Isothioureas, Ureas, and Their N-Methyl Amides from 2-Aminobenzothiazole and Chiral Amino Acids

Itzia I. Padilla-Martínez, José Miguel González-Encarnación, Efrén V. García-Báez, Alejandro Cruz and Ángel Andrés Ramos-Organillo

1 Instituto Politécnico Nacional-UPIBI, Laboratorio de Química Supramolecular y Nanociencias, Av. Acueducto s/n, Barrio la Laguna Ticomán 07340, México City, Mexico; ipadillamar@ipn.mx (I.I.P.-M.); jos3miguelgiez@gmail.com (J.M.G.-E.); efren1003@yahoo.com.mx (E.V.G.-B.)
2 Facultad de Ciencias Químicas, Universidad de Colima, Km 9 Carr. Colima-Coquimatlán, Coquimatlán 28400, Colima, Mexico; aaramos@ucol.mx

Correspondence: alcralmx@hotmail.com; Tel.: +52-555-729-6000 (ext. 56323)

Academic Editor: Sven Mangelinckx
Received: 15 August 2019; Accepted: 10 September 2019; Published: 18 September 2019

Abstract: In this investigation, the reaction of 2-dithiomethylcarboimidatebenzothiazole with a series of six chiral amino acids was studied. The reaction proceeds through the isolable sodium salt of SMe-isothiourea carboxylates as intermediates, whose reaction with methyl iodide in stirring DMF affords SMe-isothiourea methyl esters. The presence of water in the reaction leads to the corresponding urea carboxylates as isolable intermediates, whose methyl esters were obtained. Finally, the urea N-methyl amide derivatives were isolated when SMe-isothiourea or urea methyl esters were reacted with methylamine in the presence of water. The structures of synthesized compounds were established by 1H and 13C nuclear magnetic resonance and the structures of SMe-isothiourea methyl esters derived from (l)-glycine, (l)-alanine, (l)-phenylglycine, and (l)-leucine, by X-ray diffraction analysis. This methodology allows to functionalize 2-aminobenzothiazole with SMe-isothiourea, urea, and methylamide groups derived from chiral amino acids to get benzothiazole derivatives containing coordination sites and hydrogen bonding groups. Further research on the biological activities of some of these derivatives is ongoing.

Keywords: 2-aminobenzothiazole; 2-dithiomethylcarboimidatebenzothiazole; α-amino-acids; S-methyl-isothioureas; urea-carboxylate methyl esters and urea N-methyl amides

1. Introduction

Benzothiazole is an aromatic bicyclic ring system that consists of a thiazole ring fused with a benzene ring. The benzothiazole moiety is small but a very interesting compound with wide biological activities. At the beginning of the 1970s, it was found that benzothiazole derivatives possessed pharmacological antiviral [1–3], antibacterial [3–6], antimicrobial [7–9], fungicidal [10,11], antiallergic [12–14], antidiabetic [15–17], antitumoral [18–21], anti-inflammatory [22,23] and anthelmintic [24–26] activities.

A continuous interest in this class of compounds follows nowadays and numerous efforts to synthesize new biologically active heterocyclic compounds derived from the benzothiazole moiety have been made in the last 50 years. Several of these derivatives were found to possess anticonvulsant [27–29] and antioxidant [30–32] activities. In this context, some results related to molecules containing benzothiazole nuclei in medicinal chemistry have been summarized elsewhere [33,34].

On the other hand, guanidines are an important class of compounds that are found widely throughout nature and as biologically active synthetic compounds, and several uses in organic chemistry are known [35–38]. For example, the natural amino acid arginine has a guanidine group as
side chain, whilst cimetidine, a synthetic guanidine-derived compound, was the first drug used to treat peptic ulcers.

Typically, the reaction of amines with thioureas [39] or isothioureas [40–42] is the most commonly used method to obtain guanidines. Particularly, the isothiourea group has been bonded to a solid phase as precursor of guanidines [43]. In the last decade, it has been recognized that isothioureas can also serve as remarkably potent inhibitors for a range of enzymatic systems [44–46]. On the other hand, inhibition of nitric oxide synthase (NOS) has led to their use in the treatment of a range of life-threatening conditions, including septic shock, acute kidney failure, and rejection after transplantation surgery [47].

In this sense, we report a synthetic way to prepare symmetrical and nonsymmetrical guanidines 4 derived from 2-aminobenzothiazole 1 by the reaction of 2-dithiomethylcarboimidatebenzothiazole 2 with primary amines in refluxing ethanol [48]. The reaction proceeds through the formation of SMe-isothioureas 3, as intermediates, and the displacement of two MeSH molecules [49], Scheme 1.

![Scheme 1](attachment:Scheme1.png)

**Scheme 1.** Dithiomethylcarboimidatebenzothiazole 2, SMe-isothioureas 3 and guanidines 4 starting from 2-aminobenzothiazole 1.

In this contribution, we applied this methodology in the reaction of 2 with a series of chiral amino acids to form the corresponding SMe-isothiourea carboxylates 5, which were further transformed into the corresponding isourea carboxylates 6, methyl ester derivatives 8–10 and 12, and isourea amides 11, and 13. This methodology allows the functionalization of 2-aminobenzothiazole to introduce groups such as isothioureas, isoureas ureas, amides, and guanidines derived from chiral amino acids. These functional groups give properties such as coordinating sites, hydrogen bonding interactions, and water solubility, among others, required for the interaction with biomolecules. The reactions were carried out without modification of the chiral center configuration and all compounds were optically pure isolated as shown in the analyzed X-ray structures of compounds 8b,c and 9f.

2. Results and Discussion

2.1. Reactions and Characterization

Six amino acids Aa–f were tested: glycine (R = H, a), (l)-alanine (R = Me, b), (l)-phenylglycine (R = Ph, c), (l)-phenylalanine (R = Bn, d), (l)-valine (R = tPr, e), and (l)-leucine (R = tBu, f), represented as the zwitterions Ba–f. Each amino acid was transformed in situ into the corresponding sodium carboxylate Ca–f by reaction with one molar equivalent of sodium hydroxide in stirring ethanol for 2 h at room temperature, Scheme 2.

