Med Chem Res (2016) 25:2058–2069
DOI 10.1007/s00044-016-1614-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Syntheses, in vitro evaluation and molecular docking studies of 5-bromo-2-aryl benzimidazoles as α-glucosidase inhibitors

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Received: 23 February 2016 / Accepted: 14 June 2016 / Published online: 22 July 2016

Abstract Based on the previous reports on α-glucosidase inhibitory activity of benzimidazole class, we intend to evaluate further this class as potential inhibitors of α-glucosidase enzyme. Thus, in the current study synthesis of 5-bromo-2-aryl benzimidazole derivatives **1**–**25** was carried out. All the synthetic compounds were characterized by different spectroscopic techniques EIMS, HRMS, ^{1}H-NMR, and ^{13}C-NMR. Molecular docking was also performed on the selected compounds **1**, **4**, **7**, and **17** having varying substitution pattern in order to understand the molecular interaction of molecules with the active site of the enzyme. All compounds were evaluated for their in vitro α-glucosidase inhibitory activities. Twenty-three compounds out of twenty-five showed excellent to moderate activity in the range of $IC_{50} = 12.4–103.2$ μM. Inhibitory results were compared with the standard drug acarbose ($IC_{50} = 38.25 \pm 0.12$ μM). Compounds **1** ($IC_{50} = 37.82 \pm 0.08$ μM), **9** ($IC_{50} = 37.76 \pm 0.05$ μM), **12** ($IC_{50} = 24.96 \pm 0.09$ μM), **16** ($IC_{50} = 21.15 \pm 0.08$ μM) and **17** ($IC_{50} = 8.34 \pm 0.02$ μM) showed excellent inhibition as compared to standard drug acarbose ($IC_{50} = 38.25 \pm 0.12$ μM). Especially, **17** ($IC_{50} = 8.34 \pm 0.02$ μM) was found to be five-fold more active than the standard.

Keywords Benzimidazole · In vitro α-Glucosidase inhibition · Structure-activity relationship · Diabetic complications · Obesity

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Introduction

Benzimidazole is a bicyclic and heterocyclic ring structure consisting of a fused benzene and imidazole ring system (Brink and Folkers, 1949). Some benzimidazole derivatives are abundant in marine natural products, like in marine sponge (Calcul et al., 2003). All seven positions are available for substitution in benzimidazole, but the most biological active analogs are 1, 2, 5, di- or tri-substituted analogs. Many drugs possess benzimidazole moiety as the core part of their structures, for example, omeprazole, mebendazole, albendazole, and astemizole. This indicates the importance of benzimidazole as a privileged pharmacophore (Dinparast et al., 2016; Castillo et al., 2016; Song et al., 2015; Gao et al., 2015; Mariappan et al., 2015; Mavrova et al., 2015; Błaszczak-Świątkiewicz et al., 2014; Desai et al., 2014; Zhang et al., 2012; Guo et al., 2008; Sur et al., 2005; Olbe et al., 2003).

Literature search shows that benzimidazole and its derivatives possess a wide spectrum of biological activities such as

antimicrobial, antiviral, antitumor, antioxidant, antiinflammatory, antihypertensive, anticoagulant, antidiabetic, antiallergic, antihistaminic, antitubercular, anti-HIV, antihelmentic, antidepressant, and analgesic activity (Bansal and Silakari, 2012; Nakano et al., 2000; Achar et al., 2010; Kazimierczuk et al., 2002; Ozden et al., 2005; Walia et al., 2011).

Diabetes mellitus is responsible for about 5 % of the deaths of the global population. Type 2 diabetes mellitus is the most common type of disease, in which α-glucosidase enzyme catalyzes the carbohydrates and converts it into absorbable monosaccharide in the small intestine (Gao et al., 2007). α-Glucosidase hydrolyzes the α-glucosidal bond of linear and branched isomaltose oligosaccharides and releases α-D-glucose, which is the main cause of hyperglycemia (Van de Laar, 2008). Inhibition of this enzyme is one of the simplest ways to treat type 2 diabetes mellitus by delaying the intestinal glucose absorption process (Rhabasa-Lhoret et al., 2004). Acarbose, miglitol, and voglibose are inhibitors of α-glucosidase, which are being clinically used for the treatment of type 2 diabetes mellitus (Meneilly et al., 2000; Lesley and Caroline, 2000) and can be used as antidiabetic, anti-HIV, anti-obesity, and anticancer agents (Gallienne et al., 2006; Groopman, 1990; Zitzmann et al., 1999).

However, these drugs are 50 % less effective than other antidiabetic agents such as metformin and sulfonylurea, as well as have some associated side effects such as diarrhea, flatulence, and abdominal discomfort (Ag, 1994). Therefore, it is a restrictive aspect to use the drug alone and thus it is often used in combination with other antidiabetic drugs to improve the efficacy. Hence it is an utmost important task to develop safer medication for diabetes.

Our group has explored several classes of heterocyclic compounds including benzimidazole for their potential therapeutic effects (Khan et al., 1999, 2000, 2002, 2003, 2013; Saify et al., 1999; Zaidi et al., 2001; Zawawi et al., 2015; Rahim et al., 2015; Taha et al., 2015) and also explored many classes of compounds for their α-glucosidase inhibitory activities (Niaz et al., 2015; Taha et al., 2015; Rahim et al., 2015; Kashtoh et al., 2014; Khan et al., 2014).

There are only few reports available regarding the α-glucosidase inhibitory activity of benzimidazole class members such as benzimidazole pthalimide containing amino acid (structure **A**) (Mobinikhaledi et al., 2015) and aryl substituted benzimidazole (structures **B** and **C**) (Kumar et al., 2010) (Fig. 1). Therefore, we decided to further explore this class regarding α-glucosidase inhibitory activity in order to get the more potent inhibitor.

In the light of previous reports, we synthesized 5-bromobenzimidazole analogs **1–25** (general structure **D**) in order to identify some more molecules having α-glucosidase inhibitory potential with less or no cytotoxicity. To the best of our knowledge, structures of compounds **1**, **2**, **4**, **6**, **9** (Dandegaonker and Shastri, 1965), **11**, **12**, **16**, **17** (Cui et al., 2011), **18**, **19**, and **21** (Dandegaonker and Shastri, 1965) are previously known, whereas rest of the molecules are new.

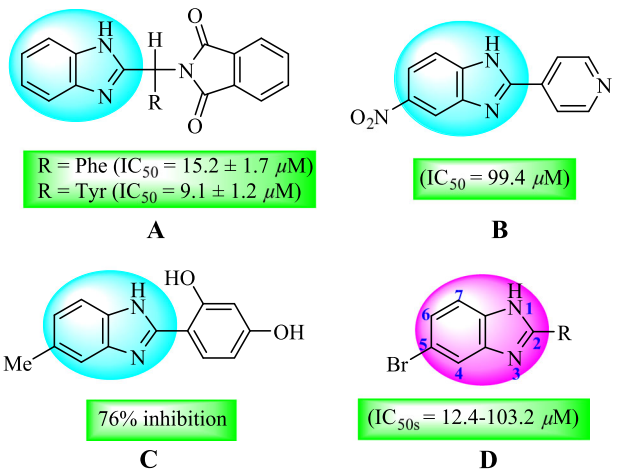


Fig. 1 Rationale of the current study

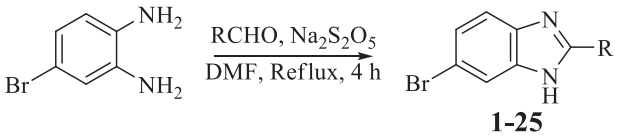
Results and discussion

Chemistry

Benzimidazoles **1–25** were synthesized by treating commercially available 4-bromo-1,2-benzenediamine with different aromatic aldehydes in *N*,*N*-dimethylformamide in the presence of a catalytic amount of sodium metabisulfite ($Na_2S_2O_5$) (Scheme 1). 1,2-Diamino groups of 4-bromo-1,2-benzenediamine undergo cyclization reaction with the aromatic aldehydes to afford desired benzimidazole moieties. The reaction mixture was refluxed for 4 h to afford the products in the form of precipitates, which were collected via filtration and crystallized in ethanol to get the pure products in high yields. Synthesized derivatives were characterized by different spectroscopic techniques such as EIMS, HRMS, ^{1}H-NMR, and ^{13}C-NMR.

