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A REVIEW ON STRUCTURE ACTIVITY RELATION SHIP OF AND THEIR ORAL HYPOGLYCEMIC AGENTSTHERAPEUTIC SIGNIFICANCE.

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ABSTRACT :

Biguanides constitute a versatile class of compounds with significant therapeutic value and a wide range of biological activities. While metformin remains the cornerstone of biguanide-based therapy for type 2 diabetes mellitus, extensive research has led to the synthesis of novel biguanide derivatives with enhanced pharmacological properties. Structural modifications of the biguanide framework, including incorporation into heterocyclic systems, aromatic ring substitutions, halogenation, and coordination with metal ions, have been shown to markedly influence biological activity. Structure–activity relationship (SAR) investigations indicate that factors such as electronic effects, lipophilicity, molecular size, and hydrogen-bonding capability play critical roles in determining target affinity, cellular permeability, potency, and selectivity.

The incorporation of biguanide groups into heterocyclic scaffolds, including benzimidazole, imidazole, triazole, and pyrimidine derivatives, has produced compounds exhibiting not only improved antidiabetic activity but also promising anticancer, antimicrobial, anti-inflammatory, and cardioprotective effects. In addition, functional group modifications, particularly halogen substitution, have contributed to improved metabolic stability and favorable pharmacokinetic characteristics. Emerging studies on Schiff base-derived biguanides and metal-complex analogues further demonstrate the potential of these compounds as innovative therapeutic agents against cancer and microbial infections.

This review provides a comprehensive overview of recent advances in the SAR of biguanide derivatives and examines the relationship between structural features and pharmacological performance. The therapeutic applications of these compounds across metabolic, oncological, and infectious diseases are discussed, along with current challenges and future prospects in rational drug design. Understanding these SAR patterns may support the development of next-generation biguanide-based drugs with enhanced efficacy, selectivity, and safety. [46,41,39,40]

KEY WORDS:

Biguanides, Metformin, Structure–Activity Relationship, Heterocyclic Derivatives, Antidiabetic Activity, Anticancer Activity, Antimicrobial Activity, Schiff Bases, Metal Complexes, Drug Design.

1. INTRODUCTION:

Biguanides represent an important class of bioactive compounds that have attracted considerable scientific interest due to their broad spectrum of pharmacological activities and therapeutic applications. The origins of biguanide research can be traced to investigations of *Galega officinalis* (French lilac), a medicinal plant traditionally used for the treatment of symptoms associated with diabetes. The isolation of guanidine-related compounds from this plant led to the development of synthetic biguanides, including metformin, phenformin, and buformin. Although some early members of this class were discontinued because of safety concerns, metformin demonstrated a favorable efficacy and safety profile and subsequently became the most widely prescribed oral medication for the management of type 1 diabetes mellitus.

The clinical success of metformin has stimulated extensive research into the biological properties of biguanides beyond glycemic control. In addition to their well-established antihyperglycemic effects, accumulating evidence suggests that biguanides possess anticancer, anti-inflammatory, antimicrobial, cardioprotective, and neuroprotective activities. Epidemiological studies reporting reduced cancer incidence and improved clinical outcomes among diabetic patients receiving metformin have further accelerated interest in the therapeutic potential of this class. Consequently, numerous structural modifications of the biguanide scaffold have been explored to enhance potency, selectivity, pharmacokinetic behavior and tissue distribution.

The pharmacological activity of biguanides is strongly influenced by their chemical structure. Structure–activity relationship (SAR) studies have demonstrated that alterations in lipophilicity, electronic properties, steric characteristics, and hydrogen-bonding capacity significantly affect cellular uptake, target interactions, and biological efficacy. Incorporation of the biguanide moiety into heterocyclic frameworks such as benzimidazole, imidazole, triazole, and pyrimidine systems has yielded compounds with improved therapeutic profiles and expanded biological activities. Similarly, aromatic substitutions, halogen incorporation, Schiff base formation, and metal-complex conjugation have generated derivatives exhibiting enhanced metabolic stability and promising pharmacological effects.

At the molecular level, biguanides are known to influence multiple cellular pathways. Their antidiabetic activity is primarily associated with the regulation of glucose metabolism and cellular energy homeostasis, often involving activation of AMP-activated protein kinase (AMPK. In cancer research, biguanides have been shown to interfere with mitochondrial bioenergetics, suppress proliferative signalling pathways, and modulate tumor metabolism. Recent studies have also identified novel mechanisms involving lysosomal signalling and receptor modulation, highlighting the complexity of their biological actions. Furthermore, emerging evidence suggests that certain biguanide derivatives may interact with neuronal targets such as N-methyl-D-aspartate (NMDA) receptors, opening new possibilities for drug repurposing in neurodegenerative and neurological disorders.

The continuous search for safer and more effective therapeutic agents has encouraged the design and synthesis of structurally diverse biguanide derivatives. Understanding how specific structural modifications influence biological activity is essential for the rational development of next-generation compounds with improved efficacy and reduced adverse effects. Therefore, comprehensive evaluation of SAR trends remains a crucial component of modern biguanide research.

