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Original article

The inhibition effects of some sulfonamides on human serum paraoxonase-1 (hPON1)

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ABSTRACT

Background: Paraoxonase 1 (PON1) is an antiatherogenic and organophosphate hydrolyzer enzyme. It has important roles including protecting low density lipoprotein (LDL) against oxidation and the detoxification of highly toxic substances. Reducing the levels of this enzyme in patients with diabetes mellitus, cardiovascular diseases, hyperthyroidism, and chronic renal failure is a major risk.
Methods: Here, we report on the purification of the human serum PON1 using simple methods and determine the interactions between some sulfonamides and the enzyme.
Results: We found that some sulfonamides exhibit potential inhibitor properties for the human serum PON1 with IC_{50} values in the range of 24.10–201.45 μM and K_i values in the range of 4.41 ± 0.52–150.23 ± 20.73 μM. The sulfonamides showed different inhibition mechanisms. We determined that sulfonamides **1, 2, 4, 5, 8,** and **9** showed a non-competitive inhibition effect whereas sulfonamides **3, 6** and **7** showed competitive inhibition.
Conclusion: Use of drugs containing the sulfonamides molecule groups with crucial biological activity would be very dangerous in some cases.

Introduction

The human serum paraoxonase-1 (PON1) enzyme is an ester hydrolase and is synthesized in the liver. This enzyme is related to high-density lipoprotein (HDL), which is calcium dependent and has a molecular weight of 43–45 kDa. Previously, paraoxonase was thought to be a lactonase due to its physiological effects. However, the biological function and the physiological substrate of this enzyme have not yet been determined [1].

During normal cell metabolism, free oxygen radicals are continuously produced, and oxidative stress occurs. Increased oxidative stress has a significant role in both psoriatic disease and atherosclerosis. HDL (high density lipoprotein) cholesterol aids in inhibiting lipid oxidation by PON1, a part of the antioxidant enzymatic proteins family found on HDL particles. Recently, it has been shown that positive cardiovascular outcomes are not just based on rising plasma levels of HDL cholesterol but also on the anti-atherogenic, anti-inflammatory, and anti-oxidant, function of HDL because of PON1 enzymatic activity [2,3]. PON1 plays a role as an antioxidant enzyme by protecting HDLs and low-density lipoproteins (LDHs) from oxidative stress, which is thought to be related to a number of different vascular diseases such as atherosclerosis. Decreased PON1 activity is thought to be a biomarker for the conversion of HDL to a dysfunctional pro-atherogenic and pro-inflammatory state and increased systemic oxidative stress and has been related to the development of cardiovascular disease. It has been shown that diminished PON1 enzymatic activity encourages the development of adverse cardiovascular cases [4,5].

Sulfonamide compounds are the basis for a variety of drug classes known as sulfamide drugs. Molecules containing sulfonamide moiety (SO_2NH_2) in the structure are called sulfonamides. Due to pharmaceutic and various biological processes in agricultural areas, these compounds have to be taken into account [6–9]. The main sulfonamide compounds of the type RSO_2NH_2 comprise an important class of drugs. They have different types of pharmacological factors such as antiviral, antibacterial, and anticancer activities; and protease inhibition, cyclooxygenase 2 (COX2) inhibition, carbonic anhydrase (CA) inhibition, and diuretic action. Some other biological activities of sulfonamides including acylsulfonamides, benzenesulfonamides, hetaryl sulfonamides, phenolic sulfonamides, and secondary sulfonamides have been studied by researchers [10–14]. These compounds are also used in the treatment of trachoma, meningitis, conjunctivitis, streptococcal pharyngitis, malaria, bacillary dysentery, toxolasmosis, and nocardiosis [15,16].