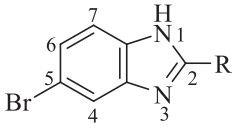
Biological activities

5-Bromo-2-aryl benzimidazole derivatives **1–25** were evaluated for their α-glucosidase inhibitory potential (Table 1). All compounds were found to be active and



Scheme 1 Syntheses of 5-bromo-2-aryl benzimidazole derivatives **1–25**

Table 1 In vitro α-glucosidase inhibitory activity of 5-bromo-2-aryl benzimidazole derivatives **1–25**



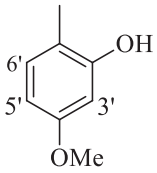
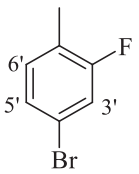
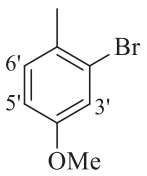
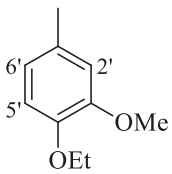
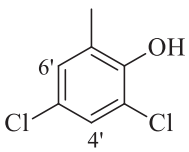
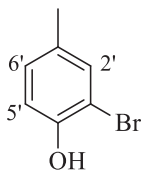
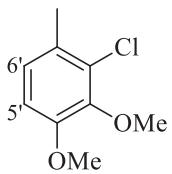
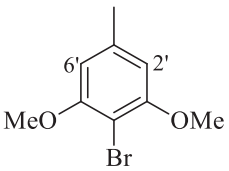
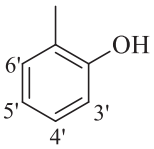
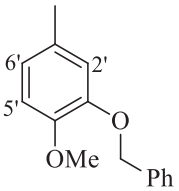
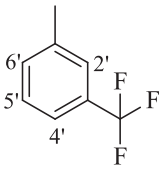
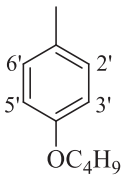
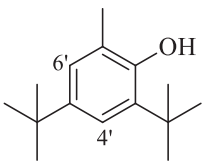
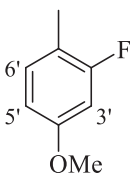
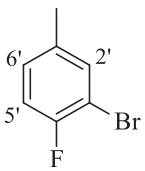
S. No.	*R*	($IC_{50} \pm SEM$)
1		37.82 ± 0.08
2		145.21 ± 0.16
3		54.62 ± 0.07
4		131.95 ± 0.12
5		61.34 ± 0.08
6		102.26 ± 0.17
7		158.23 ± 0.12
8		96.87 ± 0.11
9		37.76 ± 0.05
10		97.35 ± 0.14
11		92.63 ± 0.05
12		24.96 ± 0.09
13		97.31 ± 0.12
14		119.78 ± 0.12
15		174.62 ± 0.19

Table 1 continued

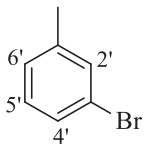
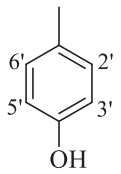
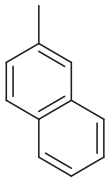
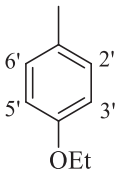
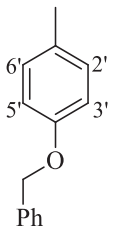
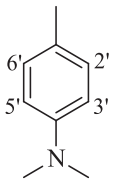
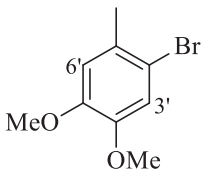
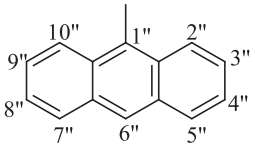
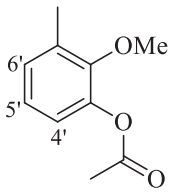
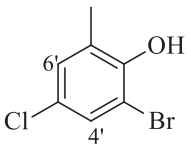
S. No.	*R*	($IC_{50} \pm SEM$)
16		21.15 ± 0.08
17		8.34 ± 0.02
18		102.82 ± 0.06
19		119.78 ± 0.11
20		114.27 ± 0.12
21		117.76 ± 0.13
22		92.47 ± 0.16
23		86.36 ± 0.11

Table 1 continued

S. No.	*R*	($IC_{50} \pm SEM$)
24		NA
25		NA
Standard = Acarbose		38.25 ± 0.12

SEM *standard error of mean,* NA *not active,* Std *standard inhibitor for* α*-glucosidase*

showed their potential in terms of IC_{50} values within the range of 8.34–174.62 μM when compared with the standard drug acarbose ($IC_{50} = 38.25 \pm 0.12$ μM), only two molecules **24** and **25** showed no activity. Compounds **1** ($IC_{50} = 37.82 \pm 0.08$ μM), **9** ($IC_{50} = 37.76 \pm 0.05$ μM), **12** ($IC_{50} = 24.96 \pm 0.09$ μM), **16** ($IC_{50} = 21.15 \pm 0.08$ μM), **17** ($IC_{50} = 8.34 \pm 0.02$ μM) showed excellent and compounds **3** ($IC_{50} = 54.62 \pm 0.07$ μM) and **5** ($IC_{50} = 61.34 \pm 0.08$ μM) showed good inhibitory potential as compared to standard acarbose (Table 1). However, other analogs exhibited moderate inhibitory potential.

Limited structure-activity relationship studies revealed that the activity of this series of compound mainly depends upon the substitutions on the phenyl part of benzimidazole moiety at position 2, their nature and respective positions of substituents. Compound **17** ($IC_{50} = 8.34 \pm 0.02$ μM) having 4-hydroxyl substitution was found to be five-fold more active than the standard ($IC_{50} = 38.25 \pm 0.12$ μM), analog **16** having 3-bromo substitution, residue **12** having 4-butoxy substitution, molecule **9** having 2-hydroxyl substitution and moiety **1** having 2-hydroxy, and 4-methoxy substitution on the phenyl part at position 2 of benzimidazole showed excellent inhibitory potential as compared to standard acarbose. In order to understand the mechanism of α-glucosidase inhibition, mode of binding inside the binding pocket of enzyme of these benzimidazoles and to confirm the assay results, molecular docking studies were carried out.