This review discusses the chemical diversity, structure–activity relationships, and pharmacological properties of biguanide derivatives. Particular emphasis is placed on the impact of structural modifications on therapeutic performance in metabolic disorders, cancer, infectious diseases, and emerging neurological applications. The current challenges and future opportunities in the development of biguanide-based therapeutics are also highlighted. [46,38,39]

2.METFORMIN:

Metformin: Absorption, Distribution, Therapeutic Concentrations, and Elimination [20,10]

Metformin (dimethylbiguanide) is the most commonly prescribed first-line medication for the management of type 2 diabetes mellitus (T2D). It belongs to the biguanide class of antidiabetic drugs and is currently the only biguanide in widespread clinical use due to its favorable safety profile compared with older agents such as phenformin and buformin. Although metformin was synthesized in the 1920s and its glucose-lowering effects were recognized early, its clinical application became established after studies in the 1950s demonstrated its efficacy in diabetic patients.

Metformin is administered orally as either immediate-release (IR) or extended-release (XR) formulations. Typical daily doses range from 500 mg to 2550 mg, with IR formulations generally taken two or three times daily and XR preparations administered once daily. Following oral administration, metformin dissolves readily in the gastrointestinal tract. However, because the molecule is highly hydrophilic and positively charged at physiological pH, it cannot diffuse passively across biological membranes. Instead, its absorption and tissue distribution depend on specialized membrane transport proteins.

Several organic cation transporters participate in metformin transport, including OCT1, OCT2, OCT3, PMAT, MATE1, MATE2K, and OCTN1. In the intestine, PMAT and OCT family transporters facilitate drug uptake across enterocytes. OCT3 is mainly located on the apical membrane of intestinal epithelial cells and mediates metformin entry into the cells, whereas OCT1 is predominantly found on the basolateral membrane and transports metformin into the circulation. These transporters are also expressed in metabolically important tissues such as the liver and skeletal muscle, allowing metformin to accumulate at its sites of action.

The liver is a major target organ for metformin. Hepatic uptake is largely mediated by OCT1 and OCT3, resulting in intracellular concentrations that are substantially higher than those found in plasma. Experimental studies in rodents have shown that liver concentrations may be several-fold greater than circulating levels, reflecting active transporter-mediated accumulation. Similar findings have been reported in isolated hepatocytes, where intracellular metformin concentrations exceed extracellular concentrations by approximately five- to eight-fold.

Unlike many drugs, metformin exhibits negligible binding to plasma proteins. Consequently, it distributes rapidly throughout body fluids and tissues. In patients receiving standard therapeutic doses (approximately 1.5–2.5 g/day), plasma concentrations generally range between 4 and 15 μm, although transient peak levels may be higher after individual doses. Studies have reported plasma concentrations of approximately 8–12 μm after a single 500 mg dose and around 20–25 μm following a 1.5 g dose. Average steady-state concentrations during routine therapy are commonly observed near 4–10 μm.

Metformin accumulation is particularly pronounced in the gastrointestinal tract. Measurements obtained from patients receiving chronic treatment have demonstrated intestinal tissue concentrations that are tens to hundreds of times higher than plasma concentrations. Such findings support the hypothesis that the gut plays an important role in the therapeutic actions of metformin, in addition to its well-established hepatic effects.

Although direct measurements of hepatic metformin concentrations in humans are limited, pharmacokinetic modelling and animal studies suggest that liver concentrations may reach approximately 60–90 μm during conventional treatment. In rodents, plasma concentrations around 15 μm are often associated with liver concentrations near 40 μm. Much higher concentrations have been observed in experimental studies employing supratherapeutic doses, particularly in cancer research models.

