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REVIEW PAPER OPEN ACCESS

Heterocyclic pyrazoline's derivatives exhibiting promising potential antidiabetic activity

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ABSTRACT

Diabetes mellitus (DM) represents a complicated metabolic disorder with an increasing global incidence, necessitating the identification of effective therapeutic agents. Out of the various approaches, heterocyclic pyrazoline derivatives have surfaced as promising candidates because of their extensive pharmacological properties, encompassing anti-diabetic, anti-inflammatory, and antioxidant characteristics. This review offers a thorough analysis of pyrazoline derivatives, emphasizing their mechanisms of action, including the inhibition of vital metabolic enzymes, enhancement of insulin sensitivity, and decrease in oxidative stress. Structure-activity relationship (SAR) investigations have illustrated the potential for specific modifications on the pyrazoline nucleus to enhance biological effectiveness. Additionally, recent progress in molecular docking and in vivo investigations underscores their therapeutic promise. In spite of its promise, more pharmacokinetic, pharmacodynamic, and clinical studies are essential to validate these compounds as effective anti-diabetic agents. This study integrates existing knowledge on pyrazolines and pinpoints future research directions, aiming to encourage novel diabetes treatment strategies.

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INTRODUCTION

Diabetes mellitus is a long-lasting, multifactorial metabolic disorder characterized by ongoing hyperglycemia resulting from reduced insulin production, insulin action, or both (Baynes, 2022).

It represents a significant public health issue globally, with concerning rises in prevalence leading to considerable morbidity, mortality, and financial burden. Present diabetic interventions, including insulin therapy and oral hypoglycemic agents like sulfonylureas, biguanides, and DPP-4 inhibitors, have proven effective in managing blood glucose levels (Mohajan and Mohajan, 2024; Bailey and Krentz, 2024; Weinberg Sibony *et al.*, 2023). Nevertheless, these medications are often associated with considerable drawbacks, such as limited effectiveness in advanced disease stages, adverse effects, and an absence of preventive strategies for long-term complications like cardiovascular disease, nephropathy, neuropathy, and retinopathy.

Pyrazolines, which are a category of five-membered heterocyclic compounds containing two adjacent nitrogen atoms in their composition (HM and Dubey, 2024), have garnered significant interest in medicinal chemistry due to their diverse pharmacological effects, encompassing anti-inflammatory (Yan *et al.*, 2022; Elgohary *et al.*, 2023; Mantzanidou *et al.*, 2021), antimicrobial (Jain and Singhal, 2020; Aksöz *et al.*, 2020; TN *et al.*, 2023), anticancer (Haider *et al.*, 2022; Matiadis and Sagnou, 2020; Nasab *et al.*, 2023; Rana *et al.*, 2021), and analgesic characteristics. A recent investigation has highlighted the promise of pyrazolines as anti-diabetic agents (Ibraheem *et al.*, 2020; Kumar *et al.*, 2021; Uğraş *et al.*, 2024). The therapeutic efficacy of pyrazolines in diabetes stems from their ability to influence key biological targets that play a role in glucose metabolism and insulin sensitivity (Thilagavathi *et al.*, 2022).

These mechanisms include the inhibition of α-glucosidase and α-amylase enzymes, stimulation of insulin secretion, enhancement of glucose uptake in peripheral tissues, and mitigation of oxidative stress and inflammation, all of which are linked to the development of diabetes and its related complications (Shahwan *et al.*, 2022; Singh *et al.*, 2022; Choudhury *et al.*, 2018; Kumar *et al.*, 2011).

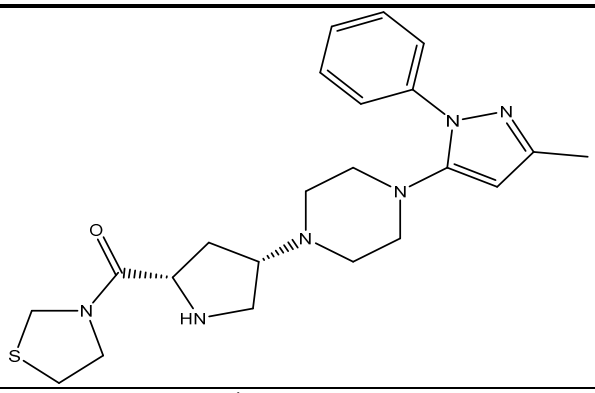
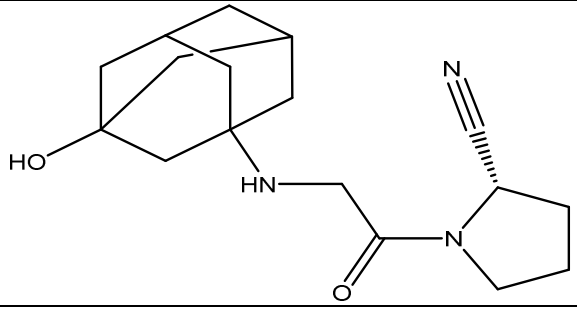
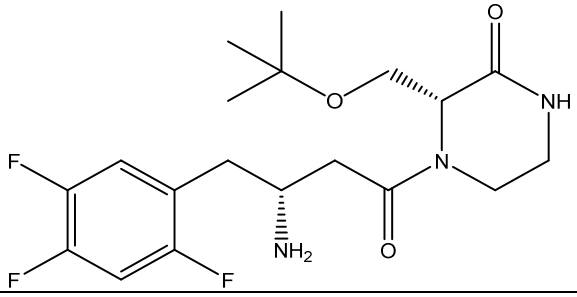
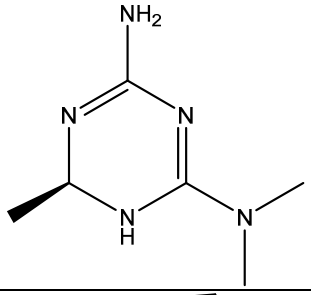
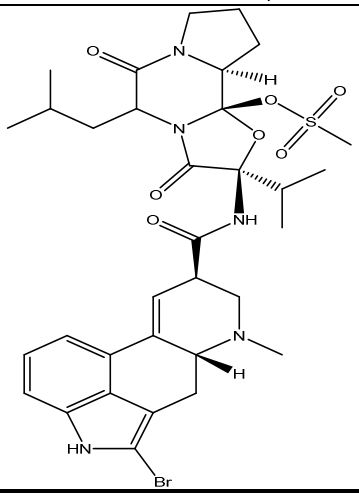
Pyrazolines exhibit a broad spectrum of biological activities aside from their anti-diabetic effects, rendering them versatile candidates for drug development. They possess strong anti-inflammatory properties as they inhibit pro-inflammatory cytokines and enzymes such as cyclooxygenase (COX), which play a crucial role in chronic inflammatory diseases (Subramanian *et al.*, 2008).

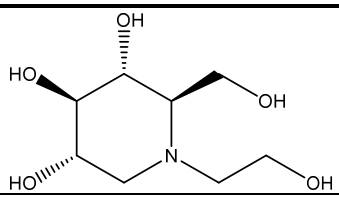
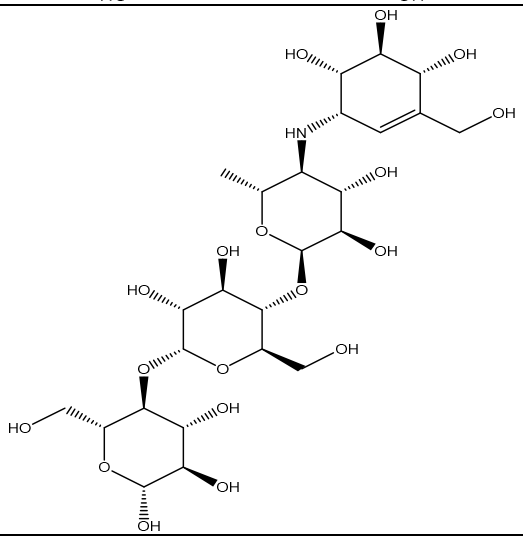
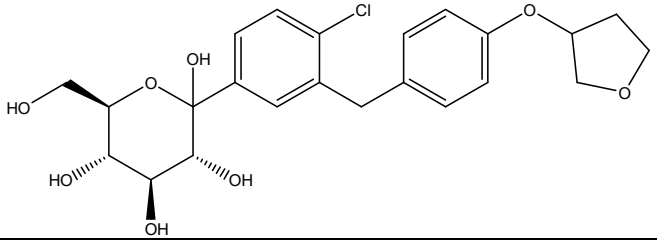
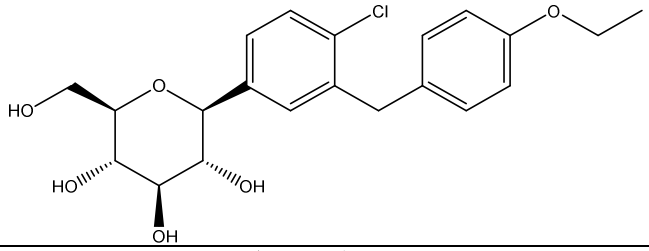
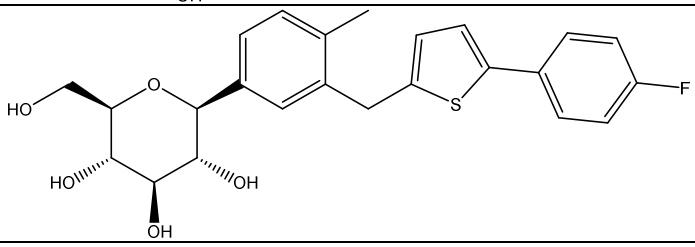
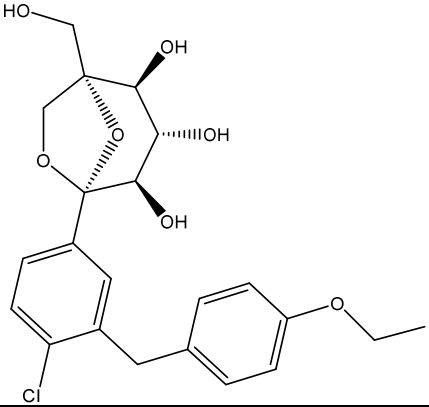
Their antimicrobial efficacy encompasses a variety of bacterial and fungal species, underscoring their importance in combating infectious diseases. Pyrazolines have also demonstrated promise as anticancer agents by triggering apoptosis, halting the cell cycle, and obstructing angiogenesis (Ikram *et al.*, 2018). In addition, their antioxidant properties allow them to mitigate oxidative stress, a common factor in numerous chronic conditions. These varied biological activities emphasize the therapeutic potential of pyrazolines and establish a foundation for their future advancement as multifunctional pharmaceutical agents (Ali *et al.*, 2014).

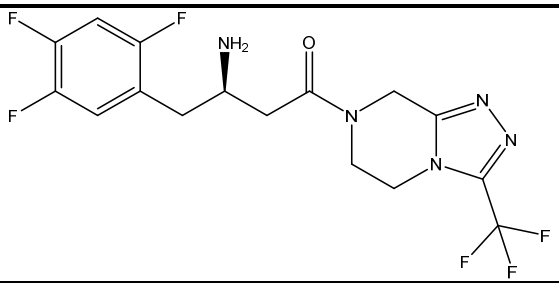
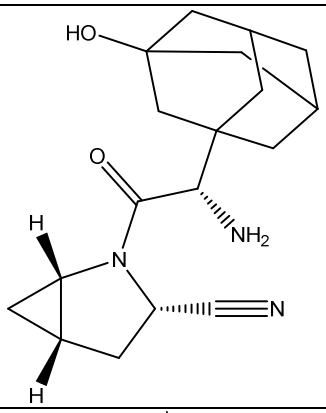
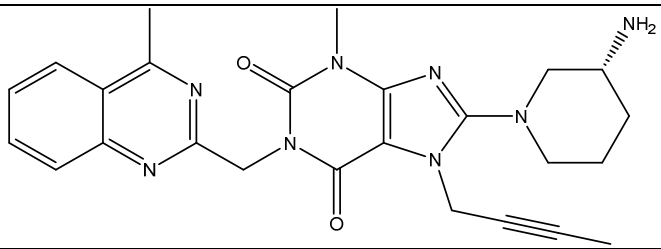
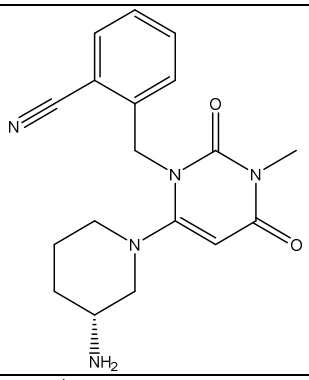
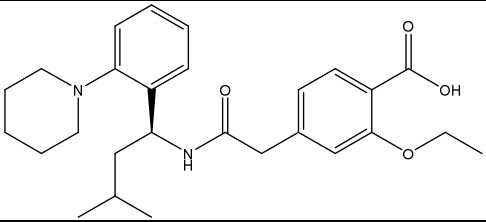
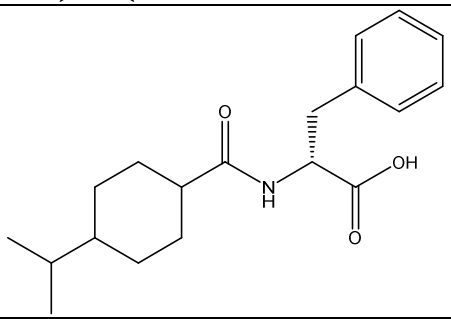
The molecular structure of pyrazolines enables extensive structural modifications, facilitating the creation of a variety of derivatives with particular biological properties (Park *et al.*, 2021).

