76)
10d	76	White powder	148–150	3436, 3198, 1613, 1568		57.42 (62.68)	4.57 (4.48)	19.05 (20.89)
10e	89	White powder	145–147	3418, 3200, 1597, 1560		63.14 (63.83)	4.98 (4.96)	19.95 (19.86)
10f	90	Colorless crystals	184–186	3395, 3161, 1609, 1547		66.99 (67.08)	5.70 (5.59)	17.72 (17.39)
10g	60	White powder	127–129	3400, 1613, 1580	344(19)	68.19 (69.76)	4.72 (4.65)	16.17 (16.28)
10h	90	Brownish liquid		1602, 1574	220(100)	54.80 (54.54)	5.49 (5.45)	24.24 (25.45)
10i	92	Colorless crystals	136–137	3210, 3080, 1588, 1524		59.63 (60.0)	6.24 (6.15)	21.71 (21.54)
10j	89	Brownish liquid			300(100)	63.2512 (64.00)	5.9812 (6.66)	19.12 (18.66)

Table 4. X-ray crystal data of compounds **10g**, **10i** and **9a**.

Compound	10f	10i	9a
Unit cell information			
Cell axes [Å]**a**	11.3477[13]	14.3400[20]	5.6230[10]
b	9.0463[11]	7.8188[12]	8.2300[9]
c	16.5004[19]	24.1730[40]	17.2290[10]
Cell angles [deg]α	90.000[0]	90.000[0]	90.000[0]
β	101.858[2]	101.858[2]	90.000[0]
γ	90.000[0]	90.000[0]	90.000[0]
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	P 2₁/c	P na2₁	P 2₁/c
Molecular Formula	$C_{18}H_{18}N_4S$	$C_{13}H_{16}N_4S$	$C_8H_5N_3S$
Density [g cm^{-1}]	1.29	1.28	1.46
Formula weight	322.4	520.7	175.2
No. Form. Units Z	4	4	4
Reflection data			
No. Meas.	15334	22566	3406
No. Uniq.	2920	4245	1544
No. Obs.	2630	3049	1278
Current refinement			
No. Reflen.	2920	4245	1544
No. Param.	208	325	110
Delta-rho[eÅ^{-3}]max, min	0.242, −0.280	0.922, −0.272	0.274, −0.283
R_all, R_obs	0.054, 0.049	0.102, 0.073	0.054, 0.049
wR2_all, wR2_aobs	0.125, 0.121	0.189, 0.166	0.127, 0.116

3.2. General Procedure to Get Isothiourea Intermediates **8**

In a 100 mL flask, dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate **5** (1.0 g, 3.94 mmol) was dissolved in ethanol (10 mL), three molar equivalents of ammonia, or one molar equivalent of the respective aliphatic or aromatic amine were added and the mixture was stirred for 72 h, in the case of ammonia, 48 h in the case of alkylamine or pyrrolidine and 24 h in refluxing in the case of aniline to get the corresponding isothiourea compounds.

3.3. General Procedure to Obtain Guanidines **10**

In a 100 mL flask, isothiourea compound **5** (1.0 g, 3.94 mmol) was dissolved in ethanol (10 mL) with one molar equivalent of the corresponding amine and refluxed for 16 h to get guanidines **10b–e**,**g–j** or from carboimidate **5** with 2 molar equivalents of the amine in refluxing ethanol for 16 h, in the case of alkylamines, or refluxing DMF, in the case of aniline, to get the corresponding guanidine compounds **10h**,**j**. The solvent was eliminated by evaporation; the resulting solid was washed with cold ethanol, ketone or chloroform, then dissolved in ethanol and after precipitation or crystallization, filtered and air dried to give a white solid.

