ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

Molecular Modeling and Synthesis of Indoline-2,3-dione-Based Benzene Sulfonamide Derivatives and Their Inhibitory Activity against α-Glucosidase and α-Amylase Enzymes

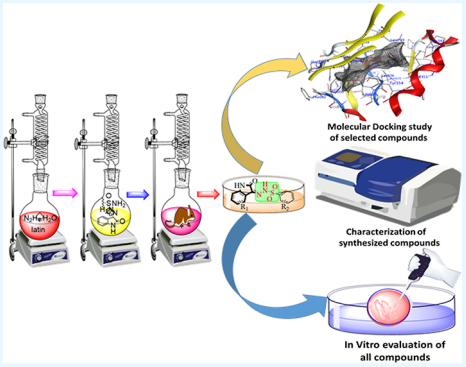
Liaqat Rasheed, Wajid Rehman,* Fazal Rahim, Zahid Ali, Ashwag S. Alanazi, Rafaqat Hussain, Imran Khan, Mohammed M. Alanazi, Muhammad Naseer, Magda H. Abdellattif, Riaz Hussain, Shoaib Khan, Muhammad Taha, and Syed Adnan Ali Shah

Cite This: *ACS Omega* 2023, 8, 15660−15672

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Diabetes is also known as a critical and noisy disease. Hyperglycemia, that is, increased blood glucose level is a common effect of uncontrolled diabetes, and over a period of time can cause serious effects on health such as blood vessel damage and nervous system damage. However, many attempts have been made to find suitable and beneficial solutions to overcome diabetes. Considering this fact, we synthesized a novel series of indoline-2,3-dione-based benzene sulfonamide derivatives and evaluated them against α-glucosidase and α-amylase enzymes. Out of the synthesized sixteen compounds (**1**−**16**), only three compounds showed better results; the IC_{50} value was in the range of 12.70 ± 0.20 to 0.90 ± 0.10 μM for α-glucosidase against acarbose 11.50 ± 0.30 μM and 14.90 ± 0.20 to 1.10 ± 0.10 μM for α-amylase against acarbose 12.20 ± 0.30 μM. Among the series, only three compounds showed better inhibitory potential such as analogues **11** (0.90 ± 0.10 μM for α-glucosidase and 1.10 ± 0.10 μM for α-amylase), **1** (1.10 ± 0.10 μM for α-glucosidase and 1.30 ± 0.10 μM for α-amylase), and **6** (1.20 ± 0.10 μM for α-glucosidase and 1.60 ± 0.10 μM for α-amylase). Molecular modeling was performed to determine the binding affinity of active interacting residues against these enzymes, and it was found that benzenesulfonohydrazide derivatives can be indexed as suitable inhibitors for diabetes mellitus.



1. INTRODUCTION

The use of isatin was found to be extensive in drug discovery. Various naturally occurring compounds contain an isatin structure, which is also used to synthesize a different biologically active heterocycle. Isatin contains a five-membered −N-containing ring and a benzene ring. Literature shows isatin has numerous biological activities such as anticancer,[1] antidepressant, antibiotic,[2] sedative, anticonvulsant, anxiogenic,[3] antifungal, antidiabetic, antibacterial,[4] etc. Diabetes is also known as a chronic epidemic disorder that plagues the world. As of 2019, approximately 463 million people of the world were diabetic. Moreover, it is predicted that the number of diabetic patients would increase by approximately up to 700 million by 2045.[5] Increased glucose level occurs in the blood due to diabetes, which can lead to serious side effects such as coronary heart disease, stroke, liver damage, nephropathy, retinopathy, and peripheral nephropathy over time.[6] Furthermore, both the oral cavity and small intestine contain a variety of digestive enzymes that are involved in starch hydrolysis.[7,8] Among them, α-glucosidase is synthesized through a fast and efficient method,[9−11] as well as α-amylase plays a crucial role in regulating the postprandial glucose concentration,[12] so they are considered necessary enzymes for the digestion of starch and glycogen, respectively. Inhibiting either α-glucosidase or α-amylase is therefore a successful strategy to reduce postprandial hyperglycemia. While the inhibition profile of these enzymes prevents the transformation of carbohydrates in the circulatory system, lowering the high glucose level in the blood after a meal that contains both simple and complex carbohydrates may therefore be a key strategy in the treatment of type 2 diabetes.[13]

Various drugs such as miglitol, voglibose, and acarbose are used to treat type 2 diabetes. These are responsible for controlling α-amylase and α-glucosidase enzymes. Their use has been constrained, however, by the unpleasant side effects and high price.[14] About 5% of the world's population has diabetes, making it difficult for medical professionals to manage it without side effects. As a result, the importance of research into these agents has increased, and scientists are now

Received: February 22, 2023
Accepted: April 7, 2023
Published: April 19, 2023

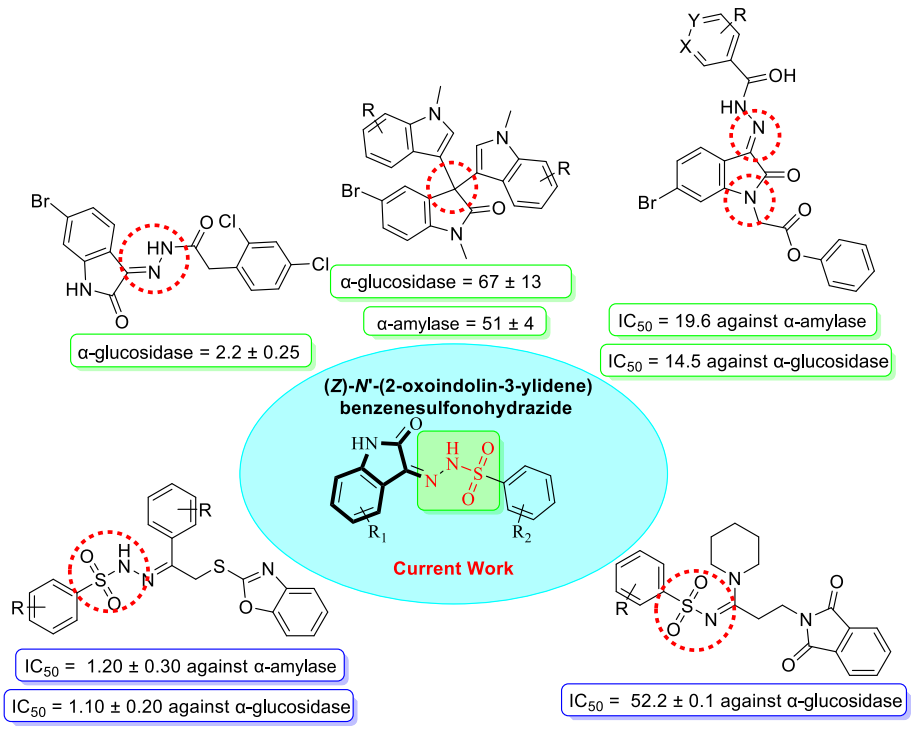
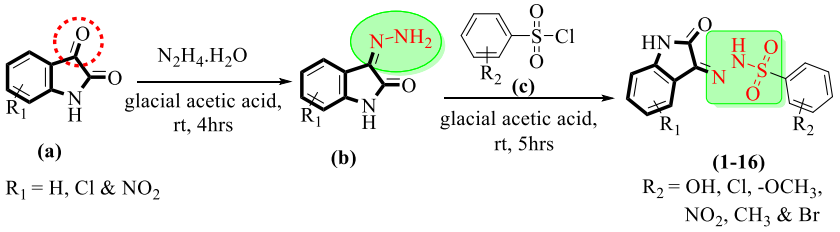


Figure 1. Rationale of the current work.