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In the current study, we purified hPON1 from human serum by using a rapid and simple procedure and determined the *in vitro* effects of some sulfonamides [5-bromothiophene 2-sulfonamide (**1**), naphthalene-2- sulfonamide (**2**), 4,5-dichlorothiophene-2-sulfonamide (**3**), 2,5-dichlorothiophene-3-sulfonamide (**4**), 5-(2-aminoethyl)thiophene-2-sulfonamide (**5**), 5-(aminomethyl) thiophene-2-sulfonamide (**6**), 5-chlorothiophene-2-sulfonamide (**7**), 5-chloro-3-methyl-1-benzothiophene-2-sulfonamide (**8**), and 6-aminopyridine-3-sulfonamide (**9**)] on PON1 activity (Fig. 1).

Material and methods

Chemicals

All chemicals were obtained from Sigma Chemical Co. Standard protein markers for electrophoresis were obtained from Thermo.

Paraoxonase activity assay

hPON1 activity was measured using paraoxon (diethyl p-nitrophenyl phosphate) as a substrate (1 mM) in 50 mM glycine/NaOH (pH 10.5) including 1 mM $CaCl_2$ at 412 nm [17].

Purification of PON1

Human serum proteins were isolated using ammonium sulfate precipitation. 60% to 80% ammonium sulfate saturation was dissolved in 100 mM Na-phosphate buffer (pH 7.0) and dialyzed against the same buffer. It was applied to the DEAE-Sephadex ion exchange column and eluated with 0 up to 1.5 M NaCl. Combined enzyme fractions from the ion exchange column were applied to the Sephadex G-100 column. After this column, tubes showing high activity were tested using the SDS-PAGE technique [18].

Protein quantity assay

A quantitative amount of enzyme was determined according to the Bradford procedure at 595 nm, spectrophotometrically [19]. Bovine serum albumin was used as standard protein [20,21].

Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE)

According to the Laemmli procedure [22], the purity and presence of PON1 were observed by the SDS-PAGE technique. The procedure was performed according to our previous studies [23–25]. After this procedure, a single band was seen for PON1.

In vitro *inhibition studies*

The inhibition effects of sulfonamides were investigated at least five different inhibitor concentrations on PON1. IC_{50} was defined as the concentration of a compound causing 50% inhibition, and it was calculated from activity (%)–[sulfonamide] graphs for each compound. The K_i values and inhibition types were found by Lineweaver and Burk's curves [26].

