

RESEARCH ARTICLE

New antihyperglycemic, α -glucosidase inhibitory, and cytotoxic derivatives of benzimidazoles

Jaladi Ashok Kumar¹, Ashok Kumar Tiwari², Amtul Zehra Ali², Kuncha Madhusudhana², Boreddy Srinivas Reddy², Sistala Ramakrishna², and Bhimapaka China Raju¹

¹Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad, India, and ²Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad, India

Abstract

Glycosidases play an important role in a wide range of physiological and pathological conditions, and have become potential targets for the discovery and development of agents useful for the treatment of diseases such as diabetes, cancer, influenza, and even AIDS. In this study, several benzimidazole derivatives were prepared from *o*-phenylenediamine and aromatic and heteroaromatic carboxaldehydes in very good yields, using $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ as the most efficient catalyst. Synthesized compounds were assayed for their activity on yeast and rat intestinal α -glucosidase inhibition and cytotoxic activity against colon carcinoma cell line HT-29. Compound **3e** exhibited 95.6% and 75.3% inhibition of yeast and rat intestinal α -glucosidase enzyme, while showing 74.8% cytotoxic activity against the HT-29 cell line at primary screening concentrations of 2.1 mM for yeast and rat intestinal α -glucosidase enzyme and 0.2 mM for cytotoxic activity against the HT-29 cell line, respectively. Compound **3c** displayed 76% and 34.4% inhibition of yeast and rat intestinal α -glucosidase enzyme, and 80.4% cytotoxic activity against the HT-29 cell line at similar primary screening concentrations. The IC_{50} value for the most potent intestinal α -glucosidase inhibitor compound **3e** was found to be 99.4 μM . The IC_{50} values for the most active cytotoxic compounds **3c** and **3e** were 82 μM and 98.8 μM , respectively. Both compounds displayed significant antihyperglycemic activity in starch-induced postprandial hyperglycemia in rats. This is the first report assigning yeast and rat intestinal α -glucosidase enzyme inhibition, cytotoxic activity against the HT-29 cell line, and antihyperglycemic activity to benzimidazole compounds **3c** and **3e**.

Keywords: Benzimidazoles; carbonyl compounds; α -glucosidase inhibition; cytotoxic activity; HT-29 cell line; starch tolerance test; antihyperglycemic activity

Introduction

Benzimidazoles are heterocyclic compounds having various biological activities, among which albendazole, mebendazole, and thiabendazole are widely used antihelminthic drugs¹. Furthermore, benzimidazole compounds are also reported to possess biological activities such as inhibition of the angiotensin receptor TIE-2 and tyrosine kinase receptor VEGFR-2 (vascular endothelial growth factor receptor-2)², antitumor activity³, thrombopoietin receptor agonistic activity⁴, γ -aminobutyric acid (GABA) agonistic activity⁵, antibacterial activity⁶, antiprotozoal⁷ and antimicrobial activity⁸, topoisomerase inhibition⁹, neuropeptide Y1 receptor antagonistic activity¹⁰, and inhibition of angiotensin II¹¹. Recently, benzimidazole derivatives have been found to be active on several targets useful for the development of

antidiabetic therapeutics, e.g. inhibitors of dipeptidyl peptidase IV¹² and activators of peroxisome proliferator-activated receptor- γ (PPAR- γ)^{13,14}.

In the course of our study to find α -glucosidase inhibitors from various sources, we observed benzimidazoles to be potent inhibitors of yeast as well as intestinal α -glucosidase. Intestinal α -glucosidase inhibitors have become an important therapeutic tool in mitigation of postprandial hyperglycemia (PPHG). PPHG has emerged as a prominent and early defect in type 2 diabetes¹⁵ and as a predictor of cardiovascular or even all-cause mortality, as well as an independent risk factor for atherosclerosis¹⁶. Several epidemiological studies have observed that subjects with type 2 diabetes have an increased risk for the development of colorectal cancer¹⁷.