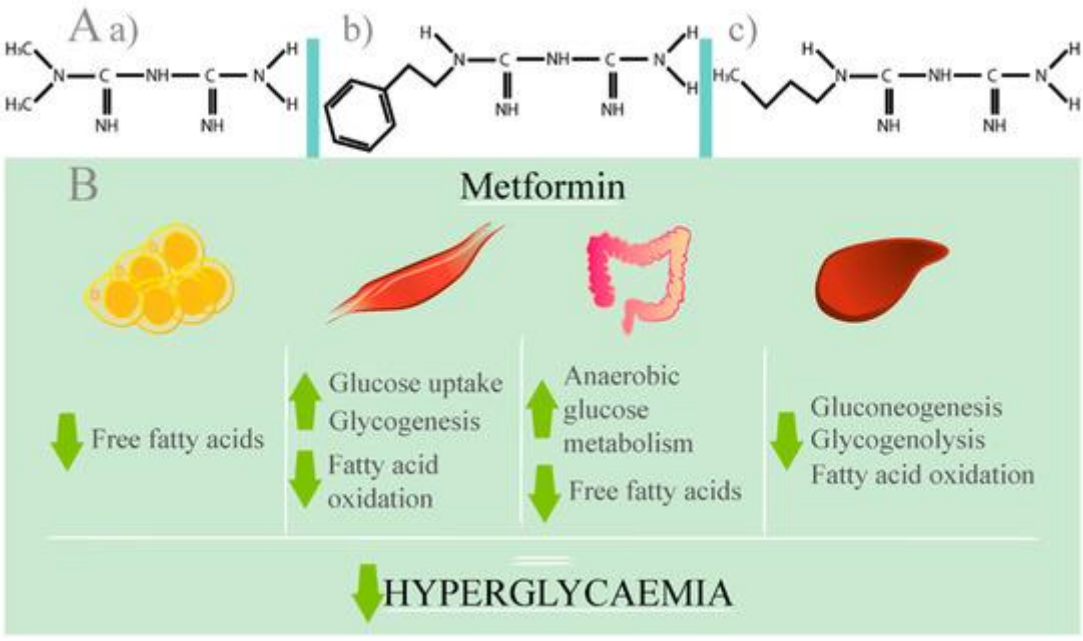
Metformin pharmacokinetics are characterized by rapid elimination from the circulation. Following intravenous administration, plasma concentrations decline quickly over several hours. The drug is not metabolized by the

liver and is excreted unchanged through the kidneys. Renal handling of metformin involves active secretion by transport proteins located in renal tubular cells. OCT2 mediates uptake from the bloodstream into tubular epithelial cells, while MATE1 and MATE2K transport metformin into the tubular lumen for urinary excretion. OCT1 and OCT3 may also contribute to renal transport processes.

Renal clearance of metformin is high, typically ranging between approximately 500 and 650 mL/min, indicating substantial active tubular secretion in addition to glomerular filtration. The plasma elimination half-life generally falls between 1.5 and 5 hours. Because renal excretion is the primary route of elimination, impaired kidney function significantly reduces metformin clearance and increases systemic exposure. Genetic variations affecting OCT and MATE transporter activity can also influence drug disposition and individual responses to therapy.

Analytical determination of metformin in biological samples is important for pharmacokinetic and therapeutic studies. Although mass spectrometry-based techniques provide excellent sensitivity and specificity, they require specialized equipment and expertise. High-performance liquid chromatography (HPLC) remains one of the most widely used methods for quantifying metformin in plasma and tissues because of its simplicity, accuracy, and cost-effectiveness. Various chromatographic approaches employ mobile phases containing combinations of acetonitrile, methanol, phosphate buffers, ammonium salts, or acidic modifiers to achieve reliable separation and detection.

Overall, metformin demonstrates efficient transporter-mediated absorption, extensive tissue distribution with preferential accumulation in the liver and intestine, minimal protein binding, and elimination through unchanged renal excretion. These pharmacokinetic characteristics contribute significantly to its effectiveness and safety as the cornerstone therapy for type 2 diabetes mellitus.



Metformin: Absorption, Distribution, Therapeutic Concentrations, and Elimination

3.PHENFORMIN:

Phenformin is a lipophilic biguanide derivative structurally related to metformin, distinguished by the presence of a phenethyl substituent attached to the terminal nitrogen atom of the biguanide nucleus. This structural modification significantly increases its hydrophobicity compared to metformin, influencing both its

pharmacokinetic behavior and biological activity. Initially introduced as an oral antihyperglycemic agent for the treatment of type 2 diabetes mellitus, phenformin demonstrated potent glucose-lowering effects. However, its clinical use was largely discontinued because of an elevated risk of lactic acidosis, particularly in patients with impaired renal function or other predisposing conditions.

The increased lipophilicity of phenformin enhances its ability to cross biological membranes, resulting in greater intracellular accumulation and pharmacological potency than metformin. Unlike metformin, which relies heavily on organic cation transporters for cellular uptake, phenformin can enter cells more readily through passive diffusion. Nevertheless, transporter-mediated mechanisms still contribute to its distribution, especially within mitochondria and renal tissues. Studies have shown that transport proteins such as OCTN1 and OCT2 play important roles in the mitochondrial uptake and renal handling of phenformin, respectively.

Following oral administration, phenformin is rapidly absorbed and distributed throughout the body. It undergoes partial hepatic metabolism, primarily through hydroxylation reactions mediated by cytochrome P450 enzymes, particularly CYP2D6. Both the parent drug and its metabolites are predominantly eliminated through renal excretion. Variability in metabolic enzyme activity and transporter expression can substantially influence systemic drug exposure and toxicity. Individuals with reduced CYP2D6 activity or impaired renal clearance may experience elevated plasma concentrations, increasing the likelihood of adverse effects.

Beyond its antidiabetic activity, phenformin has attracted considerable interest for its potential anticancer properties. Due to its efficient cellular uptake and mitochondrial accumulation, phenformin exerts a stronger inhibitory effect on mitochondrial oxidative phosphorylation than metformin. This disruption of cellular energy production leads to metabolic stress, activation of AMP-activated protein kinase (AMPK), and suppression of anabolic pathways involved in cell growth and proliferation. Consequently, phenformin has demonstrated significant antitumor activity in a variety of preclinical cancer models, including pancreatic, breast, lung, and melanoma cancers.

