An Original Traceless Linker Strategy for Solid-Phase Synthesis of *N*,*N*′,*N*″-Substituted Guanidines

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Abstract: An original sequence for solution- and solid-phase synthesis of *N*,*N*′,*N*″-trisubstituted guanidines is described. The sequence involves as key intermediate a bis-electrophilic chlorothioformamidine that is stable, easy to prepare and also easy to handle. Supported chlorothioformamidine, prepared in two steps from Merrifield resin, undergoes smooth nucleophilic addition of a primary amine to afford the corresponding supported isothiourea. The guanidine is obtained in satisfactory yield and good purity through a functionalizing-release process by heating the supported isothiourea in the presence of a primary amine in toluene at 100 °C. Compatibility of this sequence with several functional groups is demonstrated.

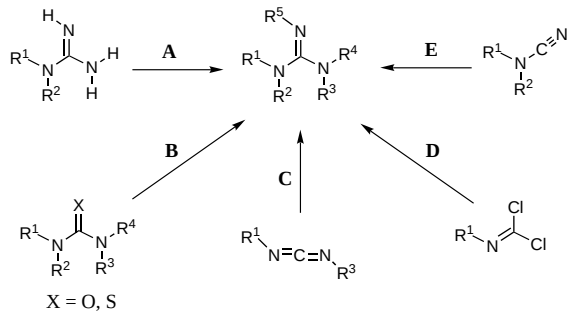
Keywords: combinatorial chemistry · guanidines · nucleophilic substitutions · solid-phase synthesis · traceless linkers

Introduction

Guanidines are found in most living organisms. They are the core features of many biologically active molecules. For instance among amino acids, arginine plays a key role in many peptides for receptor binding and enzymatic activity.[1] Complex molecules that incorporate single or multiple guanidines units have been isolated from microorganisms and several synthetic guanidine-containing drugs are known as HIV protease inhibitors, NMDA receptor antagonists or DNA binding agents.[2] Moreover synthetic guanidines found wide applications in the engineering of advanced synthetic molecular recognition devices, sensors, organic materials, and phase-transfer catalysts.[3]

This polyvalence might be partly explained by the wide range of biophysical properties that guanidines can display. For instance, pK_a values of guanidines range from 14 for alkyl- to 7 for benzoyl-substituted guanidines. Similarly, the hydrogen bonding pattern and metal ion coordination properties of to guanidines are modulated by the nature and the degree of substitution. In addition remarkable stability is conferred to the guanidinium skeleton by the so-called Y aromaticity, that is resonance through three canonical forms.[4]

As a consequence, guanidine synthesis has been intensively investigated for many years both in solution-phase chemistry and more recently in solid-phase synthesis. In solution-phase chemistry, five major routes for the synthesis of polysubstituted guanidines can be distinguished and classified according to the precursor involved[5] (Scheme 1).



Scheme 1. Methods for the preparation of guanidines from different precursor.

Substituted guanidines are prepared by reaction of alkyl or aryl guanidines with various electrophiles under basic conditions (path A). This approach leads to mixtures of products except for sterically hindered electrophiles which react with free guanidines to give monosubstituted adducts. All other methods involve an electrophilic precursor of the guanidine moiety, which reacts with a nucleophilic primary or secondary amine. The electrophilic precursor can be generated from various functions. Thiouroniums for instance (path B, X = S),

