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Exploration of Some Bis-Sulfide and Bis-Sulfone Derivatives as Non-Classical Aldose Reductase İnhibitors

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Aldose reductase (AR, ALR2; EC 1.1.1.21), an enzyme that converts glucose to fructose on the polyol pathway, is an important member of the Aldo-keto reductase superfamily. ALR2 is part of the rate-limiting step, which is associated with diabetic complications in this process, and plays a role in regulating reactive oxygen species induced by growth factors and cytokines. Despite the fact that sulfides and sulfones have been discovered to have a variety of other biological functions, in the current study, we assessed the ALR2 inhibitory potential of the derivatives of bis-sulfide (**5 a–i**) and bis-sulfone (**6 a–i**) in order to further our interest in designing and discovering powerful ALR2 inhibitors. The results of the biological investigations showed that all of the derivatives exhibit activity against ALR2, with K_I values ranging from 0.53 ± 0.03 to 4.20 ± 0.06 μM. Among these agents, 2,6-bis((4-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 h**), 2,6-bis((3-nitrophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 c**), and 2,6-bis((3-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 g**) exhibited prominent inhibitory activity with K_I constants of 0.53 ± 0.03 μM, 0.65 ± 0.04 μM, and 0.71 ± 0.05 μM, respectively, against ALR2 and were found to be more potent than epalrestat (K_I = 0.79 ± 0.01 μM) is currently, the only ALR2 inhibitor (ALR2I) utilized in treatment. Additionally, *in silico* molecular docking experiments were carried out to explain how these bis-sulfides (**5 a–i**) and bis-sulfones (**6 a–i**) interacted with the target enzyme ALR2's binding site. According to the ADME-Tox study, these compounds are predicted to be ALR2Is with appropriate drug-like characteristics. The study's findings on sulfides and sulfones could be exploited to create innovative therapeutics that prevent diabetes complications.

Introduction

The sulfides and sulfones synthesis has great importance in medicinal and synthetic organic chemistry.[1–4] In the literature, 1,4-Michael addition reactions are the most commonly used method for C–S bond formation.[5,6] 1,4-Michael addition of thiols to α-β-unsaturated ketones for bis-sulfide synthesis a key reaction in organic synthesis.[7–11] It is well known that this technique is crucial in the development of bioactive substances.[12,13] As an important class of biological molecules, bis-sulfone compounds are widely used in organic synthesis, materials, and pharmaceuticals.[14] The synthesis of the sulfone compounds from the sulfides can be carried out with oxidizing inorganic reagents (Cr_2O_5, $FeBr_3$-HNO_3, $KMnO_4$, $NaClO_4$, H_5IO_6, HgO-I_2, HIV_9O_{28}, oxodiperoxomolybdenum complexes, etc.), heavy metal salts ($TaCl_5$, $NbCl_5$, Cp′Mo(CO)$_3$Cl etc.), together with H_2O_2, peroxides (H_2O_2, H_2O_2/AcOH) and peroxy acids (*m*-CPBA, *o*-iyodoperbenzoik acide, benzenseleninik peroxyacide).[15–23] In chemical, biological, and pharmacological applications, molecules with sulfide and sulfone groups have been reported to have some biological activity (Figures 1 and 2).[24–29]

High blood glucose levels brought on by insufficient insulin production or metabolic insulin resistance characterize diabetes mellitus (DM), a chronic metabolic illness.[30–32] Long-term hyperglycemia and insulin resistance generate a variety of metabolic abnormalities in the target organs and eventually result in many microvascular and macrovascular problems.[33–35] Two critical theories claimed to be the significant switches in

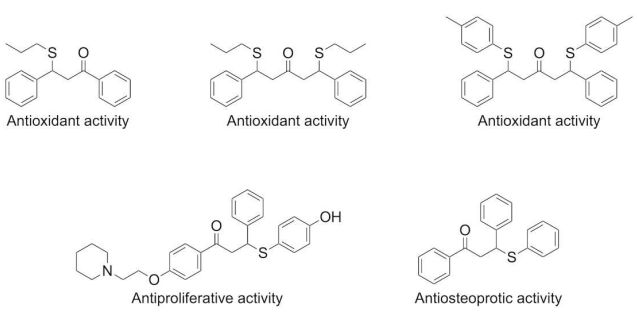

Figure 1. Some biological properties of sulfide and bis-sulfide derivatives.

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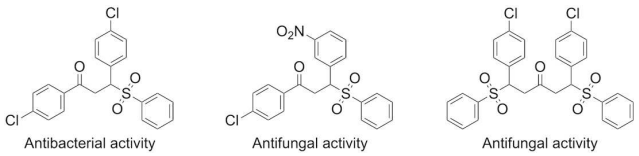

Figure 2. Some biological properties of sulfone and bis-sulfone derivatives.

the evolution of DM are the polyol pathway and an oxidative stress-mediated unified mechanism.[36–40]

The cytosolic reduced NADPH-dependent oxidoreductase enzyme[41] aldose reductase (AR, ALR2; EC 1.1.1.21)[42] is a member of the superfamily of Aldo-keto reductases.[43] ALR2 is the first enzyme studied in the polyol route of glucose metabolism, which converts glucose to fructose through sorbitol.[44–46] Given that tissue-based diseases, such as diabetes mellitus consequences like cataracts,[47] nephropathy,[48] neuropathy,[49] and retinopathy,[50] have been linked to glucose overutilization via the polyol pathway, it is very intriguing for medicinal chemistry. ALR2 has received much attention from researchers worldwide to develop potent ALR2 inhibitors (ALR2Is) as it prevents or delays the onset and progression of these complications (Figure 3).