Scheme 1. Synthesis of Indoline-2,3-dione-Based Benzene Sulfonamide Derivatives



competing to develop fresh, potent, and secure therapeutic agents for the treatment of diabetes.[15−17]

Our research group continuously synthesized bioactive compounds through adopting biocompatible methodologies, such as isatin[18−20] and sulfonamide[21,22] (Figure 1); herein, we report the synthesis of (*Z*)-3,5-dichloro-*N*′-(5-chloro-2-oxoindolin-3-ylidene)-2-hydroxybenzenesulfonohydrazide moieties. Furthermore, all of the synthesized hybrid analogues are assessed against α-amylase and α-glucosidase enzymes.

2. RESULTS AND DISCUSSION

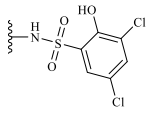
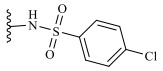
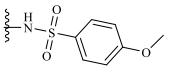
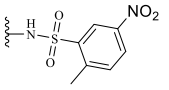
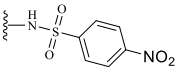
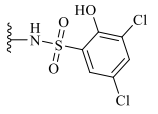
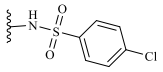
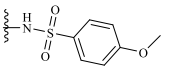
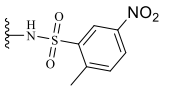
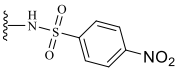
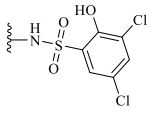
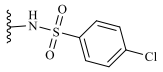
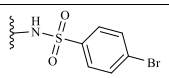
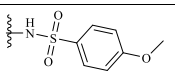
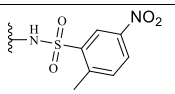
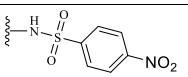
2.1. Chemistry. Indoline-2,3-dione-based substituted benzene sulfonamide scaffolds were prepared (**1**−**16**) by treating substituted indoline-2,3-dione (0.02 mmol) (a) with the hydrazine hydrate (0.02 mmol) in the presence of glacial CH_3COOH to reflux for 4 h to synthesize substituted 3-hydrazonoindolin-2-one as the intermediate product (b). Furthermore, the intermediate (b) (0.02 mmol) was treated with the substituted benzene sulfonyl chloride (c) and refluxed for 5 h under a catalytic amount of CH_3COOH to yield the substituted isatin-based substituted benzene sulfonamide derivatives (**1**−**16**) Scheme 1.

3. BIOLOGICAL ACTIVITY

3.1. In Vitro α-Glucosidase and α-Amylase Activity (1−16). The biological profile of isatin showed different biological significances when tested with α-glucosidase and α-amylase enzymes and their inhibition profiles (Table 1). The comparison criteria for the same substituted compound and their SAR values were found in varied ranges due to the presence of different substituents at the varied position of the isatin moiety and the aromatic ring linked to the sulfonamide group. In this regard, the nitro-substituted isatin moiety is compared with each other bearing another nitro group at the aromatic ring of the sulfonamide moiety. In addition, the difference in their IC_{50} value is the factor behind the shifting of the value due to the presence of different functional groups at the varied position. They may be electron-withdrawing or -donating groups; thus, the changes occurred with a substituent, number/s, as well as their position on the aromatic ring. Nitro-substituted compounds (**4**, **5**, **9**, **10**, **15**, and **16**) displayed a varied range of α-glucosidase inhibitory profiles with IC_{50} values of 12.60 ± 0.30, 12.40 ± 0.10, 12.10 ± 0.30, 12.70 ± 0.20, 13.70 ± 0.20, and 11.40 ± 0.20 μM respectively, as well as these compounds showed α-amylase inhibitory activity with IC_{50} values of 13.30 ± 0.30, 13.20 ± 0.20, 13.20 ± 0.30, 13.20 ± 0.20, 14.90 ± 0.20, and 12.30 ± 20 μM, respectively. Both he nitro substituent, the electron-with-

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

Table 1. α-Glucosidase and α-Amylase Inhibitory Potentials and Solubility of Synthesized Isatin-Based Benzene Sulfonamide Analogues (1−16)

S. NO.	Structure	IC_{50} ± SEM[a] *Alpha*-glucosidase [μM]	IC_{50} ± SEM[a] *Alpha*-amylase [μM]	Solubility
1		1.10 ± 0.10	1.30 ± 0.10	DMSO
2		3.20 ± 0.10	4.10 ± 0.10	DMSO
3		7.30 ± 0.20	8.20 ± 0.20	DMSO
4		12.60 ± 0.30	13.30 ± 0.30	DMSO
5		12.40 ± 0.10	13.20 ± 0.20	DMSO
6		1.20 ± 0.10	1.60 ± 0.10	DMSO
7		3.30 ± 0.10	3.70 ± 0.10	DMSO
8		11.20 ± 0.10	11.60 ± 0.10	DMSO
9		12.10 ± 0.30	13.20 ± 0.30	DMSO
10		12.70 ± 0.20	13.20 ± 0.20	DMSO
11		0.90 ± 0.10	1.10 ± 0.10	DMSO
12		2.50 ± 0.10	3.10 ± 0.10	DMSO
13		12.30 ± 0.30	12.80 ± 0.30	DMSO
14		12.10 ± 0.20	13.10 ± 0.20	DMSO
15		13.70 ± 0.20	14.90 ± 0.20	DMSO
16		11.40 ± 0.20	12.30 ± 20	DMSO
Standard Acarbose		11.50 ± 0.30	12.20 ± 0.30	---

drawing group, and the aromatic moiety in isatin displayed good to poor activity as acarbose against α-glucosidase and α-amylase activity (0.45 ± 0.02 and 0.34 ± 0.02 respectively), but it is not found to be a potent molecule. The nitro group

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

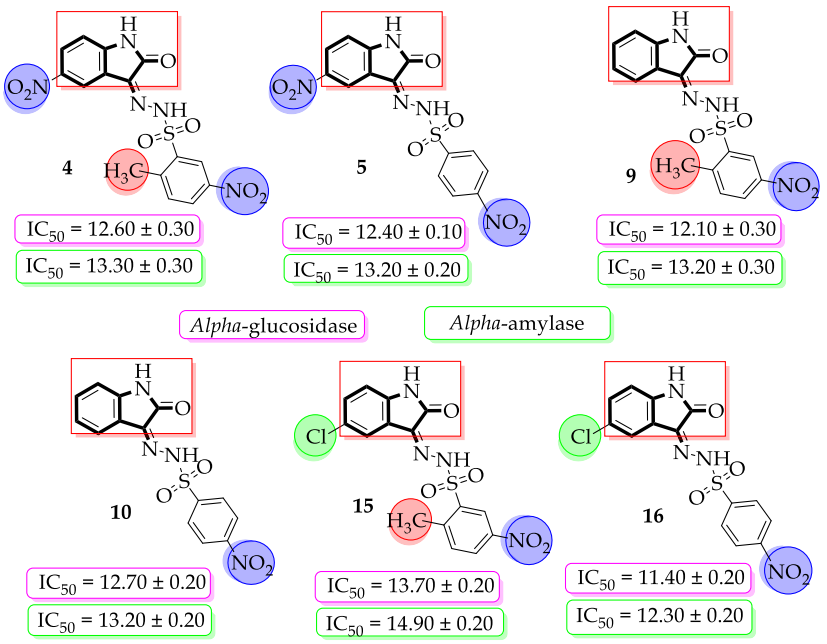


Figure 2. SAR study of analogues **4**, **5**, **9**, **10**, **15**, and **16**.

