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Assessment of the inhibitory effects and molecular docking of some sulfonamides on human serum paraoxonase 1

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Abstract

Paraoxonase-1 (PON1) is an organophosphate hydrolyzer and antiatherogenic enzyme. Due to the PON1's crucial functions, inhibitors and activators of PON1 must be known for pharmacological applications. In this study, we investigated the *in vitro* effects of some sulfonamides compounds on human serum PON1 (hPON1). For this aim, we purified the hPON1 from human serum with high specific activity by using simple chromatographic methods, and after the purification processes, we investigated *in vitro* interactions between the enzyme and some sulfonamides (2-amino-5-methyl-1,3-benzenedisulfonamide, 2-chloro-4-sülfamoilaniline, 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, sulfisomidine, and 5-amino-2-methylbenzenesulfonamide). IC_{50}, K_i values, and inhibition types were calculated for each sulfonamide. 2-amino-5-methyl-1,3-benzenedisulfonamide and 2-chloro-4-sülfamoilaniline exhibited noncompetitive inhibition effect, whereas 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine exhibited mixed type inhibition. On the other hand, 5-amino-2-methylbenzenesulfonamide showed competitive inhibition and so molecular docking studies were performed for this compound in order to assess the probable binding mechanism into the active site of hPON1.

KEYWORDS

atherosclerosis, inhibition, molecular docking, paraoxonase-1, sulfonamide

1 | INTRODUCTION

Atherosclerosis is an inflammatory disease, and is one of the leading causes of death in the developing world.[1] Oxidized low-density lipoprotein (LDL) plays a central role in the progression of atherosclerosis. Human paraoxonase-1 (hPON1), a high-density lipoprotein (HDL)-associated serum esterase/lactonase, protects HDL and LDL from oxidative modifications. Thus, PON1 is protective against the development of atherosclerosis.[2]

Paraoxonase is an important enzyme family, and in recent years, it has gained significance in a wide range of research applications especially due to its detoxification functionality and antiatherogenic activity.[3] Paraoxonase was identified in the early 1950s after Abraham Mazur's note about an animal enzyme capable of hydrolyzing organophosphates.[4] Due to this enzyme's capability of hydrolyzing paraoxon, a toxic metabolite of pesticide parathion, this enzyme was named paraoxonase.[5] The paraoxonase gene family was discovered as a multigene family in 1996 by Primo-Parmo and colleagues, and they were named PON1, PON2, and PON3.[6] PON1, PON2, and PON3 are located side by side in the long arm of chromosome 7 q21.3-22.1 in humans, and they are located in chromosome 6 in mice. These genes show an approximate similarity at a 65% amino acid level and at a 70% the nucleotide level.[7] However, PON1, PON2, and PON3 show differences in terms of their intracellular localizations, catalytic activities, and substrate specificities.[8] PONs possess physiologically significant hydrolytic activities for drug metabolism and detoxification of the nerve agents.[9] However, research has mainly focused on the PON1 due to its well-documented role in preventing oxidation of LDL and HDL, and hence protecting against atherosclerosis. PON1 activity levels are vital not only for cardiovascular diseases, but also for others associated with oxidative stress. Because of this, the changes in PON1 enzyme activity could endanger life.[8] Thus, the determination of PON1 inhibitors and activators are very important.

Many drugs and chemical substances show their effects on metabolism through enzymes. That is, they stop or enhance the activity of a particular enzyme. Nowadays, drugs that function as enzyme inhibitors constitute a significant proportion of the currently used therapeutically active agents. Therefore, the investigation of the effects of medical active compounds on metabolic enzymes is very important for drug design studies.[10] In this study, we examined the *in*