Classical ARIs are generally classified into two groups according to their chemical structure, and these are acetic acid compounds and spirohydantoin derivatives.[51] These small molecule ALR2Is have been identified and tested in a large number of *in vitro* and *in vivo* studies up to this point. Due to pharmacokinetic issues, limited *in vivo* efficacy, or unfavorable side effects, they have not yet received market approval. For the treatment of diabetic neuropathy, from the acetic acid derivatives, only epalrestat (EPR) is commercially accessible as an ALR2I authorized drug.[52–54] ALR2Is with a better pharmacokinetic profile and fewer side effects are required as a result of these reasons.

These 18 inhibitors, the bis-sulfide[55] (**5a–i**) and bis-sulfone[56] (**6a–i**) derivatives have previously been shown to have potent inhibitory activity against some carbonic anhydrase isoforms (*h*CA I and *h*CA II) and cholinesterases (AChE and BChE). These compounds (**5a–i**) and (**6a–i**) were examined *in vitro* and *in silico* as non-classical ALR2Is in this investigation.

Results and Discussion

Biological evaluation and structure-activity relationship

A key enzyme for the polyol pathway,[57] which is an alternative pathway for the metabolism of a small quantity of non-

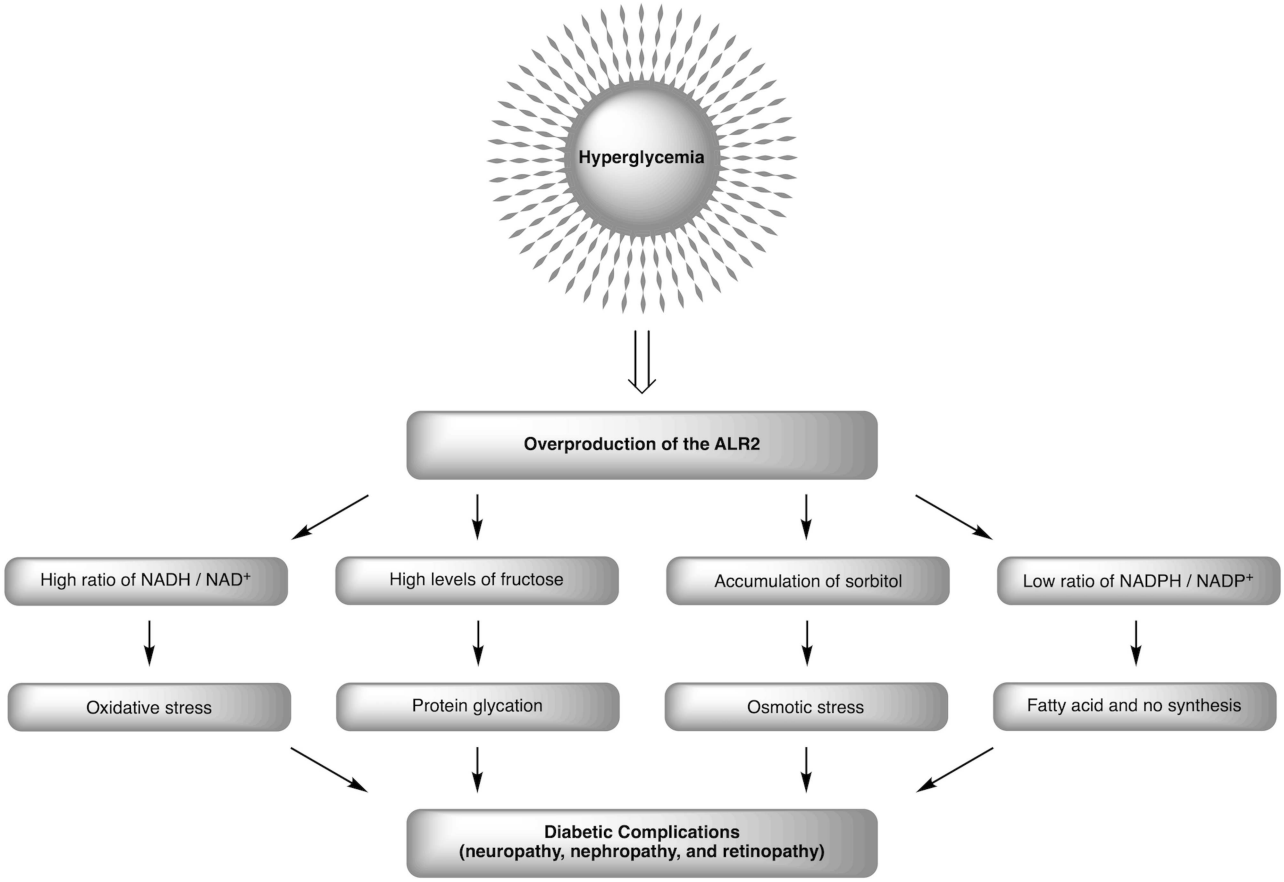

Figure 3. Schematic of the role of aldose reductase (ALR2) in diabetic complications.[49]