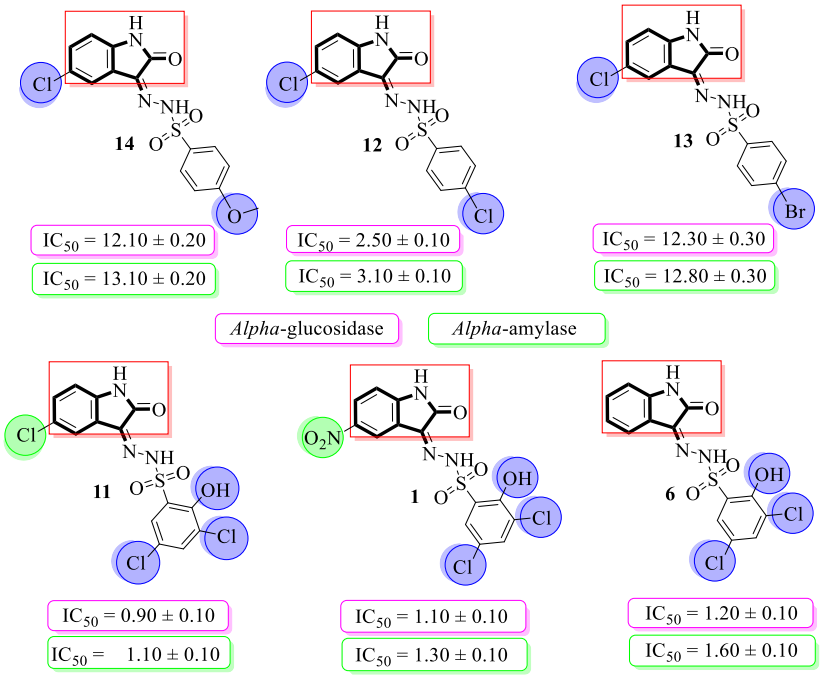


Figure 3. SAR profiles of compounds **1**, **6**, **11**, **12**, **13**, and **14**.

deactivates the ring for further substitutions; therefore, the interactions of the molecule with the active site of the enzyme are reduced. The reduction in the inhibitory property of the molecule is also related to the position of the substituent; therefore, the activity of nitro-substituted molecules also varied in the inhibitory profile. Steric hindrance is the factor related to the electron-withdrawing group, which reduces the interactions toward the targeted enzyme. Finally, the result was found from this comparison that the nitro-bearing electron-withdrawing group decreased the activity due to the nature, number/s, and position of substituents at isatin and aromatic moieties. The poor interaction shown by the above-mentioned compounds was only due to the presence of the nitro group, which clearly reduced the interactions of the molecule up to some extent when compared with standard acarbose drug (Figure 2).

Through SAR study, it was suggested that the core skeleton of isatin-based sulfonamide was known to have promising activity against α-glucosidase and α-amylase enzymes. However, this core skeleton based on isatin-bearing sulfonamide showed interesting α-glucosidase and α-amylase profiles on the attachment of either the electron-withdrawing group around isatin and Ph-ring of the sulfonamide moiety or electron-donating group that makes the Ph-ring or isatin either a more electron-deficient or electron-rich center, which becomes more susceptible for interactions with α-glucosidase and α-amylase through various types of bonding and hence

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

Table 2. Interacting Residues of Benzenesulfonohydrazide Derivatives with α-Amylase PDB = 2BFH

Cpd	ligand interaction	receptor	interactions	distance (Å)	E (K cal/mol)
1	N 1	O LEU 12 (A)	H-donor	2.75	−3.0
	C 24	OG1 THR 21 (A)	H-donor	3.38	−0.5
	O 29	O ALA 30 (A)	H-donor	2.51	−2.7
	O 28	N ILE 28 (A)	H-acceptor	2.77	−3.2
	O 28	N ALA 30 (A)	H-acceptor	3.17	−2.1
6	N 1	O TYR 7 (A)	H-donor	2.81	−3.8
	O 29	OE1 GLN 13 (A)	H-donor	2.68	−4.2
	N 18	CA CYS 1 (A)	H-acceptor	3.26	−1.4
	N 18	N ALA 2 (A)	H-acceptor	2.98	−0.5
	O 28	CA CYS 1 (A)	H-acceptor	2.92	−0.7
11	O 27	NE2 GLN 3 (A)	H-acceptor	2.94	−2.4
	O 28	OH TYR 18 (A)	H-acceptor	2.85	−1.3
acarbose	O 12	O LEU 12 (A)	H-donor	2.68	−0.9
	O 14	O VAL 10 (A)	H-donor	2.74	−2.0
	O 16	O SER 9 (A)	H-donor	2.70	−2.3
	O 21	O TYR 18 (A)	H-donor	2.81	−1.6
	O 38	O HIS 19 (A)	H-donor	2.77	−2.0
	O 40	OE1 GLU 6 (A)	H-donor	2.68	−3.0
	O 59	O ALA 2 (A)	H-donor	2.88	−0.6
	O 59	SG CYS 14 (A)	H-donor	3.42	−0.5
	O 82	O LEU 12 (A)	H-donor	2.70	−1.1
	O 16	N LEU 12 (A)	H-acceptor	2.81	−2.4
	O 21	N CYS 14 (A)	H-acceptor	3.10	−2.2
	O 59	N ALA 2 (A)	H-acceptor	3.01	−2.4
	O 75	N CYS 1 (A)	H-acceptor	2.84	−6.3
	O 80	CA CYS 1 (A)	H-acceptor	2.99	−0.7

Table 3. Docking Score and Energy of Benzenesulfonohydrazide Derivatives with α-Amylase PDB = 2BFH

Cpd	S	RMSD_refine	E-conf	E-place	E-scorel	E-refine	E-score2
1	−5.3682	2.4699	110.8853	−37.619	−9.3788	−27.7250	−5.3682
6	−5.0202	1.5207	78.1380	−56.7132	−9.6889	−25.1460	−5.0202
11	−5.4659	1.9785	79.7430	−56.6826	−9.6461	−26.3125	−5.4659
acarbose	−6.4340	2.3285	252.1367	−92.8034	−11.4467	−35.3851	−6.4340

plays a vital role in inhibiting α-glucosidase and α-amylase enzyme; therefore, alteration in the nature or number/s and position of substituents of either the strong electron-withdrawing group or electron-donating group nature has a significant effect on the inhibition profile of isatin-based sulfonamide analogues. The analogue **11** bearing the chloro moiety of less electron-withdrawing nature on either end of isatin and a Ph-ring of sulfonamide was found to show interesting α-glucosidase and α-amylase inhibitory potential. This interesting inhibition profile shown by analogue **11** was due to the attachment of the dichloro group in the meta-position of the Ph-ring and the OH group in the ortho-position of sulfonamide, as well as isatin holds this −Cl moiety in their skeleton that makes up the Ph-ring and isatin electron-deficient center, so these −Cl groups on both sides of analogue **11** seemed to play a key role in interaction with α-glucosidase and α-amylase enzymes and showed excellent activity. Furthermore, the inhibition potential of analogues **1** and **6** dropped down rapidly upon replacing the −Cl and NO_2 moiety present on the isatin ring. These analogues **1** and **6** differ from analogue **11** only in the nature of substituents (−Cl & NO_2) around the isatin ring. The decline in activity was shown by analogue **1** bearing the $-NO_2$ moiety and **6** having no substitution on the isatin ring, which was shown to display poor interaction with α-glucosidase and α-amylase enzyme and hence showed less activity than **11**. However, the activity of analogue **11** was enhanced by replacing the $-NO_2$ moiety of isatin with less EWG nature, such as the −Cl group as in analogues **1** and **6** that bear nitro-substituted and unsubstituted isatin along with the di-Cl- and OH moiety-substituted Ph-ring of sulfonamide.

Interestingly, the inhibition potential against α-glucosidase and α-amylase was enhanced significantly by the addition of a moiety with less EWG nature and more EDG nature as well as having the tendency of the formation of H-bonding with the active site of α-glucosidase and α-amylase. Analogue **11** was found to be a more potent inhibitor of α-glucosidase and α-amylase among the current synthesized series. This analogue bears two −Cl groups and one −OH group on the Ph-ring of sulfonamide along with chloro-substituted isatin. These moieties, such as −OH and −Cl, strongly attract electronic density toward itself and make the isatin-sulfonamide skeleton more susceptible to interaction with α-glucosidase and α-amylase. In addition, the activity of analogues **1** and **6** sharply decreased upon replacing the −Cl group linked to isatin with $-NO_2$ and hydrogen atoms in analogue **1** that holds $-NO_2$ substitution on the isatin ring and **6** that holds the unsubstituted isatin ring (Figure 3).