4. Conclusions

We have demonstrated the preparation of symmetric and non-symmetric guanidines from the reaction of dimethyl benzo[*d*]thiazol-2-ylcarbonodithioimidate (**5**) and primary or secondary amines in refluxing ethanol, through the displacement of two molecules of HSMe. The reaction proceeds through isothiourea intermediates which, in strongly basic media, are transformed in (*Z*)-2-cyanamidabenzothiazoles. Alkylamines are nucleophilic enough to easily perform both substitutions leading to guanidines, whereas the second substitution with aniline requires harsh conditions. Intramolecular hydrogen bonding between the NH of the aniline group and benzothiazole nitrogen in *S*-methylisothiourea **8d**, leads to a *cis*-disposition between them and thus controlling the stereochemistry of the second substitution. The NH of alkylamines is not acidic enough to form intramolecular hydrogen bonding and intermolecular interactions are found instead. In any case the preferred rotamer observed in the solid state is *trans* to the sulfur atom of benzothiazole ring.

Acknowledgments

References

1. Lednicer, D., Mitscher, L.A., Eds. *The Organic Chemistry of Drugs Synthesis*; Wiley: New York, NY, USA, 1980; Volume II.
2. Mori, A., Cohen, B.D., Lowenthal, A., Eds. *Historical, Biological, Biochemical and Clinical Aspects of the Naturally Occurring Guanidino Compounds*; Plenium: New York, NY, USA, 1985.
3. Berlinck, R.G.S. Some aspects of guanidine secondary metabolites. *Fortschr. Chem. Org. Naturst.* **1995**, *66*, 119–295.
4. Burgess, K., Ed. *Solid-Phase Organic Synthesis*; John Wiley Sons: New York, NY, USA, 2000.
5. Xian, M.; Li, X.; Tang, X.; Chen, X.; Zheng, Z.; Galligan, J.J.; Kreulen, D.L.; Wang, P.G. *N*-Hydroxyl derivatives of guanidine based drugs as enzymatic NO donors. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2377–2380.
6. Durant, G.J. Guanidine derivatives acting at histaminergic receptors. *Chem Soc. Rev.* **1985**, *14*, 375–398.
7. Echavarren, A.; Galan, A.; Lehn, J.M.; De Mendoza, J. Chiral recognition of aromatic carboxylate anions by an optically active abiotic receptor containing a rigid guanidinium binding subunit. *J. Am. Chem. Soc.* **1989**, *111*, 4994–4995.
8. Simoni, D.; Invidiata, F.P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G.P. Facile synthesis of 2-nitroalkanols by tetramethylguanidine (TMG)-catalyzed addition of primary nitroalkanes to aldehydes and alicyclic ketones. *Tetrahedron Lett.* **1997**, *38*, 2749–2752.
9. Isobe, T.; Fukuda, K.; Ishikawa, T. Modified guanidines as potential chiral superbases. 1. Preparation of 1,3-disubstituted 2-iminoimidazolidines and the related guanidines through chloroamidine derivatives. *J. Org. Chem.* **2000**, *65*, 7770–7773.

10. Isobe, T.; Fukuda, K.; Tokunaga, T.; Seki, H.; Yamaguchi, K.; Ishikawa, T. Modified guanidines as potential chiral superbases. 2. Preparation of 1,3-unsubstituted and 1-substituted 2-iminoimidazolidine derivatives and a related guanidine by the 2-chloro-1,3-dimethyl-imidazolinium chloride-induced cyclization of thioureas. *J. Org. Chem*. **2000**, *65*, 7774–7778.

11. Isobe, T.; Fukuda, K.; Yamaguchi, K.; Seki, H.; Tokunaga, T.; Ishikawa, T. Modified guanidines as potential chiral superbases. 3. Preparation of 1,4,6-triazabicyclooctene systems and 1,4-disubstituted 2-iminoimidazolidines by the 2-chloro-1,3-dimethylimidazolinium chloride-induced cyclization of guanidines with a hydroxyethyl substituent. *J. Org. Chem*. **2000**, *65*, 7779–7785.

12. Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. Optical resolution of (±)-1,2-bis(2-methylphenyl)ethylene-1,2-diamine as a chiral framework for 2-iminoimidazolidine with 2-methylphenyl pendant and the guanidine-catalyzed asymmetric Michael reaction of *tert*-butyl diphenyliminoacetate and ethyl acrylate. *J. Org. Chem.* **2008**, *73*, 133–141.