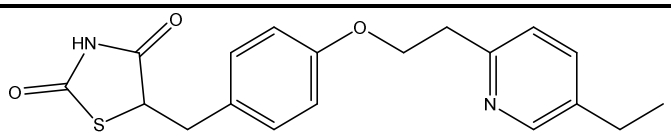
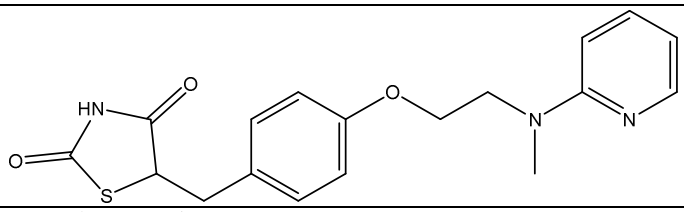
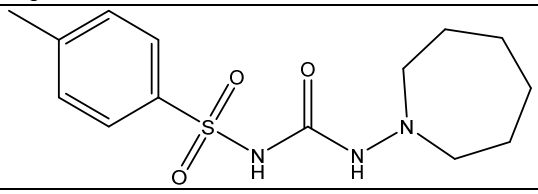
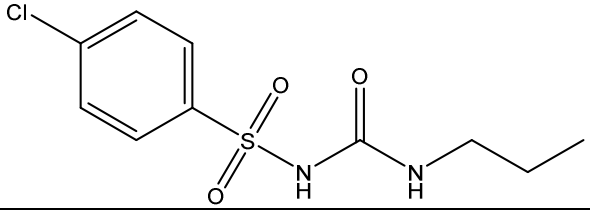
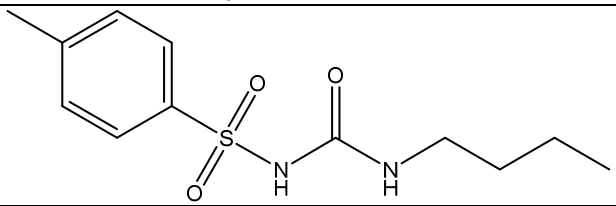
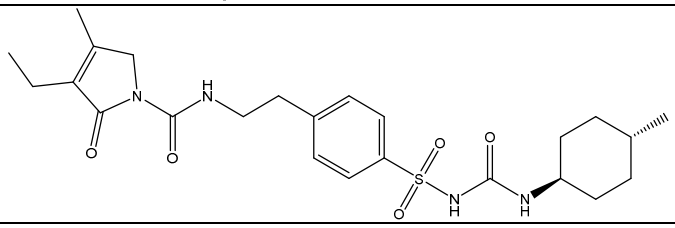
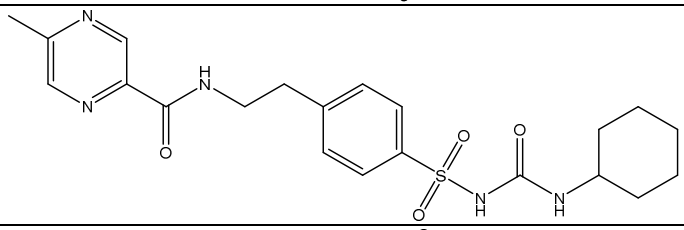
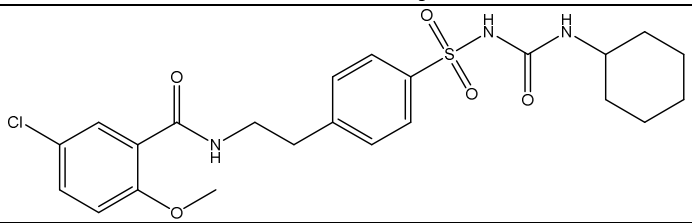
Investigations into structure-activity relationships (SAR) have identified vital functional groups and substitution patterns that influence the anti-diabetic effectiveness of pyrazolines (Chen *et al.*, 2001) (Table 1). For instance, incorporating electron-donating or withdrawing groups at designated positions on the aromatic ring of pyrazolines can significantly enhance their effectiveness and specificity for diabetic targets (García-Mediavilla *et al.*, 2007). In addition, hybrid compounds that comprise the pyrazoline core along with other pharmacophores have shown synergistic effects, broadening the therapeutic potential of this drug family.

Table 1. Important marketed drugs for diabetes treatment

Sl	Name of drug	Chemical structure	Reference
1.	Teneligliptin		(Patil *et al.*, 2013; Kadan *et al.*, 2016)
2.	Vildagliptin		(Kumbhare *et al.*, 2012; Kostyuk *et al.*, 2011)
3.	Evogliptin		(La Casa *et al.*, 2000)
4.	Imeglimin		(Mamun-Or-Rashid *et al.*, 2014; Sharma and Nazareth, 2021)
5.	Cycloset		(Patil and Maheshwari, 2013)

6.	Miglitol		(Niture *et al.*, 2014; Selvaraj *et al.*, 2013)
7.	Acarbose		(Kazmi *et al.*, 2012; Devi *et al.*, 2011; Janbaz *et al.*, 2014)
8.	Empagliflozin		(Zhao *et al.*, 2012; Ahangarpour *et al.*, 2014)
9.	Dapagliflozin		(Saeed *et al.*, 2012)
10.	Canagliflozin		(Dkhil *et al.*, 2015)
11.	Ertugliflozin		(Prabu and Shagirtha, 2012)

12.	Sitagliptin		(Sultana *et al.*, 2020)
13.	Saxagliptin		(Jain *et al.*, 2024; Elmalahany *et al.*, 2023)
14.	Linagliptin		(Hossain *et al.*, 2020)
15.	Alogliptin		(Mohanty *et al.*, 2022)
16.	Repaglinide		(Foroumadi *et al.*, 2022; Haddad *et al.*, 2024)
17.	Nateglinide		(Haque, 2024; Kale *et al.*, 2024)

18.	Pioglitazone		(Tamimi *et al.*, 2023; Afzal *et al.*, 2021)
19.	Rosiglitazone		(Xu *et al.*, 2022; Lee *et al.*, 2023)
20.	Tolazamide		(Araújo *et al.*, 2023; Khan, 2024)
21.	Chlorpropamide		(Das *et al.*, 2024; Majid *et al.*, 2023)
22.	Tolbutamide		(SS *et al.*, 2024; Saha, 2020)
23.	Glimepiride		(Li *et al.*, 2024; Razzaq *et al.*, 2021; Abdallah *et al.*, 2023)
24.	Glipizide		(Khan *et al.*, 2024; Nagulancha and Vandavasi, 2023)
25.	Glyburide		(Vázquez *et al.*, 2024; Saeedan *et al.*, 2021; Mukherjee *et al.*, 2020)

Despite their considerable potential, the clinical advancement of pyrazolines as anti-diabetic medications remains at a preliminary stage (Boudjou *et al.*, 2013). Preclinical investigations have produced encouraging outcomes regarding glucose-lowering effectiveness and low toxicity; however, thorough assessments of pharmacokinetics, pharmacodynamics, and long-term safety must be conducted before these medications can proceed to clinical trials. In addition, employing computational methods like molecular docking and

QSAR modeling can significantly accelerate the drug development process by predicting pyrazoline interactions with essential diabetic targets and guiding rational drug development (Rani *et al.*, 2016).

Pyrazoline derivatives exhibiting anti-diabetic activity

In 2018, Bhutani *et al.* examined new benzothiazoles combined with oxadiazole-Mannich bases on OGTT and STZ-induced diabetes in healthy rats. Compound 1 reduced glucose levels in the STZ model by 161. 39 ± 4. 38 mg/dL, which is like glibenclamide therapy (140. 29 ± 1. 24 mg/dL). The other medications evaluated demonstrated antihyperglycemic efficacy that varied from modest to outstanding (Fig. 1).

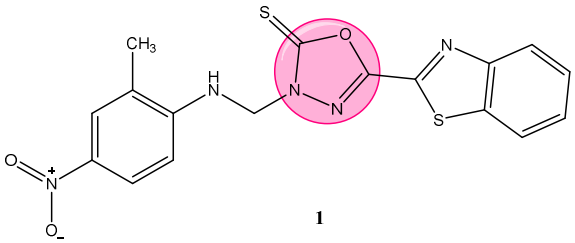


Fig. 1. Synthesized pyrazoline derivatives by Bhutani *et al.* (2018)

In 2018, Kazmi *et al.* described the one-pot multicomponent approach for designing and synthesizing three series of diamine-bridged bis-coumarinyl oxadiazole conjugates. The generated conjugates were assessed for their capacity to impede glucosidases. Compound 2, which contains the 4,4′-oxydianiline linker, inhibits alpha-glucosidase enzymes with an IC_{50} value of merely 0. 07 ± 0. 001 µM (acarbose: 38. 2 ± 0. 12 µM), establishing it as the primary and selective inhibitor. It exhibited approximately 545 times greater inhibitory activity than reference medications. Compound 2 substantially inhibited intestinal maltase-glucoamylase (IC_{50} = 0. 04 ± 0. 02 µM) in comparison to acarbose (IC_{50} = 0. 06 ± 0. 01 µM). This compound has an IC_{50} value of 0. 08 ± 0. 002 µM and serves as the main inhibitor of the β-glucosidase enzyme. The inhibition mechanism was investigated through Michaelis-Menten kinetic experiments. All synthesized compounds were docked against the glucosidase enzyme. The results revealed multiple coordinated interactions with catalytic residues, potentially stabilizing inhibitors at the active site. Furthermore, β-glucosidase inhibitors were effectively identified using compounds that exhibited strong binding interactions with amino acid residues (Kazmi *et al.*, 2018) (Fig. 2, Table 2).

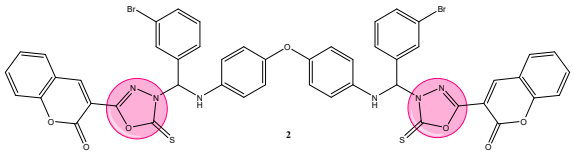


Fig. 2. Synthesized pyrazoline derivatives by Kazmi *et al.* (2018)

Table 2. IC_{50} values of the synthesized derivative 2

Compound	IC_{50} (µM)
2	0.07 ± 0.001 (alpha-glucosidase)
	0.04 ± 0.02 (intestinal maltase-glucoamylase)
	0.08 ± 0.002 (beta-glucosidase)

Taha *et al.* (2021) recognized hybrid analogues of oxindole-derived oxadiazoles as potential α-glucosidase inhibitors. In comparison to acarbose (IC_{50} = 895. 09 ± 2. 04 µM), all compounds demonstrated significant inhibition of this enzyme, exhibiting IC_{50} values between 1. 25 ± 0. 05 and 268. 36 ± 4. 22 µM. This research highlights a novel category of effective α-glucosidase inhibitors that require additional investigation (Fig. 3).

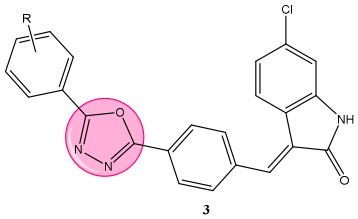


Fig. 3. Synthesized pyrazoline derivatives by Taha *et al.* (2021)

In 2018, Yousuf *et al.* produced, analyzed, and evaluated a range of 2-aryl and 4-arylidene substituted pyrazolones against α-amylase through in silico studies. Compound 4 demonstrates the most significant inhibitory impact against α-amylase, showing an IC_{50} of 1. 61 ± 0. 16 µM. Kinetic studies

were performed on the strongest compounds in the series, with compound 47 displaying a mixed type of inhibition. SAR studies indicated that the addition of an electron-donating hydroxy group at the ortho position and an electron-withdrawing dichloro group at the meta position, as seen in compound 4, led to considerable inhibitory effects. Molecular docking studies revealed that compound 4 engages with the Asp300 and His201 residues. The acidic Asp300 donates hydrogen to the hydroxyl group, while His201 accepts hydrogen from the oxygen atom of the pyrazolone ring (Dey *et al.*, 2019) (Fig. 4).

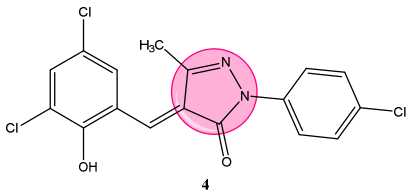


Fig. 4. Synthesized pyrazoline derivatives by Yousuf *et al.* (20218)

In 2018, Nazir *et al.* investigated the sequential transformation of indolyl butanoic acid into 1,3,4-oxadiazole-2-thiols and performed multiple chemical transformations. Various amine derivatives were reacted with 2-bromoacetyl bromide to act as an electrophile, producing 2-bromo-N-phenyl/arylacetamides through a series of parallel reactions. A nucleophilic 1,3,4-oxadiazole-2-thiol analogue was subsequently utilized on the electrophilic compounds, resulting in several N-substituted derivatives (compounds 5a and 5b). This research explored the anti-diabetic potential of all synthesized compounds by inhibiting the α-glucosidase enzyme and analyzing them in silico. Additionally, their hemolytic activity was used to determine their cytotoxicity profile, and all of the compounds exhibited low cytotoxicity. The most potent compounds (5a and 5b) exhibited IC_{50} values of 9. 46 ± 0. 03 µM and 9. 37 ± 0. 03 µM, respectively. Future studies might utilize these compounds to develop more effective anti-diabetic therapies owing to their moderate to good inhibitory capacity (IC_{50} = 12. 68 ± 0. 04 to 37. 82 ± 0. 07 µM) (Fig. 5).