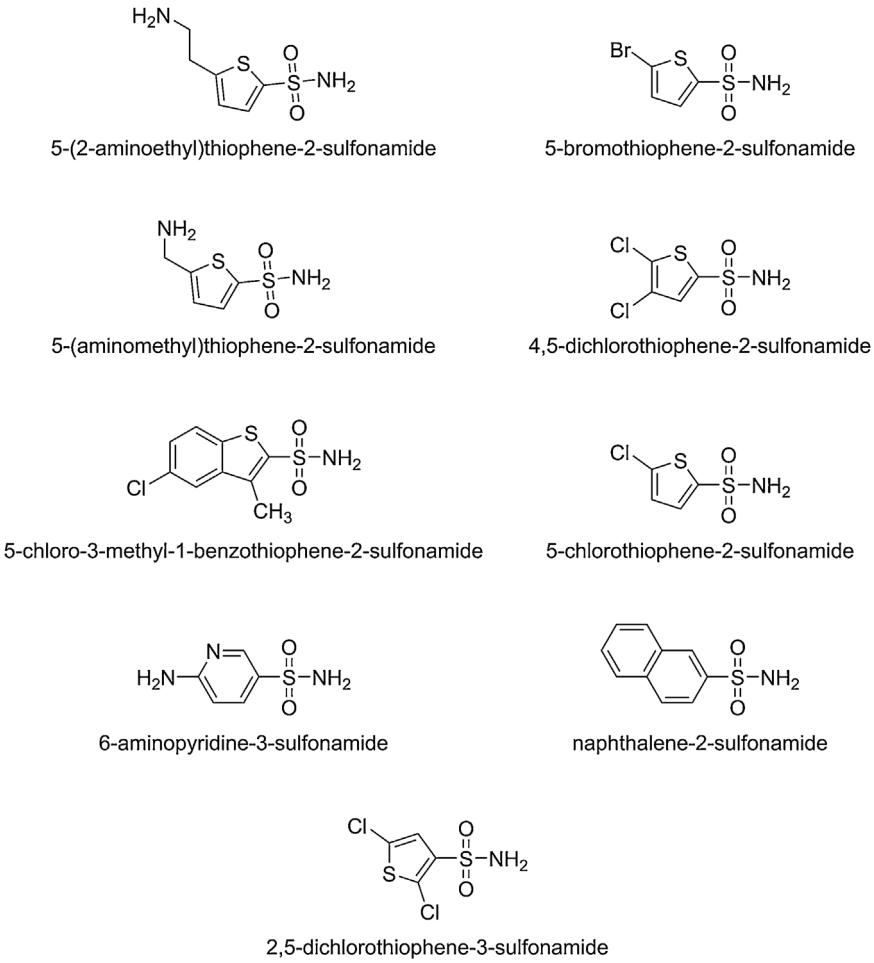

Fig. 1. The molecular structure of sulfonamides used in this study.

Results

In the present study, PON1 was purified from human serum using simple chromatic methods. The enzyme was obtained with 111.27-fold purification and with a specific activity of 1936.11 EU/mg protein (Table 1). The SDS-PAGE procedure was performed after the purification of the PON1 enzyme, and the molecular mass of the enzyme found to be approximately 43 kDa. (Fig. 2). Then, the *in vitro* inhibition impacts of **1–9** molecules on the purified enzyme were determined. IC_{50} values were found to be 201.45, 147.34, 24.10 193.56, 81.–13, 73.23, 85.35, 27.34, and 112.47 μM for 1–9 respectively. To determine K_i values and inhibition types for each sulfonamide molecule, Lineweaver–Burk graphs were drawn. K_i values were found to be 150.23 ± 20.73, 98.23 ± 5.69, 4.41 ± 0.52, 145.76 ± 3.12, 67.23 ± 8.22, 18.72 ± 4.68, 75.45 ± 4.08, 18.25 ± 2.12, and 92.26 ± 10.41 μM for 1–9 respectively (Table 2). We determined that compound **1, 2, 4, 5, 8,** and **9** showed non-competitive inhibition effect whereas compound **3, 6,** and **7** showed competitive inhibition.

Discussion

Oxidative stress can be identified as a disturbance in the prooxidant-antioxidant balance in favor of the former, leading to potential tissue and cellular injury [27]. Free oxygen radicals are generated in extreme amounts when oxidative stress occurs [28]. They have a crucial role in carcinogenesis and show high mutagenic activity [29,30]. There are antioxidant defense mechanisms to protect mammalian cells from reactive oxygen species such as PON, glutathione peroxidases, catalases, and superoxide dismutases [31]. The human body battles to balance its antioxidant and oxidant systems to carry on its biological functions.

It is well known that enzymes are crucial bio-catalyzers in metabolism. Therefore, all substances taken into the body may interact with various enzymes, especially some enzymes called drug-target and chemical target. PON is a mammalian lactonase that is found in the liver [32]. A decrease of PON1 activities may be related to some metabolic or genetic disorders such as diabetes mellitus, rheumatoid arthritis, cardiovascular diseases, chronic renal failure, age-related macular degeneration, and hyperthyroidism [33]. Moreover, PON1 has a significant role in the prevention of atherosclerosis and HDL metabolism [34]. Numerous studies have revealed that PON1 is a central contributor to the antioxidant capacity of HDL [35,36]. PON prevents the oxidation of both HDL and LDL by this antioxidant property. Thus, there is a close physiological connection between HDL and PON1 in plasma [37]. Free radical-induced liver impairment would result in a depletion of peroxisome proliferator-activated receptors (PPAR) gene expression and, as a result, in PON1 gene expression. It would also induce an inhibition of the ATP-binding cassette transporter (ABCA1), a depletion in serum PON1 concentration, and a depletion in HDL synthesis. Hence, serum lactonase activity would be depleted after these changes and because of a direct inhibition by free radicals. PON1 levels would also be raised as a result of decreased protein degradation (Fig. 3) [38].