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phosphorylated glucose,[58] ALR2 is an NADPH-dependent oxidoreductase[59] that catalyzes the conversion of glucose to sorbitol in a hyperglycemic condition.[60] Sorbitol dehydrogenase enzyme reduces sorbitol to fructose. Osmotic stress brought on by sorbitol accumulation[61] and redox imbalance[62] following NADPH depletion cause organ destruction and cell damage,[63] which leads to cataract development,[64] neuropathy,[65] and other diabetes problems like nephropathy[66] and retinopathy.[67] ALR2 inhibition has thus been acknowledged as a crucial approach for avoiding and reducing long-term diabetic problems. To date, many structurally unique ALR2Is have been created, and some have shown excellent ALR2 inhibitory action.[68] However, most ALR2Is have not yet achieved clinical success because of their adverse effects or pharmacokinetic complications.[69,70] Therefore, this research will summarize new insights into the properties and functions of some of the bis-sulfide (**5a**–**i**) and bis-sulfone (**6a**–**i**) derivatives by inhibiting the ALR2 enzyme and its potential role in the prevention of diabetes.

In the light of all this information, this bis-sulfide (**5a**–**i**) and bis-sulfone (**6a**–**i**) derivatives, previously reported to have potent inhibitory activity versus some carbonic anhydrase isoforms (*h*CA I and *h*CA II) and cholinesterases (AChE and BChE),[55,56] was evaluated as non-classical ALR2Is against the pure ALR2 that was isolated from sheep kidney tissue. All derivatives (**5a**–**i** and **6a**–**i**) are typically proven to exhibit activity against ALR2 with micromolar level concentrations, according to the *in vitro* and *in silico* inhibitory evaluation utilizing EPR as a positive standard. The K_I constants of the bis-sulfides (**5a**–**i**) and bis-sulfones (**6a**–**i**) were determined to be from 0.53 ± 0.03 to 4.20 ± 0.06 μM, respectively (Table 1).

Among the tested 18 inhibitors, compound **5h**, which carried chloro moiety in the para position, is found to have excellent activity versus ALR2 up to 1.5 times compared to the reference agent EPR ($K_I = 0.79 \pm 0.01$ μM, $R^2 = 0.9992$) (Figure 4). But, the **5c** compound with a nitro moiety in the meta position displays slightly less activity than **5h** with the K_I of 0.65 ± 0.04 μM ($R^2 = 0.9942$). As opposed to that, the meta position chloro substituent ($K_I = 0.71 \pm 0.05$ μM, $R^2 = 0.9927$) of compound **5g** has less activity (**5h**, $K_I = 0.53 \pm 0.03$ μM, $R^2 = 0.9968$) than the para position substituent, but it has 1.1-fold more activity than EPR. Generally, bis-sulfide (**5a**–**i**) compounds are more active than the bis-sulfone (**6a**–**i**) derivatives. Derivatives **5i**, **5b**, and **5d** exhibit inhibition with the K_I constants of 1.70 ± 0.04 μM, 1.78 ± 0.09 μM, and 1.83 ± 0.03 μM against ALR2, and their K_I values are higher than that of the standard drug. The same findings are also made in the **5a**, **5e**, and **5f** as well, with the K_I values of 2.37 ± 0.05 μM, 3.11 ± 0.06 μM, and 2.14 ± 0.07 μM, respectively. Further, bis-sulfone derivatives, **6a**–**i** showed K_I values ranging from 1.88 ± 0.03 to 4.20 ± 0.06 μM, which are less efficient than the standard drug.

In this direction, other researches have indicated that some bis-sulfide and bis-sulfone agents show effective inhibition versus ALR2. In this context, the study by Mylari et al.[71] identified 6-phenylsulfonylpyridazin-2H-3-one, compound **8**, which exhibited modest inhibition of ALR2, both *in vitro* and *in vivo*. This reaction between 3,6-dichloropyridazine and the matching bis-sulfide produced the bis-sulfone when it is oxidized with peracid. However, this labile bis-sulfone underwent hydrolysis during an aqueous workup to produce derivative **8**. They discovered that the first SAR focused on phenyl substituents and produced the derivative **8l**, 6-(2,4-dichlorophenylsulfonyl)-2*H*-pyridazin-3-one, which was more effective than compound **8** under both *in vitro* and *in vivo* settings.

Table 1. Inhibition data of ALR2 with the bis-sulfide (**5a**–**i**) and bis-sulfone (**6a**–**i**) derivatives and standard drug epalrestat.

Compound ID	K_I (μM)	R^2	Inhibition type
5a	2.37 ± 0.05	0.9979	Noncompetitive
5b	1.78 ± 0.09	0.9881	Noncompetitive
5c	0.65 ± 0.04	0.9942	Competitive
5d	1.83 ± 0.03	0.9989	Noncompetitive
5e	3.11 ± 0.06	0.9979	Noncompetitive
5f	2.14 ± 0.07	0.9942	Noncompetitive
5g	0.71 ± 0.05	0.9927	Competitive
5h	0.53 ± 0.03	0.9968	Competitive
5i	1.70 ± 0.04	0.9962	Noncompetitive
6a	2.05 ± 0.03	0.9988	Noncompetitive
6b	2.02 ± 0.03	0.9989	Noncompetitive
6c	2.93 ± 0.05	0.9986	Noncompetitive
6d	3.00 ± 0.05	0.9985	Noncompetitive
6e	4.20 ± 0.06	0.9988	Noncompetitive
6f	1.95 ± 0.03	0.9989	Noncompetitive
6g	3.38 ± 0.08	0.9967	Noncompetitive
6h	2.03 ± 0.05	0.9972	Noncompetitive
6i	1.88 ± 0.03	0.9981	Noncompetitive
EPR[a]	0.79 ± 0.01	0.9992	Noncompetitive

[a] Standard drug epalrestat.