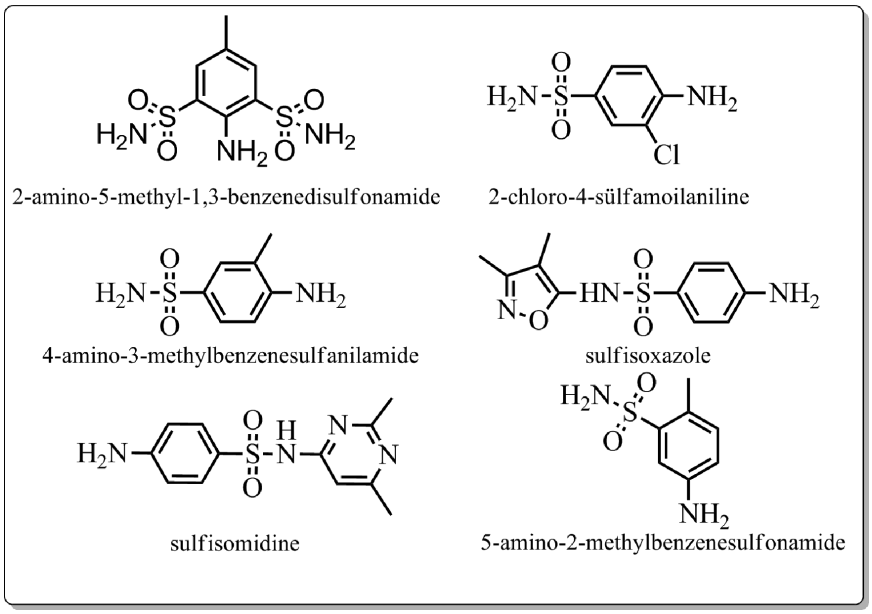

FIGURE 1 The molecular structures of sulfonamides used in this study

vitro effects of some sulfonamide compounds on human serum PON1 activity.

Sulfonamides are compounds that have a general structure of R-S (= O_2)-NH_2. They interfere with PABA (p-aminobenzoic acid) in the biosynthesis of tetrahydrofolic acid, which is a basic growth factor essential for the metabolic process of bacteria. Therefore, sulfonamides are an important class of medicinally active compounds,[11–16] and they are used as preventive and chemotherapeutic agents against various diseases.[17] Sulfonamides possess many types of biological activities such as antibacterial,[18] anti-carbonic anhydrase, hypoglycemic, diuretic, antithyroid,[19] anti-hypertensive,[20] antiviral,[21] antiprotozoal,[22] antifungal,[23] anti-inflammatory, and antitumor activity.[24] In this study, we examined the *in vitro* effects of 2-amino-5-methyl-1,3-benzenedisulfonamide, 2-chloro-4-sülfamoilaniline, 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, sulfisomidine, and 5-amino-2-methylbenzenesulfonamide (Figure 1) on purified human serum PON1 activity. IC_{50}, K_i constants, and inhibition mechanism of these compounds were firstly determined for hPON1 in this study.

2 | MATERIAL AND METHODS

2.1 | Chemicals and instruments

The chemicals for electrophoresis, sulfonamides, DEAE-Sephadex A50, Sephadex G100, paraoxon, and other chemicals used in experimental procedures were obtained from Sigma–Aldrich Co. (Sigma–Aldrich Chemie GmbH, Taufkirchen, Germany).

2.2 | Paraoxonase activity assay

The paraoxonase activity assay was based on the estimation of p-nitrophenol at a 412 nm. Paraoxon (diethyl p-nitrophenyl phosphate) was used as a substrate. The assays were performed using a spectrophotometer (CHEBIOS UV–VIS). An approximate 1 mL total volume of the enzymatic reaction mix contained a 50 mM glycine/NaOH buffer (pH 10.5) containing 1 mM$CaCl_2$, 1 mM paraoxon, and enzyme solution. One enzyme unit was defined as the amount of enzyme that catalyzes the hydrolysis of 1 μmol of paraoxon at 25°C.[25]

2.3 | Purification of PON1 from human serum

Twenty milliliters of human serum was treated with Triton X-100. Then, an ammonium sulfate (60–80%) precipitation was applied as in our previous studies. The resulting enzyme solution was dialyzed against 100 mM sodium phosphate buffer (pH 7.0). The dialyzed enzyme solution was loaded onto the DEAE-Sephadex A50 anion-exchange column previously equilibrated with the 100 mM Na-phosphate buffer (pH 7.0). The column was washed with a 100 mM Na-phosphate buffer to remove other impurities. A linear gradient of 0–1.5 M NaCl was used to elute the enzyme. The activity measurements were made at 412 nm in all the elutions, and the active fractions were pooled. Then, this enzyme solution was loaded onto the Sephadex G-100 column equilibrated with a 100 mM Na-phosphate buffer (pH 7.0). Both the qualitative protein identification (280 nm) and enzyme activity (412 nm) were monitored in the eluates. The tubes observed in the enzyme activity were combined for other kinetic studies. All purification procedures were performed at 4°C. These processes were performed as in our previous studies.[3,8] The enzyme purity was controlled according to Laemmli's procedure.[26]