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

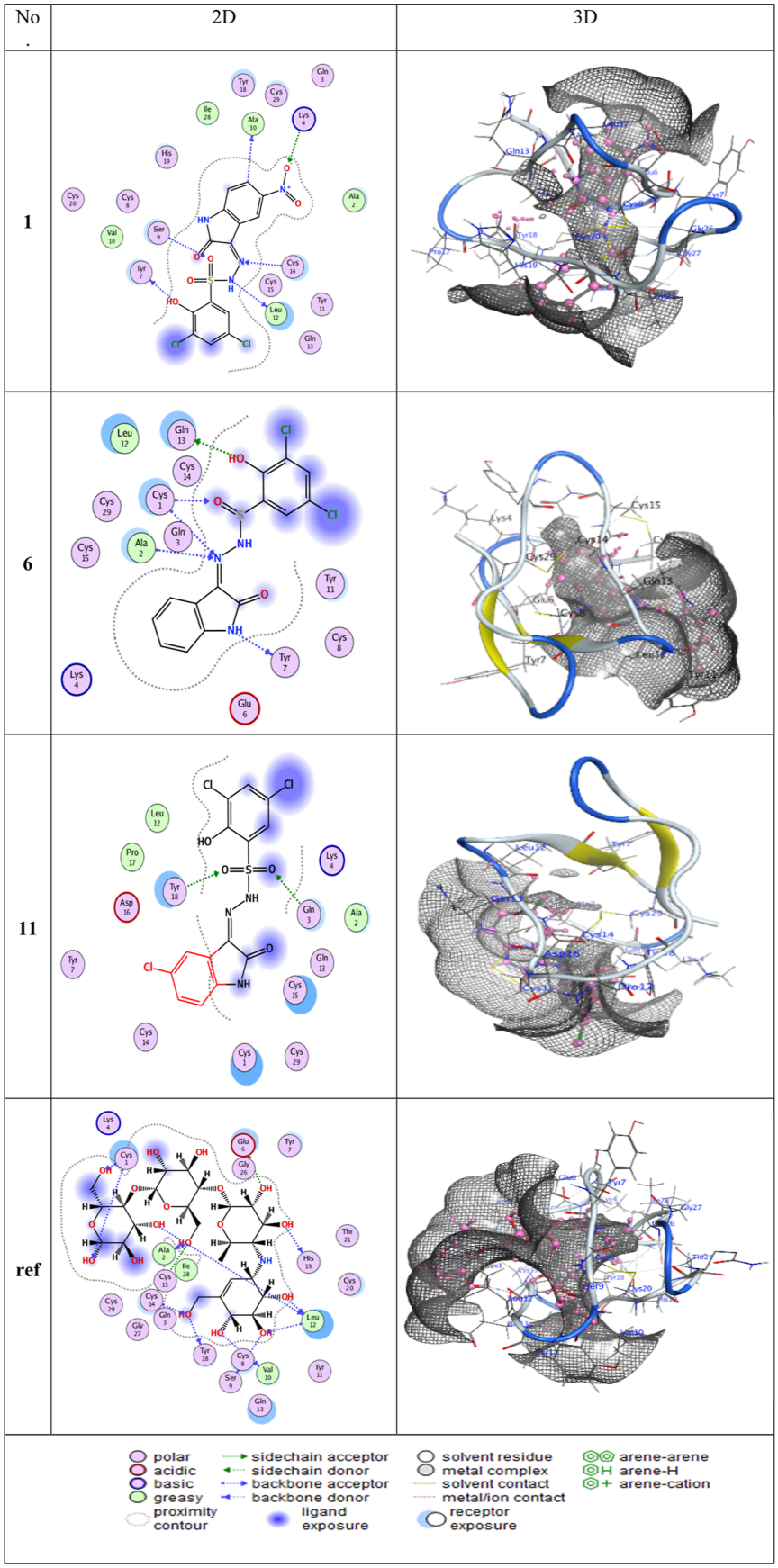


Figure 4. Interactions of benzenesulfonohydrazide derivatives with α-amylase PDB = 2BFH.

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

Table 4. Interacting Residues of Benzenesulfonohydrazide Derivatives with α-Glucosidase PDB = 5KZW

Cpd	ligand interaction	receptor	interactions	distance (Å)	E (K cal/mol)
1	O 4	N ASN 635 (A)	H-acceptor	2.83	−3.8
	O 4	ND2 ASN 635 (A)	H-acceptor	3.03	−1.5
	N 17	N LEU 636 (A)	H-acceptor	3.17	−0.5
	O 28	NE2 GLN 633 (A)	H-acceptor	2.91	−2.0
	5-ring	CB ASN 635 (A)	Pi-H	3.79	−0.5
	6-ring	5-ring HIS 295 (A)	pi−pi	4.03	−0.0
6	N 1	O LEU 632 (A)	H-donor	3.01	−1.7
	N 16	O VAL 639 (A)	H-donor	2.78	−7.4
	O 4	N PHE 634 (A)	H-acceptor	3.27	−1.2
	6-ring	CB PHE 634 (A)	Pi-H	4.40	−0.7
11	N 1	O LEU 632 (A)	H-donor	2.86	−4.3
	O 29	O PHE 634 (A)	H-donor	2.78	−1.4
	O 4	N LEU 636 (A)	H-acceptor	2.74	−3.5
	O 4	N LEU 637 (A)	H-acceptor	3.39	−0.7
	O 28	N GLY 605 (A)	H-acceptor	3.10	−2.0
acarbose	O 21	O LEU 641 (A)	H-donor	2.69	−1.7
	O 38	O ILE 631 (A)	H-donor	2.64	−3.3
	O 84	O LEU 632 (A)	H-donor	2.63	−2.0
	O 21	N LEU 641 (A)	H-acceptor	2.87	−1.7
	O 40	N PHE 634 (A)	H-acceptor	2.73	−1.9
	O 42	N ASN 635 (A)	H-acceptor	3.29	−1.0
	O 61	ND2 ASN 635 (A)	H-acceptor	2.91	−2.6

Table 5. Docking Score and Energy of Benzenesulfonohydrazide Derivatives with α-Glucosidase PDB = 5KZW

Cpd	S	RMSD_refine	E-conf	E-place	E-scorel	E-refine	E-score2
1	−7.0226	1.2880	137.7378	−90.4338	−12.2435	−35.6661	−7.0226
6	−6.6688	1.3264	93.7095	−74.2225	−11.1232	−33.8192	−6.6688
11	−7.0509	1.8482	82.8002	−86.7855	−11.5197	−30.3678	−7.0509
acarbose	−9.0807	1.6945	250.1247	−102.9935	−12.5275	−45.6802	−9.0807

4. MOLECULAR DOCKING

The use of molecular docking simulation in drug discovery and design has considerably increased during the last few years since this computational technique can provide helpful information about the binding affinity between the discovered drug and a target protein. Therefore, it constitutes a suitable method to predict the inhibition of a target protein in considerably less time and cost.[23] Furthermore, a possible hypothesis of the mechanism of action of the discovered drug is proposed. The interaction of the ligand and protein residue results obtained from docking of ligands **1**, **6**, **11**, and acarbose as a reference with α-amylase PDB = 2BFH is described in Table 2. In contrast, the docking score energies are represented in Table 3 with RMSD values less than 3 Å. The docking score energies showed variation near acarbose values. Although acarbose has the highest value, the sequence of values is −6.4, −5.46, −5.36, and −5.02 for acarbose, **11**, **1**, and **6**, respectively. While Figure 4 reports the 2D and 3D snaps of the docked complexes, the results of the interaction of the ligand and protein residue obtained from docking of ligands **1**, **6**, **11**, and **acarbose** as a reference with α-glucosidase PDB = 5KZW are represented in Table 4.

