Journal of Chemical Reviews

2024, Volume 6, Issue 3

Review Article

Synthesis and Biological Evaluation of Five- and Six-Membered Heterocycles as an Anti-Diabetic Agent: An Overview

Gautam P. Sadawarte[1,*], Jamatsing D. Rajput[1] Amol D. Kaleb[2], Vasant B. Jagrut[3,*]

[1]*Department of Chemistry, B.P. Arts, S.M.A. Science and K.K.C. Commerce College, Chalisgaon, Dist-Jalgaon 424101 (M.S.), India*
[2]*Department of Chemistry, Lal Bahadur Shastri Sr. College, Partur, Dist-Jalna 431501 (M.S.), India*
[3]*Department of Chemistry, Swami Vivekanand Senior College, Mantha, Dist-Jalna 431504 (M.S.), India*

Use your device to scan and read the article online

Citation: G.P. Sadawarte, J.D. Rajput, A.D. Kaleb, V.B. Jagrut, **Synthesis and Biological Evaluation of Five- and Six-Membered Heterocycles as an Anti-Diabetic Agent: An Overview.** *J. Chem. Rev.,* **2024,** *6*(3), 331-352.

https://doi.org/10.48309/JCR.2024.437575.1303

Article info:
Received: 23 February 2024
Revised: 01 April 2024
Accepted: 26 May 2024
ID: JCR-2402-1303
Checked for Plagiarism: Yes
Language Editor Checked: Yes

Keywords:
Heterocycles 5, 6 membered ring, Sulphonamide, Anti-diabetic, Biological activity

ABSTRACT

In medicinal chemistry, heterocycles represent a unique place as a valuable source of therapeutic drugs. Over 75% of pharmaceuticals that are presently on the market and have received FDA approval contain heterocyclic moieties of nitrogen and sulfur. A substantially higher proportion of novel medications based on nitrogen and sulfur is expected in the upcoming ten years. Novel N-heterocyclic moieties have important physiological characteristics and a growing variety of intriguing uses in medicinal chemistry. We have combined the in this review the recent advances on novel 5, 6 membered heterocycles containing nitrogen, sulphur atom, and their unique biological activities that have been documented in the last ten years. The trends in this review are highlighted about 5, 6 membered heterocycles like sulphonamide, pyrimidine based moieties in drug design.

Gautam Prabhakar Sadawarte: He has completed his B.Sc. from Milind College of science Chhatrapati Sambhaji Nagar affiliated to Dr. Babasaheb Ambedkar Marathwada University Chhatrapati Sambhaji Nagar (M.S.) India. He did his M.Sc. from Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University Chhatrapati Sambhaji Nagar (M.S.) India. Currently he is working as Assistant Professor in Chemistry at CESs, BP Arts SMA Science and KKC Commerce College Chalisgaon, Maharashtra, India. He has more than 15 years teaching experience.

***Corresponding Author: Gautam P. Sadawarte** (gautamsadawarte@gmail.com), **Vasant B. Jagrut** (jagrutvb@gmail.com)*

Jamatsing D. Rajput: He has completed his B.Sc. degree from Dr. P.R. Ghogare Science College, Dhule (M.S.) India. He did his M.Sc., Ph.D. and Post-doc from North Maharashtra University, Jalgaon (M.S.)India. Currently he is working as Assistant Professor in Chemistry at CESs, BP Arts SMA Science and KKC Commerce College Chalisgaon, (M.S.) India. He has more than 5 years teaching and research experience in the felid of organic chemistry.

Amol Diliprao Kale: He has completed graduation in B.Sc. at L.B.S.Sr. College , Partur And completed PG in chemistry at Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University Chhatrapati Sambhaji Nagar (M.S.) India. Recently he working as Assistant professor at L.B.S.Sr. College , Partur (M.S.) India. He has more than 10 years teaching experience.

Vasant Bhagwan Jagrut: He has completed his B.Sc. and M.Sc. from Amravati University Amravati (M.S.) India. He did his Ph.D. from Swami Ramanand Tirth Marathwada University Nanded, (M.S.) India. Currently he is working as Associate Professor in Chemistry at Swami Vivekanand Sr. College, Mantha, Dist. Jalna (M.S.) India. He has more than 24 years teaching experience.

Content

1. Introduction

Along with the advancement of organic chemistry, heterocyclic chemistry history began in the 1800s. There have been some notable advancements since alloxan (1) [1] was first created in 1818 by Luigi Valentino Brugnatelli. Hakimi, F., suggested that synthesized 2-arylbenzoxazoles derivatives were achieved by condensation reaction of aromatic aldehydes with 2-aminophenol at 50 °C without the use of solvent and by employing heterogeneous catalyst [2]. Baghernejad, B., synthesized 2-amino-4H-pyran derivatives [3-4], using a one-pot reaction between indole and isatin in reflux conditions, oxindole derivatives with good yield [5]. The discovery of many wide-ranging medicinal drugs is mostly due to the fact that pyridine-based ring structures have a significant influence on pharmacological activity and are utilized so frequently in the drug development process [6]. A heterocyclic compounds have great significance in medicinal chemistry. In organic chemistry, major class of organic compounds belongs in the heterocyclic compound. Heterocyclic compounds cyclic compounds contains a ring which has at least one hetero atom i.e. nitrogen along with carbon atoms [7]. Heterocyclic compounds are significantly used in medicinal chemistry, industrial application, and physiology. The bulk of pharmaceuticals, most biomass (cellulose and related materials), hormones, pheromones, marine creature products, vitamins, antibiotics like penicillin and cephalosporin, nucleic acids, and many natural and manufactured colours are examples of naturally occurring substances in heterocycles [8]. Heterocycles have been recognized as an important structural component in medicinal chemistry. Additionally, they are commonly found in bio-molecules at high quantities including vitamins, enzymes, natural products, and biologically active compounds with properties such as antifungal, antibacterial, anticonvulsant, anti-allergic, enzyme inhibitors, herbicidal activity, antidiabetic, anti-HIV, and insecticidal agents [9].

Most of the synthetic heterocyclic compounds is are used as drug anticonvulsants (**2a** and 2b) [10], Hypnotics (3a, 3b) [11], antineoplastics [12], anticancer activity (4)[13], antifungal [14], antibacterial (5) [15], anti-allergic (6,7,8) [16], enzyme inhibitors(10) [17], herbicidal activity (11,12) [18-19], anti-HIV [20], anti-inflammatory [21-22], antioxidant (13,14,15,16) [23-25], anti-diabetic (17,18,19,20) [26-31], and insecticidal agents (21,22,23,24) [32] (**Figure 1**).

2. Some Bio-Active Heterocyclic Compounds

Salve M. T. *et al.* analyzed a novel class of 1,3,4-oxadiazole derivative sulphonamide hybrid anti-diabetic drugs (25) [33], John B. Wright, *et al.* shows the anti-diabetic activity of 3,5-dimethylpyrazoles (26), were reported 41 pyrazole derivatives having excellent hypoglycemic activity which are comparable with STD drug molecule (**Figure 2**) [34]. New 2-thiouracil-5-sulphonamide derivatives were synthesised by Fathalla O. A. *et al.* [35] has antibacterial and antifungal activity. Sequences of substituted phosphonates containing the thiazolidinedione moiety were synthesized by Sujatha B. *et al.* yielded that the compounds showed an effective role in anti-diabetic activity [36].

Thiosemicarbazides (28), triazoles (29), oxadiazoles (30) and thiazolidinones (31) are heterocyclic derivatives of mono- and *bis*-dipicolinic acid that Maja Molnar *et al.* created as antifungal and antioxidant agents [37].Mina Bolous *et al.* have been synthesized Spirooxindolo-pyrrolidine tethered indole/imidazole hybrid (32), and their antifungal activities against fungal strains were determined (**Figure 3**). The results show that spirooxindolo-pyrrolidine heterocyclic scaffolds potentially signify a comprehensive class of chemical agents with remarkable antifungal activity [38]. Heterocycles containing sulphur and or nitrogen plays a significant function in nature and are being thoroughly researched as therapeutic agents. Recently, increasing focus has been placed on the biological assessment of five- and six-membered heterocycles possessing sulphuryl urea and heteroaryl pharmacophore. In the

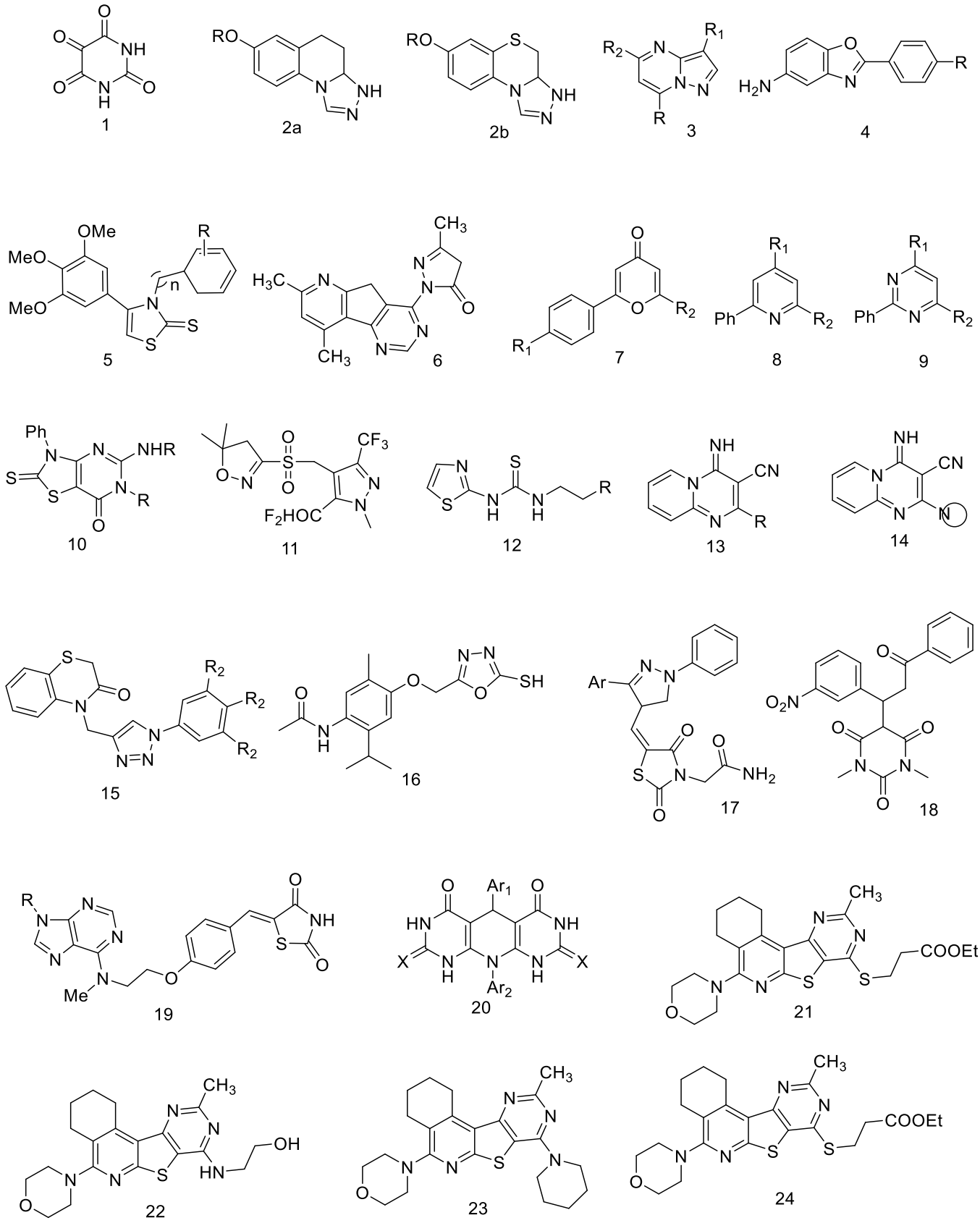

Figure 1. Some heterocyclic drug molecules

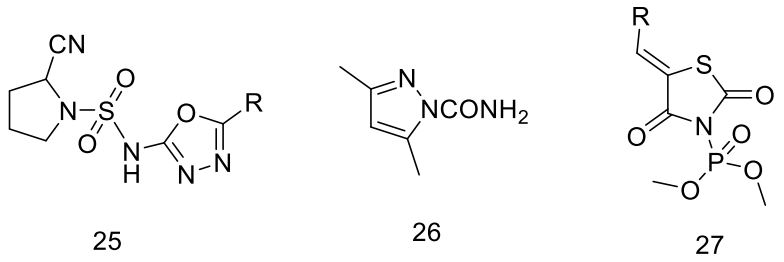

Figure 2. Biologically active 1,3,4-oxadiazole, dimethylpyrazoles, and phosphonated thiazolidinediones

