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Communication

Synthesis of the Guanidine Derivative: *N*-{[(7-(4,5-Dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene)amino](phenylamino)methylene}benzamide

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Abstract: The guanidine derivative *N*-{[(7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene)amino](phenylamino)methylene}benzamide (**3**) has been obtained by the reaction of one measure of *N*-{[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene]carbamothioyl}benzamide (**2**) with one measure of aniline in the presence of mercury(II) chloride and triethylamine in anhydrous dimethylformamide. The structure of product **3** was confirmed by ^{1}H and ^{13}C-NMR, infrared spectroscopy, and elemental analysis.

Keywords: guanidine derivative; imidazoline derivative; imidazo-triazole derivative

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1. Introduction

The guanidine scaffold is present in an impressive number of naturally occurring compounds with a broad range of biological activities [1–3]. The considerable number of papers dealing with the synthesis and applications of guanidine derivatives over the past decades shows their great importance in the field of chemistry and medicine. Thus, the guanidine frame is utilized in clinically used marketed drugs as depicted in Figure 1. For instance, guanidine is present in streptomycin and was recently developed for the treatment of influenza neuraminidase inhibitors-zanamivir, peramivir. The use of debrisoquine, guanethidine, guanabenz, and guanadrel in the treatment of hypertension is well established. Other examples of medically used guanidine derivatives include the histamine receptor antagonists cimetidine and famotidine, which are frequently used in the treatment of heartburn and peptic ulcers. Metformin is an example of an orally administered antihyperglycemic agent from the biguanide class used in the treatment of type 2 diabetes, whereas amiloride is a potassium-sparing diuretic used to treat high blood pressure. Iobenguane, an aryl-alkyl-guanidine analog of noradrenaline, is commonly used as a radio(^{131}I)-labelled pharmaceutical in medicinal diagnostic techniques or as an antineoplastic agent [4]. In addition, this moiety constitutes a promising lead structure suitable for the development of potential chemotherapeutic agents [5–7]. Of special interest are their anticancer properties [8], which may be correlated with a caspase-3/7 activation [9] or interference with the kinase MAPK/ERK pathway [10]. It should be noted that synthetic guanidine-methylglyoxal-bis(guanylhydrazone), known as mitoguazone (CAS No. 459-86-9) induces cell apoptosis and has the potential use in acute leukemia, as well as Hodgkin's and non-Hodgkin's lymphoma, treatment.

