ChemistrySelect

Research Article
doi.org/10.1002/slct.202104489

Chemistry Europe
European Chemical Societies Publishing

www.chemistryselect.org

Biological Chemistry & Chemical Biology

Evaluation of Naphthalenylmethylen Hydrazine Derivatives as Potent Inhibitors on, Antiatherogenic Enzymes, Paraoxonase I and Acetylcholinesterase Activities

Hanif Shirinzadeh,[a] Esra Dilek,[b] and Zuhal Alım*[c]

Acetylcholinesterase (AChE) and paraoxonase 1 (PON1) are two important serum ester hydrolases that have antiatherosclerotic effect by inhibiting the oxidation of lipid peroxides. In addition, AChE inhibitors are target molecules for the treatment of Alzheimer's. Naphthalene derivatives are important molecules in the field of pharmacology due to their wide range of biological activities. In this study, the inhibition effects of naphthalenylmethylen hydrazine derivatives on these two metabolic enzymes were investigated. IC_{50} values of these molecules were determined in the range of 0.158 μM to 6.862 μM against PON1, 0.0214 μM to 0.675 μM against AChE. As a result, naphthalenylmethylen hydrazine derivatives had strong inhibition effect on both enzymes. In this context, we hope that the results obtained in this study contribute to the determination of the side effects of current and new naphthalene-based pharmacological compounds to be developed. And also be effective in the synthesis studies of new AChE inhibitors.

Introduction

Paraoxonase (PON1; EC 3.1.8.1) and acetylcholinesterase (AChE; AChE; E.C.3.1.1.7) are serum ester hydrolases that can hydrolyze lipid peroxides.[1,2] PON1 is an enzyme in calcium-dependent glycoprotein structure, located on high-density lipoprotein (HDL) in serum, showing esterase activity.[3,4] PON1, with a molecular mass of 43–45 kDa, is synthesized as a protein consisting of 354 aa in the liver and released into the blood.[5–7] PON1 is found in the blood completely dependent on HDL, and HDL stimulates the rapid release of PON1 from the liver and stabilizes the enzyme.[8,9] PON1 hydrolyzes toxic metabolites of organophosphate pesticides, certain carbamates, aromatic and aliphatic lactones, aromatic esters and oxidized lipids.[10,11] Since the PON1 enzyme has high potency to hydrolyze many pesticides and insecticides in the organophosphate structure, hence the PON1 enzyme has a significant role in the detoxification of organophosphates.[12–14] Apart from that, serum PON1 also shows antioxidant and anti-atherogenic effects by degrading oxidized lipids and preventing LDL oxidation.[15,16] Low PON1 activity is closely associated with increased atherosclerosis and the development of cardiovascular diseases.[3,4,17,18] Acetylcholinesterase (AChE; E.C.3.1.1.7) is an important metabolic enzyme that catalyzes the hydrolysis of acetylcholine to acetic acid and choline.[19–21] Unlike PON1, the activity of AChE is inhibited by organophosphates, however AChE is like PON1 prevents oxidation of LDL by hydrolyzing lipid peroxides and reduces the development of atherosclerosis.[1,2,22,23] The previous studies indicate that low serum AChE activity is associated with poor outcomes in the coronary artery and stroke diseases.[23] Furthermore, in view of the fact that AChE ends the nerve transmission by hydrolyzing acetylcholine to acetic acid and choline in the cholinergic synapses of the nervous system, somatic system and central nervous system, AChE could be a potential target enzyme for the development of drugs to be used in the treatment of Alzheimer's disease.[21,24–27] Whereas the inhibitors of AChE (such as tacrine, donepezil, rivastigmine, galantamine) are effective in the treatment of Alzheimer's disease.[21,28] And according to their outstanding metabolic functions, it is extremely important to identify inhibitors of PON1 and AChE enzymes.