Address for Correspondence: Ashok Kumar Tiwari, Pharmacology Division, Indian Institute of Chemical Technology, Hyderabad-500 607, India; Bhimapaka Chinaraaju, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 607, India. Tel: 91-40-27191725; 91-40-27191617. Fax: 91-40-27160512. E-mail: astiwari@yahoo.com; chinaraajuict@yahoo.co.in

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Therefore, the search for agents that mitigate postprandial hyperglycemia and possess cytotoxic activity against colon cancer cell lines may offer an opportunity for the development of novel therapeutics for diabetic patients. In this communication we report the synthesis of various benzimidazoles **3a-h** by the condensation of *o*-phenylenediamines (**1a-h**) with aromatic and heteroaromatic carbonyl compounds (**2a-h**) in the presence of a catalytic amount of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in dry MeOH at room temperature. Compounds **3a-h** were evaluated for their *in vitro* α -glucosidase inhibitory activity and cytotoxic activity on colon carcinoma line HT-29, as well as antihyperglycemic property in starch-induced postprandial hyperglycemia in rats.

Experimental

Chemistry

^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz and an Avance 300 MHz spectrometer in CDCl_3 and $\text{DMSO}-d_6$ using tetramethylsilane (TMS) as internal standard. All chemical shifts are reported as δ (ppm) values. Infrared (IR) spectra were recorded on a Nicolet 740 Fourier transform (FTIR) spectrometer. Mass spectra were obtained on an Agilent liquid chromatography (LCMS) instrument. Melting points were determined in open glass capillary tubes on a Mettler FP 51 apparatus and are uncorrected. All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (mesh); spots were visualized under ultraviolet (UV) light. Merck silica gel (60–120; 100–200 mesh) was used for chromatography. All reactions were carried out using reagent-grade solvents, and the reagents were purchased from Sigma-Aldrich.

General procedure for the preparation of benzimidazoles **3a-h**

To a stirred solution of *o*-phenylenediamine (**1a**, 1 mmol) and catalyst $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (20 mol%) in anhydrous methanol (5 mL) was added a solution of carbonyl compound (**2a**, 1 mmol) under a nitrogen atmosphere over a period of 5 min at room temperature, and the contents were stirred at the same temperature for 4 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and the crude product was subjected to column chromatography purification to afford 2-(2-chloro-5-methyl-3-pyridyl)-1H-benzo[d]imidazole **3a** as solid in 82% yield. Mp: 213–215°C; IR (KBr): 3443, 2922, 1569, 1436, 1071, 889 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 2.42 (s, 3H, CH_3), 7.24–7.36 (m, 2H, aromatic), 7.62–7.72 (m, 2H, aromatic), 8.28 (s, 1H, heteroaromatic), 8.72 (s, 1H, heteroaromatic); ^{13}C NMR (CDCl_3 , 75 MHz): δ 22.14, 120.71, 127.86, 130.93, 138.26, 143.92, 146.50, 150.31, 152.62, 155.82; LCMS: [$\text{M}^+ + 1$] 243, 245.

Compounds **3b-h** were synthesized similarly.

2-(2-chloro-5-methyl-3-pyridyl)-6-nitro-1H-benzo[d]imidazole. **3b** 68% Yield; solid; Mp: 261–263°C; IR (KBr): 3363,

2924, 1619, 1439, 1339, 1189, 1064, 947 cm^{-1} ; ^1H NMR (CDCl_3 + $\text{DMSO}-d_6$, 300 MHz): δ 2.42 (s, 3H, CH_3), 7.78 (d, $J=10$ Hz, 1H, aromatic), 8.22 (d, 1H, heteroaromatic), 8.32 (s, 1H, aromatic), 8.38 (s, 1H, heteroaromatic), 8.66 (s, 1H, heteroaromatic); LCMS: [$\text{M}^+ - 1$] 287, 289.

