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2-Hydroxyethyl substituted NHC precursors: Synthesis, characterization, crystal structure and carbonic anhydrase, α-glycosidase, butyrylcholinesterase, and acetylcholinesterase inhibitory properties

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ABSTRACT

This study contains novel a serie synthesis of *N*-heterocyclic carbene (NHC) precursors that 2-hydroxyethyl substituted. The NHC precursors have been prepared from 1-(2- hydroxyethyl)benzimidazole and alkyl halides. The novel NHC precursors have been characterized by using ^{1}H NMR, ^{13}C NMR, FTIR spectroscopy and elemental analysis techniques. Molecular and crystal structures of **2a, 2d, 2e, 2f** and **2g** were obtained with single-crystal X-ray diffraction studies. These novel NHC precursor's derivatives effectively inhibited the α-glycosidase, cytosolic carbonic anhydrase I and II isoforms (hCA I and II), butyrylcholinesterase (BChE) and acetylcholinesterase (AChE). Inhibition constant (K_i) were found in the range of 0.30–9.22 nM for α-glycosidase, 13.90–41.46 nM for hCA I, 12.82–49.95 nM for hCA II, 145.82–882.01 nM for BChE, and 280.92–1370.01 nM for AChE, respectively.

1. Introduction

Heterocyclic compounds are very important both industrially and biologically. These compounds are found in the vast majority of new drugs synthesized in the pharmaceutical industry [1]. Imidazole, imidazolidine and benzimidazole compounds are important five-membered nitrogen heterocyclic compounds. Azolium salts are known to exhibit biologic activity such as antitumor [2], antibacterial [3] and antimicrobial activity [4]. They are also used as ligands for the synthesis metal-*N*-heterocyclic carbene (NHC) complexes [5] that feature improved stability, selectivity and high catalytic reactivity. Since, the stable NHCs were synthesized in the organic and organometallic chemistry appeared very important developments. These stable compounds have attracted great interest by chemists [6,7] due to their unique properties such as strong σ-acidity and poor π-basicity, air and moisture stability and regulation. Thanks to these properties, NHCs have a variety of applications areas ranging from catalysts to biological systems [8–10]. Also, some enzyme inhibition studies of NHC precursors have been recently performed. In particular, the benzimidazole salts have been published as NHC precursors in the studies [11,12].

Carbonic anhydrases (CA, E.C.4.2.1.1) are ubiquitous zinc metalloenzymes outspread across the phylogenetic tree [13,14] and expressed in most living organisms and are encoded by seven distinct gene families, including α-, β-, γ-, δ-, ζ-, n- and θ-CAs. There are sixteen distinct CA isoforms commonly recorded in mammals belongs to α-CA family [15]. These isoforms catalyze a critical, yet simple, reaction: the reversible hydration of carbon dioxide molecule to a proton (H^+) and bicarbonate anion (HCO_3^-) [16,17]. CAs facilitates deprotonation of water molecule to produce the forcefully main hydroxide anion (OH^-) under physiological situations. OH^- is the reactive type in the hydration of CO_2 molecule helping to creation and release of HCO_3^- [18,19].

Cholinesterases (ChEs) are divided into two significant types conforming to discrepancies in their inhibitor specificities and

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natural substrates: acetylcholinesterase (AChE, E.C.3.1.1.7) and butyrylcholinesterase (BChE, E.C.3.1.1.8) [20]. AChE; which includes of a ~120 kDa unit is responsible for the catalysis of neurotransmitter acetylcholine (ACh) to its corresponding choline and acetate in cholinergic synapses [21,22]. ACh plays a fundamental role in memory and cognitive functions [23]. AChE has a high particular catalytic act that catalysis about 25000 compounds of ACh per second [24]. BChE includes of a 60 kDa unit and is a nonspecific ChE enzyme, acting on ACh, butrylcholine, and diverse choline esters [25]. Also, BChE enzyme was recorded alongside β-amyloid compounds in the central neural device, which estimated that it might play a main role in their creation [26]. Currently, AChE inhibitors (AChEI) are the important kind of authorized drugs on the market toward mild to severe Alzheimer's disease (AD) [27,28].

