Biguanidines, guanylureas and guanylthioureas

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Dedicated to Prof. Bruce E. Maryanoff and Prof. Cynthia A. Maryanoff in honor of their outstanding contributions to organic chemistry

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Abstract
Classical and more recent preparations of biguanidines, guanylureas and guanylthioureas are summarized, together with their biological activity and other applications. Biguanides are depicted in their most stable tautomeric form, modified where necessary from that in the literature.

Keywords: Biguanides, guanylureas, guanylthioureas, hypoglycemic agents, spasmolytic agents

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1. Introduction

Biguanidines are an interesting class of compounds with many known or potential applications. We were unable to locate any recent review of the synthesis and biological properties of the structurally related biguanidines 1, guanylureas 2 and guanylthioureas 3 (Figure 1). Consequently, we have now attempted to review both classical and more recent procedures for the preparation of biguanidines, guanylureas, and guanylthioureas together with their industrial applications.

2. Biguanides

2.1 Structure of biguanides
In the literature, structures of biguanides continue to be commonly depicted as shown for 4, which lead to a misleading perception. In fact, X-ray crystallographic analysis,\(^1\) \(^1\)\(^5\)N NMR spectroscopy,\(^2\) molecular modeling\(^3\) and tautomer stability studies\(^4\) have confirmed that biguanides should be represented as 5 (Figure 2), where there is an absence of hydrogen on the bridging nitrogen. Hence, throughout this review we have represented biguanides according to form 5, modifying the literature structures where necessary.

2.2 Methods of preparation
The synthesis most commonly utilized for substituted biguanidines 8 is the reaction of primary amine salts 7 with cyanoguanidine 6 (Scheme 1).
Treatment of dialkylcyanamide 9 with hydrogen chloride at 60 °C to 150 °C gave alkylguanylchloroformamidine hydrochlorides 10. Reaction these with aqueous ammonia or amines gave the corresponding biguanides 11 (Scheme 2).\(^5\)

Scheme 1

In 1960 Priyadarjan Ray reviewed complexes of biguanidines with metals, reporting preparations of biguanidines up to 1958.\(^6\a\) In 1968 Kurzer and Pitchfork reviewed the chemistry of biguanides.\(^6\b\) In 1960 Shirai and Sugino found that the biguanidine 16 can be obtained in good yield from O-alkylisoureas 12 and guanidine 13 in ethanol as solvent (Scheme 3).\(^7\)

Scheme 2
Amines add to the cyanoguanidine 6 in the presence of FeCl₃ or ZnCl₂ under mild conditions: thus, cyanoguanidine 6 and butylamine 18 in the presence of FeCl₃ gave butylbiguanide 19 at 20 °C (Scheme 4).\(^8\)

A monosaccharide 22 containing the biguanide functionality had no hypoglycemic activity (Scheme 5) at the doses tested.\(^9\) The isothiocyanate 20 was treated with guanidine 13 to afford 21, which was then treated with ethyl iodide, followed by an excess of phenylethylamine to give 22 (a 7:3 mixture of β/α anomers).
Scheme 5

Compounds $24$ [6-biguanidino-1,2;3,5-bis-O-(1-methylethylidene)-6-deoxy-α-D-glucofuranose] and $26$ [methyl 6-biguanidino-6-deoxy-2,3,4-O-tribenzyl-α-D-glucopyranoside] exhibit hypoglycemic activity close to that of Phenformin $63$ and Metformin $64$ (see Figure 5) as measured by the inhibition of rise of blood glucose levels, and were prepared as shown in Scheme 6.$^9$

Scheme 6
A high-purity biguanide derivative 28 was prepared by treatment of the phenoxyalkylamine salt 27 with cyanoguanidine 6 in high yields (Scheme 7).\(^{10}\)

\[
\begin{align*}
\text{OCH}_2\text{CHNH}_2\text{H}_X & \quad \text{N}_2\text{N} \quad \text{NH}_2 \quad \text{CN} \\
\text{R}_1^1 & \quad \text{R}_2^2 \\
27 & \quad 6 \\
\rightarrow & \\
\text{OCH}_2\text{CHNH} & \quad \text{N}_2\text{N} \quad \text{NH}_2 \\
\text{R}_1^1 & \quad \text{R}_2^2 = \text{alkyl group} \\
28 & \quad X = \text{halogen}
\end{align*}
\]

