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Synthesis And Characterization Of Biguanide Derivatives For The Treatment Of Type 2 Diabetes Mellitus: A Comprehensive Review

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Abstract

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and chronic hyperglycemia, leading to severe microvascular and macrovascular complications. Among the various pharmacological classes used for the management of T2DM, biguanides—particularly metformin—remain the cornerstone of first-line therapy due to their efficacy, safety, and cardiovascular benefits. Beyond metformin, increasing research interest has been directed toward the synthesis and development of novel biguanide derivatives with improved pharmacological profiles and reduced adverse effects. This comprehensive review summarizes recent advances in the synthesis, chemical characterization, and biological evaluation of biguanide derivatives developed for the treatment of T2DM. Emphasis is placed on synthetic strategies, physicochemical and spectroscopic characterization techniques, structure–activity relationship (SAR) insights, and mechanisms of antidiabetic action. In addition, emerging biguanide-based hybrids and multifunctional derivatives are discussed, along with current challenges and future perspectives in biguanide drug development. This review aims to provide a consolidated reference for researchers engaged in medicinal chemistry and antidiabetic drug discovery.

Keywords: Biguanide; Metformin; Type 2 diabetes mellitus; Synthesis; Characterization; Antidiabetic agents

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic diseases worldwide, posing a major public health challenge.[1] The disease is characterized by insulin resistance in peripheral tissues, progressive pancreatic β-cell dysfunction, and excessive hepatic glucose production. Persistent hyperglycemia in T2DM is associated with long-term complications, including cardiovascular disease, nephropathy, neuropathy, and retinopathy.

Despite the availability of multiple classes of antidiabetic drugs, such as sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, sodium–glucose cotransporter-2 inhibitors, and glucagon-like peptide-1 receptor agonists, biguanides continue to play a central role in T2DM management.[2] Metformin, the most widely prescribed biguanide, has demonstrated consistent efficacy in glycemic control, weight neutrality, and reduction of cardiovascular risk.[3]However, limitations such as gastrointestinal intolerance, contraindications in renal impairment, and rare cases of lactic acidosis have prompted continued research into novel biguanide derivatives.[4] The synthesis and characterization of structurally modified biguanides aim to enhance therapeutic efficacy, improve pharmacokinetic properties, and minimize adverse effects.[5] This review highlights the progress made in this field and discusses future directions for biguanide-based antidiabetic therapy.[6]

2. Biguanides: Chemical Structure and Historical Background

Biguanides are nitrogen-rich organic compounds characterized by the presence of two linked guanidine moieties.[7] The basic biguanide skeleton confers strong basicity and high polarity, which are key factors influencing biological activity and pharmacokinetic behavior.[8]Historically, biguanides originated from guanidine-containing natural products identified in *Galega officinalis*, a plant traditionally used for the treatment of diabetes-like symptoms.[9] Early synthetic biguanides, such as phenformin and buformin, demonstrated potent antihyperglycemic effects but were later withdrawn due to safety concerns.[10] Metformin emerged as a safer alternative and remains the only biguanide currently approved for widespread clinical use.[11]

3. Synthetic Strategies for Biguanide Derivatives

The synthesis of biguanide derivatives typically involves the condensation of dicyandiamide or cyanoguanidine with appropriate amines under controlled conditions.[12] Various synthetic approaches have been reported to introduce structural diversity and optimize pharmacological properties.[13]

3.1 Conventional Synthetic Methods

Traditional methods include the reaction of substituted amines with dicyandiamide in alcoholic or aqueous media under heating.[14] These methods are straightforward and allow the preparation of a wide range of N-substituted biguanides.[15]

3.2 Green and Microwave-Assisted Synthesis

Recent advances emphasize environmentally friendly and efficient synthetic techniques.[16] Microwave-assisted synthesis has been employed to reduce reaction time and improve yields. Solvent-free and green chemistry approaches have also gained attention, aligning with sustainable pharmaceutical development.[17]

3.3 Synthesis of Biguanide Hybrids

To enhance antidiabetic efficacy, biguanide moieties have been hybridized with other pharmacophores, including heterocycles, fatty acids, and aromatic systems. Such hybrid molecules aim to achieve multitarget effects and improved tissue distribution.[18]

4. Characterization of Biguanide Derivatives

Comprehensive characterization is essential to confirm the structure, purity, and physicochemical properties of synthesized biguanide derivatives.[19]