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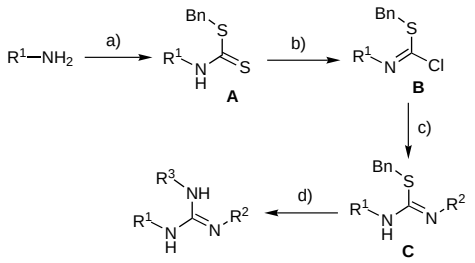
are prepared by alkylation of thiourea with reagents, such as trialkyl oxonium salts or alkyl halides. Treatment of thiourea with chlorinating agents, for example phosphoryl chloride, affords chlorouronium salts which are reactive guanidine precursors. Similarly electrophilic imino N^2 centers are generated from ureas (path B, X = O), by treatment with strong alkylating or chlorinating agents. Carbodiimides (path C), obtained by dehydration or desulfurization of ureas or thioureas, react smoothly with an amine to yield trisubstituted guanidines. Bis-electrophilic precursors which react successively with two mono- or di-substituted amines to give *N*,*N*′-polysubstituted guanidines were also reported. For example carbonimidic dichloride is prepared by chlorination of isothiocyanate (path D). *N*,*N*-Disubstituted guanidine can be obtained by reaction of an amine group with a guanylating agent, for example cyanamide (path E), *N*,*N*′-di-(*tert*-butoxycarbonyl)thiourea or *N*,*N*′-bis-Boc-1-guanylpyrazole.

Several approaches for solid-phase synthesis of guanidines have already been reported in the literature. Early approaches were often based on synthetic schemes derived from solution-phase chemistry,[6] that is the reaction of a resin-bound carbodiimide with an amine in solution. These approaches do not fully benefit from the use of the solid support. The linkage between the resin and the guanidine precursor through an ester or amide functionality leave a carboxylic acid residue on the cleaved product. More recent work focussed on the development of traceless linkers for guanidine solid-phase synthesis.[7] For instance *N*,*N*′-bis-(*tert*-butoxycarbonyl)thio-pseudourea was used as a masked guanidine scaffold which after derivatization could be cleaved from the resin upon treatment with a primary amine.[8] However, only mono- or bis-*N*,*N*-substituted guanidines were prepared through this process.

Results and Discussion

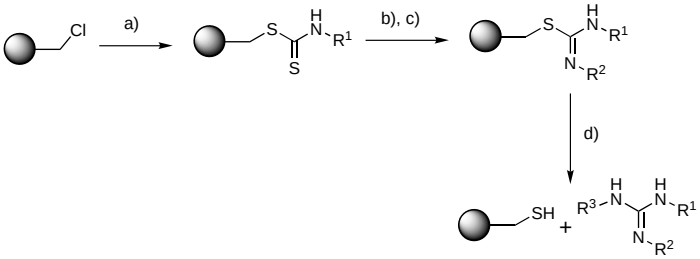
Herein we describe an original sequence for solution- and solid-phase synthesis of *N*,*N*′,*N*″-trisubstituted guanidines in good yield under mild conditions. The sequence involves as key intermediate a bis-electrophilic chlorothioformamidine **B** (Scheme 2). Compared with the above mentioned bis-electrophilic guanidine precursor such as carbonimidic dichloride (path D), chlorothioformamidine is more stable and both easy to prepare, and to handle.



Scheme 2. Synthesis of guanidines through two consecutive nucleophilic additions of amines on the bis-electrophilic isothiourea intermediate generated from a dithiocarbamate precursor. a) BnCl, CS_2, THF, rt, 12 h. b) $COCl_2$, toluene, 60 °C, 12 h. c) R^2NH_2, toluene, 60 °C, 12 h. d) R^3NH_2, toluene, 100 °C, 60 h.

A preliminary study was conducted in solution to determine the scope and limitation of this synthetic scheme. Dithiocarbamate **A** is obtained by reaction of an amine with carbon disulfide in the presence of benzyl chloride. This reaction was extensively studied and is described to work with many alkyl halides.[9] However, benzyl chloride was chosen for this study because it mimics the Merrifield resin. The dithiocarbamate is quantitatively converted into the corresponding chlorothioformamidine **B** by treatment at 60 °C with phosgene in toluene for 12 h. In the presence of an amine this intermediate undergoes nucleophilic addition at 60 °C to afford isothiourea **C**. No double addition was observed at this stage. The second addition which leads to the urea formation could be effected by heating the isothiourea at 100 °C in the presence of an excess of a third amine. For this last reaction different solvents were evaluated. After 6 h reaction, conversion reached 80 % in DMSO and 50 % in toluene, while in acetonitrile or dioxane conversion was only around 20 %. NMR analysis of the crude mixture from reaction mixture carried out in DMSO showed the presence of unidentified side products. Since purity of the crude is a crucial issue with regard to the use of this sequence for SPS, toluene appeared as the most suitable solvent. We then carried out a series of experiments in which we tested all possible combinations of primary and secondary amines in each step.

