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Benzimidazole derivatives as new α-glucosidase inhibitors and *in silico* studies

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ABSTRACT

Newly synthesized benzimidazole hydrazone derivatives **1–26** were evaluated for their α-glucosidase inhibitory activity. Compounds **1–26** exhibited varying degrees of yeast α-glucosidase inhibitory activity with IC_{50} values between 8.40 ± 0.76 and 179.71 ± 1.11 μM when compared with standard acarbose. In this assay, seven compounds that showed highest inhibitory effects than the rest of benzimidazole series were identified. All the synthesized compounds were characterized by different spectroscopic methods adequately. We further evaluated the interaction of the active compounds with enzyme with the help of docking studies.

1. Introduction

Postprandial hyperglycemia resulting from defects of insulin secretion β-cells play an important role in the development of both types of diabetes mellitus [1,2]. One of the therapeutic approaches to control postprandial hyperglycemia is to retard absorption of glucose by the inhibition of α-glucosidase in intestinal carbohydrate digestion [3]. Oral hypoglycemic agents like α-glucosidase inhibitors are used for treatment of diabetes but they have their own limitations due to selective mechanism of action. A few examples of leading inhibitors such as acarbose and miglitol, are often reported to cause diarrhea and other intestinal disturbances, with corresponding bloating, flatulence, cramping and abdominal pain [4]. Therefore, alternative α-glucosidase inhibitors may become therapeutics of interest in managing both types of diabetes. In the continuous effort to discover new bioactive compounds, a new series of benzimidazole derivatives as α-glucosidase inhibitors were synthesized. Benzimidazole nucleus is an important pharmacophore with unique chemical and biological properties [5–10]. Benzimidazoles have been found to possess anti-inflammatory, antidiabetic, antispasmodic, antihistaminic, analgesic, antimicrobial, antiproliferative, antitumor, anti-HIV-RT, antiulcer, anticancer, anti-tubercular, and cycloxygenase inhibitor activities [11–20]. We have reported few heterocyclic hydrazones [21] as potent inhibitors for α-glucosidase so, in continuation of our work we synthesized novel benzimidazole derivatives and tested for α-glucosidase.

2. Results and discussion

2.1. Chemistry

The synthesis of the target compounds began with the synthesis of sodium metasulfite adduct according to literature protocol [21]. The resulting sulfite adduct was refluxed with 4,5-dimethyl-*O*-phenylenediamine in DMF for 6 h to give out the arylester substituted benzimidazole. The benzohydrazide of benzimidazole was formed by refluxing arylester of benzimidazole with methanolic hydrazine hydrate. The synthesis of new benzimidazole benzohydrazide Schiff bases **1–26** was accomplished (Table 1) by reacting different aldehydes with benzimidazole benzohydrazide in *n*-butanol in the presence of catalytic amount of acetic acid, as shown in Scheme 1. The structures of all compounds were

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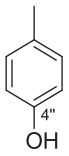
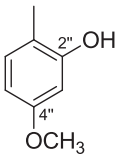
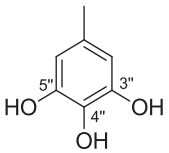
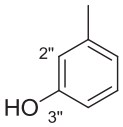
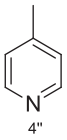
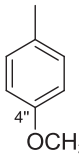
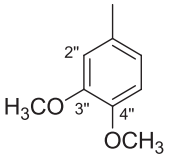
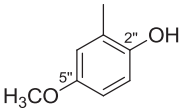
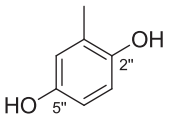
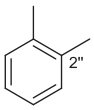
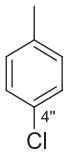
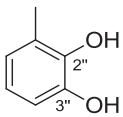
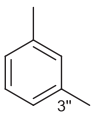
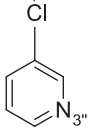
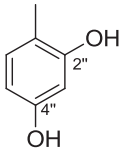
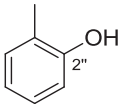
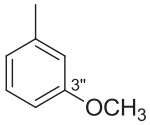
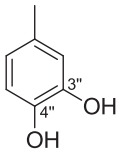
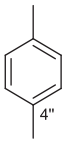
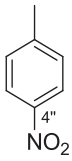
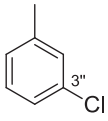
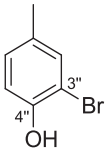
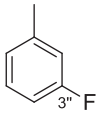
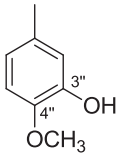
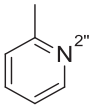
Table 1
α-Glucosidase inhibitory potential of benzimidazole hydrazone derivatives **1–26**.

No.	R	IC_{50} ± SEM (μM)	No.	R	IC_{50} ± SEM (μM)	No.	R	IC_{50} ± SEM (μM)
1		26.02 ± 1.32	**10**		8.44 ± 0.76	**19**		8.40 ± 0.76
2		32.53 ± 0.62	**11**		147.53 ± 1.04	**20**		32.63 ± 0.50
3		179.71 ± 1.11	**12**		8.44 ± 0.68	**21**		32.09 ± 0.68
4		8.74 ± 0.40	**13**		24.84 ± 0.76	**22**		24.82 ± 1.52
5		9.99 ± 0.69	**14**		23.53 ± 0.29	**23**		46.02 ± 1.04
6		8.74 ± 1.60	**15**		18.21 ± 1.53	**24**		15.06 ± 1.53
7		12.49 ± 1.16	**16**		18.30 ± 0.5	**25**		19.35 ± 0.76
8		22.36 ± 0.29	**17**		34.53 ± 0.21	**26**		157.86 ± 0.76
9		28.95 ± 1.04	**18**		25.72 ± 0.68	**27**	Acarbose	774.5 ± 1.94

confirmed by their spectral evidence (IR, 1D NMR, ESI mass spectroscopy) and melting point.

2.2. α-Glucosidase inhibitory activity

Identification of potential α-glucosidase inhibitors were done by *in vitro* screening of 26 benzimidazole derivatives using Baker's yeast α-glucosidase enzyme. Compounds **1–26** exhibited varying degrees of yeast α-glucosidase inhibitory activity with IC_{50} values between 8.40 ± 0.76 and 179.71 ± 1.11 μM when compared with standard acarbose (IC_{50} = 774.5 ± 1.94 μM). Acarbose was not very potent in inhibition of yeast α-glucosidase under our assay conditions. This was expected since acarbose has been shown to be a potent inhibitor of mammalian sucrose and maltase and less potent against yeast and bacterial forms [22–24]. In this assay, seven compounds that showed significant inhibitory effects than the rest of benzimidazole series (Table 1) were identified. These are the compounds with IC_{50} values ranging from 8.40 ± 0.76 to 12.49 ± 1.16 μM. Our study showed that compound **19** having three hydroxyls group at *meta–para* position over the phenyl ring was the most potent α-glucosidase inhibitor with IC_{50} value (IC_{50} = 8.40 ± 0.76) as compared to compound **7** (IC_{50} = 12.49 ± 1.16) having only two hydroxyls group at the same position. Whereas the other five active compound **4**, **5**, **6**, **10** and **12** with IC_{50} values ranging from 8.44 ± 0.68 to 9.99 ± 0.69 μM having two substituents over the phenyl ring with one hydroxyl group at