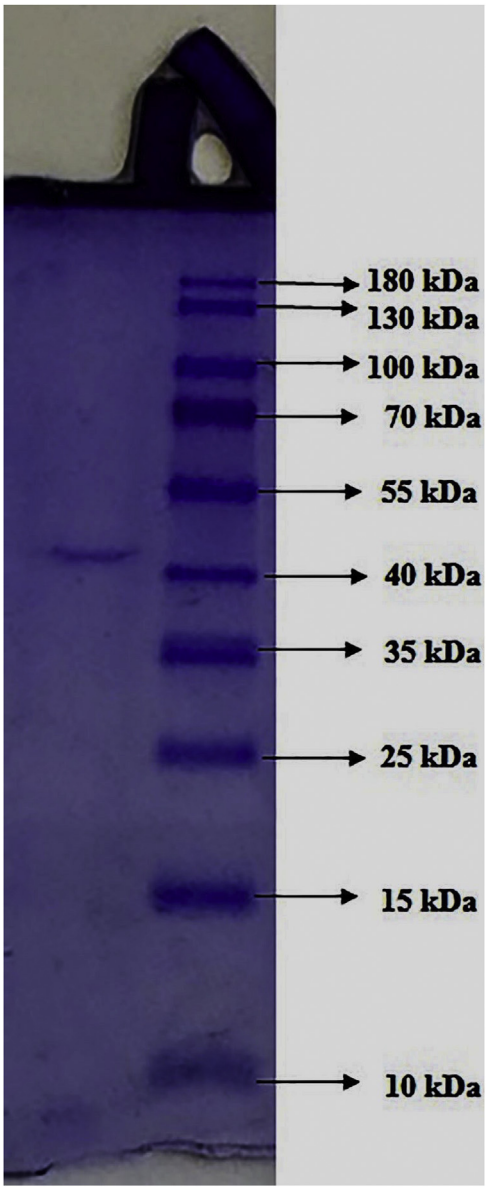

Fig. 2. SDS-PAGE analysis of PON1 to confirm the purify of the enzyme was carried out according to the Laemmli method. Samples were applied the electrophoresis, and the protein bands were obtained with Coomassie blue staining. The standard protein marker was purchased from Thermo.

PON1 has a crucial role in the living metabolism according to the information mentioned above. Also, this enzyme is important with regard to its pharmacokinetic role and is worthy of future research [39]. Recently, researchers have reported a number of studies on the different properties of PON1. On the other hand, few studies have been carried out on the connections between certain chemicals or drugs and PON1 activity, for instance, the impact of anticancer agents on hPON1 enzyme activity. These drugs exhibited an inhibition effect on the PON1

Table 1
Summary of the PON1 purification procedure from human serum.

Purification Steps	Total volume (mL)	Activity (EU/mL)	Protein (mg/mL)	Total protein (mg)	Total activity (EU)	Specific activity (EU/mg)	Purification fold	Yield (%)
Serum	30	124.38	7.15	214.50	3731.40	17.40	1	100
Ammonium sulfate precipitation (%60–80) and dialysis	22	110.29	5.17	113.74	2426.38	21.33	1.23	65.03
DEAE-Sephadex A50 anion exchange chromatography	14	66.23	0.313	4.38	927.22	211.69	12.17	24.81
Sephadex G-100 gel filtration chromatography	6	34.85	0.018	0.108	209.10	1936.11	111.27	5.59

Table 2
IC_{50}, K_i values and inhibition types of some sulfonamides on PON1.