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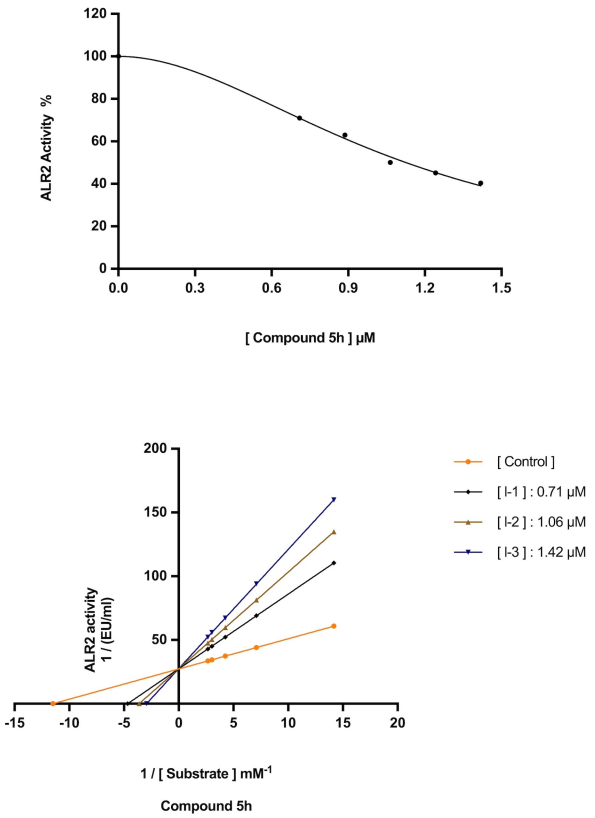

Figure 4. *In vitro* inhibition effects of 2,6-bis((4-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5h**) against ALR2 activity. IC_{50} graph is shown on the left. Lineweaver-Burk plot, displayed on the right, was used to determine the K_i constant and inhibition type of derivative **5h**. For this purpose, five different amounts of dl-glyceraldehyde and three different inhibitor doses for derivative **5h** were examined.

Computational studies

A thorough SAR research was carried out to examine the behavior of these series of compounds inside the EPR binding site of ALR2 in order to learn more about the binding mechanisms of the synthesized bis-sulfide (**5a–i**) and bis-sulfone (**6a–i**) derivatives.

By using Schrödinger Small-Molecule Drug Discovery Suite 2022–1 for Mac to re-dock the co-crystallized EPR into the active site of ALR2 (PDB ID: 4JIR; Resolution: 2.00 Å; Species: Homo sapiens), evaluated the effectiveness of the Glide XP (Schrödinger, LLC, NY, USA) docking technology. The Glide XP docking algorithm was capable of these bis-sulfide (**5a–i**) and bis-sulfone (**6a–i**) compounds to the ALR2 active pocket, as indicated by the RMSD value of 1.06 Å between the EPR conformation and the best pose produced by this protocol.

The primary contact established by potent inhibitors 2,6-bis((4-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5h**, with a docking score of −7.41 kcal/mol and an MM-GBSA value of −63.84 kcal/mol), 2,6-bis((3-nitrophenyl)(phenylthio)methyl)cyclohexan-1-one (**5c**, with a docking score of −6.96 kcal/mol and an MM-GBSA value of −61.05 kcal/mol), and 2,6-bis((3-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5g**, with a docking score of −6. 61 kcal/mol and an MM-GBSA value of −55.31 kcal/mol) of this bis-sulfide (**5a–i**) and bis-sulfone (**6a–i**) series are π-π stacking between the phenyl ring of the core scaffold and Trp20 residue, and nonetheless, a few hydrophobic interactions with Val47, Trp111, Tyr209, Pro218, and Cys298 residues within the binding cavity. Also, both **5c** (distances of 2.48 Å and 2.03 Å) and **5g** (distances of 3.00 Å and 2.91 Å) established H-bond within the binding cavity with residues Tyr48 and His110, respectively. Interestingly, compounds **5h** and **5c** interacted with residues Phe122 and Trp219. Especially, derivative **5h** formed π-π stacking interaction with Trp111 (Figures 5–7).

All of the derivatives of bis-sulfide (**5a–i**) and bis-sulfone (**6a–i**) were evaluated *in silico* using the ADME-Tox prediction software QikProp and the SwissADME platform. Selected results are presented in Table 2. All parameters computed confirmed