Recent investigations have also suggested that phenformin may possess therapeutic potential beyond metabolic disorders and oncology. Emerging evidence indicates that certain biguanides, including phenformin, can modulate neuronal signalling pathways and interact with N-methyl-D-aspartate (NMDA) receptors, highlighting possible applications in neurodegenerative and neurological diseases. Although these findings remain at an early stage, they illustrate the expanding pharmacological scope of biguanide-based compounds.

Despite its withdrawal from routine diabetic therapy, phenformin remains an important molecule in medicinal chemistry and drug discovery. Its higher potency compared with metformin provides valuable insights into the relationship between lipophilicity, cellular transport, mitochondrial targeting, and biological activity. Understanding these structure–activity relationships may facilitate the design of next-generation biguanide derivatives that retain therapeutic efficacy while minimizing the risk of toxicity.[52,53]

PHENFORMIN

Structural Features | Pharmacological Activities | Limitations

- Biguanide nucleus
- Phenethyl group
- High lipophilicity

- Antidiabetic
- Anticancer
- Neuroprotective

Lactic Acidosis Risk

Enhanced Cell Permeability

Mechanism of Action

Increased Cellular Uptake

Mitochondrial Complex I Inhibition

↓ ATP Production

AMPK Activation

Glucose Lowering & Inhibition of Tumor Cell Grow

- PHENFORMIN

High Lipophilicity

Enhanced Cellular Uptake

Mitochondrial Complex I Inhibition

AMPK Activation

Antidiabetic | Anticancer | Neuroprotective

Activity Activity Potential

▼

Risk of Lactic Acidosis[36,45].

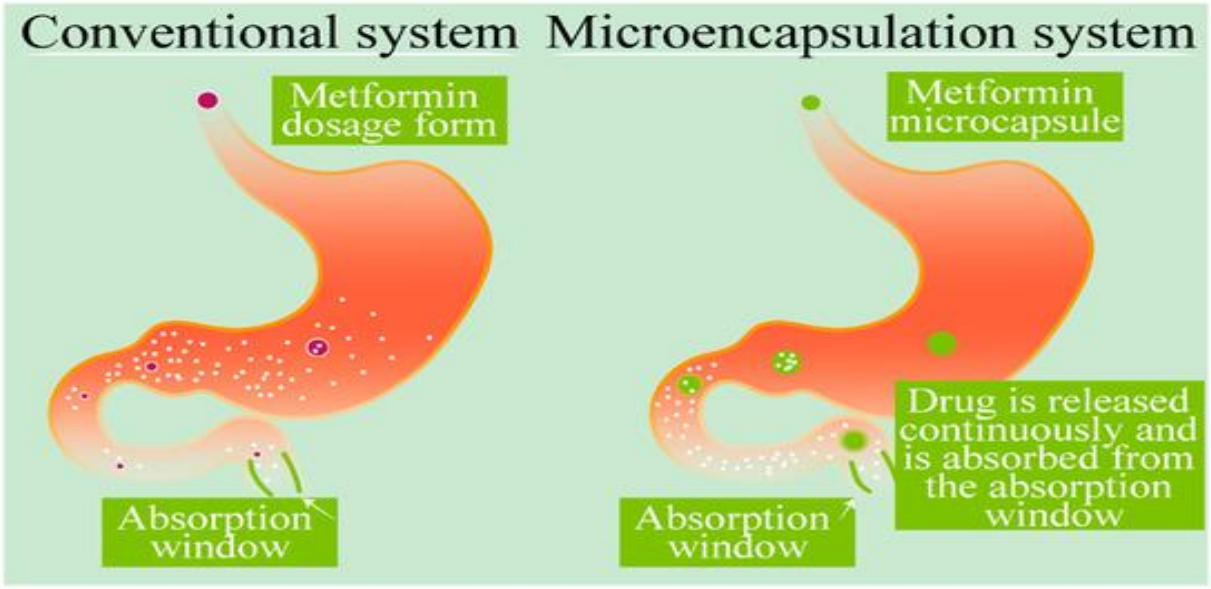
2.1: ENCAPSULATION OF METFORMIN:

controlled-release formulation for metformin aims to prolong the drug's residence time in the gastrointestinal tract so that it is released steadily at its primary absorption site, the small intestine. This approach is important because conventional oral metformin delivery suffers from limited absorption efficiency and variable bioavailability[2,3,41,45], which restricts its effectiveness and potential application beyond type 2 diabetes management.