Molecular docking

Docking studies were carried out using MOE-Dock as docking software implemented in molecular operating

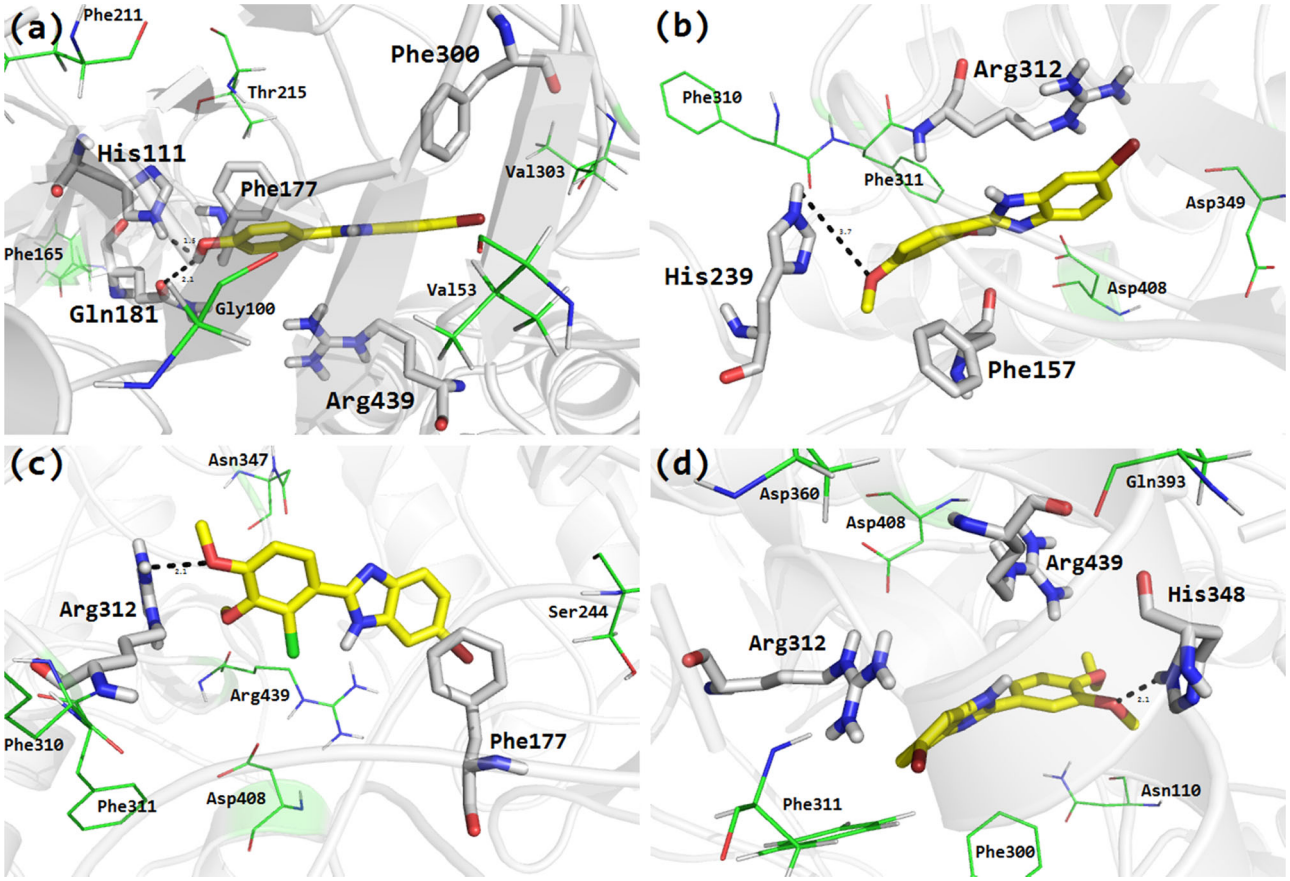


Fig. 2 Predicted binding mode of **a** compound **17**, **b** compound **1**, **c** compound **7**, and **d** compound **4** in the active site of α-glucosidase

environment (MOE) (www.chemchomp.com). The docking scores demonstrated that these compounds showed interactions with active site residues of the enzyme. Docking score is the binding free energy calculated by the GBVI/WSA scoring function, which is the score of the last stage showing the overall fitness of compound in the pocket. For all scoring functions, lower scores indicate more favorable poses. The unit for all scoring functions is kcal/mol. The docking conformation of the most active compound **17** in the series showed six interactions with important active site residues (Fig. 2a). The hydroxyl group at the phenyl ring established two hydrogen bonds with His111 and Gln181, respectively. The phenyl ring of the compound formed arene–arene and arene–cation interactions with active site residues Phe177 and Arg439, respectively. Furthermore, the imidazole ring of the compound formed arene–arene and arene–cation interactions with Phe300 and Arg439, respectively. The presence of electron donating group OH at position 4 of the phenyl ring increases the electron density; as a result more interactions were observed for this compound. This strong bonding network might be one of the reasons for compound **17** to be the most active in the series. Like compound **17**, good interactions were observed for compounds **1**, **3**, **5**, **9**, **12**, and **16**. All these compounds have electron donating moiety at phenyl ring and thus have increased electron density that might be responsible for the good interactions between these compounds and active site residues. The lower activities of compounds **1**, **3**, **5**, and **12** as compare to compound **17** might be due to the presence of methoxy or chlorine moieties at the phenyl ring that produce steric hindrance between these compounds and active site residues of the enzyme as indicated by the lower docking scores of these compound. For example, in case of compound **1**, only four interactions were observed between the compound and active site residues of the enzyme (Fig. 2b). The oxygen atom of the methoxy group of compound **1** forms a hydrogen bond with His239, the phenyl ring of the compound forms arene–arene interaction with Phe157, whereas the imidazole ring of the compound establishes two arene–cation interactions with Arg312. In the case of least-active compounds **15**, **7**, **2**, and **4** mild interactions were observed. The mild interactions observed in case of these compounds might be due to the presence of more steric hindrance on the phenyl ring of these compounds as compared to compound **17**. For example, in the case of compound **7**, only two interactions were observed.