![Scheme 2](attachment:Scheme2.png)

**Scheme 2.** Generation of sodium carboxylates C from neutral amino acids A.

The reaction of one molar equivalent of 2-dithiomethylcarboimidatebenzothiazole 2 with the corresponding amino-acid carboxylates Ca–f at refluxing ethanol for eight hours was carried out. In these conditions, the reaction proceeds by nucleophilic attack of the amino group of the amino-carboxylates C to the carbonimidothioate group of compound 2, with elimination of
were carried out using anhydrous ethanol and stirring for 4 days at room temperature to avoid
proportion with respect to the aromatic hydrogen atoms. In the

| \( 5c \) |
| \( 5a-f \) |
| \( 8a-f \) |
| \( 9e,f,HI \) |
| \( 10a-f \) |
| \( 11a-f \) |
| \( 12e.f \) |
| \( 13e,f \) |

Scheme 3. Synthesis of SMe-isothiourea carboxylates \( 5a-f \), isourea-carboxylates \( 6a-f \), their corresponding methyl esters \( 8a-f \), \( 9e,f,10a-f \), and \( 12e,f \), isourea-amides \( 11a-f \) and urea-amides \( 13e,f \) derived from benzothiazole and amino acids.

In the case of the reaction of compound \( 2 \) with valine- \( (Ce, \ R = \ ^{1}Pr) \) or leucine- \( (Cf, \ R = \ ^{1}Bu) \) carboxylates, an insoluble yellowish solid appeared in the reaction mixture, which was identified as compound \( 7 \). The \( ^{1}H \) NMR spectrum shows two singlets at 2.6 ppm (SMe) and 3.9 (NMe) each in a 3:4 proportion with respect to the aromatic hydrogen atoms. In the \( ^{13}C \) NMR spectrum, the signals for SMe, NMe, and the thiocarbonyl group at 18.6, 33.7, and 208.7 ppm, respectively, appeared. To explain these results, a sigmatropic rearrangement of compound \( 2 \) to form compound \( 7 \) in 15% yield is proposed, as depicted in Scheme 3, in agreement with \( ^{1}H \) and \( ^{13}C \) NMR data.

Isorea carboxylate compound \( 6c \) was isolated as byproduct in 20% yield, from the remaining mother liquors of \( 5c \). No signal for the SMe group was present in the NMR spectra of compound \( 6c \), but two interchangeable protons with deuterium were observed at 11.8 ppm, corresponding to the isourea OH, and at 8.3 ppm, attributed to the urea NH. \( ^{1}H \) and \( ^{13}C \) NMR spectroscopic data of compound \( 6c \) are listed in Tables S5 and S6, respectively. The substitution of the remaining SMe group in compound \( 5c \) by one molecule of water afforded compound \( 6c \) as one of the two possible tautomers, Table S5.

To improve the yields of the sodium salt of SMe-isotiourea carboxylates \( 5b-f \), the reactions were carried out using anhydrous ethanol and stirring for 4 days at room temperature to avoid
hydrolysis. In these conditions, the reaction proceeds more slowly to afford the corresponding SMe-isothiourea-carboxylates 5b–f in 62–95% yields. On the other hand, the complete hydrolysis of SMe-isothiourea-carboxylates 5b–f in a refluxing mixture of ethanol:water 1:1 was carried out. In these conditions, the second thiometanol gas molecule was eliminated to afford the corresponding isourea-carboxylates 6b–e as the only products in 65–75% yields. The hydrolysis of compound 5a required more drastic conditions such as refluxing in DMF/H2O mixtures to obtain 6a in 40% yield.

![Scheme 4. Sygmatropic rearrangement of compound 2. The numbers on the atoms are the 1H and 13C chemical shifts in CDCl3.](image)

The corresponding SMe-isothiourea carboxylate methyl esters 8a–d were obtained in 56–83% yields after the methylation of carboxylates 5a–d with one molar equivalent of methyl iodide in DMF as solvent, whose 1H and 13C NMR chemical shifts are listed in Tables S7 and S8, respectively. In general, their spectra are very similar compared to the corresponding carboxylates 5a–d, except for the OMe group signals which are in the 3.75–3.83 and 45–53 ppm ranges in 1H and 13C NMR spectra, respectively. The 13C NMR data of esters 8c,d in CDCl3 show broad signals for C2, C9, and C11, suggesting that the usually fast proton exchange between N3 and N12 through tautomeric equilibria becomes slower because of the steric effects of the phenyl and benzyl moieties from the amino-acid residue.

The use of one equivalent of iodomethane in the reaction of SMe-isothiourea-carboxylates 5e or 5f, afforded the respective methyl esters 8e (49% yield) or 8f (51% yield) in mixture with the corresponding N3-Me methyl esters 9e (8% yield) or 9f (25% yield) and their hydroiodides 9e-HI or 9f-HI. Compound 5f was reacted with two molar equivalents of CH3I; however, compounds 8f and 9f-HI remained. This last compound precipitated from the reaction mixture and was separated for further analysis. A 1H and 13C chemical shifts comparison between compounds 9e, 9f-HI, and 9f is depicted in Figure 1. The characteristic 1H (13C) NMR signals of 9f-HI, are the SMe group at δ 3.1 (18.3), N–Me at 3.8 (56.5), and N–H at 9.1 ppm. The high frequency shift of the NH suggests a hydrogen bonding interaction with the sulfur atom and/or with the carbonyl oxygen atom, Figure 1. The nitrogen atom of the N–Me group on the benzothiazole produces an electronic effect on C4 of the aromatic ring, shifting it to low frequencies: 114.1 ppm for 9f-HI and ≈ 110 ppm for 9e and 9f.