Researching of therapeutic active compounds with a specific pharmacological activity is a challenging task in drug development. Indole and its derivatives have always attracted the attention of researchers in terms of pharmacological activity. In terms of pharmacological activity, Indole and its derivatives have always attracted the attention of researchers, and numerous studies indicated the antioxidant,[29] antimicrobial,[30] anticancer[31] and carbonic anhydrase inhibitör[32] activities of indole derivatives. The replacement of the indole ring with another ring, which is isostere for indole has attracted the attention of most researchers, One of the

[a] H. Shirinzadeh
Department of Pharmaceutical Chemistry,
Faculty of Pharmacy,
Erzincan Binali Yildirim University,
Yalnizbag, Erzincan, Turkey
[b] E. Dilek
Department of Biochemistry,
Faculty of Pharmacy,
Erzincan Binali Yildirim University,
Yalnizbag, Erzincan, Turkey
[c] Z. Alım
Department of Chemistry,
Faculty of Science and Arts,
Kırşehir Ahi Evran University,
Bagbaşi, Kırşehir, Turkey
E-mail: zuhal.alim@ahievran.edu.tr

Supporting information for this article is available on the WWW under https://doi.org/10.1002/slct.202104489

isostere rings is naphthalene.[33] The naphthalene skeleton with varying structural modifications has a wide spectrum of biological activities, from anticancer activity to antidepressants. Nowadays, numerous naphthalene-based drugs are approved by the FDA and used clinically.[34] For instance, in Agomelatine which was confirmed as an antidepressant agent for the treatment of major depressive disorders indole ring has been replaced with naphthalene.[35]

Combining some pharmacophores in the same molecule that may lead to new compounds with significant biological activity, is one of the methods for developing the new drugs. Therefore, based on our previous studies on indole derivatives, indole ring was replaced with naphthalene ring than some derivatives of imine substitution of naphthalene ring were synthesized. 1H, 13C NMR, mass spectra and elemental analysis data of the synthesized compounds have been published[32] and it was determined that these compounds have strong inhibition effect on carbonic anhydrase activity. In the current study, the possible inhibitory effects of the same compounds **1 a**–**1 h** (Figure 1) on human serum PON1 (hPON1) and AChE enzymes, which have antiatherogenic effects, were investigated.

Results and Discussion

Naphthalene is an aromatic molecule with a cytotoxic effect. It has been determined that naphthalene derivatives have a wide range of biological activities such as anticancer, antimicrobial, anti-inflammatory, antiviral, antituberculosis, antihypertension, antidiabetic, antineurodegenerative, antipsychotic, anticonvulsant, antidepressant. Today, many naphthalene-based molecules (for example: naphyrone, tolnaftate, duloxetine, lasofoxifene, naproxen, propranolol etc) have been approved as drugs and are used in the clinic.[34] Due to its wide variety of biological activities, naphthalene derivatives have gained importance in drug discovery and development research. In this study, we examined the inhibition effects of naphthalenyl methylene hydrazine derivatives (**1 a**–**1 h**) on hPON1 and AChE activities.

The PON1 enzyme, which is associated with HDL, is one of the most important endogenous antioxidant enzymes with paraoxonase, arylesterase and lactonase activities.[9] The antioxidant property of PON1 and the presence of homocysteine thiolactonase activity give PON1 antiatherosclerotic properties.[36] Therefore, PON1 activity in serum is inversely proportional to the risk of cardiovascular disease.[37,38] In many studies, it has been determined that low serum PON1 activity is proportional to increased atherosclerosis and cardiovascular diseases.[39–41] In addition, in various studies, PON1 activity was found to be low in individuals who are prone to atherosclerosis such as diabetes,[42] familial hypercholesterolemia[43] and kidney disorders[44] and in patients with obesity,[45] cancer,[46] Alzheimer's,[47] Parkinson's,[48] and schizophrenia[49] Therefore, it is vital to know the changes in PON1 activity, especially in individuals at risk of vascular disease. Therefore, it is very