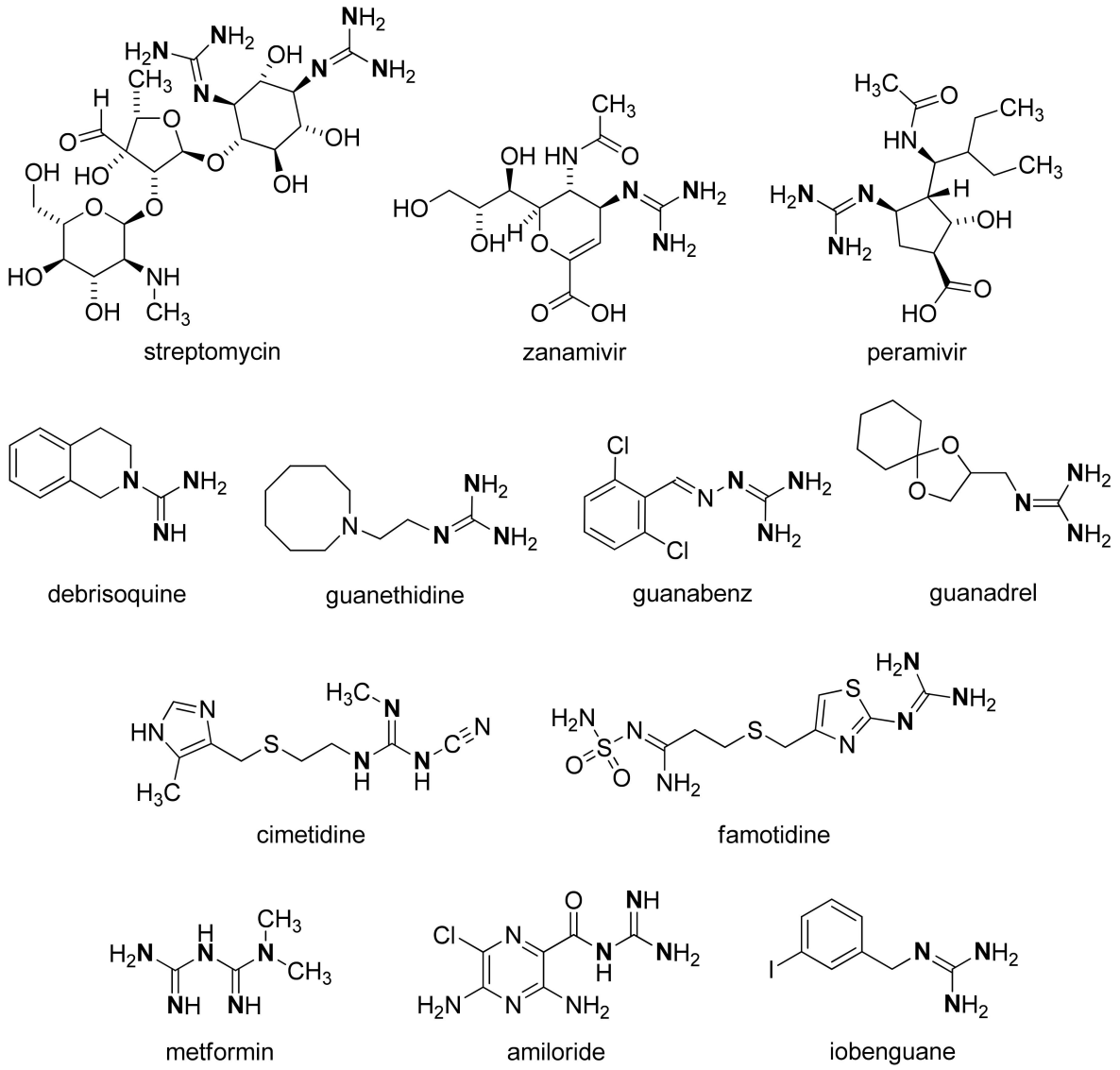


Figure 1. Chemical structures of guanidine containing drugs.

An important strategy in the development of preclinically and clinically valuable opioids is functionalization and modification of the highly versatile carbonyl group in position 6 of the morphinan-6-one ring of well-known opioid agonists. The 6-guanidine analogues derived from 6-aminomorphinanes showed potent opioid receptor agonist activities and antinociceptive properties [11].

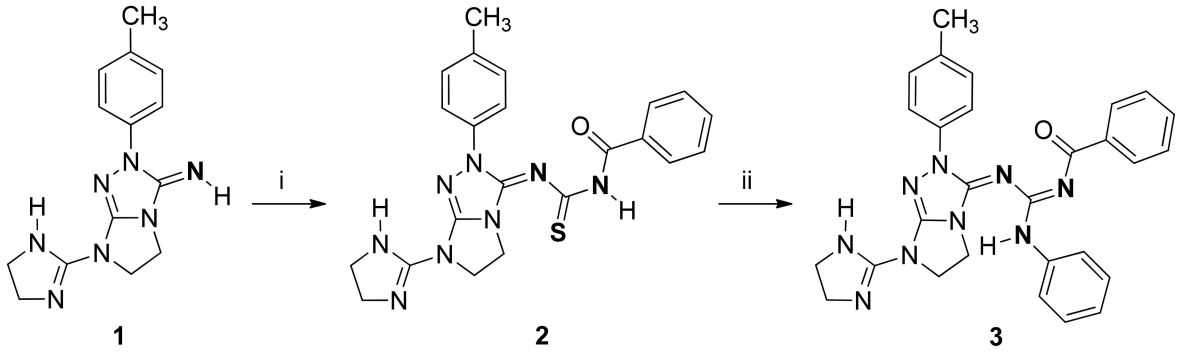
On the other hand, guanidines are classified as highly basic compounds, so-called superbases with pK_a values of conjugated acids at about 13. The super-basic character and their resonance stability upon protonation are conferred to the 'Y-aromaticity'. Due to its forklike structure, guanidine moiety has the ability to interact with water molecules forming strong hydrogen bonds. Guanidinium ions belong to one of the most hydrophilic organic groups [12–14].