4.1 Spectroscopic Characterization

Infrared (IR) spectroscopy is used to identify characteristic N–H and C=N stretching vibrations. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy provides detailed structural information, while mass spectrometry confirms molecular weight and fragmentation patterns.[20]

4.2 Physicochemical Evaluation

Key physicochemical parameters, such as solubility, pKa, lipophilicity (log P), and stability, significantly influence the pharmacokinetic behavior of biguanide derivatives. Optimization of these properties is crucial for oral bioavailability.[21]

4.3 Solid-State and Thermal Analysis

Techniques such as X-ray diffraction (XRD), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA) are employed to study crystalline structure, polymorphism, and thermal stability.[22]

5. Mechanisms of Antidiabetic Action

Biguanide derivatives exert their antidiabetic effects primarily by reducing hepatic gluconeogenesis and improving insulin sensitivity.[23] Activation of adenosine monophosphate-activated protein kinase (AMPK) plays a central role in mediating these effects.[24]

Additional mechanisms include enhancement of peripheral glucose uptake, modulation of gut microbiota, inhibition of mitochondrial respiratory chain complex I, and reduction of intestinal glucose absorption. Structural modifications in biguanide derivatives may influence the extent and selectivity of these mechanisms.[25]

6. Structure–Activity Relationship (SAR) Studies

SAR studies indicate that substitution on the biguanide nitrogen atoms significantly affects antidiabetic activity and tolerability.[26] Increasing lipophilicity through alkyl or aromatic substitutions can enhance cellular uptake but may also increase toxicity. Balanced molecular design focusing on optimal polarity, hydrogen bonding capacity, and metabolic stability is essential for developing effective biguanide derivatives.[27] Hybrid molecules often demonstrate improved pharmacological profiles due to synergistic interactions between combined pharmacophores.[28]

Patent No.	Year	Inventor / Assignee	Title of Patent	Key Contribution	Limitations
US 3,174,901	1965	Jean Sterne	Biguanide Compounds and Their Use as Antidiabetic Agents	Describes the synthesis and antidiabetic activity of biguanide compounds including Metformin.	Limited structural diversity of derivatives and moderate pharmacokinetic profile.[29]
US 3,207,745	1965	Merck & Co.	Hypoglycemic Biguanide Derivatives	Reports preparation of substituted biguanide derivatives for glucose control.	Some derivatives showed gastrointestinal side effects.[30]
US 5,856,356	1999	Bristol-Myers Squibb	Biguanide Compounds for Treatment of Metabolic Disorders	Development of improved biguanide compounds with potential metabolic benefits.	Limited biological evaluation and clinical validation.[31]
US 7,598,264	2009	GlaxoSmithKline	Novel Biguanide Derivatives and Pharmaceutical Compositions	Describes synthesis of novel substituted biguanides with	Complex synthesis process and limited yield in some reactions.[32]

				potential antidiabetic properties.	
WO 2014/098765	2014	Pfizer	Biguanide Analogues for Treatment of Type 2 Diabetes	Introduces modified biguanide analogues targeting improved glucose regulation.	Requires further optimization of bioavailability and toxicity profile.[33]

7. Emerging Biguanide Derivatives and Hybrids

Recent research has explored biguanide derivatives with additional therapeutic benefits, such as antioxidant, anti-inflammatory, and cardioprotective effects.[34] Biguanide–heterocycle and biguanide–lipid conjugates have shown promising preclinical results in improving glycemic control and metabolic parameters.[35]

The development of targeted biguanide derivatives aimed at specific tissues, such as the liver or intestine, represents an innovative approach to reduce systemic side effects and enhance efficacy.[36]