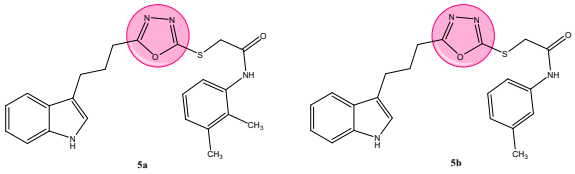


Fig. 5. Synthesized pyrazoline derivatives by Nazir *et al.* (2018)

In 2018, Bhutani *et al.* created hybrid compounds comprising benzothiazole-1,3,4-oxadiazole-4-thiazolidinone. The OGTT in non-diabetic rats and streptozotocin-induced diabetic rat models were employed to evaluate the seven compounds that exhibited the highest docking scores. All of the examined substances significantly reduced blood glucose levels, with outcomes that varied from good to moderate. The anti-diabetic properties of three compounds (6a, 6b, and 6c) were more effective than those of the standard medication pioglitazone, which showed a glucose concentration of 178. 32 ± 1. 88 mg/dL, compared to the lower glucose concentrations of 157. 15 ± 1. 79 mg/dL, 154. 39 ± 1. 71 mg/dL, and 167. 36 ± 2. 45 mg/dL reported for 6a-c. Acarbose (IC_{50} = 18. 5 ± 0. 20 µM) was noted as the most effective alpha-glucosidase inhibitor among the seven derivatives evaluated. Three of its derivatives, compounds 6a, 6d, and 6e, displayed lower IC_{50} values (0. 21 ± 0. 01 µM, 9. 03 ± 0. 12 µM, and 11. 96 ± 0. 40 µM, respectively), suggesting they were less potent than the original acarbose. This means that these distinct hybrids could act as a basis for the creation of new agents (Fig. 6, Table 3).

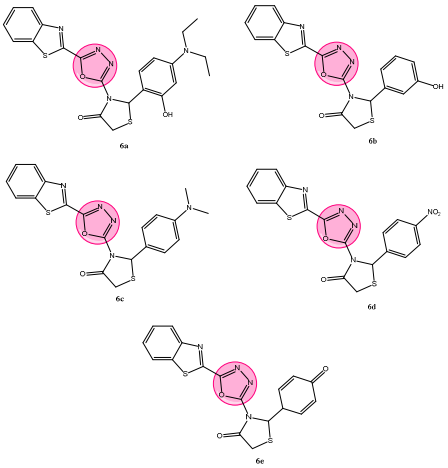
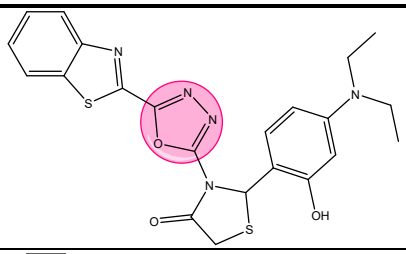
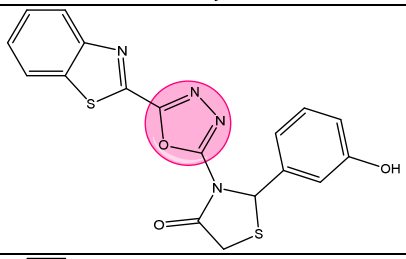
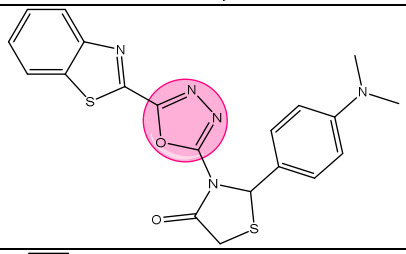
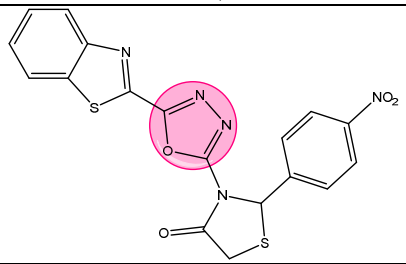
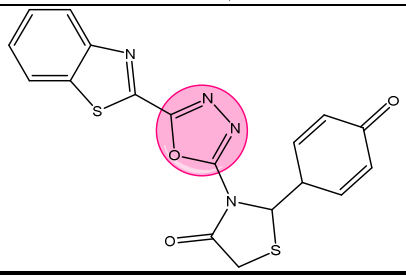


Fig. 6. Synthesized pyrazoline derivatives by Bhutani *et al.* (2018)

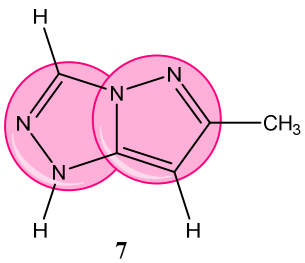
Table 3. IC_{50} values of the synthesized derivatives 6a-e

Sl	Structure	Compound name	IC_{50} value (µM)
1.		6a	0.21 ± 0.01
2.		6b	N/A
3.		6c	20.36 ± 2.41
4.		6d	9.03 ± 0.12
5.		6e	11.96 ± 0.4

In 2019, Bakri *et al.* developed new condensed 1,2,4-triazoles and examined their biological activity and molecular modeling. The α-amylase inhibition test showed that compound 7 exhibited the strongest inhibitory potency, with an IC_{50} of 109. 43 ± 6. 12 µM, in contrast to the standard drug acarbose (IC_{50} = 618. 87 ± 0. 76 µM) (Pandit *et al.*, 2021) (Fig. 7, Table 4).

Table 4. IC50 value of the synthesized derivative 7

Sl	Compound name	IC_{50} value (µM)
1.	7	109.43 ± 6.12
2.	Acarbose	618.87 ± 0.76



7

Fig. 7. Synthesized pyrazoline derivative by Bakri *et al.* (2019)

In 2019, Singh *et al.* produced, characterized, and evaluated rhodanine derivatives as well as rhodanine-

pyrazole conjugates for their ability to inhibit α-glucosidase and α-amylase. The para-hydroxy-substituted pyrazole-rhodanine derivative (compound 8) exhibited the strongest inhibitory activity against α-amylase (IC_{50} = 6. 377 × 10^{-5} mol/l), which is 1. 5 times greater than the standard drug acarbose (IC_{50} = 1. 038 × 10^{-4} mol/l) (Fig. 8, Table 5).

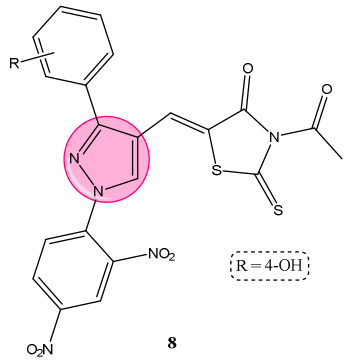


Fig. 8. Synthesized pyrazoline derivatives by Singh *et al.* (2019)

Table 5. IC_{50} values of the synthesized derivative 8

Sl	Compound name	IC_{50} value (mol/l)
1.	8	6.377 × 10^{-5}
2.	Acarbose	1.038 × 10^{-4}

In 2019, Reddy *et al.* created and evaluated new amide-containing fused pyrazolo-pyrimidine derivatives to assess their antidiabetic capabilities. In an in vitro α-amylase inhibitory assay, compound 9a, which featured o- and m-substituted phenyl rings, was identified as the most effective inhibitor (IC_{50} = 1. 60 ± 0. 48 μM). The next most effective molecule was 9b, exhibiting an IC_{50} of 1. 64 ± 0. 03 μM and containing a p-nitro substituent on the phenyl ring (Fig. 9, Table 6).

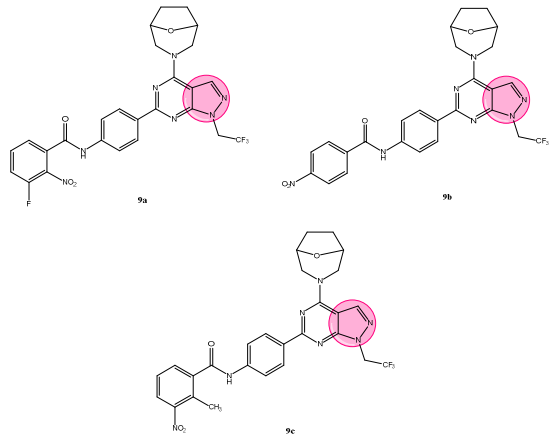
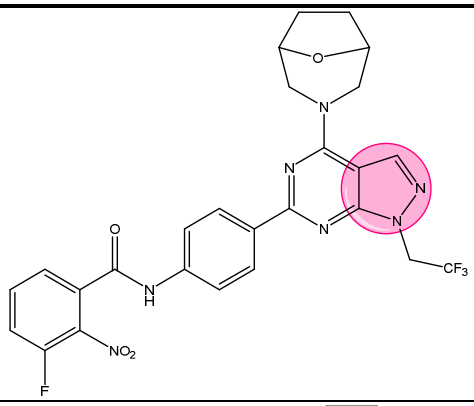
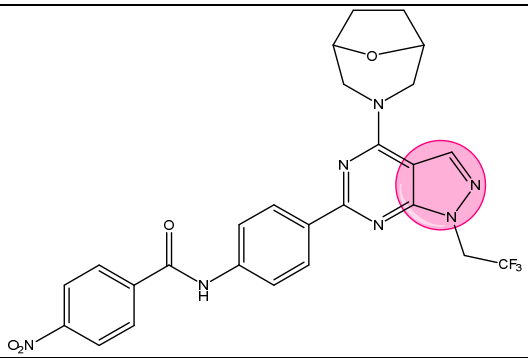
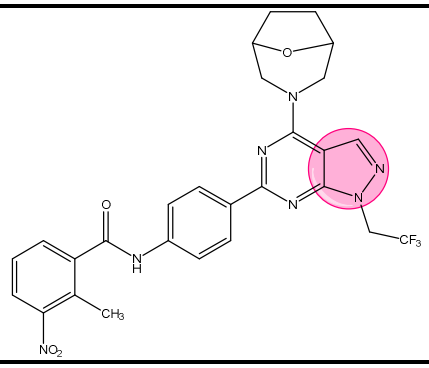


Fig. 9. Synthesized pyrazoline derivatives by Reddy *et al.* (20219)

Table 6. IC_{50} values of the synthesized derivatives 9a-c

Sl	Structure	Compound name	IC_{50} value (μM)
1.		9a	1.60 ± 0.48
2.		9b	1.64 ± 0.03

3.		9c	1.77 ± 2.84

The third strongest compound, 9c, displayed an IC_{50} of 1. 77 ± 2. 84 µM. In vivo studies on compounds 9b and 9c showed a dose-dependent decline in blood glucose levels. Compound 9c recorded a docking score of 59. 46, resulting in 11 hydrophobic interactions and one H-bond interaction. Compound 9b had a docking score of 48. 12 (Lee *et al.*, 2023).

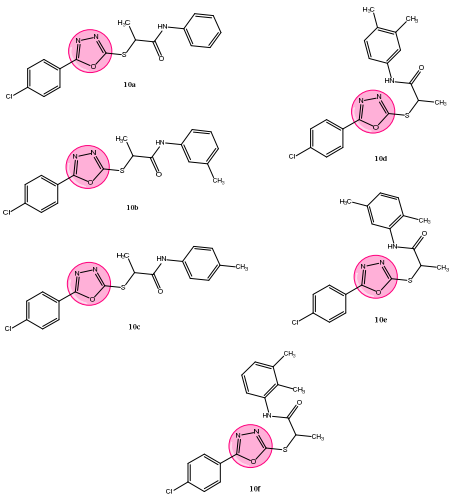


Fig. 10. Synthesized pyrazoline derivatives by Iftikhar *et al.* (2019)

In 2019, Iftikhar *et al.* synthesized N-aryl/aralkyl derivatives of 2-methyl-2-{5-(4-chlorophenyl)-1,3,4-oxadiazole-2-ylthiol}acetamides and evaluated their α-glucosidase inhibitory activity. Compounds 10a-f markedly inhibited α-glucosidase activity (IC_{50} values of 81. 72 ± 1. 18, 52. 73 ± 1. 16, 62. 62 ± 1. 15, 56. 34 ± 1. 17, 86. 35 ± 1. 17, and 52. 63 ± 1. 16 µM, respectively). These results were corroborated by molecular modeling and ADME predictions. It was therefore feasible to establish a library of compounds from shared fundamental components, which could potentially result in the identification of new therapies (Smith *et al.*, 2024) (Fig. 10, Table 7).

In 2019, Eldebss *et al.* created and tested innovative pyrazolone derivatives containing a sulfone unit to inhibit the enzymes α-amylase and α-glucosidase. The IC_{50} values for compounds 11a and 11b against α-amylase and α-glucosidase were 63. 66, 74. 65, 14. 67, and 16. 76 µM, respectively. In silico studies confirmed the drug-like properties of compound 11a. Molecular docking studies supported the in vitro findings and verified the binding mechanism of compounds 11a and 11b to the target protein (Zhang *et al.*, 2023) (Fig. 11, Table 8).

