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Research Article

Synthesis, Structural Elucidation and α-Glucosidase Inhibitory Activity of New Hydrazide Derivatives

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Abstract: Diabetes mellitus (DM) is a chronic and progressive metabolic disorder affecting over 422 million people globally. It arises from insufficient insulin production or the inability of cells to respond to insulin, leading to disruptions in carbohydrate, fat, and protein metabolism. Over time, DM can result in severe complications such as cardiovascular diseases, kidney failure, and vision loss. Effective management of DM includes therapeutic strategies aimed at stabilizing blood glucose levels. Among these, α-glucosidase enzyme inhibitors play a crucial role by slowing carbohydrate digestion and reducing postprandial blood glucose spikes. In this study, new hydrazide derivatives linked to non-steroidal anti-inflammatory drugs (NSAIDs) were synthesized and evaluated as potential α-glucosidase enzyme inhibitors. Structural characterization of these derivatives was performed using techniques such as ^{1}H-NMR, FTIR, and mass spectrometry (MS). All of these compounds were tested *in vitro* for their α-glucosidase enzyme inhibition activity. Among the synthesized derivatives, ethyl 2-{3-[3-(trifluoromethyl)anilino]benzoyl}hydrazine-1-carboxylate (compound **3d**), an etofenamate derivative, revealed the highest inhibitory potential with IC_{50} values of 188.30±0.1 μg mL^{-1} when compared with standard acarbose having IC_{50} value 190.70±2.05 μg mL^{-1}. These findings highlight the potential of NSAID-linked hydrazide derivatives as promising candidates for the development of novel DM therapies.

Keywords: Carboxylate, Diabetes Mellitus, Glucosidase, Hydrazide, NSAID

Yeni Hidrazid Türevlerinin Sentezi, Yapı Aydınlatma ve α-Glukozidaz İnhibitör Etki Çalışmaları

Öz: Diabetes mellitus (DM), dünya çapında 422 milyondan fazla insanı etkileyen kronik ve ilerleyici bir metabolik hastalıktır. Yetersiz insülin üretimi veya hücrelerin insüline yanıt verememesi sonucu ortaya çıkar ve karbonhidrat, yağ ve protein metabolizmasında bozulmalara yol açar. Zamanla DM, kardiyovasküler hastalıklar, böbrek yetmezliği ve görme kaybı gibi ciddi komplikasyonlara neden olabilir. DM'nin etkili yönetimi, kan şekeri seviyelerini stabilize etmeyi amaçlayan terapötik stratejileri içerir. Bunlar arasında, α-glukozidaz enzim inhibitörleri, karbonhidrat sindirimini yavaşlatarak ve yemek sonrası kan şekeri yükselmelerinin azaltılmasında önemli bir rol oynar. Bu çalışmada, steroid olmayan anti-inflamatuar ilaçlarla (NSAİİ) bağlantılı yeni hidrazid türevleri sentezlenmiş ve potansiyel α-glukozidaz enzim inhibitörleri olarak değerlendirilmiştir. Bu türevlerin yapısal karakterizasyonu, ^{1}H-NMR, FTIR ve kütle spektrometrisi (MS) gibi teknikler kullanılarak gerçekleştirilmiştir. Bu bileşiklerin tümü, α-glukozidaz enzim inhibisyon aktiviteleri açısından *in vitro* yöntemle test edilmiştir. Sentezlenen türevler arasında etofenamat türevi olan etil 2-{3-[3-(triflorometil)anilino]benzoil}hidrazin-1-karboksilat (bileşik **3d**), 190.70±2.05 μg mL^{-1} IC_{50} değerine sahip standart akarbozla karşılaştırıldığında 188.30±0.1 μg mL^{-1} IC_{50} değeriyle en yüksek inhibisyon gösteren bileşik olduğu sonucuna varılmıştır. Bu bulgular, NSAİİ bağlantılı hidrazid türevlerinin yeni DM tedavilerinin geliştirilmesi için umut verici adaylar olabileceğini göstermektedir.

