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*Proceeding Paper*

# Computational Screening And Synthesis Of Some Isatin-Thiadiazole Hybrids Potentially Targating Diabetes †

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**Abstract**

This study explores the design, synthesis and preliminary in silico screening of novel thiadiazole-isatin hybrid derivatives targeting diabetes mellitus. Building on thiadiazole and isatin compounds' demonstrated antidiabetic potential, the research objectives were to design and synthesize thiadiazole-isatin hybrids and evaluate their antidiabetic potential. Methodology encompassed literature review, computational screening using molecular docking, ADME prediction and Lipinski's rule and synthesis of thiadiazole intermediates from thiosemicarbazide combined with isatin derivatives. Key findings revealed compounds 2a and 2b exhibiting favorable binding affinity with human aldose reductase, monoglyceride lipase, GLP-1 and alpha-amylase, satisfying Lipinski's rule for optimal drug-likeness. Docking scores ranged from −10.6 to −7.0 for 2a and −10.2 to −7.0 for 2b. Thiadiazole-isatin derivatives, particularly 2a and 2b, demonstrate promise as antidiabetic agents through multi-enzyme inhibition, warranting pre-clinical and in vitro validation. This research offers a novel therapeutic strategy for diabetes management and potential pharmaceutical lead compounds. Future directions include experimental validation, in vitro and in vivo efficacy studies and structure-activity relationship exploration, contributing to innovative antidiabetic therapies.

**Keywords:** thiadiazole-isatin hybrids; molecular docking; ADME prediction; Lipinski's rule,GLP-1 receptor binding; MGL; alpha-amylase inhibition; aldose reductase inhibitors

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## 1. Introduction

Heterocyclic substances possess garnered many interest due to the several significant biological and therapeutic uses they have. Because heterocyclic molecules are useful and have been extensively studied synthetically, research interest in them is growing quickly. They span the area nearly 90% of new drugs contains them, and they are found b/w chemistry and biology, where a lot of scientific study and use takes place [1]. Heterocyclic compounds are of great interest in organic chemistry as they have strong coordination ability, high electron-blocking capacity and wide of applications [2]. In medical chemistry,

heterocyclic molecules are primarily of interest.Together with the mother scaffold's effective substituent groups, the ring structures' size and type clearly demonstrated their physicochemical characteristics [3]. "Heterocyclic" comes from "heteros" a Greek word," which means "distinct." These are substances essentially organic cyclic structures that contain a heteroatom. Common heteroatoms include nitrogen, oxygen, and sulfur; other elements such as Additionally, Se, P, Si, and B combine to form heterocyclic molecules [4]. Besides, they are widely distributed in natural and synthetic bio-active compounds, such as alkaloids, antibiotics, amino acids, vitamins, hormones, hemoglobin, dyes and many other therapeutic agents [5]. Alkaloids, cardiac glycosides, antibiotics and insecticides are some of the heterocycles of importance to human and animal health. The substitution of carbon for a heteroatom having an N or S family in aromatic rings, electron pair donation availability, and electronegativity difference that characterizes these closed-ring systems as fundamental in circular systems. [6]. Nitrogen heterocycles are the most essential pharmacophore and significant class of compounds, however, sulfur containing heterocycles are frequently present in FDA approved drug and reported to possess various activities anticancer, antimicrobial, antidiabetic, anti-inflammatory, antimalarial, anti- Alzheimer's and antifungal [7].One atom of sulfur and two nitrogen atoms make up chain framework of the thiadiazole. thiadiazole has 4 distinct isomeric structures. One of the most prevalent and significant components found in the fundamental structure of an array of natural goods, medications, is thiadiazole. Since the discovery of powerful sulfa medications that include this nucleus, the pace of advancement pertaining to thiadiazole has significantly increased. Thiadiazole and its derivatives are well known for being important scaffolds in pharmacology. '1-3-4-thiadiazoles' show a variety of inhibitory activities, encompassing enzymes and inhibitors of human platelet aggregation, as well as inhibitors that are antibacterial, anti-inflammatory, anticancer, antioxidant, antitubercular, neuroprotective, and antiviral. These compounds have exceptional pharmacological applications. Some drugs are available in marketing to containing Thiadiazole moiety. Additionally, some natural products, including Polycarpathiamines (A) and (B), which are Dendrodoine was taken from the Ascidian Polycarpa aurata., which is derived from Penicillium thiamines B and the marine algae Dendrodoa grossularia (13) (which come from Penicillium oxalicum via extraction), contain the 1,2,4-thiadiazole nucleus, as demonstrated [8].Fischer originally described 1,3,4-thiadiazoles in 1882, and Busch went on to develop them. Thiadiazoles with amino, hydroxyl, and mercapto substituents can take on a variety of tautomeric forms. In its completely conjugated form, the ring of 1,3,4-thiadiazole structure, which contains three different types of atoms, doesn't exhibit automerism. However, tautomerism is achievable in the presence of specific substituents. Because of the S (sulfur) atom's inductive effect, this base is incredibly weak with a reasonably elevated aromaticity, the 1,3,4-thiadiazole ring. While it can experience a ring cleavage with an aquatic foundation, In aqueous acid solutions, it is reasonably stable. Additionally, the ring is demonstrated to exist extremely electron-poor because of the nitrogen atoms effect of electron withdrawal', making it largely resistant to electrophilic substitution, while vulnerable to an assault by nucleophiles. Conversely, the ring gets very active, reacts rapidly to generate an assortment of derivatives when substitutions were introduced as its 5′ & 2′ locations [9].