To address these limitations, researchers have explored nano- and microencapsulation strategies. These systems are designed to protect metformin from rapid dissolution and enhance its controlled release profile. Various formulation techniques have been studied for this purpose. For example, solvent evaporation methods using polymers such as ethyl cellulose and Eudragit systems have been widely investigated to create sustained-release microcarriers. Similarly, spray drying techniques allow the formation of fine encapsulated particles with improved stability and release control. Another promising approach is ionic gelation, which commonly involves natural polymers like alginate combined with other biocompatible materials to form gel-based delivery matrices capable of gradual drug release.

These encapsulation technologies are often compared with conventional dosage forms, highlighting the advantages of modified-release systems in maintaining more consistent plasma drug levels and reducing dosing frequency. In addition to microencapsulation, nanotechnology-based systems have also been explored to further enhance targeting and absorption efficiency. Although these nano formulations show encouraging results, challenges remain in optimizing their long-term safety, scalability, and cost-effectiveness for clinical use.

Overall, ongoing research in advanced drug delivery systems not only seeks to improve metformin's pharmacokinetic profile but also opens possibilities for repurposing it in other conditions, including metabolic disorders and certain types of cancer, due to its broader biological activity.



CONVENTIONAL SYSTEM MICROENCAPSULATION SYSTEM

4.MECHANISM OF ACTION OF BIGUANIDES :LESSONS FROM TYPE 2 DIABETES MELLITUS :

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes observed in the population and a leading cause of death. T2DM is characterized by insulin resistance, βcell dysfunction, and elevated hepatic glucose output mainly attributed to an increase in gluconeogenesis[4,7].

Biguanides have been used for the treatment of type 2 diabetes mellitus (T2DM) for more than 70 years and metformin is the most prescribed oral anti-diabetic agent worldwide, taken by over 150 million people annually. Metformin prevents body weight gain and does not cause hypoglycemia, which is frequently associated with the use of other antidiabetic drugs. Moreover, metformin may have therapeutic potential in the treatment of conditions such as nephropathy, polycystic ovary syndrome, and cardiovascular diseases, often associated with diabetes or insulin resistance.

The pleiotropic properties of metformin suggest that the drug acts on multiple tissues, but the underlying mechanism of action remains debated.

Most of the studies on the mechanism of action of biguanides, especially metformin, have been conducted in T2DM models, trying to identify the primary target and the consequences of its alteration. These studies have then ignited investigation in tumor models, to determine if the effectors and mechanisms operating in diabetes could also be responsible for the antitumor properties of these drugs.

The main and best studied site of the antidiabetic action of biguanides is the liver, where these drugs reduce hepatic gluconeogenesis, through various mechanisms discussed below. However, other studies have also proposed the gut and skeletal muscle as additional sites responsible for the blood-glucose-lowering properties of biguanides.

Liver as a Target Tissue:

A clinical study using ^{13}C nuclear magnetic resonance spectroscopy showed that metformin reduces fasting plasma glucose concentrations in diabetic patients by decreasing hepatic glucose production (HGP) by about 25% and gluconeogenesis (two to three times higher in diabetics than in control patients) by about 35%, without affecting glycogenolysis.

Several mechanisms have been identified for the action of biguanides in hepatic gluconeogenesis and glucose production, which are generally thought to be mediated by the interaction of the drugs with two main cell compartments: mitochondria (energy or redox alterations) or lysosomes