Two major limitations were found: for tri-substituted isothuourea the nucleophilic substitution of the thioalkyl residue did not proceed and secondary amines did not react with *N*,*N*′-bis-substituted isothiourea. In both cases the isothioureas were recovered without degradation after 12 h at 100 °C in the presence of an excess of amine. An increase in temperature to 140 °C did also not bring the reaction to proceed. Thus, it appeared that the nucleophilic substitution of thioalkyl residue is highly sensitive to steric hindrance. Hence, only primary amines can be used in this sequence. Nevertheless the procedure and the diversity of available primary amines led us to develop a SPS strategy based on the described pathway (Scheme 3).



Scheme 3. Traceless linker strategy for solid-phase synthesis of *N*,*N*′,*N*″-substituted guanidines. a) Merrifield resin, CS_2, THF, RT, 12 h. b) $COCl_2$, toluene, 60 °C, 12 h. c) R^2NH_2, toluene, 60 °C, 12 h. d) R^3NH_2, toluene, 100 °C, 60 h.

In a previous paper we showed that the use of chloromethylpolystyrene (Merrifield resin) instead of benzyl chloride in the first step resulted in the quantitative formation of resin-bound dithiocarbonate.[10] The treatment of this supported dithiocarbamate with an excess of oxalyl chloride at 60 °C for 12 h gives the expected resin-bound chlorothioformimidate.

Noteworthy, a prolonged reaction time led to a decreased yield of the final guanidine. This is presumably due to partial cleavage of the benzylic resin-dithiocarbonate bond as evidenced by the weaker intensity of the chlorothioformimidate IR signal. After washing, an excess of primary amine is added to a suspension of resin-bound chlorothioformimidate in toluene. The mixture is shaken at 60 °C for 12 h to give the supported isothiourea after thorough washing of the resin. The thermolytic cleavage is then performed by heating a suspension of resin in the presence of an excess of primary amine in toluene at 100 °C for 60 h.

After the reaction mixture was concentrated in vacuo, ^{1}H-NMR analysis of the residue showed that only the desired guanidine along with the excess of amine used in the cleavage step were present in the crude cleavage mixture. Guanidines are polar, basic, and hydrophilic compounds, which are known to be difficult to purify. Since tedious purification is not compatible with high-throughput process, guanidines purification were carried out simply by diluting the concentrated crude reaction mixtures in methylene chloride and precipitation by addition of ether. Using this procedure the purity of the final compounds is found to be over 90 % by HPLC and ^{1}H-NMR analysis. The yields indicated in Scheme 4 are given for the product recovered by precipitation and calculated from the theoretical initial loading of the starting Merrifield resin (1.2 mequiv per g). It is noteworthy that if the purification are performed by preparative TLC the isolated yield are increased by more than 20 %.