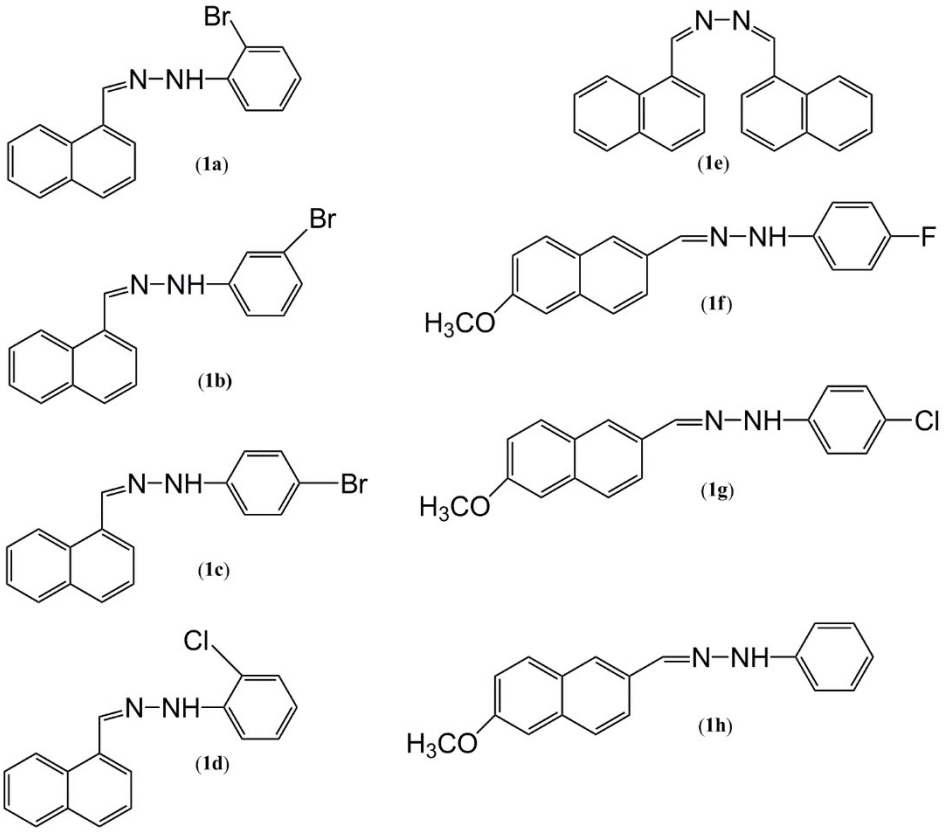

Figure 1. The molecular structures of naphthalenylmethylen hydrazine derivatives (**1 a**–**1 h**) used in this study.

important to know the drugs and chemicals that change this enzyme activity. To date, the inhibitory effects of, various chemicals such as some sulfonamides,[50] some indazoles[4] naphthoquinones, benzoquinones, anthraquinones,[51] and many drug groups such as anticancer drugs,[3] antiepileptic drugs,[9] calcium channel blockers,[11] antihypertension drugs,[52] on PON1 activity have been investigated. Another serum hydrolase associated with the risk of heart attack is AChE. It also hydrolyzes lipid peroxides, preventing LDL oxidation and reducing the risk of atherosclerosis. Studies have shown that AChE activity is decreased in the serum and heart tissues of patients who have had a heart attack.[1,2,23] Apart from this, the AChE enzyme is the main enzyme in the development of treatment methods for Alzheimer's disease.[27] AChE inhibition is the most effective and successful method used to date in the treatment of Alzheimer's disease. Today, there are AChE inhibitors (tacrine, donepezil, rivastigmine, galantamine) used in the treatment of Alzheimer's disease. However, due to the serious side effects of these inhibitors, studies to identify new AChE inhibitors continue.[21] It is very important to know the inhibitors of these two enzymes (PON1 and AChE) because of their relationship with both the prevention of atherosclerosis and other diseases such as Alzheimer's. In this study, inhibition effects of naphthalenyl methylene hydrazine derivatives (**1a**–**1h**) on PON1 and AChE activities were investigated. Inhibitory effects of **1a**–**1h** compounds on hPON1 and AChE activity were determined by IC_{50} (inhibitor concentration that halves the activity) and K_i (enzyme-inhibitory dissociation equilibrium constant) values. IC_{50} values of **1a**–**1h** were found in ranging of 0.158 μM to 6.862 μM for hPON1. K_i constants of **1a**–**1h** excluding **1e** were found as 0.357 ± 0.041 μM, 0.273 ± 0.093 μM, 0.272 ± 0.061 μM, 0.494 ± 0.146 μM, 0.195 ± 0.027 μM, 0.272 ± 0.027 μM, 8.72 ± 1.63 μM, for hPON1, respectively (Table 1). According to obtained results, **1f** had the strongest inhibition effect (Figure 2), while **1h** had the weakest inhibition effect. It was thought that the **1f** showed this strong inhibition effect with its fluorine group, unlike **1h**. The **1e** compound did not change the hPON1 activity.

For AChE IC_{50} values of **1a**–**1h** were found in ranging of 0.0214 μM to 0.675 μM. And K_i constants of **1a**–**1h** were found as 0.030 ± 0.008 μM, 0.012 ± 0.003 μM, 0.011 ± 0.003 μM, 0.055 ± 0.009 μM, 0.476 ± 0.072 μM, 0.012 ± 0.010 μM, 0.022 ± 0.013 μM, 0.676 ± 0.086 μM for AChE, respectively (Table 2). According to these results, **1c** had the strongest inhibition effect (Figure 3), while **1h** had the weakest inhibition effect on AChE.