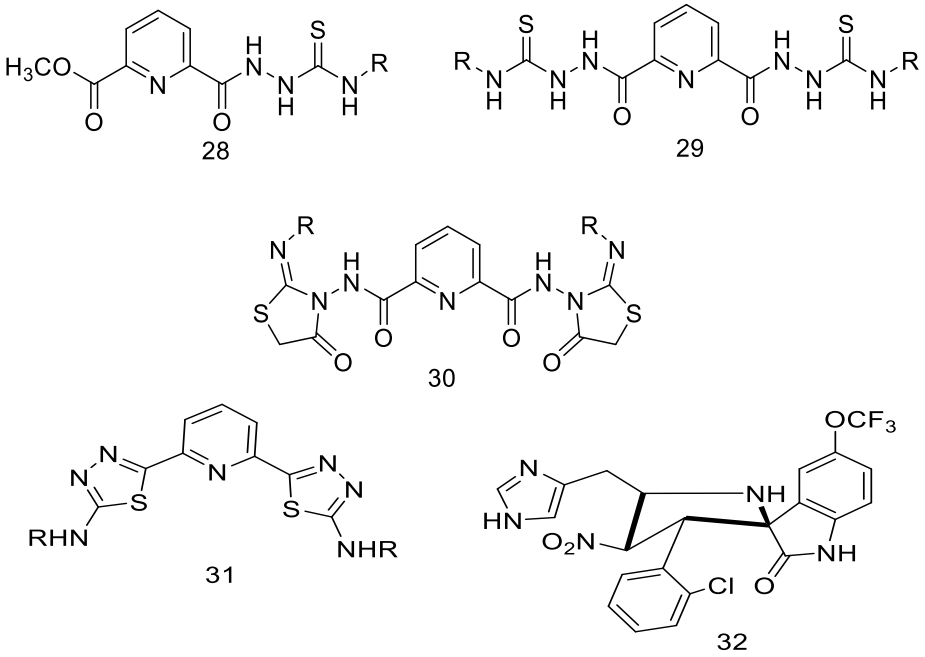

Figure 3. Biologically active thiosemicarbazides, triazoles, oxadiazoles, thiazolidinones, and spirooxindolo-pyrrolidine

modern world, DM is one of the most common degenerative diseases. With more than 171 million diabetics as of 2000, India has overtaken the rest of the world as the world's diabetic epicentre [39]. The estimated 5.8 million people with diabetes mellitus, of which 90% are classified as having non-insulin dependent diabetes mellitus, suffer from a complex, chronic, progressive condition that eventually might negatively impact the function of their kidneys, eyes, brain system, and vascular system (NIDDM) [40]. Obesity and peripheral insulin resistance are present in the majority of NIDDM patients. Diabetes mellitus is linked to poor glucose metabolism, which raises blood glucose levels and produces more free radicals. Unfortunately, no current medicine is used to treat metabolic disorders completely. Sulphonylureas cause hypoglycemia, lactic acidosis is made more likely by the use of metaformin, and bloating and flatulence are made worse by the use of acarbose [41].

The explorations of many classes of thiazolidinedione compounds have been receiving an intense research in recent years (33-37), and many of these compounds have a wide range of pharmacological actions (**Figure 4**). It is known that several of these compounds with pyridine nuclei have special anti-inflammatory, analgesic, antibacterial, anticancer, antifungal, anti-mycobacterial, anticonvulsant, anti-

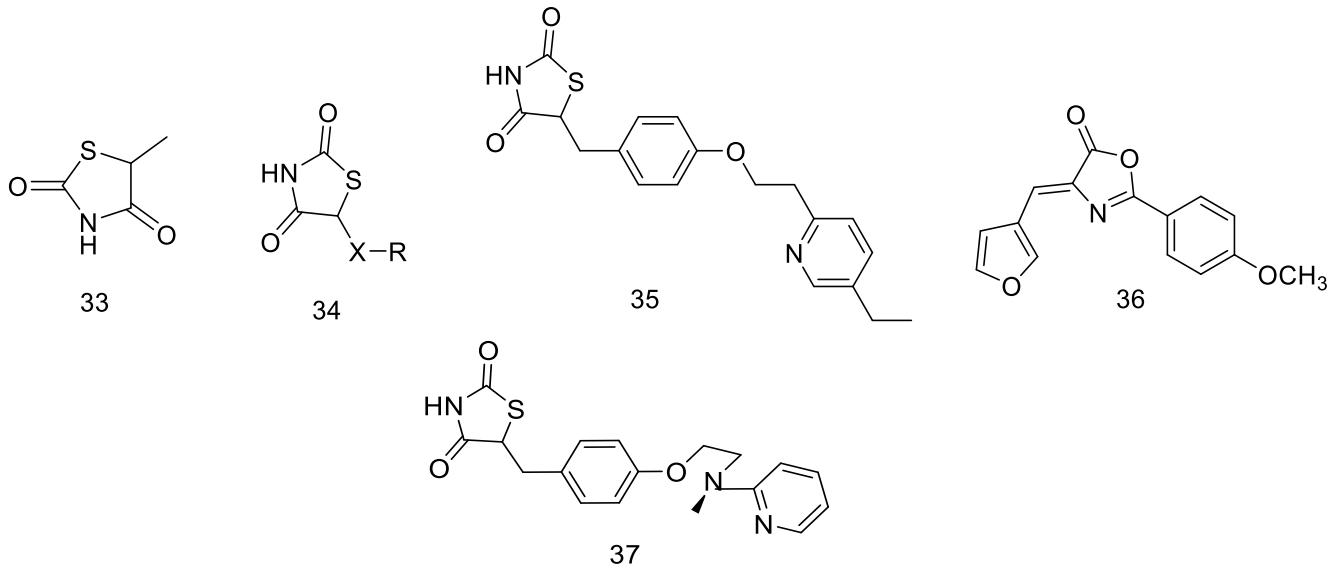

Figure 4. Biologically active thiazolidinediones

diabetic, and antiviral properties. The pyridine ring has so far been modified in a way that has boosted efficacy and decreased toxicity with a remarkable extent successfully.

3. Diabetes Drugs

Biguanides: Metformin typically the first medication that doctors advise take metformin to manage type 2 diabetes. It stimulates the body to utilize the insulin which lowers the blood sugar. Naturally, it reduces the production of sugar by the liver.

Sulfonylureas: Glipizide, glimepride, and glyburide. These medications increase insulin production from the pancreas, lowering blood sugar levels.

Meglitinides: nateglinide and repaglinide. These medicines help the pancreas to produce more insulin.

Thiazolidinediones (TZDs): Pioglitazone and rosiglitazone. These medicines improve insulin's physiological action.

Alpha-glucosidase inhibitors: Acarbose and miglitol. They hinder the process of breaking down of carbohydrates.

DPP-4 inhibitors: alogliptin, linagliptin, saxagliptin, and sitagliptin. It encourage human pancreas to produce more insulin after meals.

SGLT2 inhibitors: Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. They instruct the kidneys to eliminate excess blood sugar through urine [42].

4. Anti-Diabetic Heterocycles

For the evaluation of the anti-diabetic activity, Pattan *et al.* introduced the synthesis of a number of compounds (38a-38l). Among these, compound (38h) has demonstrated a significant level of anti-diabetic action, whereas compound (38a, 38b, 38e) has demonstrated a more moderate level of anti-diabetic activity (**Figure 5**) [43].

Rajput *et al.* reported new class of Diindolyl methanes (DIMs) derivatives (39a-39c) significant biological activities such as anticancer, antioxidant and *α*-amylase inhibitory activities. All the synthesized diindolyl methanes (DIMs)

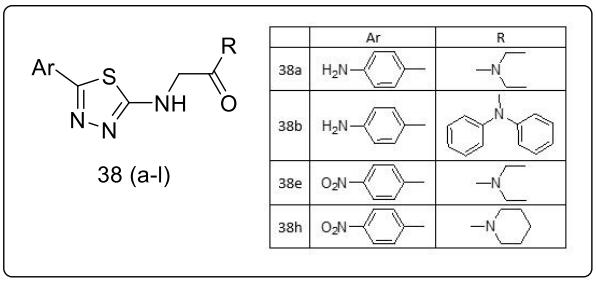

Figure 5. Anti-diabetic active 1, 3, 4-thiadiazol-2-yl)piperidine derivatives

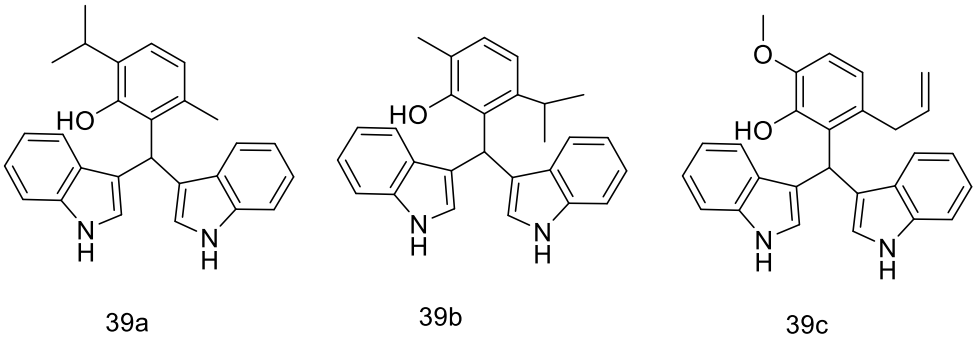

Figure 6. Anti-diabetic active diindolyl methanes (DIMs) derivatives

derivatives show excellent *α*-amylase inhibitory activity at lower to higher concentration (**Figure 6**) [44].

A series of chromonyl-2,4-thiazolidinediones/imidazolidinediones/2-thioxo-imidazolidine-4-ones (40a, 40b) was prepared by Meltem Ceylan-Ünlüsoy *et al.* and its insulinotropic activities tested in INS-1 cells (**Figure 7**) [45].