In the course of our previous research aimed at the synthesis of novel 6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-imine derivatives, it was observed that their reactivity with aryl isothiocyanates gave rise to the formation of corresponding thioureas [15]. This observation prompted us to investigate their further transformations. Our attention has been focused on the guanidine moiety. It should be noted that thioureas are commonly used starting materials in the synthesis of guanidines, and the conversion of a thiourea derivative usually requires its initial activation.

The commercial method for preparing guanidines is the reaction of ammonia or ammonia derivatives with *S*-methylisothiouronium salts, and one of the by-products of this process is methanethiol (CH_3SH), flammable gas with a distinctively putrid smell [16]. Alternatively, guanidines may be obtained via the reaction of ammonia or amines with cyanamides, carbodiimides, chloroform-amidines or dichloroisocyanides. The starting materials, as well as by-products, of the mentioned procedures are moisture sensitive or corrosive. A more plausible method for the synthesis of guanidine derivatives from thioureas utilizes nucleophilic displacement of the activated sulphur [16]. The activation of the sulphur atom in the thiourea moiety can also be achieved in the presence of the transitional metal salt. Noteworthy is the fact that the use of mercury salt has made it possible to obtain guanidine derivatives with the use of an aromatic amine with weaker nucleophilic properties under mild conditions [17]. In this case, the experimental procedure seems to be facile, and the reaction may be carried out at ambient temperatures and without any volatile by-products [18,19].

2. Results and Discussion

As outlined in Scheme 1, the title compound, guanidine derivative: *N*-{[(7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene)amino](phenylamino)methylene}benzamide (**3**), was synthesized by reaction of *N*-{[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene]carbamothioyl}benzamide (**2**) with an equal amount of aniline in the presence of mercury(II) chloride ($HgCl_2$) and triethylamine (Et_3N) in anhydrous dimethylformamide (DMF).



i: Ph-CO-N=C=S, DCM, 20-22°C, 12 h

ii: Ph-NH_2, $HgCl_2$, Et_3N, DMF, 20-22°C, 7 days

Scheme 1. Synthesis of guanidine derivative **3**.

For the preparation of *N*-{[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene]carbamothioyl}benzamide (2), 7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-imine (**1**) was reacted with an equal amount of benzoyl isothiocyanate in a halogenated hydrocarbon solvent (anhydrous dichloromethane, DCM) at room temperature.

Looking for a convenient procedure for the preparation of a tri-substituted guanidine, we chose a 2-chloropyridinium salt, known as Mukaiyama's reagent, as a coupling agent [20–22]. This method provides a certain advantage over traditional procedures. The reaction completes within a significantly shorter time and under mild conditions. Unfortunately, in the case of compound **2**, this method was unsuccessful, even over a longer period (24–72 h) and at elevated temperatures (70–100 °C).

As noted previously, an alternative and improved method for the preparation of guanidines utilizes mercury salt. The presence of an electron-withdrawing group linked to thiourea moiety and the use of mercury chloride ($HgCl_2$) acting as a Lewis acid makes the carbon atom in position 2 of the thiourea group more susceptible to nucleophilic attack. It

should be pointed out that the use of copper(II) sulphate in the presence of SiO_2 instead of mercury salt has failed.

Generally, the mixture of *N*-{[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene]carbamothioyl}benzamide (**2**), aniline, mercury(II) chloride, and triethylamine required stirring for 7 days to give a grey-black precipitate of mercury(II) sulphide, complex salts, and the desired guanidine derivative **3**. The reaction was carried out in anhydrous dimethylformamide at room temperature. In the next step, crude product **3** was isolated using thin-layer preparative chromatography.