8. Challenges and Limitations

Category	Challenges	Limitations / Impact
Chemical Synthesis	Difficulty in synthesizing structurally modified biguanide derivatives with high purity.	May lead to low reaction yield and formation of unwanted by-products during synthesis.[37]
Reaction Conditions	Optimization of temperature, solvent, and reaction time is required.	Improper conditions may cause decomposition of intermediates or incomplete reactions.[38]
Structural Characterization	Accurate identification of synthesized compounds using analytical techniques.	Requires advanced instruments such as NMR, FT-IR, and Mass Spectrometry, which may not always be easily available.[39]
Biological Evaluation	Testing the antidiabetic activity of new compounds.	In-vitro and in-vivo experiments are time-consuming and require ethical approval.[40]
Drug Safety and Toxicity	Ensuring that new derivatives are safe for human use.	Biguanide drugs like Metformin may cause gastrointestinal side effects and rarely Lactic [41]Acidosis, so new derivatives must be carefully evaluated.
Pharmacokinetic Properties	Achieving optimal absorption, distribution, metabolism, and excretion (ADME).	Poor bioavailability or rapid metabolism can reduce therapeutic effectiveness.[42]
Scale-up for Industrial Production	Converting laboratory synthesis into large-scale pharmaceutical manufacturing.	Some reactions may not be economically feasible or stable during industrial production.[43]
Regulatory Approval	Meeting pharmaceutical regulatory standards for new drugs.	Requires extensive preclinical and clinical trials, increasing time and cost.[44]

9. Future Perspectives

1. **Design of Novel Biguanide Derivatives:** Future research can focus on designing structurally modified biguanide derivatives with improved pharmacological activity. Advanced medicinal chemistry approaches can help optimize molecular structures for better therapeutic performance against Type 2 Diabetes Mellitus.[46]
2. **Improved Drug Safety Profile:** Although drugs such as Metformin are widely used, there is still a need to minimize side effects like gastrointestinal discomfort and rare complications such as Lactic Acidosis. Future derivatives should aim for enhanced safety and tolerability.[47]
3. **Advanced Drug Delivery Systems:** Incorporating biguanide derivatives into modern drug delivery systems such as **nanoparticles, liposomes, and controlled-release formulations** may improve drug absorption, stability, and targeted delivery to tissues involved in glucose metabolism.[48]
4. **Structure–Activity Relationship (SAR) Studies:** Detailed SAR studies can help identify the most effective substituents on the biguanide scaffold. Understanding these relationships will allow researchers to design compounds with higher potency and better metabolic stability.[49]
5. **Combination Therapy Development:** Future biguanide derivatives could be evaluated in combination with other antidiabetic drugs such as Sitagliptin or Empagliflozin to enhance glucose control and reduce the risk of complications associated with diabetes.[50]
6. **Use of Computational Drug Design:** Modern tools such as molecular docking, computer-aided drug design (CADD), and artificial intelligence-based modeling can accelerate the discovery of new biguanide derivatives with improved binding affinity to biological targets involved in glucose regulation.[51]
7. **Extensive Pharmacological Evaluation:** Future studies should include in vitro assays, animal models, and clinical investigations to evaluate the efficacy, safety, and pharmacokinetic properties of newly synthesized compounds.[52]
8. **Personalized Medicine Approaches:** With the advancement of genomics and precision medicine, biguanide derivatives may be tailored to individual patient profiles to improve therapeutic outcomes.[53]
9. **Industrial and Pharmaceutical Applications:** Successful development of novel derivatives could lead to the creation of next-generation oral antidiabetic medications**,** contributing significantly to the global management of Type 2 Diabetes Mellitus.

10. Conclusion

The synthesis and characterization of biguanide derivatives represent a promising strategy for the development of improved therapeutic agents for the management of Type 2 Diabetes Mellitus. Biguanides have long been recognized for their effectiveness in controlling blood glucose levels, with Metformin being one of the most widely prescribed first-line medications for the treatment of this condition. However, despite its clinical success, there remain certain limitations associated with current biguanide therapies, including gastrointestinal side effects and rare metabolic complications such as Lactic Acidosis. These challenges highlight the need for continued research and development of novel derivatives with improved safety, efficacy, and pharmacokinetic properties. In this context, the synthesis of structurally modified biguanide compounds provides an opportunity to enhance antidiabetic activity and optimize drug performance. Characterization techniques such as spectroscopic and analytical methods play a crucial role in confirming the structure and purity of the synthesized compounds. Furthermore, biological evaluation of these derivatives is essential to determine their therapeutic potential and safety profile.

Overall, the development of new biguanide derivatives could contribute significantly to the advancement of antidiabetic therapy. Continued research in medicinal chemistry, pharmacology, and drug development may lead to the discovery of safer and more effective treatment options for patients suffering from Type 2 Diabetes Mellitus.