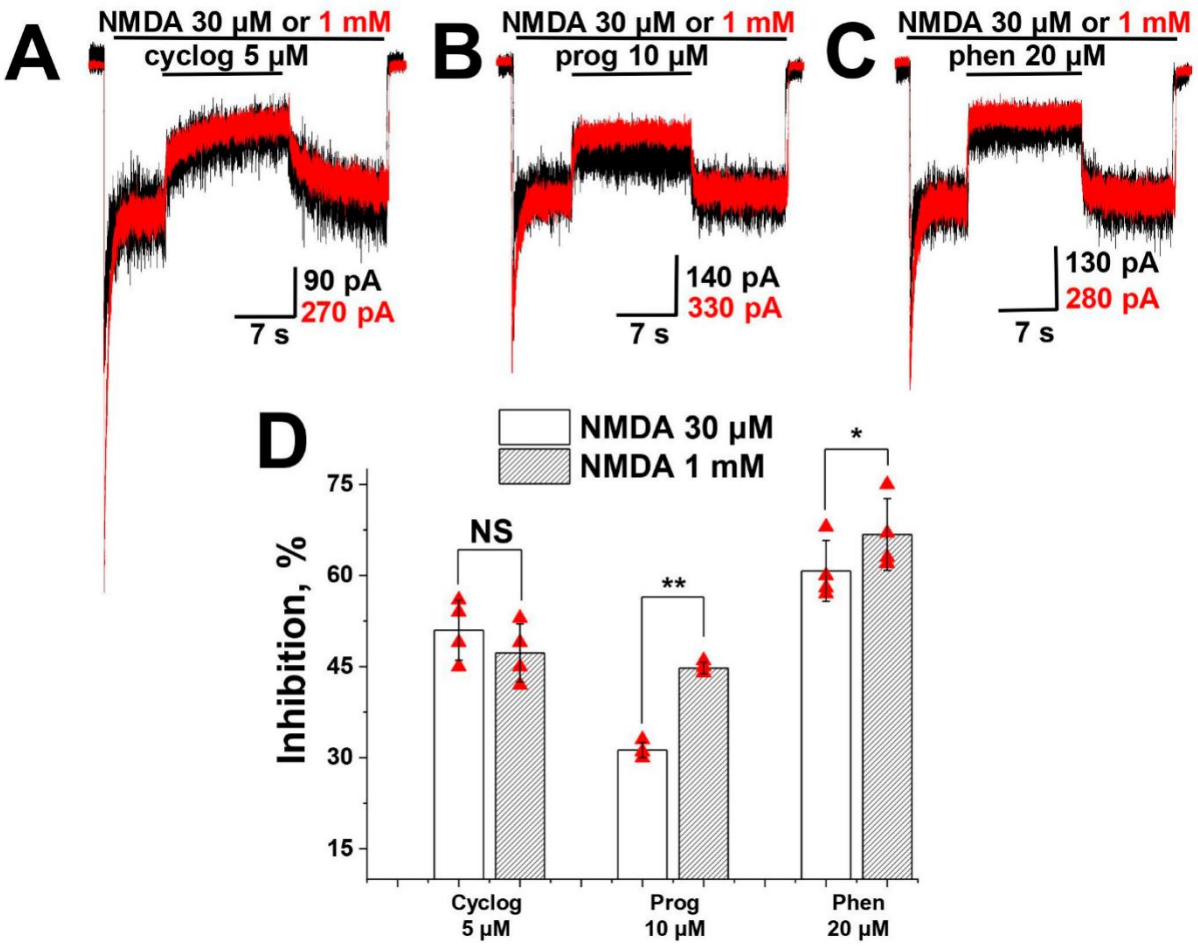
5.AGONISTIC DEPENDENCE:

Determine whether the inhibitory effects of proguanil, cycloguanil, and phenformin on NMDA receptors are competitive or non-competitive, receptor responses were evaluated at two different NMDA concentrations: 30 µm, which elicited approximately 40% of the maximal response (340 ± 120 pA, n = 7), and 1000 µm, which produced nearly 90% of the maximal response (720 ± 260 pA, n = 7). Representative recordings and summarized results

An increase in agonist concentration did not reduce the inhibitory actions of any of the tested compounds. Since competitive antagonists typically exhibit diminished inhibition at higher agonist concentrations, these findings indicate that the inhibitory mechanisms of proguanil, cycloguanil, and phenformin are not competitive in nature. Similar non-competitive behavior has also been reported previously for other amidine- and guanidine-containing compounds.

Agonist concentration dependence of biguanide-mediated inhibition of NMDA receptors. Representative traces illustrate the effects of 5 µM cycloguanil (A), 10 µM proguanil (B), and 20 µm phenformin (C) on NMDA receptor currents evoked by 30 µM and 1 mM NMDA. Panel (D) summarizes the quantitative data. Cycloguanil

displayed agonist-independent inhibition, whereas proguanil and phenformin produced stronger inhibition at the higher agonist concentration. These observations further support a non-competitive mode of inhibition for all three compounds. Statistical significance was assessed using a paired t-test, where NS indicates a non-significant difference ($p > 0.05$), * denotes $p < 0.005$, and ** denotes $p < 0.001$.



6.Chemical Structure of Biguanides:

The fundamental structure of biguanides consists of a highly basic nitrogen-rich framework represented as:

$HN=C(NH)-NH-C(NH)-NH_2$

This biguanide nucleus serves as the essential pharmacophore responsible for biological activity. Structural modifications around this nucleus significantly affect the drug's pharmacological properties. [39,46]

Structure–Activity Relationship (SAR) of Biguanide Derivatives:

7.1. Importance of the Biguanide Nucleus:

The biguanide moiety is indispensable for antihyperglycemic activity. Any significant alteration or disruption of this core structure results in a marked reduction or complete loss of biological activity. Therefore, the intact biguanide framework is considered the primary requirement for therapeutic effectiveness. [40,46

7.2. Effect of Alkyl Substitution:

Substitution of alkyl groups on the terminal nitrogen atoms enhances the pharmacological activity of biguanides. These substituents influence drug absorption, distribution, and interaction with biological targets. Small alkyl groups generally improve oral bioavailability while maintaining a favorable safety profile. [39,41]

7.3. Influence of Lipophilicity:

The degree of lipophilicity plays a crucial role in determining potency. Increased lipophilicity improves membrane permeability and enhances glucose-lowering effects. However, excessive lipophilicity may also increase tissue accumulation and toxicity. The relative potency of major biguanides follows the order:

Phenformin > Buformin > Metformin

Although phenformin is more potent, its higher lipophilicity contributes to a greater risk of adverse effects. [1,45]

7.4. Dimethyl Substitution in Metformin:

Metformin contains two methyl groups attached to one terminal nitrogen atom. This modification provides an optimal balance between efficacy and safety. The dimethyl substitution improves oral absorption and reduces the risk of severe adverse reactions, particularly lactic acidosis.