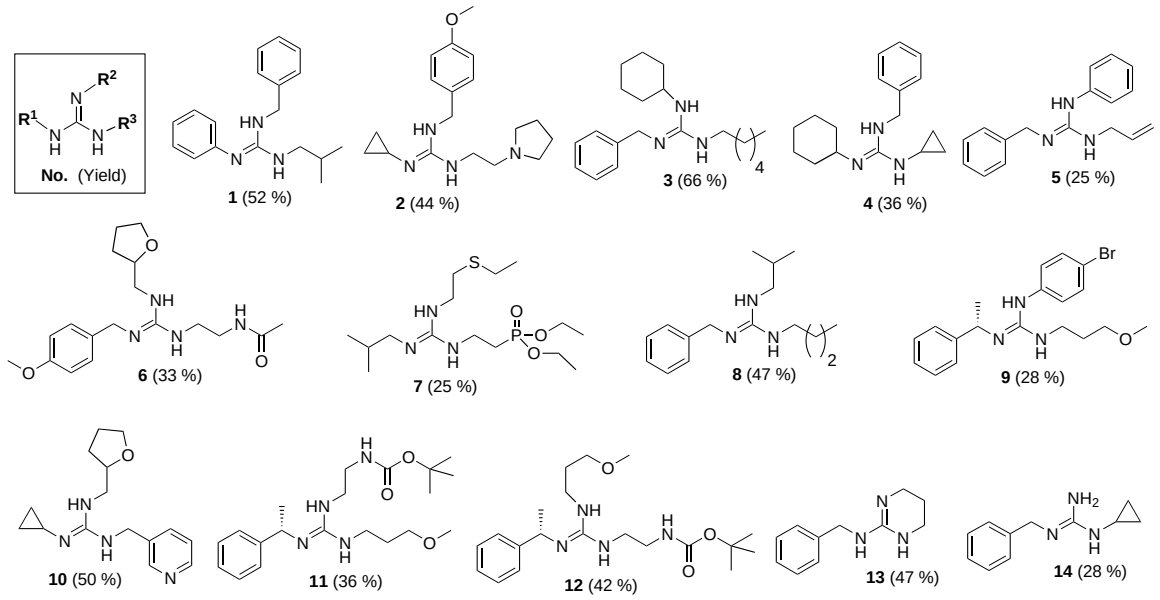
After each SPS step, resins were analyzed by single bead IR microscopy and ^{13}C-NMR sprectroscopy. All intermediates showed characteristic IR signals that allowed the monitoring of the successive transformations. In particular, the NH signals were characteristic for dithiocarbamates at around 3350, 3255 cm^{-1} and 1375, 1325 cm^{-1}, for the isothioureas at 3420 cm^{-1} while chlorothioformamidines, which did not show any NH signal, showed a characteristic band at around 1645 cm^{-1}. Other signals at 1090 cm^{-1} and 1615 cm^{-1} were also characteristic of the dithiocarbamate and isothiourea fonctions, respectively.

Our procedure allows traceless synthesis of guanidine by three successive reactions of primary amine. To illustrate the compatibility of the reaction conditions with various functional groups, some representative amines were tested.

As was anticipated, the reaction sequence is compatible with a wide variety of structures and functional groups. In the first step, only nonfunctionalized alkyl-, aryl-, and allylamines were involved to avoid possible side reactions with oxalyl chloride in the activation step. In the later steps more complex amines bearing various functionalities were used (see Scheme 4), that is ether **6**, **10**, and **11**, thioether **7**, carbamate **11**, and **12**, amides **6**, tertiary amine **2**, phosphinate **7** and the aromatic heterocycle **10**. In all cases the desired polyfunctional tri-substituted guanidines were obtained with satisfactory yields and good purities. Interestingly, the use of aqueous ammonia in the second step allows the preparation of *N*,*N*′-disubtituted guanidines such as **14**.

Additional diversity can be introduced on the guanidine scaffold by derivatization of a suitably functionalized isothiourea intermediate. For instance, the aryl bromide substituted isothiourea intermediate **9** would be an ideal substrate for preparation through palladium coupling reactions of biphenyl-containing guanidine libraries and *N*-Boc substituted isothiourea **12** would allow after deprotection, introduction of an additional diversity by amide, carbamate, or sulfonamide formation.