4-(6-methyl-1H-benzo[d]imidazol-2-yl)-1,3-benzenediol. **3c** 78% Yield; solid; Mp: 248–249°C; IR (KBr): 3559, 3356, 2922, 1740, 1616, 1494, 1426, 1250, 1040, 970 cm^{-1} ; ^1H NMR (CDCl_3 + $\text{DMSO}-d_6$, 300 MHz): δ 2.42 (s, 3H, CH_3), 6.40 (d, $J=8$ Hz, 1H, aromatic), 6.50 (s, 1H, aromatic), 6.98 (s, 1H, aromatic), 7.30 (s, 1H, aromatic), 7.38 (d, $J=12$ Hz, 1H, aromatic), 7.62 (d, $J=12$ Hz, 1H, aromatic); ^{13}C NMR (CDCl_3 + $\text{DMSO}-d_6$, 75 MHz): δ 21.19, 103.00, 104.55, 107.45, 123.69, 127.24, 131.62, 152.04, 159.78, 160.62; LCMS: [$\text{M}^+ - 1$] 239.

6-Nitro-2-(3-pyridyl)-1H-benzo[d]imidazole. **3d** 64% Yield; solid; Mp: 242–244°C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.42–7.54 (m, 1H, aromatic), 7.70 (d, $J=8$ Hz, 1H, heteroaromatic), 8.18 (d, $J=10$ Hz, 1H, heteroaromatic), 8.52–8.58 (m, 2H, heteroaromatic), 8.78 (s, 1H, aromatic), 9.46 (s, 1H, heteroaromatic). LCMS: [$\text{M}^+ + 1$] 240.

6-Nitro-2-(4-pyridyl)-1H-benzo[d]imidazole. **3e** 62% Yield; solid; Mp: 224–226°C; ^1H NMR (CDCl_3 , 300 MHz): δ 7.26 (s, 1H, aromatic), 7.44–7.52 (m, 1H, aromatic), 7.74 (brs, 1H, NH), 7.92–8.02 (m, 1H, aromatic), 8.26 (d, $J=10$ Hz, 1H, heteroaromatic), 8.54 (d, 1H, heteroaromatic), 8.68 (d, $J=8$ Hz, 2H, heteroaromatic); LCMS: [$\text{M}^+ + 1$] 241.

6-Methyl-2-(3-pyridyl)-1H-benzo[d]imidazole. **3f** 76% Yield; solid; Mp: 244–246°C; IR (KBr): 3448, 3006, 2917, 1736, 1574, 1448, 1425, 1314, 1274, 1186, 962 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 2.46 (s, 3H, CH_3), 6.98 (d, $J=10$ Hz, 1H, aromatic), 7.28–7.52 (m, 3H, aromatic + heteroaromatic), 8.48 (d, $J=10$ Hz, 1H, heteroaromatic), 8.66 (d, $J=8$ Hz, 1H, aromatic), 9.34 (d, $J=8$ Hz, 1H, heteroaromatic); ^{13}C NMR (CDCl_3 + $\text{DMSO}-d_6$, 75 MHz): δ 21.26, 123.93, 126.24, 131.76, 133.56, 147.35, 148.45, 150.25; LCMS: [$\text{M}^+ + 1$] 210.

6-Methyl-2-(4-pyridyl)-1H-benzo[d]imidazole. **3g** 68% Yield; solid; Mp: 218–219°C; IR (KBr): 3448, 3038, 1683, 1606, 1483, 1373, 1235, 1000, 960 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 2.50 (s, 3H, CH_3), 7.04 (d, $J=8$ Hz, 1H, aromatic), 7.42 (s, 1H, aromatic), 7.58 (d, $J=8$ Hz, 1H, aromatic), 8.04 (d, $J=10$ Hz, 2H, heteroaromatic), 8.70 (d, $J=8$ Hz, 2H, heteroaromatic); LCMS: [$\text{M}^+ + 1$] 210.

