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Guanidine Group: Definition and Pharmaceutical Applications.

Majeed Khalaf[1], Dheaa Zageer[1,2], Zainab Hussain[3], Hadeel Adil[1], Salam Mohammed[4], and Emad Yousif[1]*

[1]Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq.
[2]Forensic DNA Center for Research and Training, Al-Nahrain University, Baghdad, Iraq.
[3]Department of Chemistry, College of Science, Misan University, Misan, Iraq.
[4]College of Engineering and Architecture, University of Nizwa, Birkat Almouz, 616 Nizwa, Oman.

ABSTRACT

In the past couple of decades, the interest of guanidinium groups in biological, pharmaceutical and supra molecular applications has been ignited. They are valuable precursors of numerous medicinally important molecules and are assets in biological research. The chemical properties of the guanidinium group as well as its ability to form H-bonds, charge pairing and cation-π interactions opens up a large number of possibilities in molecular recognition.

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Corresponding author

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Guanidine Definition

Guanidine, also called carbamidine, is a nitrogen organic base, has been widely used in the synthesis of heterocyclic compounds incorporating at least two nitrogen atoms. This moiety is present in the side-chain of the amino acid arginine and plays an important role in the interaction with enzymes or receptors through hydrogen bonding and/or electrostatic interactions [1]. The guanidine group defines chemical and physicochemical properties of many compounds of medical interest. Trimethoprim **1**, sulfadiazine **2**, and Gleevec (imatinib mesilate) **3** are examples of pharmaceutically important guanidine-containing heterocycles (Figure 1). In peptides, residue of arginine has a guanidine structure in the protonated form as guanidinium ion, which functions as an efficient identi_cation moiety of anionic substrates such as carboxylate, nitronate, and phosphate functionalities. The guanidinium ion is also involved in many enzymatic transformations, because it can orient specific substrates based on their electronic characteristic and it is able to form a transition state assembly with the substrates to reduce the activation energy or to stabilize anionic intermediates [2].

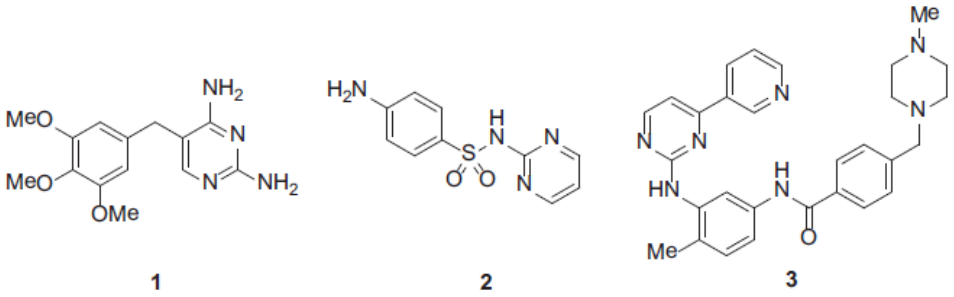

Figure 1: Typical compounds containing a guanidine substructure.

Chemical structure

Guanidine can be thought of as a nitrogenous analogue of the carbonic acid functional group. That is, the C=O group in carbonic acid is replaced by a C=NH group, and each OH is replaced by a NH_2 group [3]. A detailed crystallographic analysis of guanidine was elucidated 148 years after its first synthesis, despite the simplicity of the molecule [4]. In 2013, the positions of the hydrogen atoms and their displacement parameters were accurately determined using single-crystal neutron diffraction [5]. (Figure 2).

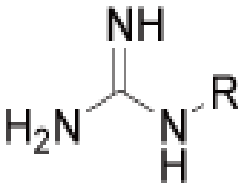

Figure 2: Chemical structure of guanidine.

Important of Guanidine group

As we mentioned that guanidinium moiety is found in Arginine amino acid, this amino acid is found in numerous enzyme active sites and cell recognition motifs. Horseradish peroxidase, fumarate reductase and creatine kinase [6] are just a few enzymes that have arginine containing active sites. The tripeptide sequence RGD (Arg-Gly-Asp) is a common cell recognition motif responsible for the binding of the integrin receptors. This sequence has been used as a lead structure for the development of different integrin antagonists. while carboxylic guanidino analogs are used as influenza neuroaminidase inhibitors . Guanidinium-based molecules are also extensively used as cardiovascular drugs, antihistaminines, anti-inflammatory agents, antidiabetic drugs, antibacterial and antifungal drugs, antiprotozal and other antiparasitic drugs and antiviral drugs.