Scheme 7

The aryl-alkylamine hydrochlorides 29 and dicyandiamide 6 give the 1-aralkyl biguanides 30 at 120-150 °C. (Scheme 8).\(^{11}\)

\[
\begin{align*}
\text{OCH}_2\text{CHNH}_2\text{HCl} & \quad \text{N}_2\text{N} \quad \text{NH}_2 \quad \text{CN} \\
\text{F} & \quad \text{Et} \\
29 & \quad 6 \\
\rightarrow & \\
\text{OCH}_2\text{CHNH} & \quad \text{N}_2\text{N} \quad \text{NH}_2 \\
\text{F} & \quad \text{Et} \\
30
\end{align*}
\]

Scheme 8

The biguanide transfer reagent 31 converted glycine, β-alanine, 3-aminopropanoic acid, and taurine into the desired biguanide analogs 32a-d (Scheme 9).\(^{12}\)

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \quad \text{SCH}_3 \\
\text{N}_2\text{N} \quad \text{H}_2 & \quad \text{N} \quad \text{R} \\
31 & \quad 2 \text{eq. Et}_3\text{N} \\
\rightarrow & \quad \text{aq. EtOH, 60 °C} \\
\text{N}_2\text{N} \quad \text{H}_2 & \quad \text{N} \quad \text{NH}_2 \\
32a-d & \quad R = -\text{CH}_2\text{-COOH} \\
& \quad -\text{CH}(\text{CH}_3)\text{-COOH} \\
& \quad -\text{CH}_2\text{CH}_2\text{-COOH} \\
& \quad -\text{CH}_2\text{CH}_2\text{-SO}_3\text{H}
\end{align*}
\]

Scheme 9
Organ’s group\(^\text{13}\) produced an array of alkyl- and aryl-based biguanide compounds \(34\) and \(36\) using microwave irradiation, starting from the substituted benzylamine \(33\) and anilines \(35\) with dicyandiamide \(6\) in average yields of 40\% (Scheme 10). These compounds showed significant inhibitory activity of dihydrofolate reductase (DHFR).

\[
\begin{align*}
R^1\text{-}C_6H_4\text{-NH}_2 + \text{H}_2\text{N}-\text{N}=\text{CN} & \xrightarrow{\text{conc. HCl (1.05 eq)}} \xrightarrow{\text{heat, solvent}} \text{R}^1\text{-C}_6\text{H}_4\text{-N}N\text{-N}\text{Cl} \\
R^1\text{-C}_6\text{H}_4\text{-NH}_2 + \text{H}_2\text{N}-\text{N}=\text{CN} & \xrightarrow{\text{conc. HCl (1.05 eq)}} \xrightarrow{125^\circ\text{C}, 15 \text{ min, solvent}} \text{N}N\text{Cl} \\
\end{align*}
\]

Yields 22-58\% and 2-85\%.

Scheme 10

LeBel and his group synthesized the mono-substituted aryl-biguanides \(38\) from \(37\) and dicyandiamide, \(6\), by heating the mixture under reflux conditions for 12 h, in a modification of the method reported by Curd and Rose (Scheme 11).\(^\text{1a}\)

\[
\begin{align*}
\text{NH}_3\text{Cl}^- + \text{H}_2\text{N}-\text{N}=\text{CN} & \xrightarrow{\text{H}_2\text{O/heat}} \text{NH}_2\text{N}-\text{N}=\text{CN} \\
\end{align*}
\]

Scheme 11

Neelakantan synthesized the 1,5-diarylbiguanides \(41\) by using a one-pot procedure, from aniline derivatives \(40\) and phenylcyanoguanidine \(39\) at 100 °C (Scheme 12).\(^\text{14}\)

\[
\begin{align*}
\text{R}\text{-C}_6\text{H}_4\text{-NH}_2 + \text{H}_2\text{N}-\text{Ar} & \xrightarrow{\text{HCl}} \xrightarrow{\text{H}_2\text{O/heat}} \text{N}N\text{Cl} \\
\end{align*}
\]

Yields: 30-75\%.