6-Nitro-2-(2-pyridyl)-1-(2-pyridylmethyl)-1H-benzo[d]imidazole. **3h** 64% Yield; solid; Mp: 173–175°C; IR (KBr): 3424, 3060, 1587, 1510, 1466, 1436, 1337, 1150, 992 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 6.34 (s, 2H, CH_2), 7.06 (d, $J=10$ Hz, 1H, aromatic), 7.14–7.22 (m, 1H, aromatic), 7.37–7.43 (m, 1H, heteroaromatic), 7.53–7.58 (m, 1H, heteroaromatic), 7.86–7.93 (m, 2H, heteroaromatic), 8.24 (d, $J=12$ Hz, 1H, heteroaromatic), 8.44 (s, 1H, aromatic), 8.50 (d, $J=12$ Hz, 1H, heteroaromatic), 8.58 (d, $J=6$ Hz, 1H, heteroaromatic), 8.65 (d, $J=6$ Hz, 1H, heteroaromatic); ^{13}C NMR (CDCl_3 , 75 MHz): δ 51.49, 108.13, 119.27, 120.09, 121.19, 122.73, 125.14, 125.20, 136.39, 136.92, 137.19, 146.96, 148.80, 148.89, 149.44, 149.60, 154.20, 156.27; LCMS: [$\text{M}^+ + 1$] 332.

Biological evaluation

Chemicals

Yeast α -glucosidase and rat intestinal acetone powder as a source of intestinal α -glucosidase, *p*-nitrophenyl α -D-glucopyranoside (*p*NPG), soluble potato starch, DMEM (Dulbecco's modified Eagle's medium), MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide), trypsin, and EDTA (ethylenediaminetetraacetic acid) were purchased from Sigma Chemical Co., St. Louis, MO, USA. Fetal bovine serum (FBS) was purchased from Gibco. Other chemicals of analytical grade were procured from indigenous manufacturers. The HT-29 (colon cancer) cell line was obtained from the National Center for Cell Science (NCCS), Pune, India.

In vitro α -glucosidase inhibitory assay

α -Glucosidase inhibitory activities were determined as per earlier reported methods^{18,19}. Rat intestinal acetone powder in normal saline (100: 1; w/v) was sonicated thoroughly and the supernatant was used as a source of crude intestinal α -glucosidase after centrifugation. In brief, 10 μ L of test sample (5 mg/mL DMSO solution) was reconstituted in 100 μ L of 100 mM phosphate buffer (pH 6.8) in a 96-well microplate and incubated with 50 μ L of crude intestinal α -glucosidase for 5 min before 50 μ L substrate (5 mM *p*NPG prepared in same buffer) was added. Release of *p*-nitrophenol was measured at 405 nm spectrophotometrically (SpectraMax Plus³⁸⁴; Molecular Devices Corp., Sunnyvale, CA, USA) 5 min after incubation with substrate. Individual blanks for test samples were prepared to correct background absorbance where substrate was replaced with 50 μ L of buffer. The control sample contained 10 μ L of dimethylsulfoxide (DMSO) in place of

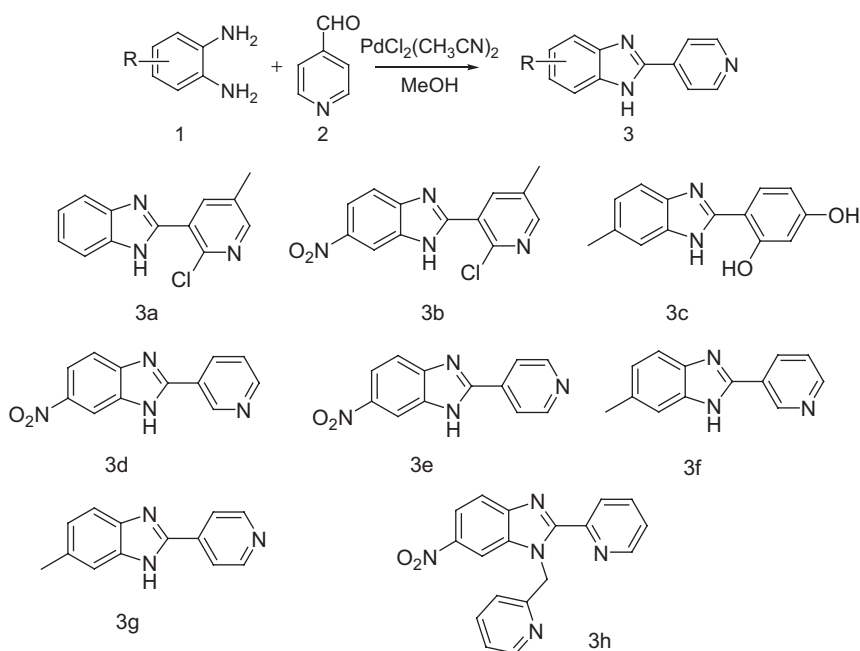
test sample. The percentage of enzyme inhibition was calculated as $(1 - B/A) \times 100$ where *A* represents the absorbance of control without test sample, and *B* represents the absorbance in the presence of test sample. The IC_{50} values were determined by applying logarithmic regression analysis to the data for at least five concentration dilutions of the compound.