At the same time, the inhibition power of **1g** and **1b** compounds was found to be very close to that of **1c**. In current study, it was determined that the inhibition effect of all naphthalenyl methylene hydrazine derivatives (**1a**–**1h**) on AChE activity was much stronger than on hPON1 activity. Tacrine was used as a reference inhibitor for AChE. Although **1a**–**1h** compounds had a strong inhibitory effect on AChE at micromolar concentration, their inhibition power was lower than tacrine. In the literature, there are some studies in which various naphthalene-based molecules have been identified as potent AChE inhibitors.[53,54] At the same time, the inhibition types of molecules showing an inhibitory effect on hPON1 and AChE activities were determined in this study. **1f** and **1g** compounds showed competitive inhibition effect on hPON1.

Table 1. The IC_{50} values, K_i constants and inhibition types determined for **1a**–**1h** compounds having inhibitory effects on hPON1.

Compounds	hPON1 IC_{50} (μM)	R^2	K_i (μM)	Inhibition Type
1a	0.348	0.9984	0.357 ± 0.041	Noncompetitive
1b	0.208	0.9966	0.273 ± 0.093	Noncompetitive
1c	0.224	0.9943	0.272 ± 0.061	Noncompetitive
1d	0.343	0.9788	0.494 ± 0.146	Noncompetitive
1e	–	–	–	–
1f	0.158	0.9945	0.195 ± 0.027	Competitive
1g	0.199	0.9979	0.272 ± 0.027	Competitive
1h	6.862	0.9933	8.72 ± 1.63	Noncompetitive

Table 2. The IC_{50} values, K_i constants and inhibition types determined for **1a**–**1h** compounds having inhibitory effects on AChE.

Compounds	AChE IC_{50} (μM)	R^2	K_i (μM)	Inhibition Type
1a	0.0346	0.9977	0.030 ± 0.008	Noncompetitive
1b	0.0230	0.9948	0.012 ± 0.003	Noncompetitive
1c	0.0214	0.9935	0.011 ± 0.003	Noncompetitive
1d	0.034	0.9908	0.055 ± 0.009	Noncompetitive
1e	0.673	0.9923	0.476 ± 0.072	Noncompetitive
1f	0.0278	0.9832	0.012 ± 0.010	Noncompetitive
1g	0.0219	0.9708	0.022 ± 0.013	Noncompetitive
1h	0.675	0.9998	0.676 ± 0.086	Noncompetitive
Tacrine	0.014	0.9940	0.010 ± 004	Competitive

*Tacrine was used as standard inhibitor for AChE.