Novel oxazolone compounds were synthesized by Marippan G. *et al.* utilising 4-methoxy benzoyl chloride (41) divergence in the anti-diabetic action (**Figure 8**) [46].

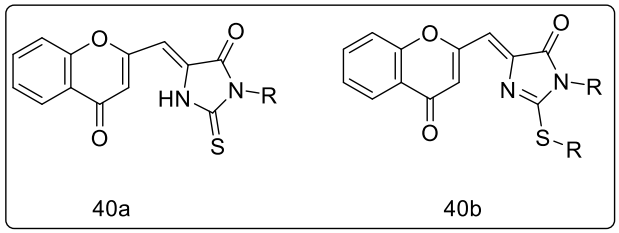

Figure 7. Anti-diabetic active thioxo-imidazolidine-4-ones derivatives

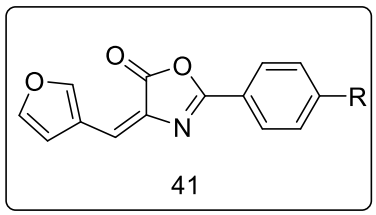

Figure 8. Anti-diabetic active oxazolone derivatives

Sridevi P. *et al.* extracted and synthesized the derivatives of 4-hydroxy isoleucine MI, EII, and BVII showed greater anti diabetic activity [47], Shingalpur R. V. *et al.* synthesized 4-thiazolidinones(42) and 1,3,4-oxadiazoles containing 2-mercapto benzimidazole(43) moiety screened for anticonvulsant and antidiabetic activity (**Figure 9**) [48].

Deepti Kini and Manjunath Ghate synthesized 3-[5'-methyl-2'-aryl-3'-(thiazol-2''-yl amino) thiazolidin-4'-one] coumarin products (44) has oral hypoglycemic activity (**Figure 10**) [49].

Figure 9. Anti-diabetic active 4-thiazolidinones 1,3,4-oxadiazoles derivatives

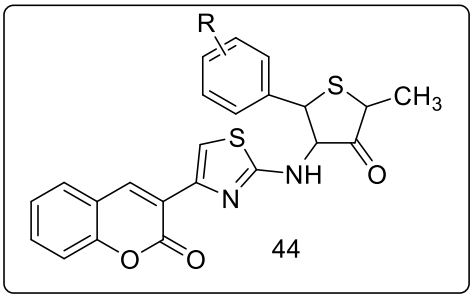

Figure 10. Anti-diabetic active thiazolidin-4'-one coumarin derivatives

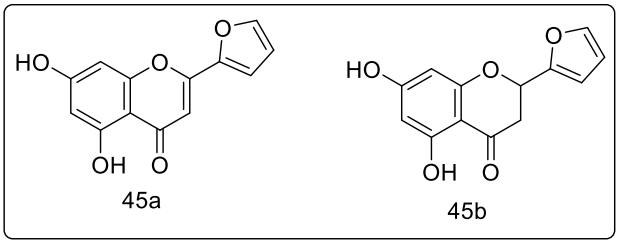

Figure 11. Anti-diabetic active dihydroxyflavones derivatives

After creating two series of flavonoids, 5,7-dihydroxyflavanones and 5,7-dihydroxyflavones (45a, 45b), and screening them for possible anti-diabetic activity, Liu-Shuan Chang *et al.* found that the majority of the flavonoids exhibited impressive *in vitro* activity (**Figure 11**) [50].

Mariappan, G. created and tested a novel series of benzothiazole(46) compounds *in vivo* to look into its hypoglycemic action using streptozotocin-induced diebetic (**Figure 12**) [51]. As proposed by Sonia Rocha *et al.*, chalcones are unquestionably effective on anti-diabetic medications that target a variety of therapeutic targets, including DPP-4, GLUT4, SGLT2, alpha-amylase, alpha-glucosidase, and ALR [52-53].

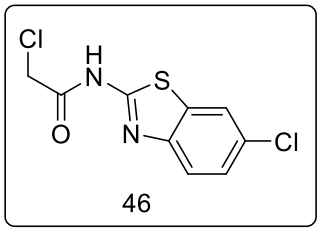

Figure 12. Anti-diabetic active chalcones derivatives

Farid M. S. *et al.* synthesized sulphanyl urea(47,48,49) [54], utilizing the common medication Gliclazide at a dosage of 200 mg/kg, which has the potential to be an anti-diabetic agent [55].

2, 4-disubstituted furan derivatives (50) were synthesized by Babu S. P. and Suresh Babu K. and their anti-diabetic properties were assessed [56]. Utilizing a microwave synthesiser, Lipika Pandey *et al.* synthesized oxazolan derivatives (51), the resulting molecules significantly lowered blood sugar levels in diabetic rats (**Figure 13**) [57].

A series of *N*-(4-phenylthiazol-2-yl)benzenesulfonamides (52) were synthesized by Nouraddin Hosseinzadeh *et al.* by reacting 2-amino thiazol with aromatic sulfonyl chloride. Using a streptozotocin-induced diabetic rat model, all the compounds were tested *in vivo* for their oral hypoglycemic efficacy [58]. Mahapatra S.P. *et al.* synthesized 3-phthalimidoethyl-4-acetyl substituted benzanilides (53), and they assessed their potential for lowering blood sugar levels using male Wistar albino rats (**Figure 14**) [59].

N-(6-chlorobenzothiazol-2-yl)-2-(substituted amino) acetamide was synthesized by Mariappan G. *et al.* and reported their anti-diabetic potential against drug molecules [60]. Sulfonylureas (55) have anti-diabetic properties which were synthesized by Ameya A. Chavan *et al.* According to Chetna Kharbanda *et al.*, the efficiency of all the synthetic compounds as oral anti-diabetic drugs have been principally evaluated by loading glucose into normal in rats (**Figure 15**).

It has been noted that seven substances considerably inhibited the rise in plasma glucose levels when compared to the usual medication glibenclamide [61]. Synthesized novel 3-trifluoro methyl pyrazolesulfonyl-urea and thiourea compounds were tested as antibacterial and anti-diabetic drugs by Faidallah H. M. *et al.* [62]. Somaye Karimiana designed series of dihydropyrimidinone derivatives having excellent *β*-glucuronidase inhibitory activity [63]. The new dibenzofuran carboxylic acids (56) were synthesized and evaluated by Lakshminarayana N. *et al.* potential anti-diabetic drugs [64]. A series of

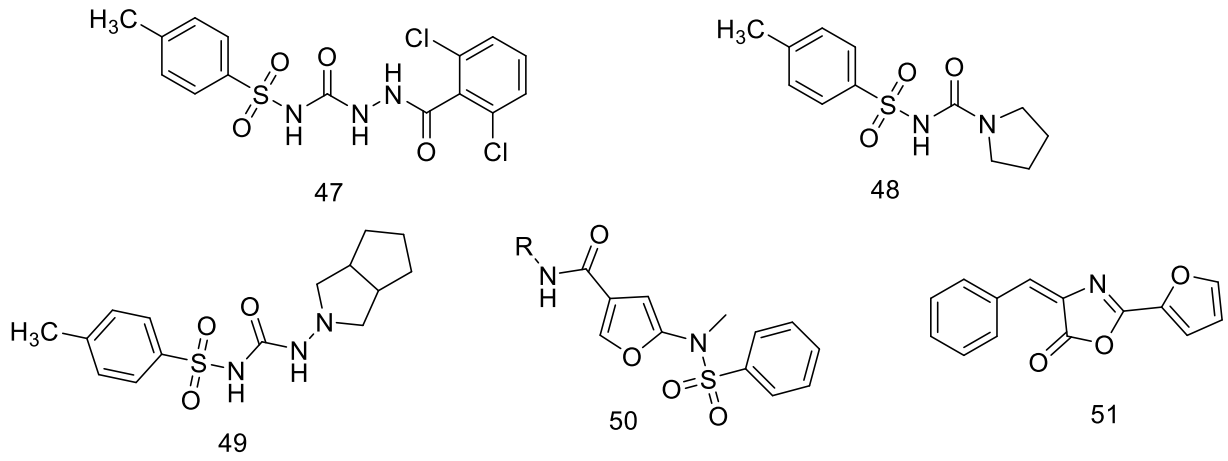

Figure 13. Anti-diabetic active sulphanyl urea derivatives

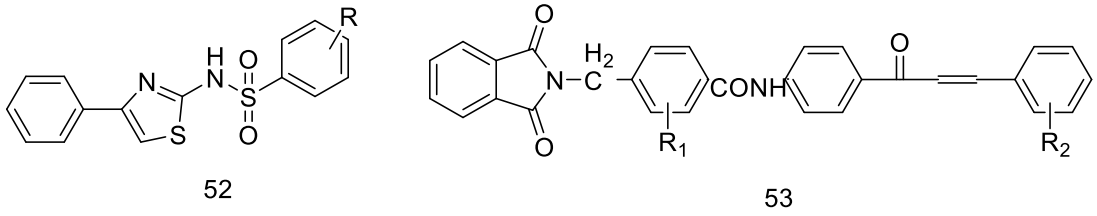

Figure 14. Anti-diabetic active benzenesulfonamides and benzenesulfonamides derivatives

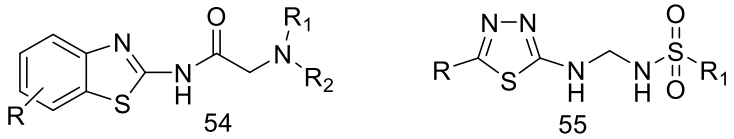

Figure 15. Anti-diabetic active acetamide derivatives

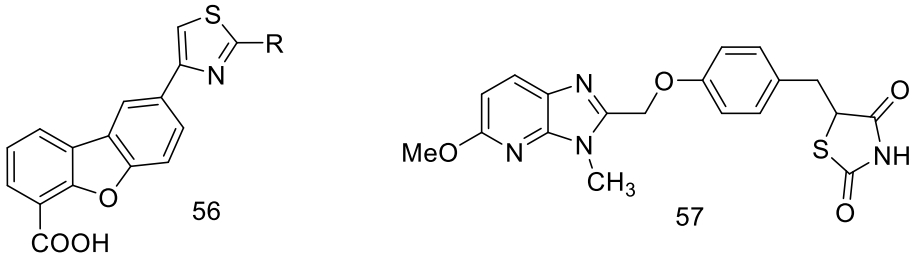

Figure 16. Anti-diabetic active dibenzofuran and imidazoylpyridine thiazolidinediones derivatives

imidazoylpyridine thiazolidinediones was reported by Oguchi *et al.* (57) starting from the pyridines, who created a series of conformationally constrained analogues of (Rosiglitazone) and 20 (Rivoglitazone) imidazopyridine TZDs (**Figure 16**) [65]. Soylem *et al.* synthesized pyridinylmethanone, nicotinonitrile, pyran-3-carbonitrile, pyrazolopyridine, chromenopyridine, and *N*-butyrylpyrazolyl-1-butanone derivatives (58,59,60), which were then tested for their anti-diabetic activities at micro molar concentrations (**Figure 17**) [66]. New thiazole-pyridine (61,62)derivatives were created by Suri Babu Patchipala *et al.* and compounds were then tested for their anti-diabetic activity

by Swiss albino mice housed *in vivo*, compared to glibenclamide, synthetic molecules show promise for lowering blood sugar levels (**Figure 18**) [67]. Dihydro-6*H*-chromeno[4,3-*b*]isoxazolo[4,5-e]pyridine heterocycles (63) were synthesized using a one-pot, three-component, eco-friendly technique, and their anti-diabetic action was tested against type 2 diabetes mellitus (**Figure 19**) [68].