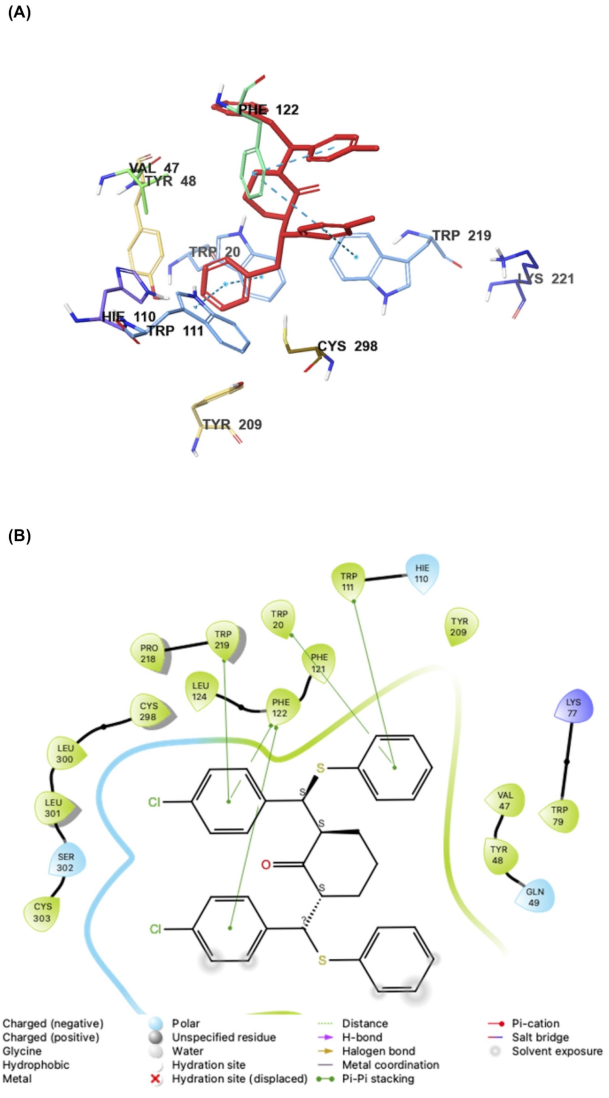

Figure 5. Molecular docking of aldose reductase enzyme (ALR2, PDB code: 4JIR) with 2,6-bis((4-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5h**). **(A)** 3D docking pose of derivative **5h** within the binding pocket of 4JIR. A blue dashed line in the 3D panel depicts interactions involving π-π stacking. **(B)** 2D binding interaction of 4JIR with derivative **5h**.

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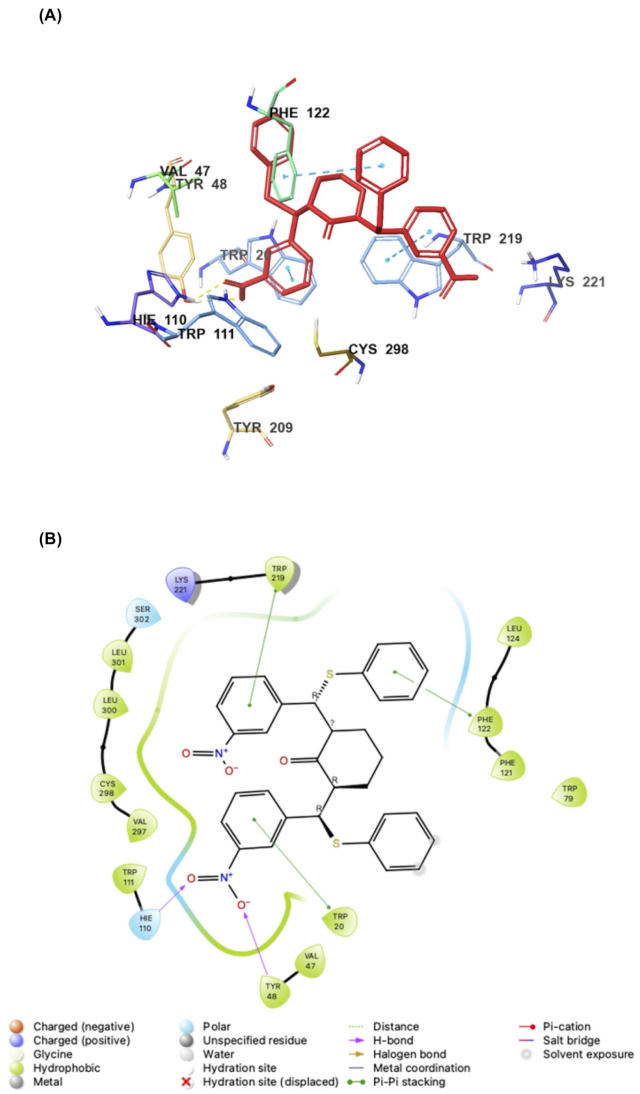

Figure 6. Molecular docking of aldose reductase enzyme (ALR2, PDB code: 4JIR) with 2,6-bis((3-nitrophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 c**). **(A)** 3D docking pose of derivative **5 c** within the binding pocket of 4JIR. A yellow and blue dashed line in the 3D panel depicts interactions involving hydrogen bonds and π-π stacking, respectively. **(B)** 2D binding interaction of 4JIR with derivative **5 c**.

