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Biology-oriented drug synthesis (BIODS) of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl aryl ether derivatives, *in vitro* α-amylase inhibitory activity and *in silico* studies

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ABSTRACT

A new library of 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl aryl ether derivatives (**1** –**2 3**) were synthesized and characterized by EI-MS and ^{1}H NMR, and screened for their α-amylase inhibitory activity. Out of twenty-three derivatives, two molecules **19** (IC_{50} = 0.38 ± 0.82 μM) and **23** (IC_{50} = 1.66 ± 0.14 μM), showed excellent activity whereas the remaining compounds, except **10** and **17**, showed good to moderate inhibition in the range of IC_{50} = 1.77–2.98 μM when compared with the standard acarbose (IC_{50} = 1.66 ± 0.1 μM). A plausible structure-activity relationship has also been presented. In addition, *in silico* studies was carried out in order to rationalize the binding interaction of compounds with the active site of enzyme.

1. Introduction

Diabetes being a severe disease is the most raising problem in the world. Estimated data was collected in 2010 which stated that 285 million peoples were affected by this disease which may increase to 439 million by 2030 [1,2]. Almost 95% of diabetes cases are characterized by changing blood glucose level because of insulin resistance [3]. This situation leads to cardiovascular diseases, high blood pressure, stroke, blindness, and kidney failure [4]. Inhibition of α-amylase enzyme in the digestive system is one of the best options to maintain the postprandial glucose level [5]. α-Amylase is a protein enzyme that involves in the hydrolyses of α-bonds of complex α-linked polysaccharides like starch and glycogens. While these fragment involve in degradation of α-glycosides in small intestine. This enzyme hydrolyses non-reducing glucose to enter into blood stream [6]. Postprandial hyperglycemia occurs due to reduce rate of glucose absorption which occur due to delay of carbohydrate digestion in the body [7].

Imidazole ring is a common structural motif of pharmacologically active scaffolds, covering a broad spectrum of targets. The pharmacological interest of the nitroimidazoles has been recognized, as these are extensively being used in therapy against amoebic, giardial, trichomonal, and anaerobic infections or as hypoxic cell radio-sensitizers [8]. Metronidazole and substituted imidazoles are well-tolerated drugs that are potentially active against leishmania, but their use in the treatment of cutaneous and visceral leishmaniasis has produced conflicting results [9]. Clotrimazole is an antifungal medication commonly used in the treatment of fungal infections such as vaginal yeast infections, oral thrush and ringworm. The imidazole moiety which incorporates both p-excessive and p-deficient characteristics has proven to be a master key in the range of drug target families [10]. Compounds with the imidazole scaffold are known as inhibitors of p38 MAPK [11], JNK

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[12], BRAF kinase [13], transforming growth factor b-1 (TGF-b1) type-1 receptor kinase [14] and acyl-CoA: cholesterol *O*-acyl transferase (ACAT) [15]. Imidazoles substituted with 2-arylamino functionality have been reported to have potent and selective agonist activity at a 2-adrenoceptors [16].

In the array of our recently recognized terminology "biology-oriented drug synthesis" (BIODS) by the scientific world [17,18], which is purely dedicated to explore further biological potential of already existing drug candidates after some structural modification by simple one or two step synthesis. As far as metronidazole is concern, we recently reported the *β*-glucuronidase inhibitory activity of 2-(2-methyl-5-nitro-1*H*-imidazol-1-yl)ethyl aryl carboxylate derivatives [18]. In recent past, we have reported benzimidazole derivatives as potential class of antiglycating agents [19]. Which encouraged us to evaluate the library of 1-(2-(aryloxy) ethyl)-2-methyl-5-nitro-1H-imidazole derivatives (**1** –**2 3**) for *α*-amylase inhibitory activity due to have some structural resemblance (Fig. 1).

Current study is comprised of the synthesis of aryl ethers of metronidazole (**1** –**2 3**) and their *in vitro* *α*-amylase inhibitory activity and *in silico* studies.

2. Experimental

2.1. General methods

All nuclear magnetic resonance experiments had been carried out using on Avance Bruker 500 MHz. Elemental analysis was performed on Carlo Erba Strumentazion-Mod-1106, Italy. Electron impact mass spectra (EI-MS) were recorded on a Finnigan MAT-311A, Germany. Thin layer chromatography (TLC) was performed on pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany). Chromatograms were visualized by UV at 254 and 365 nm.

2.2. General procedure for synthesis of 2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethyl aryl ethers (1 –2 3)

2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethanol (I) was treated with sodium hydride in dried THF followed by addition of 1.1 equilivlant benzyl halide to give 1-(2-(benzyloxy)ethyl)-2-methyl-5-nitro-1H-imidazole. The reaction completion was monitored by TLC. The product was purified through Column chromatography.

2.2.1. 1-(2-(Benzyloxy)ethyl)-2-methyl-5-nitro-1H-imidazole

Yield: 87%; m.p. 290 °C; ^{1}H NMR (500 MHz, DMSO) *δ* 7.85 (s, 1H), 7.36 (m, 1H), 7.30 (m, 4H), 4.85 (s, 2H), 4.38 (d, *J* = 7.7 Hz, 2H), 3.83 (d, *J* = 7.7 Hz, 2H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): *δ* 152.4, 139.5, 138.9, 133.8, 129.2, 129.2, 129.0, 128.8, 128.8, 74.6, 70.8, 44.2, 15.1; HR-ESI-MS: *m*/*z* calcd for $C_{13}H_{15}N_3O_3$, [M]+ 261.2810; Found 261.2819; Anal. Calcd: C, 59.76; H, 5.79; N, 16.08; Found C, 59.75; H, 5.80; N, 16.09.

