Bioorganic & Medicinal Chemistry 24 (2016) 1392–1401

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Functionalized imidazolium and benzimidazolium salts as paraoxonase 1 inhibitors: Synthesis, characterization and molecular docking studies

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ARTICLE INFO

Article history:
Received 1 January 2016
Revised 3 February 2016
Accepted 8 February 2016
Available online 8 February 2016

Keywords:
Benzimidazolium
Coumarin
Imidazolium
Inhibition
Molecular docking
Paraoxonase 1

ABSTRACT

Paraoxonase (PON) is a key enzyme in metabolism of living organisms and decreased activity of PON1 was acknowledged as a risk for atherosclerosis and organophosphate toxicity. The present study describes the synthesis, characterization, PON1 inhibitory properties and molecular docking studies of functionalized imidazolium and benzimidazolium salts (**1a**–**5g**). The structures of all compounds were elucidated by IR, NMR, elemental analysis and structures of compounds **2b** and **2c** were characterized by single-crystal X-ray diffraction. Compound **1c**, a coumarin substituted imidazolium salt showed the best inhibitory effect on the activity of PON1 with good IC_{50} value (6.37 μM). Kinetic investigation was evaluated for this compound and results showed that this compound is competitive inhibitor of PON1 with K_i value of 2.39 μM. Molecular docking studies were also performed for most active compound **1c** and one of least active compound **2c** in order to determine the probable binding model into active site of PON1 and validation of the experimental results.

1. Introduction

Paraoxonase 1 (PON1) is the best studied member of the mammalian enzyme family including PON1, PON2 and PON3. PON1 is the calcium-dependent and high-density lipoprotein (HDL) associated enzyme that has 355 amino acids with a molecular mass of 43 kDA.[1–3] PON1 catalyses the hydrolysis of lactones,[4] thiolactones,[5] aromatic esters[6] and organophosphates,[7] but physiological substrate of this enzyme is still unknown. PON1 is a key enzyme in metabolism especially for two reasons; (i) it hydrolyses organophosphates such as serin and soman and protects the nervous system against the neurotoxicity of organophosphates[7] and (ii) it prevents the oxidation of low-density lipoproteins and reduced levels of oxidized lipids are involved in the initiation of atherosclerosis so decreased activity of PON 1 was acknowledged as a risk for atherosclerosis.[3] Therefore all factors affecting on PON1 activity have to be well understood. It is known that almost all chemical reactions in metabolism of living organisms are catalyzed by enzymes and they are important drug targets and effects of bioactive compounds on PON1 activity must also be examined.

Heterocyclic rings are widely found in the structures of large number of natural products and they are part of various biologically active compounds so synthesis of heterocyclic compounds is important target for organic chemists. Therefore, synthesis and biological evaluation of heterocyclic compounds are still the subject of intensive research area.[8–15] In addition, cyclic structures are more conformationally restricted than their acyclic analogues and this fact make them more selective and bioactive.[16,17]

Azoles and coumarins are well known and widely investigated class of compounds among the heterocyclic compounds. Imidazole, triazole and benzimidazole derived compounds have attracted great interest due to their wide range of pharmacological properties including anticancer, antitumor, antimicrobial, antiviral, anti-inflammatory and anticoagulant.[8–13] Coumarin derivatives have been widely investigated owing to their diverse pharmacological

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http://dx.doi.org/10.1016/j.bmc.2016.02.012
0968-0896/

properties such as anticoagulant, anticancer, anti-HIV, antimicrobial[14,15] and carbonic anhydrase inhibitor.[18] As shown, these small heterocyclic compounds act as highly functional scaffolds and their vital role in drug design cannot be denied.

In our previous paper, we reported the inhibition of PON1 by some hydroxy coumarin-benzimidazole hybrid compounds (doi:10.3109/14756366.2015.1043297)[19] In the present study, we have synthesized nine imidazolium and eight benzimidazolium derivatives which containing coumarin, triazole, benzimidazole, benzoxazinone and some aryl or alkyl groups as substituent. The synthesized compounds were characterized by IR, NMR, elemental analysis and single-crystal X-ray diffraction. Among the various activities of these compounds, anti-coagulant effects of coumarin and benzimidazole derivatives make them more attractive especially for interactions with PON. Herein, we examined the in vitro effects of these twenty compounds which were functionalized with different substituents. Moreover, in order to determine the probable binding interactions, molecular docking studies were performed on PON1 active site.