Anahtar Kelimeler: Diabetes Mellitus, Glukosidaz, Hidrazid, Karboksilat, NSAİİ

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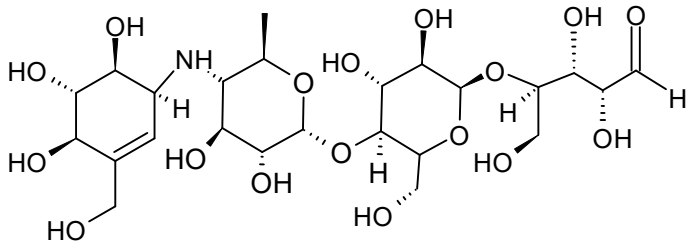
1. Introduction

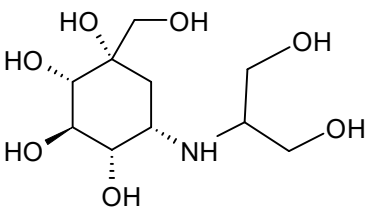
Diabetes mellitus (DM) is a chronic metabolic disorder marked by elevated blood glucose levels, leading to various complications such as cardiovascular diseases, chronic inflammation, and increased risk of infections (Tripathi & Srivastava, 2006; Fowler, 2008; Antar et al., 2023). The World Health Organization reports that approximately 422 million people are affected by diabetes globally, with Type 2 Diabetes Mellitus (T2DM) accounting for over 90% of cases. The incidence of T2DM is expected to rise, with more than 590 million individuals projected to be affected by 2035 (Zheng et al., 2018).

T2DM is characterized by insulin resistance and inadequate insulin secretion by pancreatic β-cells. Effective management focuses on controlling hyperglycemia to prevent chronic complications. Current treatments include oral hypoglycemic agents, such as sulfonylureas, thiazolidinediones, metformin, and α-glucosidase inhibitors. The α-glucosidase enzyme plays a crucial role in carbohydrate digestion by breaking down disaccharides and oligosaccharides into glucose (Dirir et al., 2022). Inhibitors of α-glucosidase delay carbohydrate digestion and absorption, helping to stabilize blood glucose levels and prevent postprandial hyperglycemia.

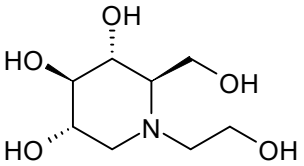
Three α-glucosidase inhibitors -acarbose, voglibose, and miglitol- manage T2DM by reducing glucose formation in the intestine (Figure 1). However, these drugs are often associated with side effects such as flatulence, diarrhea, and abdominal discomfort (Scott & Spencer, 2000; Dabhi et al., 2013; Gao et al., 2018). As a result, there is a continuing need to develop new and more effective α-glucosidase inhibitors to improve treatment outcomes and reduce adverse effects.



Acarbose



Voglibose



Miglitol

Figure 1. α-glucosidase inhibitors.

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of medications commonly used to alleviate pain and reduce inflammation. Unlike steroids, NSAIDs work by inhibiting the activity of enzymes known as cyclooxygenases (COX), particularly COX-1 and COX-2, which play a significant role in prostaglandin synthesis (Rao et al., 2010). Researchers are focusing on maintaining the core skeletal structures of NSAIDs while synthesizing various derivatives through modifications, and they are working to demonstrate that these resultant molecules are biologically active (Aydın et al., 2014; Şenkardeş et al., 2016; Koç et al., 2022).

Numerous studies have explored the α-glucosidase inhibitory activities of compounds derived from NSAIDs (Kausar et al., 2021; Daud et al., 2024). In 2022, (S)-flurbiprofen hydrazide-hydrazone derivatives were synthesized and their α-glucosidase inhibitory activities were evaluated. The most potent inhibitor in this series was (E)-2-(2-fluoro-[1,1′-biphenyl]-4-yl)-*N*′-(1-

phenylbutylidene)propanehydrazide, which exhibited an impressive IC_{50} value of 0.93 μM (Alam et al., 2022). A study by Sardar et al. examined the glucosidase activities of hydrazide derivatives synthesized from diclofenac. The results concluded that most of the synthesized compounds exhibited stronger α-glucosidase inhibitory effects than standard acarbose (Sardar et al., 2024a). Another investigations identified oxadiazole derivatives starting from ibuprofen and naproxen as potent α-glucosidase inhibitors (Daud et al., 2022; Sardar et al., 2024b). These findings indicate that NSAID-derived compounds have the potential for modulating metabolic processes such as α-glucosidase inhibition.

Herein, a series of NSAID-linked hydrazide derivatives were synthesized, and the structures of all derivatives were confirmed using different techniques, including elemental analysis, ^{1}H-NMR, FTIR and MS techniques. Furthermore, all derivatives were screened for their in vitro α-glucosidase inhibitory activities.

2. Material and Methods

2.1. Chemicals and methods

All the chemicals, such as solvents and reagents were purchased from Sigma/Aldrich and Merck, and were used as such without any purification and distillation. The IR spectra were recorded on a Schimadzu FTIR 8400S spectrometer and the wave numbers were given in cm^{-1}. ^{1}H-NMR spectra were recorded on BRUKER NMR spectrometer and are reported relative to deuterated solvent signals. Elemental analyses were determined by CHNS-932 (LECO) analyzer. Low-resolution mass spectra (LR-MS), which can only separate and detect ions with integer masses and have a resolution of less than 2000, were obtained using the Shimadzu LC-MS/MS-8030 system Shimadzu Corporation, Kyoto, Japan). Thin-layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany).