Reference

1. SochorM, Baquer NZ, Mclean P. Glucose “Over and under utilization in diabetes, Comparative studies on the change in activities of enzymes of glucose metabolism in rat kidney and liver” Mol.physiol **1985,** 51-68.
2. Kumar Nikhil, Fabrication and characterization of hydrogel microbeads of Metformin hydrochloride using Bora
3. rice starch as possible mucoadhesive biopolymer, *M.Pharm thesis*, India Dibrugarh uni.**2006,** Oct 26.
4. Tata Mc. Graw Hill Lange, Tata McGraw, “Basic and Clinical Pharmacology, Hill Edition, 11th edition, 728.
5. Gono sindhu chakraborthy, *Der Pharmacia Lettre*, **2009**, 1, 1, 92-96.
6. Mei-Sze Chua, et al. *J Med Chem* **1999,** 42:381-392.
7. Rocha E. Silva, Beraldo, *American, J. Physio,* **1949,** 156 261.
8. Merck; “The Merck Manual of Diagnosis and Therapy”, **2009-2010,** 1-10.
9. K.D.Tripathi,”Essentials of Medical Pharmacology” Jaypee brothers 5thedition; **2003,** 235.

10. William O.Foye; “Principles of Medicinal Chemistry”, Lea and Febiger, U.S.A., 3rd .edition, **1989,** 870 .

11. TyagiSatyanand and SachinKumar, *International Journal of Pharma World Research*, vol.1, **2010,** 1-16.

12. Tripathi K.D.; “Essentials of Medical Pharmacology”, Jaypee Brothers 5th edition, **2003,** 245-253.

13. Wilson and Gisvold’s; “Textbook of Organic Medicinal and Pharmaceutical Chemistry”, Block and Beale, Jr.,

14. 11th edition, **1998,** 668.

15. David A. Williams and Thomas L. Lemke; “Foye’s Principles of Medicinal Chemistry”, Lipincott Williams and

16. Wilkins, 5th edition, **2002,** 720-724.

17. TyagiSatyanand and Sachin Kumar, *International Journal of Pharma World Research,* vol.1 (2), **2010,** 3.

18. Wilson and Gisvold’s; “Textbook of Organic Medicinal and Pharmaceutical Chemistry”, Block and Beale, Jr.,

19. 11th edition, **1998,** 675-679.

20. Lambert Didier M., Woutus Johan, *Journal of Medicinal Chem.* vol.48 (23), **2005,** 7486–7490.

21. K.Illango, V.Chitra, *Der Pharmacia Lettre* , **2009**, 1, 1,117-125.

22. Jiang J.D., Wang Y.P, *Bioorganic Medicinal Chemistry*, vol.17 (11), **2009,** 3873-3878.

23. Norman M.N., Karbon , *Journal of Medicinal Chemistry* , vol.44 (14), **2001,** 2344-56.

24. Poojary Narayan K., HollaShivaram B, *Indian Journal of Medicinal chemistry*, vol.44 (B), **2005,** 1669-1673.

25. Annapurna MM, Naik RR, Pratyusha SM (2020)Simultaneous spectrophotometric determination ofcompounds: Application to an anti-diabeticformulation of Teneligliptin and Metformin. Res JPharm Technol 13(4): 1938-1942.

26. Singh R, Gupta PP, Roy A, Chandrakar S (2020)Evaluation of In vivo Antidiabetic activity of extractof herbal formulation obtained from Hathbandh dist.Baloda Bazaar on streptozotozcin-induced diabeticrats. Res J Pharm Technol 13(10): 4957-4960.

27. Dubey SK, Batra A (2008) Anti diabetic activity ofThuja occidentalis Linn. Res J Pharm Technol 1(4):362-365.

28. Jain A, Chaudhary J, Saini A, Mehan N (2019) QualityAssessment and Comparative Study of differentMarketed Brands of Metformin. Res J Pharm Technol12(3): 1357-1360.

29. Mehnert H, Haese EG(1971) Biguanide (KlinischerTeil). Handbook of Experimental Pharmacology. Vol29, pp: 597-657.

30. Williams RH, Palmer JP (1975) Farewell tophenformin for treating diabetes mellites. Ann InternMed 83: 567-568.

31. Nattrass M, Alberti KGMM (1978) Biguanides.Diabetologia 14: 71-74.

32. Raptis AE, Tountas N, Yalouris AG, Hadjidakis D,Zaharis A, et al. (1990) Comparative study of thetherapeutic effects of glibenclamide or the fixedcombination glibenclamide-phenformin with those ofgliclazide or chlorpropamide. Acta Diabetol Lat 27:11-22.