Balakrishna Kalluraya *et al.* synthesized different 2-[3-(6-methylpyridinyl)]-5-aryl-[1,3,4]-oxadiazole (64), 2-[3-(6-methylpyridinyl)]-4-substitutedaminomethyl-[1,3,4]-oxadiazole-5-thione (65) and 2-[3-(6-methyl pyridinyl)]-5-substituted benzylthio-[1,3,4]-oxadiazole (66) were screened for their antidiabetic and showing good α-amylase as well α-glucosidase inhibition activity (**Figure 20**) [69].

Mubeen A. *et al.* created a series of compounds (67), which contain an acetohydrazide moiety linked with 3-pyridine through a tetrazole ring (**Figure 21**). Molecular docking studies, the substances that is most effective at lowering blood sugar. An excellent pact was obtained since best docked poses displayed significant binding features based on interactions between oxygen and aromatic moieties [70]. Dhanraj Patidar *et al.* synthesized novel 3, 6-disubstituted-2-pyridinecarboxamide derivatives (68, 69) they noted that the anti-

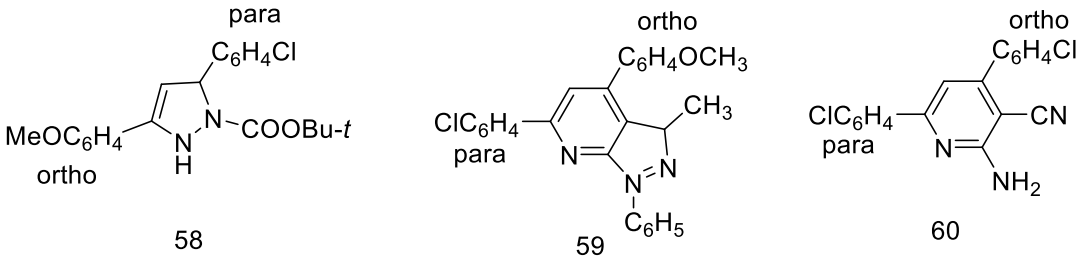

Figure 17. Anti-diabetic active pyridinylmethanone, nicotinonitrile, pyran-3-carbonitrile, pyrazolopyridine derivatives

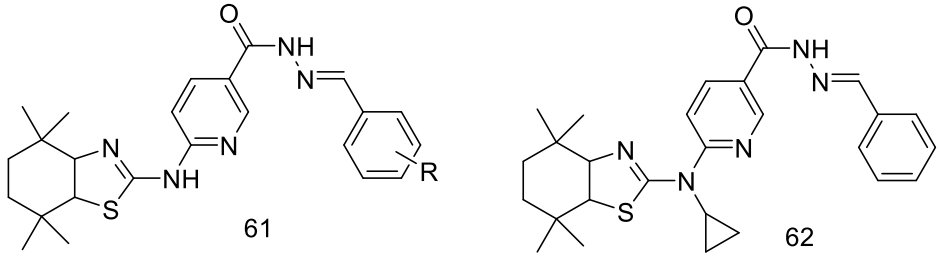

Figure 18. Anti-diabetic active thiazole-pyridine derivatives

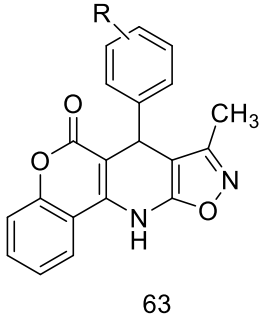

Figure19. Anti-diabetic active pyridine heterocyclic derivatives

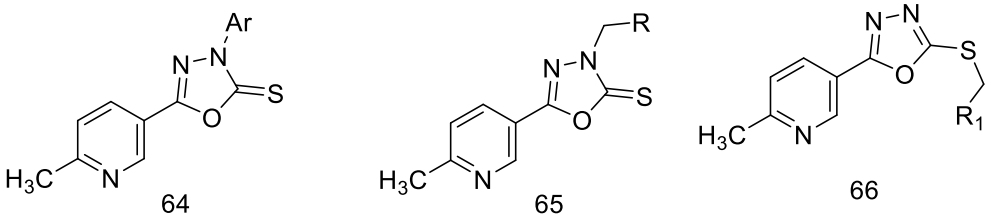

Figure 20. Anti-diabetic active oxadiazole derivatives

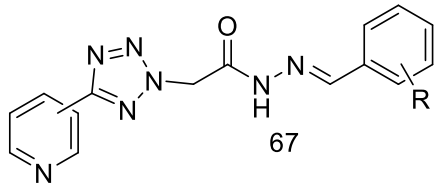

Figure 21. Anti-diabetic active acetohydrazide derivatives

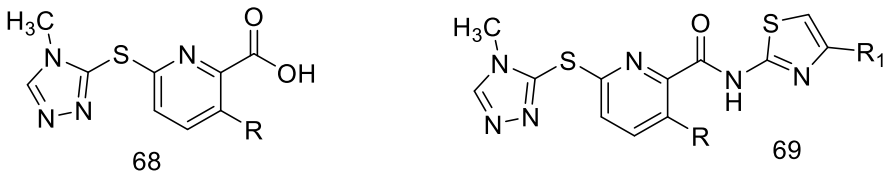

Figure 22. Anti-diabetic active disubstituted-2-pyridinecarboxamide derivatives

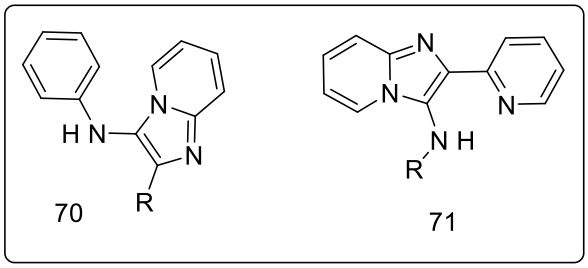

Figure 23. Anti-diabetic active substituted imidazo[1,2- *a*]pyridin-3-amine derivatives

hypoglycemic activity was enhanced by the substitution of the pyridine ring at position 3 with a hydrophobic group like the methyl group (**Figure 22**) [71]. Different 2-substituted imidazo[1,2-*a*]pyridin-3-amine were synthesised by T.V. Rao Kota *et al.* which display antidiabetic activity (**Figure 23**) [72].

In a study conducted by Khan, Z.A. *et al.*, the preclinical anti-diabetic effects of a novel synthesised drug, *N*'-2,*N*'-4,*N*'-6-*tris*(4-hydroxybenzylidene)pyridine-2,4,6-tricarbohydrazide, were examined in mice that had been given alloxan to induce diabetes found that TPTH had strong anti-diabetic effects [73]. Two series of 2,5-disubstituted-3-imidazol-2-yl-pyrrolo[2,3-*b*]pyridines (72) and thieno[2,3-*b*]pyridines (73) were studied by Bahekar, R.H. *et al.* Using a RIN5F cell-based assay, the *in vitro* glucose-dependent insulinotropic activity of each test compound was assessed. All test compounds that demonstrated *in vivo* anti-diabetic activities of the most potent compounds from both series were evaluated (**Figure 24**) [74].

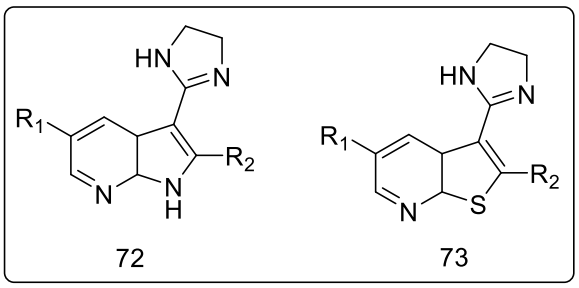

Figure 24. Anti-diabetic active substituted pyridines derivatives

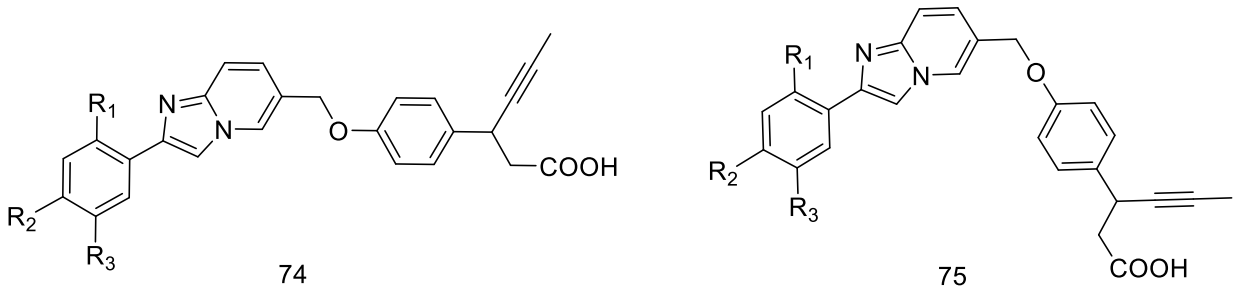

Figure 25. Anti-diabetic active imidazo [1, 2-*a*]pyridine derivatives

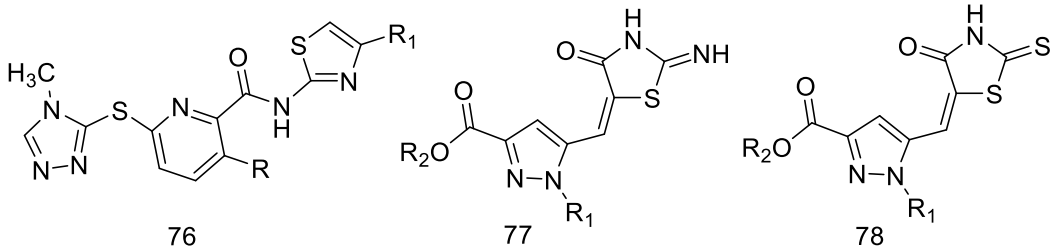

Figure 26. Anti-diabetic active pyrazole-3-carbonic derivatives

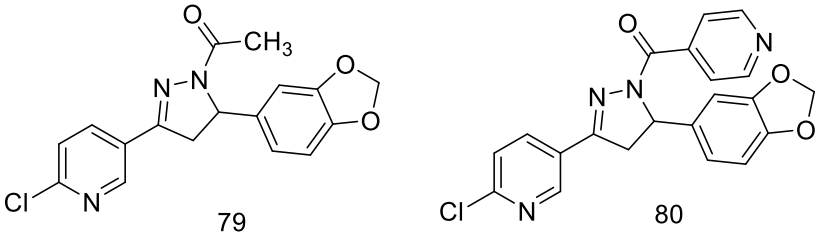

Figure 27. Anti-diabetic active chalcone-piperonal derivatives

A number of new compounds with imidazo [1,2-*a*]pyridine (74,75) skeletons were synthesised by Ye Z. *et al.* as GPR40. The evident drop in blood glucose in both normal and diabetic mice, that did not face any hepatotoxicity risk, indicates that this agonist is effective [75]. The 3, 6-disubstituted 2-pyridinecarboxamide derivatives [76] produced by Patidar D. *et al*. and tested for their anti-diabetic activity (**Figure 25**) [76].