7.5. Aromatic Substitution:

Introduction of aromatic groups, as seen in phenformin, increases lipid solubility and pharmacological potency. However, such modifications also increase the likelihood of drug accumulation in tissues, thereby elevating the risk of toxicity. [39,40]

7.6. Basicity and Biological Activity:

Biguanides are strongly basic compounds. Their basic nature facilitates interactions with cellular targets involved in glucose metabolism. A reduction in basicity generally leads to decreased therapeutic activity. [41,40]

8.CONCLUSION:

The study of biguanide derivatives has evolved from a narrow focus on antidiabetic therapy to a broad and multidisciplinary field encompassing medicinal chemistry, pharmacology, oncology, microbiology, and drug delivery science. Over several decades, these compounds have demonstrated remarkable therapeutic versatility, establishing themselves as one of the most significant classes of bioactive molecules in modern medicine. The continued scientific interest in biguanides is largely driven by their unique ability to influence multiple biological pathways while maintaining a relatively simple and adaptable chemical structure. As a result, the biguanide scaffold remains an attractive platform for the development of novel therapeutic agents designed to address both existing and emerging healthcare challenges.

A central finding emerging from the investigation of biguanide derivatives is the critical role played by chemical structure in determining biological activity. The biguanide nucleus itself serves as the primary pharmacophore responsible for therapeutic action, and preservation of this core framework is essential for maintaining biological effectiveness. At the same time, strategic structural modifications around the nucleus can profoundly influence pharmacological properties, including potency, selectivity, tissue distribution, metabolic stability, and safety. Structure–activity relationship studies have consistently demonstrated that alterations in lipophilicity, electronic characteristics, steric properties, and hydrogen-bonding capabilities significantly affect the interaction of biguanides with their biological targets. These observations highlight the importance of rational molecular design in optimizing therapeutic outcomes.

Among the various members of the biguanide family, metformin remains the most successful and clinically relevant compound. Its widespread use as a first-line treatment for type 2 diabetes mellitus reflects a favorable balance between efficacy and safety. Unlike earlier biguanides, metformin possesses pharmacokinetic characteristics that minimize toxicity while maintaining effective glucose-lowering activity. Its transporter-mediated absorption, extensive tissue distribution, negligible plasma protein binding, and renal elimination

contribute to its well-established therapeutic profile. Furthermore, decades of clinical experience have provided substantial evidence supporting its long-term effectiveness and tolerability. Consequently, metformin continues to serve as the reference compound against which newly synthesized biguanide derivatives are evaluated.

The success of metformin has stimulated extensive research aimed at understanding the mechanisms underlying its therapeutic actions. Although the reduction of hepatic glucose production remains a key component of its antidiabetic effect, contemporary studies indicate that metformin influences multiple cellular processes. Regulation of energy metabolism, modulation of mitochondrial function, activation of AMP-activated protein kinase [42,43,48], and interactions with lysosomal signaling pathways all contribute to its pharmacological activity. These diverse mechanisms help explain the broad range of biological effects associated with metformin and provide a foundation for exploring additional therapeutic applications beyond glycemic control.

Phenformin represents another important member of the biguanide family and offers valuable insights into the relationship between chemical structure and biological activity. The presence of a phenethyl substituent increases the lipophilicity of phenformin, resulting in enhanced cellular uptake and greater pharmacological potency compared with metformin. However, this increased potency is accompanied by a substantially greater risk of adverse effects, particularly lactic acidosis. The clinical history of phenformin illustrates the delicate balance that must be achieved between therapeutic efficacy and patient safety during drug development. Despite its withdrawal from routine diabetic treatment, phenformin remains an important research tool and continues to attract attention because of its potent anticancer properties[34,40,50].

One of the most significant advances in biguanide research has been the development of heterocyclic derivatives. Incorporation of the biguanide moiety into heterocyclic frameworks such as benzimidazole, imidazole, triazole, and pyrimidine systems has generated compounds with enhanced biological activity and exanded therapeutic potential. These structural modifications can improve receptor binding, optimize pharmacokinetic properties, and increase molecular stability. In many cases, heterocyclic biguanides exhibit stronger pharmacological effects than traditional derivatives while simultaneously demonstrating broader activity profiles. Such compounds provide important opportunities for the development of multifunctional drugs capable of targeting complex disease processes through multiple mechanisms of action.

The introduction of aromatic substituents has also played a crucial role in enhancing the therapeutic performance of biguanide derivatives. Aromatic groups can increase lipophilicity, strengthen molecular interactions with biological targets, and improve membrane permeability. These effects frequently translate into enhanced pharmacological potency. However, excessive lipophilicity may also promote tissue accumulation and increase toxicity. Therefore, aromatic substitution strategies must be carefully optimized to achieve an appropriate balance between efficacy and safety. The lessons learned from compounds such as phenformin continue to guide modern efforts to design structurally modified biguanides with improved therapeutic indices.