2.4 | Protein determination

The quantitative protein assay was performed according to the Bradford method. Bovine serum albumin was used as a standard.[27]

TABLE 1 Summary of the PON1 Purification Procedure from Human Serum

Purification Steps	Activity (EU/mL)	Total Volume (mL)	Protein (mg/mL)	Total Protein (mg)	Total Activity (EU)	Specific Activity (EU/mg)	Yield (%)	Purification Fold
Serum sample	105.4	20	7.1	142	2108	14.84	100	1
Ammonium sulfate precipitation (60-80%)	102.2	15	5.2	78	1533	19.65	72.72	1.32
DEAE-Sephadex A-50 anion-exchange chromatography	68	12	0.176	2.112	816	386.36	38.71	26.04
Sephadex G-100 gel filtration chromatography	55.2	6	0.0128	0.0768	331.2	4312.5	15.71	290.6

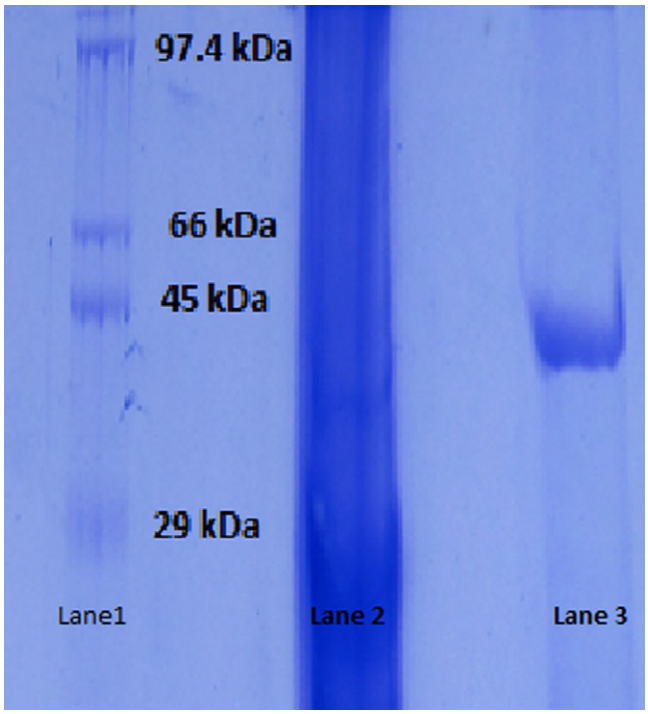

FIGURE 2 Sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis of purified human serum PON1. Lane 1, standard proteins (kDa); lane 2, human serum sample; lane 3, purified human serum PON1

2.5 | *In vitro* interaction studies of sulfonamides with hPON1

The *in vitro* effects of 2-amino-5-methyl-1,3-benzenedisulfonamide, 2-chloro-4-sülfamoilaniline, 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, sulfisomidine, and 5-amino-2-methylbenzenesulfonamide on the hPON1 were examined. The human serum PON1 activity was measured at different sulfonamide concentrations. Activity%-[Sulfonamide] graphs were plotted for each compound and sulfonamide concentrations that produced a 50% inhibition (IC_{50}) were calculated from these graphs. In addition, Lineweaver–Burk graphs were used for the determination of the K_i and inhibition type.[28]

2.6 | Molecular docking studies

The crystal structure of serum PON1 in complex with 2-hydroxyquinoline (PDB ID: 3SRG)[29] at a resolution of 2.19 Å was prepared by the Protein Preparation Wizard of Schrödinger by eliminating the 2-hydroxyquinoline and all the water molecules from its crystal structure, determining the bond order, adding the hydrogen atoms, and adjusting the physiological pH 7 using the PROPKA software. Lastly, the restrained minimization of the added hydrogen atoms was made with a cut off of 0.3 Å.[30] The ligand preparation tool of a Maestro was used to create the 3D of 5-amino-2-methylbenzenesulfonamide. In addition, all the protonated states of the ligand in the pH range 7 ± 2 were generated using an Epik in

TABLE 2 IC_{50}, K_i Values, and Inhibition Types of Sulfonamide Compounds for hPON1

