A Comprehensive Review on the Synthesis of Mannich Base Compounds as Potential Anti-diabetic Agents

Sharmila Chaudhary[1], Shweta Gupta[2], Shiv Dev Singh[3], Priya Kumar[4]
[1]*Research Scholar, Department of Pharmacy, Mahatma Jyotiba Phule Rohilkhand University, Bareilly, Uttar Pradesh, India*
[2,3]*Assistant Professor, Department of Pharmacy, Mahatma Jyotiba Phule Rohilkhand University, Bareilly, Uttar Pradesh, India*
[4]*Assistant Professor, Department of Pharmaceutical Chemistry, Aditya Bangalore Institute of Pharmacy Education and Research, Bangalore, India*

***Abstract*—This review explores the antidiabetic potential of Mannich base-modified heterocyclic compounds. These compounds were tested for inhibitory activity against alpha-amylase, a critical enzyme in glucose metabolism, and shown considerable suppression, indicating their potential for glycemic management. Furthermore, benzothiazole-oxadiazole Mannich base conjugates displayed significant antidiabetic effectiveness in an alloxan-induced diabetic rat model, which was confirmed by their inhibition of lipase, alpha-glucosidase, and acetylcholinesterase.**

The synthesized compounds were structurally characterized using infrared spectroscopy, proton nuclear magnetic resonance, carbon-13 nuclear magnetic resonance, elemental analysis, and mass spectrometry, confirming their identification and demonstrating their promise as antidiabetic possibilities. These findings indicate that Mannich base-modified heterocycles present a promising multi-target approach for diabetes management and medication development.

***Index Terms*—Mannich base, Anti-diabetic activity, heterocyclic-containing compound.**

I. INTRODUCTION

The Mannich reaction produces β-amino carbonyl compounds, also called Mannich bases. These compounds are produced by combining primary or secondary amines with non-enolizable aldehydes and enolizable ketones. The nucleophilic addition of an amine to a non-enolizable aldehyde result in a resonance-stabilized iminium ion or imine salt. The carbanion, formed from an acid molecule with active hydrogens, attacks the imine, resulting in the formation of the Mannich base. Mannich bases have an electrophilic core carbon atom and two geminal heteroatoms, including nitrogen, making them valuable intermediates in organic synthesis. The Mannich reaction is well-known for its ability to form carbon-carbon bonds and is commonly utilized to synthesize aminocarbonyl derivatives.[1][2] Mannich bases have received a lot of interest because of their diverse biological functions. They have anti-inflammatory, anti-filarial, cancer-prevention, anti-fungal, anti-bacterial, anti-convulsant, anti-helmintic, and other various activities. Their broad pharmacological potential makes them valuable building blocks in the synthesis of bioactive molecules, enabling the development of medications with specific therapeutic objectives. The Mannich process, with its several modifications, provides a reliable methodology for generating aminocarbonyl compounds and related derivatives. [3-25]

II. SYNTHESIS OF HETEROCYCLIC MANNICH BASES

Given the rising occurrence of multidrug-resistant (MDR) diseases and cancers, Mannich bases are gaining popularity as prospective options for generating new medications and tailored drug delivery systems. Recent improvements in Mannich reaction procedures include the use of chiral catalysts, nanocrystalline copper particles, poly(amidoamine)-catalyzed reactions, and microwave-assisted methods. These advancements have increased the effectiveness of the process, allowing for the creation of

enantiomerically pure molecules with improved pharmacological properties. Furthermore, the Mannich reaction can improve medications' lipophilic or hydrophilic characteristics, hence increasing water solubility and bioavailability. Some Mannich bases can also act as prodrugs, releasing active medicinal substances under regulated hydrolysis conditions.

Blicke, Karbe, Nobles, Reichert, and Thompsons have all conducted substantial research on the Mannich reaction, emphasizing its importance in chemical synthesis and drug creation. Mannich bases have showed promise as a treatment for metabolic illnesses such as type 2 diabetic mellitus (T2DM).Novel anti-diabetic medicines were discovered by synthesizing β-aminoketone compounds, including those having a nabumetone moiety, using a one-pot, two-step Mannich process. SAR studies show that the sulphanilamide unit in β-aminoketones strongly contributes to anti-diabetic efficacy [26].