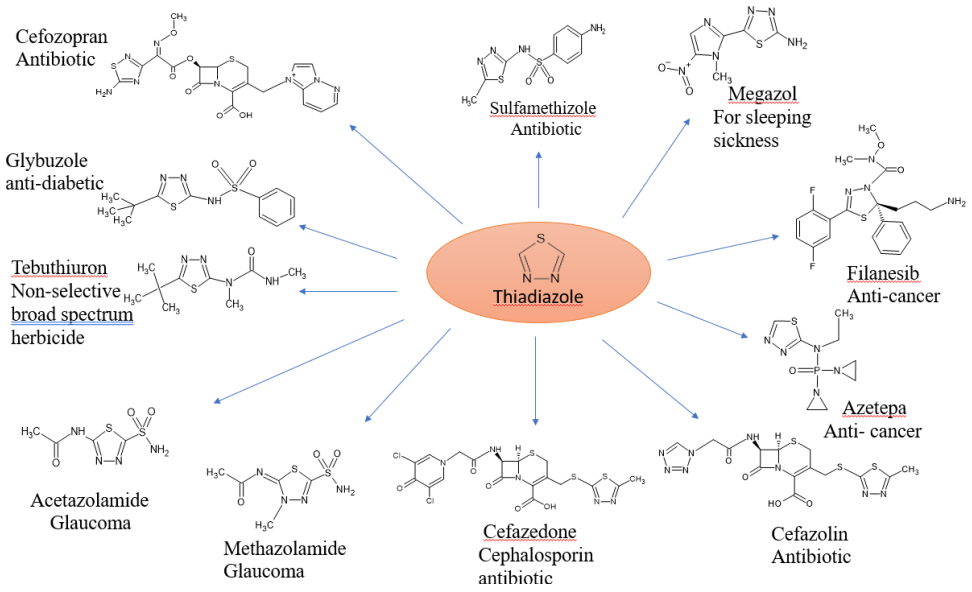


**Figure 1.** Representative medicinal scaffolds featuring the Thiadiazole ring system.

*Rationale of Design*

Isatin is an important heterocyclic scaffold with diverse pharmacological properties. Structural modification through an amide linkage to bioactive 1,3,4-thiadiazoles enhances rigidity and target interactions. The substituted thiadiazole ring adds pharmacophoric features improving binding affinity. Aromatic substituents (R = –H, –Cl, –$NH_2$, –$NO_2$, –OH) modulate activity by influencing electronic and steric properties. Thus, isatin–amide–thiadiazole conjugates are expected to show significant enzyme inhibitory activity through combined pharmacological potential and substituent fine-tuning.