![Figure 1. 1H and 13C NMR data in CDCl3 of compounds 9e, 9f-HI, and 9f.](image)

The isourea-carboxylates 6a–d can also be methylated to afford the isourea methyl esters 10a–d in 30–90% yields, Scheme 3. However, the methylation reaction of the sodium salts of isourea-carboxylates 6e or 6f afforded the corresponding methyl esters 10e (66%) or 10f (54%) in mixture with their N–Me esters 12e (24%) or 12f (21%). 1H and 13C NMR data of compounds 10a–f are listed in Tables S9 and S10, respectively, and those of urea-methyl esters 12e and 12f are depicted in Figure 2.
Isourea carboxylate methyl esters 10a–f or 12e,f were reacted with methylamine to afford their corresponding isourea amides 11a–f or urea-amides 13e,f in 60–97% yield or 20% and 46% yields, respectively. The $^1$H and $^{13}$C NMR spectra of compounds 11a–f are listed in Tables S11 and S12 and those of compounds 13e,f are depicted in Figure 2. The $^1$H NMR spectrum of isourea-amides 11a–f show three deuterium labile hydrogen atoms in the 8.4–10.9, 7.0–10.6, and 7.1–8.1 ppm ranges, as well as the characteristic doublet in 2.5–3.0 ppm range for the NHMe group. The C4 NMR frequencies were found at approximately 110 ppm in both NMe esters 12e,f and their amides 13e,f. The 10 ppm shift to low frequencies compared with their NH analogues $^{13}$e were reacted with methylamine to a complex mixture of several methylated compounds. The reaction of compounds $^{13}$e or urea-amides $^{13}$e,f was due to the electronic effect of the NHMe group on C4. In compounds 13e and 13f, the urea NH appears as a doublet at 5.9 ($^3J = 9.3$ Hz) and 5.7 ppm ($^3J = 8.2$ Hz); and the amide NH appears at lower frequency as a quartet at 6.6 ($^3J = 4.4$ Hz) and 6.4 ppm ($^3J = 4.7$ Hz), respectively.

Isothiourea carboxylate methyl esters 8a–f contain both SMe and OMe groups, which are susceptible to substitution with nucleophiles such as methylamine. The reaction of compounds 8a with one molar equivalent of methylamine produces a complex mixture of several methylated compounds. However, in the presence of an excess of methylamine, the isourea-amide compound 11a precipitated as a white solid. In these conditions, the SMe group was substituted because of the formation of MeNH$_2$OH in aqueous medium. The last procedure was also used with the urea methyl esters 8b–f and 9e,f to obtain compounds 11b–f and 13e,f in 45–60% yields.

2.2. Molecular Structure of Compounds 8a–c and 9f

The SMe-isothiourea methyl esters (S)-8a–c and (S)-9f were purified by crystallization from ethanol and suitable crystals for X-ray diffraction analysis were isolated. The molecular structures of compounds 8a and 8c, displayed in Figures 3 and 4, show that the N12H is engaged in intramolecular three-centered hydrogen bonding interaction with the benzothiazole nitrogen and carbonyl oxygen atoms. The distances and angles associated with this N3--H12--O14 interaction are N12H--N3 = 2.01 Å, 132° (8a) and 2.03 Å, 132° (8c); N12H--O14 = 2.31 Å, 107° (8a) and 2.21 Å, 111° (8c), forming the corresponding adjacent six (S6) and five (S5)-membered rings. This hydrogen bonding interaction fixes the stereochemistry of the imine N10--C11 bond and only the (E) isomer of 8a and 8c was produced. In addition, the lateral side chain is almost in the same plane of the benzothiazole, including the carbon atoms of both OMe and SMe groups. In general, the SMe group is the most deviated from the mean plane [N(10)-C(11)-S(23)-C(24) = 6.18(1)°] compared with the OMe group [O(14)-C(14)-O(15)-C(16) = 1.48(1)°].

![Figure 2. $^1$H and $^{13}$C NMR data in CDCl$_3$ of urea carboxylate methyl esters 12e, 12f, and their corresponding urea NMe amides 13e, 13f.](image-url)
In the structure of compound (S)-8b, displayed in Figure 5, only the intramolecular hydrogen bonding interaction with benzothiazole nitrogen atom was observed, N12H···N3 (2.06 Å, 133°), forming the corresponding six-membered ring (S6). Therefore, the isothiourea group is in the same plane of the benzothiazole, including the chiral carbon atom, N(10)-C(11)-N(12)-C(13) −178.71(1)° and S(23)-C(11)-N(12)-C(13) 0.16(1)°. In this case, the carbon atom of the SMe group is deviated from the benzothiazole ring planes, N(10)-C(11)-S(23)-C(24) = 5.19(1)° and the carboxylate group is almost perpendicular to the plane of the molecule C(14)-(C(13)-N(12)-C(11) = −85.82(1).

**Figure 3.** X-ray diffraction structure of compound 8a. Bond lengths (Å): S(1)-C(2) 1.7624(1), S(1)-C(8) 1.7342(1), S(23)-C(11) 1.7599(1), S(23)-C(24) 1.7927(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.3855(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.301(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1), N(3)-C(2) 1.3115(1), N(3)-C(9) 1.3855(1), N(3)-C(9) 1.3621(1), N(10)-C(2) 1.372(3), N(10)-C(11) 1.306(3), N(12)-C(11) 1.3308(1), N(12)-C(13) 1.4402(1).
The first interaction causes both exocyclic nitrogen atoms to be almost in the plane of the ring. The second interaction is between the exocyclic nitrogen atom and the carbonyl carbon atom, which results in a deviation of the nitrogen atom from the plane of the ring. The structure of compound 9f is displayed in Figure 6. Two intramolecular noncovalent bonding interactions were observed, one of them is that of N14 with benzothiazole sulfur atom, S···N14 (2.68 Å), the other of S12 with carbonyl carbon atom S12···C16 (3.125 Å), forming in both cases a five-membered ring. The first interaction causes both exocyclic nitrogen atoms to be almost in the plane of the ring.
same plane of the benzothiazole rings, including the chiral carbon and methylene carbon atoms of the isobutyl group. The SMe group is approximately 10° deviated from the mean plane, S12-C11-N10-C2 −169.8(4) compared with a small deviation of N10 [N10-C2-N3-C23 −3.6(7)] and C11 [S1-C2-N10-C11 2.1(7)]. The second interaction maintain the C=O and the isopropyl groups to be opposite each other deviated from the mean plane C16-C15-N14-C11 −70.1(5) and N14-C15-C19-C20 −66.1(6), respectively. Intermediate bond lengths values between single and double character for C2-N3 [1.330(5) Å], C2-N10 [1.309(6) Å], N10-C11 [1.369(5) Å], whereas double bond for C11-N14 [1.283(6) Å] and single bond for N14-C15 [1.461(6) Å] were observed.