In vitro assay for cytotoxic activity

HT-29 (colon cancer) cells were plated at a density of 1×10^3 cells per well in 100 μ L of DMEM supplemented with 10% FBS medium in a 96-well plate and grown for 24 h. The cells were then exposed to a series of concentrations of test compounds for 24 h and the viability of cells was measured with the MTT method as reported earlier²⁰. Briefly, the above media were replaced with 90 μ L of fresh serum-free DMEM and 10 μ L of MTT reagent (5 mg/mL) and plates were incubated at 37°C for 4 h; thereafter the above media were replaced with 200 μ L of DMSO and incubated for 15 min. The absorbance at 570 nm was measured on a spectrophotometer (SpectraMax; Molecular Devices). The values for each point were calculated from triplicate wells. IC_{50} values were determined applying logarithmic regression analysis to the data for at least three dilutions.

Animal experiment

The study of antihyperglycemic activity was done according to a method reported earlier²¹. Male Wistar rats weighing between 195 and 215 g were obtained from the National Institute of Nutrition (CPCSEA Reg. No. 154, Government of India), Hyderabad. The animals were housed in standard polyvinyl cages. The room temperature was maintained at $22 \pm 1^\circ\text{C}$ with an alternating 12 h light/dark cycle. Food and water were provided *ad libitum*. Experiments were



Scheme 1. Reaction route for the synthesis of benzimidazoles and their structures.

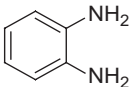
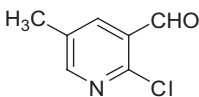
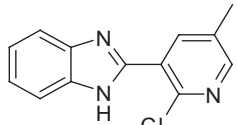
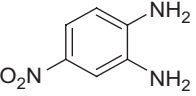
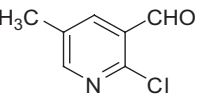
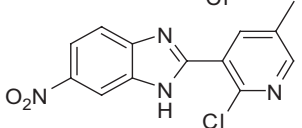
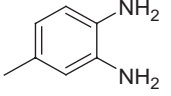
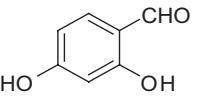
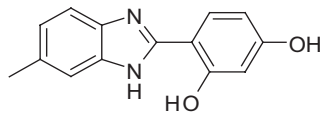
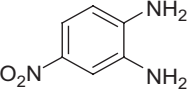
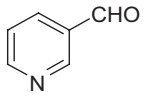
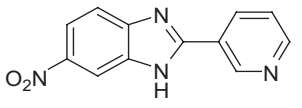
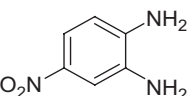
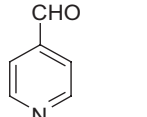
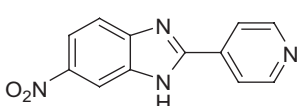
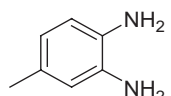
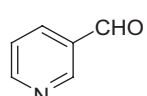
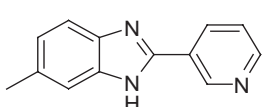
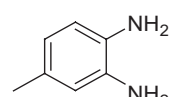
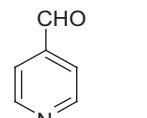
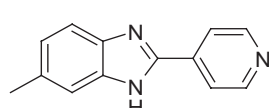
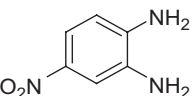
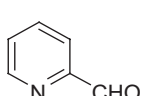
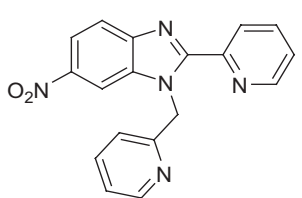
performed as per the Institutional Animal Ethics Committee norms. The rats were divided into three groups, viz. control, and **3c** and **3e** groups, containing six rats in each group. All animals were subjected to overnight fasting. The next day, forenoon blood was collected from the retro-orbital plexus in EDTA-containing tubes, and basal (0 h) plasma glucose levels were measured by the glucose-oxidase test method using a blood autoanalysis instrument (Bayer Express Plus). Test compounds were suspended in normal saline and administered orally in a dose of 50 mg/kg body weight. The control group of animals was given only normal saline. Fifteen minutes after test sample treatment, animals were fed with soluble starch dissolved in normal saline at a dose of 2 g/kg body weight. Thereafter, blood was collected at intervals of 30, 60, 90, and 120 min post-starch feeding. Plasma was separated out for glucose measurement as described above.