Heterocyclic Mannich bases with pyridine, quinoline, and thiazole rings have been created to improve the biological characteristics of these compounds. These heterocycles are found in both natural and synthetic medications and provide a variety of pharmacological effects, including anti-diabetic properties. Similarly, quinoline-based Mannich compounds were studied for their antidiabetic benefits in animal models, and they revealed significant glucose-lowering efficacy. [27]

SAR investigations on Mannich bases have revealed important structural characteristics that govern their biological action. Electron-donating and electron-drawing groups on the heterocyclic ring can dramatically affect the compounds' potency. Furthermore, the selection of amine and aldehyde in the Mannich reaction plays a critical role in defining the resulting compound's pharmacological activity. [28]

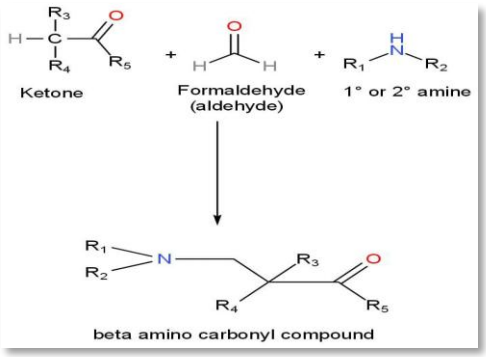


Fig 1 Mannich Base Reaction

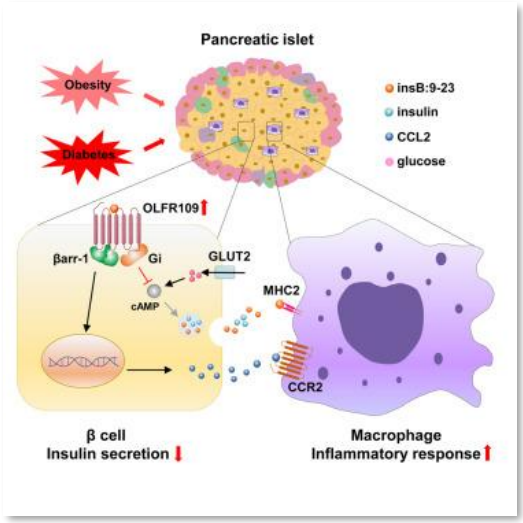


Fig 2 Diabetes Receptor

III. ANTI-DIABETIC ACTIVITY

Tang GuangXia synthesized, two sets of β-amino ketones with a p-aminobenzoic acid group (TM-1 and TM-2) were produced utilizing a modified technique. Mannich reaction methodology. The antidiabetic potential of the produced compounds was then investigated in vitro. Compound 1e (Fig 3) showed high α-glucosidase inhibition (α-GI) activity, reaching 66.50%. Furthermore, six compounds displayed peroxisome proliferator-activated receptor (PPAR) relative activation activity greater than 80%, with compound 2i demonstrating an extraordinarily high PPAR activation of 130.91%. [29]

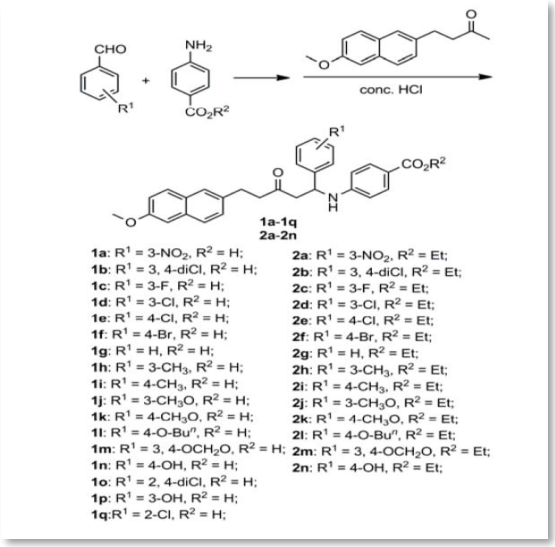
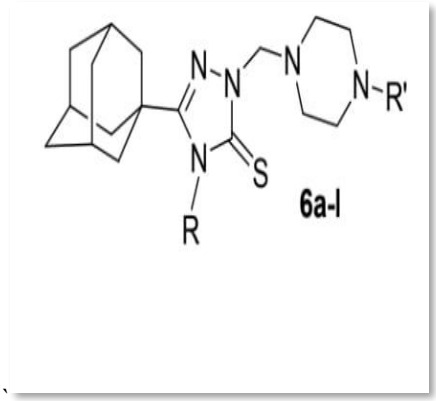