Mykhaylo Bratenko and colleagues synthesized 4-(1, 3-thiazolidine-5-ylidene)pyrazole-3-carbonic acid (77,78) and its esters with hypoglycemic activity [77]. Chalcone-piperonal (79,80) were produced by Abdullah A. A. *et al*. using the Claisen-Schmidt reaction and demonstrated their *in vitro* anti-diabetic activity (**Figure 26, 27**) [78].

A straightforward, effective, and direct approach for converting carboxylic acids into thioamides in the presence of ammonium phosphorodithioates was described by Babak Kaboudin *et al.* [79]. Meng-Tian Zeng et *al.* synthesized thioamides derived from tetramethylthiuram and aryl aldehydes when di-*tert*-butyl peroxide disulfide and CuI are presented [80]. The styrenes phenylethanethioamides and benzothioamides were produced by Zhang P. *et al.* using a selective base-controlled method [81].

Endothiopeptides were transformed into thiazoles by Uli Kazmaier *et al.* utilising TMSCl-NaI under microwave irradiation [82].

Thioamides, a type of sulfur-containing heterocycle, serve as intermediates in the production of numerous different compounds

with uses in both synthetic and pharmaceutical chemistry[83], building blocks in pharmaceuticals [84-86], asymmetric synthesis [87], powerful inhibitors of the enzymes thyroid peroxidase and dihydroorotate dehydrogenase (DHODH)[88], hyperthyroidism, tuberculosis and leprosy[89-90], and nematodes[91].

The cyclic ketones 1*H*-indole-2,3-dione (isatin) and glycine methyl ester were produced *in situ* by Toumi A. *et al.* using a one-pot azomethine ylide synthesis. This was done in conjunction with (*Z*)-5-arylidine-2-thioxothiazolidin-4-ones, and it highlighted the effective high yield construction of rhodanine-fused spiro [pyrrolidine-2,3'-oxindoles](81) scaffolds with antidiabetic properties [92].

Afzal H. R. *et al.* were synthesized and characterized new Schiff bases of pioglitazone (82) and demonstrated the anti-diabetic inhibitory effects of alpha-amylase *in vitro* in a rat model of diabetes induced by streptozotocin and nicotinamide (**Figure 28**) [93].

By reacting different coumarinyl schiff bases with thioglycollic acid Bhat K. I. *et al.* were able to synthesize 4-thiazolidinone derivatives. Intermediate coumarinyl schiff bases were created by combining 4-hydroxyl coumarin with various substituted anilines newly created substances have antidiabetic action [94].

Dominic E. J. *et al.* examined the use of azomethines for the environmentally friendly and solvent-free synthesis of isatoic anhydride in a microwave oven [95].

The pyridine-based significant class of chemicals with pharmacological characteristics includes derivatives of nicotinic and isoniazid such as anti-tubercular for their antimicrobial activity against *Mycobacterium tuberculosis in vitro* [96-100], anticancer against to human cancer cell with potent cytotoxicity[101], antifungal activities *in vitro* against the *var. capsulatum* and dimorphic fungus *Histoplasma capsulatum* [102], potential multi-target profiles for the treatment of Alzheimer's disease [103]. Anti-diabetic medications are prescribed globally, their mechanisms of action for reducing blood glucose vary, and they can have side effects that compromise the effectiveness and course of treatment. Globally, the incidence of diabetes is rising, and this is correlated with their expanding management. Although it's unclear if this is due to the effects of anti-diabetic medications or just diabetes itself, diabetes raises the risk of both cancer [104] and death from neoplasms [105].

Their research indicates that while a small number of anti-diabetic medications exhibit antitumor properties, the majority of them raise the risk of cancer.

Literature reveals that 2, 4-thiazolidinedione based amide derivatives, pyrimidine-fused derivatives, sulphonamide derivatives, sulphanyl urea, pyrazolesulfonyl-urea and thiourea derivatives, indole/imidazole/ benzimidazole, thiadiazoles, oxazolone derivatives, coumarin derivatives, arylamidebiguanide hydrochloride salts, chalcone, furan derivatives, substituted benzanilides, benzothiazole derivatives pyrimidine-2,4,6-trione derivatives, synthesized pyridinylmethanone, nicotinonitrile, pyrazolopyridine, chromenopyridine, pyran-3-carbonitrile, *N*-butyrylpyrazolyl-1-butanone, 4-oxadiazole bearing 6-methyl pyridine moiety, acetohydrazides, 3,6-disubstituted-2-pyridinecarboxamide derivatives, Imidazo pyridin-3-amine derivatives, 3-imidazol-2-yl-pyrrolo pyridines and thienopyridines, imidazo

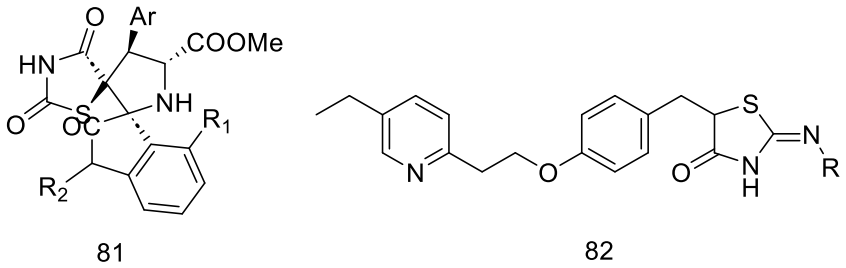

Figure 28. Anti-diabetic active Spiro and Schiff bases of pioglitazone derivatives

pyridine skeleton, 6-disubstituted 2-pyridinecarboxamide derivatives, 4-(1,3-thiazolidine-5-ylidene)pyrazole-3-carbonic acid and its esters, chalcone-piperonal derivatives, azomethine ylides, and pioglitazone having anti-diabetic activity.

5. Conclusion

The heterocyclic compounds have great significance in the medicinal chemistry. Due to the enormous applications of heterocycles which provides diverse biological activities such as anticancer, antimalarial, anti-bacterial, antifungal, antiviral, antihistamine, anti-HIV, etc. The heterocyclic compounds are utilised as an effective medicine for many diseases like malaria, cancer, diabetes, bacterial disease, inflammatory disease, etc. A five and six membered heterocyclic compounds plays an important role in medicinal chemistry. Many researchers have been reported a variety of 5 and 6 membered heterocycles showed a high biological activity. Here we have accounted the synthesis as well as applications of biologically active heterocycles containing 5 and 6 membered ring. Hence, 5 and 6 membered heterocycles like sulphonamide derivatives, pyrimidine-fused derivatives are important class of organic compounds for the new drug development. Because of the wide range of biological and pharmacological activities of 5 and 6 membered heterocycles, numerous synthetic routes have been developed for their synthesis.

Acknowledgements

We are greatly thankful to the Principal, B. P. Arts, S.M.A. Science & K.K.C. Commerce College, Chalisgaon, for his support as guidance and for presentation of the research work and also thankful to the Principal and HOD, Chemistry of Deogiri College Aurangabad for providing research facility.

Authors' contributions

All authors contribute to the work.

Conflict of Interest

The authors declared that they have no conflict of interest.

Orcid

Gautam P. Sadawarte
https://orcid.org/0000-0003-2002-0052

Jamatsing D. Rajput
https://orcid.org/0000-0002-4588-1345

Amol D. Kale
http://orcid.org/0009-0004-5535-1964

Vasant B. Jagrut
https://orcid.org/0000-0002-3328-1991

Reference

[1]. E. Campaigne, Adrien Albert and the rationalization of heterocyclic chemistry, *Journal of Chemical Education*, **1986**, *63*, 860. [Crossref], [Google Scholar], [Publisher]

[2]. F. Hakimi, M. Taghvaee, E. Golrasan, Synthesis of benzoxazole derivatives using Fe_3O_4@ SiO_2-SO_3H nanoparticles as a useful and reusable heterogeneous catalyst without using a solvent, *Advanced Journal of Chemistry, Section A*, **2023**, *6*, 188-197. [Crossref], [Google Scholar], [Publisher]

[3]. B. Baghernejad, M. Fiuzat, Synthesis of 2-amino-4*H*-pyran derivatives in aqueous media with nano-SnO_2 as recyclable catalyst, *Asian Journal of Nanoscience and Materials*, **2021**, *4*, 171-177. [Crossref], [Google Scholar], [Publisher]

[4]. Baghernejad, B., Fiuzat, M. Synthesis of 2-amino-4*H*-pyran derivatives in aqueous media with nano-SnO_2 as recyclable catalyst, *Journal of Medicinal and Nanomaterials Chemistry,* **2023,** *5*, 235-242. [Crossref], [Publisher]

[5]. B. Baghernejad, A. Zakariayi, One-Pot synthesis of oxindoles derivatives as effective antimicrobial agents by nano-magnesium aluminate as an effective aatalyst, *Asian Journal of Nanoscience and Materials*, **2022**, *5*, 225-233. [Crossref], [Google Scholar], [Publisher]

[6]. E. Athulya Chandran, V. M., N. Mathew Valooran, R.A. Kumar, A Recent update on pyridine derivatives as a potential lead for diabetes mellitus, *Journal of Chemical Reviews,* **2023,** *5*, 159-182. [Crossref], [Publisher]

[7]. T. Qadir, A. Amin, P.K. Sharma, I. Jeelani, H. Abe, A review on medicinally important heterocyclic compounds, *The Open Medicinal Chemistry Journal*, **2022**, *16*. [Crossref], [Google Scholar], [Publisher]

[8]. H. Ruwandeepika, G. Fernando, T. Jayaweera, An overview of biomedical, biotechnological, and industrial applications of actinomycetes, *Natural Products from Actinomycetes: Diversity, Ecology and Drug Discovery*, **2022**, 475-508. [Crossref], [Google Scholar], [Publisher]

[9]. Mokhtary, M., Mahooti, K. Recent advances in the synthesis of highly substituted piperidine analogs with biological activities, *Advanced Journal of Chemistry, Section A,* **2024,** 7, 163-189. [Crossref], [Publisher]

[10]. M. Bian, X.Q. Deng, G.H. Gong, C.X. Wei, Z.S. Quan, Synthesis and anticonvulsant activity evaluation of 6-substituted-[1, 2, 4] triazolo [3, 4-a](tetrazolo [5, 1-*a*]) phthalazine derivatives, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2013**, *28*, 792-800. [Crossref], [Google Scholar], [Publisher]

[11]. P.G. Baraldi, F. Fruttarolo, M.A. Tabrizi, R. Romagnoli, D. Preti, E. Ongini, H. El-Kashef, M.D. Carrión, P.A. Borea, Synthesis of a new series of pyrazolo [1, 5-*a*] pyrimidines structurally related to zaleplon, *Journal of Heterocyclic Chemistry*, **2007**, *44*, 355-361. [Crossref], [Google Scholar], [Publisher]

[12]. H. Lage, E. Aki-Sener, I. Yalcin, High antineoplastic activity of new heterocyclic compounds in cancer cells with resistance against classical DNA topoisomerase II-targeting drugs, *International Journal of Cancer*, **2006**, *119*, 213-220. [Crossref], [Google Scholar], [Publisher]