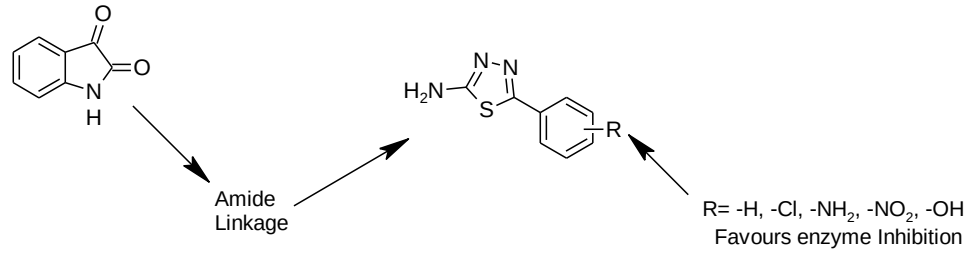


**Figure 2.** Rationale of 1,3,4-thiadiazole Compound.

## 2. Materials and Methods

The designed compounds were evaluated through in-silico analysis for antidiabetic activity (aldose reductase and MAGL) and further synthesized for in vitro efficacy studies. Computational tools confirmed their pharmacological, physicochemical, and bioactivity properties, supporting their selection for synthesis. Solvents (LR grade) from Central Drug House Pvt. Ltd., E. Merck, and S. D. Fine Chemicals Ltd. were purified prior to use. Melting points were determined by the capillary method. IR spectra were recorded on a Shimadzu IR Affinity-1 FTIR spectrophotometer, and ^1H NMR spectra on a Bruker DRX-300/400 spectrometer using TMS as an internal standard in DMSO/$CDCl_3$. Ethanol (99.5%) was employed, obtained from rectified spirit (95.6%) through purification to absolute ethanol. The proposed research work can be broadly divided into two parts. The first part was based on design and synthetic work, while the second part dealt with physicochemical evaluation and chemical docking of the substances. Various "5-phenyl-1,3,4-

thiadiazol-2-amine" was replaced (1a-1f) on reation with Isatin gave substituted amides as final products.

***Synthesis of 5-phenyl-1,3,4-thiadiazol-2-amine (1a-1f):***

A series of (1a–1f): Benzoic acid (0.1 mol) and thiosemicarbazide (0.1 mol) were gently refluxed in 30 mL of phosphorous oxychloride for 30 min. Next, the mixture took time to cool.before water (90 mL) was carefully added. The mixture of DMF and ethanol (9:1) was filtered, dried, and crystallized, yielding a white solid in 65% yield. After the solid separated, it was collected by filtration, resuspended in water, and then made basic with aqueous KOH to isolate the final product.[10,11]

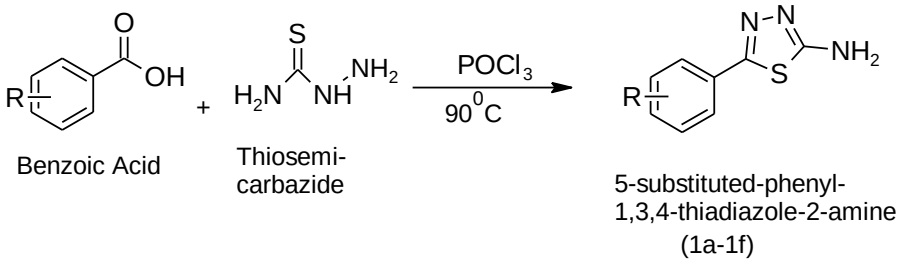


**Figure 3.** Synthetic reaction to obtain 5-phenyl-1,3,4-thiadiazol-2-amine as first step.

***Synthesis of Final 1,3,4-Thiadiazole Derivatives (2a-2f)***

In the solution of (100 mg, 0.0036 mole) in ethanol (20 mL), Isatin (0.52 gm) was added and reflux was introduced for condensation. 60 °C was the constant outside temperature. When the condensation of mixture starts GAA was introduced to the mixture to provide acidic condition to the reaction mixture. Monitoring of reaction is done by TLC in DCM:MeOH (9:1). After confirmation of final product reacting mixture was placed at room temperature. Reaction mixture undergoes neutralization reaction via concentrated from Ice on ice bath. A solid precipitate formed after complete neutralization the final product was obtained by filtering, washing with water, drying, and recrystallizing it with ethanol.

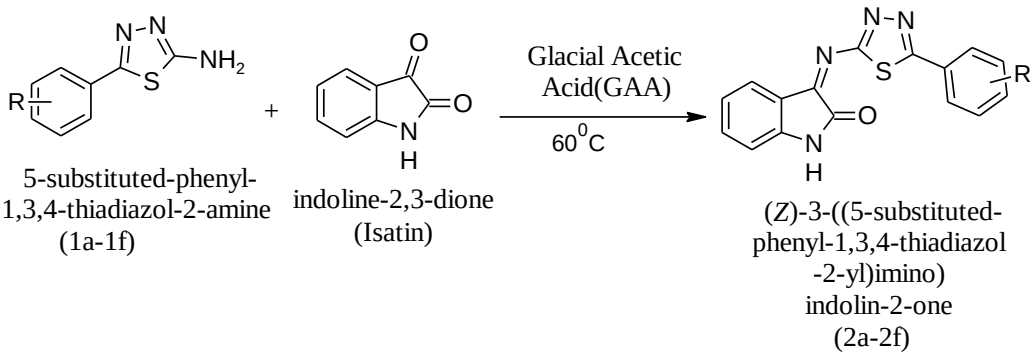


**Figure 4.** Synthetic reaction to obtain substituted 5-phenyl-1,3,4-thiadiazole-2-amine derivates as final compounds.

## 3. Result

### Chemistry

Each one of the designed compounds were examined via in-silico computational analysis for their antidiabetic activity (aldose reductase and monoacylglyceryl lipase (MAGL)) and These products underwent additional synthesis, and the resulting in vitro efficacy was investigated. All the designed compounds were also accepted by other online