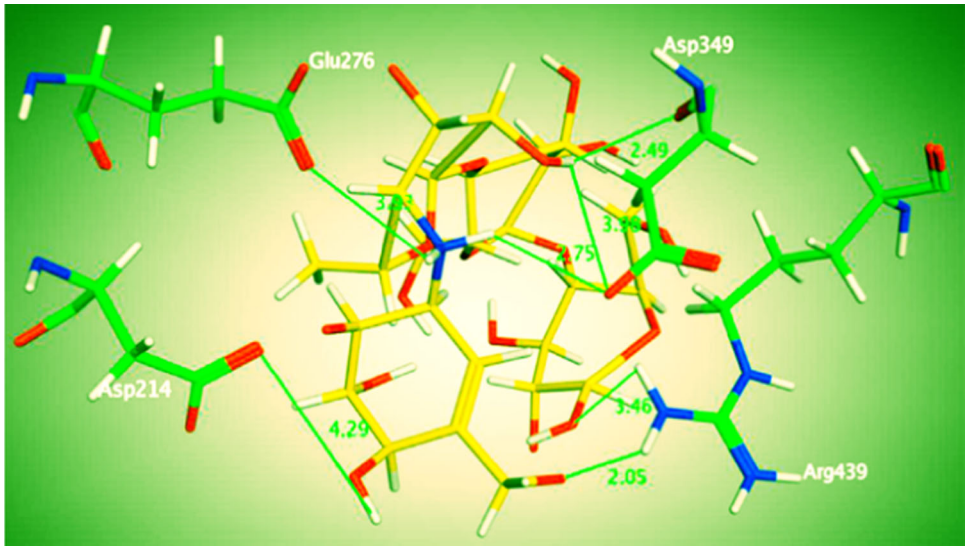


Fig. 3 Binding interaction of acarbose in the binding pocket of α-glucosidase

The oxygen atom of methoxy group of compound **7** established hydrogen bond with active site residue Arg312, while the imidazole ring of the compound formed arene–arene interaction with active site residue Phe177 (Fig. 2c). Similarly, the docking conformation of compound **4** showed that oxygen atom of the methoxy moiety of the compound formed hydrogen bond with active site residue His348, whereas the phenyl and imidazole rings of the compound established arene–cation interactions with Arg439 and Arg312, respectively (Fig. 2d). Overall the docking results showed that the electron donating moieties on the phenyl ring of these compounds promote the interaction with the active site residues and thus increase the activity. However, increasing the number of different moieties on the phenyl ring increases the steric hindrance and thus decreases the number of interactions, resulting in lowering the activity. To test the adopted protocols and to compare the molecular docking study of the synthetic compounds, the standard inhibitor acarbose was docked into the active site of our developed α-glucosidase model. The acarbose fitness in the binding pocket and interaction with the important active site residues is shown in Fig. 3, which reflects a good correlation.

Conclusion

5-Bromo-2-aryl benzimidazole derivatives **1**–**25** were screened for α-glucosidase inhibitory potential. Compounds **1** ($IC_{50} = 37.82 \pm 0.08$ µM), **9** ($IC_{50} = 37.76 \pm 0.05$ µM), **12** ($IC_{50} = 24.96 \pm 0.09$ µM), **16** ($IC_{50} = 21.15 \pm 0.08$ µM), and **17** ($IC_{50} = 8.34 \pm 0.02$ µM) showed potent α-glucosidase inhibitory activity as compared to standard acarbose ($IC_{50} = 38.25 \pm 0.12$ µM). Molecular docking studies were carried out to identify their mode of binding, which revealed that further chemical modifications on these molecules could have resulted in lead molecules with high degree of inhibitory activity and selectivity towards α-glucosidase enzyme.

Materials and methods

Reagents were purchased from Sigma-Aldrich, USA. All reagents and solvents were of analytical grade and used as received. Thin layer chromatography was performed on precoated silica gel, GF-254. Spots were visualized under ultraviolet light at 254 and 366 nm. Mass spectra were recorded under electron impact (EI) on MAT 312 and MAT 113D mass spectrometers. The ^{1}H-NMR were recorded on a Bruker AM spectrometer, operating at 300, 400, and 500 MHz. The chemical shift values are presented in ppm (δ) relative to tetramethylsilane (TMS) as an internal standard and the coupling constants (J) are in Hz.

In vitro α-glucosidase inhibition assay

α-Glucosidase inhibitory potential of all the synthetic benzimidazoles was measured by the reported method (Rahim et al., 2015). Typically, α-glucosidase activity was measured in phosphate buffer 50 mM of pH 6.8 that contains 5 % v/v dimethylsulfoxide, and PNP glycoside was used as a substrate. The inhibitors were pre-incubated with enzyme for half an hour at 37 °C. Then substrate was added and the enzymatic reaction was performed for 60 min at 37 °C. Absorbance was measured spectrophotometrically at 400 nm. The assay was carried in triplicate at five different concentrations around the IC_{50} values that were roughly calculated in the first turn of the experiments, and the mean values were adopted.

General experimental procedure for the syntheses of 5-bromo-2-aryl benzimidazole derivatives 1–25

4-Bromo-1,2-diaminobenzene (1 mmol) and different substituted aromatic aldehydes (1 mmol) in *N*,*N*-dimethylformamide (10 mL) were taken into a 100 mL round-bottomed flask. Catalytic amount of sodium metabisulfite ($Na_2S_2O_5$) was added into the reaction mixture and refluxed for 4 h. Reaction progress was carefully monitored by thin layer chromatography. After completion of reaction, it was added into chilled distilled water (100 mL). Precipitates were formed and filtered to afford products. Crude products were crystallized from ethanol to get pure products in high yields.

*2-(5-Bromo-1H-benzo[d]imidazol-2-yl)-5-methoxyphenol (**1**)*

Yield: 82 %; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.88 (d, 1H, $J_{6',5'} = 9.3$ Hz, H-6′), 7.79 (d, 1H, $J_{4,6} = 1.8$ Hz, H-4), 7.56 (d, 1H, $J_{7,6} = 8.7$ Hz, H-7), 7.4 (dd, 1H, $J_{6,4} = 1.8$, $J_{6,7} = 8.4$ Hz, H-6), 6.59 (m, 2H, H-3′, H-5′), 3.85 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 162.2 (C, C-4′), 156.1 (C, C-2′), 152.7 (C, C-2) , 141.3 (C, C-8), 140.6 (C, C-9), 129.8 (CH, C-6′), 126.1 (CH, C-6), 118.8 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7), 110.5 (C, C-1′), 107.3 (CH, C-5′), 104.4 (CH, C-3′), 55.9 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 318 (M^+, 100), 320 (M+2, 96), 289 (14), 277 (21), 196 (5), 168 (7), 90 (4); HRMS (EI) calcd. for $C_{14}H_{11}BrN_2O_2$: *m/z* = 318.0004, found 318.0010.

*5-Bromo-2-(4-bromo-2-fluorophenyl)-1H-benzo[d] imidazole (**2**)*

Yield: 85 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.16 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.85 (dd, 2H, $J_{6,4/5',3'} = 1.6$, $J_{6,7/5',6'} = 9.2$ Hz, H-6, H-5′), 7.64 (d, 1H, $J_{3',5'} = 2$ Hz, H-3′), (d, 1H, $J_{4,6} = 1.6$ Hz, H-4), 7.4 (m, 1H, H-6′); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 160.4 (C, C-2′), 152.7 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 131.2 (CH, C-6′), 127.6 (CH, C-5′), 126.4 (CH, C-6), 124.6 (C, C-4′), 122.3 (C, C-1′), 121.1 (CH, C-3′), 118.6 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7); EIMS: *m/z* (rel. abund. %), 368 (M^+, 94), 370 (M+2, 100), 372 (M+4, 70), 291 (20), 228 (49), 154 (40), 127 (11); HRMS (EI) calcd. for $C_{13}H_7Br_2FN_2$: *m/z* = 367.8960, found 367.8968.

*5-Bromo-2-(2-bromo-4-methoxyphenyl)-1H-benzo[d] imidazole (**3**)*

Yield: 75 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.4 (d, 1H, $J_{4,6} = 2$ Hz, H-4), 8.19 (dd, 1H, $J_{6,4} = J_{6,5} = 8.8$ Hz, H-6), 7.75 (d, 1H, $J_{3',5'} = 1.6$ Hz, H-3′), 7.54 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.35 (dd, 1H, $J_{5',3'} = 2$, $J_{5',6'} = 8.8$ Hz, H-5′), 7.27 (d, 1H, $J_{6',5'} = 8.8$ Hz, H-6′), 3.99 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 158.5 (C, C-4′), 152.7 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 130.8 (C, C-1′), 130.6 (CH, C-6′), 126.1 (CH, C-6), 121.3 (C, C-2′), 118.8 (CH, C-4), 118.3 (CH, C-3′), 117.7 (C, C-5), 117.4 (CH, C-7), 113.7 (CH, C-5′), 55.7 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 380 (M^+, 51), 382 (M+2, 100), 383 (M+4, 45), 367 (16), 352 (49), 339 (40), 303 (11), 288 (20); HRMS (EI) calcd. for $C_{14}H_{10}$ Br_2N_2O: *m/z* = 379.9160, found 379.9166.