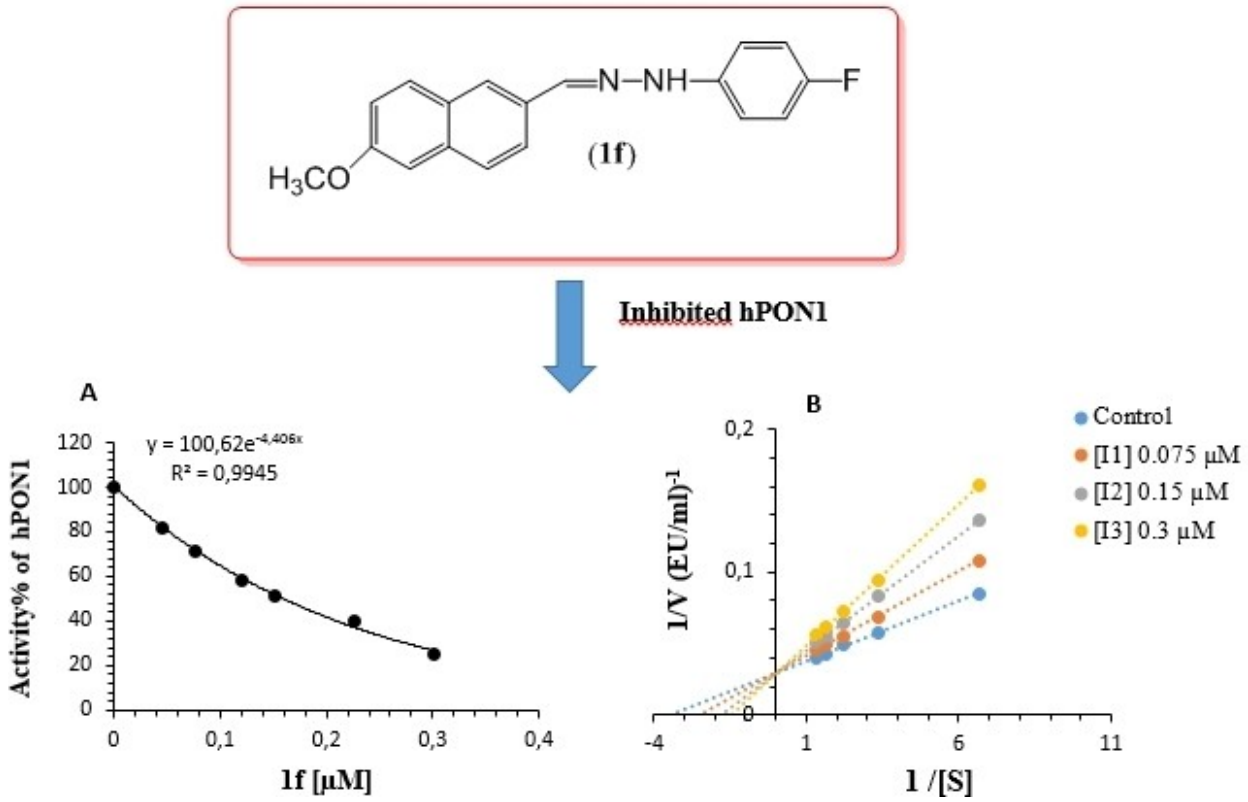

Figure 2. IC_{50} graph (A) and Lineweaver-Burk graph (B) of **1 f** for hPON1.

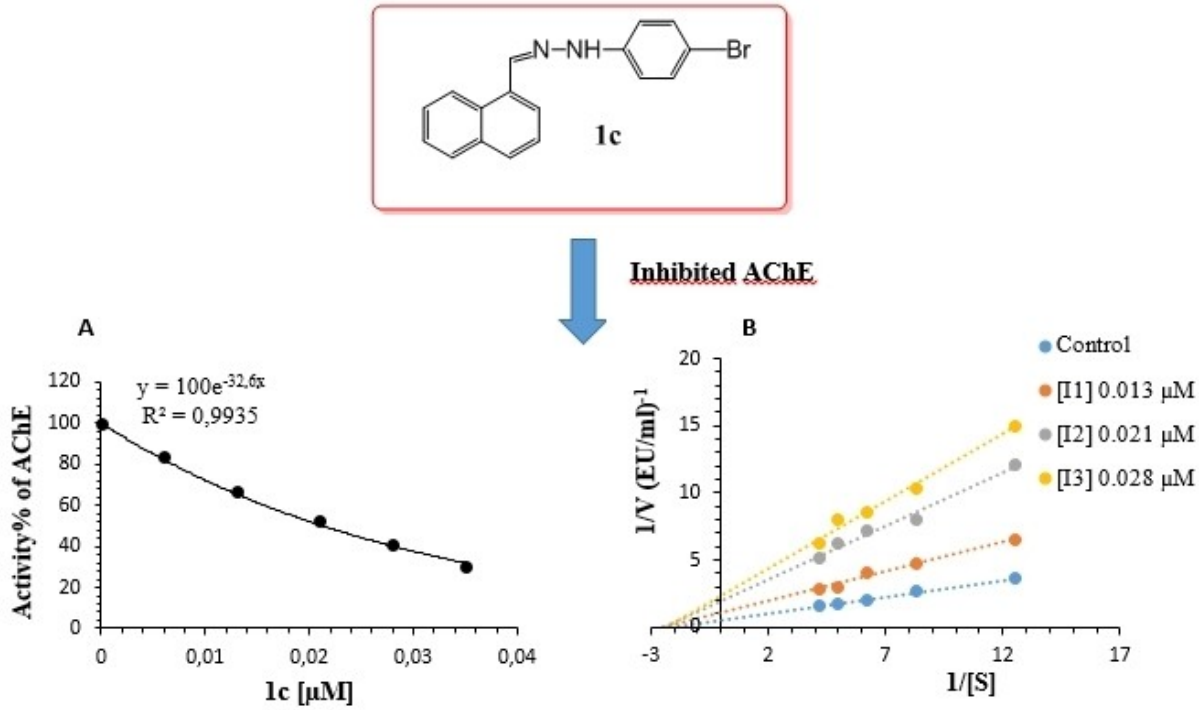

Figure 3. IC_{50} graph (A) and Lineweaver-Burk graph (B) of **1 c** for AChE.