computational tools for pharmacological activities, physicochemical properties and bioactivity properties. Hence they were chosen for synthesis as per given reaction scheme.

***(Z)-3-((5-phenyl-1,3,4-thidiazole-2-yl)imino)indolin-2-one synthesis process(2a)*** Yield: 35%, M.P.: 160 °C, Appearance: White crystals, $^1$H NMR (400 MHz): δ 7.33 (1H, ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.52-7.76 (5H, 7.58 (ddd, *J* = 8.2, 1.2, 0.4 Hz), 7.60 (dddd, *J* = 7.8, 7.4, 1.3, 0.4 Hz), 7.61 (tdd, *J* = 7.4, 1.6, 1.5 Hz), 7.69 (ddd, *J* = 8.2, 7.6, 1.5 Hz)), 8.06 (2H, dtd, *J* = 7.8, 1.5, 0.4 Hz), 8.93 (1H, ddd, *J* = 7.8, 1.5, 0.4 Hz). IR(cm$^{-1}$): 3462(N-H, Stretch), 3075-3110(C-H, Stretch), 1769(C=O, Stretch), 1672(C=N, Stretch), 1604(C=C, Bend), 1496 (C=C, Stretch), 1342 (C-N Stretch), 1265 (N-N, Stretch).

***(Z)-3-((5-(2-chlorophenyl)-1,3,4-thidiazole-2-yl)imino)indolin-2-1 (2b)*** Yield: 36%, M.P.: 180 °C, Apperance: Brownish Crystals, $^1$H NMR (400 MHz): δ 7.32 (1H, ddd, *J* = 7.8, 7.6, 1.2 Hz), 7.45-7.87 (5H, 7.53 (ddd, *J* = 7.9, 7.6, 1.7 Hz), 7.57 (ddd, *J* = 8.2, 1.2, 0.4 Hz), 7.62 (td, *J* = 7.6, 1.2 Hz), 7.68 (ddd, *J* = 8.2, 7.6, 1.5 Hz), 7.80 (ddd, *J* = 7.9, 1.2, 0.4 Hz)), 8.06 (1H, ddd, *J* = 7.6, 1.7, 0.4 Hz), 8.92 (1H, ddd, *J* = 7.8, 1.5, 0.4 Hz).

***(Z)-3-((5-(4-nitrophenyl)-1,3,4-thidiazole-2-yl)imino)indolin-2-1 (2c)*** Yield: 38%,M.P.: 170 °C, Apperance: Brownish crystals, $^1$H NMR (400 MHz): δ 7.42-7.58 (2H, 7.49 (ddd, *J* = 7.5, 7.1, 1.9 Hz), 7.52 (ddd, *J* = 7.9, 1.9, 0.5 Hz)), 8.01-8.18 (3H, 8.08 (ddd, *J* = 7.9, 7.5, 1.5 Hz), 8.12 (ddd, *J* = 8.8, 1.6, 0.5 Hz)), 8.26 (2H, ddd, *J* = 8.8, 1.5, 0.5 Hz), 8.67 (1H, ddd, *J* = 7.1, 1.5, 0.5 Hz).

***(Z)-3-((5-(3,5-Dinitrophenyl)-1,3,4-thidiazole-2-yl)imino)indolin-2-1 (2d)*** Yield: 40%, M.P.: 190 °C, Apperance: Yellowish crystal, $^1$H NMR (400 MHz): δ 7.42-7.60 (2H, 7.49 (ddd, *J* = 7.5, 7.0, 1.9 Hz), 7.54 (ddd, *J* = 8.0, 1.9, 0.5 Hz)), 8.01 (1H, ddd, *J* = 8.0, 7.5, 1.4 Hz), 8.54 (1H, ddd, *J* = 7.0, 1.4, 0.5 Hz), 8.88 (1H, t, *J* = 1.7 Hz), 9.00 (2H, dd, *J* = 1.7, 1.3 Hz).