The structure of novel guanidine derivative **3** was confirmed by IR, ^{1}H-, ^{13}C-NMR spectroscopic data, as well as mass spectrometry, and elementary analysis (see the Supplementary Materials). The broadband at 3397 cm^{-1} of the IR spectrum of compound **3** is attributable to the N-H group. The strong absorption bands of the C=O and C=N groups are observed in the range of 1667–1616 cm^{-1}. In the ^{1}H-NMR spectrum of **3**, the characteristic methylene protons CH_2-CH_2 of the fused imidazo-triazole moiety and 4,5-dihydro-1*H*-imidazole ring are found as multiplet in the range of 3.47–3.60 ppm, with the integration of four protons and a singlet at 4.26 ppm with the integration of four protons, respectively. A singlet corresponding to the proton of the N-H group of 4,5-dihydro-1*H*-imidazole ring is present at 6.17 ppm. The signals of fourteen aromatic protons are found as a triplet, two dublets, multiplet, and three dublets in the range of 7.08–8.13 ppm. Finally, a broad singlet attributable to the proton of guanidine moiety appears at 12.73 ppm. In the ^{13}C-NMR spectrum recorded for **3**, the aliphatic carbons of 4,5-dihydro-1*H*-imidazole and imidazo-triazole rings are found in the range of 44.39–51.52 ppm. Moreover, the ^{13}C-NMR spectrum revealed three signals of quaternary carbon atoms: C_{7a}=N, C_3=N of fused imidazo-triazole, and C_2=N of the 4,5-dihydro-1*H*-imidazole ring at 146.86, 151.26, and 154.96 ppm, respectively. The quaternary carbon of guanidine moiety appears at 159.26 ppm, whereas a signal of the carbonyl group C=O is located at 174.95 ppm.

To obtain better insight into the structure of the guanidine derivative in polar solvent (DMSO), we performed quantum chemical calculations using density functional (B3LYP/6.31G*) for two possible tautomers of the title guanidine derivative, *N*-{*N*-[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene]-*N*′-phenylcarbamimidoyl}benzamide (**3a**) and *N*-{[(7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(*p*-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ylidene)amino](phenylamino) methylene}benzamide (**3b**) by using the Spartan program suite (Spartan version 14 V 1.1.4.) (Figure 2).

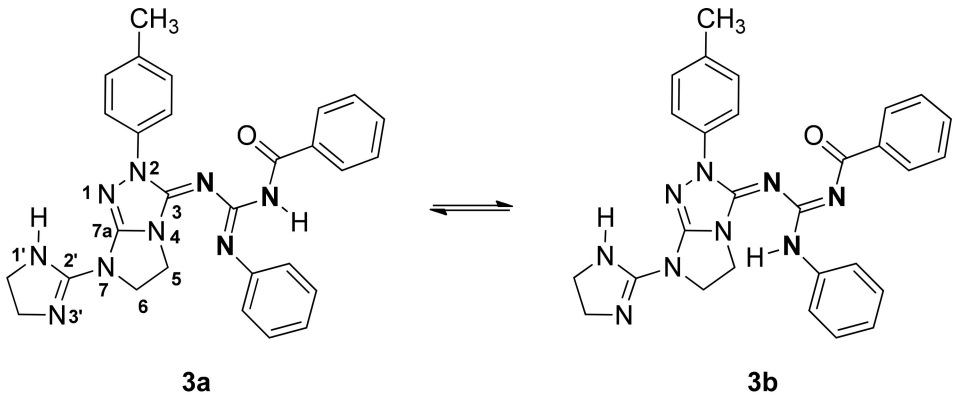


Figure 2. Tautomers **3a** and **3b**.

The tautomer **3b** was calculated to be slightly lower in energy than **3a** ($\Delta E = -0.65$ kJ/mol). Moreover, on the basis of their calculated dipole moments, the tautomer **3b** (μ = 6.73 D) would be predicted to predominate over the tautomer **3a** (μ = 5.51 D) in a polar solvent.