*5-Bromo-2-(4-ethoxy-3-methoxyphenyl)-1H-benzo[d] imidazole (**4**)*

Yield: 76 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.80 (d, 1H, $J_{4,6} = 2$ Hz, H-4), 7.74 (dd, 1H, $J_{6',2'} = 2$, $J_{6',5'} = 8.8$ Hz, H-6′), 7.72 (d, 1H, $J_{2',6'} = 1.6$ Hz, H-2′), 7.51 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.32 (dd, 1H, $J_{6,4} = 1.6$, $J_{6,7} = 8.4$ Hz, H-6), 7.09 (d, 1H, $J_{5',6'} = 8$ Hz, H-5′), 4.16 (m, 2H, CH_2), 3.92 (s, 3H, OCH_3), 1.42 (t, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 150.5 (C, C-4′), 150.3 (C, C-3′), 141.0 (C, C-8), 140.6 (C, C-9), 126.3 (CH, C-6), 123.1 (C, C-1′), 122.0 (CH, C-6′), 118.8 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7), 111.8 (CH, C-1′) , 111.3 (CH, C-5′), 64.7 (CH_2, OCH_2), 56.4 (CH_3, OCH_3) 14.7 (CH_3, OCH_2CH_3); EIMS: *m/z* (rel. abund. %), 346 (M^+, 100), 348 (M+2, 93), 317 (47), 289 (15), 260 (5), 192 (2); HRMS (EI) calcd. for $C_{16}H_{15}BrN_2O_2$: *m/z* = 346.0317, found 346.0310.

*2-(5-Bromo-1H-benzo[d]imidazol-2-yl)-4,6-dichlorophenol (**5**)*

Yield: 72 %; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 7.97 (d, 1H, $J_{4,6} = 2.4$ Hz, H-4), 7.86 (bd.s, 1H, H-6′), 7.65 (d, 1H, $J_{7,6} = 8.7$ Hz, H-7), 7.54 (d, 1H, $J_{4',6'} = 2.4$ Hz, H-4′), 7.48 (dd, 1H, $J_{6,4} = 1.8$, $J_{6,7} = 8.4$ Hz, H-6); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 154.4 (C, C-2′), 152.7 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 131.7 (CH, C-4′), 127.4 (C, C-5′), 126.8 (CH, C-6′), 126.2 (CH, C-6), 126.0 (C, C-3′), 121.3 (C, C-1′), 118.6 (CH, C-4), 117.7 (C, C-5), 117.3 (CH, C-7); EIMS: *m/z* (rel. abund. %), 356 (M^+, 78), 358 (M+2, 100), 360 (M+4, 58), 295 (19), 277 (5), 249 (5), 213 (4), 179 (7), 90 (4), 63 (6); HRMS (EI) calcd. for $C_{13}H_7BrCl_2N_2O$: *m/z* = 355.9119, found 355.9113.

*2-Bromo-4-(5-bromo-1H-benzo[d]imidazol-2-yl)phenol (**6**)*

Yield: 71 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 11.05 (s, 1H, NH), 8.32 (d, 1H, $J_{4,6} = 2$ Hz, H-4), 8.01 (dd, 1H, $J_{6',2'} = 1.6$, $J_{6',5'} = 8.4$ Hz, H-6′), 7.79 (d, 1H, $J_{2',6'} = 0.8$ Hz, H-2′), 7.56 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.04 (dd, 1H, $J_{6,4} = 1.6$, $J_{6,7} = 8.4$ Hz, H-6), 7.13 (d, 1H, $J_{5',6'} = 8.8$ Hz, H-5′); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 156.7 (C, C-4′), 152.8 (C, C-2), 141.3 (C, C-8), 140.5 (C, C-9), 133.1 (CH, C-2′), 129.6 (CH, C-6′), 126.3(CH, C-6), 123.8 (C, C-1′),

118.8 (CH, C-4), 118.4 (CH, C-5′), 117.6 (C, C-5), 117.3 (CH, C-7), 114.2 (C, C-3′); EIMS: *m/z* (rel. abund. %), 366 (M^+, 100), 368 (M+2, 100), 370 (M+4, 100), 239 (2), 287 (31), 259 (13), 208 (25), 179 (18); HRMS (EI) calcd. for $C_{13}H_8\ Br_2N_2O$: *m/z* = 365.9003, found 365.9007.

*5-Bromo-2-(2-chloro-3,4-dimethoxyphenyl)-1H-benzo[d] imidazole (**7**)*

Yield: 56 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.91 (d, 1H, $J_{6',5'}$ = 8.8 Hz, H-6′), 7.81 (d, 1H, $J_{4,6}$ = 1.6 Hz, H-4), 7.60 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.38 (dd, 1H, $J_{6,4}$ = 1.6, $J_{6,7}$ = 8.4 Hz, H-6), 7.22 (d, 1H, $J_{5',6'}$ = 8.8 Hz, H-5′), 3.98 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8(C, C-2), 151.0 (C, C-4′), 150.8 (C, C-3′), 141.2 (C, C-8), 140.5 (C, C-9), 131.6 (C, C-1′), 126.1 (CH, C-6), 122.3 (CH, C-6′) 118.7 (CH, C-4), 118.5 (C, C-5), 117.6 (CH, C-7), 117.5 (C, C-2′), 109.2 (CH, C-5′), 56.3 ($2CH_3$, OCH_3); EIMS: *m/z* (rel. abund. %), 366 (M^+, 100), 368 (M+2, 100), 370 (M+4, 98), 353 (31), 325 (55), 310 (23), 288 (16), 244 (30) 184 (17), 166 (10); HRMS (EI) calcd. for $C_{15}H_{12}\ BrClN_2O_2$: *m/z* = 365.9771, found 365.9777.

*5-Bromo-2-(4-bromo-3,5-dimethoxyphenyl)-1H-benzo[d] imidazole (**8**)*

Yield: 42 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.80 (d, 1H, $J_{4,6}$ = 1.6 Hz, H-4), 7.58 (d, 1H, $J_{7,6}$ = 9.2 Hz, H-7), 7.55 (s, 2H, H-2′, H-6′), 7.39 (dd, 1H, $J_{6,4}$ = 2, $J_{6,7}$ = 8.8 Hz, H-6), 4.00 (s, 6H, $2OCH_3$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 158.4 (C, C-3′), 158.4 (C, C-5′), 152.7 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 131.4 (C, C-1′), 126.1 (CH, C-6), 118.9 (CH, C-4), 117.6 (C, C-2), 117.4 (CH, C-7), 105.6 (CH, C-2′) , 105.6 (CH, C-6′), 99.6 (C, C-4′), 55.0 (CH_3, OCH_3), 55.0 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 410 (M^+, 79), 412 (M+2, 100), 414 (M+4, 80), 381 (8), 352 (4), 331 (7), 301 (17), 273 (21), 247 (9), 206 (11); HRMS (EI) calcd. for $C_{15}H_{12}Br_2N_2O_2$: *m/z* = 409.9266, found 409.9261.