Scheme 12
Molina et al synthesized the penta-substituted biguanides 43 by reacting 1,3-diaryl-2,4-bis-(heteroarylimino)-1,3-diazetidines 42 with primary amines in dry methylene chloride at room temperature in 47-96% yield (Scheme 13). \(^{15}\)

\[
\begin{align*}
\text{Het} & \quad \text{Ar} \quad \text{Het} \quad + \quad R-NH_2 \\
\begin{array}{c}
\text{42} \\
\end{array} & \Rightarrow \\
\begin{array}{c}
\text{Het} \quad \text{N} \quad \text{N} \quad \text{Het} \\
\text{Ar} \quad \text{NH} \quad \text{HN} \quad R \\
\end{array} \\
\begin{array}{c}
\text{43} \\
\end{array}
\end{align*}
\]

Scheme 13

Gelbard et al synthesized \(N\)-alkylated biguanides 44-46 through addition of 1,1,3,3-tetramethylguanidine (TMG) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) to di-isopropylcarbodiimide (DiP) and dicyclohexylcarbodiimide (DCCI) as shown in Scheme 14. \(^{16a}\)

\[
\begin{align*}
\text{DiP} & \quad + \quad \text{TMG} \quad \rightarrow \quad 94\% \\
\begin{array}{c}
\text{44} \\
\end{array} \\
\begin{array}{c}
\text{iPr} \quad \text{NH} \quad \text{NMe}_2 \\
\text{N} \quad \text{N} \\
\text{iPr} \quad \text{NMe}_2 \\
\end{array} \\
\begin{array}{c}
\text{DiP} \\
\text{TBD} \\
\text{DCCI} \\
\end{array} & \quad + \quad \text{TMG} \quad \rightarrow \quad 62\% \\
\begin{array}{c}
\text{45} \\
\end{array} \\
\begin{array}{c}
\text{NH} \quad \text{NMe}_2 \\
\text{N} \quad \text{N} \\
\end{array} \\
\begin{array}{c}
\text{DiP} \\
\text{TBD} \\
\end{array} & \quad + \quad \text{TBD} \quad \rightarrow \quad 43\% \\
\begin{array}{c}
\text{46} \\
\end{array} \\
\begin{array}{c}
\text{NH} \\
\text{N} \\
\text{iPr} \\
\text{iPr} \\
\end{array}
\end{align*}
\]

Scheme 14

Gelbard et al also synthesized a polystyrene-supported biguanide 48 by the nucleophilic addition of 1,1,3,3-tetramethylguanidine (TMG) to the polymeric carbodiimide 47. They showed
that the biguanide 48 was an excellent recyclable catalyst for the transesterification of triglycerides (Scheme 15).\textsuperscript{16a,b}

Scheme 15

Vicente and coworkers synthesized the porphyrin derivative 50 containing a biguanidine unit by treatment of the mono-amino porphyrin 49 in dicyanamide in the presence of HCl and isopropanol at 90 °C for 18 h (Scheme 16).\textsuperscript{17} The fluorescence quantum yield determined for 50 is higher at low pH (<6) and showed low dark-toxicity toward human carcinoma HEp2 cells.

Scheme 16

A series of polymeric biguanide hydrochlorides 53, 56, 59 containing hexamethylene groups was synthesized by developing methods for melt- and solution- polymerization, based on the
reaction of cyano groups with amine hydrochlorides (Schemes 17-19). The polybiguanide salts in both aqueous and polar non-aqueous solutions showed typical solution viscosity features of polyelectrolytes. The polybiguanides readily formed colored complexes with copper ions.

\[
\begin{align*}
\text{Scheme 17. Melt polymerization.} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 18. Solution polymerization.} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 19. Melt polymerization.} \\
\end{align*}
\]
2.3 Biological properties of biguanides

2.3.1 Antimalarial activity. Malaria is an infectious disease causing enormous public health problems. The disease is caused by protozoan parasites of the genus *Plasmodium*. Biguanides possess antimalarial activity and (N-(4-chlorophenyl)-N’-(isopropyl)-imidodicarbonimidic diamide (Proguanil) 60 (Figure 3) has been used as an antimalarial drug.19a-k