Sulfonamides	IC_{50} (mM)	K_i (mM)		Inhibition Type
2-amino-5-methyl-1,3-benzenedisulfonamide	0.185	0.301 ± 0.0521		Noncompetitive
2-chloro-4-sülfamoilaniline	0.314	0.151 ± 0.0545		Noncompetitive
4-amino-3-methylbenzenesulfanilamide	0.490	K_i	K_i'	Mixed
		0.210 ± 0.0170	0.239 ± 0.116	
Sulfisoxazole	0.520	K_i	K_i'	Mixed
		0.447 ± 0.074	3.396 ± 0.537	
Sulfisomidine	0.922	K_i	K_i'	Mixed
		1.156 ± 0.464	5.048 ± 2.675	
5-amino-2-methylbenzenesulfonamide	1.490	0.587 ± 0.281		Competitive

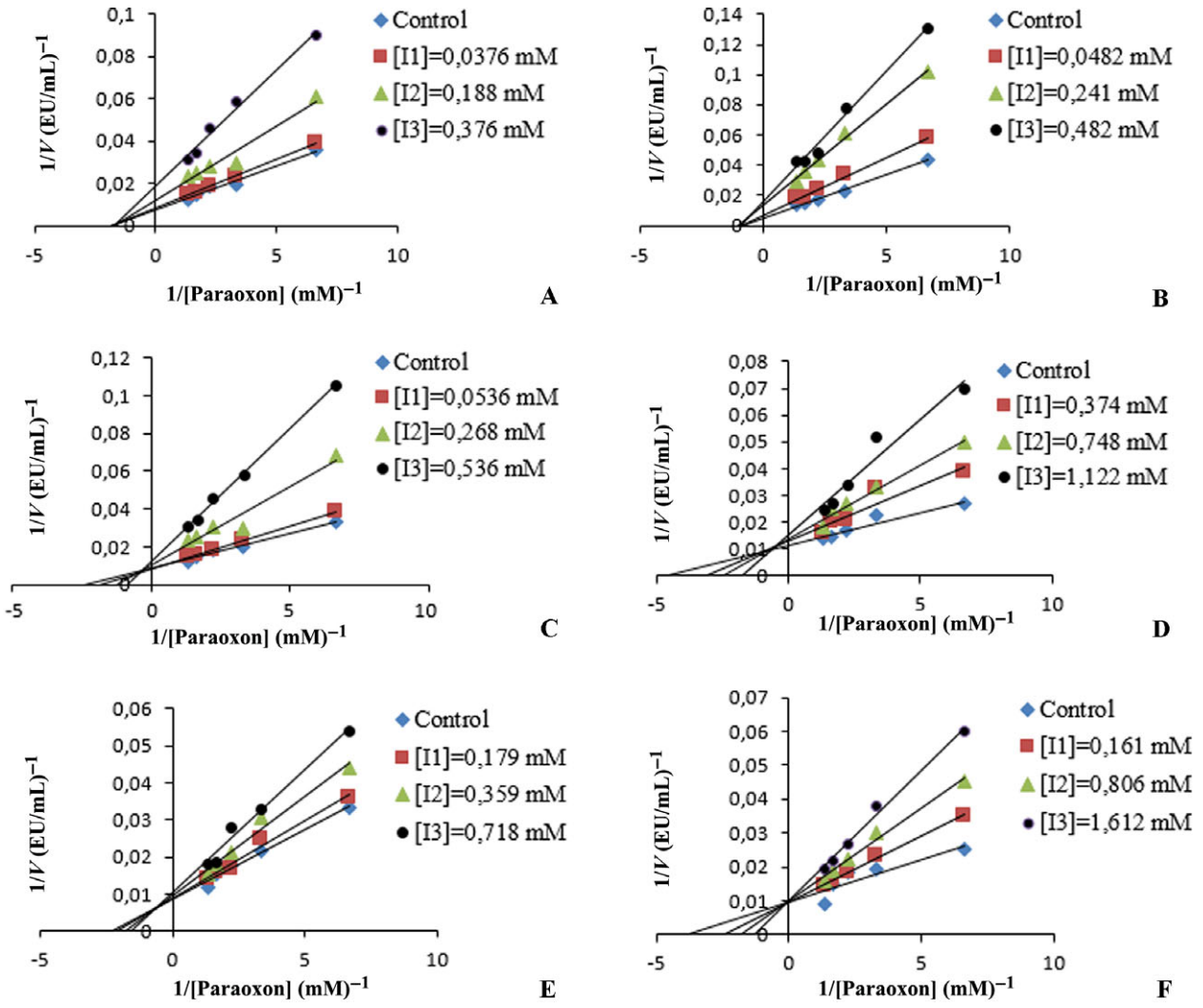

FIGURE 3 Lineweaver–Burk graphs of 2-amino-5-methyl-1,3-benzenedisulfonamide (A), 2-chloro-4-sülfamoilaniline (B), 4-amino-3-methylbenzenesulfanilamide (C), sulfisoxazole (D), sulfisomidine, and 5-amino-2-methylbenzenesulfonamide (E) for determination of K_i and inhibition type