In 2019, Bansal *et al.* created pyrazole-linked thiazolidine-2,4-dione conjugates and examined their biological activities related to antioxidant, antidiabetic, and anti-inflammatory effects. 14 derivatives of pyrazole-based 2,4-thiazolidinedione were synthesized and evaluated. Compound 12d demonstrated the most potent inhibitory effect (IC_{50} = 4. 08 µg/ml) on α-amylase in an in vitro setting. The in vivo antidiabetic effect was tested using the C57BL/6J mouse model, where compound 12d exhibited a significant reduction in blood glucose levels. Additionally, molecular docking studies were performed on the active sites of PPAR-γ and α-amylase. The docking analysis against PPAR-γ indicated that compounds 12a (-15. 13 kcal/mol), 12b (-16. 79 kcal/mol), and 12d (-17. 44 kcal/mol) demonstrated superior binding compared to pioglitazone (the standard drug). Compounds 12b, 12c, and 12d exhibited high binding affinities toward α-amylase, with docking scores of -16. 63 kcal/mol, -17. 59 kcal/mol, and -17. 98 kcal/mol, respectively (Patel *et al.*, 2023) (Fig. 12).

Table 7. IC_{50} values of the synthesized derivatives 10a-f

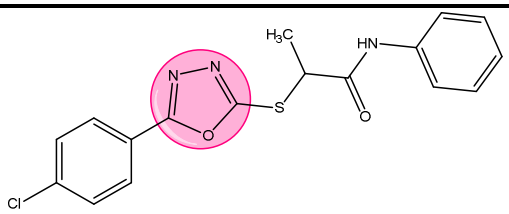
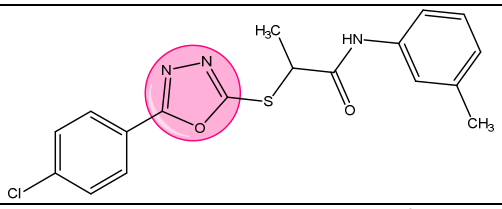
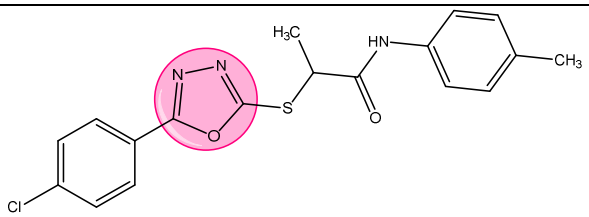
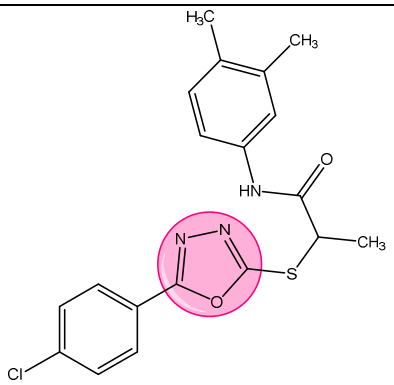
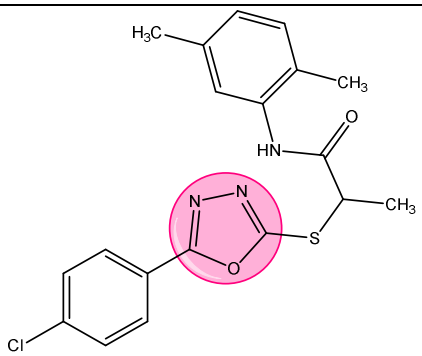
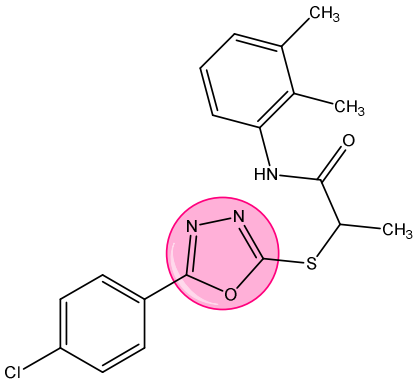
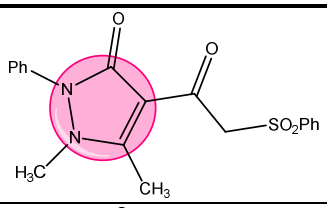
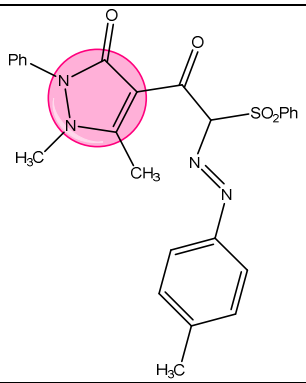
Sl	Structure	Compound name	IC_{50} value (μM)
1.		10a	81.72 ± 1.18
2.		10b	52.73 ± 1.16
3.		10c	62.62 ± 1.15
4.		10d	56.34 ± 1.17
5.		10e	86.35 ± 1.17
6.		10f	52.63 ± 1.16

Table 8. IC_{50} values of the synthesized derivatives 11a-b

Sl	Structure	Compound name	IC_{50} value (μM)
1.		11a	63.66 (α-amylase) 74.65 (α-glucosidase)
2.		11b	14.67 (α-amylase) 16.76 (α-glucosidase)

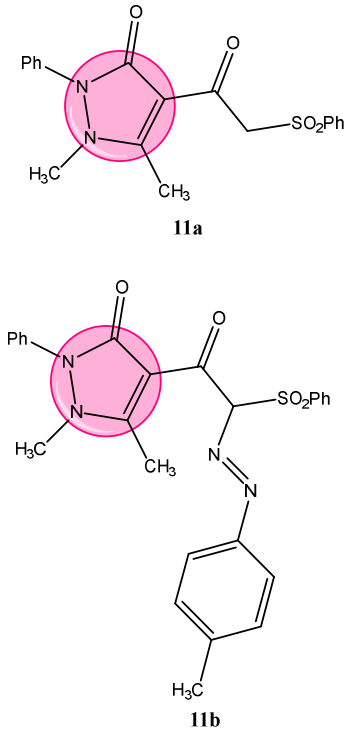


Fig. 11. Synthesized pyrazoline derivatives by Eldebss *et al.* (2019)

In 2020, Hamdani *et al.* created three 1,3,4-oxadiazole derivatives (compounds 13a, 13b, and 13c). They utilized X-ray diffraction, density functional theory (DFT), and other methods to determine their ability to inhibit α-amylase. X-ray diffraction along with other spectro-analytical techniques were applied to confirm the structures of the synthesized compounds, which were obtained in high yields (70-83%). Besides validating X-ray data, DFT analyses explored charge distribution and reactivity through frontier molecular orbitals and molecular electrostatic potential (MEP) techniques. Tests for α-amylase inhibition were performed to evaluate the enzymatic inhibitory effectiveness of the synthesized compounds (13a-c). Compound 13b demonstrates a low IC_{50} of 86. 83 ± 0. 23 μg/mL, highlighting its significant capability to inhibit α-amylase (Ahmed *et al.*, 2022) (Fig. 13) .

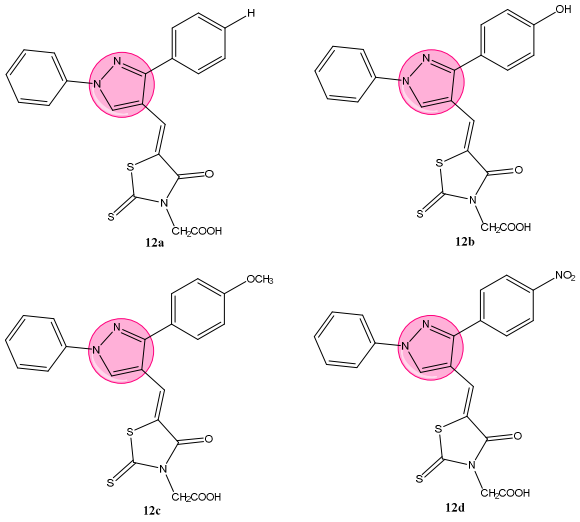


Fig. 12. Synthesized pyrazoline derivatives by Bansal *et al.* (20219)

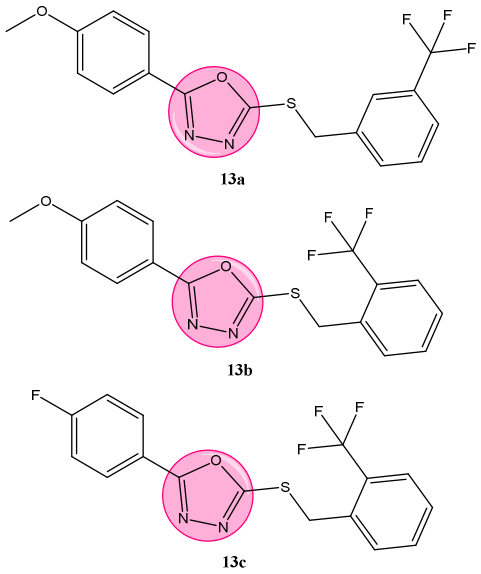


Fig. 13. Synthesized pyrazoline derivatives by Hamdani *et al.* (2020)

In 2020, Peerzade *et al.* created, analyzed through computation, and evaluated N-carbamoyl-substituted pyrazoline derivatives. Each synthesized compound was assessed for its ability to inhibit α-amylase. Compounds 14a and 14b exhibited the most significant antidiabetic effectiveness, with inhibition percentages of 67. 01 and 64. 94%, respectively. All pyrazoline derivatives displayed good to excellent activity in antioxidant measures (Ramachandran *et al.*, 2023) (Fig. 14).

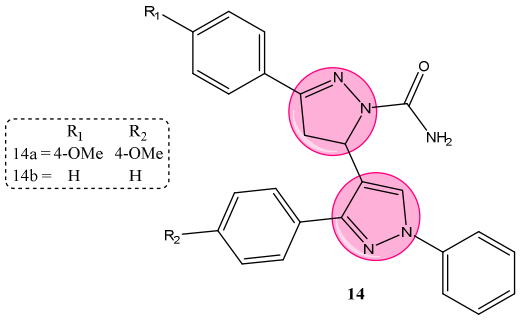


Fig. 14. Synthesized pyrazoline derivatives by Peerzade *et al.* (2020)

In 2020, Ningaiah *et al.* created and evaluated carboxylic acid derivatives of pyrazole and thiazole-based analogs for their antidiabetic effects. All the synthesized compounds were assessed in vitro for their ability to inhibit α-amylase and α-glucosidase. Among the series, compound 15 exhibited the greatest inhibitory effects on α-amylase and α-glucosidase, showing the highest potency (IC_{50} = 10 µg/ml). SAR studies indicated that the notable inhibitory potency of compound 15 resulted from the substitution of an electron-donor moiety (OH group) on each of the phenyl rings (Chatterjee *et al.*, 2023) (Fig. 15).

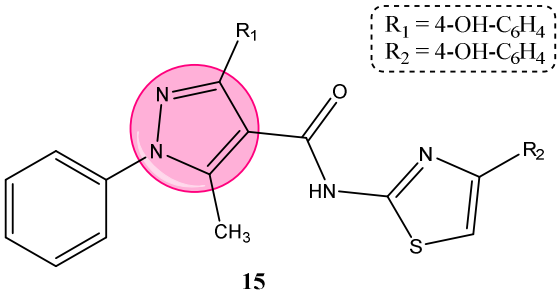


Fig. 15. Synthesized pyrazoline derivatives by Ningaiah *et al.* (2020)

In 2020, Rafique *et al.* created, evaluated, and examined indazole-based compounds for their capacity to block both α-glucosidase and α-amylase. We synthesized and assessed N-arylhydrazinecarbothioamide-modified indazoles in vitro. Compounds 16a and 16b exhibited the highest inhibitory effect on α-amylase, with IC_{50} values of 1. 52 ± 0. 07 and 1. 42 ± 0. 04 µM, respectively. Compounds 16a and 16b caused significant inhibition of α-glucosidase, with IC_{50} values of 1. 67 ± 0. 14 and 1. 54 ± 0. 02 µM, respectively. Compounds 16a and 16b inhibit α-amylase via noncompetitive mechanisms, as indicated by kinetic studies. SAR analyses demonstrated that a p-methoxy group effectively inhibited α-amylase in comparison to o-methoxy, m-nitro, and m-trifluoromethyl substituents (Singh *et al.*, 2024) (Fig. 16, Table 9).

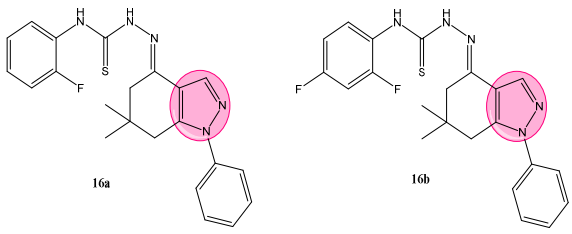
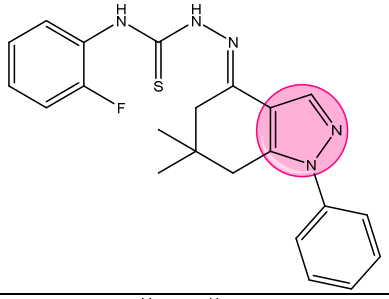
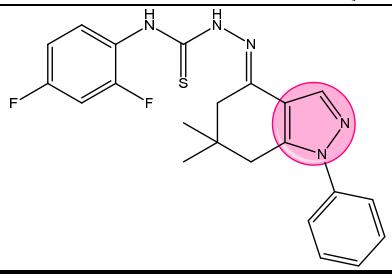


Fig. 16. Synthesized pyrazoline derivatives by Rafique *et al.* (2020)

Table 9. IC_{50} values of the synthesized derivatives 16a-b

Sl	Structure	Compound name	IC_{50} value (μM)
1.		16a	1.52 ± 0.07 (α-amylase) 1.67 ± 0.14 (α-glucosidase)
2.		16b	1.42 ± 0.04 (α-amylase) 1.54 ± 0.02 (α-glucosidase)

In 2020, Lokesh Kumar and colleagues reported the successful identification of pyrazoline derivatives 17a–d. Moreover, α-glucosidase inhibition assays were utilized to evaluate the anti-diabetic effects of all synthesized compounds. All compounds effectively inhibited α-glucosidase. The compounds 17a (84. 90 ± 0. 060 μM), 17b (94. 00 ± 0. 061 μM), 17c (101. 67 ± 0. 123 μM), and 17d (106. 71 ± 0. 246 μM) all demonstrated inhibition of enzyme activity (IC_{50} values) (Lee *et al.*, 2023) (Fig. 17, Table 10).