3. Materials and Methods

Melting points were measured on an IA 9100 apparatus (Electrothermal, Staffordshire, UK) and are uncorrected. IR spectra were recorded using a 3100 FT-IR Excalibur Series spectrophotometer (Varian, Randolph, MA, USA) equipped with an ATR system. Mass spectra were obtained in a 3900-GC/MS system (Varian, Palo Alto, CA, USA) with an electron ionization mode. Elemental analyses (EA) were performed on a 2400 elemental analyzer (Perkin-Elmer, Waltham, MA, USA). 1H- and 13C-NMR spectra were recorded on a Varian Mercury 300 (1H, 300.08; 13C, 75.46 MHz) instrument in DMSO-d6 solutions for compounds 5a–f and 6a–f, and CDCl3 in solutions for compounds 8a–f, 9a–f, 10a–f, 11a–f, 12e–f, and 13e–f. SiMe4 was used as the internal reference. Chemical shifts are in ppm and 1J(H-H) in hertz.

Crystals suitable for X-ray analysis of 8a, 8b, 8c, and 9f were obtained after solvent evaporation from saturated ethanol solutions. Single-crystal X-ray diffraction data were recorded on a D8 Quest CMOS (Bruker, Karlsruhe, Germany) or Nonius Kappa (Rotterdam, the Netherlands) area detector diffractometers with Mo Kα radiation, λ = 0.71073 Å. A table listing the crystallographic data is provided as Supplementary Material in Table S2. The structures were solved by direct methods using SHELXS97 [50] program of WinGX package [51]. The final refinement was performed by full-matrix least-squares methods on F2 with SHELXL97 [50] program. The program Mercury was used for visualization, molecular graphics, and analysis of crystal structures [52]. The software used to prepare material for publication was PLATON [53]. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC numbers 1949131 (8a), 1949129 (8b), 1413575 (8c) and 1949130 (9f). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-01-223-336-033 or E-Mail: deposit@ccdc.cam.ac.uk).

3.1. Experimental Section

2-Aminobenzothiazole 1, CS2, iodomethane, glycine, (l)-alanine, (l)-phenyl-glycine, (l)-phenylalanine, (l)-valine, (l)-leucine, DMF, ethyl alcohol and NaOH were commercial products, which were used as received. Yields, physical appearances, melting points, IR frequencies, and elemental analysis of compound 5a–f and 8a–f are listed in Table S1.

3.2. General Method for Isothiourea Carboxylates 5a–f

Amino acid (3.94 mmol), NaOH (3.94 mmol), and 15 mL of ethanol were added into a 100 mL round flask and the mixture was stirred for 2 h at room temperature. Then, compound 2 (1.0 g, 3.94 mmol) was added and the mixture was stirred for additional 96 h at room temperature.

3.2.1. Sodium (E)-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Acetate 5a

As a general method, starting from 0.295 g of glycine, compound 5a precipitated from the reaction mixture, ethanol was eliminated, the resulting mixture was cooled to room temperature and 10 mL of acetone were added, the resulting suspension was filtered and washed with cold acetone, obtaining 5a.3H2O as a cream color powder (1.14 g, 82%); mp = 220 °C (dc).
3.2.2. Sodium (S,E)-(+)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Propionate 5b

As a general method, starting from 0.35 g of l-alanine, ethanol was evaporated from the homogeneous reaction mixture, the resulting gummy product was dissolved in 10 mL of acetone and filtered, acetone was eliminated and a transparent yellowish ionic liquid compound 5b\(\cdot\)\(\text{H}_2\text{O}\) was obtained (1.08 g, 78%), which resulted to be soluble in chloroform.

3.2.3. Sodium (R,E)-(+)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Phenyl-Acetate 5c

As a general method, starting from 0.594 g of l-phenylglycine, ethanol was eliminated from the reaction mixture and then suspended in acetone (10 mL). The suspension was filtered and the remaining solid washed with cold acetone and dried to obtain a white powder (1.29 g, 86%).

3.2.4. Sodium (S,E)-(−)-2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-3-Phenyl-Propionate 5d

As a general method, starting from 0.650 g of l-phenylalanine, from the same procedure as 5b, compound 5d was obtained as brownish liquid (1.26 g, 81%).

3.2.5. Sodium (S,E)-(−)-2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-3-Methyl-Butanonate 5e

As a general method, starting from 0.673 g of l-valine, from the same procedure as 5b, compound 5e was obtained as clear liquid (1.09 g, 80%).

3.2.6. Sodium (S,E)-(−)-2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-4-Methyl-Pentanonate 5f

As a general method, starting from 0.516 g of l-leucine, from the same procedure as 5b compound 5f was obtained as yellowish liquid (1.17 g, 81%).

3.3. General Method for Isourea Carboxylates 6a–f

Starting from isourea carboxylates 5a–f (3.0 mmol), 10 mL of ethanol and 10 mL of water were added into a 100 mL round flask and the mixture was refluxed for 72 h. For isourea 5a, DMF was used instead of ethanol. The solvent was evaporated from the reaction mixture and the residue suspended in acetone, the suspension was cooled and filtered, the precipitate was washed with acetone and dried. In the hydrolysis of isoureas 5e,f, the reaction mixture was filtered and the solvents were evaporated. 5 mL of acetone were added and 50 mL of CHCl\(_3\) were slowly added, the mixture was stirred until a beige solid precipitates, which was filtered and washed with CHCl\(_3\) to get 6e,f.

3.3.1. Sodium (3-Benzothiazol-2-Yl-Isoureido)-Acetate 6a

0.32 g, 40% yield; white powder; mp = 210 °C (dc).

3.3.2. Sodium 2-(3-Benzothiazol-2-Yl-Isoureido)-Propionate 6b

White powder; 0.6 g, 70% yield; mp = 205 °C (dc).

3.3.3. Sodium (3-Benzothiazol-2-Yl-Isoureido)-Phenyl-Acetate 6c

White powder; 0.75 g, 72% yield; mp = 250 °C (dc).

3.3.4. Sodium 2-(3-Benzothiazol-2-Yl-Isoureido)-3-Phenyl-Propionate 6d

White powder; 0.81 g, 75% yield; mp = 149–150 °C.

3.3.5. Sodium 2-(3-Benzothiazol-2-Yl-Isoureido)-3-Methyl-Buturate 6e

White powder; 0.61 g, 65% yield; mp = 199–201 °C.
3.3.6. Sodium 2-(3-Benzothiazol-2-Yl-Isoureido)-4-Methyl-Pentanonate 6f
White powder; 0.69 g, 70% yield; mp = 201–203 °C.