the Maestro[31,32] The co-crystallized 2-hydroxyquinoline in the active site was used as centered for the docking box, and the grid files were generated using the receptor grid generation section. The docking score, presenting the prediction of binding energies, was obtained using the Glide/XP docking protocols.[33,34]

3 | RESULTS

In this study, we purified a PON1 enzyme from human serum by using DEAE–Sephadex anion exchange and sephadex G-100 gel filtration chromatography. The enzyme was obtained with a specific activity of

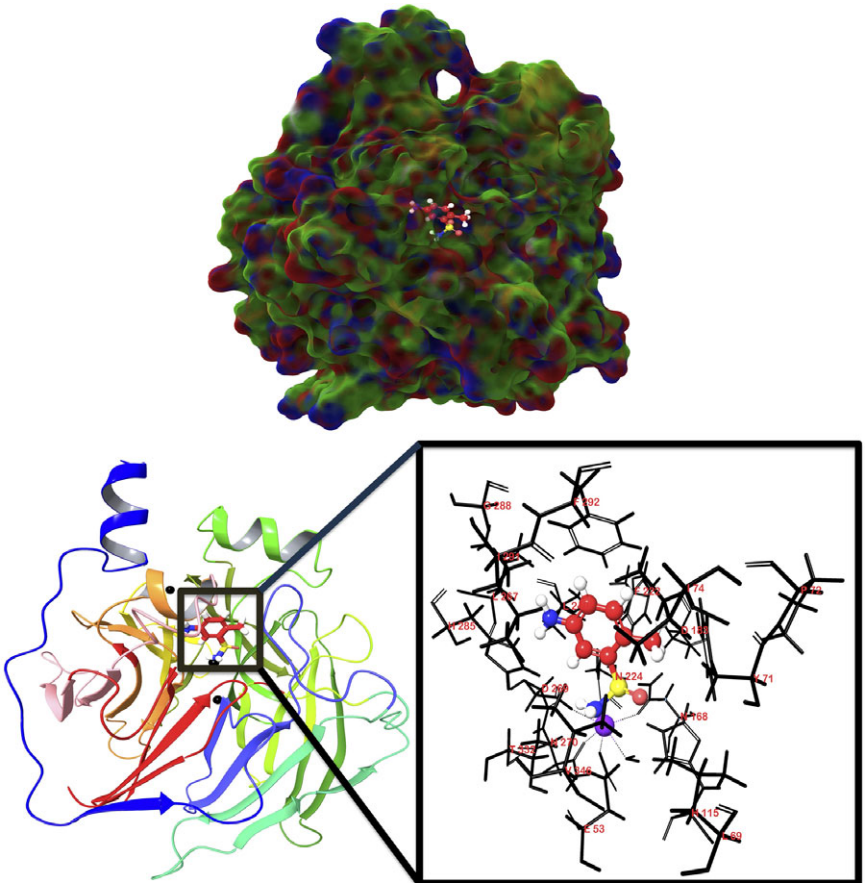

FIGURE 4 Docking pose of 5-amino-2-methylbenzenesulfonamide in ligand binding site of hPON1 (PDB ID: 3SRG)