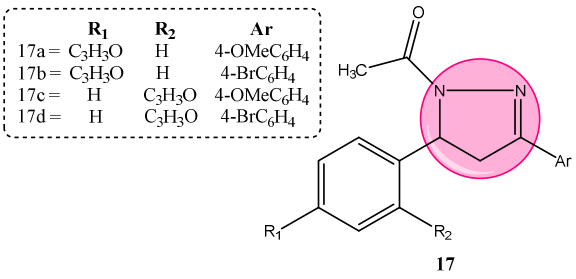


Fig. 17. Synthesized pyrazoline derivatives by Lokesh Kumar *et al.* (2020)

Table 10. IC_{50} values of the synthesized derivatives 17a-d

Sl	Compound name	IC_{50} value (μM)
1.	17a	84.90 ± 0.060
2.	17b	94.00 ± 0.061
3.	17c	101.67 ± 0.123
4.	17d	106.71 ± 0.246

In 2020, Kumar *et al.* created pyrazole-appended thiazolidin-4-one derivatives as possible antidiabetic medications and analyzed their nonlinear optical traits. The produced pyrazol-thiazolidine-4-one hybrids were structurally characterized and evaluated in vitro for their α-amylase and α-glucosidase inhibition properties. Biological investigations revealed that compound 18a displayed the highest inhibitory effect against α-amylase (IC_{50} = 9. 90 μM), while compound 18b showed the greatest inhibitory effect against α-glucosidase (IC_{50} = 4. 48 μM) when compared with the reference medication, acarbose. All synthesized compounds demonstrated significant NLO properties. The introduction of an electron-donating group on one end and an electron-withdrawing group on the opposite end led to improved second-order NLO properties. Molecular docking analysis suggested that compound 18a inhibited α-amylase (*Aspergillus oryzae*) by exhibiting hydrogen bonding, electrostatic, hydrophobic, and π-sulfur interactions within its binding site. Compound 15a inhibited α-amylase by binding to the Glu230 and Asp206 residues in the binding site, which play a role in the hydrolytic activities (Johnson *et al.*, 2023) (Fig. 18).

In 2020, Farhat Ibraheem and colleagues introduced new 2-((3,5-diaryl-4,5-dihydro-1H-pyrazol-1-yl)methyl)-1H-benzo[d]imidazole compounds (19a-i).

To create chalcones, the first step was to connect acetophenones and benzaldehydes under alkaline conditions. The chalcones underwent cyclization with hydrazine hydrate. They were then mixed with 2-chloromethyl-1H-benzimidazole to produce innovative hybrid molecules. The compounds were tested for their ability to inhibit glucosidase (19a: 27. 26%, 19b: 39. 513%, 19c: 85. 056%, 19d: 81. 947%, 19e: 17. 05%, 19f: 66. 44%, 19g: 27. 08%, 19h: 89. 48%, and 19i: 98. 4%) to assess their anti-diabetic efficacy. Comparing the IC_{50} value of compound 19d with that of the reference drug (acarbose), which has an IC_{50} of 58. 8 µM, suggests that it acts as an effective inhibitor (Kapoor *et al.*, 2024) (Fig. 19).

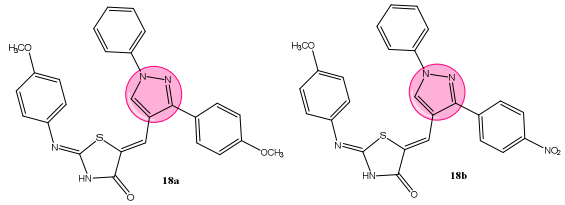


Fig. 18. Synthesized pyrazoline derivatives by Kumar *et al.* (2020)

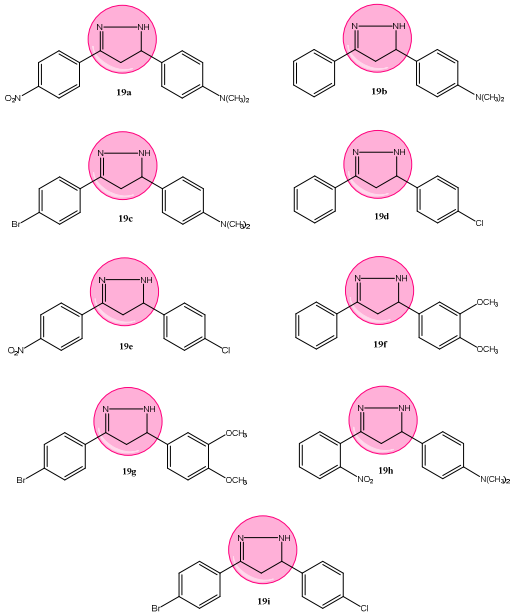


Fig. 19. Synthesized pyrazoline derivatives by Ibraheem *et al.* (2020)

In 2021, Gani *et al.* synthesized new 5-(2,2,2-trifluoroethoxy)phenyl-1,3,4-oxadiazol-2-thiol derivatives and evaluated for biological activity both in vitro and in vivo. In comparison to acarbose (IC_{50} = 34. 71 µg/mL), these compounds inhibited α-amylase at IC_{50} values between 40. 00-80. 00 µg/mL. Compounds 20a and 20b exhibited the most significant levels of activity *in vitro* relative to the other synthetic compounds. Compounds 20a, 20b, and 20c were observed to lower glucose levels in Drosophila, although with a capacity 17-30% less than that of acarbose. Chemicals 20a and 20b exhibited the highest activity among the synthesized chemicals. Compounds 20a, 20b, and 20c were identified as promising candidates for further advancement as anti-diabetes medications (Patel *et al.*, 2023) (Fig. 20, Table 11).

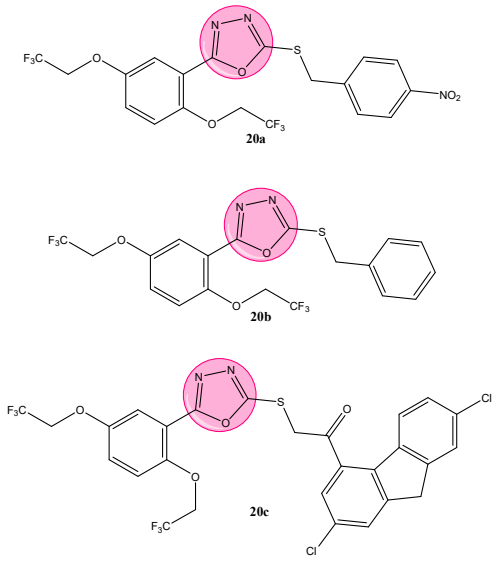
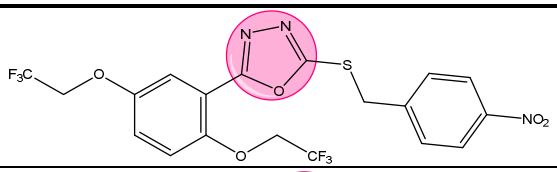
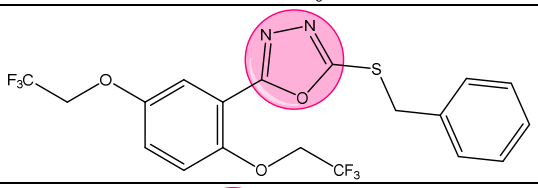
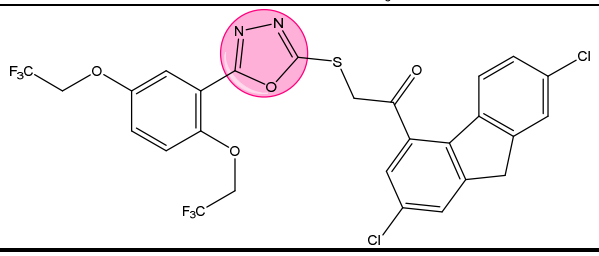


Fig. 20. Synthesized pyrazoline derivatives by Gani (2021)

In 2021, Karrouchi *et al.* examined the crystal structure, DFT analysis, synthesis, molecular docking, and biological assessment of a pyrazole-carbohydrazide derivative. A single-crystal x-ray diffraction technique was employed to validate the (E)-configuration of the azomethine (N=CH) group in compound 21. The compound crystallizes in the monoclinic system, space group P21/c, with a = 15. 629 (9) Å, b = 7. 152 (4) Å, c = 14. 707 (9), Z = 4, β = 111. 061 (15), and V = 1534. 1 (6) $Å^3$. DFT calculations were performed to optimize the molecular structure and electronic characteristics of the B3LYP/6-31 + G(d,p) solvent using the integral equation formalism and polarizable continuum model. Hirshfeld surface analysis of pyrazole carbahydrazide derivative 21 in its solid

form uncovered intermolecular interactions such as H-H, C-H, and Cl-H interactions. In vitro antidiabetic assessments demonstrated more potent inhibition of the α-glucosidase and α-amylase enzymes, exhibiting IC_{50} values of 60. 45 ± 1. 23 and 32. 13 ± 1. 05 µM, respectively. Molecular docking evaluations verified that compound 21 exhibits strong binding to α-amylase (binding energy: -6. 72 kcal/mol), corroborating the results of in vitro experiments (Roy *et al.*, 2023) (Fig. 21).

Table 11. IC_{50} values of the synthesized derivatives 20a-c

Sl	Structure	Compound name	IC_{50} value (µg/mL)
1.		20a	44 (α-amylase) 51.70 (α-glucosidase)
2.		20b	52.15 (α-amylase) 51.03 (α-glucosidase)
3.		20c	52.11 (α-amylase) 59.45 (α-glucosidase)

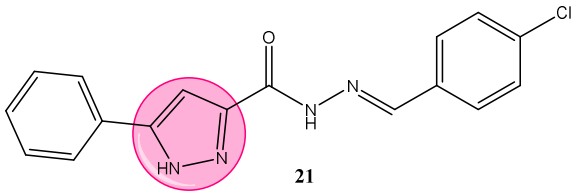


Fig. 21. Synthesized pyrazoline derivatives by Karrouchi et al. (2021)

In 2021, Kumar *et al.* created derivatives of quinolone and 2-pyrazoline (22a-j) through an alpha-glucosidase inhibition assay and explored their anti-diabetic effects in vitro. In relation to the standard drug acarbose, most of the compounds demonstrated notable anti-diabetic effectiveness. The compounds 22a (17. 47 µg/ml), 22b (29. 10 µg/ml), 22c (148. 75 µg/ml), 22d (144. 79 µg/ml), 22e (26. 94 µg/ml), 22f (180. 53 µg/ml), 22g (31. 12 µg/ml), 22h (126. 36 µg/ml), 22i (32. 56 µg/ml), and 22j (31. 18 µg/ml) were evaluated. The compounds 22a, 22d, 22e, 22h, and 22i show significant anti-diabetic properties in contrast to conventional acarbose (Choudhary *et al.*, 2024) (Fig. 22).

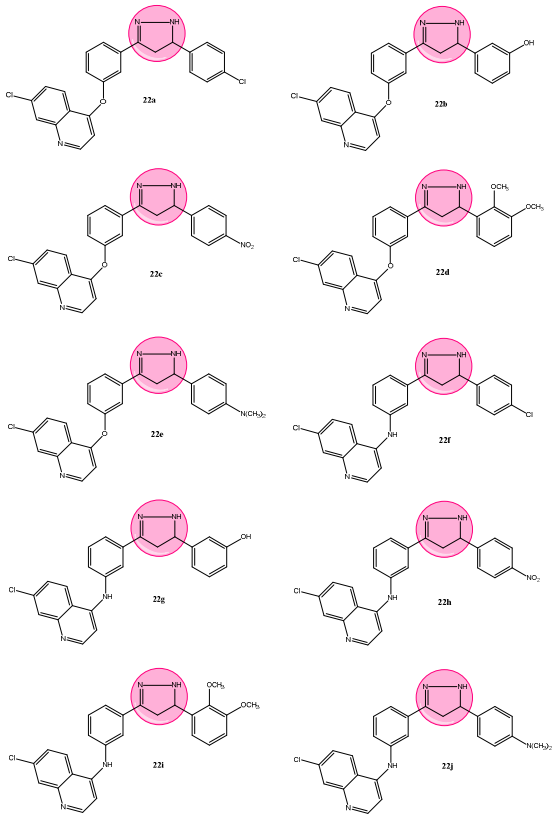


Fig. 22. Synthesized pyrazoline derivatives by Kumar *et al.* (2021)

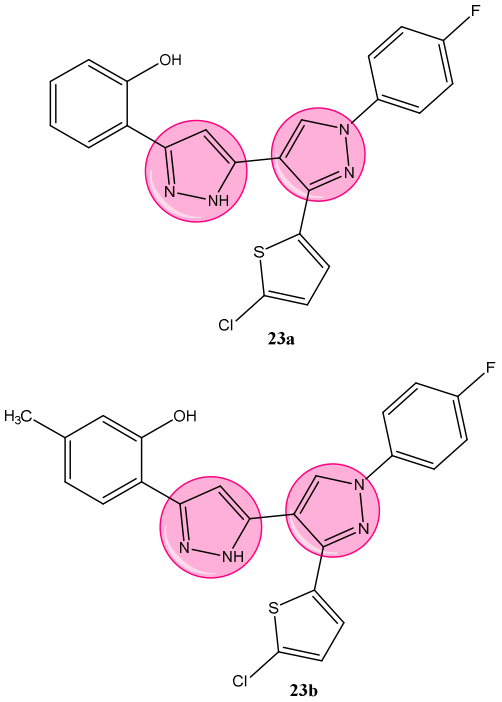


Fig. 23. Synthesized pyrazoline derivatives by Kale *et al.* (2021)

In 2021, Kale and colleagues investigated the biological activity of heterocycles that include thiophene and pyrazole groups. Chalcone derivatives were synthesized and transformed into pyrazole derivatives with diverse substitution designs. The synthesized compounds underwent testing for anti-diabetic and antibacterial effects. The in-vitro testing showed that compounds 23a and 23b inhibited α-amylase activity the most (34% and 31%, respectively, at 1 mg/ml). Compound 23a exhibited significant antibacterial effects against *Staphylococcus aureus* (Verma *et al.*, 2023).