13. Saito, N.; Ryoda, A.; Nakanishi, W.; Kumamoto, T.; Ishikawa, T. Guanidine-catalyzed asymmetric synthesis of 2,2-disubstituted chromane skeletons by intramolecular oxa-Michael addition. *Eur. J. Org. Chem.* **2008**, 2759–2766.

14. Zhang, G.; Kumamoto, T.; Heima, T.; Ishikawa, T. Access to the nicotine system by application of a guanidine-catalyzed asymmetric Michael addition of diphenyliminoacetate with 3-pyridyl vinyl ketone. *Tetrahedron Lett*. **2010**, *51*, 3927–3930.

15. Thai, K.; Gravel, M. Design, synthesis, and application of chiral electron-poor guanidines as hydrogen-bonding catalysts for the Michael reaction. *Tetrahedron: Asymmetry* **2010**, *21*, 751–755.

16. Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. Modified guanidines as chiral superbases: The first example of asymmetric silylation of secondary alcohols. *Chem. Commun*. **2001**, 243–244.

17. Tang, Y.; Li, X.; Lian, C.; Zhu, J.; Deng, J. Synthesis of a water-soluble cationic chiral diamine ligand bearing a diguanidinium and application in asymmetric transfer hydrogenation. *Tetrahedron: Asymmetry* **2011**, *22*, 1530–1535.

18. Baker, T.J.; Luedke, N.W.; Tor, Y.; Goodman, M. Synthesis and Anti-HIV Activity of guanidinoglycosides. *J. Org. Chem*. **2000**, *65*, 9054–9058.

19. Hui, Y.; Ptak, R.; Pallansch, M.; Chang, C.-W.W. Synthesis of novel guanidine incorporated aminoglycosides, guanidinopyranmycins. *Tetrahedron Lett*. **2002**, *43*, 9255–9257.

20. Izdebski, J.; Witkowska, E.; Kunce, D.; Orlowska, A.; Baranowska, B.; Radzikowska, M.; Smoluch, M. New potent hGH-RH analogues with increased resistance to enzymatic degradation. *J. Peptide Sci*. **2002**, *8*, 289–296.

21. Schow, S. Cyanamide. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed.; Wiley: Sussex, UK, 1995; pp. 1408–1410.

22. Palmer, D.C. *O*-Methylisourea. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed.; Wiley: Sussex, UK, 1995; pp. 3525–3526.

23. Bergeron, R.J.; Mcmanis, J.S. Total synthesis of (±)-15-deoxyspergualin. *J. Org. Chem.* **1987**, *52*, 1700–1703.

24. Dumas, D.J. Total synthesis of peramine. *J. Org. Chem*. **1988**, *53*, 4650–4653.

25. Moroni, M.; Kokschy, B.; Osipov, S.N.; Crucianelli, M.; Frigerio, M.; Bravo, P.; Burger, K. First synthesis of totally orthogonal protected α-(trifluoromethyl)- and α-(difluoromethyl)arginines. *J. Org. Chem*. **2001**, *66*, 130–133.

26. Bernatowics, M.S. 1*H*-Pyrazyle-1-carboxamidine Hydrochloride. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.D., Ed.; Wiley: Sussex, UK, 1995; pp. 4343–4344.

27. Linton, B.R.; Carr, A.J.; Orner, B.P.; Hamilton, A.D. A Versatile one-pot synthesis of 1,3-substituted guanidines from carbamoyl isothiocyanates. *J. Org. Chem.* **2000**, *65*, 1566–1568.

28. Manimala, J.C.; Anslyn, E.B. Solid-phase synthesis of guanidinium derivatives from thiourea and isothiourea functionalities. *Eur. J. Org. Chem.* **2002**, *2002*, 3909–3922.