On the other hand, diabetes mellitus (DM) is a metabolic disturbance, which determined by hyperglycaemia, caused by either impaired insulin deficiency or impaired insulin resistance [29]. In small intestine, polysaccharide and oligosaccharides are hydrolysed to monosaccharide, such as fructose and glucose, by α-glycosidase (E.C.3.2.1.20) secreted from intestine mucoid cells [30]. Also, α-glycosidase enzyme hydrolyses the final phase in the digestive action of carbohydrates [31]. α-Glycosidase inhibitors can reduce the uptake of dietary carbohydrates and repress postprandial hyperglycaemia and also could be effective for therapy of diabetic disease [32].

In our study, we reported the facile synthesis of well-defined 2-hydroxyethyl substituted NHC precursors **2a-g**. The molecular and crystal structures of NHC precursors **2a**, **2d, 2e, 2f** and **2g** were established through single-crystal X-ray diffraction methods. Another goal of this study was to investigate their inhibition potential of the novel NHC precursor's derivatives against hCA I, and II isoenzymes, AChE, BChE, and α-glycosidase enzymes.

2. Experimental

All synthesis involving 2-hydroxyethyl substituted NHC precursors **2a-g** were carried out under an inert atmosphere in flame-dried glassware using standard Schlenk techniques. The solvents commercially purchased were used without exposure to any purification and drying process. All other reagents were commercially available by Aldrich Chemical Co. and used without further purification. Melting points were identified in glass capillaries under air with an Electrothermal-9200 melting point apparatus. FTIR spectra were saved in the range 400–4000 cm^{-1} on Perkin Elmer Spectrum 100 FTIR spectrometer. Proton (^1H) and Carbon (^{13}C) NMR spectra were recorded using either a Bruker AS 400 Merkur spectrometer operating at 400 MHz (^1H), 100 MHz (^{13}C) in $CDCl_3$ with tetramethylsilane as an internal reference. Elemental analyses were performed by İnönü University Scientific and Technology Centre (Malatya, TURKEY).

2.1. Synthesis of 1-(2-hydroxyethyl)benzimidazole, *1*

1-(2-hydroxyethyl)benzimidazole **1** was synthesized differently from the method described in the literature [33–35]. For the synthesis of **1**, benzimidazole (3.54 g. 30 mmol) and KOH (1.85 g. 33 mmol) was added in ethanol (25 mL). The reaction mixture was stirred for 1 h at room temperatures. Then was added 2-iodoethanol (5.16 g. 30 mmol). The reaction mixture was stirred for 12 h at 80 °C temperatures. The solvents were evaporated under vacuum to afford the product as a viscous liquid. This product was purified by distillation, and product was obtained as a white solid. Yield: 4.00 g. (86%). m.p.: 97–99 °C; $\nu_{(CN)}$: 1498.0 cm^{-1}. Anal. Calc. for $C_9H_{10}N_2O$: C: 66.65; H: 6.21; N: 17.27. Found: C: 66.69; H: 6.24; N: 17.29. ^1H NMR (400 MHz, DMSO-d_6), δ 1.26 (t, 1H, J = 8 Hz $-NCH_2CH_2O\boldsymbol{H}$); 3.94 (s, 2H, $-NC\boldsymbol{H_2}CH_2OH$); 4.14 (s, 2H, $-NCH_2C\boldsymbol{H_2}OH$); 7.17–7.92 (m, 4H, Ar-***H***); 8.95 (s, 1H, 2-C***H***). ^{13}C NMR (100 MHz, DMSO-d_6), δ 47.4 ($-NCH_2CH_2OH$); 60.1 ($-NCH_2CH_2OH$); 111.1–119.7–122.0–122.7–134.4 and 143.6 (Ar-*C*); 144.9 (2-*C*H).