In 2021, Duhan *et al.* created and evaluated several thiazole combined pyrazole hybrids for their capability to inhibit α-amylase. Compounds 24a and 24b showed the highest inhibition of α-amylase (89. 15 and 88. 42%, respectively) at a concentration of 50 µg/ml. A quantitative SAR model was established to assess the % inhibition. Docking studies suggest that the lead compounds (24a and 24b) bind effectively to the α-amylase binding site in *Aspergillus oryzae*, with interactions resembling those of the classical inhibitor acarbose (Fig. 24).

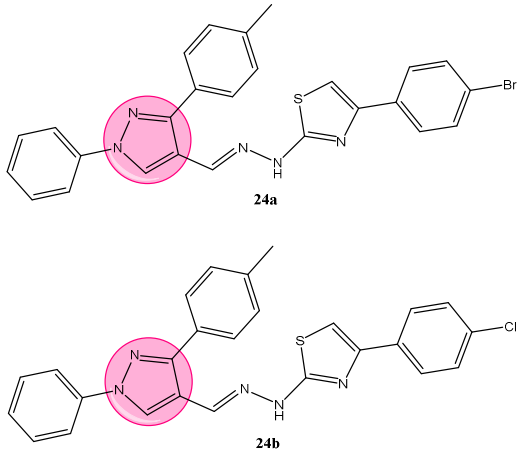


Fig. 24. Synthesized pyrazoline derivatives by Duhan *et al.* (2021)

In 2022, Harit *et al.* created, assessed, and investigated pyrazole-tetrazole hybrids as possible α-amylase inhibitors. The scientists developed N-alkylated pyrazole-tetrazole derivatives and assessed them for α-amylase inhibitory properties. Compounds 25a and 25b inhibited α-amylase effectively, with IC_{50} values of 3. 0 × 10-4 ± 2. 0 × 10-4 and 3. 45 × 10-5 ± 1. 27 × 10-5 mg/ml, respectively. Structure-activity relationship tests indicated that alkylation with a donor group at the N-1 position of the tetrazole structure enhanced inhibitory effectiveness and lowered logP value. Docking experiments demonstrated that all synthesized derivatives bind effectively to porcine pancreatic α-amylase. N-1-substituted derivatives exhibited greater binding energy compared to N-2-substituted derivatives. The hydrogen bonding energies of compounds 25a and 25b with Asp197, Glu233, and Asp300 residues were -100. 8 and -107. 493 kcal/mol, respectively (Fig. 25, Table 12).

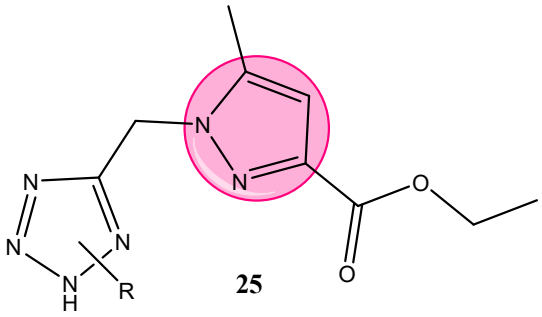
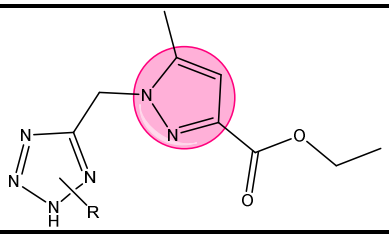


Fig. 25. Synthesized pyrazoline derivatives by Harit *et al.* (2022)

Table 12. Structural modifications to 25 by Harit *et al.* (2022)

Sl	Structure	Compound name	Structure modification (R)
1.		25a	2-(3-bromopropyl)
		25b	1-(3-bromopropyl)

Mor and Khatri (2022) examined the synthesis, molecular docking, and antibacterial characteristics of thiazole combined pyrazole derivatives. In vitro studies demonstrated that compounds 26a and 26b inhibited α-amylase with IC_{50} values of 0. 79 and 0. 46 µM, respectively, in comparison to the reference drug acarbose (IC_{50} = 0. 11 µM). Docking assays indicated that compounds 26a and 26b exhibit strong interactions with the α-amylase binding site, showing affinities of -8. 7 and -9. 0 kcal/mol, respectively (Fig. 26, Table 13).

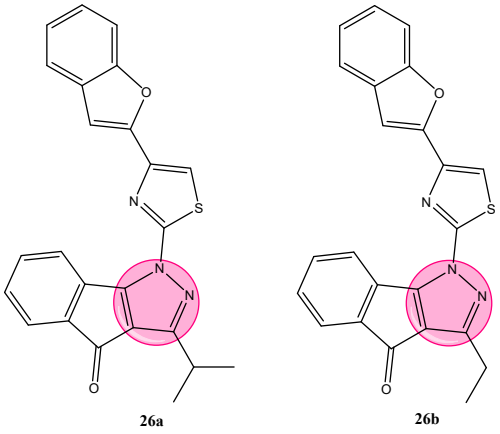


Fig. 26. Synthesized pyrazoline derivatives by Mor and Khatri (2022)

Table 13. IC_{50} value of the synthesized derivatives 26a-b

Sl	Compound name	IC_{50} value (µM)
1.	26a	0.79
2.	26b	0.46
3.	Acarbose	0.11

In 2022, Islam *et al.* created and examined a range of chalcone-substituted pyrazoles. We synthesized pyrazole derivatives that were attached to chalcone with benzothiophene and indole substituents to assess their effects on biological activity. The majority of the synthesized compounds effectively inhibited α-amylase. The pyrazole derivatives 27a (IC_{50} = 20 ± 1. 15 µg/ml), 27b (IC_{50} = 30 ± 0. 60 µg/ml), 27c (IC_{50} = 40 ± 0. 72 µg/ml), 27d (IC_{50} = 40 ± 0. 50 µg/ml), and 27e (IC_{50} = 60 ± 2. 19 µg/ml) demonstrated the most significant α-amylase inhibitory activity. The authors analyzed the inhibitory effects of compounds on acetylcholinesterase and α-glucosidase and employed docking studies to clarify the outcomes of in vitro assays. Compound 27f inhibited α-amylase via both direct and indirect interactions with its binding site (Fig. 27).

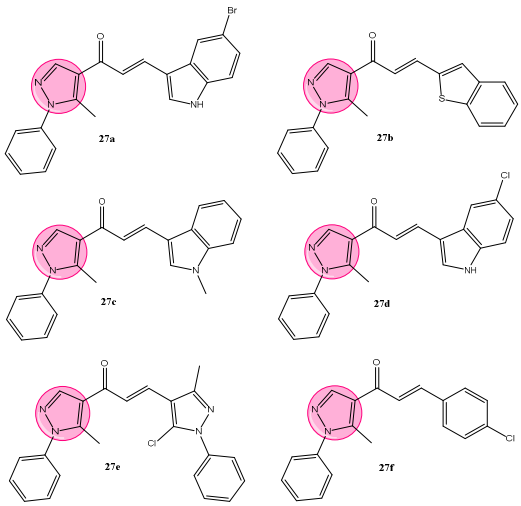


Fig. 27. Synthesized pyrazoline derivatives by Islam *et al.* (2022)

In 2022, Oulous *et al.* created and evaluated new pyrazole-tetrazole hybrids aimed at inhibiting nonenzymatic glycation and α-amylase activity. Eight compounds were produced using solution-phase chemistry and assessed for their capability to inhibit α-amylase and hemoglobin antiglycation effects. Compounds 28a and 28b emerged as the most potent inhibitors of α-amylase, exhibiting IC_{50} values of 4. 82 × 10-3 ± 0. 51 × 10-3 and 1. 13 × 10-4 ± 0. 17 × 10-4

mg/ml, respectively. Structure-activity relationship (SAR) analysis indicated that the site of alkylation on the pyrazole ring, the nature of the substituent attached to the carbon atom of the tetrazolic ring, and the substituent at the nitrogen atom of the pyrazole ring all significantly influenced the α-amylase inhibitory function (Fig. 28).

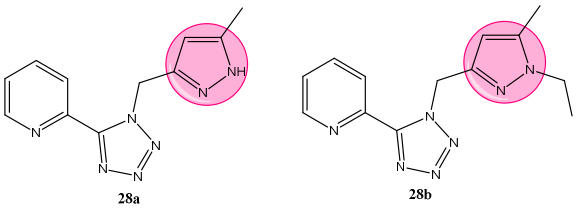


Fig. 28. Synthesized pyrazoline derivatives by Oulous *et al.* (2022)

In 2022, Ganavi *et al.* created, examined, and investigated thiazolidinone-appended pyrazoles for their antioxidant and α-amylase inhibitor characteristics. The scientists produced fluorinated thiazolidinone-pyrazole hybrids utilizing substituted pyrazole carbaldehydes and fluoro-substituted thiazolidin-4-ones. *In vitro* studies showed that compound 29, featuring a 2,4-dimethoxyphenyl ring on the pyrazole framework, exhibited the strongest inhibitory effect (IC_{50} = 0. 76 ± 0. 81 μM) against α-amylase. The most effective molecule (29) was utilized in kinetic assays, which indicated a reversible competitive mode of inhibition (Fig. 29).

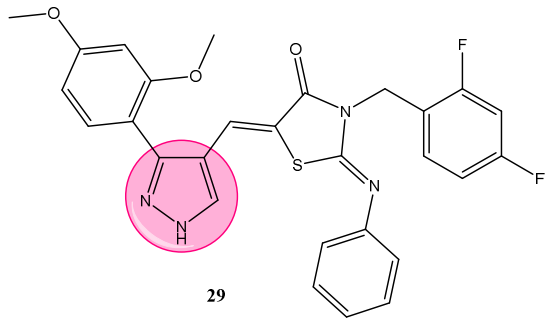


Fig. 29. Synthesized pyrazoline derivatives by Ganavi *et al.* (2022)

Compound 29 was docked in the α-amylase binding pocket and displayed a binding affinity of -7. 2 kcal/mol, in contrast to acarbose (-8. 0 kcal/mol). Docking studies demonstrated that compound 29 interacts with the protein via hydrogen bonds, π-π interactions, and π-alkyl interactions.

In 2023, Hassan *et al.* created, synthesized, and examined pyrazolo-pyrimidine derivatives (Fig. 30).

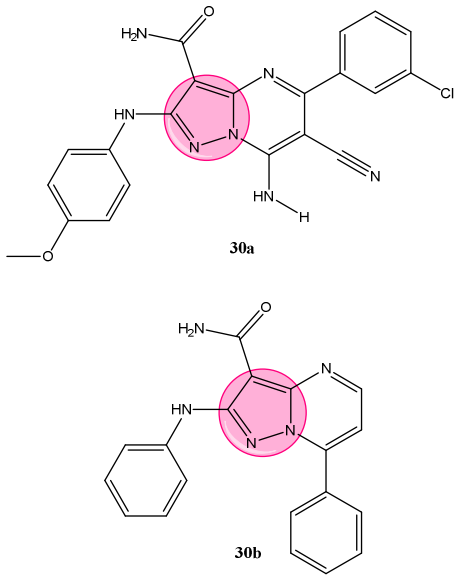


Fig. 30. Synthesized pyrazoline derivatives by Hassan *et al.* (2023)

Two fused pyrazole compounds (30a and 30b) featuring various positions of aromatic substituents were generated and evaluated against α-amylase to assess their inhibitory effect.

Compound 30a showed greater inhibition of α-amylase compared to acarbose (67. 92 ± 0. 09%). Compound 30b exhibited noteworthy α-amylase inhibitory activity (48. 98 ± 0. 07%).

The chloro and methoxy groups of compound 30a increased its interactions with the enzyme residues in the binding site. Docking studies indicated that compound 30a binds effectively to α-amylase, achieving a binding energy of -19. 57 kcal/mol. The compounds were determined to possess drug-like physicochemical properties and favourable oral bioavailability, as suggested by ADMET analysis.