Results and discussion

Chemistry

Due to the importance of benzimidazoles, a few methods have been reported in the literature, which include reaction of *o*-aryldiamines with carboxylic acids or their derivatives under strong acidic conditions at high temperatures^{22,23}. Cyclodehydration of *o*-aryldiamines with aldehydes in the presence of oxidative reagents is another method to synthesize benzimidazoles²⁴. Single electron transformation (SET) reactions of 2-nitroaniline with benzaldehyde in the presence of indium/BNP²⁵ as well as the reductive cyclization of 2-nitroaniline in the presence of Na₂S₂O₄ are also reported for the synthesis of benzimidazoles. However, all of these methods have drawbacks in terms of using expensive reagents, oxidation processes, severe conditions, long reaction times, and tedious work-up procedures. It is also

Table 1. Synthesis of benzimidazoles.

Entry	Diamines (1)	Carbonyl Compounds (2)	Product (3)	Yield (%) [*]
a				82
b				68
c				78
d				64
e				62
f				76
g				68
h				64

^{*}Isolated and unoptimized yields; compounds were characterized by spectral data. Biological activity.

known that catalysts based on palladium are very important in organic synthesis, particularly in the total synthesis of natural products for carbon-carbon bond formation²⁶. $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ is considered an important catalyst among all palladium catalysts. We carried out the synthesis of benzimidazoles by the condensation of *o*-phenylenediamine and substituted *o*-phenylenediamines (**1a-h**, 1 mmol) with aryl and heteroaryl carbonyl compounds (**2a-h**, 1 mmol) in the presence of a catalytic amount of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ in anhydrous methanol at room temperature²⁷. The mode of reaction is the formation of a Schiff base (^1H NMR, δ 8.45 singlet, 1H), followed by intramolecular cyclization resulting in benzimidazoles (**3a-h**; Scheme 1 and Table 1) in 62–82% yield. Compounds such as 2-(2-chloro-5-methyl-3-pyridyl)-1*H*-benzo[*d*]imidazole (**3a**) and 2-(2-chloro-5-methyl-3-pyridyl)-6-nitro-1*H*-benzo[*d*]imidazole (**3b**) were prepared by the condensation of *o*-phenylenediamine (**1a**) and nitro *o*-phenylenediamine (**1b**) with 2-chloro-5-methylpyridine-3-carboxaldehyde (**2a**) in very good yields. The compound 2-chloro-5-methylpyridine-3-carboxaldehyde (**2a**) was prepared by the Vilsmeier reaction of an enamide as per our earlier reported method²⁸. 6-Nitro-2-(2-pyridyl)-1-(2-pyridylmethyl)-1*H*-benzo[*d*]imidazole (**3h**) was prepared by the condensation of nitro *o*-phenylenediamine (**1b**) with 2 mol of 2-pyridinecarboxaldehyde (**2h**). The synthesized compounds were characterized by spectral data (^1H NMR, IR, and MS).