Guanidinium derivatives (Impromidine and related compounds) are also used as histamine H_2-receptor agonists and as NPY Y_1-receptor antagonists [7]. Guanidinium-containing compounds such as guanidinoacetic acid are used as artificial sweeteners [8], bicyclic guanidines catalyze the enantioselective Strecker synthesis and modified guanidines are also used as potential chiral super bases. The guanidinium ion and its many derivatives have been widely studied in the context of anion binding [9] .

The guanidinium moiety is one of the most hydrophilic functional groups known. Solvation by water is so efficient that despite the favorable binding pattern, ion pairing with carboxylates and phosphates in aqueous solution is negligible (K_S < 5 M-1). Bridging by water molecules may even allow the electrostatic repulsion to be overcome and lead to face-to-face dimerization of two guanidinium cations. The extreme basicity of guanidine (13.5), which is conserved or even enhanced by prudent substitution [10].

Application of Guanidine

Guanidine based pharmaceutical compounds

A large number of natural and synthetic guanidine compounds are being used as therapeutic compound having broad spectrum of medicinal activity. The biguanidine group also appears in a number of important therapeutic agents [11]. Some of the examples are as under:

Drugs for central nervous system

Neuropeptide Y (NPY) plays an important role as a neurotransmitter in the central and peripheral nervous system. In human four receptor subtypes, referred as NPY-Y_1, Y_2, Y_4 and Y_5 receptors, mediate the biological effects of NPY. NG-Acyl argininamides are NPY Y1 receptor (Y1R) antagonist. In central nervous system Y1R activation produces the sedative effects and is involved in the stimulation of food intake.

Cardiovascular drugs & antihypertensive drugs

Amiloride, Triamterene (potassium sparing diuretic that promotes the loss of sodium and water from the body without depleting potassium), Doxazosin mesylate, Prazosin, Terazosin, (alpha blockers, that lower blood pressure by relaxing blood vessels), Clonidine, Guanabenz, Guanethidine, Moxonidine, Aproclonidine, Guanfacine, (lower the blood pressure by activating alpha receptors in the central nervous system which open the peripheral arteries); Trimazosin, Guanadrel, Guanaxone, Guanazodine and Guanochlor are the well known examples of guanidine based drugs [12].

Antihistamines drugs

Cimeitadine, Famotidine and Dispacamide are well known medicines used for the treatment of ulcer.

Antidiabetic drugs

Metformin, Phenformin and 3-guanidinopropionicacid are being used for the treatment of diabetes. It is reported that hetero-aryl guanidine derivatives also exhibit the antidiabetic activity. R. H. Bahekar et al. tested several substituted guanidines and found N-(2-methyl,5-chloro-1H-indol-3-yl)-guanidine as an effective antidiabetic compound [13].

Antibiotic drugs

Streptomycine, Trimethoprim (mainly used for urinary tract infection) and Chlorhexidine are the guanidine derivatives used as antibiotic drugs. Polyhexamethylene biguanidine is used as a disinfectant for swimming pools, fabrics conditioning and wound care. Pyrrolidine bis-cyclic guanidines are reported to be active against Gram-positive methicillin-resistant pathogens Staphylococcus aureus (MRSA) [14]. C. Kratzer et al. reported a novel polymeric guanidine Akacid plus exhibiting excellent in vitro antimicrobial activity against different strains of bacteria and fungi [15]. Another copolymer of guanidine hydrochloride and hexamethylene diamine with crosslinking of epichlorohydrin was reported by L. Qian et al. having antimicrobial activity. The

presence of four-membered ring containing quaternary ammonium group was found to improve the antimicrobial activity.