Accordingly, it was understood that **1f** and **1g** bind to the active site of the hPON1 enzyme, thereby reducing the enzyme's catalytic activity. On the other hand, **1a**, **1b**, **1c**, **1d**, **1h** showed a non-competitive inhibition effect on hPON1. In this case, it was thought that these compounds bind to a place other than the active site of the enzyme, reducing the turnover number of the enzyme and causing inhibition. All of the **1a**–**1h** compounds showed a non-competitive inhibition effect on AChE. According to this result, it was thought that **1a**–**1h** compounds exhibited an inhibition effect by binding outside the active site of AChE.

Conclusion

As a conclusion, it was determined that the new naphthalenylmethylen hydrazine derivatives (**1a**–**1h**) had strong inhibition effects on the activities of hPON1 and AChE, as two important serum ester hydrolase enzymes with anti-atherosclerotic activity. Decreased hPON1 and AChE activity is closely associated with the development of atherosclerosis. In this regard, we hope that the results of this study will contribute to the determination of the side effects of current naphthalene-based drugs and new naphthalene-based pharmacological compounds to be developed. In addition, AChE inhibitors are target molecules in pharmacological studies for the development of drugs used in the treatment of Alzheimer's disease. it is believed that naphthalenylmethylen hydrazine derivatives (**1a**–**1h**), whose inhibitory effect on AChE activity was determined in this study, will contribute to the design studies of new AChE inhibitors.

Supporting Information Summary

Experimental Section of the current article, synthesis and *in vitro* inhibition studies are provided in the supporting information.

Author Contribution Statement

E. Dilek carried out inhibition studies of hPON1 and AChE. Analysis of the results was done by E. Dilek and Z. Alim. Synthesis studies were carried out by H. Shirinzadeh. The writing and language correction of the article were done by E. Dilek, Z. Alim, and H. Shirinzadeh.

Acknowledgements

The authors appreciate the Scientific Research Council of Erzincan Binali Yildirim University for their support of the Project (Project No: SAG-A-240215-0120).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: Acetylcholinesterase · Enzyme · Inhibition · Naphthalene · Paraoxonase 1