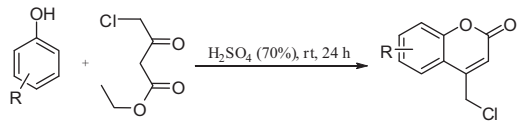
2. Results and discussion

2.1. Synthesis and spectral characterization of compounds (1a–5g)

Compounds **C1**–**3** were synthesized by the procedure described in literature by Frasinyuk[20] as shown in Scheme 1. Synthesis and structures of imidazolium salts (**1a**–**3c**) and benzimidazolium salts (**5a**–**g**) were outlined in Schemes 2 and 3, respectively. These compounds were synthesized by direct quaternization of 1-alkylimidazole and 1-alkylbenzimidazole derivatives with different alkyl chlorides in DMF. All compounds were obtained in good yields between 54% and 95%. In ^{1}H NMR spectra of imidazolium salts **1a**,**c**, **2a**,**c** and **3a**,**c**, signals of acidic NC*H*N protons were located in the range of 9.36–9.92 ppm while these signals were obtained in the range of 10.34–11.30 ppm for benzimidazolium salts (**5a**–**g**). These signals of acidic hydrogens are in good agreement with literature.[21] For compounds **3a**–**c**, signals of free —N*H* hydrogens were located in the range of 13.41–13.49 ppm. Signal of free —N*H* hydrogen of compound **5g** was located at 11.08 ppm. In IR spectra of all coumarin derived compounds (**C1**–**3**, **1a**–**c**, **5e**,**f**), sharp carbonyl peaks were observed in the range of 1707–1723 cm^{-1}. Two carbonyl peaks were observed at 1702 and 1685 cm^{-1} for compound **5g**. Elemental analysis of all compounds was also supportive for depicted structures. Hence, all of the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR and elemental analysis in satisfactory manner.

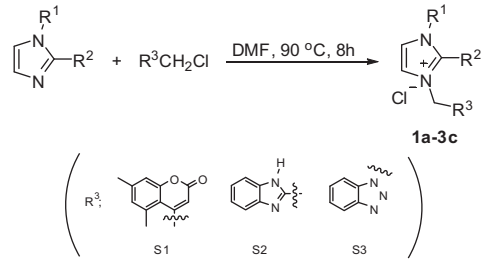
2.2. Structural description of the compounds 2b and 2c

The solid-state structures of compounds **2b** and **2c** have been determined by single crystal X-ray analysis. The perspective ORTEP-3 views of the compounds with the adopted atomic numbering scheme are depicted in Figures 1 and 2, while selected bond lengths and angles are given in Table 1. The crystallization charac-



C1, R: 5,7-$(CH_3)_2$; **C2**, R: 7,8-$(CH_3)_2$; **C3**, R: 6-$C(CH_3)_3$

Scheme 1. Synthesis of compounds **C1**–**3**.



Compound no	R^1	R^2	R^3
1a	-CH_3	-H	S1
1b	-CH_3	-CH_3	S1
1c	-$CH_2CH_2CH_2CH_3$	-H	S1
2a	-CH_3	-H	S2
2b	-CH_3	-CH_3	S2
2c	-$CH_2CH_2CH_2CH_3$	-H	S2
3a	-CH_3	-H	S3
3b	-CH_3	-CH_3	S3
3c	-$CH_2CH_2CH_2CH_3$	-H	S3

Scheme 2. Synthesis and structures of imidazolium salts.

teristics of the two compounds are different, with compounds **2c** and **2b** crystallizing in the space groups $P2_1/c$ and $P\bar{1}$, respectively. In both compounds, the charge is balanced by a Cl^- anion. The asymmetric unit in the crystal structure of compound **2b** contains the two independent molecules, labelled A and B, and one water solvent molecule. In the following discussion, parameters for molecule B are quoted in square brackets.

The imidazole ring is planar with an rms deviation of 0.0012 Å for compound **2c**, and 0.0023 Å [0.0034 Å] for compound **2b**. The bonding within the imidazole ring indicates a pattern of delocalization that extends from atom N4 to atom N5 through atom C8, the N4—C8 {1.313(3) Å in compound **2c**, 1.346(2) Å [1.3388(19) Å] in compound **2b**} and N5—C8 {1.322(3) Å in compound **2c**, 1.323 (2) Å [1.333(2) Å] in compound **2b**} distances being significantly shorter than the N4—C10 {1.376(3) Å in compound **2c**, 1.380(2) Å [1.379(2) Å] in compound **2b**} and N5—C9 {1.373(3) Å in compound **2c**, 1.371(2) Å [1.380(2) Å] in compound **2b**} distances. The N1—C7 bond lengths of 1.446(3) and 1.440(2) Å [1.445(2) Å] in compounds **2c** and **2b**, respectively, show the C—N single bond character. The N1—C6 and N3—C1 bond lengths in the benzotriazole ring are 1.356(3) and 1.378(3) Å in compound **2c**, and 1.365 (2) and 1.379(3) Å [1.359(2) and 1.377(3) Å] in compound **2b**, and N1—N2 and N2—N3 bond lengths are 1.359(3) and 1.301 (3) Å in compound **2c**, and 1.356(2) and 1.291(2) Å [1.3615(19) and 1.298(3) Å] in compound **2b**, respectively. These shorter lengths suggest that the C—N and N—N bonds in benzotriazole ring have part double bond character. In these bond lengths, the N2—N3 bond is relatively shorter, which shows that the N2—N3 distance has relatively stronger double bond character. All nitrogen atoms in the benzotriazole ring (N1, N2 and N3) are sp^2 hybridized and occupy positions in the plane of the aromatic moiety. The rms deviation of the benzotriazole ring atoms from their mean plane is 0.0104 Å and 0.0124 Å [0.0089 Å] for compounds **2c** and **2b**, respectively. The triazole and benzene rings of the benzotriazole moiety are inclined to one another at an angle of 0.793(13)° in