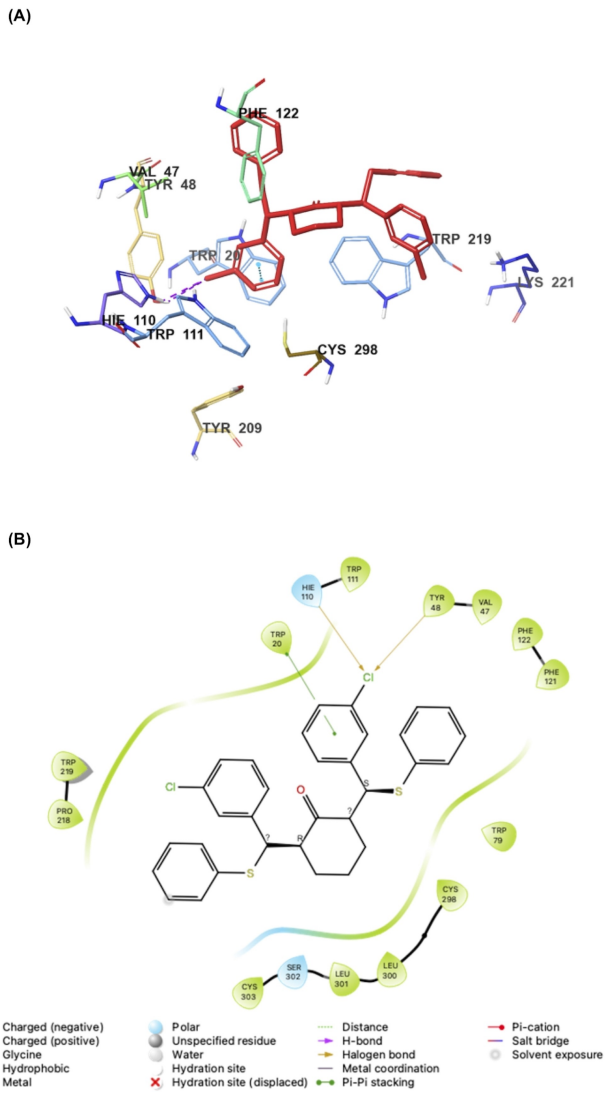

Figure 7. Molecular docking of aldose reductase enzyme (ALR2, PDB code: 4JIR) with 2,6-bis((3-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 g**). **(A)** 3D docking pose of derivative **5 g** within the binding pocket of 4JIR. A magenta and blue dashed line in the 3D panel depicts interactions involving halogen bonds and π-π stacking, respectively. **(B)** 2D binding interaction of 4JIR with derivative **5 g**.

these bis-sulfides (**5 a–i**) and bis-sulfones (**6 a–i**) as adhering to the three and five rules violations of Jorgensen[72] and Lipinski,[73,74] respectively, and being suitable hit agents with drug-like qualities.

Conclusion

Though many different biological activities of sulfides and sulfones have been reported, herein, we have studied the ALR2 inhibitory potential of the derivatives of bis-sulfide (**5 a–i**) and bis-sulfone (**6 a–i**). All derivatives exhibited inhibitory activity versus ALR2 with K_I constants ranging between 0.53 ± 0.03 to 4.20 ± 0.06 μM. Among them, 2,6-bis((4-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 h**), 2,6-bis((3-nitrophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 c**), and 2,6-bis((3-chlorophenyl)(phenylthio)methyl)cyclohexan-1-one (**5 g**) were the most prominent and identified as potential leads as ALR2Is with K_I values of 0.53 ± 0.03 μM, 0.65 ± 0.04 μM, and 0.71 ± 0.05 μM, respectively, as compared with the K_I value of 0.79 ± 0.01 μM standard agent, EPR. In order to explain the interactions of the derivatives of bis-sulfide (**5 a–i**) and bis-sulfone (**6 a–i**) at binding sites, molecular docking experiments have also been carried out. It was discovered that these compounds are ALR2Is with appropriate drug-like qualities based on an *in silico* ADME-Tox. The bis-sulfide (**5 a–i**) and bis-sulfone (**6 a–i**) agents reported in this work may be exploited to create lead medicinal medicines that prevent diabetes complications.

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Table 2. ADME-Tox related parameters of the bis-sulfide (**5a–i**) and bis-sulfone (**6a–i**) derivatives and standard drug epalrestat (EPR).

Compound ID	MW[a]	#rtvFG[b]	CNS[c]	Dipole[d]	Volume[e]	QPpolrz[f]	QPlogPoct[g]	QPlogPw[h]	QPlogBB[i]	#Metab[j]	HOA%[k]	PSA[l]	Rule of five[m]	Rule of three[n]	PAINS[o]
5a	494.71	1	0	6.02	1527.92	55.82	20.87	7.26	−0.11	6	100.00	22.97	1	1	0
5b	594.83	1	0	5.78	1818.23	68.89	25.50	8.66	−0.14	4	100.00	23.06	2	1	0
5c	584.70	1	−2	4.36	1677.12	59.48	23.68	9.45	−2.15	8	79.52	113.06	2	2	0
5d	584.70	1	−2	2.29	1684.24	59.72	23.69	9.57	−2.41	6	75.75	113.02	2	1	0
5e	530.69	1	1	6.41	1549.82	55.99	21.28	6.71	0.24	6	100.00	20.49	2	1	0
5f	530.69	1	1	3.78	1562.45	56.47	21.24	6.81	0.12	4	100.00	22.98	2	1	0
5g	563.60	1	1	5.06	1573.39	56.79	21.63	6.62	0.37	6	100.00	18.96	2	1	0
5h	563.60	1	1	3.75	1569.76	56.31	21.33	6.39	0.36	4	100.00	19.86	2	1	0
5i	652.50	1	1	2.77	1628.25	58.96	22.20	6.79	0.21	6	100.00	22.01	2	1	0
6a	558.71	1	−2	1.18	1551.43	56.10	24.83	14.33	−1.15	6	88.72	91.56	1	0	0
6b	658.83	1	−2	11.76	1804.30	67.06	29.89	15.09	−1.10	4	87.76	88.78	2	1	0
6c	648.70	1	−2	10.55	1672.77	58.61	28.18	16.23	−2.75	8	42.87	179.62	2	1	0
6d	648.70	1	−2	6.74	1671.95	58.51	27.62	16.26	−2.87	6	40.72	179.50	2	1	0
6e	594.69	1	−1	9.05	1566.66	55.70	25.76	13.55	−0.79	6	92.14	90.19	1	0	0
6f	594.69	1	−1	11.28	1568.03	55.93	26.18	13.62	−0.71	4	94.63	88.15	1	0	0
6g	627.60	1	−1	10.44	1618.81	57.78	26.82	13.55	−0.62	6	84.46	89.40	2	0	0
6h	627.60	1	−1	8.31	1615.11	57.46	26.41	13.53	−0.74	4	81.61	91.58	2	0	0
6i	716.50	1	−1	11.38	1642.14	58.73	27.35	13.62	−0.60	6	85.78	88.82	2	0	0
EPR[p]	319.39	0	−1	6.31	982.62	31.29	14.97	8.09	−0.95	2	84.98	89.03	0	0	0