In summary, we reported an original and efficient synthetic protocol for the synthesis of *N*,*N*′,*N*″ trisubstituted guanidines. The reported reaction sequence is well adapted for SPS since it allows in a four-step process the addition of three primary amines under reaction conditions compatible with a wide variety of functional groups. Moreover since the reaction conditions are suitable for automation and high-throughput synthesis, it appears possible to prepare large libraries of guanidines by this traceless linker strategy.



Scheme 4. Representative guanidines prepared by solid-phase synthesis strategy reported in this paper.

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Experimental Section

General: All chemicals were obtained from commercial suppliers. The Merrifield resin (200–400 mesh) was purchased from Novabiochem. Filtration devices equipped with 5 μm pore size PTFE membrane were purchased from Whatman. Solvents for reactions were distilled prior to use. Analytical grade solvents were used for both reactions and resin washing. One-bead IR analysis was carried out using a Perkin–Elmer 2000 FT spectrometer coupled to a Perkin–Elmer Autoimage microscope. NMR analyses were performed on Bruker 300- and 200-Avance DPX spectrometer.

Typical procedures for SPS—Preparation of supported dithiocarbamate: Carbon disulfide (0.12 mL, 2 mmol), *N*-ethyldiisopropylamine (0.21 mL, 1.24 mmol), and amine (1.86 mmol) were added successively at RT to a suspension of Merrifield resin (1 g, 1.24 mmol) in THF (10 mL). The mixture was shaken for 12 h at room temperature. The excess reagents were removed by washing the resin four times alternately with THF (15 mL), CH_2Cl_2 (15 mL), and MeOH (15 mL). After drying under vacuum, IR analysis of the resin showed the characteristic bands of the solid-phase supported dithiocarbamate at around 3350 (NH), 3255 (NH), 1375, 1325, 1090, and 1060 cm^{-1}.

Activation step: An excess of phosgene (3.7 mmol) was added to a suspension of the polymer-bound dithiocarbamate (1 g) in toluene (10 mL) at room temperature. The mixture was heated at 60 °C for 12 h to promote chlorothioformimidate formation. The resin was then filtered and washed four times with toluene (15 mL) and CH_2Cl_2 (15 mL). After drying under vacuum, IR analysis of the resin showed the characteristic signal of the supported chlorothioformimidate at 1645 cm^{-1}.

Formation of supported isothiourea: The chlorothioformimidate resin recovered from the previous step was then treated with an excess of primary amine (3.7 mmol) in toluene (8 mL) for 12 h at 60 °C. The resulting resin was then filtered off and washed four times alternately with CH_2Cl_2 (15 mL) and MeOH (15 mL). After drying under vacuum, IR analysis of the resin showed the characteristic bands of the solid-phase supported isothiourea at 1615 cm^{-1}.

Thermolytic cleavage: An excess of primary amine (3.7 mmol) was added to the polymer-bound isothiourea (recovered from the previous step) in toluene (10 mL). The mixture was heated at 100 °C for 60 h. The resin was then filtered off and washed four times alternately with CH_2Cl_2 (15 mL) and MeOH (15 mL). The filtrate was concentrated under vacuum to afford the crude mixture containing the guanidine and excess of amine. The crude was then dissolved in a minimum amount of CH_2Cl_2 (1 mL). Dropwise addition of ether (15 mL) resulted in precipitation of the guanidine, which was recovered by filtration. ^{1}H-NMR and HPLC/mass spectroscopy analysis were performed for each compound.

Analytical data

***N*-Phenyl,*N*′-isobutyl,*N*″-benzyl-guanidine (1)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $^3J = 6.8$ Hz, 6H), 1.77 (tseptet, $^3J = 6.8$ Hz, 6.4 Hz, 1H), 2.98 (d, $^3J = 6.4$ Hz, 2H), 4.44 (s, 2H), 7.01–7.28 (m, 10H); MS (IC/NH_4^+) m/z: 282 $[M-H]^+$.