2.2. Synthetic procedure

2.2.1. Preparation of compounds 2a-d:

In this study, flurbiprofen, diflunisal, etofenamate and naproxen hydrazides **(2a-d)** were prepared using literature methods (Küçükgüzel et al., 2003; Aboul-Fadl et al., 2011; Aydın et al., 2013; Han et al., 2018). 0.01 mol of diflunisal, naproxen or flurbiprofen dissolved in methanol (20 mL) is treated with concentrated sulfuric acid (1 mL) and heated under reflux for 3 hours. After esterification is complete, the reaction mixture is treated with a 5% $NaHCO_3$ solution and washed with water.

The resulting ester compounds **(1a-c)** (0.01 mol) and etofenamate **(1d)** are dissolved in methanol (20 mL). Hydrazine hydrate (4.5 mL) is added, and the mixture is heated under reflux for 2-4 hours, then cooled, and the precipitated solid is washed with water. The product is crystallized from methanol/ethanol.

*2-(6-methoxynaphthalen-2-yl)propanehydrazide **(2a)***

Yield 78%. mp 136-137 °C (lit. 137 °C, Han et al., 2018*)*

*2',4'-difluoro-4-hydroxy[1,1'-biphenyl]-3-carbohydrazide **(2b)***

Yield 90%. mp 199-201°C (lit 200-202 °C, Küçükgüzel et al., 2003*)*

*2-(2-fluoro[1,1'-biphenyl]-4-yl)propanehydrazide **(2c)***

Yield 86%. mp 96-98 °C (lit. 96 °C, Aydın et al., 2013*)*

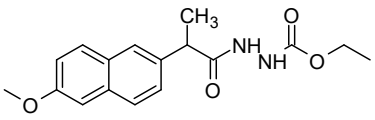
*2-[3-(trifluoromethyl)anilino]benzohydrazide **(2d)***

Yield 76%. mp 134-135 °C (lit. 136-138 °C, Aboul-Fadl et al., 2011*)*

2.2.2. General procedure for synthesis of compounds 3a-d:

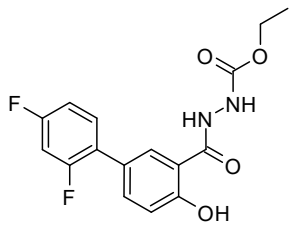
A mixture of acid hydrazide **(2a-d)** (0.002 mol) and ethyl chloroformate (0.002 mol) in toluene in the presence of triethylamine (TEA) was stirred and heated under refluxed for 7-10 h. After cooling and partial evaporation of the solvent, the precipitate obtained was filtered, dried and crystallized from ethanol (Madhavilatha et al., 2018).

Ethyl 2-[2-(6-methoxynaphthalen-2-yl)propanoyl]hydrazine-1-carboxylate (3a)



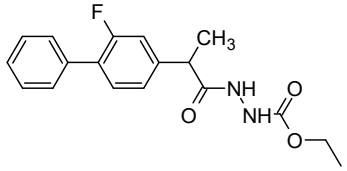
Yield 63 %; m.p. 158-160°C; FT-IR υ_{max} (cm^{-1}): 3285, 3223 (N-H); 1718 (C=O ester); 1676 (C=O amide). ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.17 (t, 3H, CH_2-C**H**$_3$); 1.44 (d, 3H, CH-C**H**$_3$); 3.76 (q, 1H, C**H**-CH_3); 3.86 (s, 3H, OC**H**$_3$); 4.00 (q, 2H, C**H**$_2$-CH_3); 7.13-7.82 (m, 6H, Ar-**H**); 9.01 (s, 1H, N**H**); 9.89 (s, 1H, N**H**). Anal. Calcd for $C_{17}H_{20}N_2O_4$.1/4 C_2H_5OH: C, 64.11; H, 6.61; N, 8.54; Found: C, 64.26; H, 6.28; N, 8.50. LR-MS (ESI) (m/z): calc. for $(M+H)^+$: 317.150, found: 317.30. Calc. for $(M-H)^-$: 315.135, found: 315.25.