[13]. M. Ansari, M. Shokrzadeh, S. Karima, S. Rajaei, M. Fallah, N. Ghassemi-Barghi, M. Ghasemian, S. Emami, New thiazole-2 (3*H*)-thiones containing 4-(3, 4, 5-trimethoxyphenyl) moiety as anticancer agents, *European Journal of Medicinal Chemistry*, **2020**, *185*, 111784. [Crossref], [Google Scholar], [Publisher]

[14]. M.O. Karataş, B. Olgundeniz, S. Günal, İ. Özdemir, B. Alıcı, E. Çetinkaya, Synthesis, characterization and antimicrobial activities of novel silver (I) complexes with coumarin substituted *N*-heterocyclic carbene ligands, *Bioorganic & Medicinal Chemistry*, **2016**, *24*, 643-650. [Crossref], [Google Scholar], [Publisher]

[15]. M.E. Azab, M.M. Youssef, E.A. El-Bordany, Synthesis and antibacterial evaluation of novel heterocyclic compounds containing a sulfonamido moiety, *Molecules*, **2013**, *18*, 832-844. [Crossref], [Google Scholar], [Publisher]

[16]. Y. Honma, Y. Sekine, T. Hashiyama, M. Takeda, Y. Ono, K. Tsuzurahara, Studies on antiallergic agents. I. Phenyl-substituted heterocycles with a 5-tetrazolyl or *N*-(5-tetrazolyl) carbamoyl group, *Chemical and Pharmaceutical Bulletin*, **1982**, *30*, 4314-4324. [Crossref], [Google Scholar], [Publisher]

[17]. R. Rubbiani, L. Salassa, A. De Almeida, A. Casini, I. Ott, Cytotoxic gold (I) *N*-heterocyclic carbene complexes with phosphane ligands as potent enzyme inhibitors, *ChemMedChem*, **2014**, *9*, 1205-1210. [Crossref], [Google Scholar], [Publisher]

[18]. M. Nakatani, M. Ito, T. Yoshimura, M. Miyazaki, R. Ueno, H. Kawasaki, S. Takahashi, Y. Todoroki, Synthesis and herbicidal activity of 3-{[(hetero) aryl] methanesulfonyl}-4, 5-dihydro-1, 2-oxazole derivative; Discovery of the novel pre-emergence herbicide pyroxasulfone, *Journal of Pesticide Science*, **2016**, *41*, 133-144. [Crossref], [Google Scholar], [Publisher]

[19]. Y. Liang, S. Fan, W.Y. Mo, H.W. He, A facile synthesis and herbicidal activities of novel fluorine-containing thiazolo [4, 5-*d*] pyrimidin-7 (6*H*)-ones, *Journal of Fluorine Chemistry*, **2007**, *128*, 879-884. [Crossref], [Google Scholar], [Publisher]

[20]. T. Venkatachalam, E.A. Sudbeck, C. Mao, F.M. Uckun, Anti-HIV activity of aromatic and

heterocyclic thiazolyl thiourea compounds, *Bioorganic & Medicinal Chemistry Letters*, **2001**, *11*, 523-528. [Crossref], [Google Scholar], [Publisher]

[21]. R.A. Waghmare, Synthesis and in vitro anti-inflammatory activity of 5-arylidene-1-[(2 (methyl suphonyl amino) thiazol-4-yl) methyl]-2-thioxoimidazolidin-4-ones, *Asian Journal of Research in Chemistry*, **2017**, *10*, 739-744. [Crossref], [Google Scholar], [Publisher]

[22]. R.A. Waghmare, D.L. Lingampalle, V. Patil, A. Asrondkar, Synthesis and in vitro anti-inflammatory activity of some 1-(4-methyl sulphonyl amino methyl) phenyl-3, 5-diaryl-pyrazolines, *International Journal of ChemTech Research*, **2017**, *10*, 201-206. [Google Scholar]

[23]. M.H. Shaikh, D.D. Subhedar, M. Arkile, V.M. Khedkar, N. Jadhav, D. Sarkar, B.B. Shingate, Synthesis and bioactivity of novel triazole incorporated benzothiazinone derivatives as antitubercular and antioxidant agent, *Bioorganic & Medicinal Chemistry Letters*, **2016**, *26*, 561-569. [Crossref], [Google Scholar], [Publisher]

[24]. S. Vartale, N. Halikar, Y. Pawar, K. Tawde, Synthesis and evaluation of 3-cyano-4-imino-2-methylthio-4*H*-pyrido [1, 2-*a*] pyrimidine derivatives as potent antioxidant agents, *Arabian Journal of Chemistry*, **2016**, *9*, S1117-S1124. [Crossref], [Google Scholar], [Publisher]

[25]. D. Suresh, D. Jamatsing, S. Pravin, S. Ratnamala, Synthesis, characterization and antioxidant activity of carvacrol containing novel thiadiazole and oxadiazole moieties, *Modern Chemistry and Applications*, **2016**, *4*, 2. [Google Scholar], [Publisher]

[26]. M.J. Naim, M.J. Alam, F. Nawaz, V. Naidu, S. Aaghaz, M. Sahu, N. Siddiqui, O. Alam, Synthesis, molecular docking and anti-diabetic evaluation of 2, 4-thiazolidinedione based amide derivatives, *Bioorganic Chemistry*, **2017**, *73*, 24-36. [Crossref], [Google Scholar], [Publisher]

[27]. B.Y. Kim, J.B. Ahn, H.W. Lee, S.K. Kang, J.H. Lee, J.S. Shin, S.K. Ahn, C.I. Hong, S.S. Yoon, Synthesis and biological activity of novel substituted pyridines and purines containing 2, 4-thiazolidinedione, *European Journal of Medicinal Chemistry*, **2004**, *39*, 433-447. [Crossref], [Google Scholar], [Publisher]

[28]. F. Panahi, R. Yousefi, M.H. Mehraban, A. Khalafi-Nezhad, Synthesis of new pyrimidine-fused derivatives as potent and selective antidiabetic *α*-glucosidase inhibitors, *Carbohydrate Research*, **2013**, *380*, 81-91. [Crossref], [Google Scholar], [Publisher]

[29]. A. Trapero, A. Llebaria, A prospect for pyrrolidine iminosugars as antidiabetic α-glucosidase inhibitors, *ACS Publications, Journal of Medicinal Chemistry*, **2012**, *55*, 10345-10346. [Crossref], [Google Scholar], [Publisher]

[30]. G.P. Sadawarte, N.K. Halikar, A.D. Kale, V.B. Jagrut, Sodium oxalate mediate synthesis and α-amalyase inhibition assay of 5-substituted-3-phenyl-2-thioxoimidazolidin-4-ones, *Polycyclic Aromatic Compounds*, **2024**, *44*, 521-527. [Crossref], [Google Scholar], [Publisher]

[31]. G. Sadawarte, S. Jagatap, M. Patil, V. Jagrut, J.D. Rajput, Synthesis of substituted pyridine based sulphonamides as an antidiabetic agent, *European Journal of Chemistry*, **2021**, *12*, 279-283. [Crossref], [Google Scholar], [Publisher]

[32]. A.M.K. El-Dean, A.A. Abd-Ella, R. Hassanien, M.E. El-Sayed, R.M. Zaki, S.A. Abdel-Raheem, Chemical design and toxicity evaluation of new pyrimidothienotetrahydroisoquinolines as potential insecticidal agents, *Toxicology Reports*, **2019**, *6*, 100-104. [Crossref], [Google Scholar], [Publisher]

[33]. M.T. Salve, S.B. Jadhav Sr, Synthesis, characterization and antidiabetic evaluation of sulfonamide in corporated with 1, 3, 4-oxadiazole derivatives, *Indian Journal of Pharmaceutical Education and Research*, **2021**, *55*, 1145-1150. [Crossref], [Google Scholar], [Publisher]

[34]. J.B. Wright, W.E. Dulin, J.H. Markillie, The antidiabetic activity of 3, 5-dimethylpyrazoles, *Journal of Medicinal Chemistry*, **1964**, *7*, 102-105. [Crossref], [Google Scholar], [Publisher]

[35]. O. Fathalla, S. Awad, M. Mohamed, Synthesis of new 2-thiouracil-5-sulphonamide

derivatives with antibacterial and antifungal activity, *Archives of Pharmacal Research*, **2005**, *28*, 1205-1212. [Crossref], [Google Scholar], [Publisher]

[36]. B. Sujatha, S. Chennamsetty, V. Chintha, R. Wudayagiri, K. Prasada Rao, Synthesis and anti-diabetic activity evaluation of phosphonates containing thiazolidinedione moiety, *Phosphorus, Sulfur, and Silicon and the Related Elements*, **2020**, *195*, 586-591. [Crossref], [Google Scholar], [Publisher]

[37]. M. Molnar, V. Pavić, B. Šarkanj, M. Čačić, D. Vuković, J. Klenkar, Mono-and *bis*-dipicolinic acid heterocyclic derivatives–thiosemicarbazides, triazoles, oxadiazoles and thiazolidinones as antifungal and antioxidant agents, *Heterocyclic Communications*, **2017**, *23*, 35-42. [Crossref], [Google Scholar], [Publisher]

[38]. M. Bolous, N. Arumugam, A.I. Almansour, R.S. Kumar, K. Maruoka, V.C. Antharam, S. Thangamani, Broad-spectrum antifungal activity of spirooxindolo-pyrrolidine tethered indole/imidazole hybrid heterocycles against fungal pathogens, *Bioorganic & Medicinal Chemistry Letters*, **2019**, *29*, 2059-2063. [Crossref], [Google Scholar], [Publisher]

[39]. S. Wild, G. Roglic, A. Green, R. Sicree, H. King, Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030, *Diabetes Care*, **2004**, *27*, 1047-1053. [Crossref], [Google Scholar], [Publisher]

[40]. D. Soumya, B. Srilatha, Late stage complications of diabetes and insulin resistance, *Journal of Diabetes & Metabolism*, **2011**, *2*, 1000167. [Crossref], [Google Scholar], [Publisher]

[41]. S.P. Kushwaha, S.K. Rawat, P. Kumar, K. Tripathi, Coupling antioxidant and antidiabetic assets of 2, 4-thiazolidinedione derivatives, *Asian Journal of Pharmaceutical Analysis*, **2011**, *1*, 71-73. [Crossref], [Google Scholar], [Publisher]

[42]. A. Chaudhury, C. Duvoor, V.S. Reddy Dendi, S. Kraleti, A. Chada, R. Ravilla, A. Marco, N.S. Shekhawat, M.T. Montales, K. Kuriakose, Clinical review of antidiabetic drugs: Implications for type 2 diabetes mellitus management, *Frontiers in Endocrinology*, **2017**, *8*, 6. [Crossref], [Google Scholar], [Publisher]

[43]. D.S. Musmade, S.K. Parjane, A.V. Daithankar, Synthesis and biological evaluation of some 1, 3, 4-thiadiazoles, *Journal of Chemical and Pharmaceutical Research*, **2009**, *1*, 191-198. [Google Scholar], [Publisher]

[44]. N. Sachan, S. Thareja, R. Agarwal, S.S. Kadam, V.M. Kulkarni, Substituted biphenyl ethanones as antidiabetic agents: Synthesis and in-vivo screening, *International Journal of PharmTech. Research*, **2009**, *1*, 1625-1631. [Google Scholar], [Publisher]