Fig 3 Mannich reaction methodology

Ebtehal S. Al-Abdullah synthesized N-Mannich bases by combining Novel N-Mannich derivatives of 4-Substituted-5-(1-adamantyl)- Triazoline in positions 1, 2, and 4. The -3- produced by reacting4-Ethyl or allyl-5-(1-adamantyl)-1,2,4-triazole-3-thione or 4-Ethyl or allyl-5-(1-adamantyl)-1,2,4-triazole-3-thione reacted with formaldehyde solution and many 1-substituted piperazines.The Orally active blood sugar-lowering effects of selected compounds were assessed in diabetic rats induced with streptozotocin (STZ). Compounds 6a, 6f, 6g, and 6l (Figure 4) had strong hypoglycaemic effects that outperformed gliclazide in effectiveness. [30]



6a: R = Et, R' = Et
6b: R = Et, R' = COOEt
6c: R = Et, R' = Ph
6d: R = Et, R' = 2-MeOC$_6$H$_4$
6e: R = Et, R' = PhCH$_2$
6f: R = Et, R' = 2-Pyridyl
6g: R = Allyl, R' = Et
6h: R = Allyl, R' = COOEt
6i: R = Allyl, R' = Ph
6j: R = Allyl, R' = 2-MeOC$_6$H$_4$
6k: R = Allyl, R' = PhCH$_2$
6l: R = Allyl, R' = 2-Pyridyl

Fig 4: Substitutions for Novel N-Mannich derivatives

Bhutani R investigated newly proposed benzothiazole-linked oxadiazole-Mannich bases (Figure 5) and validated their structures with NMR, mass spectrometry, infrared, and elemental analyses. Nine compounds were chosen based on their docking scores and tested for in vivo antidiabetic efficacy utilizing an oral tolerance to glucose test (OGTT).. The results showed that compound M14 had greatest drop in blood glucose levels, comparable to conventional medication glibenclamide.[31]

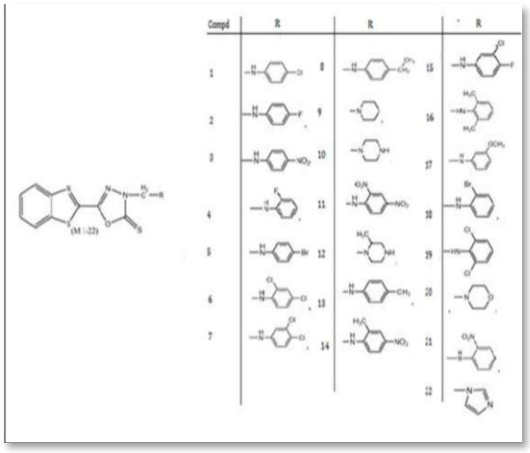


Fig 5 benzothiazole-linked oxadiazole-Mannich bases

Gopi C reported that Figure 6 depicts the synthesis of novel Semicarbazone derivatives of 1-(3-(N, N-dimethylamino)-1-(5-substituted thiophene-2-yl) propylidene using N, N-dimethylamine hydrochloride, semicarbazide, 1-(thiophen-2-yl) ethanone, and formaldehyde. The compounds' structures were determined using various spectroscopy. Addition, to the compounds were examined for their antidiabetic and anti-inflammatory properties.[32]

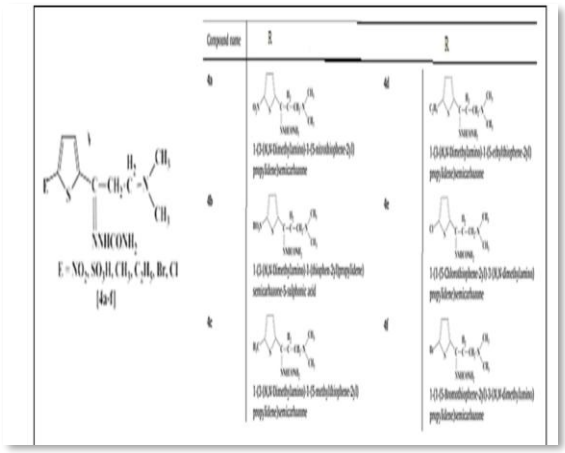


Fig 6-(3-(N,N-Dimethyl amino)-1-(5-substituted thiophene-2-yl) propylidene derivatives