Ethyl 2-(2',4'-difluoro-4-hydroxy[1,1'-biphenyl]-3-carbonyl)hydrazine-1-carboxylate (3b)



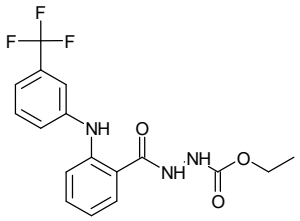
Yield 76 %; m.p. 160-162°C; FT-IR υ_{max} (cm^{-1}): 3333 (O-H); 3173 (N-H); 1697 (C=O ester); 1645 (C=O amide). ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.23 (t, 3H, CH_2-C**H**$_3$); 3.86 (s, 3H, OC**H**$_3$); 4.09 (q, 2H, C**H**$_2$-CH_3); 7.06-8.02 (m, 6H, Ar-**H**); 9.36 (s, 1H, N**H**); 10.49 (s, 1H, N**H**); 12.02 (s, 1H, O**H**). Anal. Calcd for $C_{16}H_{14}F_2N_2O_4$: C, 57.14; H, 4.20; N, 8.33; Found: C, 57.35; H, 4.26; N, 8.03. LR-MS (ESI) (m/z): calc. for $(M+H)^+$: 337.099, found: 337.30. Calc. for $(M-H)^-$: 335.084, found: 335.20.

Ethyl 2-[2-(2-fluoro[1,1'-biphenyl]-4-yl)propanoyl]hydrazine-1-carboxylate (3c)



Yield 69 %; m.p. 196-197°C; FT-IR υ_{max} (cm^{-1}): 3288 (N-H); 1716 (C=O ester); 1676 (C=O amide). ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.17 (t, 3H, CH_2-C**H**$_3$); 1.38 (d, 3H, CH-C**H**$_3$); 3.70 (q, 1H, C**H**-CH_3); 4.04 (q, 2H, C**H**$_2$-CH_3); 7.24-7.55 (m, 8H, Ar-**H**); 9.05 (s, 1H, N**H**); 9.93 (s, 1H, N**H**). Anal. Calcd for $C_{18}H_{22}FN_2O_3$.1/2 H_2O: C, 63.71; H, 5.94; N, 8.25; Found: C, 63.52; H, 6.00; N, 8.20. LR-MS (ESI) (m/z): calc. for $(M+H)^+$: 331.145, found: 331.30. Calc. for $(M-H)^-$: 329.130, found: 329.30.

Ethyl 2-{3-[3-(trifluoromethyl)anilino]benzoyl}hydrazine-1-carboxylate (3d)



Yield 77 %; m.p. 172-173°C; FT-IR υ_{max} (cm^{-1}): 3338, 3230 (N-H); 1728 (C=O ester); 1645 (C=O amide). ^{1}H-NMR (300 MHz), (DMSO-d_6/TMS) δ ppm: 1.22 (t, 3H, CH_2-C**H$_3$**); 4.08 (q, 2H, C**H$_2$**-CH_3); 7.00-7.69 (m, 8H, Ar-**H**); 9.25 (s, 1H, N**H**); 9.39 (s, 1H, N**H**); 10.37 (s, 1H, N**H**). Anal. Calcd for $C_{17}H_{16}F_3N_3O_3$: C, 55.59; H, 4.39; N, 11.44; Found: C, 55.32; H, 4.39; N, 11.42. LR-MS (ESI) (m/z): calc. for $(M+H)^+$: 368.121, found: 368.30. Calc. for $(M-H)^-$: 366.106, found: 366.25.

2.3. Biological evaluation

2.3.1. α-Glucosidase inhibition assay

The method for assessing antidiabetic activity described by Ramakrishna et al. was modified and implemented with slight alterations (Ramakrishna et al., 2017; Şen et al., 2019). A 10 µl sample (ranging from 250 to 0.49 µg mL^{-1}) was mixed with 40 µL of 0.1 M sodium phosphate buffer (pH 6.9) and 100 µl of α-glucosidase enzyme (obtained from Saccharomyces cerevisiae, 1 U/mL) prepared in the same buffer. The mixtures were incubated at 25°C for 10 minutes. Subsequently, 50 µl of 5 mM p-nitrophenyl-α-D-glucopyranoside (pNPG) prepared in the buffer. The mixtures were then incubated at 25°C for an additional 5 minutes, and absorbance changes at 405 nm were measured before and after incubation using a microplate reader. Acarbose (135-16.88 µg mL^{-1}) was used as the standard. The percentage inhibition of enzyme activity by the samples was calculated using the following formula:
Percentage inhibition of α-glucosidase enzyme (%): $(A_{control}-A_{sample})/A_{control}\times100$

- $A_{control}$, represents the absorbance of the control containing all components except the sample (replaced with DMSO).
- A_{sample}, represents the absorbance of the sample containing all components.

The inhibition concentration of the samples that reduced 50% of the α-glucosidase enzyme activity (IC_{50}) was determined by plotting the inhibition graph against the concentrations of the samples using GraphPad Prism 5 software. Measurements were repeated four times.