[45]. M. Ceylan-Ünlüsoy, E.J. Verspohl, R. Ertan, Synthesis and antidiabetic activity of some new chromonyl-2, 4-thiazolidinediones, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **2010**, *25*, 784-789. [Crossref], [Google Scholar], [Publisher]

[46]. G. Mariappan, B. Saha, S. Datta, D. Kumar, P. Haldar, Design, synthesis and antidiabetic evaluation of oxazolone derivatives, *Journal of Chemical Sciences*, **2011**, *123*, 335-341. [Crossref], [Google Scholar], [Publisher]

[47]. P. Sridevi, M. Raju, V. Verma, P. Rangarao, Synthesis of derivatives of 4-hydroxy isoleucine from fenugreek and evaluation of their antidiabetic activity, *International Journal of Phytopharmacology*, **2014**, 4, 06-10. [Crossref], [Google Scholar]

[48]. R.V. Shingalapur, K.M. Hosamani, R.S. Keri, M.H. Hugar, Derivatives of benzimidazole pharmacophore: Synthesis, anticonvulsant, antidiabetic and DNA cleavage studies, *European Journal of Medicinal Chemistry*, **2010**, *45*, 1753-1759. [Crossref], [Google Scholar], [Publisher]

[49]. D. Kini, M. Ghate, Synthesis and oral hypoglycemic activity of 3-[5'-methyl-2'-aryl-3'-(thiazol-2"-yl amino) thiazolidin-4'-one] coumarin derivatives, *Journal of Chemistry*, **2011**, *8*, 386-390. [Crossref], [Google Scholar], [Publisher]

[50]. W.M. Basyouni, S.Y. Abbas, M.F. El Shehry, K.A. El-Bayouki, H.F. Aly, A. Arafa, M.S. Soliman,

New biguanides as anti-diabetic agents, Part II: synthesis and anti-diabetic properties evaluation of 1-arylamidebiguanide derivatives as agents of insulin resistant type II diabetes, *Archiv der Pharmazie*, **2017**, *350*, 1700183. [Crossref], [Google Scholar], [Publisher]

[51]. G. Mariappan, P. Prabhat, L. Sutharson, J. Banerjee, U. Patangia, S. Nath, Synthesis and antidiabetic evaluation of benzothiazole derivatives, *Journal of the Korean Chemical Society*, **2012**, *56*, 251-256. [Crossref], [Google Scholar], [Publisher]

[52]. S. Rocha, D. Ribeiro, E. Fernandes, M. Freitas, A systematic review on anti-diabetic properties of chalcones, *Current Medicinal Chemistry*, **2020**, *27*, 2257-2321. [Crossref], [Google Scholar], [Publisher]

[53]. C.T. Hsieh, T.J. Hsieh, M. El-Shazly, D.W. Chuang, Y.H. Tsai, C.T. Yen, S.F. Wu, Y.C. Wu, F.R. Chang, Synthesis of chalcone derivatives as potential anti-diabetic agents, *Bioorganic & Medicinal Chemistry Letters*, **2012**, *22*, 3912-3915. [Crossref], [Google Scholar], [Publisher]

[54]. F.M. Sroor, S.Y. Abbas, W.M. Basyouni, K.A. El-Bayouki, M.F. El-Mansy, H.F. Aly, S.A. Ali, A.F. Arafa, A.A. Haroun, Synthesis, structural characterization and in vivo anti-diabetic evaluation of some new sulfonylurea derivatives in normal and silicate coated nanoparticle forms as anti-hyperglycemic agents, *Bioorganic Chemistry*, **2019**, *92*, 103290. [Crossref], [Google Scholar], [Publisher]

[55]. D. Sola, L. Rossi, G.P.C. Schianca, P. Maffioli, M. Bigliocca, R. Mella, F. Corlianò, G.P. Fra, E. Bartoli, G. Derosa, State of the art paper Sulfonylureas and their use in clinical practice, *Archives of Medical Science*, **2015**, *11*, 840-848. [Crossref], [Google Scholar]

[56]. S.P. Babu, K.S. Babu, Synthesis and antidiabetic activity of 2, 4-disubstituted furan derivatives, *Der Pharma Chemica*, **2012**, *4*, 2178-2186. [Crossref], [Google Scholar], [Publisher]

[57]. L. Pandey, R. Karki, A. Theengh, J.B.G. Mariappan, Microwave assisted synthesis of some novel oxazolone derivatives as oral hypoglycemic agents, *Hetero Group Journal*, **2013**, *2*, 061-067. [Google Scholar], [Publisher]

[58]. N. Hosseinzadeh, S. Seraj, M.E. Bakhshi-Dezffoli, M. Hasani, M. Khoshneviszadeh, S. Fallah-Bonekohal, M. Abdollahi, A. Foroumadi, A. Shafiee, Synthesis and antidiabetic evaluation of benzenesulfonamide derivatives, *Iranian Journal of Pharmaceutical Research: IJPR*, **2013**, *12*, 325. [Google Scholar], [Publisher]

[59]. S.P. Mahapatra, P. Ghode, D. Jain, S. Chaturvedi, B. Maiti, T. Maity, Synthesis and hypoglycemic activity of some phthalimide derivatives, *J. Pharm. sci. res*, **2010**, *2*, 567-578. [Google Scholar], [Publisher]

[60]. G. Mariappan, P. Prabhat, L. Sutharson, J. Banerjee, U. Patangia, S. Nath, Synthesis and antidiabetic evaluation of benzothiazole derivatives, *Journal of the Korean Chemical Society*, **2012**, *56*, 251-256. [Crossref], [Google Scholar], [Publisher]

[61]. A.A. Chavan, N.R. Pai, Sulfonylureas as dual acting agents-synthesis and biological activity, *Journal of the Chinese Chemical Society*, **2007**, *54*, 771-777. [Crossref], [Google Scholar], [Publisher]

[62]. H.M. Faidallah, K.A. Khan, A.M. Asiri, Synthesis and biological evaluation of new 3-trifluoromethylpyrazolesulfonyl-urea and thiourea derivatives as antidiabetic and antimicrobial agents, *Journal of Fluorine Chemistry*, **2011**, *132*, 131-137. [Crossref], [Google Scholar], [Publisher]

[63]. S. Karimian, Y. Moghdani, M. Khoshneviszadeh, S. Pirhadi, A. Iraji, M. Khoshneviszadeh, Rational design, synthesis, in vitro, and in silico studies of dihydropyrimidinone derivatives as β-glucuronidase inhibitors, *Journal of Chemistry*, **2021**, *2021*, 1-10. [Crossref], [Google Scholar], [Publisher]

[64]. G. Navarrete-Vázquez, M.G. Morales-Vilchis, S. Estrada-Soto, J.J. Ramírez-Espinosa, S. Hidalgo-Figueroa, C. Nava-Zuazo, H. Tlahuext, I. Leon-Rivera, J.L. Medina-Franco, F. López-Vallejo, Synthesis of 2-{2-[(*α*/*β*-naphthalen-1-ylsulfonyl) amino]-1, 3-thiazol-4-yl} acetamides

with 11*β*-hydroxysteroid dehydrogenase inhibition and in combo antidiabetic activities, *European Journal of Medicinal Chemistry*, **2014**, *74*, 179-186. [Crossref], [Google Scholar], [Publisher]

[65]. M. Oguchi, K. Wada, H. Honma, A. Tanaka, T. Kaneko, S. Sakakibara, J. Ohsumi, N. Serizawa, T. Fujiwara, H. Horikoshi, Molecular design, synthesis, and hypoglycemic activity of a series of thiazolidine-2, 4-diones, *Journal of Medicinal Chemistry*, **2000**, *43*, 3052-3066. [Crossref], [Google Scholar], [Publisher]

[66]. E.A. Soylem, M.G. Assy, G.M. Morsi, Michael cyclization of polarized systems: synthesis and in vitro anti-diabetic evaluation of some novel pyrimidine, pyridine, pyrazole and pyrazolo [3, 4-*b*] pyridine derivatives, *Croatica Chemica Acta*, **2017**, *90*, 461-469. [Crossref], [Google Scholar]

[67]. S.B. Patchipala, V.R. Pasupuleti, A.V. Audipudi, H. babu Bollikolla, Synthesis, in-vivo anti-diabetic & anticancer activities and molecular modelling studies of tetrahydrobenzo [*d*] thiazole tethered nicotinohydrazide derivatives, *Arabian Journal of Chemistry*, **2022**, *15*, 103546. [Crossref], [Google Scholar], [Publisher]

[68]. L. Suresh, P.S.V. Kumar, P. Onkar, L. Srinivas, Y. Pydisetty, G. Chandramouli, Synthesis and in vitro evaluation of dihydro-6 H-chromeno [4, 3-*b*] isoxazolo [4, 5-*e*] pyridine derivatives as potent antidiabetic agents, *Research on Chemical Intermediates*, **2017**, *43*, 5433-5451. [Crossref], [Google Scholar], [Publisher]

[69]. P. Shyma, K. Balakrishna, K. Peethambar, M. Vijesh, Synthesis, characterization, antidiabetic and antioxidant activity of 1, 3, 4-oxadiazole derivatives bearing 6-methyl pyridine moiety, *Der Pharma Chemica*, **2015**, *7*, 137-145. [Google Scholar]

[70]. M. Arif, F. Jabeen, A. Saeed, I.Z. Qureshi, N. Mushtaq, A new class of potential anti-diabetic acetohydrazides: Synthesis, in vivo anti-diabetic activity and molecular docking studies, *Bangladesh Journal of Pharmacology*, **2017**, *12*, 319-332. [Crossref], [Google Scholar], [Publisher]

[71]. D. Patidar, A. Jain, P. Senger, Design, synthesis, characterization and biological evaluation of some novel 3, 6-disubstituted-2-pyridinecarboxamide derivatives as antidiabetic agents, *Journal of Cardiovascular Disease Research*; **2021**, 12. [Crossref], [Google Scholar]

[72]. T.V. Kota, H.B. Gandham, P.D.Sanasi, Green synthesis, characterization and antidiabetic activity of 2-substituted Aryl/Alkyl-*N*-Aryl/Alkyl imidazo [1, 2-*a*] pyridin-3-amine derivatives, *Asian Journal of Chemistry*, **2018**, *30*. [Crossref], [Google Scholar], [Publisher]

[73]. Z.A. Khan, M. Ahmad, S.H. Kamran, R. Anwar, F. Mobasher, T.-u. Rehman, S. Riaz, Preclinical anti-diabetic evaluation of *N*'-2, *N*'-4, *N*'-6-tris (4-hydroxybenzylidene) pyridine-2, 4, 6-tricarbohydrazide, *Latin American Journal of Pharmacy*, **2019**, *38*, 531-538. [Google Scholar], [Publisher]

[74]. R.H. Bahekar, M.R. Jain, P.A. Jadav, V.M. Prajapati, D.N. Patel, A.A. Gupta, A. Sharma, R. Tom, D. Bandyopadhya, H. Modi, Synthesis and antidiabetic activity of 2, 5-disubstituted-3-imidazol-2-yl-pyrrolo [2, 3-*b*] pyridines and thieno [2, 3-*b*] pyridines, *Bioorganic & Medicinal Chemistry*, **2007**, *15*, 6782-6795. [Crossref], [Google Scholar], [Publisher]