Compounds name	Compounds No	IC_{50} (μM)	K_i (μM)	Inhibition type
5-Bromothiophene 2-sulfonamide	**1**	201.45	150.23 ± 20.73	Noncompetitive
Naphthalene-2- sulfonamide	**2**	147.34	98.23 ± 5.69	Noncompetitive
4,5-Dichlorothiophene-2-sulfonamide	**3**	24.10	4.41 ± 0.52	Competitive
2,5-Dichlorothiophene-3-sulfonamide	**4**	193.56	145.76 ± 3.12	Noncompetitive
5-(2-aminoethyl)thiophene-2-sulfonamide	**5**	81.13	67.23 ± 8.22	Noncompetitive
5-(aminomethyl)thiophene-2-sulfonamide	**6**	73.23	18.72 ± 4.68	Competitive
5-Chlorothiophene-2-sulfonamide	**7**	85.35	75.45 ± 4.08	Competitive
5-Chloro-3-methyl-1-benzothiophene-2-sulfonamide	**8**	27.34	18.25 ± 2.12	Noncompetitive
6-Aminopyridine-3-sulfonamide	**9**	112.47	92.26 ± 10.41	Noncompetitive

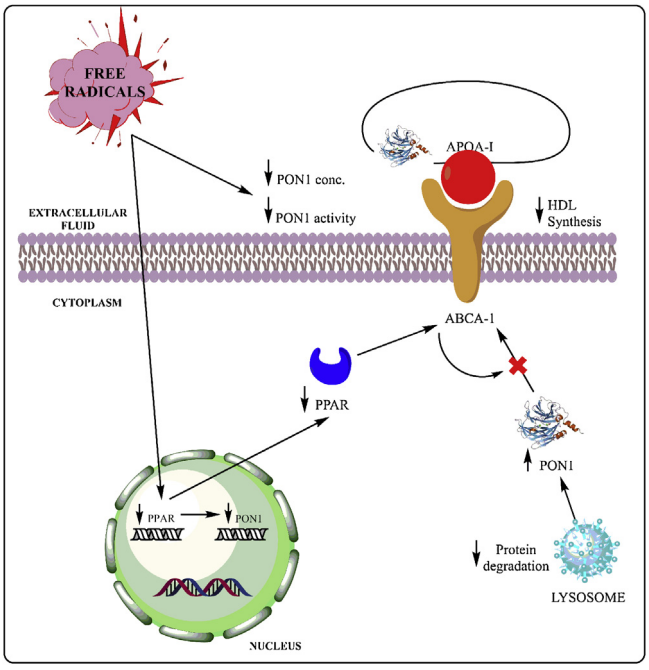

Fig. 3. The systematic demonstration of the effect of free radicals on PON1 [38].

enzyme. IC_{50} values were in the range of 0.011–23.3 mM [40]. Alım et al. [41] showed the *in vitro* impact of indazoles on hPON1. They found that IC_{50} values in a range of 72.9–358 μM against hPON1. In another study, Beydemir and Demir [42] studied the effect of epilepsy drugs on PON enzyme activity. They found that all studied compounds showed inhibition effects. There are a few studies about the inhibition of PON1 by sulfonamides in the literature. Alım et al. [43] studied the effect of some sulfonamides on PON1 activity and found IC_{50} values of studied sulfonamides in a range of 0.185–1.49 mM against hPON1. They determined that 2-chloro-4-sulfamoilaniline and 2-amino-5-methyl-1,3-benzenedisulfonamide showed a non-competitive inhibition effect whereas sulfisomidine, sulfisoxazole, and 4-amino-3-methylbenzenesulfanilamide showed a mixed-type inhibition. In addition, Ekinci et al. [44] investigated the *in vitro* impact of some sulfonamides such as homosulfanilamide furosemide, sulfosalazine, mafenide, 1,3,4-thiadiazole-2-sulfonamide, and acetazolamide on enzyme activity. They found IC_{50} values of six sulfonamides in a range of 0.18–1.24 mM against hPON1. Our results were more effective compared to other studies.