*2-(5-Bromo-1H-benzo[d]imidazol-2-yl)phenol (**9**)*

Yield: 76 %; ^{1}H-NMR: (300 MHz, DMSO-d_6): δ 7.80 (d, 1H, $J_{4,6}$ = 1.5 Hz, H-4), 7.73 (m, 1H, H-5′), 7.68 (d, 1H, $J_{6',5'}$ = 7.8 Hz, H-6′), 7.59 (d, 1H, $J_{7,6}$ = 8.7 Hz, H-7), 7.39 (m, 2H, H-6, H-4′), 7.02 (m, 1H, H-3′); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 154.2 (C, C-2′), 152.8 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 131.8 (CH, C-6′), 130.3 (CH, C-4′), 126.3 (CH, C-6), 121.9 (CH, C-5′), 118.6 (C1, C-1′), 118.4 (CH, C-4), 117.6 (C, C-5), 117.6 (CH, C-3′), 117.3 (CH, C-7); EIMS: *m/z* (rel. abund. %), 286 (M^+, 100), 288 (M+2, 89), 236 (10), 192 (7), 157 (10); HRMS (EI) calcd. for $C_{13}H_9BrN_2O$: *m/z* = 287.9898, found 287.9894.

*2-(3-(Benzyloxy)-4-methoxyphenyl)-5-bromo-1H-benzo[d] imidazole (**10**)*

Yield: 63 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.88 (d, 1H, $J_{4,6}$ = 1.6 Hz, H-4), 7.81 (d, 1H, $J_{2',6'}$ = 1.2 Hz, H-2′), 7.79 (dd, 1H, $J_{6,4}$ = 1.6, $J_{6,7}$ = 8.4 Hz, H-6), 7.60 (d, 1H, $J_{7,6}$ = 8.8 Hz, H-7), 7.51 (d, 2H, $J_{2'',3''} = J_{6'',5''}$ = 7.2 Hz, H-2′′, H-6′′), 7.44 (t, 3H, $J_{3''(2'',4'')} = J_{4''(3'',5'')} = J_{5''(3'',4'')}$ = 7.2 Hz, H-3′′, H-4′′, H-5′′), 7.37 (d, 1H, $J_{6',5'}$ = 7.2 Hz, H-6′), 7.23 (d, 1H, $J_{5',6'}$ = 8.8 Hz, H-5′), 5.19 (s, 2H, CH_2), 3.39 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 149.6 (C, C-4′), 148.5 (C, C-3′), 141.3 (C, C-8), 140.6 (C, C-9), 136.5 (CH_2, OCH_2), 128.8 (CH, C-3′′), 128.6 (CH, C-5′′), 127.7 (CH, C-4′′), 127.2 (CH, C-6′′), 127.0 (CH, C-2′′), 126.1 (CH, C-6), 123.8 (C, C-1′), 122.5 (CH, C-6′), 118.5 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7), 112.2 (CH, C-2′), 111.1 (CH, C-5′), 71.2 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 391 (M^+, 33), 393 (M+2, 42), 317 (58), 291 (4), 246 (2); HRMS (EI) calcd. for $C_{21}H_{17}BrN_2O_2$: *m/z* = 392.0524, found 392.0529.

*5-Bromo-2-(3-(trifluoromethyl)phenyl)-1H-benzo[d] imidazole (**11**)*

Yield: 68 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.95 (d, 1H, $J_{6',5'}$ = 7.6 Hz, H-6′), 7.84 (m, 4H, H-4, H-2′, H-4′, H-5′), 7.59 (d, 1H, $J_{7,6}$ = 8.8 Hz, H-7), 7.39 (dd, 1H, $J_{6,4}$ = 1.6, $J_{6,7}$ =8.8 Hz, H-6); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 137.7 (C, C-2′), 135.3 (CH, C-6′), 131.4 (C, C-3′), 129.6 (CH, C-5′), 126.3 (CH, C-6), 125.4 (CH, C-2′), 125.0 (CH, C-4′), 124.2 (C, CF_3), 118.8 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7); EIMS: *m/z* (rel. abund. %), 340 (M^+, 99), 342 (M+2, 99), 322 (100), 301 (29), 241 (44), 152 (14); HRMS (EI) calcd. for $C_{14}H_8BrF_3N_2$: *m/z* = 339.9823, found 339.9828.

*5-Bromo-2-(4-butoxyphenyl)-1H-benzo[d]imidazole (**12**)*

Yield: 51 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.13 (d, 2H, $J_{2',6'} = J_{6',5'}$ = 8.8 Hz, H-2′, H-6′), 7.79 (s, 1H, H-4), 7.68 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.41 (d, 1H, $J_{6,7}$ = 8.4 Hz, H-6), 7.16 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.4 Hz, H-3′, H-5′), 4.09 (t, 2H, OCH_2), 1.75 (m, 2H, CH_2), 1.48 (m, 2H, CH_2), 0.96 (t, 2H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.5 (C, C-4′), 152.8 (C, C-2), 141.2 (C, C-8), 140.6 (C, C-9), 129.8 (CH, C-2′), 129.8 (CH, C-6′), 126.0 (CH, C-6), 118.9 (CH, C-4), 117.4 (C, C-4), 117.3 (CH, C-7), 114.8 (CH, C-3′), 114.8 (CH, C-5′), 112.2 (C, C-1′), 68.6 (CH_2, OCH_2), 31.7 (CH_2, O-CH_2CH_2), 19.1 (CH2, O-$CH_2CH_2CH_2$), 14.2 (CH_2, $OCH_2CH_2CH_2CH_3$); EIMS: *m/z* (rel. abund. %), 344 (M^+, 55), 346 (M+2, 56), 319 (3), 289 (100), 260 (6), 209 (6);

HRMS (EI) calcd. for $C_{17}H_{17}BrN_2O$: *m/z* = 344.0524, found 344.0528.

*2-(5-Bromo-1H-benzo[d]imidazol-2-yl)-4,6-di-tert-butylphenol (**13**)*

Yield: 65 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.91 (d, 1H, $J_{6',4'}$ = 2 Hz, H-6′), 7.74 (m, 2H, H-4, H-7), 7.43 (d, 1H, $J_{6,7}$ = 8 Hz, H-6), 7.37 (d, 1H, $J_{4',6'}$ = 2 Hz, H-6′), 1.42 (s, 9H, $3CH_3$), 1.34 (s, 9H, $3CH_3$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 145.4 (C, C-2′), 142.5 (C, C-5′), 141.2 (C, C-8), 140.6 (C, C-9), 138.3 (C, C-3′), 126.3(C, C-6), 126.1 (CH, C-4′), 124.8 (CH, C-6′), 118.6 (CH, C-4), 117.4 (C, C-1′), 117.6 (C, C-5), 117.4 (CH, C-7), 34.9 (C, $C(CH_3)_3$), 34.7 (C, $C(CH_3)_3$), 31.5 (CH_3, $C(CH_3)_3$), 31.5 (CH_3, $C(CH_3)_3$), 31.5 (CH_3, $C(CH_3)_3$), 31.4 (CH_3, $C(CH_3)_3$), 31.4 (CH_3, $C(CH_3)_3$), 31.4 (CH_3, $C(CH_3)_3$); EIMS: *m/z* (rel. abund. %), 400 (M^+, 40), 402 (M +2, 34), 387 (100), 359 (25), 343 (21), 329 (21), 250 (3); HRMS (EI) calcd. for $C_{21}H_{25}BrN_2O$: *m/z* = 400.1150, found 400.1154.