[a] Molecular weight of the molecule (130.0–725.0). [b] Number of reactive functional groups (0–2). [c] Predicted central nervous system activity (−2 (inactive) to +2 (active)). [d] Computed dipole moment of the molecule (1.0–12.5). [e] Total solvent-accessible volume in cubic angstroms using a probe with a 1.4 Å Radius (500.0–2000.0). [f] Predicted polarizability in cubic angstroms (13.0–70.0). [g] Predicted octanol/gas partition coefficient (8.0–35.0). [h] Predicted water/gas partition coefficient (4.0–45.0). [i] Predicted brain/blood partition coefficient (−3.0–1.2). [j] Number of likely metabolic reactions (#Metab: 1–8). [k] Predicted human oral absorption on 0 to 100% scale (poor $<25\%$, high $>80\%$). [l] Van der Waals surface area of polar nitrogen and oxygen atoms (7.0–200.0). [m] Number of violations of Lipinski's rule of five (max. 4). [n] Number of violations of Jorgensen's rule of three (max. 3). [o] Pan-assay interference compounds alert. [p] Standard drug epalrestat.

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Experimental Section

Chemistry

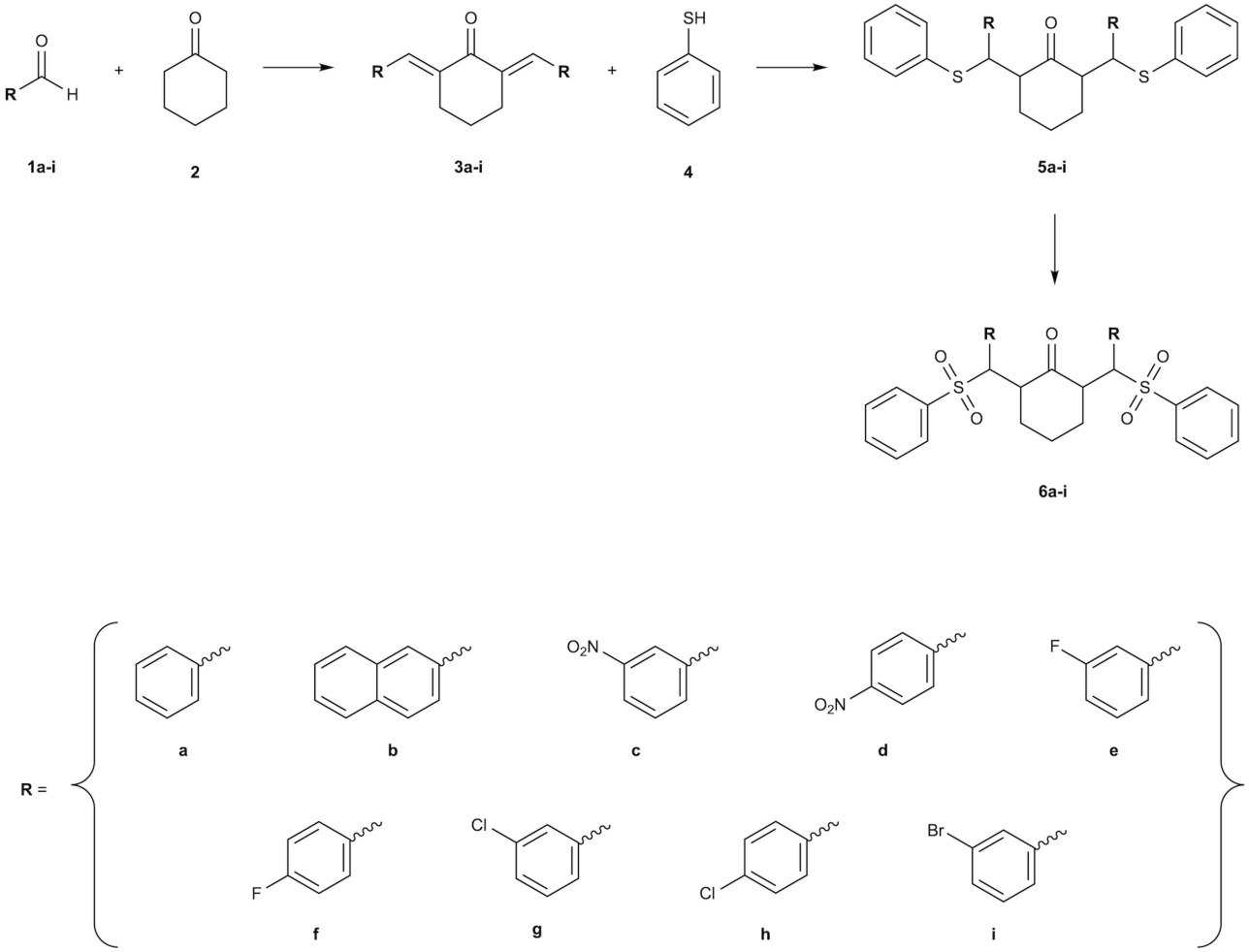
Bis-sulfide (**5 a**–**i**) and bis-sulfone (**6 a**–**i**) derivatives were synthesized according to our previous studies.[55,56] We used bis-chalcone derivatives in the synthesis of these compounds (Scheme 1). Bis-chalcones were synthesized according to our procedure by the condensation of cyclohexanone with aromatic aldehydes.[75] By reacting 1,4-Michael addition of bis-chalcones with thiophenol, we were able to synthesize bis-sulfides (**5 a**–**i**) using our previous methods.[56] At room temperature and under straightforward reaction conditions, bis-sulfides (**5 a**–**i**) were changed into bis-sulfones (**6 a**–**i**) by the employment of the oxidant *meta*-chloroperbenzoic acid (*m*-CPBA) (Scheme 1).[55] Spectroscopic details of the compounds are given in both this literature and Supplementary Information.