2.2.2. 2-methyl-1-(2-((4-methylbenzyl)oxy)ethyl)-5-nitro-1H-imidazole

Yield: 89%; m.p. 294 °C; ^{1}H NMR (500 MHz, DMSO) *δ* 7.84 (s, 1H), 7.19 (dd, *J* = 7.4, 0.7 Hz, 2H), 7.11 (dd, *J* = 7.4, 0.9 Hz, 2H), 4.86 (s, 2H), 4.36 (d, *J* = 7.7 Hz, 2H), 3.82 (d, *J* = 7.7 Hz, 2H), 2.52 (s, 3H), 2.21 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): *δ* 151.4, 138.5, 136.9, 132.8, 132.6, 128.8, 128.8, 126.9, 126.9, 73.4, 69.7, 43.2, 21.1, 14.1; HR-ESI-MS: *m*/*z* calcd for $C_{14}H_{17}N_3O_3$, [M]+ 275.3080; Found 275.3087; Anal. Calcd: C, 61.08; H, 6.22; N, 15.26; Found C, 61.07; H, 6.23; N, 15.24.

2.2.3. 1-(2-((4-Methoxybenzyl)oxy)ethyl)-2-methyl-5-nitro-1H-imidazole

Yield: 88%; m.p. 301 °C; ^{1}H NMR (500 MHz, DMSO) *δ* 7.86 (s, 1H), 7.10 (dd, *J* = 7.4, 0.7 Hz, 2H), 6.98 (dd, *J* = 7.4, 0.9 Hz, 2H), 4.83 (s, 2H), 4.37 (d, *J* = 7.7 Hz, 2H), 3.87 (d, *J* = 7.7 Hz, 2H), 3.83 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): *δ* 160.0, 152.2, 139.3, 133.6, 132.0, 130.0, 130.0, 114.5, 114.5, 74.2, 70.5, 56.1, 44.0, 14.9; HR-ESI-MS: *m*/*z* calcd for $C_{14}H_{17}N_3O_4$, [M]+ 291.3070; Found 291.3084; Anal. Calcd: C, 57.72; H, 5.88; N, 14.42; Found C, 57.70; H, 5.89; N, 14.43.

2.2.4. 1-(2-((3,5-Dimethoxybenzyl)oxy)ethyl)-2-methyl-5-nitro-1H-imidazole

Yield: 90%; m.p. 305 °C; ^{1}H NMR (500 MHz, DMSO) *δ* 7.86 (s, 1H), 6.68 (dd, *J* = 0.9, 0.7 Hz, 2H), 6.39 (dd, *J* = 0.7, 0.9 Hz, 1H), 4.82 (s, 2H), 4.34 (d, *J* = 7.7 Hz, 2H), 3.86 (d, *J* = 7.7 Hz, 2H), 3.80 (s, 6H), 2.55 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6): *δ* 157.2, 157.2, 150.3, 145.9, 137.4, 131.7, 102.7, 102.7, 99.7, 71.4, 68.6, 54.1, 54.1, 42.1, 13.0; HR-ESI-MS: *m*/*z* calcd for $C_{15}H_{19}N_3O_5$, [M]+ 321.3330; Found 321.3323; Anal. Calcd: C, 56.07; H, 5.96; N, 13.08; Found C, 56.08; H, 5.94; N, 13.07.

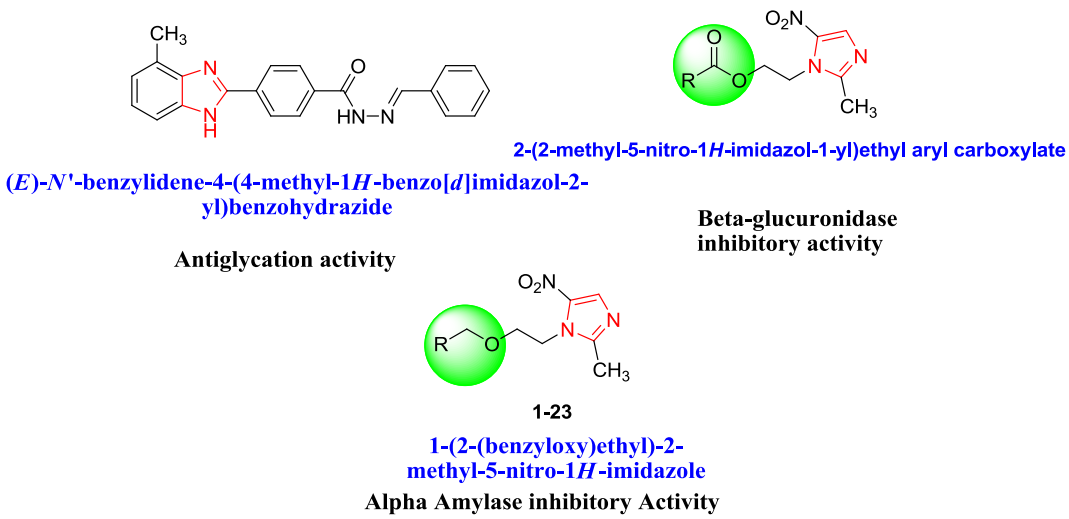

Fig. 1. Rationale of the current study.