*5-Bromo-2-(2-fluoro-4-methoxyphenyl)-1H-benzo[d] imidazole (**14**)*

Yield: 84 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.15 (m, 1H, H-3′), 7.82 (d, 1H $J_{4,6}$ = 1.2 Hz, H-4), 7.60 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.42 (dd, 1H, $J_{6,4}$ = 1.6, $J_{6,7}$ = 8.8 Hz, H-6), 7.13 (dd, 1H, $J_{6',3'}$ = 2, $J_{6',5'}$ = 13.6 Hz, H-6′), 7.03 (dd, 1H, $J_{5',3'}$ = 2, $J_{5',6'}$ = 8.8 Hz, H-5′), 3.87 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.7 (C, C-4′), 159.1 (C, C-2′), 152.8 (C, C-2), 141.0 (C, C-8), 140.6 (C, C-8), 130.2 (CH, C-6′), 126.3(CH, C-6), 118.6 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7), 115.7 (C, C-1′), 110.3 (CH, C-5′), 102.8 (CH, C-3′), 55.6 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 320 (M^+, 98), 322 (M+2, 100), 307 (36), 279 (15), 259 (11), 241 (3); HRMS (EI) calcd. for $C_{14}H_{10}BrFN_2O$: *m/z* = 319.9961, found 319.9966.

*5-Bromo-2-(3-bromo-4-fluorophenyl)-1H-benzo[d] imidazole (**15**)*

Yield: 88 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.49 (dd, 1H, $J_{6',2'}$ = 2, $J_{6',5'}$ = 6.4 Hz, H-6′), 8.22 (m, 1H, H-5′), 7.81 (s, 1H, H-2′), 7.62 (m, 2H, H-4, H-7), 7.39 (dd, 1H, $J_{6,4}$ = 1.6, $J_{6,7}$ = 8.8 Hz, H-6); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 165.3 (C, C-4′), 152.7 (C, C-2), 141.3 (C, C-8), 140.8 (C, C-9), 134.6 (CH, C-2′), 128.3 (CH, C-6′), 126.7 (C, C-1′), 126.1(CH, C-6), 118.9 (CH, C-4), 118.3 (CH, C-5′), 117.6 (C, C-5), 117.3 (CH, C-7), 110.4 (CH, C-3′); EIMS: *m/z* (rel. abund. %), 368 (M^+, 71), 370 (M+2, 100), 372 (M+4, 68), 289 (25), 262 (3), 210 (34), 187 (9); HRMS (EI) calcd. for $C_{13}H_7Br_2FN_2$: *m/z* = 367.8960, found 367.8965.

*5-Bromo-2-(3-bromophenyl)-1H-benzo[d]imidazole (**16**)*

Yield: 76 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.36 (s, 1H, H-4), 8.18 (d, 1H, $J_{6',5'}$ =7.6 Hz, H-6′), 7.84 (s, 1H, H-2′), 7.76 (d, 1H, $J_{4',5'}$ = 8 Hz, H-4′), 7.62 (d, 1H, $J_{7,6}$ = 8.8 Hz, H-7), 7.57 (t, 1H, $J_{5',4'} = J_{5',6'}$ = 8 Hz, H-5′), 7.42 (d, 1H, $J_{6,7}$ = 8.4 Hz, H-6); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.7 (C, C-2), 141.0 (C, C-8), 140.6 (C, C-9), 131.8 (CH, C-2′), 131.5 (CH, C-5′), 131.2 (C, C-1′), 128.2 (CH, C-4′), 126.6 (CH, C-6′), 126.2 (CH, C-6), 122.0 (CH, C-3′), 118.6 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7); EIMS: *m/z* (rel. abund. %), 350 (M^+, 87), 352 (M+2, 100), 354 (M+4, 94), 290 (2), 271 (25), 246 (2), 192 (45), 176 (7); HRMS (EI) calcd. for $C_{13}H_8Br_2N_2$: *m/z* = 349.9054, found 349.9058.

*4-(5-Bromo-1H-benzo[d]imidazol-2-yl)phenol (**17**)*

Yield: 0.11 g (71 %); ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.07 (dd, 2H, $J_{2',6'/6',2'}$ = 1.6, $J_{2',3'/6',5'}$ = 6.8 Hz, H-2′, H-6′), 7.71 (d, 1H, $J_{4,6}$ = 1.6 Hz, H-4), 7.49 (d, 1H, $J_{7,6}$ = 8.8 Hz, H-7), 7.31 (dd, 1H, $J_{6,4}$ = 2 $J_{6,7}$ = 8.4 Hz, H-6), 6.99 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.8 Hz, H-3′, H-5′); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 158.6 (C, C-4′), 152.7 (C, C-2), 141.3 (C, C-8), 140.6 (C, C-9), 130.5 (CH, C-2′), 130.5 (CH, C-6′), 126.3 (CH, C-6), 118.8 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7), 116.6 (CH, C-3′), 116.6 (CH, C-5′), 113.2 (C, C-1′); EIMS: *m/z* (rel. abund. %), 288 (M^+, 100), 290 (M+2, 91), 261 (4), 209 (9), 182 (8), 170 (2), 144 (4); HRMS (EI) calcd. for $C_{13}H_9BrN_2O$: *m/z* = 287.9898, found 287.9892.

*5-Bromo-2-(naphthalen-2-yl)-1H-benzo[d]imidazole (**18**)*

Yield: 65 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.72 (s, 1H, H-4), 8.36 (dd, 1H, $J_{8',2'}$ = 1.6, $J_{8',7'}$ = 8.8 Hz, H-8′), 8.06 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 8.04 (m, 1H, H-3′), 7.99 (m,1H, H-6′), 7.81 (d, 1H, $J_{2',8'}$ = 1.6 Hz, H-2′), 7.81 (m, 3H, H-4′, H-5′, H-7′), 7.39 (dd, 1H, $J_{6,4}$ = 2 $J_{6,7}$ = 8.4 Hz, H-6); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 141.2 (C, C-8), 140.6 (C, C-9), 133.8 (C, C-1′), 133.7 (C, C-9′), 133.2 (C, C-10′), 131.8 (CH, C-8′), 128.3 (CH, C-4′), 128.3 (CH, C-7′), 126.3 (CH, C-6), 126.1 (CH, C-5′), 126.1 (CH, C-6′), 125.8 (CH, C-2′), 124.6 (CH, C-8′), 118.6 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7); EIMS: *m/z* (rel. abund. %), 322 (M^+, 100), 324 (M +2, 92), 242 (22), 216 (3), 189 (2), 153 (7); HRMS (EI) calcd. for $C_{17}H_{11}BrN_2$: *m/z* = 322.0106, found 322.0101.