***(Z)-3-((5-(4-aminophenyl)-1,3,4-thidiazole-2-yl)imino)indolin-2-1 (2e)*** Yield: 42%, M.P.: 195 °C, Apperance: Pale yellow crystal, $^1$H NMR (400 MHz): δ 6.78 (2H, ddd, *J* = 8.3, 1.2, 0.4 Hz), 7.28-7.46 (2H, 7.34 (ddd, *J* = 8.2, 1.3, 0.4 Hz), 7.40 (td, *J* = 7.6, 1.3 Hz)), 7.64-7.81 (3H, 7.70 (ddd, *J* = 8.3, 1.7, 0.4 Hz), 7.73 (ddd, *J* = 8.2, 7.6, 1.5 Hz)), 8.58 (1H, ddd, *J* = 7.6, 1.5, 0.4 Hz).

***(Z)-3-((5-(4-hydroxyphenyl)-1,3,4-thidiazole-2-yl)imino)indolin-2-1 (2f)*** Yield: 45%, M.P.: 200 °C, Appearance: Whitish crystal, $^1$H NMR (400 MHz): δ 7.16 (2H, ddd, *J* = 8.6, 1.2, 0.4 Hz), 7.29-7.47 (2H, 7.35 (ddd, *J* = 8.2, 1.3, 0.4 Hz), 7.41 (td, *J* = 7.6, 1.3 Hz)), 7.61-7.79 (3H, 7.69 (ddd, *J* = 8.2, 7.6, 1.5 Hz), 7.73 (ddd, *J* = 8.6, 1.7, 0.4 Hz)), 8.90 (1H, ddd, *J* = 7.6, 1.5, 0.4 Hz).

The IR spectra were recorded using a Shimadzu IR Affinity-1 FTIR spectrophotometer (KBr disc method). The ^1H NMR spectra were obtained on a Bruker DRX-300/400 using DMSO or $CDCl_3$ with TMS as the internal standard. Signal patterns were designated as d, t, q, m, s, and bs with chemical shifts in δ (ppm). The ^1H-NMR spectrum strongly supports synthesis of the target compound. A singlet at δ 5.60 ppm corresponds to methylene (–CH2–) protons introduced during coupling of benzotriazole with quinoline carbohydrazide, serving as a structural marker. Absence of this resonance in starting materials confirms the new –CH2– linkage. The downfield shift (δ 5.60 ppm) arises from deshielding by adjacent N and C=O groups, substantiating connectivity. Thus, the methylene proton peak provides unambiguous evidence for successful formation of the Isatin-thiadiazole GI hybrid system.

### *3.1. Molecular Docking Studies*

Molecular docking was performed using Glide 7.0, with Schrodinger suite version 10.1 used to generate ligand interaction diagrams and visualize protein–ligand interactions. Glide XP Docking was employed after minimizing ligand energy, and docking was performed to obtain binding affinities. Binding energy, which reflects the strength of ligand–protein interaction, was used to identify the best configuration for each target.

Molecules with the highest binding affinity for each protein were selected for further analysis. The PDB IDs used as antidiabetic targets were 1US0 (aldose reductase), 4W93 (alpha amylase), 5UZN (monoglycerol lipase), and 3IOL (glycogen like protein).

*3.2. Physicochemical Studies*

Predicting physicochemical characteristics is important in developing antidiabetic medications with improved pharmacological profiles. Toxicity, digital pharmacological action, physico-chemical properties, and oral bioavailability of developed molecules were assessed using Molinspiration and Property Explorer. Molecular weight (MW), lipid solubility (cLogP), hydrophilicity (clogS), toxicity, number of rotatable bonds (nROTB), drug likeness, and Lipinski's rules were computed. Toxicities predicted by Osiris Property Explorer and Data Warrior indicated no mutations, tumors, irritation, or adverse effects on reproduction. Higher lipophilicity with low water solubility is a key characteristic for improved pharmacological profiles. All synthesized compounds had solubility (clogS) within the satisfactory range (<−4). Lipophilicity-related clogP quantifies drug-likeness, effectiveness, pharmacokinetics, and toxicity, with favorable profiles at values less than 5. TPSA values were computed, showing poor membrane permeability and low CNS bioavailability, though values greater than 60 Å are chosen for oral molecules. Compounds with negative or null drug-likeness values were excluded. These tools help screen active compounds.