Anti-inflammatory drugs

Leucettamine extracted from a sponge and then totally synthesized has been shown to poses a role as mediator of inflammation [16]. H. MavarManga et al. extracted N1,N2-diisopentylguanidine and N1,N2,N3-triisopentylguanidine from Alchornea cordifolia (plant in Africa) which exhibited significant antiinflammatory activity [17]. 3,4-dimethoxyphenethyl-β-guanidine extracted from 10 Aplidium orthium (New Zealand) is reported as potential anti-inflammatory compound.

Antiprotozoal drugs

Guanidine based drugs are used against the diseases produced by protozoa or other lower animals. Paludrine and Chlorguanide are antimalarial drugs. Melarsoprol is uesd for the last stage treatment of Human African Trypanasomiasis (HAT) "sleeping sickness" caused by the protozoan parasites Trypanasoma brucei [18]. Woster and coworkers have reported some alkylpolyaminoguanidines and alkylpolyaminobiguanidines as potent antitripanosomal compounds [19]. H Berber et al. synthesized 5-benzyl-6-trifluoromethyl-2,4-diaminopyrimidines and 6-aryl-5- trifluoroethyl-2,4-diaminopyrimidines and tested for their in vitro anti-toxoplasmosis activity (disease produced by protozoa Toxoplasma gondii).

Influenza inhibitor

Zanamivir is drug containing guanidine moiety and is effective against all types of flu. P. Chand et al. synthesized guanidine derivatives of pyridine and reported as influenza inhibitors [20].

Anti-obesity drugs

Metformin and 3-guanidinopropionicacid are used to control the excessive weight of the body. Aminoguanidines and diaminoguanidines analogues of 3- guanidinopropionicacid are also synthesized and found effective [21]. Biguanidines and NG-Acyl argininamides are also reported to regulate the food intake and obesity control.

Anticoagulant

substituted guanidines especially acylguanidines are reported as thrombin inhibitor (Factor Xa inhibitor) for the treatment of uncontrolled blood coagulation [22].

Anti-viral drugs

Fomivirsen is used to treatment of cytomegalovirus (CMV) retinitis and AIDS. 4-carbamoyl-5-(4,6-diamino-2,5-dihydro-1,3,5-triazin-2-ylimidazole-1-β-D ribofuranoside is also reported to exhibit activity against different viral strands [23].

Histamine receptors and arginine-type NPY Y1 receptor antagonists

G-proteincoupled receptors (GPCRs; a large family proteins imbibed in the cell membrane and act as transmembrane receptors that sense the signals outside the cells and activate the transduction pathway and ultimately cellular response e.g. Histamine receptor, neuropeptide receptors) represent a major class of biological targets in drug discovery and certain studies are available on the exploration of guanidine-acylguanidine as histamine H2, H3, H4 receptor and arginine-type NPY Y_1 receptor antagonists [24].

NHE-1 inhibitors

Na^+/H^+ exchanger (NHE) system is a mechanism which is used to maintain the intracellular physiological pH. During injuries the accumulation of intracellular protons leads to the activation of Na^+/H^+ exchanger, which exchanges intracellular H^+ for extracellular Na^+ to regulate intracellular pH. Although it is an

essential mechanism but an excessive stimulation of NHE results in an increase in Na^+ concentration. Since Na^+ and Ca^{2+} transport are coupled the situation leads to raised intracellular Ca^{2+}. This cellular Ca^{2+} overload is assumed to be involved in ischemic and reperfusion injuries, like arrhythmias, myocardial contracture, stunning, tissue necrosis and certain physiological disorders in the body. Most of the NHE-1 inhibitors have acylguanidine structure with quite diverse aryl ring templates including benzene, pyrazole, quinoline, and indole, etc. [25].

Others drugs

Tizanidine (muscle relaxant); Romifidine (vetnary medicine, sedative or analgesic); Brimonidine (to treat ocular hypertension, effect on optical nerves due to high blood pressure); Amidinoureas (in treating irritable bowel syndrome, gastrointestinal, spasmolytic and cardiovascular disorders and parasitic infestations) are the drugs containing the guanidine moiety [26].

CONCLUSION

In this review, the important of guanidine compounds in different fields especially the medicinal activity of these compounds have been studied, and we concluded that these compounds have very active role in this field.

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