a 4312.5 EU/mg protein with a 290.6-fold purification, and a yield of 15.71% (Table 1). The SDS-PAGE was performed after the purification of the enzyme, and the electrophoretic pattern is shown in Figure 2. After the purification steps, the *in vitro* inhibition effects of 2-amino-5-methyl-1,3-benzenedisulfonamide, 2-chloro-4-sülfamoilaniline, 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, sulfisomidine, and 5-amino-2-methylbenzenesulfonamide on the purified enzyme were investigated. Both the IC_{50} and K_i values of the sulfonamide compounds were determined via Activity%–[Sulfonamide] and Lineweaver–Burk graphs ($1/V–1/[S]$), respectively. The IC_{50} values were found to be 0.185, 0.314, 0.490, 0.520, 0.922, and 1.490 mM for 2-amino-5-methyl-1,3-benzenedisulfonamide, 2-chloro-4-sülfamoilaniline, 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, sulfisomidine, and 5-amino-2-methylbenzenesulfonamide, respectively (Table 2). The K_i constants were obtained from the Lineweaver–Burk graphs ($1/V–1/[S]$) (Figure 3), and an inhibition type was found for each sulfonamide. 2-amino-5-methyl-1,3-benzenedisulfonamide and 2-chloro-4-sülfamoilaniline exhibited non-competitive inhibition, and the K_i values were found to be 0.301 ± 0.0521 0.151 ± 0.0545 mM, respectively. 4-Amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine exhibited mixed type inhibition. K_i values were found to be 0.210 ± 0.0170, 0.447 ± 0.074, and 1.156 ± 0.464 mM for 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine, respectively. K_i' values were found to be 0.239 ± 0.116, 3.396 ± 0.537, and 5.048 ± 2.675 mM for 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine, respectively. The 5-amino-2-methylbenzenesulfonamide exhibited competitive inhibition, and the K_i value was found to be 0.587 ± 0.281 mM. The molecular docking studies were performed for this compound in order to assess the probable binding mechanism into the active site of the hPON1. The crystallographic structure of the serum PON1 (PDB ID: 3SRG)[29] was used as the receptor for the docking. The 5-amino-2-methylbenzenesulfonamide determined as a competitive type of inhibition was docked at the ligand binding site of the hPON1 using the Glide XP protocol and Gilde XP score, which was obtained as −6.09 kcal/mol. This score predicts the affinity between the ligand and the hPON1 receptor. 3D image and 2D diagram of the docking pose of 5-amino-2-methylbenzenesulfonamide in the ligand binding site of the hPON1 receptor is represented in Figures 4 and 5.

4 | DISCUSSION

The PON1 enzyme activity level is vital both in cardiovascular diseases and other diseases associated with increased oxidative stress and inflammation.[35,36] Because of this, the diminished PON1 activity is associated with many diseases such as familial hypercholesterolemia,[37] type 1 and type 2 diabetes mellitus,[38] chronic kidney failure,[39] aging,[40] neurological disorders,[41,42] and