Analyzing and Screening ADME Results

Molecule 2a showed good docking scores with receptors human aldose reductase and monoglyceride lipase. 2a showed docking score of −10.6, −9.8, and −7.4 with human aldose reductase, monoglyceride lipase, GLP-1 and alpha amylase respectively. However, poor score (–6.8) was observed with alpha amylase. The best docking results obtained with 2b were −10.2, −9.4, −7.5 and −7.0 with human aldose reductase, monoglycerol lipase, GLP-1 and alpha amylaae respectively. 2c also gave best dock score of −7.8 with human aldose reductase; however, poor scores were obtained with other three targets. Compound 2e was found to be best against aldose reductase with dock score 7.7 which is comparatively less than best compounds 2a and 2b. Molecule 2d and 2f showed poor dock scores with all four targets. Overall, in case of antidiabetic properties, 2a showed highest dock with the receptor human aldose reductase.

Compounds 2a–2f were evaluated against various ADME criteria, including LogS, Lipinski's Rule of five, LogP, The BBB and surface area as polar (TPSA) permeability and gastrointestinal absorption. Compounds that met Lipinski's Rule of five and had higher gastric absorption were chosen for additional analysis; further compounds with low or medium risk or no toxicity were also selected for additional analysis. Compound 2a was selected as the final hit compound for additional study.