29. Bowser, A.M.; Madalengoitia, J.S. A 1,3-Diaza-Claisen rearrangement that affords guanidines. *Org. Lett.* **2004**, *6*, 3409–3412.

30. McAlpine, I.J.; Armstrong, R.W. Stereoselective synthesis of a tricyclic guanidinium model of cylindrospermopsin. *Tetrahedron Lett.* **2000**, *41*, 1849–1853.

31. Santagada, V.; Fiorino, F.; Severino, B.; Salvadori, S.; Lazarus, L.H.; Bryant, S.D.; Caliendo, G. A convenient synthesis of *N*-Fmoc-*N*,*N'*-bis-Boc-7-guanyl-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (Fmoc-*N*,*N'*-bis-Boc-7-guanyl-Tic-OH, GTIC). *Tetrahedron Lett.* **2001**, *42*, 3507–3509.

32. De Mong, D.E.; Williams, R.M. The asymmetric synthesis of (2*S*,3*R*)-capreomycidine. *Tetrahedron Lett.* **2001**, *42*, 3529–3532.

33. Nagasawa, K.; Koshino, H.; Nakata, T. Stereoselective synthesis of tricyclic guanidine systems: confirmation of the stereochemistry of batzelladine F left-hand tricyclic guanidine portion. *Tetrahedron Lett.* **2001**, *42*, 4155–4158.

34. Ghosh, A.K.; Hol, W.G.J.; Fan, E. Solid-phase synthesis of *N*-acyl-*N'*-alkyl/aryl disubstituted guanidines. *J. Org. Chem.* **2001**, *66*, 2161–2164.

35. Powell, D.A.; Phillip, D.; Ramsden, P.D.; Batey, R.A. Phase-transfer-catalyzed alkylation of guanidines by alkyl halides under biphasic conditions: A convenient protocol for the synthesis of highly functionalized guanidines. *J. Org. Chem.* **2003**, *68*, 2300–2309.

36. Yong, Y.F.; Kowalski, J.A.; Lipton, M.A. A new reagent for solid and solution phase synthesis of protected guanidines from amines. *Tetrahedron Lett.* **1999**, *40*, 53–56.

37. Gers, T.; Kunce, D.; Markowski, P.; Izdebski, J. Reagents for efficient conversion of amines to protected guanidines. *Synthesis* **2004**, 37–42.

38. Cunha, S.; Rodriguez, M.T., Jr. The first bismuth(III)-catalyzed guanylation of thioureas. *Tetrahedron Lett.* **2006**, *47*, 6955–6956.

39. Porcheddu, A.; Giacomelli, G.; Chinghine, A.; Masala, S. New cellulose-supported reagent: A sustainable approach to guanidines. *Org. Lett.* **2004**, *6*, 4925–4927.

40. Deprez, P.; Vevert, J.P. Efficient two-step syntheses of sulfonylguanidines from sulfonamides. *Synth. Commun.* **1996**, *26*, 4299–4310.

41. Levallet, C.; Lerpiniere, J.; Ko, S.Y. The HgCl₂-promoted guanylation reaction: The scope and limitations. *Tetrahedron* **1997**, *53*, 5291–5304.

42. Atwal, K.S.; Ahmed, S.Z.; O'Reilly, B.C. A facile synthesis of cyanoguanidines from thioureas. *Tetrahedron Lett.* **1989**, *30*, 7313–7316.

43. Wilson, L.J.; Klopfenstein, S.R.; Li, M. A traceless linker approach to the solid phase synthesis of substituted guanidines utilizing a novel acyl isothiocyanate resin. *Tetrahedron Lett.* **1999**, *40*, 3999–4002.

44. Wang, H.; Ye, C.; Jin, H.; Liu, J.; Wu, J. An expeditious approach to 1-(isoquinolin-1-yl)guanidines via a three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, with carbodiimide. *Tetrahedron* **2011**, *67*, 5871–5877.