2.2. Synthesis of 1-(2-hydroxyethyl)-3-benzylbenzimidazolium chloride, *2a*

For the synthesis of **2a**, benzyl chloride (1.27 g, 10 mmol) and 1-(2-tetrahydro-pyran-2-yloxyethyl)benzimidazole (2.46 g, 10 mmol) was added in dry DMF (4 mL). The reaction mixture was stirred for 22 h at 70–80 °C and 2 h at 100–110 °C temperatures. The excess of DMF was evaporated in vacuum. Dry diethyl ether was added to the reaction mixture and the white solid was filtered off. The product was obtained as a mixture of two salts, separated and not separated from the pyran ring, and could not be purified at these conditions. The product mixture was stirred with 36% HCl solution in 25 mL of methanol for 1 h at room temperature [36]. The methanol was completely removed. The crude product was crystallized in a mixture of ethyl alcohol-diethyl ether (1/3). The synthesized compound was converted to the 1-(2-hydroxyethyl)-3-benzylbenzimidazolium chloride. It has been proved by spectroscopic methods that this is been. Yield: 2.51 g; (87%); m.p.: 105–106 °C; $\nu_{(CN)}$: 1557.0 cm^{-1}; ν(OH): 3150-3628 cm^{-1}. Anal. Calc. for $C_{16}H_{17}ClN_2O$: C: 66.55; H: 5.93; N: 9.70. Found: C: 66.79; H: 6.11; N: 9.58. ^1H NMR (400 MHz, $CDCl_3$); δ 2.17 (s, 1H, $-NCH_2CH_2O\boldsymbol{H}$); 4.14 (t, 2H, J = 4 Hz $-NC\boldsymbol{H_2}CH_2OH$); 4.77 (t, 2H, J = 4 Hz $-NCH_2C\boldsymbol{H_2}OH$); 5.79 (s, 2H, $-NC\boldsymbol{H_2}(C_6H_5)$; 7.27–7.76 (m, 9H, Ar-*H*); 10.98 (s, 1H, 2-C***H***). ^{13}C NMR (100 MHz, $CDCl_3$); δ 49.7 ($-NCH_2CH_2OH$); 51.7 $-NCH_2(C_6H_5)$; 58.8 $-NCH_2CH_2OH$); 113.1–113.6–117.0–128.2–129.2–129.4–131.2–131.9 and 132.6 (Ar-*C*); 143.6 (2-*C*H).

2.3. Synthesis of 1-(2-hydroxyethyl)-3-benzylbenzimidazolium bromide, *2b*

For the synthesis of **2b,** 1-benzylbenzimidazole (2.08 g, 10 mmol) and 2-bromoethanol (1.25 g, 10 mmol) was added in DMF (4 mL). The reaction mixture was stirred for 24 h at 70–80 °C and 2 h. at 100–110 °C temperatures. Then the solvents were evaporated under vacuum to afford the product as a white solid. The crude product was recrystallized from ethyl alcohol/diethyl ether (1:3) at room temperature. Yield: 2.70 g (81%). m.p.: 104–105 °C; $\nu_{(CN)}$: 1479.8 cm^{-1}. Anal. Calc. for $C_{16}H_{17}BrN_2O$: C: 57.67; H: 5.14; N: 8.41. Found: C: 57.64; H: 5.16; N: 8.44. ^1H NMR (400 MHz, $CDCl_3$-d_6); δ 2.62 (t, 1H, J = 6 Hz $-NCH_2CH_2O\boldsymbol{H}$); 4.12 (t, 2H, J = 6 Hz $-NC\boldsymbol{H_2}CH_2OH$); 4.76 (t, 2H, J = 6 Hz $-NCH_2C\boldsymbol{H_2}OH$); 5.80 (s, 2H, $-NC\boldsymbol{H_2}(C_6H_5)$; 7.28–7.84 (m, 9H, Ar-*H*); 10.65 (s, 1H, 2-C***H***). ^{13}C NMR (100 MHz, $CDCl_3$-d_6); δ 49.9 ($-NCH_2CH_2OH$); 51.6 $-NCH_2(C_6H_5)$; 59.0 ($-NCH_2CH_2OH$); 113.6–113.7–127.0–127.1–128.3–129.2–129.4–131.2–131.9 and 132.6 (Ar-*C*); 142.7 (2-*C*H).

2.4. Synthesis of 1-(2-hydroxyethyl)-3-benzylbenzimidazolium hexafluorophosphate, *2c*

For the synthesis of **2c**, 1-(2-hydroxyethyl)-3-benzylbenzimidazolium bromide **2b** (1.67 g, 5 mmol) and ammonium hexafluorophosphate (0.82 g, 5 mmol) was added in chloroform (5 mL) [37]. The reaction mixture was stirred for 24 h at room temperatures. Then the solvents were evaporated under vacuum to afford the product as a white solid. The crude product was recrystallized from ethyl alcohol/diethyl ether (1:3) at room temperature.