Inhibition of glycosidases has recently become important not only due to their interesting role in delineating enzyme mechanisms and the control of postprandial hyperglycemic excursion in diabetes mellitus, but also in development of newer therapeutics targeted at, for example, cancer, viral infections including human immunodeficiency virus (HIV) and influenza, and lysosomal storage diseases, with a number of drugs in current clinical use²⁹. All the compounds were tested *in vitro* first, for α -glucosidase inhibitory activity. Compounds were screened using two models of α -glucosidase enzyme sources: one from yeast that represents α -glucosidase type-I³⁰ that has been extensively used as a model for screening potential inhibitors against viral diseases and cancer³¹, and another from rat intestine that represents α -glucosidase type-II³⁰ that serves as a potential target for screening compounds that may be developed as antihyperglycemic agents against carbohydrate-induced postprandial hyperglycemic excursion³². It is evident from Figure 1A that compounds **3c**, **3e**, and **3g** displayed potent inhibitory activity for yeast α -glucosidase.

Despite the fact that amino acid sequences in the catalytic site of the α -glucosidase family are highly conserved, the aglycon specificity is different³³. It has been advised, therefore, to use enzymes of target tissues or organs for screening of agents for viral diseases, cancer, or diabetes³⁴. Excessive intake of a high-calorie, quickly digestible high-carbohydrate diet results in abnormal surges in the blood glucose level, referred to as PPGH³⁵. Slowing the digestion and absorption of digestible dietary carbohydrates by intestinal α -glucosidase inhibitors in particular, which reduce the rate of enzymatic

digestion of starch and delay the release of glucose molecules for absorption, has shown promise in reducing PPHG, hyperinsulinemia, and unwanted consequences on pancreatic function along with the development of hemodynamic disturbances^{36–37}. When compounds under study were screened for their rat intestinal α -glucosidase inhibitory activity, only **3e** could display strong inhibitory potential for enzyme inhibition also (Figure 1B, IC_{50} = 99.4 μM).

Evaluation of the cytotoxic activity of these compounds was done on colon cancer cell line HT-29. It was observed that at a primary screening concentration of 0.2 μM , compounds **3c** and **3e** displayed 80.4% and 74.8% cytotoxic activity (Figure 1C). The IC_{50} values for compounds **3c** and **3e** were calculated to be 82 μM and 98.75 μM , respectively.

Because compounds **3c** and **3e** possessed both α -glucosidase inhibitory as well as cytotoxic activity, they were selected for evaluation of antihyperglycemic activity *in vivo* on starch-induced hyperglycemia in rats. Both compounds significantly reduced starch-induced postprandial