3.4. General Method for SMe-Isothiourea Carboxylate Methyl Esters 8a–f and 9e,f or Isourea Carboxylate Methyl Esters 10a–f and Urea Methyl Ester 12e,f

In a 100 mL round flask, 3.0 mmol of the corresponding isothiourea carboxylate 5a–f or urea carboxylate 6a–f were dissolved in DMF (10 mL), methyl iodide (3.5 mmol) were added and the mixture was stirred for 12 h on an ice bath and then 12 h at room temperature. At the end of the reaction, 50 mL of water were added and the corresponding ester was extracted with CHCl₃. Chloroform was eliminated and the O-methyl compounds were purified by crystallization in ethanol. Compounds 9e or 9f were separated from 8e or 8f by crystallization from their ethanol mixture. Compounds 12e or 12f were separated from 10e or 10f using a chloroform/acetone 10:1 mixture in a silica gel chromatography column. 12e and 12f were precipitated from hexane.

3.4.1. (E)-2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Acetic Acid Methyl Ester 8a
White crystals; 0.73 g, 83% yield; mp = 145–146 °C.

3.4.2. (S,E)-(+-)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Propionic Acid Methyl Ester 8b
White crystals; 0.74 g, 80% yield; mp = 100–101 °C.

3.4.3. (S,E)-(+-)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-Phenyl-Acetic Acid Methyl Ester 8c
White crystals; 0.83 g, 75% yield; mp = 133–134 °C.

3.4.4. (S,E)-(−)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-3-Phenyl-Propionic Acid Methyl Ester 8d
White crystals; 0.64 g, 56% yield; mp = 84–85 °C.

3.4.5. (S,E)-(−)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-3-Methyl-Butanoic Acid Methyl Ester 8e
Viscous liquid; 0.49 g, 49% yield.

3.4.6. (S,E)-(−)2-(3-Benzothiazol-2-Yl-2-Methyl-Isothioureido)-4-Methyl-Pentanonic Acid Methyl Ester 8f
Viscous liquid; 0.53 g, 51% yield.

3.4.7. 3-Methyl-2-[2-Methyl-3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Isothioureido]-Butyric Acid Methyl Ester 9e
White crystals; 0.084 g, 8% yield; mp = 163–164 °C; MS: M + H = 352.1 (79.1%).

3.4.8. 4-Methyl-2-[2-Methyl-3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Isothioureido]-Pentanoic Acid Methyl Ester 9f
White crystals; 0.27 g, 25% yield; mp = 177–178 °C; MS: M + H = 366.0 (80.1%).

3.4.9. (3-Benzothiazol-2-Yl-Isoureido)-Acetic Acid Methyl Ester 10a
White powder; 0.65 g, 82% yield; mp = 170–180 °C; MS: M + H = 266.06 (85%).

3.4.10. 2-(3-Benzothiazol-2-Yl-Isoureido)-Propionic Acid Methyl Ester 10b
White powder; 0.68 g, 86% yield; mp = 149–150 °C; MS: M + H = 280.07 (85.6%).
3.4.11. (3-Benzothiazol-2-Yl-Isoureido)-Phenyl-Acetic Acid Methyl Ester 10c
White powder; 0.73 g, 72% yield; mp = 112–114 °C; MS: M + H = 342.1 (83.1%).

3.4.12. 2-(3-Benzothiazol-2-Yl-Isoureido)-3-Phenyl-Propionic Acid Methyl Ester 10d
White powder; 0.32 g, 30% yield, 70–71 °C (mp), MS: M + H = 356.1 (80.6%).

3.4.13. 2-(3-Benzothiazol-2-Yl-Isoureido)-3-Methyl-Butyric Acid Methyl Ester 10e
Viscous liquid; 0.6 g, 66% yield; MS: M + H = 308.1 (82.7%).

3.4.14. 2-(3-Benzothiazol-2-Yl-Isoureido)-4-Methyl-Pentanoic Acid Methyl Ester 10f
Viscous liquid; 0.52 g, 54% yield; MS: M + H = 321.0 (84.1%).

3.4.15. 3-Methyl-2-[3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Ureido]-Butyric Acid Methyl Ester 12e
White powder; 0.23 g, 24% yield; mp = 100–101 °C; MS: M + H = 322.1 (83%).

3.4.16. 4-Methyl-2-[3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Ureido]-Pentanoic Acid Methyl Ester 12f
White powder; 0.21 g, 21% yield; mp = 87–89 °C; MS: M + H = 336.1 (82%).

3.5. General Method for Isourea Amides 11a–f or Urea-Amides 13e,f
In a 100 mL round flask, 3.00 mmol of the corresponding isourea carboxylate methyl esters 10a-f or urea methyl esters 12e,f were dissolved in ethanol (10 mL), methyl amine 40% in water (3.5 mmol) were added and the mixture was refluxed for 24 h. At the end of the reaction, the precipitate was filtered and washed with plenty of acetone.

3.5.1. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-Acetamide 11a
White powder; 0.63 g, 80% yield; mp = 260–270 °C (dc); MS: M + H = 265.1 (82.1%).

3.5.2. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-Propionamide 11b
White powder; 0.81 g, 97% yield; mp = 250–260 °C (dc), MS: M + H = 279.09 (84.8%).

3.5.3. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-2-Phenyl-Acetamide 11c
White powder; 0.98 g, 96% yield; mp = 270–290 °C (dc); MS: M + H = 341.1 (77.9%).

3.5.4. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-3-Phenyl-Propionamide 11d
White powder; 1.06 g, 93% yield, mp = 270–280 °C (dc); MS: M + H = 355.1 (77.5%).

3.5.5. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-3-Methyl-Butiramide 11e
White powder; 0.55 g, 60% yield; mp = 205–207 °C (dc), MS: M + H = 307.12 (80.1%).

3.5.6. 2-[3-(3H-Benzothiazol-2-Ylidene)-Ureido]-N-Methyl-4-Methyl-Pentylamide 11f
White powder; 0.6 g, 63% yield; mp = 138–140 °C; MS: M + H = 321.1 (76.1%).

3.5.7. 3,N-Dimethyl-2-[3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Ureido]-Butiramide 13e
White powder; 0.2 g, 20% yield; mp = 205–206 °C; MS: M + H = 321.1 (79.1%).