![Figure 3](image)

Jensen *et al.* recently synthesized 34 analogs of the biguanide PS-15 (61a) and a prodrug of diaminotriazine WR-99210 (62). Several of them, such as 61b (PS-33) and 61c (PS-26), maintain or exceed the *in vivo* activity of PS-15 and do not require the use of highly regulated starting materials (Figure 4).19f

![Figure 4](image)

2.3.2 Hypoglycemic agents. Diabetes mellitus is one of the most serious public health problems and has a rapidly increasing incidence, especially in the West. Diabetes is an enormous economic burden in the industrialized world, accounting for huge healthcare costs.20a,b Biguanides are widely used for the treatment of Type 2 diabetes mellitus [e.g., 1,1-dimethylbiguanide (metformin) 63, and phenylethylbiguanide (phenformin) 64 (Figure 5)].20c-e Metformin 63 is a
potent anti-diabetic agent currently used as a first-line treatment for patients with type 2 diabetes. In 2003, Hundal and Inzucchi reviewed the role of metformin in the treatment of patients with Type 2 diabetes and described the benefits it provides over and above its effect on glucose levels alone.

**Figure 5**

2.3.3 **Antitumor activity.** The antitumor activity of biguanides has been mentioned frequently since preliminary reports by Kundu *et al.* in 1967 on pyrimidinodiguanidines as anticancer drugs. Lugaro and co-workers found that mono- and di- substituted biguanidines exhibited antitumor activity. Sączewski and co-workers used biguanides in the synthesis of 2,4-diamino-1,3,5-triazine derivatives, which showed moderate to strong growth inhibition activity on various tumor panel cell lines between 0.148 and 56.2 µM concentrations. Ghosh and co-workers have reported antitumor properties of boron complexes with hydroxy- biguanidine.

2.3.4 **Spasmolytic agents.** Diamond and co-workers found that 1-substituted phenyl biguanides possess useful gastric anti-secretory and spasmolytic agents (Figure 6).

**Figure 6**

2.3.5 **Antiseptic properties.** Tsubouchi and co-workers synthesized 1,5-disubstituted biguanidines, and the bactericidal activity in 3,4-dichlorobenzyl derivatives was found to be high (Figure 7).
Zhang’s group synthesized the water-soluble polyhexamethylene biguanidine hydrochloride (PHBGC) 67 and the lipophilic polyhexamethylene biguanide stearate (PHBGS) 68, and tested their antimicrobial activity (Figure 8). The polymeric biguanides are effective in controlling both bacteria and fungi.

3. Guanylureas

3.1 Methods of preparation
Treatment of 2-amino-4-chloro-1,3,5-triazine 69 with water gave guanylurea 70 (Scheme 20).
The guanylurea derivatives 74 are also obtained by condensation of N-Cbz-ureido-N’-Cbz-S-methylisothiourea 72 with amines 71 in the presence of triethylamine in DMF at 20 °C, followed by hydrogenation (Scheme 21).29

\[
\begin{align*}
&\text{R} = \begin{cases} 
\text{NH} & 81\% \\
\text{O} & 75\% \\
\text{NH}_2 & 99\% \\
\text{NH}_2 & 48\% 
\end{cases}
\end{align*}
\]

Scheme 21

Guanylurea nitrate (GUN) 76a and guanylurea perchlorate (GUP) 76b were prepared by hydrolysis of cyanoguanidine (CG) 6 with the corresponding concentrated acid in aqueous solution (Scheme 22).30

\[
\text{H}_2\text{O} \quad \text{reflux} \quad \begin{cases} 
\text{A}^- = \text{NO}_3^-, \text{ClO}_4^- & 
\end{cases}
\]

Scheme 22

Katritzky and his co-workers reported the synthesis of guanylureas 80 from (benzotriazol-1-yl)carboximidamides 78 by treatment of 78 with isocyanate followed by amines (Scheme 23).31
Scheme 23

3.2 Applications of guanylureas
Salts of protonated guanylurea with dinitramide 81,32 the nitrate 76a and the perchlorate 76b anions30 (Figure 9) have been prepared for use as energetic materials.