Also, the docking score energies are represented in Table 5 with RMSD values less than 3 Å, while Figure 5 reports the 2D and 3D snaps of the docked complexes. The docking score energies showed variation near acarbose values. Although acarbose has the highest value, the sequence of values is −9.08, −7.05, −7.02, and −6.67 for acarbose, **11**, **1**, and **6**, respectively. The results of the interaction of the ligand and protein residue obtained from docking of ligands **1**, **6**, **11**, and acarbose as a reference with pancreatic lipase PDB = 2OXE are represented in Table 6, which represents that most of the interaction was via hydrogen acceptors or donors. In addition, the docking score energies are represented in Table 7 with RMSD values less than 3 Å, while Figure 6 reports the 2D and 3D snaps of the docked complexes. The docking score energies showed variation near acarbose values. Although acarbose has the highest value, the sequence of values is −6.94, −6.29, −5.87, and −5.7435 for acarbose, **1**, **6**, and **11**, respectively. Most of the interactions were found to be via hydrogen acceptors or donors for the three proteins. No one appeared to have docking score values higher than acarbose, although benzenesulfonohydrazide derivatives are indexed as suitable inhibitors for diabetes mellitus.

4.1. In Silico Drug-Likeness, Pharmacokinetic Properties, and Toxicity Evaluation. The ADMET properties for three derivatives were calculated using Lipinski's rule of five, GI absorption = high; BBB permeant = no. by admetSAR (Supporting Information).

PreADMET provides information about drugs that would likely violate rules like the rule of five and ADMET properties, while also providing the numerical values of various parameters such as blood−brain barrier permeation and gastrointestinal absorption, and performs toxicity tests, e.g., mouse carcinogenicity, hERG inhibition, and Ames test.

(Note: details of pharmacokinetics of benzenesulfonohydrazide is presented in the Supporting Information, Table S1).

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

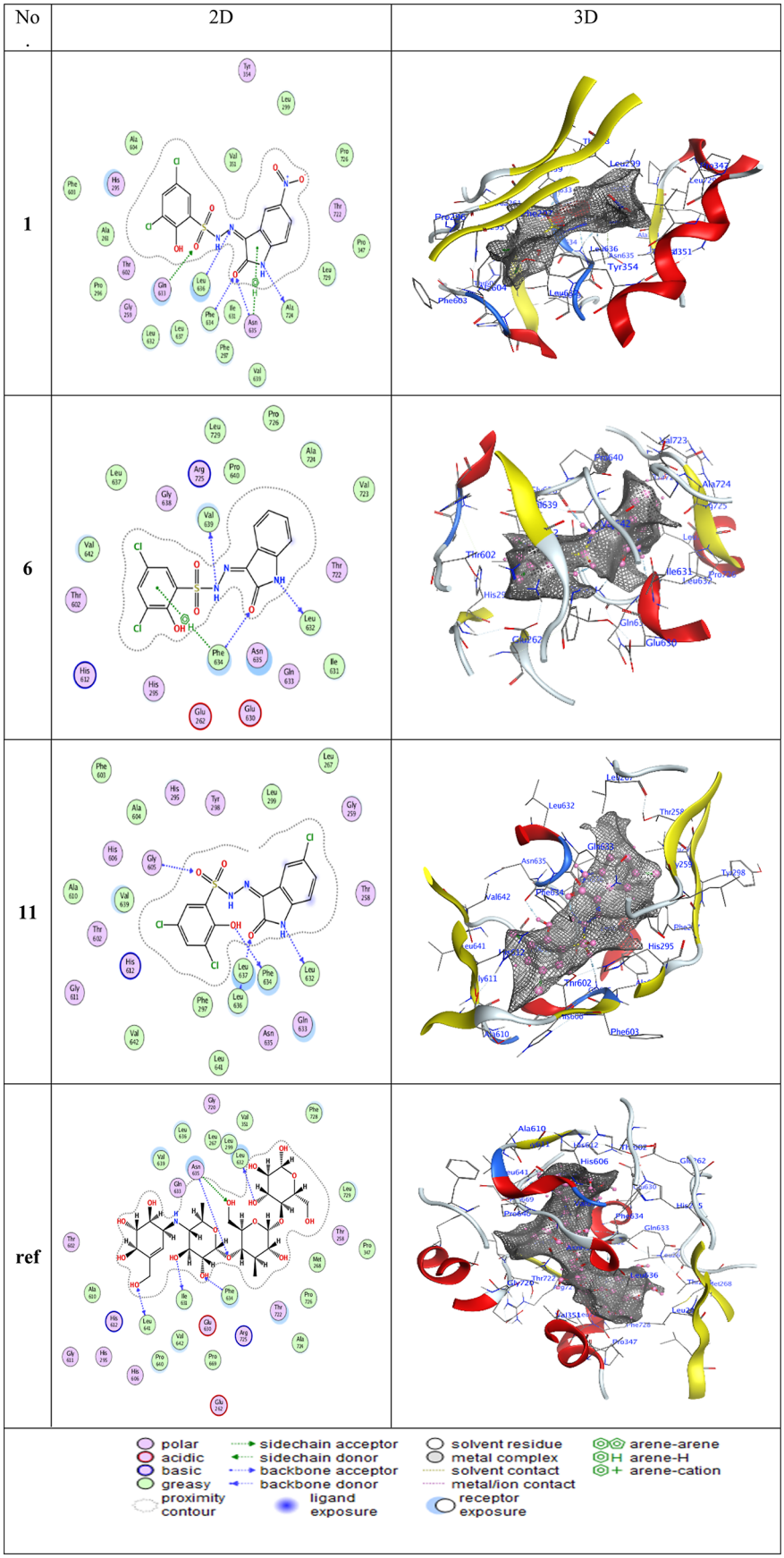


Figure 5. Interactions of benzenesulfonohydrazide derivatives with α-glucosidase PDB = 5KZW.

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

Table 6. Interacting Residues of Benzenesulfonohydrazide Derivatives with Pancreatic Lipase PDB = 2OXE

Cpd	ligand interaction	receptor	interactions	distance (Å)	*E* (K cal/mol)
1	O 61	ND2 ASN 635 (A)	H-acceptor	2.91	−2.6
	C 12	OD2 ASP 308 (A)	H-donor	3.44	−0.6
	N 15	OD2 ASP 308 (B)	H-donor	2.71	−8.1
	O 29	OD1 ASP 308 (B)	H-donor	2.53	−3.4
	N 17	NZ LYS 251 (A)	H-acceptor	3.03	−6.7
	O 27	CE LYS 251 (A)	H-acceptor	3.23	−1.2
6	N 16	OD2 ASP 308 (B)	H-donor	2.68	−6.8
11	N 15	OD2 ASP 308 (B)	H-donor	2.82	−8.6
	O 29	OD2 ASP 308 (B)	H-donor	2.53	−1.3
	O 27	NZ LYS 251 (A)	H-acceptor	2.95	−7.5
acarbose	O 12	OE1 GLU 252 (B)	H-donor	3.11	−1.7
	O 21	OE1 GLU 252 (B)	H-donor	2.64	−2.3
	O 38	OE2 GLU 252 (B)	H-donor	2.73	−3.6
	O 61	OE1 GLU 252 (A)	H-donor	2.61	−3.2
	O 63	OD1 ASP 308 (B)	H-donor	2.84	−2.1
	O 77	OE2 GLU 312 (B)	H-donor	2.63	−4.6
	O 82	OD2 ASP 308 (B)	H-donor	2.75	−2.5
	O 86	OE2 GLU 312 (B)	H-donor	2.68	−3.5
	N 88	OE2 GLU 252 (B)	H-donor	2.90	−2.0
	O 61	NZ LYS 251 (A)	H-acceptor	2.95	−6.2