3.5.8. 4-Methyl-2-[3-(3-Methyl-3H-Benzothiazol-2-Ylidene)-Ureido]-Pentanoic Acid Methylamide 13f
White powder; 0.46 g, 46% yield; mp = 210–212 °C, MS: M + H = 335.1 (79.9%).
4. Conclusions

A six sodium salt series of isothiourea-carboxylate benzothiazoles 5a–f, as well as their methyl ester derivatives 8a–f, were obtained in moderate to good yields by the reaction of dimethylcarbonimidate benzothiazole 2 with sodium salts of glycine, (l)-alanine, (l)-phenylglycine, (l)-phenylalanine, (l)-valine, and (l)-leucine in stirring ethanol at room temperature and further methylation under mild conditions. The reaction is stereo selective, only the E-isomer was isolated, the X-ray structure of (R,E)-methyl-2-((benzothiazol-2-ylmino)(methyl-thio)methylamino)-2-phenylacetate 8c confirmed the stereochemistry of the reaction. The structures of 8a and 8c are stabilized by three center hydrogen bonding interactions N3···H1–O14 between the amino N12H12 with the nitrogen atom of benzothiazole ring and the oxygen atom of the carbonyl group, forming two intramolecular adjacent S(6) and S(5) rings, respectively. This finding suggests the stereochemical assistance of the reaction by hydrogen bonding. When the same reactions were carried out in the presence of water, the urea-carboxylate benzothiazoles 6a–f were obtained. Their further methylation produced the corresponding methyl esters 10a–f. In the methylation reaction of sodium isothiourea-carboxylates 5e,f and urea-carboxylates 6e,f, the corresponding N3Me methyl esters 9e,f and 12e,f were produced as byproducts, which were isolated. Methyl esters 8a–f or 10a–f and 9e,f or 12e,f were used as starting materials to produce the corresponding urea carboximides 11a–f and 13e,f by the reaction with methyl amine. Further studies on the synthesis of chiral guanidines from SMe-isothioureas 8 are in progress.

Supplementary Materials: The following are available online. Table S1. Complementary data of SMe-isothiourea carboxylates 5a–f and their methyl esters 8a–f. Table S2. X-ray crystal data of compounds 8a, 8b, 8c and 9f. Table S3. 1H NMR data of compounds 5a–f (DMSO-d6). Table S4. 13CNMR data of compounds 5a–f (DMSO-d6). Table S5. 1H NMR data of compounds 6a–f (DMSO-d6). Table S6. 13CNMR data of compounds 6a–f (DMSO-d6). Table S7. 1HNMR data of compounds 8a–d (CDCl3). Table S8. 13C NMR data of compounds 8a–d (CDCl3). Table S9. 1H NMR data of compounds 10a–f (CDCl3). Table S10. 13CNMR data of compounds 10a–f (CDCl3). Table S11. 13C NMR data of compounds 11a–f (CDCl3). Table S12. 13C NMR data of compounds 11a–f (CDCl3).

Author Contributions: Research, A.C. and J.M.G.-E.; original draft preparation, writing-review and editing, A.C.

Funding: This research received no external funding.

Acknowledgments: A. Cruz thanks Secretaria de Investigación y Posgrado del IPN (SIP-IPN) for financial support, Grants 20180754 and 20196686 and COTEBAL-IPN as well as CONACYT, México for the sabbatical study financial support (2018–2019).

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Borthwick, A.D.; Davies, D.E.; Ertl, P.F.; Exall, A.M.; Haley, T.M.; Hart, G.J.; Jackson, D.L.; Parry, N.R.; Patikis, A.; Trivedi, N.; et al. Design and synthesis of pyrrolidine-5,5′-trans-lactams (5-oxo-hexahydropyrrolo [3, 2-b] pyrroles) as novel mechanism-based inhibitors of human cytomegalovirus protease. 4. Antiviral activity and plasma stability. J. Med. Chem. 2003, 46, 4428–4449. [CrossRef] [PubMed]
2. Akhtar, T.; Hameed, S.; Al-Masoudi, N.A.; Loddo, R.; La Colla, P. In vitro antitumor and antiviral activities of new benzothiazoles and 1,3,4-oxadiazole-2-tione derivatives. Acta Pharm. 2008, 58, 135–149. [CrossRef] [PubMed]
3. Ke, S.; Wei, Y.; Ziwen, Y.; Wang, K.; Liang, Y.; Shi, L. Novel cycloalkylthiophene-imine derivatives bearing benzothiazole scaffold: Synthesis, characterization and antiviral activity evaluation. Bioorg. Med. Chem. Lett. 2013, 23, 5131–5134. [CrossRef] [PubMed]
4. Haydon, D.J.; Stokes, N.R.; Ure, R.; Galbraith, G.; Bennett, J.M.; Brown, D.R.; Baker, P.J.; Barynin, V.V.; Rice, D.W.; Sedelnikova, S.E.; et al. An inhibitor of FtsZ with potent and selective anti-staphylococcal activity. Science 2008, 321, 1673–1675. [CrossRef] [PubMed]
5. Saeed, A.; Rafique, H.; Hameed, A.; Rasheed, S. Synthesis and antibacterial activity of some new 1-aroyl-3-(substituted-2-benzothiazolyl)thio-ureas. Pharm. Chem. J. 2008, 42, 191–195.
6. Haydon, D.J.; Bennett, J.M.; Brown, D.; Collins, I.; Galbraith, G.; Lancett, P.; Macdonald, R.; Stokes, N.R.; Pramod, K.; Chauhan, J.K.S.; et al. Creating an antibacterial with in vivo efficacy: Synthesis and characterization of potent inhibitors of the bacterial cell division protein FtsZ with improved pharmaceutical properties. J. Med. Chem. 2010, 53, 3927–3936. [CrossRef] [PubMed]

7. Scheich, C.; Puetter, V.; Schade, M. Novel small molecule inhibitors of MDR mycobacterium tuberculosis by NMR fragment screening of antigen 85C. J. Med. Chem. 2010, 53, 8362–8367. [CrossRef] [PubMed]

8. Singh, M.K.; Tilak, R.; Nath, G.; Awasthi, S.K.; Agarwal, A. Design, synthesis and antimicrobial activity of novel benzothiazole analogs. Eur. J. Med. Chem. 2013, 63, 635–644. [CrossRef]

9. Singh, M.; Gangwar, M.; Nath, G.; Singh, S.K. Synthesis, DNA cleavage and antimicrobial activity of 4-thiazolidinones-benzothiazole conjugates. Indian J. Exp. Biol. 2014, 52, 1062–1070.