Garmia Kapoor developed oxadiazole-based Mannich base derivatives of fatty acids and evaluated their

antidiabetic potential. Among the produced compounds, 5-Heptadecyl-3-((2-fluorophenylamino) methyl) -1,3,4-oxadiazole-2(3H)-thione had the greatest potency, lowering blood glucose levels in six hours, beating the conventional medication glibenclamide (103 mg/dL). Furthermore, 5-Heptadecyl-3-((2,6-dimethylphenylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione & 5-Heptadecyl-3-((2,6-dichlorophenylamino) methyl) -1,3,4-oxadiazole-2(3H)-thionealso showed substantial action. Other compounds include 3-((4-bromophenylamino)methyl).-5-heptadecyl-1,3,4-oxadiazole-2(3H)Thione, 3-((4-fluorophenylamino)methyl)-5-Heptadecyl-1,3,4-Oxadiazole-2(3H)-thione, 3-((2,4 Dichlorophenylamino) methyl)-5-heptadecyl-2(3H)-Thione-1,3,4-oxadiazole, 5-heptadecyl-3-((2-methylpiperazin-1-yl)methyl)-3-((p-toluidino)methyl) - 5-heptadecyl-1,3,4-oxadiazole-2(3H)-thione, and 3-((4-ethylphenylamino)methyl)-5-heptadecyl-2(3H)-Thione-1,3,4-oxadiazole (Figure 7) demonstrated moderate action. Based on these findings, fatty acid derivatives of oxadiazole-based Mannich bases hold potential as antihyperglycemic agents with a safer and rapid onset of action [33].

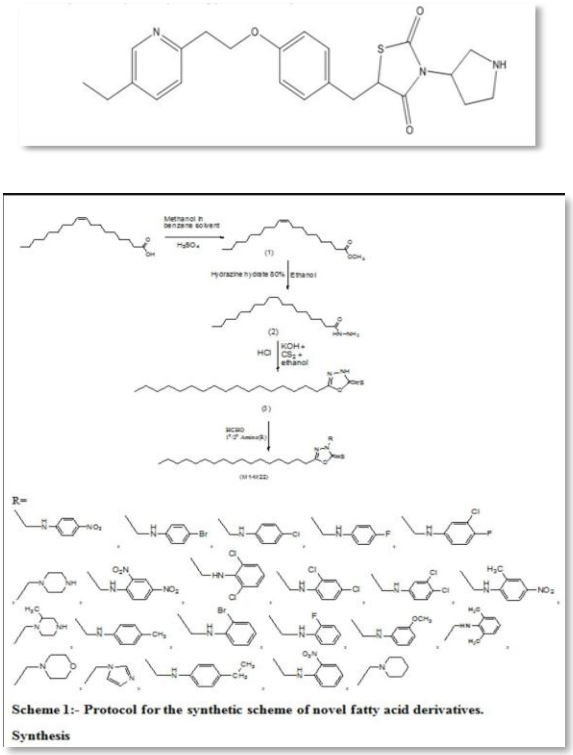


Fig 7: Mannich base derivatives of fatty acids

Ramit Kapoor proposed Mannich base derivatives of pioglitazone. The pyrrolidine derivative 3-(Pyrrolidin-3-yl)-5-(4-(2-(5-ethylpyridin-2-yl) ethoxy) benzyl) thiazolidine-2,4-dione (Figure 8) had the best yield, with a retention factor ranging from 0.45 to 0.75. Studies have demonstrated that Mannich bases have much more activity than the parent molecule. These compounds of Pioglitazone show potential as more effective antidiabetic medicines than Pioglitazone alone. [34]

Badrud Duza Mohammad found that combining oxadiazole with various structural frameworks, such as Benzothiazole, 5-(2,5,2-trifluoroethoxy)phenyl group, β-homophenylalanine derivative, 2-methyl-2-{5-(4-chlorophenyl)} group, diamine-bridged bis-coumarin compound, 5-aryl-2-(6′-nitrobenzofuran-2′-yl) structure, nitrobenzofuran compound, and oxindole molecule (Figures 9 & 10), showed promising antidiabetic activity [35].

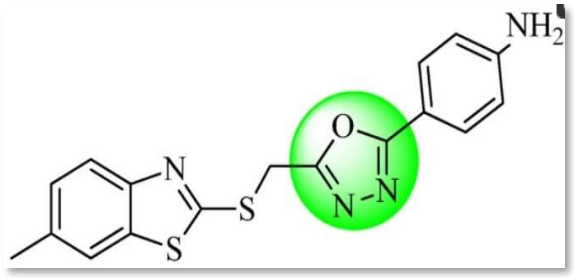


Fig 8

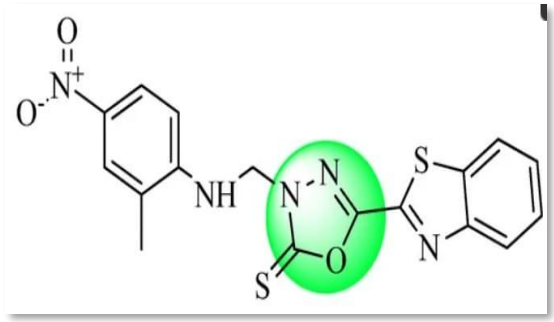


Fig 8: Benzothiazole clubbed oxadiazole-Mannich base

Chu synthesized Four series of thirty novel Mannich base analogs of magnolol and honokiol were evaluated for their α-glucosidase inhibitory activity. Compounds 3k and 3l (Figure 9) inhibited α-glucosidase more effectively than acarbose, with IC_{50} values.[36]