45. Zhang, X.; Wang, C.; Qian, C.; Han, F.; Xu, F.; Shen, Q. Heterobimetallic dianionic guanidinate complexes of lanthanide and lithium: Highly efficient precatalysts for catalytic addition of amines to carbodiimides to synthesize guanidines. *Tetrahedron* **2011**, *67*, 8790–8799.

46. Li, J.; Zhang, G.; Zhang, Z.; Fan, E. TFA-sensitive arylsulfonylthiourea-assisted synthesis of *N,N′*-substituted guanidines. *J. Org. Chem.* **2003**, *68*, 1611–1614.

47. Kurser, F.; Sanderson, P.M. Thiadiazoles. Part X. The synthesis and isomerisation of 2-aryl-5-arylamino-3-arylimino-Δ^4-1,2,4-thiadiazolines. *J. Chem. Soc.* **1960**, 3240–3249.

48. Weiss, V.S.; Kromer, H.; Prietzel, H. Uber 2-benzthiazolyl-guanidin: Biologische Wirksamkeit und verbessertes Dartellungsverfharen. *Chemiker-Zeit.* **1975**, *99*, 291, and references cited therein.

49. Téllez, F.; Cruz, A.; López-Sandoval, H.; Ramos-García, I.; Gayosso, M.; Castillo-Sierra, R.N.; Paz-Michel, B.; Nöth, H.; Flores-Parra, A.; Contreras, R. Dithiocarbamates, thiocarbamic esters, dithiocarboimidates, guanidines, thioureas, isothioureas, and tetraazathiapentalene derived from 2-aminobenzothiazole. *Eur. J. Org. Chem.* **2004**, 4203–4214.

50. Merchan, F.L.; Garín, J.; Meléndez, E. A facile synthesis of dimethyl *N*-(2-benzothiazolyl)-dithiocarbonimidates and methyl *N*-(2-benzothiazolyl)-dithiocarbamates. *Synthesis* *1982*, 590–591.

51. Garín, J.; Meléndez, E.; Merchan, F.L.; Ortíz, D.; Tejero, T. 2-(2-Benzimidazolylamino-benzothiazoles and 2-(2-imidazolidinylidenamino)-benzothiazoles. *Synthesis* **1982**, 1066–1067.

52. Garín, J.; Meléndez, E.; Merchan, F.L.; Ortíz, D.; Tejero, T. A facile synthesis of 8-arylamino- and 8-hetarylaminopurines and their 1- and 3-deaza analogs. *Synthesis* **1985**, 867–869.

53. Merchan, F.L.; Garín, J.; Meléndez, E.; Tejero, T. A facile synthesis of 2-(2-benzothiazolylamino)-1,3-heterazoles. *Synthesis* **1987**, 368–370.

54. Cruz, A.; Padilla-Martínez, I.I.; García-Báez, E.V.; Juárez, M.J. *S*-Methyl-(-*N*-aryl and -*N*-alkyl)isothioureas derived from 2-aminobenzothiazole. *ARKIVOC* **2008**, *V*, 200–209.

55. Allen, F.H.; Kenard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylos, R. Tables of bond lengths determined by X-ray and neutron diffraction. Part 1. Bond lenghts in organic compounds. *J. Chem. Soc. Perkin Trans. II* **1987**, S1–S19.

56. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. Typical Interatomic Distances: Organic Compounds. In *International Tables for Crystallography*; Wilson, A.J.C., Ed.; The International Union of Crystallography, Kluwer Academic Publishers: Dordrecht, The Netherlands, 1992; Volume C, p. 685.

57. Bruker. *SMART and SAINT*, Versions 6.02a; Bruker AXS Inc.: Madison, WI, USA, 2000.

58. Sheldrick, G.M. *SHELXS97 and SHELXL97*; University of Göttingen: Göttingen, Germany, 1997.

59. Spek, A.L. *PLATON*, Version of March 2002; University of Utrecht: Heidelberglaan, The Netherlands, 2002.

60. Farrugia, L.J. WinGX suite for small molecule single crystal crystallography. *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

Sample Availability: Samples of the compounds **10f** and **10i** are available from the authors.