10. Mittal, S.; Samota, M.K.; Kaur, J.; Seth, G.; Mittal, S.; Samota, M.K.; Kaur, J.; Seth, G. Synthesis, spectral, and antifungal evaluation of phosphorylated and thiophosphorylated benzothiazole derivatives. Phosphorus Sulfur 2007, 182, 2105–2113. [CrossRef]

11. Huang, W.; Yang, G.-F. Microwave-assisted, one-pot syntheses and fungicidal activity of polyfluorinated 2-benzylthiobenzothiazoles. Bioorg. Med. Chem. 2006, 14, 8280–8285. [CrossRef] [PubMed]

12. Yevich, J.P.; Temple, D.L.; Covington, R.R.; Owens, D.A.; Seidehamel, R.J.; Dungan, K.W. Antiallergics: 3-(1H-Tetrazol-5-yl)-4H-pyrimido[2,1-b]benzo-thiazol-4-ones. J. Med. Chem. 1982, 25, 864–868. [CrossRef] [PubMed]

13. Musser, J.H.; Brown, R.E.; Love, B.; Baily, K.; Jones, H.; Kahen, R. Synthesis of 2-(2,3-dihydro-2-oxo-1,3,4-oxadiazol-5-yl)benzo heterocycles. A novel series of orally active antiallergic agents. J. Med. Chem. 1984, 27, 121–125. [CrossRef] [PubMed]

14. Ager, I.R.; Barnes, A.C.; Danswan, G.W.; Hairsinse, P.W.; Kay, D.P.; Kennewell, P.D.; Matharu, S.S.; Miller, P.; Robson, P. Synthesis and oral antiallergic activity of carboxylic acids derived from imidazo[2,1-c][1,4]benzoxazines, imidazo[1,2-a]quinolines, imidazo[1,2-a]quinoxalines, imidazo[1,2-a]quinoxalinones, pyrrolo[1,2-a]quinoloxalines, pyrrolo[2,3-a]quinoloxalines, and imidazo[2,1-b]benzothiazoles. J. Med. Chem. 1988, 31, 1098–1115. [PubMed]

15. Pattan, S.R.; Suresh, C.; Pajar, V.D.; Reddy, V.V.K.; Rasai, V.P.; Kotti, B.C. Synthesis and antidiabetic activity of 2-amino [5'(4-sulphonylbenzylidine)-2,4-thiazolidinedione]-7-chloro-6-fluorobenzothiazole. Indian J. Chem. 2005, 44, 2404–2408.

16. Moreno-Diaz, H.; Villalobos-Molina, R.; Ortiz-Andrade, R.; Díaz-Coutiño, D.; Medina-Franco, J.L.; Webster, S.P.; Binnie, M.; Estrada-Soto, S.; Ibarra-Barajas, M.; León-Rivera, I.; et al. Antidiabetic activity of N-(6-substituted-1,3-benzothiazol-2-yl)benzenesulphonamides. Bioorg. Med. Chem. Lett. 2008, 18, 2871–2877. [CrossRef] [PubMed]

17. Mariappan, G.; Prabhat, P.; Sutharson, L.; Banerjee, J.; Patangia, U.; Nath, S. Synthesis and antidiabetic evaluation of benzothiazole derivatives. J. Korean Chem. Soc. 2012, 56, 251–256. [CrossRef]

18. Yan, Y.; Xie, X.; Zhu, N.; Liu, G. Benzothiazoles exhibit broad-spectrum antitumor activity: Their potency structure-activity and structure-metabolism relationships. Eur. J. Med. Chem. 2014, 76, 67–78.

19. Gabr, M.T.; El-Gohary, N.S.; El-Bendary, E.R.; El-Kerdawy, M.M. Synthesis and in vitro antitumor activity of new series of benzothiazole and pyrimido[2,1-b]benzothiazole derivatives. Eur. J. Med. Chem. 2014, 85, 576–592. [CrossRef]

20. Gabr, M.T.; El-Gohary, N.S.; El-Bendary, E.R. El-Kerdawy, M.M. New series of benzothiazole and pyrimido[2,1-b]benzothiazole derivatives: Synthesis, antitumor activity, EGFR tyrosine kinase inhibitory activity and molecular modeling studies. Med. Chem. Res. 2015, 24, 860–878. [CrossRef]

21. Yurttas, L.; Tay, F.; Demirayak, S. Synthesis and antitumor activity evaluation of new 2-(4-amino-phenyl)benzothiazole derivatives bearing different heterocyclic ring. J. Enzyme Inhib. Med. Chem. 2015, 30, 458–465. [PubMed]

22. Paramashivappa, R.; Kumar, P.P.; Rao, S.P.V.; Rao, S. Design, synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. Bioorg. Med. Chem. Lett. 2003, 13, 657–660. [PubMed]

23. Deshmukh, V.K.; Raviprasad, P.; Kulkarni, P.A.; Kuberkar, S.V. Design, synthesis and biological activities of novel 4H-pyrimido [2,1-b][1,3] benzothiazole derivatives. Int. J. Chem. Tech. Res. 2011, 3, 136–142.

24. Munirajasekhar, D.; Himaja, M.; Sunil, V.M. Synthesis and anthelmintic activity of 2-amino-6-substituted benzothiazoles. Int. Res. J. Pharm. 2011, 2, 114–117.
25. Suresh, C.H.; Rao, J.V.; Jayaveera, K.N.; Subudhi, S.K. Synthesis and anthelmintic activity of 3-(2-hydrazinobenzothiazoles)-substituted indole-2-one. Int. Res. J. Pharm. 2011, 2, 257–261.

26. Balaji, P.N.; Ranganyakulu, D.; Yadav, K.R.; Jayamma, J.; Kumar, S.; Sivaramaiah, C. Anthelmintic and anti-microbial activities of synthesized heterocyclic pyrazole and its derivatives from fluoro substituted hydrazino benzothiazole. Int. J. Pharm. Tech. Res. 2014, 6, 1970–1975.