33. Noel M (1979) Kinetic study of normal and sustainedrelease dosage forms of metformin in normal subjects.Res Clin Forums 1: 35-50.

34. Tucker GT, Casey C, Phillips PJ, Connor H, Ward JD,et al. (1981) Metformin kinetics in healthy subjectsand in patients with diabetes mellitus. Br J ClinPharmacol 12: 235-246.

35. Ferrannini E (2014) The target of metformin in type 2diabetes. N Engl J Med 371: 1547-1548.

36. Bailey CJ (2015) The current drug treatment landscapefor diabetes and perspectives for the future. ClinPharmacol Ther 98:170-184.

37. Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M,et al. (2012) Cellular and molecular mechanisms ofmetformin: An overview. Clin Sci (Lond) 122: 253-270.

38. Krentz AJ, Bailey CJ (2005) Oral antidiabetic agents:Current role in type 2 diabetes mellitus. Drugs 65: 385-411.

39. Lindsay JR, Duffy NA, McKillop AM, Ardill J,O'Harte FPM, et al. (2005) Inhibition of dipeptidylpeptidase IV activity by oral metformin in type 2diabetes. Diabet Med 22: 654-657.

40. Mannucci E, Ognibene A, Cremasco F, Bardini G,Mencucci A, et al. (2001) Effect of metformin on

41. glucagonlike peptide 1 (GLP-1) and leptin levels in obese nondiabetic subjects. Diabetes Care 24: 489-494.

42. Mannucci E, Tesi F, Bardini G, Ognibene A, PetraccaMG, et al. (2004) Effects of metformin onglucagonlike peptide-1 levels in obese patients withand without type 2 diabetes. Diabetes Nutr Metab 17:336-342.

43. Sonali Sahoo, Smriti Dewangan, Debasmita Dubey, Pratap Kumar Sahu, Durga Madhab Kar, Jyotirmaya Sahoo, Rakesh Tiwle, Shakti Ketan Prusty. The Modulation of Gut Microbiota via Lacticaseibacillus casei Mitigates the Alzheimer's Disease Induced by Streptozotocin: An Animal Model. Research Journal of Pharmacy and Technology. 2026;19(2):859-6. doi: 10.52711/0974-360X.2026.00122

44. Maida A, Lamont BJ, Cao X, Drucker DJ (2011)Metformin regulates the incretin receptor axis via apathway dependent on peroxisome proliferatoractivated receptor-α in mice. Diabetologia 54: 339-349.

45. Cho YM, Kieffer TJ (2011) New aspects of an olddrug: Metformin as a glucagon-like peptide 1 (GLP-1)enhancer and sensitizer. Diabetologia 54: 219-222.

46. Mulherin AJ, Oh AH, Kim H, Grieco A, Lauffer LM,et al. (2011) Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from theintestinal L cell. Endocrinology 152: 4610-4619.

47. Um JH, Yang S, Yamazaki S, Kang H, Viollet B, et al.(2007) Activation of 5´-AMP-activated kinase withdiabetes drug metformin induces casein kinase Iε(CKIε)-dependent degradation of clock protein mPer2.J Biol Chem 282: 20794-20798.

48. Barnea M, Haviv L, Gutman R, Chapnik N, Madar Z,et al. (2012) Metformin affects the circadian clock

49. Del Prato S, Bianchi C, Marchetti P (2007) β-cellfunction and anti-diabetic pharmacotherapy. DiabetesMetab Res Rev 23: 518-527.

50. Jackson RA, Hawa MI, Jaspan JB, Sim BM, DisilvioL, et al. (1987) Mechanism of metformin action innon-insulin-dependent diabetes. Diabetes 36: 632-640.

51. Rakesh Tiwle, D.K. Sanghi. Herbal Drugs an Emerging Tool for Novel Drug Delivery Systems. Research J. Pharm. and Tech. 6(9): September 2013; Page 962-966

52. Van Gaal LF, De Leeuw IH (2003) Rationale andoptions for combination therapy in the treatment oftype 2 diabetes. Diabetologia 46(Suppl 1): M44-M50.

53. Rakesh Tiwle, Varsha Rawat, Smriti Dewangan. Characterization, Antimicrobial Activity and Antioxidant Properties of Grewia tiliifolia Root Mucilage as a Binder Excipient. Research Journal of Pharmacy and Technology. 2025;18(7):3037-4. doi: 10.52711/0974-360X.2025.00435