Table 7. Docking Score and Energy of Benzenesulfonohydrazide Derivatives with Pancreatic Lipase PDB = 2OXE

Cpd	*S*	RMSD_refine	E-conf	E-place	E-scorel	E-refine	E-score2
1	−6.2941	1.8014	116.2517	−43.0674	−9.1904	−36.4991	−6.2941
6	−5.8701	1.4067	97.5553	−43.7238	−10.6220	−31.5003	−5.8701
11	−5.7435	2.0796	91.8629	−78.4393	−9.8605	−30.9717	−5.7435
acarbose	−6.9432	1.7990	241.7659	−77.7495	−11.3245	−40.5970	−6.9432

5. CONCLUSIONS

This work contains a class of novel (*Z*)-3,5-dichloro-*N*′-(5-chloro-2-oxoindolin-3-ylidene)-2-hydroxybenzenesulfonohydrazide derivatives which were synthesized and evaluated for their α-amylase and α-glucosidase enzymes. Out of these sixteen compounds (**1**−**16**), only three compounds showed better inhibitory potentials such as analogue **11** (0.90 ± 0.10 μM for α-glucosidase and 1.10 ± 0.10 μM for α-amylase), **1** (1.10 ± 0.10 μM for α-glucosidase and 1.30 ± 0.10 μM for α-amylase), and **6** (1.20 ± 0.10 μM for α-glucosidase and 1.60 ± 0.10 μM for α-amylase). Furthermore, molecular modeling of acarbose, **11**, **1**, and **6** and RMSD values against α-amylase, α-glucosidase, and pancreatic lipase less than 3 Å, the docking score energies showed variation near acarbose values. Although acarbose has the highest value, the sequence of α-amylase, α-glucosidase, and pancreatic lipase values is (−6.4, −5.46, −5.36, and −5.02), (−9.08, −7.05, −7.02, and −6.67), and (−6.94, −6.29, −5.87, and −5.7435) for acarbose, **11**, **1**, and **6**, as well as ADMET and PreADMET tests show excellent results, so it is concluded that these derivatives are indexed as suitable inhibitors for diabetes mellitus. Analytical techniques, e.g., ^{1}H NMR, ^{13}C NMR, and HRESIMS, are applied to confirm their structures.

6. MATERIALS AND METHODS

Substituted indoline-2,3-dione (Isatin), substituted benzenesulfonyl chloride, acetic acid, and hydrazine hydrate were acquired from USA Sigma-Aldrich. In addition, solvents such as methanol, ethanol, acetone, *n*-hexane, and ethyl acetate were of analytical grade. Bruker AVANCE 500 MHz NMR spectrometers were used to record the NMR spectra of ^{1}H NMR and ^{13}C NMR, while DMSO-d_6 was use as a solvent, and tetramethylsilane was used as an internal solvent. The coupling constant (j) in hertz and chemical shift (δ) value were expressed in ppm. Unless stated otherwise, all the reactions were performed under atmospheric air pressure, and the reactions were monitored by an analytical technique such as TLC performed on specified pre-coated silica gel metal plates (Kieselgel 60, 254, E. Merck Germany). A UV−visible lamp with a short range of 365 nm and a long range of 425 nm was used to visualize spots on the TLC plates. An HRESIMS spectrometer was used to record the mass spectrum according to their m/z values.

6.1. General Procedure for the Synthesis of Isatin-Based Sulfonamide Analogues (84−99). The synthesis of substituted indoline-2,3-dione-based substituted benzene sulfonamide scaffolds was completed in two steps. Initially, substituted indoline-2,3-dione (**a**, **1:1**) was refluxed with hydrazine hydrate in the presence of glacial CH_3COOH (10 mL) for 4 h to synthesize substituted 3-hydrazonoindolin-2-one as the intermediate product (**b**). In the last step, analogues (**b**, **1:1**) were treated with the substituted benzene sulfonyl chloride (**c**) for 5 h in CH_3COOH (10 mL) to synthesize the substituted isatin-based substituted benzene sulfonamide derivatives in 61−72% yield (**1**−**16**) Scheme 1.

7. MOLECULAR DOCKING

7.1. Methodology. Benzenesulfonohydrazide derivatives were used previously.[24] In this article, different derivatives were investigated toward α-amylase, α-glucosidase, and pancreatic lipase theoretically by carrying out molecular docking studies

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

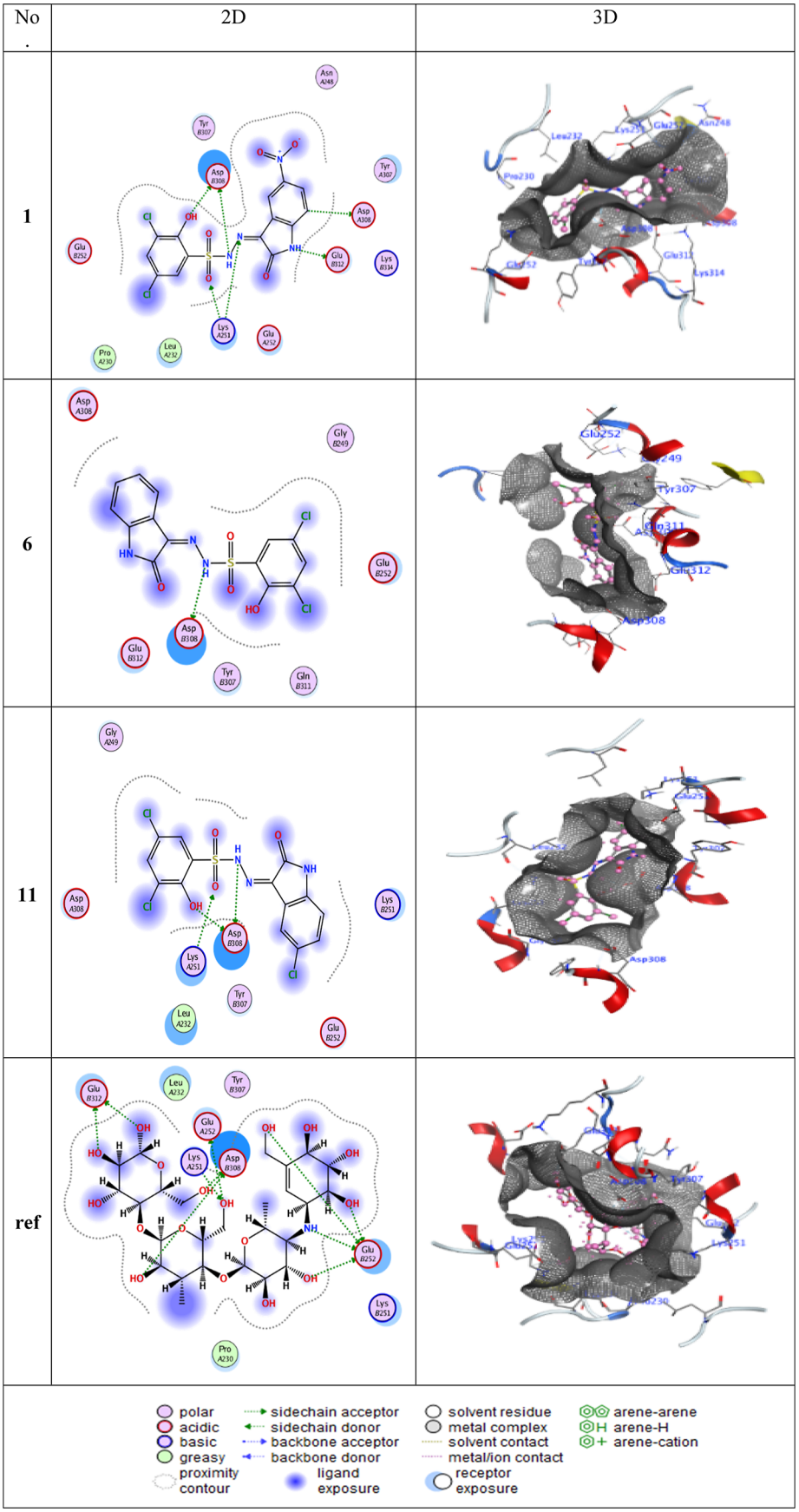


Figure 6. Interactions of benzenesulfonohydrazide derivatives with pancreatic lipase PDB = 2OXE.