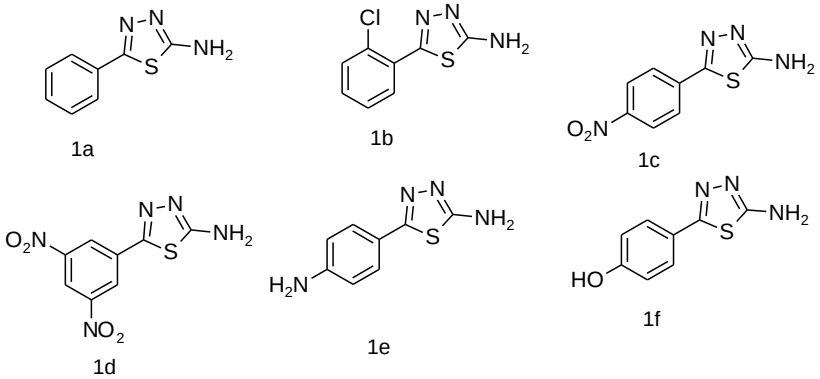

**Figure 5.** Compound of ***5-phenyl-1,3,4-thiadiazol-2-amine (1a–1f)***.

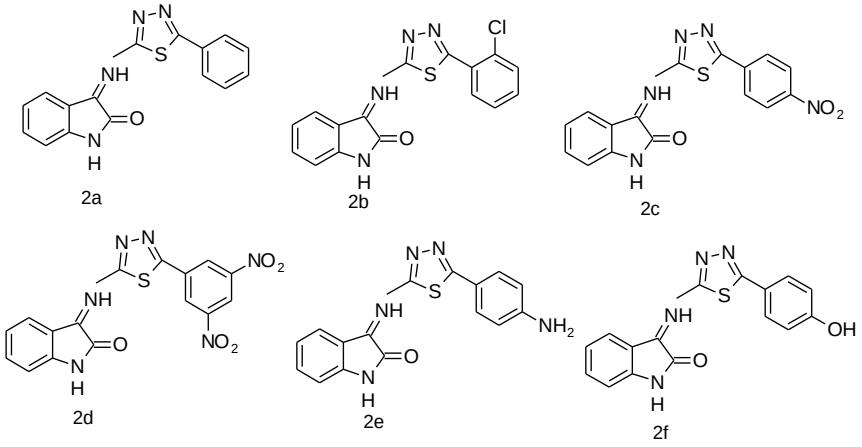


**Figure 6.** Final Derivatives of 1,3,4-thiadiazole.

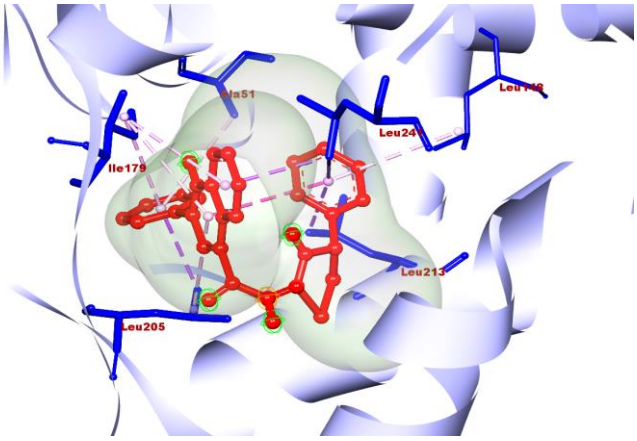


**Figure 7.** 3D amino acid interactions of 2a with the receptor Aldose reductase.

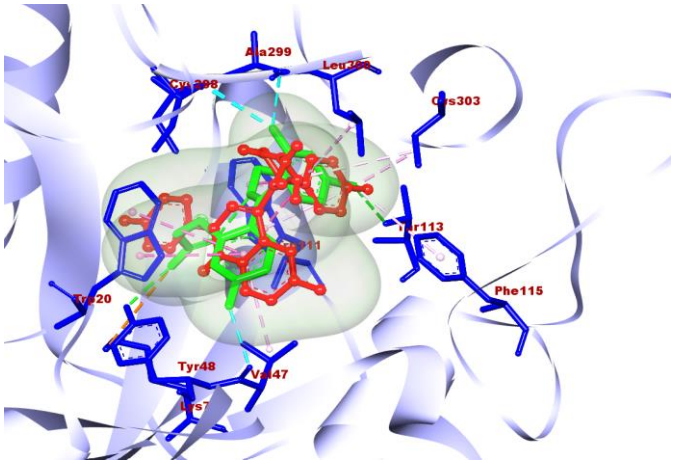


**Figure 8.** Superimposed picture of compound 2a with co-crystallized ligand of aldose reductase receptor at its active site.

**Table 1.** Molecular docking score of synthesized compounds with all four targets.

| Protein Name | PDB-ID | 2a | 2b | 2c | 2d | 2e | 2f |
|---|---|---|---|---|---|---|---|
| Aldose reductase | 1US0 | −10.6 | −10.2 | −7.8 | −7.6 | 8.1 | 7.7 |
| Alpha amylase | 4W93 | −6.8 | −7.0 | −5.8 | −5.1 | −6.2 | −5.4 |
| Monoglycerol lipase | 5ZUN | −9.8 | −9.4 | −6.9 | −6.4 | −7.5 | −6.8 |
| Glucagon like Peptide-1 | 3IOL | −7.4 | −7.5 | −6.3 | −6.1 | −7.1 | −6.7 |

**Table 2.** ADME/physicochemical properties of titled compounds.

| Code | Molecular Weight | cLogP | HBD | HBA | Nrotb | TPSA | cLogS | Drug Score | Drug Likeliness | Lipinski's Rule |
|---|---|---|---|---|---|---|---|---|---|---|
| **2a** | 306.39 | 1.70 | 2 | 5 | 1 | 106.97 | -2.60 | 0.93 | 5.98 | Yes |
| **2b** | 340.79 | 2.30 | 2 | 5 | 1 | 106.97 | -3.33 | 0.89 | 6.34 | Yes |
| **2c** | 351.34 | 0.49 | 2 | 8 | 3 | 152.79 | -2.91 | 0.76 | 0.80 | Yes |
| **2d** | 396.34 | -0.71 | 2 | 11 | 5 | 198.61 | -3.22 | 0.50 | -1.42 | Yes |
| **2e** | 321.36 | 1.98 | 2 | 6 | 2 | 115.71 | -3.61 | 0.92 | 6.21 | Yes |
| **2f** | 322.34 | 1.65 | 2 | 6 | 2 | 121.50 | -3.99 | 0.93 | 6.16 | Yes |

## 4. Conclusions

The research focused on designing, synthesizing, and in-silico screening of thiadiazole–isatin derivatives. After literature review, compounds were designed and evaluated using molecular docking, ADME prediction, and physicochemical analysis. The synthesis involved preparing thiadiazole intermediates followed by coupling with isatin. Docking studies of six compounds (2a–2f) showed that 2a and 2b passed Lipinski's rule and exhibited good binding affinity, especially with human aldose reductase and monoglyceride lipase. Compound 2a gave the best docking results and better drug-likeness compared to 2b, while others showed lower activity. Overall, compounds 2a and 2b emerged as promising lead molecules for multi-enzyme targeting agents.

**Supplementary Materials:**

**Author Contributions:** Conceptualization, N.S.; methodology, M.; software, N.S.; validation, N.S.; formal analysis, N.S.; investigation, M.; resources, N.S.; data curation, P.; writing—original draft preparation, P.; writing—review and editing, N.S.; visualization, M.; supervision, N.S.; project administration, N.S. All authors have read and agreed to the published version of the manuscript.

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**Informed Consent Statement:** Not Applicable.

**Data Availability Statement:** The original contributions presented in this study are included in the article/Supplementary Material further inquires can be directed to the corresponding author.