3. Materials and Methods

3.1. General Methods and Physical Measurements

All reagents and solvents were purchased from commercial sources and used without further purification. The melting points were determined with a Boetius apparatus and are uncorrected. The infrared spectra were recorded on a Nicolet 380FT-IR spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra of compounds **2** and **3** were registered at 20–22 °C on a Varian Unity Inova 500 (^{1}H = 500 MHz, ^{13}C = 125 MHz), using the signal of DMSO-d_6 as an internal standard. The values of chemical shifts are given in ppm and coupling constants (J) are expressed in hertz (Hz). Mass spectra were recorded on an LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan). The compounds were identified based on their molecular ions obtained through electrospray ionization. Compounds were purified using preparative chromatography. Thin-layer chromatography was performed on silica gel plates with fluorescence detection (Merck Silica Gel 254). After drying spots were detected under UV light (λ = 254 nm). Measured C, H, and N elemental analyses were within 0.4% of calculated values.

*3.2. Synthesis of N-{[7-(4,5-Dihydro-1H-imidazol-2-yl)-2-(p-tolyl)-6,7-dihydro-2H-imidazo[2,1-c][1,2,4]triazol-3(5H)-ylidene]carbamothioyl}benzamide (**2**)*

To a stirring solution of 7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(p-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-c][1,2,4]triazol-3(5*H*)-imine (**1**) (0.2833 g; 1 mmol) in anhydrous dichloromethane (5 mL) benzoyl isothiocyanate was added (0.1632 g, d = 1.214 g/mL, 0.1344 mL). The mixture was stirred at room temperature (20–22 °C) for 12 h. The progress of the reaction was controlled by TLC. After completion of the reaction, the precipitate was separated by suction, washed with a small amount of dichloromethane, and dried. The crude product was dissolved in a mixture containing: ethyl acetate, dichloromethane, acetone, methanol, and triethylamine (5:2:1:1:1, *v*/*v*/*v*/*v*/*v*), and purified on silica gel by preparative thin-layer chromatography (chromatotron, eluent: ethyl acetate:methanol, 8:2, *v*/*v*). Yield 0.14 g (31%); m.p. 174–176 °C; IR (KBr, cm^{-1}): 3404, 3311, 3065, 3033, 2922, 2876, 1708, 1675, 1556, 1509, 1383, 1317, 1158, 1136, 825, 702; ^{1}H-NMR (500 MHz, DMSO-d_6): 2.31 (s, 3H, CH_3), 3.54 (s, 4H, CH_2-CH_2), 4.33–4.38 (m, 2H, CH_2), 4.39–4.44 (m, 2H, CH_2), 6.45 (br.s, 1H, NH), 7.28 (d, J = 8.3 Hz, 2H, Ar), 7.46 (t, 2H, Ar), 7.56 (t, 1H, Ar), 7.79 (d, J = 8.3 Hz, 2H, Ar), 7.84 (d, J = 7.3 Hz, 2H, Ar), 10.63 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6+TFA): 20.87, 44.10 (two overlapping signals), 44.52, 53.07, 121.72 (two overlapping signals), 128.62 (two overlapping signals), 128.80 (two overlapping signals), 129.89 (two overlapping signals), 132.52, 134.43, 134.86, 137.58, 147.92, 150.06, 153.85, 164.87, 182.93; *m/z* (ESI): 447 [M + H]$^{+}$. Anal. Calcd for $C_{22}H_{22}N_8OS$ (446.53): C, 59.18; H, 4.97; N, 25.09. Found: C, 59.56; H, 5.01; N, 24.98.

*3.3. Synthesis of N-{[(7-(4,5-Dihydro-1H-imidazol-2-yl)-2-(p-tolyl)-6,7-dihydro-2H-imidazo[2,1-c][1,2,4]triazol-3(5H)-ylidene)amino](phenylamino)methylene}benzamide (**3**)*