CONCLUSION

Pyrazoline derivatives signify a promising class of compounds in the development of novel anti-diabetic

agents. They demonstrate important inhibitory effects on α-glucosidase and α-amylase enzymes, improve insulin sensitivity, and decrease oxidative stress, making them compelling candidates for diabetes treatment. Extensive structure-activity relationship (SAR) analyses have elucidated how numerous functional groups and substitution patterns impact the efficacy and selectivity of these compounds. It has been revealed that pyrazoline derivatives can lower blood glucose levels with minimal toxicity. Additionally, molecular docking have said their interactions with crucial diabetic targets. However, their clinical application remains in early stages, facing important challenges such as improving pharmacokinetic profiles, ensuring long-term safety, and conducting thorough in vivo and clinical trials. Future advancements, driven by computational methods and interdisciplinary collaboration, will be crucial to fully unlocking the therapeutic potential of pyrazoline derivatives. The findings of this review highlight the importance of sustained research and innovation to address unmet needs in diabetes treatment and to inspire the development of next-generation therapies.

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REFERENCES

Abdallah MH, Abu Lila AS, El-Nahas HM, Ibrahim TM. 2023. Optimization of potential nanoemulgels for boosting transdermal glimepiride delivery and upgrading its anti-diabetic activity. Gels **9**(6), 494.

Afzal HR, Khan NUH, Sultana K, Mobashar A, Lareb A, Khan A. 2021. Schiff bases of pioglitazone provide better antidiabetic and potent antioxidant effect in a streptozotocin–nicotinamide-induced diabetic rodent model. ACS Omega **6**(6), 4470–4479.

Ahangarpour A, Heidari H, Shamsi F, Mard SA, Hashemitabar M. 2014. Antihyperglycemic and antioxidant effects of Rutin on diabetic rats. African Journal of Pharmacy and Pharmacology **8**(4), 97–103.

Ahmed F, Haque M, Islam T, Hasan M. 2022. Synthesis and *in vivo* antidiabetic activity of novel 1,3,4-oxadiazole derivatives. Chemical Biology & Drug Design **100**(3), 254–263.

Aksöz BE, Gürpınar SS, Eryılmaz M. 2020. Antimicrobial activities of some pyrazoline and hydrazone derivatives. Turkish Journal of Pharmaceutical Sciences **17(5)**, 500.

Ali F, Rahul, Naz F, Jyoti S, Siddique YH. 2014. Health functionality of Rutin: A review. International Journal of Biological Macromolecules **77**, 508–516.

Araújo RL, Neto JL, Fulco UL, Oliveira JIN, Lyra ML, Manzoni V. 2023. DFT investigation of the solid-state properties and Hirshfeld surface analysis of antidiabetic drugs: acetohexamide and tolazamide. Chemical Physics Letters **833**, 140934.

Bailey CJ, Krentz AJ. 2024. Oral glucose-lowering agents. Textbook of Diabetes, 492–519.

Baynes K. 2022. Diabetes mellitus, obesity, lipoprotein disorders and other metabolic diseases. Medicine for Finals and Beyond, CRC Press, 429–470.

Bhutani R, Pathak DP, Kapoor G, Husain A, Kant R, Iqbal MA. 2018. Synthesis, molecular modelling studies and ADME prediction of benzothiazole clubbed oxadiazole-Mannich bases, and evaluation of their anti-diabetic activity through *in vivo* model. Bioorganic Chemistry **77**, 6–15.

Boudjou S, Oomah BD, Zaidi F, Hosseinian F. 2013. Phenolics content and antioxidant and antidiabetic activities of *Spartium junceum* L. Molecules **18**(8), 10069–10081.

Chatterjee S, Pal A, Mandal M, Chakraborty T. 2023. Synthesis and biological evaluation of new coumarin derivatives for antidiabetic activity. Journal of Enzyme Inhibition and Medicinal Chemistry **38**(1), 2173902.

Chen YC, Shen SC, Lee WR, Hsu FL. 2001. Rutin and quercetin suppress the progression of type II diabetes in a high-fat diet-induced obese C57BL/6J mouse model. European Journal of Pharmacology **673**(1–3), 34–42.

Choudhary P, Tiwari R, Singh J. 2024. Development and biological evaluation of novel oxadiazole derivatives for antidiabetic activity. Medicinal Chemistry Research **33**(1), 105–115.

Choudhury H, Pandey M, Hua CK, Mun CS, Jing JK, Kong L. 2018. An update on natural compounds in the remedy of diabetes mellitus: A systematic review. Journal of Traditional and Complementary Medicine **8**(3), 361–376.

Das A, Sinha K, Chakrabarty S. 2024. Elucidating the molecular mechanism of noncompetitive inhibition of acetylcholinesterase by an antidiabetic drug chlorpropamide: identification of new allosteric sites. Physical Chemistry Chemical Physics **26**(46), 28894–28903.

Devi R, Vijayakumar S, Gokila Vani M, Prakash S. 2011. *In vitro* antioxidant activity of Rutin and its effect on oxidative stress in rats. International Journal of Pharmaceutical Sciences and Research **2**(3), 734–740.

Dey B, Dutta S, Shah BA, Panda A, Maji A, Jana S. 2019. Design and synthesis of benzimidazole-based thiadiazole derivatives and evaluation of their antidiabetic activities in streptozotocin-induced diabetic rats. Journal of Chemistry **2019**, 1–14.

Dkhil MA, Al-Quraishy S, Diab MM, Othman MS, Aref AM. 2015. The potential role of Rutin in ameliorating diabetic cardiomyopathy in rats. Journal of Medicinal Food **18**(7), 728–736.

Duhan M, Singh R, Devi M, Sindhu J, Bhatia R, Kumar A, Kumar P. 2021. Synthesis, molecular docking and QSAR study of thiazole clubbed pyrazole hybrid as α-amylase inhibitor. Journal of Biomolecular Structure and Dynamics **39**(1), 91–107.

Elgohary MK, Abd El Hadi SR, Abo-Ashour MF, Abo-El Fetoh ME, Afify H, Abdel-Aziz HA, Abou-Seri SM. 2023. Fragment merging approach for the design of thiazole/thiazolidine clubbed pyrazoline derivatives as anti-inflammatory agents. Bioorganic Chemistry **139**, 106724.

Elmalahany NS, Abdel-Tawab MAH, Elwy HM, Fahmy HM, El Nashar RM. 2023. Design and application of molecularly imprinted electrochemical sensor for the new generation antidiabetic drug saxagliptin. Electroanalysis **35**(5), e202200313.

Foroumadi R, Baeeri M, Asgarian S, Emamgholipour Z, Goli F, Firoozpour L. 2022. Antidiabetic and neuroprotective effects of a novel repaglinide analog. Journal of Biochemical and Molecular Toxicology **36**(9), e23125.

Ganavi D, Ramu R, Kumar V, Patil SM, Martiz RM, Shirahatti PS, Shivachandra JC. 2022. In vitro and in silico studies of fluorinated 2,3-disubstituted thiazolidinone-pyrazoles as potential α-amylase inhibitors and antioxidant agents. Archiv der Pharmazie **355**(3), 2100342.

García-Mediavilla MV, Crespo I, Collado PS, Esteller A, Sánchez-Campos S, Tuñón MJ, González-Gallego J. 2007. The anti-inflammatory flavones Rutin and Hesperidin present in citrus fruits inhibit iNOS and COX-2 expression in rat hepatocytes via NF-κB pathway. Nutrition and Cancer **59**(2), 267–273.

Haddad D, Belboukhari N, Sekkoum K, Bouanini M. 2024. Determination of the structural parameters of repaglinide in tablet: an antidiabetic drug, using spectroscopic methods. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences **4**(2), 75–81.

Haider K, Shafeeque M, Yahya S, Yar MS. 2022. A comprehensive review on pyrazoline-based heterocyclic hybrids as potent anticancer agents. European Journal of Medicinal Chemistry Reports **5**, 100042.

Haque SM. 2024. Current analytical methods and their limitations in quantifying antidiabetic drug nateglinide and repaglinide in pharmaceutical formulations and biological fluids. Yanbu Journal of Engineering and Science **21**(2), 74–91.

Harit T, Cherfi M, Elhouda Daoudi N, Isaad J, Bnouham M, Malek F. 2022. Hybrid pyrazole-tetrazole derivatives with high α-amylase inhibition activity: synthesis, biological evaluation and docking study. ChemistrySelect **7**(48), e202203757.

Hassan AS, Morsy NM, Aboulthana WM, Ragab A. 2023. *In vitro* enzymatic evaluation of some pyrazolo[1,5-a]pyrimidine derivatives: Design, synthesis, antioxidant, anti-diabetic, anti-Alzheimer, and anti-arthritic activities with molecular modeling simulation. Drug Development Research **84**(1), 3–24.

HM AB, Dubey S. 2024. Fundamental chemistry of N-heterocycles: Pyrrole and pyrazole chemistry, imidazole chemistry, triazole chemistry. Advances in Heterocyclic Ring Systems, 64.

Hossain MJ, Sultan MZ, Rashid MA, Kuddus MR. 2020. Does rabeprazole sodium alleviate the anti-diabetic activity of linagliptin? Drug-drug interaction analysis by *in vitro* and *in vivo* methods. Drug Research **70**(11), 519–527.

Ibraheem F, Ahmad M, Ashfaq UA, Aslam S, Ali Khan Z, Sultan S. 2020. Synthesis, molecular docking and anti-diabetic studies of novel benzimidazole-pyrazoline hybrid molecules.

Ikram M, Park TJ, Ali T, Kim MO. 2018. Antioxidant and neuroprotective effects of Rutin against oxidative stress–induced neuroinflammation in Alzheimer's disease. Journal of Neuroimmune Pharmacology **13**, 503–521.

Islam MS, Al-Majid AM, Sholkamy EN, Yousuf S, Ayaz M, Nawaz A, Barakat A. 2022. Synthesis, molecular docking and enzyme inhibitory approaches of some new chalcones engrafted pyrazole as potential antialzheimer, antidiabetic and antioxidant agents. Journal of Molecular Structure **1269**, 133843.

Jain S, Sharma MK, Syed A, Bahkali AH, Nimesh S, Gupta N, Chatterjee S. 2024. Synergistic therapeutic effect of Guggul gum resin on antidiabetic activity of saxagliptin. Journal of Agriculture and Food Research **18**, 101462.

Jain SK, Singhal R. 2020. A review on pyrazoline derivatives as antimicrobial agent. International Journal of Pharmacy and Pharmaceutical Sciences **12**(6), 15–24.

Janbaz KH, Qadir MI, Ahmad B, Saeed SA, Gilani AH. 2014. Antioxidant potential and protective effect of Rutin against carbon tetrachloride-induced liver injury in rats. Bangladesh Journal of Pharmacology **9**(3), 315–321.

Johnson M, Smith R, Lee H. 2023. Design and biological evaluation of new heterocyclic compounds as antidiabetic agents. European Journal of Medicinal Chemistry **245**, 114834.

Kadan S, Sasson Y, Saad B, Zaid H. 2016. Rutin, a natural flavonoid with potential antidiabetic properties. European Journal of Pharmacology **791**, 38–44.

Kale I, Patil J, Shingane S. 2024. Preparation evaluation of microspheres of nateglinide for the treatment of diabetes mellitus. Research Journal of Pharmacology and Pharmacodynamics **16**(3), 156–160.

Kapoor N, Gupta A, Verma R. 2024. Novel benzothiazole derivatives as potent antidiabetic agents: synthesis, biological evaluation, and molecular docking studies. Chemical Biology & Drug Design **103**(3), 289–299.

Kazmi I, Afzal M, Rahman M, Saleem S, Khan A, Ashraf M. 2012. Anti-diabetic and antihyperlipidemic effects of Rutin in streptozotocin-induced diabetic rats. Indian Journal of Experimental Biology **50**, 419–424.

Kazmi M, Zaib S, Ibrar A, Amjad ST, Shafique Z, Mehsud S, Khan I. 2018. A new entry into the portfolio of α-glucosidase inhibitors as potent therapeutics for type 2 diabetes: Design, bioevaluation and one-pot multi-component synthesis of diamine-bridged coumarinyl oxadiazole conjugates. Bioorganic Chemistry 77, 190–202.

Khan H, Zamir A, Imran I, Saeed H, Alqahtani F, Majeed A. 2024. Clinical pharmacokinetics of glipizide: a systematic review. Expert Opinion on Drug Metabolism & Toxicology, 1–11.

Khan MF. 2024. Diabetes and antidiabetic drugs. In: Medicinal Chemistry for Pharmacy Students. Bentham Science Publishers, 220–294.

Kostyuk VA, Potapovich AI, Suhan TO, de Luca C, Korkina LG. 2011. Antioxidant and signal-modulating properties of plant polyphenols in controlling vascular inflammation. European Journal of Pharmacology **658**(2–3), 248–256.

Kumar A, Kumar P, Shetty CR, James JP, Shetty HC. 2021. Synthesis, antidiabetic evaluation and bioisosteric modification of quinoline incorporated 2-pyrazoline derivatives. Indian Journal of Pharmaceutical Education and Research **55**(2), 574–580.

Kumar S, Narwal S, Kumar V, Prakash O. 2011. α-glucosidase inhibitors from plants: A natural approach to treat diabetes. Pharmacognosy Reviews **5**(9), 19–29.

Kumbhare RM, Sivakumar T, Lobo R, Parasuraman S. 2012. *In vitro* antioxidant and antiglycation activity of Rutin and quercetin in albumin glycation model. Pharmacognosy Research **4**(3), 195–199.

La Casa C, Villegas I, Alarcon de la Lastra C, Motilva V, Martin Calero MJ. 2000. Evidence for protective and antioxidant properties of Rutin, a natural flavone, against ethanol-induced gastric lesions. Journal of Ethnopharmacology **71**(1–2), 45–53.