***N*-Cyclopropyl,*N*′-(4-methoxybenzyl),*N*″-(2-pyrrolidin-1-yl-ethyl)-guanidine (2)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.50-0.61$ (m, 2H), 0.76–0.81 (m, 2H), 1.30–1.59 (m, 4H), 2.27–2.61 (m, 7H), 3.22–3.31 (m, 2H), 3.69 (s, 3H), 4.48 (s, 2H), 6.74 (d, $^3J = 8.3$ Hz, 2H), 7.28 (d, $^3J = 8.3$ Hz, 2H); MS (IC/NH_4^+) m/z: 317 $[M-H]^+$.

***N*-Benzyl,*N*′-cyclohexyl,*N*″-hexyl-guanidine (3)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.81$ (t, $^3J = 6.7$ Hz, 3H), 1.09–1.84 (m, 18H), 3.34 (td, $^3J = 6.0$ Hz, 6.4 Hz, 2H), 3.69–3.82 (m, 1H), 4.56 (d, $^3J = 5.7$ Hz, 2H), 6.20 (d, $^3J = 7.9$ Hz, 1H), 7.18–7.40 (m, 5H), 8.58 (t, $^3J = 5.7$ Hz, 1H); MS (IC/NH_4^+) m/z: 316 $[M-H]^+$.

***N*-Benzyl,*N*′-cyclohexyl,*N*″-cyclopropyl-guanidine (4)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.51-0.89$ (m, 4H), 1.09–1.56 (m, 8H), 1.84–1.87 (m, 2H), 2.52–2.61 (m, 1H), 3.84–3.96 (m, 1H), 4.66 (s, 2H), 6.06 (brs, 1H), 7.21–7.44 (m, 5H), 8.52 (brs, 1H); MS (IC/NH_4^+) m/z: 272 $[M-H]^+$.

***N*-Allyl,*N*′-benzyl,*N*″-phenyl-guanidine (5)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.60$ (t, $^3J = 3.7$ Hz, 1H), 3.80 (dd, $^3J = 3.7$ Hz, 8.0 Hz, 2H), 4.38 (brs, 1H), 4.42 (s, 2H), 5.06–5.15 (m, 2H), 5.60–5.80 (m, 1H), 7.00–7.26 (m, 10H); MS (IC/NH_4^+) m/z: 266 $[M-H]^+$.

***N*-{2-[*N*′-(4-Methoxy-benzyl),*N*″-(tetrahydrofuran-2-yl-methyl)-guanidino]-ethyl}-acetamide (6)**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.59-1.98$ (m, 4H), 2.00 (s, 3H), 3.17–3.25 (m, 1H), 3.46–3.74 (m, 7H), 3.80 (s, 3H), 3.89–3.98 (m, 1H), 4.39 (s, 2H), 6.87 (d, $^3J = 8.5$ Hz, 2H), 7.25 (d, $^3J = 8.5$ Hz, 2H), 9.07 (brs, 1H); MS (IC/NH_4^+) m/z: 349 $[M-H]^+$.

***N*-{2-[*N*′-(2-Ethylsulfanyl-ethyl),*N*″-isobutyl-guanidino]-ethyl]}-phosphonic acid diethyl ester (7)**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.02$ (t, $^3J = 6.6$ Hz, 6H), 1.28 (t, $^3J = 7.3$ Hz, 3H), 1.36 (t, $^3J = 6.8$ Hz, 6H), 2.01 (tseptet, $^3J = 6.6$ Hz, 6.9 Hz, 1H), 2.17 (td, $^3J = 6.8$ Hz, 14 Hz, 2H), 2.61 (q, $^3J = 7.3$ Hz, 2H), 2.86 (t, $^3J = 6.1$ Hz, 2H), 3.10 (dd, $^3J = 5.3$ Hz, 6.9 Hz, 2H), 3.52–3.82 (m, 4H), 4.13 (qd, $^3J = 6.8$ Hz, 14 Hz, 4H), 7.70 (brs, 0.5H), 7.92 (brs, 0.5H), 8.32 (brs, 1H); MS (IC/NH_4^+) m/z: 368 $[M-H]^+$.