To a stirring solution of *N*-{[7-(4,5-dihydro-1*H*-imidazol-2-yl)-2-(p-tolyl)-6,7-dihydro-2*H*-imidazo[2,1-c][1,2,4]triazol-3(5*H*)-ylidene]carbamothioyl}benzamide (**2**) (0.2233 g, 0.5 mmol) in anhydrous dimethylformamide (5 mL), triethylamine (0.1012 g, 0.1393 mL, d = 0.726 g/mL, 1 mmol), mercury(II) chloride (0.1358 g, 0.5 mmol), and aniline (0.0466 g, 0.0456 mL, d = 1.0217 g/mL, 0.5 mmol) were added at room temperature (20–22 °C). The suspension was stirred at room temperature (20–22 °C) for 7 days (the grey-black precipitate appeared after 3 days of stirring). After 7 days, the mixture was diluted with chloroform (20 mL) and filtered. The grey-black solid was washed with a small amount of chloroform. Combined organic layers were evaporated to dryness. To the residue was added 30 mL of ethyl acetate, and the organic phase was washed with brine (3 × 15 mL), dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in chloroform and purified on silica gel by preparative thin-layer chromatography (chromatotron, eluent: ethyl acetate:methanol, 9:1, *v*/*v*) and crystallized from methanol. Yield 0.08 g (32%); m.p. 250–253 °C; IR (KBr, cm^{-1}): 3397, 3058, 3029, 2929, 2876, 1667, 1616, 1591, 1547, 1518,

1467, 1439, 1338, 1218, 750, 717; ^{1}H-NMR (500 MHz, DMSO-d_6): 2.31 (s, 3H, CH_3), 3.47–3.60 (m, 4H, CH_2-CH_2), 4.26 (s, 4H, CH_2-CH_2), 6.17 (s, 1H, NH), 7.08 (t, J = 7.3 Hz, 1H, Ar), 7.25 (d, J = 8.3 Hz, 2H, Ar), 7.30 (t, J = 7.8 Hz, 2H, Ar), 7.42–7.50 (m, 3H, Ar), 7.56 (d, J = 7.8 Hz, 2H, Ar), 7.82 (d, J = 8.3 Hz, 2H, Ar), 8.13 (d, J = 7.3 Hz, 2H, Ar), 12.73 (s, 1H, NH); ^{13}C-NMR (125 MHz, DMSO-d_6): 21.02, 44.39, 48.70, 51.52 (two overlapping signals), 121.82 (two overlapping signals), 122.16, 128.62 (two overlapping signals), 129.10 (two overlapping signals), 129.17 (three overlapping signals), 129.69 (four overlapping signals), 131.53, 135.67, 136.52, 139.15, 146.86, 151.26, 154.96, 159.26, 174.95; *m/z* (ESI): 506 $[M + H]^+$. Anal. Calcd for $C_{28}H_{27}N_9O$ (505.57): C, 66.52; H, 5.38; N, 24.93. Found: C, 66.58; H, 5.34; N, 25.12.

4. Conclusions

In conclusion, we synthesized a novel tri-substituted guanidine derivative **3** via the reaction of appropriate thiourea **2** with a primary aromatic amine in the presence of mercury(II) chloride and triethylamine. The optimization of the reaction was studied at different temperatures and in various solvents. It was found that the higher conversion of starting thiourea **2** and better yield of desired product **3** could be achieved using dimethylformamide as a solvent at an ambient temperature.

The structural modifications of this class of compounds may be gained by the introduction of different substituents at the phenyl rings using a series of aromatic amines or thiourea derivatives as starting materials. The guanidine represents an anchoring group that is a prominent scaffold for further functionalization. It will lead to a diversity of guanidine analogues.

Having in mind that the class of guanidines includes well-known drugs and that the field of potential applications for guanidines is constantly extending, the guanidine derivative **3** obtained in this work and its possible analogues may exhibit promising biological activity with potential applications in medicinal chemistry. Therefore, the guanidine derivative **3** constitutes a platform for the development of a new class of compounds that deserves further biological investigation to evaluate their potent cytotoxic activity against human tumour cell lines. This allows for a better understanding of structure-activity relationships (SARs), determining further structural modifications of this class of guanidine-containing derivatives.

Supplementary Materials: Supplementary data, including IR and NMR spectra of compounds **2** and **3**, associated with this article are available online.

Author Contributions: Ł.B. conceived, designed, and performed the experiments; Ł.B. and A.K. analyzed the data and wrote the paper. All authors have read and agreed to the published version of the manuscript.

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

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