27. Reddy, D.R.S.; Raparla, L.P.; Pradeep, K.; Ahmed, S.M.; Sindhura, J. Synthesis, analytical characterization, antimicrobial, anti-oxidant and anti-convulsant evaluation of some novel 6-fluorobenzothiazole substituted pyrazole analogues. Int. J. Pharm. Chem. 2013, 3, 72–81.

28. Joseph, J.; Janaki, G.B. Synthesis, structural characterization and biological studies of copper complexes with 2-aminobenzothiazole derivatives. J. Mater. Environ. Sci. 2014, 5, 693–704. [CrossRef]

29. Fen, R.; Christian, S. Antioxidant potential of novel 2-(4-amino-2-arylaminothiazol-5-oyl) benzothiazoles. Int. J. Pharm. Sci. 2014, 5, 74–79.

30. Yadav, A.G.; Patil, V.N.; Asrondkar, A.L.; Naik, A.A.; Ansulkar, P.V.; Bobade, A.S.; Chowdhary, A.S. Anti-oxidant and anti-microbial activities of pyrazolyl-benzothiazole derivatives using Vilsmeier-Haack reaction. Rayazan J. Chem. 2012, 5, 117–120.

31. Nessim, M.I.; Ahmed, M.H.M.; Ali, A.M.B.; Salem, A.A.; Attia, S.K. The effect of some benzothiazole derivatives as antioxidants for base stock. Int. J. Curr. Res. 2013, 5, 111–1113.

32. Choudhary, S.; Kini, S.G.; Mubeen, M. Antioxidant activity of novel coumarin substituted benzothiazole derivatives. Der. Pharm. Chem. 2013, 5, 213–222.

33. Raju, G.N.; Karumudi, B.S.; Rao, N.R. Benzothiazole-Versatile heterocyclic nucleus in medicinal chemistry: A review. Int. J. Pharm. Chem. 2015, 5, 104–114.

34. Keri, R.S.; Patil, M.R.; Patil, S.A.; Budagumpi, S. A comprehensive review in current developments of benzothiazole based molecules in medicinal chemistry. Eur. J. Med. Chem. 2015, 89, 207–251. [CrossRef] [PubMed]

35. Coles, M.P. Bicyclic-guanidines, -guanidinates and -guanidinium salts: Wide ranging applications from a simple family of molecules. Chem. Commun. 2009, 3659–3676.

36. Ishikawa, T. Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts; Johon Wiley and Sons Ltd.: Chippenham, UK, 2009.

37. Berlinck, R.G.S.; Burtoloso, A.C.B.; Trindade-Silva, A.E.; Romminger, S.; Morais, R.P.; Bandeira, K.; Mizuno, C.M. The chemistry and biology of organic guanidine derivatives. Nat. Prod. Rep. 2010, 27, 1871–1907. [PubMed]

38. Fu, X.; Tan, C.-H. Mechanistic considerations of guanidine-catalyzed reactions. Chem. Commun. 2011, 47, 8210–8222.

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

40. Liu, F.; Lu, G.-Y.; He, W.-J.; Hu, J.; Mei, Y.-H.; Zhu, L.-G. Synthesis of calix[4]arene derivatives with alkyl guanidinium or chiral bicyclic guanidinium. Synthesis 2001, 607–611.

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

42. Ibatullin, F.M.; Selivanov, S.I.; Shavva, A.G. A General procedure for conversion of s-glycosyl isothiourea derivatives into thioglycosides, thioligosaccharides and glycosyl thioesters. Synthesis 2001, 419–422. [CrossRef]

43. Porcheddu, A.; Giacomelli, G.; Chinghine, A.; Masala, S. New cellulose-supported reagent: A sustainable approach to guanidines. Org. Lett. 2004, 6, 4925–4927. [CrossRef] [PubMed]

44. Garvey, E.P.; Oplinger, J.A.; Tanoury, G.J.; Sherman, P.A.; Fowler, M.; Marshall, S.; Harmon, M.F.; Paith, J.E.; Furfine, E.S. Potent and selective inhibition of human nitric oxide synthases. Inhibition by non-amine acid isothioureas. J. Biol. Chem. 1994, 269, 26669–26676. [PubMed]

45. Di Giacomo, C.; Sorrenti, V.; Salerno, L.; Cardile, V.; Guerrera, F.; Siracusa, M.A.; Avitabile, M.; Vanella, A. Novel inhibitors of neuronal nitric oxide synthase. Exp. Biol. Med. 2003, 228, 486–490.

46. Harusawaa, S.; Sawada, K.; Magata, T.; Yoneyama, H.; Araki, L.; Usami, Y.; Hatano, K.; Yamamoto, K.; Yamamoto, D.; Yamatodani, A. Synthesis and evaluation of N-alkyl-S-[3-(piperidin-1-yl)propyl]isothioureas: High affinity and human/rat species-selective histamine H3 receptor antagonists. Bioorg. Med. Chem. Lett. 2013, 23, 6415–6420. [CrossRef] [PubMed]
47. Paesano, N.; Marzocco, S.; Vidiomini, C.; Carmela, S.; Autore, G.; De Martino, G.; Sbardella, G. Synthesis and biological evaluation of 3-benzyl-1-methyl- and 1-methyl-3-phenyl-isothioureas as potential inhibitors of iNOS. *Bioorg. Med. Chem. Lett.* 2005, 15, 539–543. [PubMed]

48. Cruz, A.; Padilla-Martínez, I.I.; García-Báez, E. A synthetic method to access symmetric and non-symmetric 2-(N,N'-disubstituted)guanidinebenzothiazoles. *Molecules* 2012, 17, 10178–10191.

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

50. Sheldrick, G.M. A short history of SHELX. *Acta Cryst.* 2008, 64, 112–122.

51. Farrugia, L.J. WinGX suite for small-molecule single-crystal crystallography. *J. Appl. Crystallogr.* 1999, 32, 837–838. [CrossRef]

52. Macrae, C.F.; Edgington, P.R.; McCabe, P.; Pidcock, E.; Shields, G.P.; Taylor, R.; Towler, M.; van de Streek, J. Mercury: Visualization and analysis of crystal structures. *J. Appl. Crystallogr.* 2006, 39, 453–457. [CrossRef]

53. Spek, A.L. Single-crystal structure validation with the program PLATON. *J. Appl. Crystallogr.* 2003, 36, 7–13. [CrossRef]

**Sample Availability:** Samples of the compounds are available from the authors.