2.4. Statistical analysis

Statistical analysis was conducted using GraphPad Prism 5.0 software. Data are presented as mean ± standard deviation. Statistical comparisons were determined using one-way ANOVA followed by Tukey's multiple comparison test. A p-value of <0.05 was considered statistically significant.

3. Results and Discussion

3.1. Chemistry

In this present work, new NSAID hydrazide derivatives **(3a-d)** were synthesized. The synthetic route for the preparation of compounds **3a-d** is outlined in Figure 2. First, compounds **2a-c** were obtained from naproxen, diflunisal, and flurbiprofen upon treatment with methanol in the presence of sulfuric acid. The NSAID hydrazides were obtained from the condensation of **2a-c** and etofenamate **(1d)** with hydrazine hydrate. In order to prepare the target compounds, ethyl chloroformate and NSAID hydrazides were heated with toluene in the presence of TEA. Among the newly synthesized compounds **(3a-d)**, compound **3a** has got only a CAS number (CAS No: 1389160-65-9) with no spectroscopic and synthesis data in Scifinder database. So, all of the synthesized compounds were checked for purity using

elemental microanalysis and melting points and fully characterized by their spectral data for the first time.

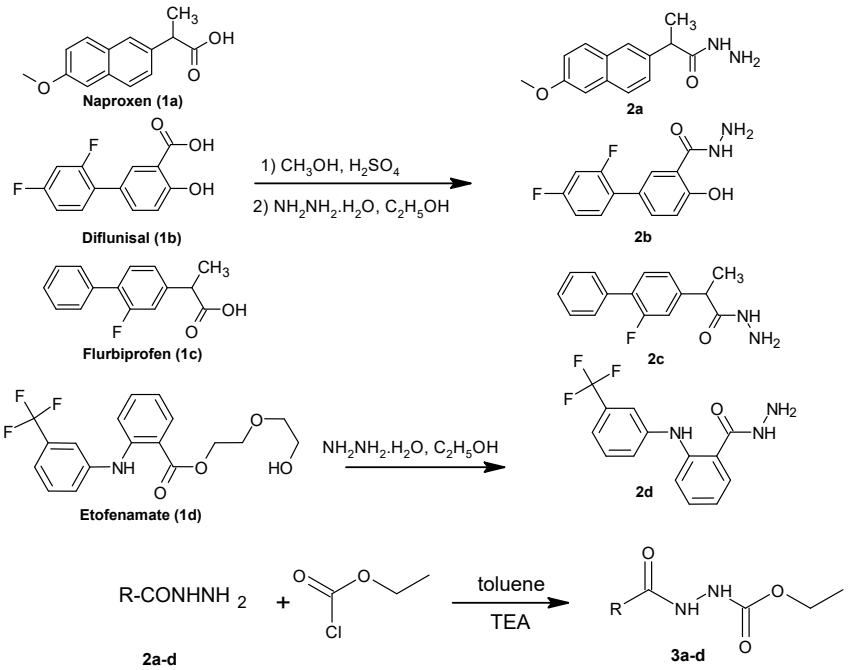


Figure 2. Synthesis of compounds **3a-d.**

The structures of the synthesized compounds were elucidated by spectral methods (IR, ^{1}H-NMR and mass spectra) and confirmed by elemental analysis. In the IR spectra, characteristic C=O ester stretching bonds (1697-1728 cm^{-1}) were observed, which are supported by the literature (Roller et al., 2005). In the ^{1}H-NMR spectra, the signal of the -O-C**H$_2$**-CH$_3$ protons of the carboxylate moiety observed 1.17-1.23 ppm as quartets, while the signals of the -O-CH$_2$-C**H$_3$** protons were at 4.00-4.09 ppm as triplets (Thakkalapally & Benin, 2005; Das et al., 2024). The mass spectra of the compounds were recorded via the electrospray ionisation technique and $(M+H)^+$ and $(M-H)^-$ seen in the spectra of all compounds. Elemental analysis results were within ±0.4 of the theoretical values for all compounds.

3.2. Biological Activity

3.2.1. α-Glucosidase enzyme inhibition results

In one of our recent studies, the alpha glucosidase inhibitory effect of hydrazide derivatives was investigated and effective compounds were found (Şenkardeş et al., 2022). In this study, compounds **3a-d** were synthesized to evaluate their potency as α-glucosidase inhibitors. The results are detailed in Table 1, highlighting IC$_{50}$ values in comparison with acarbose, which was used as the positive control.