[1] B. Fuhrman, A. Partoush, M. Aviram, *Res. Commun.* **2004**, *322*, 974–978.
[2] S. Shenhar-Tsarfaty, N. Waiskopf, K. Ofek, L. Shopin, S. Usher, S. Berliner, I. Shapira, N. M. Bornstein, Y. Ritov, H. Soreq, E. Ben Assayag, *Eur. J. Neurol.* **2013**, *20*, 891–898.
[3] Z. Alım, Ş. Beydemir, *Chem. Biol. Drug Des.* **2016**, *88*, 188–196.
[4] Z. Alım, D. Kılıç, Y. Demir, *Arch. Physiol. Biochem.* **2019**, *125*, 387–395.
[5] M. I. Mackness, B. Mackness, P. N. Durrington, A. M. Fogelman, J. Berliner, A. J. Lusis, M. Navab, D. Shih, G. C. Fonarow, *Curr. Opin. Lipidol.* **1998**, *9*, 319–324.
[6] H. Lu, J. Zhu, Y. Zang, Y. Ze, J. Qin, *Protein Expression Purif.* **2006**, *46*, 92–99.
[7] H. A. Alici, D. Ekinci, Ş. Beydemir, *Clin. Biochem.* **2008**, *41*, 1384–1390.
[8] S. Deakin, I. Leviev, M. Gomaraschi, L. Calabresi, G. Franceschini, R. W. James, *J. Biol. Chem.* **2002**, *277*, 4301–4308.
[9] Ş. Beydemir, Y. Demir, *J. Biochem. Mol. Toxicol.* **2017**, *31*, e21889.
[10] A. Bosak, A. Bavec, T. Konte, G. Šinko, Z. Kovarik, M. Goličnik, *Molecules.* **2020**, *25*, 211.
[11] C. Turkes, Y. Demir, Ş. Beydemir, *J. Biomol. Struct. Dyn.* **2022**, *40*, 77–85.
[12] L. G. Costa, T. B. Cole, A. Vitalone, C. E. Furlong, *Clin. Chim. Acta.* **2005**, *352*, 37–47.
[13] H. Ceylan, Y. Demir, Ş. Beydemir, *Protein Pept. Lett.* **2019**, *26*, 364–370.
[14] Y. Demir, N. Balcı, M. Gürbüz, *Comp. Biochem. Physiol. Part C* **2019**, *226*, 108608.
[15] K. Kowalska, E. Socha, H. Milnerowicz, *Ann. Clin. Lab. Sci.* **2015**, *45*, 226–233.
[16] D. A. Chistiakov, A. A. Melnichenko, A. N. Orekhov, Y. V. Bobryshev, *Paraoxonase and atherosclerosis-related cardiovascular diseases, Biochimie.* **2017**, *132*, 19–27.
[17] G. P. Jarvik, T. S. Hatsukami, C. Carlson, R. J. Richter, R. Jampsa, V. H. Brophy, S. Margolin, M. Rieder, D. Nickerson, G. D. Schellenberg, P. J. Heagerty, C. E. Furlong, *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 1465–1471.
[18] H. Berrougui, C. N. Momo, A. Khalil, *J. Clin. Lipidol.* **2012**, *6*, 524–533.
[19] M. B. Colovic, D. Z. Krstic, T. D. Lazarevic-Pasti, A. M. Bondzic, V. M. Vasic, *Curr. Neuropharmacol.* **2013**, *11*, 315–335.
[20] U. Atmaca, A. Yıldırım, P. Taslimi, S. T. Çelik, İ. Gülçin, C. T. Supuran, M. Çelik, *J. Biochem. Mol. Toxicol.* **2018**, *32*, e22173.
[21] Z. Köksal, Z. Alım, S. Bayrak, İ. Gülçin, H. Özdemir, *J. Biochem. Mol. Toxicol.* **2019**, *33*, e22300.
[22] S. A. Akgur, P. Ozturk, E. Y. Sozmen, Y. Delen, T. Tanyalcin, B. Ege, *J. Toxicol. Environ. Health Part A* **1999**, *58*, 469–474.
[23] S. Shenhar-Tsarfaty, R. Y. Brzezinski, N. Waiskopf, A. Finkelstein, A. Halkin, S. Berliner, O. Rogowski, D. Zeltser, I. Shapira, M. Laufer-Perl, Y. Shacham, B. Litmanowicz, S. Banai, H. Soreq, Y. Arbel, *Atherosclerosis* **2020**, *313*, 144–149.
[24] Q. Istrefi, C. Türkeş, M. Arslan, Y. Demir, A. R. Nixha, Ş. Beydemir, O. I. Küfrevioglu, *Arch. Pharm.* **2020**, *353*, 1900383.
[25] M. Kalaycı, C. Türkeş, M. Arslan, Y. Demir, Ş. Beydemir, *Arch. Pharm.* **2021**, *354*, 2000282.
[26] B. Sever, C. Türkeş, M. D. Altıntop, Y. Demir, Ş. Beydemir, *Int. J. Biol. Macromol.* **2020**, *163*, 1970–1988.
[27] T. Tunç, Z. Alım, *Russ. J. Org. Chem.* **2021**, *57*, 247–254.
[28] S. Ökten, M. Ekiz, Ü. M. Koçyiğit, A. Tutar, İ. Çelik, M. Akkurt, F. Gökalp, P. Taslimi, I. Gülçin, *J. Mol. Struct.* **2019**, *1175*, 906–915.
[29] S. Suzen, B. Tekiner-Gulbas, H. Shirinzadeh, D. Uslu, H. Gurer-Orhan, M. Gumustas, S. A. Ozkan, *J. Enzyme Inhib. Med. Chem.* **2013**, *28*, 1143–1155.
[30] H. Shirinzadeh, N. Altanlar, N. Yucel, S. Ozden, S. Suzen, *Z. Naturforsch. C* **2011**, *66*, 340–344.
[31] H. Shirinzadeh, E. Neuhaus, E. Ince Erguc, H. Gurer-Orhan, S. Suzen, *Bioorg. Chem.* **2020**, *104*, 104219.
[32] H. Shirinzadeh, E. Dilek, *J. Mol. Struct.* **2020**, *1220*, 128657.