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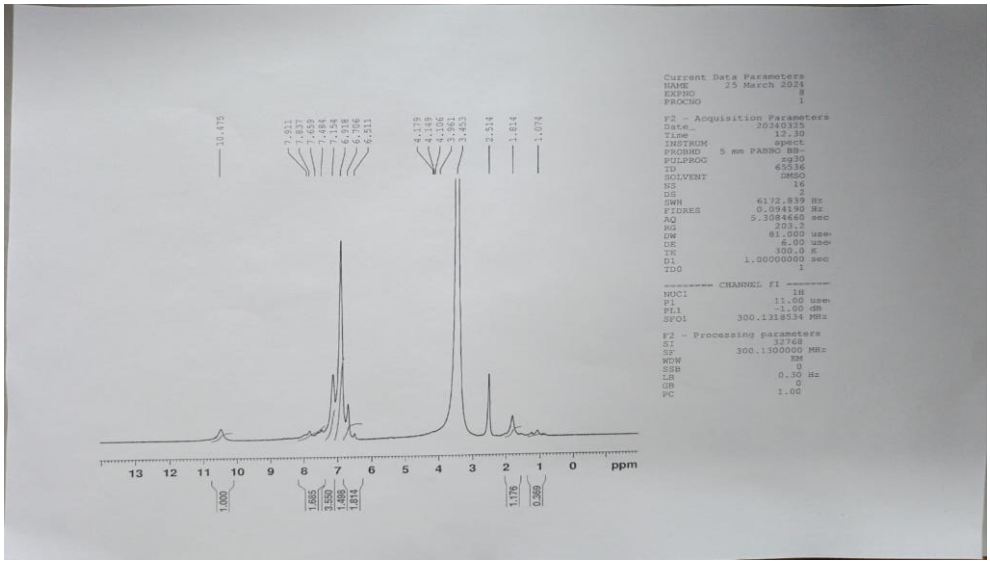
**Conflicts of Interest:** "The author declare no conflicts of interest. ".

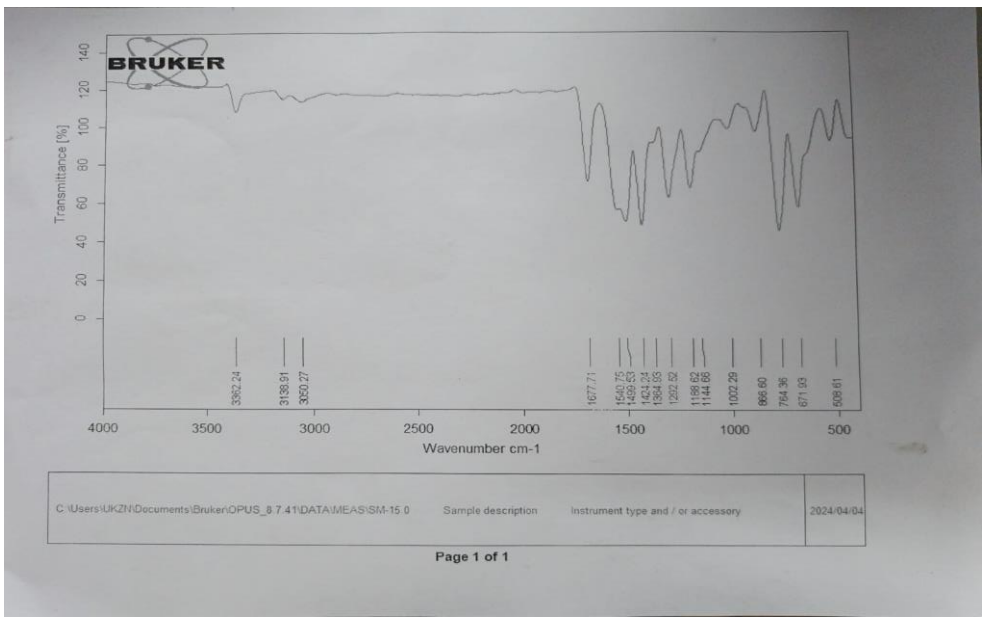
## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| TLC | Thin layer Chromatography |
| TPSA | Total polar surface area |
| LogP | lipophilicity |
| LogS | Water solubility |
| DMSO | Dimethyl Sulfoxide |
| GAA | Glacial Acetic Acid |
| $CDCl_3$ | Deuterated Chloroform |
| TMS | Trimethylsilyl |
| DMF | Dimethylformamide |
| KOH | Potassium hydroxide |
| NMR | Nuclear magnetic resonance |

### Appendix A




## Appendix B

*Refer Supplementary Information File.*

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