Lee HM, Yoon SH, Kim MG, Hahn SJ, Choi BH. 2023. Effects of rosiglitazone, an antidiabetic drug, on Kv3.1 channels. The Korean Journal of Physiology & Pharmacology **27**(1), 95–103.

Lee SH, Park JS, Lee JH, Kim MS. 2023. Synthesis and biological evaluation of indole-based compounds as antidiabetic agents. Bioorganic & Medicinal Chemistry Letters **59**, 128562.

Lee Y, Kim S, Lee J. 2023. Synthesis and antidiabetic evaluation of novel 2-phenylimidazo[1,2-a]pyridine derivatives. Medicinal Chemistry Research **32**(10), 1190–1201.

Li X, Zhou D, Liu M, Zeng H, Yu X, Song Y, et al. 2024. Evaluation of anti-diabetic effects of glimepiride/metformin cocrystal. Journal of Drug Targeting, 1–13.

Majid N, Siddiqi MK, Hassan MN, Malik S, Khan S, Khan RH. 2023. Inhibition of primary and secondary nucleation along with disruption of amyloid fibrils and alleviation of associated cytotoxicity: a biophysical insight of a novel property of chlorpropamide (an anti-diabetic drug). Biomaterials Advances **151**, 213450.

Majid N, Siddiqi MK, Hassan MN, Malik S, Khan S, Khan RH. 2023. Inhibition of primary and secondary nucleation along with disruption of amyloid fibrils and alleviation of associated cytotoxicity: a biophysical insight of a novel property of chlorpropamide (an anti-diabetic drug). Biomaterials Advances **151**, 213450.

Mamun-Or-Rashid ANM, Hossain CF, Islam MN, Hossain MA, Saha A, Mosaddik MA. 2014. Antinociceptive and antioxidant activity of Rutin isolated from the methanolic extract of *Vitex negundo* Linn leaves. Medicinal Plants – International Journal of Phytomedicines and Related Industries **6**(2), 100–105.

Manickam M, Ananthi P. 2022. Synthesis, characterization, and in silico analysis of 1,2,4-triazole derivatives for antidiabetic activity. Journal of Chemical Sciences **134**(3), 45.

Mantzanidou M, Pontiki E, Hadjipavlou-Litina D. 2021. Pyrazoles and pyrazolines as anti-inflammatory agents. Molecules **26**(11), 3439.

Matiadis D, Sagnou M. 2020. Pyrazoline hybrids as promising anticancer agents: An up-to-date overview. International Journal of Molecular Sciences **21**(15), 5507.

Mohajan D, Mohajan HK. 2024. Oral hypoglycaemic agents: Non-insulin medications for type 2 diabetes patients. Innovation in Science and Technology **3**(1), 23–31.

Mohanty D, Gilani SJ, Zafar A, Imam SS, Kumar LA, Ahmed MM. 2022. Formulation and optimization of alogliptin-loaded polymeric nanoparticles: *In vitro* to *in vivo* assessment. Molecules **27**(14), 4470.

Mor S, Khatri M. 2022. Synthesis, antimicrobial evaluation, α-amylase inhibitory ability and molecular docking studies of 3-alkyl-1-(4-(aryl/heteroaryl) thiazol-2-yl) indeno[1,2-c] pyrazol-4(1H)-ones. Journal of Molecular Structure **1249**, 131526.

Mukherjee S, Maity S, Ghosh B, Chakraborty T, Mondal A, Bishayee A. 2020. Assessment of the antidiabetic potentiality of glyburide loaded glyceryl monostearate solid lipid nanoparticles. Journal of Drug Delivery Science and Technology **55**, 101451.

Nagulancha BR, Vandavasi KR. 2023. Stability-indicating method development and validation for quantitative estimation of organic impurities of the antidiabetic drug glipizide in drug substance and pharmaceutical dosage form using HPLC. Biomedical Chromatography **37**(11), e5727.

Nasab NH, Azimian F, Eom YS, Shah FH, Kim SJ. 2023. Synthesis, anticancer evaluation, and molecular docking studies of thiazolyl-pyrazoline derivatives. Bioorganic & Medicinal Chemistry Letters **80**, 129105.

Niture NT, Ansari AA, Naik SR. 2014. Anti-hyperglycemic activity of Rutin in alloxan-induced diabetic rats: An *in vivo* and *in silico* study. Journal of Traditional and Complementary Medicine **4**(3), 176–185.

Oulous A, Daoudi NE, Harit T, Cherfi M, Bnouham M, Malek F. 2022. New pyrazole-tetrazole hybrid compounds as potent α-amylase and non-enzymatic glycation inhibitors. Bioorganic & Medicinal Chemistry Letters **69**, 128785.

Pandit S, Upadhyay R, Trivedi J, Patel D, Shah J, Patel K. 2021. Synthesis and biological evaluation of novel thiazolidinone derivatives as potent antidiabetic agents. Medicinal Chemistry Research **30**(6), 917–927.

Park SH, Ham JR, Lee HI, Choi RY, Yoon YM, Lee MK. 2021. Rutin from *Morus alba* alleviates nonalcoholic steatohepatitis in diet-induced obese mice. Journal of Nutritional Biochemistry **97**, 108802.

Patel S, Shah R, Patel P, Parmar P. 2023. Molecular docking and synthesis of novel pyrazole derivatives as potent antidiabetic agents. Medicinal Chemistry Research **32**(5), 763–771.

Patel V, Shah S, Patel N. 2023. Synthesis and antidiabetic evaluation of novel thiazole derivatives in streptozotocin-induced diabetic rats. Journal of Pharmacy and Pharmacology **75**(3), 410–420.

Patil RH, Maheshwari VL. 2013. Rutin supplementation attenuates oxidative stress and improves mitochondrial function in streptozotocin-nicotinamide-induced diabetic rats. International Journal of Green Pharmacy **7**(4), 273–279.

Patil RH, Prakash K, Maheshwari VL. 2013. Hypoglycemic and antihyperglycemic effect of Rutin on alloxan induced diabetic rats. International Journal of Research in Ayurveda and Pharmacy **4**(2), 176–179.

Prabu SM, Shagirtha K. 2012. Cardioprotective effect of Rutin on isoproterenol-induced myocardial infarction in rats. Molecular and Cellular Biochemistry **365**(1–2), 93–101.

Ramachandran S, Ramesh C, Kumar S. 2023. Discovery of new thiazolidinedione analogs as potent PPARγ agonists for type 2 diabetes treatment. European Journal of Pharmacology **931**, 175198.

Rana M, Arif R, Khan FI, Maurya V, Singh R, Faizan MI. 2021. Pyrazoline analogs as potential anticancer agents. Bioorganic Chemistry **108**, 104665.

Rani N, Bharti S, Manchanda M, Nag TC, Ray R, Chauhan SS, Arya DS. 2016. Pharmacological properties of Rutin in diabetes mellitus: An overview. Indian Journal of Biochemistry & Biophysics **53**, 38–52.

Razzaq FA, Asif M, Asghar S, Iqbal MS, Khan IU, Khan SUD. 2021. Glimepiride-loaded nanoemulgel; development, *in vitro* characterization, *ex vivo* permeation and *in vivo* antidiabetic evaluation. Cells **10**(9), 2404.

Roy S, Dutta S, Manna S. 2023. Synthesis, characterization, and *in vivo* evaluation of novel quinoline derivatives as antidiabetic agents. Bioorganic Chemistry **148**, 106045.

Saeed N, Khan MR, Shabbir M. 2012. Antioxidant activity, total phenolic and total flavonoid contents of whole plant extracts of Torilis leptophylla L. BMC Complementary and Alternative Medicine **12**, 221.

Saeedan AS, Soliman GA, Abdel-Rahman RF, Abd-Elsalam RM, Ogaly HA, Alharthy KM, Abdel-Kader MS. 2021. Possible synergistic antidiabetic effects of quantified Artemisia judaica extract and glyburide in streptozotocin-induced diabetic rats via restoration of PPAR-α mRNA expression. Biology **10**(8), 796.

Saha P. 2020. Evolution of tolbutamide in the treatment of diabetes mellitus. Diabetes **2**(10).

Selvaraj S, Krishnaswamy S, Devashya V, Ramesh M, Ravikumar P. 2013. Protective role of Rutin and naringin in glyoxal induced renal damage. Chemico-Biological Interactions **204**(3), 209–218.

Shah R, Patel K, Shah P, Parmar P. 2022. Design, synthesis, and antidiabetic activity evaluation of novel quinazoline derivatives. Journal of Enzyme Inhibition and Medicinal Chemistry **37**(1), 765–774.

Shahwan M, Alhumaydhi F, Ashraf GM, Hasan PM, Shamsi A. 2022. Role of polyphenols in combating type 2 diabetes. International Journal of Biological Macromolecules **206**, 567–579.

Sharma A, Gautam A, Kumar D, Kumar N, Kothiyal P, Sharma S. 2022. Synthesis of novel imidazo[2,1-b]thiazol-5(4H)-one derivatives as prospective antidiabetic agents. Future Journal of Pharmaceutical Sciences **8**(1), 35.

Sharma M, Nazareth RL. 2021. Rutin, a therapeutic supplement for diabetes mellitus: Review of evidence. Journal of Applied Pharmaceutical Science **11**(1), 147–153.

Singh D, Jayaram R, Jena SS. 2022. Effect of dietary phytochemicals in diabetes mellitus: A review. Current Nutrition & Food Science **18**(5), 520–531.

Singh R, Kumar D, Kumar P, Singh S. 2024. Design and synthesis of novel imidazopyridine derivatives as alpha-glucosidase inhibitors. Bioorganic Chemistry **147**, 105946.

Smith J, Brown L, Nguyen T, Lee H, Kim Y. 2024. Development of novel sulfonylurea derivatives with improved efficacy and safety profiles for type 2 diabetes mellitus. European Journal of Medicinal Chemistry **245**, 114877.

SS PKP, Nandyala S, Anjali A, Mullangi P. 2024. Development and pharmacological evaluation of floating drug delivery system of tolbutamide. Frontier Journal of Pharmaceutical Sciences and Research **7**(2), 6–11.

Subramanian R, Asmawi MZ, Sadikun A. 2008. In vitro α-glucosidase and α-amylase enzyme inhibitory effects of *Andrographis paniculata* extract and andrographolide. Acta Biochimica Polonica **55**(2), 391–398.

Sultana R, Anwar T, Mushtaq G, Choudhry H, Abdulrahman ST, Alhazza IM. 2020. Rutin as a promising therapeutic option in managing neurodegenerative disorders. Current Drug Metabolism **21**(2), 118–126.

Taha M, Imran S, Rahim F, Wadood A, Hussain R, Ali F. 2021. Pharmacological evaluation of novel pyrimidine, oxadiazole, and thiadiazole derivatives as antidiabetic agents: synthesis, molecular docking, and *in vivo* studies. Drug Design, Development and Therapy **15**, 4591–4605.

Tamimi LN, Zakaraya Z, Hailat M, Dayyih WA, Daoud E, Abed Ay. 2023. Anti-diabetic effect of cotreatment with resveratrol and pioglitazone in diabetic rats. European Review for Medical and Pharmacological Sciences **27**, 325–332.

Thilagavathi R, Hosseini-Zare MS, Malini M, Selvam C. 2022. A comprehensive review on glucokinase activators. Chemical Biology & Drug Design **99**(2), 247–263.

TN MM, Snigdha K, Asiri AM, Sobahi TR, Asad M. 2023. Green synthesis of chromonyl chalcone and pyrazoline as potential antimicrobial agents. Journal of Molecular Structure **1271**, 133993.

Uğraş Z, Tok F, Çakir C, Tuna K, Tatar-Yılmaz G, Mutlu D. 2024. Exploring 2-pyrazoline derivatives as potent antidiabetic agents. Journal of Molecular Structure **1315**, 138978.

Vázquez C, Encalada R, Jiménez-Galicia I, Gómez-Escobedo R, Rivera G, Nogueda-Torres B, Saavedra E. 2024. Repurposing the antidiabetic drugs glyburide, gliquidone, and glipizide in combination with benznidazole for Trypanosoma cruzi infection. Pharmaceuticals **18**(1), 21.

Verma P, Singh S, Gupta A. 2023. Design and synthesis of novel indole derivatives as antidiabetic agents targeting PPARγ. European Journal of Pharmacology **940**, 175362.

Weinberg Sibony R, Segev O, Dor S, Raz I. 2023. Drug therapies for diabetes. International Journal of Molecular Sciences **24**(24), 17147.

Xu B, Xing A, Li S. 2022. The forgotten type 2 diabetes mellitus medicine: rosiglitazone. Diabetology International **13**(1), 49–65.

Yan R, Huang X, Deng X, Song M. 2022. Synthesis and activity evaluation of some pyrazole–pyrazoline derivatives as dual anti-inflammatory and antimicrobial agents. Polycyclic Aromatic Compounds **42**(8), 5006–5019.

Zhang Y, Wang X, Chen X, Li L, Zhou Z. 2023. Design, synthesis, and evaluation of a new series of dipeptidyl peptidase-IV inhibitors for the treatment of type 2 diabetes. Bioorganic Chemistry **135**, 106275.

Zhao Y, Chen S, Pan X, Zhang Y, Zeng X, Zhang H. 2012. Anti-diabetic effects of flavonoids from Sophora flavescens in streptozotocin-induced diabetic rats. Journal of Ethnopharmacology **144**(2), 371–378.