Table 1. α-Glucosidase inhibition potential of **3a-d** (IC$_{50}$, µg mL^{-1})

Compound	IC$_{50}$ *
3a	648.10±3.47^{d}
3b	218.50±1.84^{b}
3c	237.40±3.32^{c}
3d	188.30±0.14^{a}
Acarbose	190.70±2.05^{a}

*Values in the table are expressed as mean ± SD (n = 4). Different letters (superscript) in the same row indicate significant differences between values ($p < 0.05$).

Because of the lower IC_{50} (the concentration of the sample required to inhibit 50% of enzyme activity) indicates higher activity, Table 1 shows that among the samples, compound **3d**, the derivative of etofenamate, exhibited the highest α-glucosidase inhibitory activity, followed sequentially by **3b**, **3c**, and **3d** ($p<0.05$).

The weak inhibitory effect of compound **3a** may be due to the absence of electron-withdrawing groups (F and –NH) found in compounds **3b-d**. The -F and -NH atoms found in compounds **3b-d** provide electron flow, making them more effective and polarizable. As seen in the literature (Sardar et al., 2024b), the reason for the compound **3d** exhibiting the strongest activity may be due to the strong hydrogen bonding interaction between the NH atom and the active residues of the enzyme.

Nawaz et al. (2022) found that several analogues with fluorine atoms attached to the benzene rings exhibited significant α-glucosidase inhibition. They also highlighted that the presence of the fluorine group plays a key role in enhancing the activity of these compounds. This may be the reason why the naproxen derived compound **(3a)** showed the lowest inhibition.

When comparing these results with similar studies examining the glucosidase activities of derivatives synthesized from flurbiprofen and naproxen (Alam et al., 2022; Rane et al., 2025), it is found that our compounds **(3a-c)** exhibit lower inhibitory activity. Furthermore, no literature reports have been found regarding the glucosidase activity of diflunisal and etofenamate derivatives.

4. Conclusion

Novel hydrazide derivatives linked to different NSAIDs were synthesized, and characterized via spectroscopic techniques. All compounds were evaluated for their α-glucosidase inhibitory potential. The synthesized derivatives exhibited a range of inhibitory activities when tested for glucosidase inhibition, using acarbose as the standard (IC_{50}=190.70±2.05 μg mL^{-1}). Biological activity results revealed that ethyl 2-{3-[3-(trifluoromethyl)anilino]benzoyl}hydrazine-1-carboxylate **(3d)** as the most potent derivative exhibited better potency (IC_{50}=188.30±0.14 μg mL^{-1}) than the clinically used drug, acarbose. This research could provide insights into the development of new therapeutic agents for conditions such as diabetes, where regulating glucosidase activity is essential for controlling blood sugar levels. Furthermore, our future goal is to perform molecular docking studies and make the necessary modifications to these compounds for improved efficacy, as well as to gather information on their stability.

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References

Aboul-Fadl, T., Abdel-Aziz, H. A., Kadi, A., Bari, A., Ahmad, P., Al-Samani, T., & Ng, S.W. (2011). Microwave-assisted one-step synthesis of fenamic acid hydrazides from the corresponding acids. *Molecules*, *16*(5), 3544-3551. https://doi.org/10.3390/molecules16053544

Alam, A., Ali, M., Rehman, N. U., Ullah, S., Halim, S. A., Latif, A., Zainab, Khan, A., Ullah, O., Ahmad, S., Al-Harrasi, A., & Ahmad, M. (2022). Bio-oriented synthesis of novel (S)-flurbiprofen clubbed hydrazone schiff's bases for diabetic management: In vitro and in silico studies. *Pharmaceuticals*, *15*(6), 672. https://doi.org/10.3390/ph15060672

Antar, S. A., Ashour, N. A., Sharaky, M., Khattab, M., Ashour, N. A., Zaid, R. T., Roh, E. J., Elkamhawy, A., & Al-Karmalawy, A. A. (2023). Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. *Biomedicine & Pharmacotherapy*, *168*, 115734. https://doi.org/10.1016/j.biopha.2023.115734

Aydın, S., Kaushik-Basu, N., Arora, P., Basu, A., Nichols, D., Talele, T. T., Akkurt, M., Çelik, İ., Büyükgüngör, O., & Küçükgüzel, Ş. G. (2013). Microwave assisted synthesis of some novel

Flurbiprofen hydrazidehydrazones as anti-HCV NS5B and anticancer agents. *Marmara Pharmaceutical Journal*, *17*(1), 26-34.

