



Applications of Guanidine in Pharmaceutical Field

Zainab Hussain¹, Majid Khalaf², Hanan Ibraheem² and Emad Yousif^{2*}

¹Department of Chemistry, College of Science, Misan University, Misan, Iraq

²Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq

ABSTRACT

In the past couple of decades, the interest of guanidinium groups in biological, pharmaceutical and supra molecular applications have 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.

Keywords: Guanidine; Drugs; Pharmaceutical

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 [1]. 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-Y₁, Y₂, Y₄ and Y₅ 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 [2].

Antihistamines drugs

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

Antidiabetic drugs

Metformin, Phenformin and 3-guanidinopropionic acid 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 [3].

Antibiotic drugs

Streptomycin, 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) [4]. C. Kratzer et al. reported a novel polymeric guanidine Akacid plus exhibiting excellent in vitro antimicrobial activity against different strains of bacteria and fungi [5]. 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 pose a role as mediator of inflammation [6]. H. MavarManga et al. extracted N1,N2-diisopentylguanidine and N1,N2,N3-triisopentylguanidine from *Alchornea cordifolia* (plant in Africa) which exhibited significant anti-inflammatory activity [7]. 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 used for the last stage treatment of Human African Trypanosomiasis (HAT) "sleeping sickness" caused by the protozoan parasites *Trypanosoma brucei* [8]. Woster and coworkers have reported some alkylpolyaminoguanidines and alkylpolyaminobiguanidines as potent antitrypanosomal compounds [9]. 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 [10].

Anti-obesity drugs

Metformin and 3-guanidinopropionic acid are used to control the excessive weight of the body. Aminoguanidines and diaminoguanidines analogues of 3-guanidinopropionic acid are also synthesized and found effective [11]. 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 [12].

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-yl)imidazole-1- β -D ribofuranoside is also reported to exhibit activity against different viral strands.

Histamine receptors and arginine-type NPY Y₁ receptor antagonists

G-proteincoupled receptors (GPCRs; a large family proteins imbedded 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 Y₁ receptor antagonists.

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 Ca²⁺ 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. [13].

Others drugs

Tizanidine (muscle relaxant); Romifidine (veterinary 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 [14].

CONCLUSIONS

In this review, the important of guanidine compounds in pharmaceutical field have been studied, and we concluded that these compounds have very active role in this field.

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