[75]. Z. Ye, C. Liu, F. Zou, Y. Cai, B. Chen, Y. Zou, J. Mo, T. Han, W. Huang, Q. Qiu, Discovery of novel potent GPR40 agonists containing imidazo [1, 2-*a*] pyridine core as antidiabetic agents, *Bioorganic & Medicinal Chemistry*, **2020**, *28*, 115574. [Crossref], [Google Scholar], [Publisher]

[76]. D. Patidar, A. Jain, P.K. Mohanty, Synthesis, characterization and pharmacological activity of 3, 6-disubstituted 2-pyridinecarboxamide derivatives as glucokinase activator, *Journal of Advanced Scientific Research*, **2020**, *11*, 150-156. [Google Scholar], [Publisher]

[77]. Bratenko M.; Perepelytsya O.; Yaremii I.; Kupchanko K.; Panasenko N. and Vovk M.; Synthesis and hypoglycemic activity of the

derivatives of 4-(1, 3-thiazolidine-5-ylidene) pyrazole-3-carbonic acid and its esters; *Biointerface Research in Applied Chemistry*; **2021**, 11, 14403-14412. [Crossref], [Google Scholar], [Publisher]

[78]. A. Asrar, M. Hussain, Synthesis And Evaluation of piperonal chalcone and its derivatives as anti-diabetic agents, *European Journal of Biomedical and Pharmaceutical sciences*, **2018**, *5*, 514-518. [Google Scholar], [Publisher]

[79]. B. Kaboudin, V. Yarahmadi, J.-y. Kato, T. Yokomatsu, A simple and novel method for the direct conversion of carboxylic acids into thioamides, *RSC Advances*, **2013**, *3*, 6435-6441. [Crossref], [Google Scholar], [Publisher]

[80]. M.T. Zeng, M. Wang, H.Y. Peng, Y. Cheng, Z.B. Dong, Copper-catalyzed synthesis of aryl thioamides from aryl aldehydes and tetramethylthiuram disulfide, *Synthesis*, **2018**, *50*, 644-650. [Google Scholar], [Publisher]

[81]. P. Zhang, W. Chen, M. Liu, H. Wu, Base-controlled three component reactions of amines, elemental sulfur, and styrenes: synthesis of thioamides under metal-free conditions, *The Journal of organic chemistry*, **2018**, *83*, 14269-14276. [Crossref], [Google Scholar], [Publisher]

[82]. U. Kazmaier, S. Ackermann, A straightforward approach towards thiazoles and endothiopeptides via Ugi reaction, *Organic & Biomolecular Chemistry*, **2005**, *3*, 3184-3187. [Crossref], [Google Scholar], [Publisher]

[83]. S. Gaikwad, M. Gaikwad, P. Lokhande, Iodine-DMSO catalyzed aromatization of polysubstituted cyclohexanone derivatives; An efficient methods for the synthesis of polyfunctionized biaryls derivatives, *Journal of Applied Organometallic Chemistry*, **2021**, *1*, 1-8. [Crossref], [Google Scholar], [Publisher]

[84]. M. Kriek, F. Martins, R. Leonardi, S.A. Fairhurst, D.J. Lowe, P.L. Roach, Thiazole synthase from Escherichia coli: An investigation of the substrates and purified proteins required for activity in vitro, *Journal of Biological Chemistry*, **2007**, *282*, 17413-17423. [Crossref], [Google Scholar], [Publisher]

[85]. O. Gharib, H. Nasr-Isfahani, M. Bakherad, H. Mighani, Synthesis of new polyurethanes based on 5,6,7,8–tetrabromo–2,3–dihydro–1,4–phthalazine dione, *Journal of Applied Organometallic Chemistry*, **2022**, *2*, 129-139. [Crossref], [Google Scholar], [Publisher]

[86]. C.H. Heathcock, S.K. Davidsen, S.G. Mills, M.A. Sanner, Daphniphyllum alkaloids. 10. Classical total synthesis of methyl homodaphniphyllate, *The Journal of Organic Chemistry*, **1992**, *57*, 2531-2544. [Crossref], [Google Scholar], [Publisher]

[87]. V. Safari Fard, Y. davoudabadi farahani, An amine/imine functionalized microporous MOF as a new fluorescent probe exhibiting selective sensing of Fe^{3+} and Al^{3+} over mixed metal ions, *Journal of Applied Organometallic Chemistry*, **2022**, *2*, 165-179. [Crossref], [Google Scholar], [Publisher]

[88]. R. Albert, H. Knecht, E. Andersen, V. Hungerford, M.H. Schreier, C. Papageorgiou, Isoxazolylthioamides as potential immunosuppressants a combinatorial chemistry approach, *Bioorganic & Medicinal Chemistry Letters*, **1998**, *8*, 2203-2208. [Crossref], [Google Scholar], [Publisher]

[89]. H.V. Barnes, T. Bledsoe, A simple test for selecting the thioamide schedule in thyrotoxicosis, *The Journal of Clinical Endocrinology & Metabolism*, **1972**, *35*, 250-255. [Crossref], [Google Scholar], [Publisher]

[90]. F. Wang, R. Langley, G. Gulten, L.G. Dover, G.S. Besra, W.R. Jacobs Jr, J.C. Sacchettini, Mechanism of thioamide drug action against tuberculosis and leprosy, *The Journal of Experimental Medicine*, **2007**, *204*, 73-78. [Crossref], [Google Scholar], [Publisher]

[91]. P. Jeschke, A. Harder, W. Etzel, W. Gau, G. Thielking, G. Bonse, K. Iinuma, Synthesis and anthelmintic activity of thioamide analogues of cyclic octadepsipeptides such as PF1022A, *Pest Management Science: Formerly Pesticide Science*, **2001**, *57*, 1000-1006. [Crossref], [Google Scholar], [Publisher]

[92]. A. Toumi, S. Boudriga, K. Hamden, M. Sobeh, M. Cheurfa, M. Askri, M. Knorr, C. Strohmann, L. Brieger, Synthesis, antidiabetic activity and molecular docking study of rhodanine-substitued spirooxindole pyrrolidine derivatives as novel *α*-amylase inhibitors, *Bioorganic Chemistry*, **2021**, *106*, 104507. [Crossref], [Google Scholar], [Publisher]

[93]. H.R. Afzal, N.u.H. Khan, K. Sultana, A. Mobashar, A. Lareb, A. Khan, A. Gull, H. Afzaal, M.T. Khan, M. Rizwan, Schiff bases of pioglitazone provide better antidiabetic and potent antioxidant effect in a streptozotocin–nicotinamide-induced diabetic rodent model, *ACS Omega*, **2021**, *6*, 4470-4479. [Crossref], [Google Scholar], [Publisher]

[94]. K.I. Bhat, A. Apoorva, A. Kumar, P. Kumar, Synthesis and antidiabetic evaluation of some new coumarin coupled 4-thiazolidinone derivatives, *Research Journal of Pharmacy and Technology*, **2019**, *12*, 5215-5218. [Crossref], [Google Scholar], [Publisher]

[95]. E. Dominic, M. Lopez, B. Thomas, Microwave-assisted addition of azomethines to isatoic anhydride, *Journal of Chemical Sciences*, **2007**, *119*, 47-51. [Crossref], [Google Scholar], [Publisher]

[96]. M.C. Lourenco, M.V. de Souza, A.C. Pinheiro, M.d.L. Ferreira, R.S. Gonçalves, T.C.M. Nogueira, M.A. Peralta, Evaluation of anti-tubercular activity of nicotinic and isoniazid analogues, *Arkivoc*, **2007**, *15*, 181-191. [Crossref], [Google Scholar], [Publisher]

[97]. M.J. Hearn, M.H. Cynamon, M.F. Chen, R. Coppins, J. Davis, H.J.-O. Kang, A. Noble, B. Tu-Sekine, M.S. Terrot, D. Trombino, Preparation and antitubercular activities in vitro and in vivo of novel Schiff bases of isoniazid, *European Journal of Medicinal Chemistry*, **2009**, *44*, 4169-4178. [Crossref], [Google Scholar], [Publisher]

[98]. D. Palke, Synthesis, physicochemical and biological studies of transition metal complexes of DHA schiff bases of aromatic amine, *Journal of Applied Organometallic Chemistry*, **2022**, *2*, 81-88. [Crossref], [Google Scholar], [Publisher]

[99]. E. Pahlavani, H. Kargar, N.S. Rad, A study on antitubercular and antimicrobial activity of isoniazid derivative, *Zahedan Journal of Research in Medical Sciences*, **2015**, *17*. [Crossref], [Google Scholar], [Publisher]

[100]. P.F. Oliveira, B. Guidetti, A. Chamayou, C. André-Barrès, J. Madacki, J. Korduláková, G. Mori, B.S. Orena, L.R. Chiarelli, M.R. Pasca, Mechanochemical synthesis and biological evaluation of novel isoniazid derivatives with potent antitubercular activity, *Molecules*, **2017**, *22*, 1457. [Crossref], [Google Scholar], [Publisher]

[101]. F.A. Rodrigues, A.C. Oliveira, B.C. Cavalcanti, C. Pessoa, A.C. Pinheiro, M.V. de Souza, Biological evaluation of isoniazid derivatives as an anticancer class, *Scientia Pharmaceutica*, **2014**, *82*, 21-28. [Crossref], [Google Scholar], [Publisher]

[102]. R. de Aguiar Cordeiro, F.J. de Farias Marques, R. de Aguiar Cordeiro, M.R. da Silva, A. Donato Maia Malaquias, C.V. Silva de Melo, J. Mafezoli, M.d.C. Ferreira de Oliveira, R.S. Nogueira Brilhante, M.F. Gadelha Rocha, Synthesis and antifungal activity in vitro of isoniazid derivatives against Histoplasma capsulatum var. capsulatum, *Antimicrobial Agents and Chemotherapy*, **2014**, *58*, 2504-2511. [Crossref], [Google Scholar], [Publisher]

[103]. D.C. Santos, R.R. Henriques, M.A.d.A.L. Junior, A.B. Farias, T.L. do Couto Nogueira, J.V.F. Quimas, N.C. Romeiro, L.L. da Silva, A.L.F. de Souza, Acylhydrazones as isoniazid derivatives with multi-target profiles for the treatment of Alzheimer's disease: Radical scavenging, myeloperoxidase/acetylcholinesterase inhibition and biometal chelation, *Bioorganic & Medicinal Chemistry*, **2020**, *28*, 115470. [Crossref], [Google Scholar], [Publisher]

[104]. E. Giovannucci, D.M. Harlan, M.C. Archer, R.M. Bergenstal, S.M. Gapstur, L.A. Habel, M. Pollak, J.G. Regensteiner, D. Yee, Diabetes and cancer: A consensus report, *CA: A Cancer journal for Clinicians*, **2010**, *60*, 207-221. [Crossref], [Google Scholar], [Publisher]

[105]. A. Tokajuk, E. Krzyżanowska-Grycel, A. Tokajuk, S. Grycel, A. Sadowska, H. Car,

Antidiabetic drugs and risk of cancer, *Pharmacological Reports*, **2015**, *67*, 1240-1250. [Crossref], [Google Scholar], [Publisher]