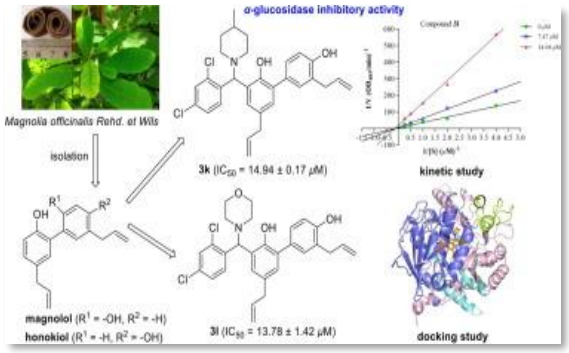


Fig 9: Compounds 3k and 3l

Senthil Kumar Raju synthesized the chemical 3-(5-Methylisoxazol-3-ylamino)-1- (3-nitrophenyl)- 5- (6-methoxynaphthalen-2-yl)-pentan-3-one (Figure 14), which has substantial biological activity. Furthermore, Mannich base derivatives of oxadiazole on position 1,3,4 containing benzothiazole scaffolds are produced & tested for anti-diabetic properties. In the streptozotocin (STZ) model, substances 5-(Benzothiazol-2-yl)-3-((3,4-dichlorophenylamino)methyl)-1,3,4-oxadiazole (Figure 10) and 3-[(2-Methyl-4-nitrophenylamino)methyl]-5-(benzothiazol-2-yl)-1,3,4-oxadiazole-2(3H)-thione (Figure 11) Demonstrated the most significant decrease in blood sugar levels, comparable to the typical medicine glibenclamide. Synthesized compounds having anti-diabetic action are reported, together with their structural information.[37]

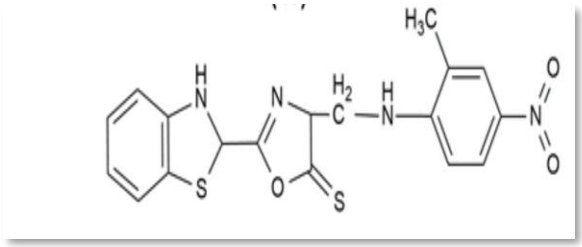


Fig 10

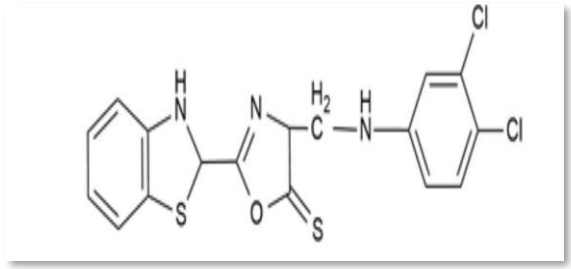


Fig 11

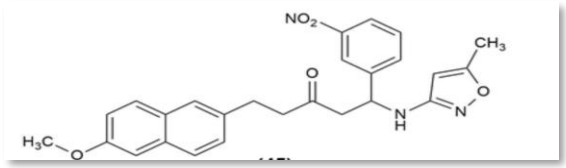


Fig 12

IV. CONCLUSION

Mannich base derivatives can lower glucose levels by inhibiting important enzymes like α-amylase, α-glucosidase, and DPP-IV, making them promising candidates for anti-diabetic medicines. So far, research has mostly focused on pyrimidine, triazole, oxadiazole, and other common pharmacophore derivatives, with numerous molecules demonstrating efficacy like mainstream medications such as metformin.

Despite these gains, there is still room for innovation. Future research can concentrate on building novel Mannich bases by integrating metal ions, creating hybrid compounds with dual therapeutic properties, and investigating understudied heterocyclic frameworks. Furthermore, using green chemistry techniques and computational drug design can improve the synthesis and screening processes. In conclusion, while progress has been made, the discovery of more selective and effective Mannich base derivatives with superior safety profiles presents a viable avenue for new anti-diabetic medicines.

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