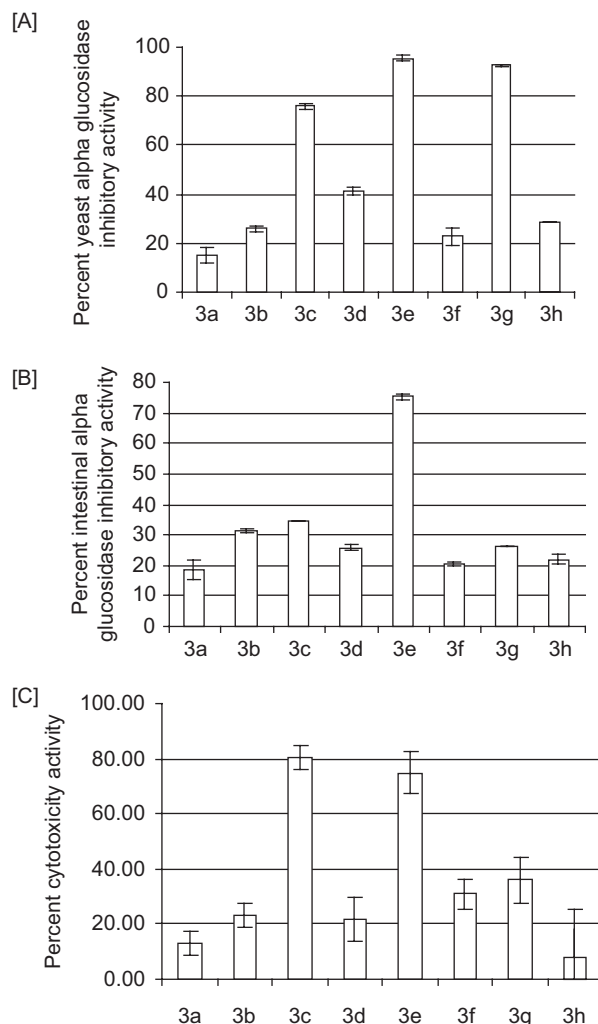


Figure 1. Percentage of activity of benzimidazole derivatives on various targets. The primary concentration at which compounds were screened was 500 $\mu\text{g}/\text{mL}$ for yeast [A] and intestinal [B] α -glucosidase inhibition assay, and 50 $\mu\text{g}/\text{mL}$ for cytotoxic activity [C]. Data represent mean \pm SD, $n=3$.

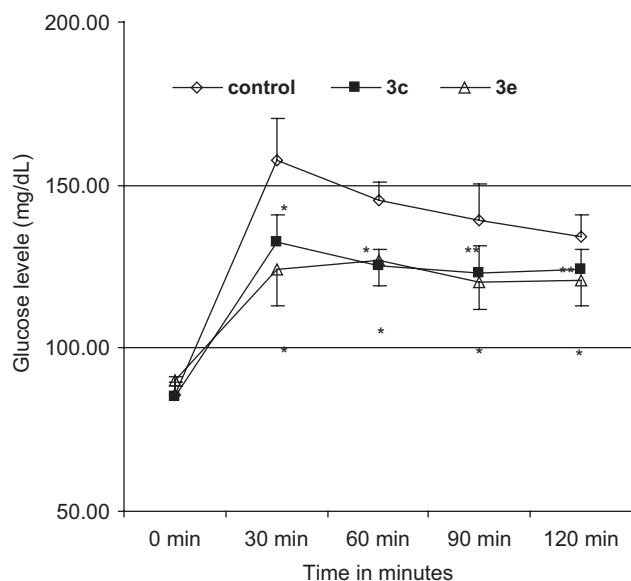


Figure 2. Antihyperglycemic activity of the compounds on starch tolerance test. For statistical analysis ANOVA followed by Dunnett's multiple comparison test was applied to compare the difference between the means. * $p < 0.01$, ** $p < 0.05$. Values represent mean \pm SD, $n = 6$.

hyperglycemic excursion in rats (Figure 2), **3e** being slightly (insignificantly) superior to **3c**.

Conclusion

Synthesis of benzimidazole compounds **3a–h** was achieved by the condensation of aromatic and heteroaromatic aldehydes with *o*-phenylenediamine and substituted *o*-phenylenediamine in the presence of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ with very good yields. Compounds **3c**, **3e**, and **3g** exhibited potent inhibition of yeast α -glucosidase enzyme. However, only **3e** could display potent intestinal α -glucosidase enzyme inhibition. Compounds **3c** and **3e** displayed cytotoxic potential also against colon cancer cell line HT-29. Furthermore, both compounds (**3c** and **3e**) displayed significant antihyperglycemic activity in starch-induced postprandial hyperglycemia in rats. These compounds, therefore, open new avenues for the development of antihyperglycemic anticancer therapeutics targeted toward the treatment of type 2 diabetes.

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