***N*-Benzyl,*N*′-butyl,*N*″-isobutyl-guanidine (8)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.78$ (d, $^3J = 6.6$ Hz, 6H), 0.79 (t, $^3J = 6.8$ Hz, 3H), 1.20 (tq, $^3J = 6.8$ Hz, 7.2 Hz, 2H), 1.45 (tt, $^3J = 6.8$ Hz, 7.2 Hz, 2H), 1.80 (tseptet, $^3J = 6.6$ Hz, 7.2 Hz, 1H), 3.08 (d, $^3J = 7.2$ Hz; 2H), 2.27 (t, $^3J = 6.8$ Hz, 2H), 4.52 (s, 2H), 7.20–7.36 (m, 5H); MS (IC/NH_4^+) m/z: 262 $[M-H]^+$.

***N*-(4-Bromo-phenyl),*N*′-(3-methoxypropyl),*N*″-(1-(+)-phenyl-ethyl)-guanidine (9)**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.57$ (d, $^3J = 6.8$ Hz, 3H), 1.70 (tt, $^3J = 5.3$ Hz, 5.1 Hz, 2H), 3.14 (s, 3H), 3.28 (t, $^3J = 5.1$ Hz, 2H), 3.34 (t, $^3J = 5.3$ Hz, 2H), 4.72 (m, 1H), 6.93 (d, $^3J = 8.6$ Hz, 2H), 7.30–7;33 (m, 5H), 7.43 (d, $^3J = 8.6$ Hz, 2H); MS (IC/NH_4^+) m/z: 390 $[M-H]^+$.

***N*-Cyclopropyl,*N*′-pyridyl-3-methyl,*N*″-(tetrahydrofuran-2-yl-methyl)-guanidine (10)**: ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.52-0.64$ (m, 2H), 0.85–0.91 (m, 2H), 1.61–1.95 (m, 4H), 2.63–2.75 (m, 1H), 3.20–3.31 (m, 1H), 3.53–3.70 (m, 3H), 3.90–3.94 (m, 1H), 4.81 (s, 2H), 7.23 (m, 1H), 7.91 (m, 1H), 8.46 (m, 1H), 8.68 (s, 1H); MS (IC/NH_4^+) m/z: 275 $[M-H]^+$.

{2-[*N*′-(3-Methoxypropyl),*N*″-(1-(+)-phenyl-ethyl)guanidino]-ethyl}-carbamic acid *tert*-butyl ester (11, 12): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 1.63 (d, $^3J = 6.0$ Hz, 3H), 1.71–1.95 (m, 2H), 3.17 (s, 3H), 3.17–3.59 (m, 8H), 4.78 (d, $^3J = 6.0$ Hz, 1H), 6.02 (brs, 1H), 7.30–7.40 (m, 5H); MS (IC/NH_4^+) m/z: 379 $[M-H]^+$.

Benzyl-(1,4,5,6-tetrahydro-pyrimidin-2-yl)-amine (13): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.68$ (quint, $^3J = 5.6$ Hz, 2H), 3.10 (t, $^3J = 5.6$ Hz, 4H), 4.37 (s, 2H), 7.17–7.28 (m, 5H), 7.73 (brs, 1H), 8.06 (brs, 1H); MS (IC/NH_4^+) m/z: 190 $[M-H]^+$.

***N*-Benzyl,*N*′-cyclopropyl-guanidine (14)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.60-0.64$ (m, 2H), 0.71–0.77 (m, 2H), 2.41–2.56 (m, 1H), 4.49 (d, $^3J = 5.7$ Hz, 2H), 4.90 (brs, 1H), 5.33 (brs, 1H), 7.30–7.35 (m, 5H); MS (IC/NH_4^+) m/z: 190 $[M-H]^+$.

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