Aydın, S., Kaushik-Basu, N., Özbaş-Turan, S., Akbuğa, J., Tiber, P. M., Orun, O., Gurukumar, K. R., Basu, A., & Küçükgüzel, Ş. G. (2014). Synthesis of 1-aroyl-3 , 5-dimethyl-1H-pyrazoles as Anti-HCV and Anticancer Agents. *Letters in Drug Design & Discovery*, *11*(2), 121-131. https://doi.org/10.2174/15701808113109990069

Dabhi, A. S., Bhatt, N. R., & Shah, M. J. (2013). Voglibose: an alpha glucosidase inhibitor. *Journal of Clinical and Diagnostic Research : JCDR*, *7*(12), 3023-3027. https://doi.org/10.7860/JCDR/2013/6373.3838

Das, A. K., Biswas, S., Pal, A., Manna, S. S., Sardar, A., Mondal, P. K., Sahoo, B., Pathak, B., & Mandal, S. (2024). A thiolated copper-hydride nanocluster with chloride bridging as a catalyst for carbonylative C–N coupling of aryl amines under mild conditions: a combined experimental and theoretical study. *Nanoscale*, *16*, 3583-3590. https://doi.org/10.1039/D3NR05912J

Daud, S., Abid, O. R., Sardar, A., Shah, B. A., Rafiq, M., Wadood, A., Ghufran, M., Rehman, W., Wahab, Z., Iftikhar F., Sultana, R., Daud, H., & Niaz, B. (2022). Design, synthesis, in vitro evaluation, and docking studies on ibuprofen derived 1,3,4-oxadiazole derivatives as dual α-glucosidase and urease inhibitors. *Medicinal Chemistry Research*, *31*(2), 316-336. https://doi.org/10.1007/s00044-021-02814-6

Daud, S., Abid, O. R, Rehman, W., Sardar, A., Alanazi, M. M., Rasheed, L., Ejaz, S. A., Fayyaz, A., Shah, B.A., & Maalik, A. (2024). Exploring the potential of new mefenamic acid derivatives as α-glucosidase inhibitors: Structure-activity relationship, in-vitro and in-silico studies. *Journal of Molecular Structure*, *1316*, 138812. https://doi.org/10.1016/j.molstruc.2024.138812

Dirir, A. M., Daou, M., Yousef, A. F., & Yousef, L. F. (2022). A review of alpha-glucosidase inhibitors from plants as potential candidates for the treatment of type-2 diabetes. *Phytochemistry Reviews : Proceedings of the Phytochemical Society of Europe*, *21*(4), 1049-1079. https://doi.org/10.1007/s11101-021-09773-1

Fowler, M. J. (2008). Microvascular and macrovascular complications of diabetes. *Clinical Diabetes*, *26*(2), 77-82. https://doi.org/10.2337/diaclin.26.2.77

Gao, X., Cai, X., Yang, W., Chen, Y., Han, X., & Ji, L. (2018). Meta-analysis and critical review on the efficacy and safety of alpha-glucosidase inhibitors in Asian and non-Asian populations. *Journal of Diabetes Investigation*, *9*(2), 321-331. https://doi.org/10.1111/jdi.12711

Han, M. İ., Bekçi, H., Cumaoğlu, A., & Küçükgüzel, S. (2018). Synthesis and characterization of 1, 2, 4-triazole containing hydrazide-hydrazones derived from (S)-Naproxen as anticancer agents. *Journal of Research in Pharmacy*, *22*(4), 559-569. https://doi.org/10.12991/jrp.2018.98

Kausar, N., Ullah, S., Khan, M. A., Zafar, H., Wahab., A., Choudhary., M. I., & Yousuf, S. (2021) Celebrex derivatives: Synthesis, α-glucosidase inhibition, crystal structures and molecular docking studies. *Bioorganic Chemistry*, *106*, 104499. https://doi.org/10.1016/j.bioorg.2020.104499

Koç, H. C., Atlihan, İ., Mega-Tiber, P., Orun, O., & Küçükgüzel, G. (2022). Synthesis of some novel hydrazide-hydrazones derived from etodolac as potential anti-prostate cancer agents. *Journal of Research in Pharmacy*, *26*(1), 1-12. https://doi.org/10.29228/jrp.97

Küçükgüzel, S. G., Mazi, A., Sahin, F., Oztürk, S., & Stables, J. (2003). Synthesis and biological activities of diflunisal hydrazide-hydrazones. *European Journal of Medicinal Chemistry*, *38*(11-12), 1005-1013. https://doi.org/10.1016/j.ejmech.2003.08.004

Madhavilatha, B., Bhattacharjee, D., Sabitha, G., Reddy, B. V. S., Yadav, J. S., Jain, N., & Reddy, B. J. M. (2018). Synthesis and in vitro anticancer activity of novel 1,3,4-oxadiazole-linked 1,2,3-triazole/isoxazole hybrids. *Journal of Heterocyclic Chemistry*, *55*(4), 863-870. https://doi.org/10.1002/jhet.3110