Halogen substitution represents another valuable approach in the optimization of biguanide derivatives. The incorporation of fluorine, chlorine, bromine, or other halogen atoms can significantly influence electronic properties, metabolic stability, and molecular interactions. In many instances, halogenated derivatives demonstrate enhanced potency, improved pharmacokinetic characteristics, and prolonged duration of action. These favorable effects are often attributed to the ability of halogen atoms to modify electron distribution within the molecule and strengthen interactions with target proteins. Consequently, halogenation remains an important strategy in the rational design of next-generation biguanide-based therapeutics.

The emergence of Schiff base-derived biguanides has further expanded the chemical diversity and therapeutic potential of this class of compounds. Schiff base formation introduces additional functional groups capable of participating in molecular recognition and target binding. These derivatives frequently exhibit enhanced biological activity and may offer improved selectivity toward specific disease-associated targets. In addition, Schiff base biguanides often serve as versatile intermediates for the synthesis of more complex therapeutic

agents. Their structural flexibility and broad pharmacological potential make them attractive candidates for future medicinal chemistry investigations.

Metal-complex biguanides constitute another innovative area of research. Coordination of biguanide ligands with metal ions can generate compounds possessing unique physicochemical and biological properties that differ substantially from those of the parent molecules. Metal complexation may alter redox behavior, facilitate cellular uptake, and enhance interactions with intracellular targets. Several metal-containing biguanide derivatives have demonstrated promising anticancer and antimicrobial activities in experimental studies. These findings suggest that the combination of biguanide pharmacophores with carefully selected metal centers may provide a productive strategy for developing novel therapeutic agents capable of overcoming limitations associated with conventional treatments.

The anticancer potential of biguanides has become one of the most intensively investigated aspects of contemporary research. Epidemiological observations indicating reduced cancer incidence among diabetic patients receiving metformin initially stimulated interest in this field. Subsequent laboratory studies confirmed that biguanides can interfere with mitochondrial energy metabolism, suppress cellular proliferation, and induce metabolic stress within tumor cells. These effects appear particularly relevant in malignancies characterized by altered metabolic requirements. Phenformin, because of its greater cellular penetration and mitochondrial accumulation, often demonstrates stronger anticancer activity than metformin in experimental models. Nevertheless, the safety profile of metformin continues to make it the preferred candidate for clinical investigation. The ongoing exploration of structurally modified biguanides may eventually lead to compounds that combine the anticancer potency of phenformin with the favorable safety characteristics of metformin.

Emerging evidence also suggests that certain biguanide derivatives possess neuroprotective and neuromodulatory properties. Experimental studies have indicated that some compounds within this class can influence neuronal signaling pathways and modulate receptor activity. Observations involving interactions with NMDA receptors and other neurological targets have generated interest in the potential application of biguanides to neurodegenerative and neurological disorders. Although this area of research remains in its early stages, it highlights the remarkable versatility of the biguanide scaffold and underscores the importance of continued investigation into previously unrecognized therapeutic opportunities.

Another major development in the field has been the advancement of drug delivery technologies designed to improve the clinical performance of biguanide-based therapies. Conventional oral administration of metformin is associated with limitations such as incomplete absorption, gastrointestinal side effects, and variable bioavailability. Encapsulation techniques, controlled-release formulations, nanoparticle systems, and targeted delivery approaches have been developed to address these challenges. Such technologies can improve therapeutic efficacy, reduce dosing frequency, enhance patient compliance, and minimize adverse effects. Furthermore, advanced delivery systems may facilitate the use of biguanides in new therapeutic settings where conventional formulations are less effect.

Future research should focus on integrating medicinal chemistry, molecular biology, computational modelling, pharmacokinetics, and advanced formulation science to accelerate the development of improved biguanide derivatives. Artificial intelligence–assisted drug design, structure-based optimization, and precision medicine approaches may further enhance the discovery of compounds with superior efficacy and safety profiles. Greater understanding of disease-specific molecular pathways is also expected to facilitate the identification of new therapeutic indications for biguanide-based agents.

In summary, biguanide derivatives represent a highly adaptable and therapeutically valuable class of compounds whose significance extends well beyond diabetes management. Structure–activity relationship investigations have demonstrated that carefully designed structural modifications can profoundly influence pharmacological behavior and therapeutic performance. Continued advances in medicinal chemistry and pharmaceutical

technology are expected to generate increasingly sophisticated derivatives capable of addressing diverse medical needs. The future of biguanide research is therefore characterized by substantial promise, with opportunities for innovation in metabolic disorders, cancer, infectious diseases, neurological conditions, and numerous other therapeutic areas [39,46,40]. Through continued scientific exploration and rational drug design, biguanides are likely to remain at the forefront of pharmaceutical research and contribute significantly to the development of safer, more effective, and more versatile therapeutic agents

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