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

using MOE (molecular operating system),[25] and pharmacokinetic studies were carried out on admetSAR.[26]

The human pancreatic α-amylase, α-glucosidase, and pancreatic lipase were retrieved from Protein Data Bank (https://www.rcsb.org/) with PDB ID: 2BFH, PDB ID: 5KZW, and PDB ID: 2OXE, respectively. These proteins were chosen based on the trial of many suitable proteins toward the prepared ligand interactions. First, the protein was retrieved with the co-crystallized acarbose ligand, which was later extracted as a separated molecule and employed as the control. MOE 2019 software[27] was used here. This software has gained particular attention in docking the prepared compounds into proteins.[28−30] Then, the structures were prepared at a pH of 7, adding hydrogen atoms and removing co-crystallized water molecules using the Quick prep tool provided by MOE software. Then, as a pre-step to validate the docking protocol, the co-crystallized ligands were re-docked against the targeted proteins. The resulting poses of the re-docked ligands were superimposed on the co-crystallized ligands, with RMSD values below 3 Å. The docking results revealed four to five poses between each compound and the targets. The most flattering pose was ranked from the more negative number of *S*-value,[31] which is a simulated approximation of the Δ*G* (K cal/mol) of the binding reflecting the tightness of the binding and a low RMSD value (Å), which reflects less perturbation during the docking process. These two parameters are recommended to validate the stability of the binding, as well as the formed "complex" (compound/target protein).

7.2. In Silico Drug-Likeness, Pharmacokinetic Properties, and Toxicity Evaluation. In the development of therapeutic drugs, most of the failures were generally related to drug-likeness, the bioavailability of the drug, pharmacokinetics, the fate of the drug in the body, and toxicity. An apparent reduction in the fraction of drug-likeness and pharmacokinetics-related failures has been reported when these parameters are identified experimentally during the drug process evaluation. Alternatively, in silico predictive models are frequently applied to obtain an early estimation of these two profiles and their toxicity. This estimation has become a standard step in designing new drug compounds. Herein, the **Preadmet server**[32] and **admetSAR server**[23] were utilized to predict the drug-likeness, pharmacokinetics properties, and toxicity of the benzenesulfonohydrazide derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01130.

Pharmacokinetics of benzenesulfonohydrazide, characterization of the isatin-based sulfonamide analogues (**1**−**16**), α-glucosidase assay protocol, and α-amylase inhibition assay (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Wajid Rehman − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan;* orcid.org/0000-0003-0128-0377; Phone: 0092-333-5779831; Email: sono_waj@yahoo.com

Authors

Liaqat Rasheed − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Fazal Rahim − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Zahid Ali − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Ashwag S. Alanazi − *Department of Pharmaceutical Sciences, College of Pharmacy, Princess Nourah Bint Abdulrahman University, Riyadh 11671, Saudi Arabia*

Rafaqat Hussain − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Imran Khan − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Mohammed M. Alanazi − *Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia*

Muhammad Naseer − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Magda H. Abdellattif − *Department of Chemistry, College of Sciences, Taif University, Taif 21944, Saudi Arabia;* orcid.org/0000-0002-8562-4749

Riaz Hussain − *Division of Science and Technology, University of Education Lahore, Lahore 54770, Pakistan;* orcid.org/0000-0002-6154-1244

Shoaib Khan − *Department of Chemistry, Hazara University, Mansehra 21120, Pakistan*

Muhammad Taha − *Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam 31441, Saudi Arabia*

Syed Adnan Ali Shah − *Atta-ur-Rahman Institute for Natural Product Discovery (AuRIns), Universiti Teknologi MARA Cawangan Selangor Kampus Puncak Alam, Selangor 42300, Malaysia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c01130

Author Contributions

CRediT authorship contribution statement—Liaqat Rasheed: methodology; Wajid Rehman and Fazal Rahim: The concept of this study was mainly from Prof Dr Wajid Rehman and Associate Professor Dr Fazal Rahim, and both were PI and Co PI of this study; Prof Dr Wajid Rehman: overall supervision and manuscript writing; Zahid Ali: manuscript drafting and formal analysis; Ashwag S. Alanazi, Rafaqat Hussain, Imran Khan, and Mohammed M. Alanazi: data curation, visualization, software, and editing; Muhammad Naseer: validation; Magda H. Abdellatif: software; Riaz Hussain and Shoaib Khan: formal analysis; Muhammad Taha: data curation; and Syed Adnan Ali Shah: editing and data analysis.

Funding

This work was supported by the Researchers Supporting Project number (RSPD2023R628), King Saud University, Riyadh, Saudi Arabia. This work was supported by Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2023R342), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors extend their appreciation to Princess Nourah bint Abdulrahman University Researchers Supporting Project number (PNURSP2023R342), Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia. The authors extend their appreciation to the Researchers Supporting Project number (RSPD2023R628), King Saud University, Riyadh, Saudi.

■ REFERENCES

(1) Liang, C.; Xia, J.; Lei, D.; Li, X.; Yao, Q.; Gao, J. Synthesis, in vitro and in vivo antitumor activity of symmetrical bis-Schiff base derivatives of isatin. *Eur. J. Med. Chem.* **2014**, *74*, 742−750.

(2) Pakravan, P.; Kashanian, S.; Khodaei, M. M.; Harding, F. J. Biochemical and pharmacological characterization of isatin and its derivatives: from structure to activity. *Pharmacol. Rep.* **2013**, *65*, 313−335.

(3) Pandeya, S. N.; Smitha, S.; Jyoti, M.; Sridhar, S. K. Biological activities of isatin and its derivatives. *Acta Pharm.* **2005**, *55*, 27−46.

(4) Varun, V.; Sonam, S.; Kakkar, R. Isatin and its derivatives: a survey of recent syntheses, reactions, and applications. *MedChemComm* **2019**, *10*, 351−368.

(5) Liu, R.; Li, L.; Shao, C.; Cai, H.; Wang, Z. The Impact of Diabetes on Vascular Disease: Progress from the Perspective of Epidemics and Treatments. *J. Diabetes Res.* **2022**, *2022*, 1−17.

(6) Marcovecchio, M.; Mohn, A.; Chiarelli, F. Type 2 diabetes mellitus in children and adolescents. *J. Endocrinol. Invest.* **2005**, *28*, 853−863.

(7) Rasouli, H.; Hosseini-Ghazvini, S. M.-B.; Adibi, H.; Khodarahmi, R. Differential α-amylase/α-glucosidase inhibitory activities of plant-derived phenolic compounds: a virtual screening perspective for the treatment of obesity and diabetes. *Food Funct.* **2017**, *8*, 1942−1954.

(8) O'Dea, K.; Wong, S. The rate of starch hydrolysis in vitro does not predict the metabolic responses to legumes in vivo. *Am. J. Clin. Nutr.* **1983**, *38*, 382−387.

(9) Peytam, F.; Adib, M.; Shourgeshty, R.; Mohammadi-Khanaposhtani, M.; Jahani, M.; Imanparast, S.; Faramarzi, M. A.; Moghadamnia, A. A.; Larijani, B.; Mahdavi, M. Synthesis and biological evaluation of new dihydroindolizino [8, 7-b] indole derivatives as novel α-glucosidase inhibitors. *J. Mol. Struct.* **2021**, *1224*, 129290.