Nawaz, M., Taha, M., Qureshi, F., Ullah, N., Selvaraj, M., Shahzad, S., Chigurupati, S., Abubshait, S. A., Ahmad, T., Chinnam, S., & Hisaindee, S. (2022). Synthesis, α-amylase and α-glucosidase inhibition and molecular docking studies of indazole derivatives. *Journal of Biomolecular Structure and Dynamics*, *40*(21), 10730-10740. https://doi.org/10.1080/07391102.2021.1947892

Ramakrishna, R., Sarkar, D., Schwarz, P., & Shetty, K. (2017). Phenolic linked anti-hyperglycemic bioactives of barley (Hordeum vulgare L.) cultivars as nutraceuticals targeting type 2 diabetes.

Industrial Crops and Products, *107*, 509-517. https://doi.org/10.1016/j.indcrop.2017.03.033

Rao, P. P. N., Kabir, S. N., & Mohamed, T. (2010). Nonsteroidal anti-inflammatory drugs (NSAIDS): progress in small molecule drug development. *Pharmaceuticals*, *3*(5), 1530-1549. https://doi.org/10.3390/ph3051530

Rane, R., Satpute, B., Patil, R., Kumar, D., Suryawanshi, M., Patil, T., Pawar, A., Gawade, B. & Sakat, S. (2025). Synthesis and molecular docking of novel biguanide-NSAIDs hybrid with dual anti-diabetic and anti-inflammatory activity. *Journal of Molecular Structure*, *1320*, 139512. https://doi.org/10.1016/j.molstruc.2024.139512

Roller, S., Zhou, H., & Haag, R. (2005). High-loading polyglycerol supported reagents for Mitsunobu- and acylation-reactions and other useful polyglycerol derivatives. *Molecular Diversity*, *9*, 305-316. https://doi.org/10.1007/s11030-005-8117-y

Sardar, A., Abid, O. R., Khan, S., Hussain, R., Daud, S., Rehman, W., Aziz, T., Shah, B. A., Alharbi, M., & Alasmari, A. F. (2024a). Identification of in vitro α-glucosidase and urease inhibitory effect, and in silico studies of Naproxen-derived 1,3,4-oxadiazole-based Schiff-base derivatives. *Journal of Molecular Structure*, *1305*, 137712. https://doi.org/10.1016/j.molstruc.2024.137712

Sardar, A., Abid, O. R., Rehman, W., Rasheed, L., Alanazi, M. M., Daud, S., Rafiq, M., Wadood, A., & Shakeel, M. (2024b). Synthesis and biological evaluation of diclofenac acid derivatives as potential lipoxygenase and α-glucosidase inhibitors. *Royal Society Open Science*, *11*(11), 240543. https://doi.org/10.1098/rsos.240543

Scott, L. J., & Spencer, C. M. (2000). Miglitol. *Drugs*, *59*(3), 521-549. https://doi.org/10.2165/00003495-200059030-00012

Şen, A., Kurkcuoglu, M., Senkardes, I., Bitis, L., & Baser, K. H. C. (2019). Chemical composition, antidiabetic, anti-inflammatory and antioxidant activity of ınula ensifolia l. essential oil. *Journal of Essential Oil Bearing Plants*, *22*(4), 1048-1057. https://doi.org/10.1080/0972060X.2019.1662333

Şenkardes, S., Özakpinar, Ö. B., Özsavci, D., Sener, A., Çevik, Ö., & Küçükgüzel, S. (2016). Synthesis of diflunisal thiazolidinones as anticancer agents. *Anti-Cancer Agents in Medicinal Chemistry*, *16*(10), 1266-1274. https://doi.org/10.2174/1871520615666150831125337

Şenkardeş, S., Kulabaş, N., & Küçükgüzel, Ş. G. (2022). Synthesis, molecular docking studies and ADME prediction of some new albendazole derivatives as α-glucosidase inhibitors. *Acta Chimica Slovenica*, *69*(3), 526-535. https://doi.org/10.17344/acsi.2022.7387

Thakkalapally, A., & Benin, V. (2005). Synthesis, structural studies and desilylation reactions of some N-2-(trimethylsilyl)ethyl-N-nitrosocarbamates. *Tetrahedron*, *61*, 4939-4948. https://doi.org/10.1016/j.tet.2005.03.044

Tripathi, B. K., & Srivastava, A. K. (2006). Diabetes mellitus: complications and therapeutics. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *12*(7), RA130-47.

Zheng, Y., Ley, S. H., & Hu, F. B. (2018). Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nature Reviews Endocrinology*, *14*(2), 88-98. https://doi.org/10.1038/nrendo.2017.151