[33] E. Landagaray, M. Ettaoussi, R. Duroux, J. A. Boutin, D. H. Caignard, P. Delagrange, P. Melnyk, P. Berthelot, S. Yous, *Eur. J. Med. Chem.* **2016**, *109*, 360–370.
[34] S. Makar, T. Saha, S. K. Singh, *Eur. J. Med. Chem.* **2019**, *161*, 252–276.
[35] M. Ettaoussi, A. Sabaouni, M. Rami, J. A. Boutin, P. Delagrange, P. Renard, M. Spedding, D. H. Caignard, P. Berthelot, S. Yous, *Eur. J. Med. Chem.* **2012**, *49*, 310–323.
[36] T. M. Van Himbergen, L. J. H. Van Tits, M. Roest, A. F. H. Stalenhoef, *Neth. J. Med.* **2006**, *64*, 34–38.
[37] B. C. Demirdogen, A. Turkanoglu, S. Bek, Y. Sanisoglu, S. Demirkaya, O. Vural, E. Arınc, O. Adalı, *Clin. Biochem.* **2008**, *41*, 1–9.
[38] F. E. Murillo-Gonzalez, N. Ponce-Ruiz, A. E. Rojas-Garcia, S. J. Rothenberg, Y. Y. Bernal-Hernandez, R. M. Cerda-Flores, M. Mackness, B. S. Barron-Vivanco, C. A. Gonzalez-Arias, J. Ponce-Gallegos, I. M. Medina-Diaz, *Clin. Chim. Acta.* **2020**, *500*, 47–53.
[39] P. N. Durrington, B. Mackness, M. I. Mackness, *Arterioscler. Thromb. Vasc. Biol.* **2001**, *21*, 473–480.
[40] G. S. Getz, C. A. Reardon, *Curr. Opin. Lipidol.* **2004**, *15*, 261–267.
[41] M. Mackness, P. Durrington, B. Mackness, *Curr. Opin. Lipidol.* **2004**, *15*, 399–404.
[42] T. Kalmar, I. Seres, Z. Balogh, M. Kaplar, G. Winkler, G. Paragh, *Diabetes Metab.* **2005**, *31*, 574–580.
[43] T. M. Van Himbergen, M. Roest, J. De Graaf, E. H. J. M. Jansen, H. Hattori, J. J. P. Kastelein, H. A. M. Voorbij, A. F. H. Stalenhoef, L. J. H. Van Tits, *J. Lipid Res.* **2005**, *46*, 445–451.
[44] T. F. Dantoine, J. Debord, J. P. Charmes, L. Merle, P. Marquet, G. Lachatre, C. Leroux-Robert, *J. Am. Soc. Nephrol.* **1998**, *9*, 2082–2088.
[45] G. Ferretti, T. Bacchetti, C. Moroni, S. Savino, A. Liuzzi, F. Balzola, *J. Clin. Endocrinol. Metab.* **2005**, *90*, 1728–1733.
[46] E. T. Elkıran, N. Mar, B. Aygen, F. Gursu, A. Karaoglu, S. Koca, *BMC Cancer.* **2007**, *7*, 48.
[47] T. F. Dantoine, M. Drouet, J. Debord, L. Merle, M. Cogne, J. P. Charmes, *Ann. N. Y. Acad. Sci.* **2006**, *977*, 239–244.
[48] T. Menini, A. Gugliucci, *Redox Rep.* **2014**, *19*, 49–58.
[49] C. Matsumoto, O. Ohmori, H. Hori, T. Shinkaj, J. Nakamura, *Neurosci. Lett.* **2002**, *321*, 165–168.
[50] Y. Demir, Z. Koksal, *Pharmacol. Rep.* **2019**, *71*, 545–549.
[51] Y. Demir, *Drug Dev. Res.* **2020**, *81*, 628–636.
[52] Y. Demir, *J. Pharm. Pharmacol.* **2019**, *71*, 1576–1583.
[53] T. Umar, S. Gusainb, M. K. Raza, S. Shalini, J. Kumar, M. Tiwari, N. Hoda, *Bioorg. Med. Chem.* **2019**, *27*, 3156–3166.
[54] F. Anwar, U. Saleem, B. Ahmad, M. Ashraf, A. U. Rehman, M. Froeyen, L. Y. Kee, I. Abdullah, M. U. Mirza, S. Ahmad, *Comput. Biol. Chem.* **2020**, *89*, 107378.

Submitted: December 21, 2021
Accepted: January 24, 2022