Biological activity study

Ammonium sulfate precipitation, DE-52 cellulose ion-exchange column, Sephadex G-100 gel-filtration column, and 2′,5′-ADP-Sepharose 4B affinity column chromatography techniques were all used to purify ALR2 from sheep kidneys in the same manner as past studies.[76–78] The Bradford's method,[79] a straightforward and speedy analytical technique at 595 nm wavelength, was used to measure the protein's quantity as described previously quantitatively.[80–83] According to Laemmli's method,[84] SDS-PAGE was used to analyze the purified enzyme fraction of ALR2 and was carried out on slab gels with an 8 percent concentration.[85–88] Solutions of the bis-sulfide (**5 a**–**i**) and bis-sulfone (**6 a**–**i**) derivatives and EPR were made using DMSO (PubChem CID: 679, Sigma D8418) at a starting concentration of 1 mg/mL. In the final reaction mixture, DMSO was present at a concentration of around 1 %.[89] To investigate the *in vitro* inhibitory mechanisms of these bis-sulfides (**5 a**–**i**) and bis-sulfones (**6 a**–**i**) against ALR2[90–92], the kinetic tests were conducted using Cerelli's method[93] at 340 nm, spectrophotometrically, and the DL-glyceraldehyde (PubChem CID: 79014) was used as the substrate.[94–97] All the samples were measured three times. In accordance with our earlier research, IC_{50} plots and Lineweaver-Burk curves[98] were made, and K_I constants, their coefficient of determination (R^2), and inhibition types were determined based on the observed data.[99,100]

Computational study

Small-Molecule Drug Discovery Suite 2022–1 for Mac (Schrödinger, LLC, NY, USA), which includes the Maestro v13, QikProp[101] v7, Protein Preparation Wizard,[102] SiteMap,[103,104] LigPrep,[105] Receptor



Scheme 1. Synthetic route for the preparation of bis-sulfide (**5 a–i**) and bis-sulfone (**6 a**–**i**) derivatives.

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Grid Generation,[106] Ligand Docking, and Prime MM-GBSA[107] v3 tools, was used to perform *in silico* studies, ADME calculations[108] and molecular docking works, as previously reported.[109–111] Protein Data Bank (http://www.rcsb.org/) was used to obtain the crystal structure of ALR2[112] (PDB ID: 4JIR; Resolution: 2.00; Species: Homo sapiens).[113] The Protein Preparation Wizard[114,115] in the Maestro panel[116] was used to optimize protein structurally. In ChemDraw program[117] v19 for Mac, bis-sulfide (**5 a–i**) and bis-sulfone (**6 a–i**) derivatives were created using drawing tools (PerkinElmer, Inc., Waltham, MA, USA). The LigPrep application[118] was used to generate the most likely ionization state in the OPLS4 force field at pH 7.0 ± 2.0 using Epik.[119,120] The Receptor Grid Generation program[121] was utilized to create energy grids with default parameters.[122] The scoring function was used to perform extra precision glide calculations (XP).[123–127] Using the VSGB energy model[128,129] and the OPLS4 force field, the MM-GBSA binding energies[130,131] were computed, which predict relative binding affinities for these bis-sulfides (**5 a–i**) and bis-sulfones (**6 a–i**).

Statistical study

Making use of GraphPad Prism v9 for Mac, data analysis and graph creation were carried out (GraphPad Software, La Jolla, California, USA). SigmaPlot v12 for Windows was used to calculate the inhibition constants (Systat Software, San Jose, California, USA). Using the additional sum-of-squares F test and the AICc method, the fit of enzyme inhibition models was examined. The data were presented as mean standard error of the mean (95 percent confidence intervals). When the *p*-value was less than 0.05, differences between data sets were deemed statistically significant

Supporting Information Summary

Characterization data and copies of FT-IR, ^{1}H NMR, and ^{13}C NMR spectra for all the compounds.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: ADME-Tox · Aldose reductase · Biological Activity · Enzymes · Inhibition

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