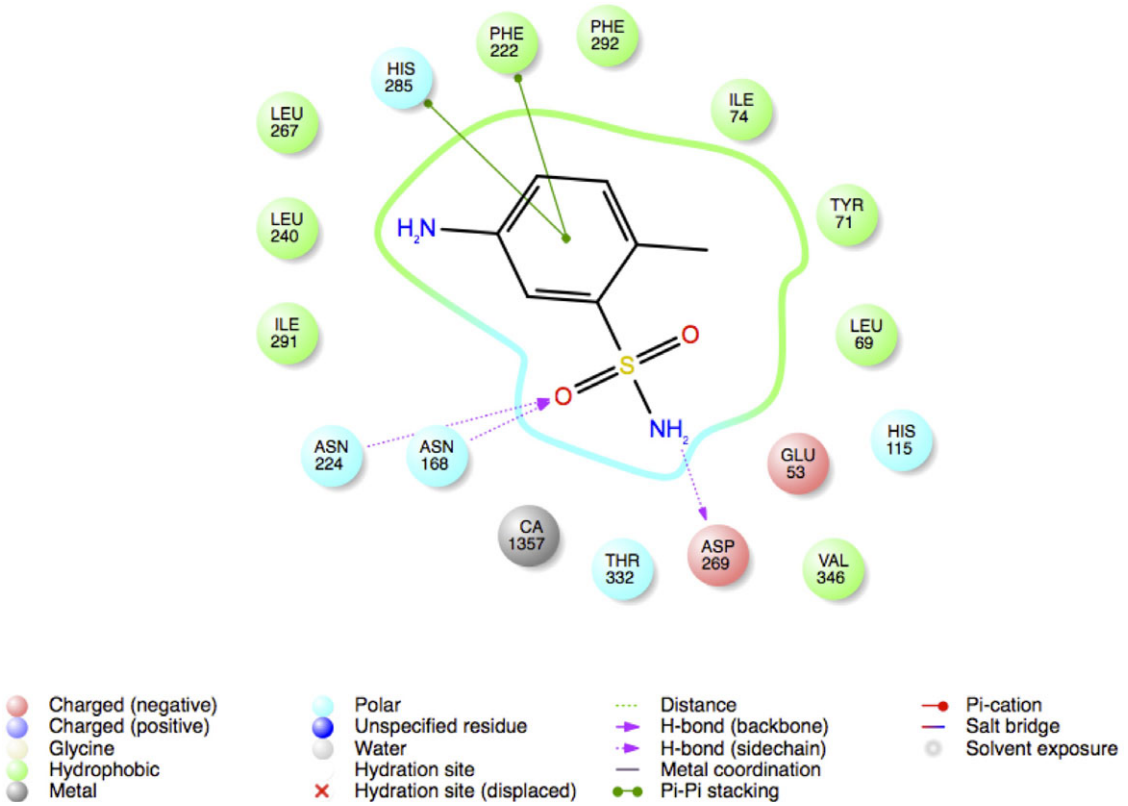

FIGURE 5 2D ligand interaction diagram of 5-amino-2-methylbenzenesulfonamide

cancer.[43] Thus, the preservation of PON1 activity is crucial for organisms.

Many studies have been conducted on the modulation of PON1 activity by drugs or chemicals in the literature.[8] In this study, we aimed to examine the *in vitro* effects of some sulfonamide compounds on human serum PON1 activity. Sulfonamides are important heterocyclic compounds with various biological activities. For instance, sulfisoxazole has antibiotic activity against a wide range of Gram-negative and Gram-positive organisms.[44] Moreover, sulfisomidine is an important antibacterial agent.[45]

In this study, the hPON1 was purified from human serum. After purification process, the *in vitro* inhibition effects of the sulfonamides on the purified enzyme were investigated. Both the IC_{50} and K_i parameters of the each sulfonamides were determined in this study from Activity%–[Inhibitor] graphs and Lineweaver–Burk graphs (1/*V*–1/[*S*]), respectively. According to the results, 2-amino-5-methyl-1,3-benzenedisulfonamide has a stronger inhibitory effect than other sulfonamides. K_i constants were obtained from the Lineweaver–Burk graph (1/*V*–1/[*S*]), and inhibition type was found for each sulfonamide. 2-Amino-5-methyl-1,3-benzenedisulfonamide and 2-chloro-4-sülfamoilaniline exhibited noncompetitive inhibition, and K_i values were found to be 0.301 ± 0.052 and 0.151 ± 0.054 mM, respectively. According to this conclusion, these sulfonamides may have a connection with somewhere other than the active site of the hPON1 enzyme. The 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine exhibited a mixed type inhibition. According to this result, the 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine lead to inhibition by binding to the free enzyme or enzyme substrate complex. The K_i values were found to be 0.210 ± 0.0170, 0.447 ± 0.074, and 1.156 ± 0.464 mM for 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine, respectively. The K_i' values were found to be 0.239 ± 0.116, 3.396 ± 0.537, and 5.048 ± 2.675 mM for 4-amino-3-methylbenzenesulfanilamide, sulfisoxazole, and sulfisomidine, respectively. 5-Amino-2-methylbenzenesulfonamide exhibited competitive inhibition, and K_i value was found to be 0.587 ± 0.281 mM. Accordingly, 5-amino-2-methylbenzenesulfonamide may have a connection with the amino acids of the hPON1 active site. In this study, the molecular docking studies were performed in order to determine the probable binding mechanism of 5-amino-2-methylbenzenesulfonamide into the active site of the PON1. The 2D ligand interaction diagram presents the key residues involved in the binding of the ligand to us and the interactions of these residues. This diagram revealed that while Asn 168, Asn 224, Thr 332, His 115, and His 285 residues construct polar interactions; Leu 69, Tyr 71, Ile 74, Phe 222, Leu 240, Leu 267, Ile 291, Phe 292, and Val 346 residues form hydrophobic interactions with 5-amino-2-methylbenzenesulfonamide. While the Asn 168, Asn 224, and Asp 269 residues form the hydrogen bond interactions; His 285 and Phe 222 construct the π–π stacking interactions with the ligand.

In conclusion, we observed that the sulfonamides decreased the enzyme activity at low concentrations. Therefore, drugs with sulfonamide in combination should be used with caution, especially on patients with metabolic diseases in which PON1 activity is important.

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