Figure 9

4. Guanylthioureas

4.1 Methods of preparation
Mono-N-substituted guanylthioureas 84 are synthesized in two steps: (i) reaction of dicyanamide with an amine and (ii) treatment of the resulting cyanoguanidine 83 with hydrogen sulfide at 80°C (Scheme 24).33
Scheme 24

Reiter and co-workers synthesized mono-N-substituted guanylioureas, \( \text{87} \), in 28-75% yields by mono-S-alkylation of dithiobiuret, \( \text{85} \), to give the corresponding thio-uronium salt \( \text{86} \), which was treated with amines to provide the desired mono- N-substituted guanylioureas \( \text{87} \) (Scheme 25).\(^{34}\)

Scheme 25

Tari and Gajary synthesized guanylioureas \( \text{92} \) by reacting dicyandiamide derivatives, \( \text{88} \), and sodium thiosulfate in acidic medium, followed by neutralization with a base (Scheme 26).\(^{35}\)

This reaction involves three steps: (a) the addition of two moles of hydrogen chloride to dicyandiamide, (b) addition of thiosulfuric acid to afford acidic hydrolysis of the product, and (c) release of the free guanyliourea by treatment with ammonium hydroxide.

\[ \text{R} = \text{H}, \text{b) } \text{R} = \text{Me}, \text{c) } \text{R} = \text{Et}, \text{d) } \text{R} = n-\text{Pr}, \text{ e) } \text{R} = i-\text{Pr}, \text{ f) } \text{R} = n-\text{Bu} \]
4.2 Applications of guanylthioureas
Guanylthiourea derivatives have immuno-stimulant and tumor cell inhibitory activity and can significantly inhibit dihydrofolate reductase (DHFR). Guanylthiourea is introduced into the structure of ion-exchange/coordinating resins having a vinylbenzyl chloride/divinylbenzene matrix in order to detect metal cations.

5. Conclusions

In this overview, we have attempted to summarize the classical and more recent preparation of biguanidines, guanylureas and guanylthioureas together with their applications. We have also modified the literature structures of biguanides to indicate the most stable tautomeric form where necessary.

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References and Notes

Biographical Sketches

Alan R. Katritzky is Kenan professor of Chemistry and Director of the Center for Heterocyclic Compounds at the University of Florida, USA. He was born in England where he studied, researched and taught at the Universities of Oxford, Cambridge and East Anglia. In 1980 he moved to his present post at the University of Florida. His research interests encompass much of heterocyclic chemistry, together with synthetic methods, physical organic chemistry and quantitative structure-property relationships. He has traveled widely, and consulted and published extensively. Further details of his current activities and news of his group and ex-group members may be found at his home page: http://www.ark.chem.ufl.edu.

Srinivasa R. Tala received his Masters in chemistry from Andhra University and Ph. D. in Organic Chemistry from Indian Institute of Technology, Delhi in 2004 under the supervision of Professor Pramod S. Pandey. His doctoral work was focused on the application of 1,3-dipolar cycloaddition reactions in the synthesis of Atorvastatin and studies on 1,3-dipolar cycloaddition reactions of nitrones. He joined Prof. Alan R. Katritzky’s research group at the Center for Heterocyclic Compounds, University of Florida, as a postdoctoral fellow in 2004. Currently he is working as a Senior Group Leader at the Center for Heterocyclic Compounds, University of Florida. His research interests include heterocyclic chemistry, benzotriazole-assisted synthetic methodologies, drug design, synthesis of peptides and biologically active compounds.
Anamika Singh received her Masters in chemistry from Banaras Hindu University and Ph. D. in organic chemistry from Indian Institute of Technology, Delhi in 2006 under the supervision of Professor Upender K. Nadir. In her doctoral work, she developed methodologies to synthesize chiral diamines and diamino acids. She started her postdoctoral research with Prof. Alan R. Katritzky at Center for Heterocyclic Compounds, University of Florida, where she was involved in benzotriazole-assisted synthetic methodology from 2005-2007. Currently, she is working as Postdoctoral fellow with Professor Carrie Haskell-Luevano at the Department of Pharmacodynamics, University of Florida with interests in drug design and synthesis of melanocortin receptor agonists, antagonists, and peptidomimetics.