(10) Sadat-Ebrahimi, S. E.; Babania, H.; Mohammadi-Khanaposhtani, M.; Asgari, M. S.; Mojtabavi, S.; Faramarzi, M. A.; Yahya-Meymandi, A.; Zareie, S.; Larijani, B.; Biglar, M.; et al. Design, synthesis, and biological evaluation of new indole-acrylamide-1, 2, 3-triazole derivatives as potential α-glucosidase inhibitors. *Polycyclic Aromat. Compd.* **2022**, *42*, 3157−3165.

(11) Niri, D. R.; Sayahi, M. H.; Behrouz, S.; Moazzam, A.; Mojtabavi, S.; Faramarzi, M. A.; Larijani, B.; Rastegar, H.; Mohammadi-Khanaposhtani, M.; Mahdavi, M. Design, synthesis, in vitro, and in silico biological evaluations of coumarin-indole hybrids as new anti-α-glucosidase agents. *BMC Chem.* **2022**, *16*, 84.

(12) Tan, Y.; Chang, S. K.; Zhang, Y. Comparison of α-amylase, α-glucosidase and lipase inhibitory activity of the phenolic substances in two black legumes of different genera. *Food Chem.* **2017**, *214*, 259−268.

(13) Puls, W. Glucosidase inhibition: A new approach to the treatment of diabetes, obesity, and hyperlipoproteinaemia. *Naturwissenschaften* **1977**, *64*, 536.

(14) Dileep, K.; Nithiyanandan, K.; Remya, C. Binding of acarbose, an anti-diabetic drug to lysozyme: a combined structural and thermodynamic study. *J. Biomol. Struct. Dyn.* **2018**, *36*, 3354−3361.

(15) Afonne, O. J.; Orisakwe, O.; Obi, E.; Orish, C.; Akumka, D. Some pharmacological properties of Synclisia scabrida III. *Indian J. Pharmacol.* **2000**, *32*, 239−241.

(16) Daisy, P.; Jasmine, R.; Ignacimuthu, S.; Murugan, E. A novel steroid from Elephantopus scaber L. an ethnomedicinal plant with antidiabetic activity. *Phytomedicine* **2009**, *16*, 252−257.

(17) Geethalakshmi, R.; Sarada, D.; Marimuthu, P.; Ramasamy, K. α-Amylase inhibitory activity of Trianthema decandra L. *Int. J. Biotechnol. Biochem.* **2010**, *6*, 369−376.

(18) Rahim, F.; Malik, F.; Ullah, H.; Wadood, A.; Khan, F.; Javid, M. T.; Taha, M.; Rehman, W.; Rehman, A. U.; Khan, K. M. Isatin based Schiff bases as inhibitors of α-glucosidase: Synthesis, characterization, in vitro evaluation and molecular docking studies. *Bioorg. Chem.* **2015**, *60*, 42−48.

(19) Santoso, M.; Ong, L. L.; Aijijiyah, N. P.; Wati, F. A.; Azminah, A.; Annuur, R. M.; Fadlan, A.; Judeh, Z. M. Synthesis, α-glucosidase inhibition, α-amylase inhibition, and molecular docking studies of 3, 3-di (indolyl) indolin-2-ones. *Heliyon* **2022**, *8*, No. e09045.

(20) Abbasi, I.; Nadeem, H.; Saeed, A.; Kharl, H. A. A.; Tahir, M. N.; Naseer, M. M. Isatin-hydrazide conjugates as potent α-amylase and α-glucosidase inhibitors: Synthesis, structure and in vitro evaluations. *Bioorg. Chem.* **2021**, *116*, 105385.

(21) Khan, S.; Rahim, F.; Rehman, W.; Nawaz, M.; Taha, M.; Fazil, S.; Hussain, R.; Shah, S. A. A.; Abdellatif, M. H. New benzoxazole-based sulphonamide hybrids analogs as potent inhibitors of α-amylase and α-glucosidase: Synthesis and in vitro evaluation along with in silico study. *Arabian J. Chem.* **2022**, *15*, 104341.

(22) Askarzadeh, M.; Azizian, H.; Adib, M.; Mohammadi-Khanaposhtani, M.; Mojtabavi, S.; Faramarzi, M. A.; Sajjadi-Jazi, S. M.; Larijani, B.; Hamedifar, H.; Mahdavi, M. Design, synthesis, in vitro α-glucosidase inhibition, docking, and molecular dynamics of new phthalimide-benzenesulfonamide hybrids for targeting type 2 diabetes. *Sci. Rep.* **2022**, *12*, 10569.

(23) Li, A. P. Screening for human ADME/Tox drug properties in drug discovery. *Drug Discovery Today* **2001**, *6*, 357−366.

(24) Tundis, R.; Loizzo, M.; Menichini, F. Natural products as α-amylase and α-glucosidase inhibitors and their hypoglycaemic potential in the treatment of diabetes: an update. *Mini-Rev. Med. Chem.* **2010**, *10*, 315−331.

(25) Swilam, N.; Nawwar, M. A.; Radwan, R. A.; Mostafa, E. S. Antidiabetic Activity and In Silico Molecular Docking of Polyphenols from Ammannia baccifera L. subsp. Aegyptiaca (Willd.) Koehne Waste: Structure Elucidation of Undescribed Acylated Flavonol Diglucoside. *Plants* **2022**, *11*, 452.

(26) Shen, J.; Cheng, F.; Xu, Y.; Li, W.; Tang, Y. Estimation of ADME properties with substructure pattern recognition. *J. Chem. Inf. Model.* **2010**, *50*, 1034−1041.

(27) Paşayeva, L.; Fatullayev, H.; Celik, I.; Unal, G.; Bozkurt, N. M.; Tugay, O.; Abdellattif, M. H. Evaluation of the Chemical Composition, Antioxidant and Antidiabetic Activity of Rhaponticoides iconiensis Flowers: Effects on Key Enzymes Linked to Type 2 Diabetes In Vitro, In Silico and on Alloxan-Induced Diabetic Rats In Vivo. *Antioxidants* **2022**, *11*, 2284.

(28) Barakat, A.; Al-Majid, A. M.; Soliman, S. M.; Lotfy, G.; Ghabbour, H. A.; Fun, H.-K.; Wadood, A.; Warad, I.; Sloop, J. C. New diethyl ammonium salt of thiobarbituric acid derivative: Synthesis, molecular structure investigations and docking studies. *Molecules* **2015**, *20*, 20642−20658.

(29) Abdellattif, M. H.; Shahbaaz, M.; Arief, M.; Hussien, M. A. Oxazinethione derivatives as a precursor to pyrazolone and pyrimidine derivatives: Synthesis, biological activities, molecular modeling, ADME, and molecular dynamics studies. *Molecules* **2021**, *26*, 5482.

(30) Lee, S.; Lee, I.; Kim, H.; Chang, G.; Chung, J.; No, K. The PreADME Approach: Web-based program for rapid prediction of physico-chemical, drug absorption and drug-like properties. *EuroQSAR 2002 Designing Drugs and Crop Protectants: processes, problems and solutions*; Blackwell Publishing Massachusetts, 2003; Vol. *2003*, pp 418−420.

(31) Cheng, F.; Li, W.; Zhou, Y.; Shen, J.; Wu, Z.; Liu, G.; Lee, P. W.; Tang, Y. *admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties*; ACS Publications, 2012.

(32) Abdellattif, M. H.; Elkamhawy, A.; Hagar, M.; Hadda, T. B.; Shehab, W. S.; Mansy, W.; Belal, A.; Arief, M.; Hussien, M. A. Novel saccharin analogs as promising antibacterial and anticancer agents:

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672

synthesis, DFT, POM analysis, molecular docking, molecular dynamic simulations, and cell-based assay. *Front. Pharmacol.* **2022**, *13*, 958379.

https://doi.org/10.1021/acsomega.3c01130
ACS Omega 2023, 8, 15660−15672