In the literature, many researchers purified the PON enzyme from different sources, employing various techniques. For example, PON3 was purified from rat liver using many column procedures with a yield of 0.4% and with a specific activity of 461 μmol min^{-1} mg^{-1} [45]. Human serum PON1 (hPON1) was purified using three simple procedures with ~ 217 fold, the specific activity of 3654.2 EU/mg protein, with a yield of 16.84% [31]. In the current study, hPON1 was purified from human serum using simple purification procedures. The enzyme was purified with a specific activity of 1936.11 EU/mg protein with ~ 111-fold purification and a yield of 5.59% (Table 1). We used the same procedure as the previous study. It was shown that specific activity (1936.11 U/mg proteins) in the current study is lower than in the previous (4612.4 EU/mg protein) studies [46,47]. Some personal and experimental factors played a significant role in this situation. It is clear that specific activities are important in enzyme purification. Depending on some conditions, specific activities can be different even if the purification procedures are the same. Generally, the purification fold and the yield of the purification support this result.

Sulfonamides have a number of biological activity properties. Antimicrobial activities of the sulfonamides depend on the substituents and their position in the benzene ring. Sulfonamides are bacteriostatic in nature. Sulfonylureas commonly used in the management of diabetes mellitus type2. They act by increasing insulin release from the beta cells in the pancreas. Sulfonamides are also used as diuretics and for their anti-epileptic, anti-cancer, and anti-inflammatory properties [48]. Due to their medicinal importance and the application of sulfonamides, the inhibition impact of these molecules on the purified PON1 enzyme were studied in the current study. It is reported that these sulfonamides, which show potential inhibitor properties for human serum PON1, reduced the enzyme activity at low concentrations (Table 2). According to our results, compound **3** showed a stronger inhibitory effect against PON1 with a K_i value of 4.41 ± 0.52 μM while compound **1** showed the lowest inhibitory effect with a K_i value of 150.23 ± 20.73 μM. We found that compounds **1, 2, 4, 5, 8,** and **9** showed a non-competitive inhibition effect. A non-competitive inhibitor exhibits its inhibitory impact by reducing the catalytic activity or turnover rate of the enzyme. Compounds **3, 6,** and **7** showed competitive inhibition. These sulfonamides may have an interaction with the amino acids of the active site.

This study showed that the K_i values order of compounds showing inhibitory potency was **3** (4.41 ± 0.52 μM) > **8** (18.25 ± 2.12 μM) > **6** (18.72 ± 4.68 μM) > **5** (67.23 ± 8.22 μM) > **7** (75.45 ± 4.08 μM) > **9** (92.26 ± 10.41 μM) > **2** (98.23 ± 5.69 μM) > **4** (145.76 ± 3.12 μM) > **1** (150.23 ± 20.73 μM) against purified PON1. The selectivity and inhibitory activity profile relates the different functional groups present in the aromatic ring in sulfonamides. A correlation can be seen between inhibition impact and the compounds used due to structural similarity. When compounds **1** and **7** were compared, compound **7** showed a better inhibitory effect than compound **1**. According to our results, chlorine ions exhibited a more inhibitory effect than bromine ions. The addition of chlorine ion position 4 on compound **7** showed the best inhibition effect (compound **3**). In addition, the binding of the amino groups from position 5 to the thiophene ring increased the inhibitory effect (compounds **5** and **6**), but increasing the number of carbons in the aliphatic chain linked to the amino group reduced the inhibition effect (compound **5** K_i: 67.23 ± 8.22 μM, compound **6** K_i :18.72 ± 4.68 μM). The following generalizations can be made according to the results of the

inhibition assay: (**i**) all studied sulfonamides inhibited purified PON1, and the (**ii**) chloro, bromo, and amino groups and the position of these substituents on the thiophene ring were significant for inhibitory activity.

Consequently, we reported that the sulfonamides showed potent inhibitor properties reduced for the hPON1 activity. Caution should be taken when drugs are used that include sulfonamides in their structure that involve crucial biological activity. Also, the results of the present study may contribute to defining new therapeutic strategies with sulfonamides.

Author contributions

Y. Demir and Z. Koksal designed experiments and analyzed results. Y. Demir performed experiments and wrote the manuscript. Z. Koksal helped with the manuscript revising and language editing.

Conflict of interest

The authors declare that no conflicts of interest exist.

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