*5-Bromo-2-(4-ethoxyphenyl)-1H-benzo[d]imidazole (**19**)*

Yield: 70 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.14 (d, 2H, $J_{2',3'} = J_{6',5'}$ = 8.8 Hz H-2′, H-6′), 7.72 (d, 1H, $J_{4,6}$ = 1.6 Hz, H-4), 7.51 (d, 1H, $J_{7,6}$ = 8.4 Hz, H-7), 7.32 (dd, 1H, $J_{6,4}$ = 2 $J_{6,7}$ = 8.4 Hz, H-6), 7.08 (d, 2H, $J_{3',2'} = J_{5',6'}$ = 8.8 Hz, H-3′, H-5′), 4.17 (m, 2H, OCH_2), 1.41 (t, 3H, CH_3);

^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.3 (C, C-4′), 152.8 (C, C-2), 141.2 (C, C-8), 140.6 (C, C-9), 129.8 (CH, C-2′), 129.8 (CH, C-6′), 126.3 (CH, C-6), 118.6 (CH, C-4), 117.7 (C, C-5), 117.3 (CH, C-7), 114.8 (CH, C-3′), 114.8 (CH, C-5′), 112.4 (C, C-1′), 64.5 (CH_2, OCH_2CH_3), 14.9 (CH_3, OCH_2CH_3); EIMS: *m/z* (rel. abund. %), 316 (M^+, 100), 318 (M+2, 100), 287 (100), 259 (98), 237 (22), 208 (67), 192 (23), 180 (91), 153 (30); HRMS (EI) calcd. for $C_{15}H_{13}BrN_2O$: $m/z = 316.0211$, found 316.0217.

*2-(4-(Benzyloxy)phenyl)-5-bromo-1H-benzo[d]imidazole (**20**)*

Yield: 69 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.16 (d, 2H, $J_{2',3'} = J_{6',5'} = 9.2$ Hz, H-2′, H-6′), 7.72 (d, 1H, $J_{4,6} = 1.2$ Hz, H-4), 7.52 (m, 3H, H-2″, H-4″, H-6″), 7.43 (t, 2H, $J_{3''(2',4'') = J5''(4'',6'')} = 7.2$ Hz, H-3″, H-5″), 7.36 (d, 1H, $J_{7,6} = 7.2$ Hz, H-7), 7.32 (dd, 1H, $J_{6,4} = 1.6$, $J_{6,7} = 8.4$ Hz, H-6), 7.19 (d, 2H, $J_{3',2'} = J_{5',6'} = 9.2$ Hz, H-3′, H-5′), 5.22 (s, 2H, OCH_2); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 159.2 (C, C-4′), 152.7 (C, C-2), 141.0 (C, C-8), 140.6 (C, C-9), 136.6 (C, C-1″), 130.2 (CH, C-2′), 130.2 (CH, C-6′), 128.7 (CH, C-3″), 128.7 (CH, C-5″), 127.7 (CH, C-4″), 127.0 (CH, C-2″), 127.0 (CH, C-6″), 126.3 (CH, C-6), 118.8 (CH, C-4), 117.6 (C, C-5), 117.5 (CH, C-7), 114.9 (CH, C-3′), 114.9 (CH, C-5′), 113.2 (C, C-1′), 70.7 (CH_2, $OCH_2C_6H_6$); EIMS: *m/z* (rel. abund. %), 378 (M^+, 16), 380 (M+2, 17), 248 (49), 218 (53), 201 (20), 189 (100), 161 (35), 135 (76); HRMS (EI) calcd. for $C_{20}H_{15}BrN_2O$: $m/z = 378.0368$, found 378.0362.

*4-(5-Bromo-1H-benzo[d]imidazol-2-yl)-N,N-dimethylaniline (**21**)*

Yield: 59 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.99 (d, 2H, $J_{2',3'} = J_{6',5'} = 9.2$ Hz, H-2′, H-6′), 7.76 (s, 1H, H-4), 7.54 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.42 (d, 1H, $J_{6,7} = 8.8$ Hz, H-6), 6.89 (d, 2H, $J_{3',2'} = J_{5',6'} = 9.2$ Hz, H-3′, H-5′), 3.03 (s, 6H, $N(CH_3)_2$); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 155.4 (C, C-4′), 152.8 (C, C-2), 141.0 (C, C-8), 140.6 (C, C-9), 128.3 (CH, C-2′), 128.3 (CH, C-6′), 126.4 (CH, C-6), 118.6 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7), 112.6 (CH, C-3′), 112.6 (CH, C-5′), 115.7 (C, C-1′), 41.2 (CH_3, $N(CH_3)_2$), 41.2 (CH_3, $N(CH_3)_2$); EIMS: *m/z* (rel. abund. %), 315 (M^+, 100), 317 (M+2, 96), 301 (13), 273 (3), 236 (11), 221 (4); HRMS (EI) calcd. for $C_{15}H_{14}BrN_3$: $m/z =$ 315.0371, found 315.0376.

*5-Bromo-2-(2-bromo-4,5-dimethoxyphenyl)-1H-benzo[d]imidazole (**22**)*

Yield: 49 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.83 (d, 1H, $J_{4,6} = 1.6$ Hz, H-4), 7.61 (s, 1H, H-3′), 7.59 (d, 1H, $J_{7,6} = 2.8$ Hz, H-7), 7.4 (dd, 1H, $J_{6,4} = 2$, $J_{6,7} = 8.8$ Hz, H-6), 3.93 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 150.3 (C, C-4′), 149.2 (C, C-5′), 141.0 (C, C-8), 140.6 (C, C-9), 133.0 (C, C-1′), 126.3 (CH, C-6), 118.6 (CH, C-4), 117.7 (C, C-5), 117.5 (CH, C-7), 115.5 (CH, C-3′), 114.4 (CH, C-6′), 113.6 (C, C-2′), 56.2 (CH_3, O CH_3), 56.1 (CH_3, O CH_3); EIMS: *m/z* (rel. abund. %), 410 (M^+, 49), 412 (M+2, 100), 414 (M+4, 51), 381 (24), 366 (19), 315 (88), 273 (23), 236 (14); HRMS (EI) calcd. for $C_{15}H_{12}Br_2N_2O_2$: $m/z = 409.9266$, found 409.9260.

*2-(Anthracen-9-yl)-5-bromo-1H-benzo[d]imidazole (**23**)*

Yield: 72 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 8.78 (s, 1H, H-6′), 8.19 (d, 2H, $J_{2',3'} = J_{10',9'} = 8.4$ Hz, H-2′, H-10′), 7.92 (s, 1H, H-4), 7.80 (d, 2H, $J_{5',4'} = J_{7',8'} = 8.8$ Hz, H-5′, H-7′), 7.71 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.57 (m, 5H, H-6, H-3′, H-4′, H-8′, H-9′); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.8 (C, C-2), 141.2 (C, C-8), 140.6 (C, C-9), 134.2 (C, C-1′), 132.1 (C, C-11′), 132.1 (C, C-13′), 130.5 (C, C-12′), 130.5 (C, C-14′), 129.7 (CH, C-6′), 128.1 (CH, C-5′), 128.1 (CH, C-7′), 126.4 (CH, C-6), 125.6 (CH, C-4′), 125.6 (CH, C-8′), 125.8 (CH, C-3′), 125.8 (CH, C-9′), 124.1 (CH, C-2′), 124.1 (CH, C-10′), 118.6 (CH, C-4), 117.6 (C, C-5), 117.3 (CH, C-7); EIMS: *m/z* (rel. abund. %), 371 (M^+, 84), 373 (M+2, 100), 313 (54), 292 (45), 264 (5), 232 (15); HRMS (EI) calcd. for $C_{21}H_{13}BrN_2$: $m/z = 372.0262$, found 372.0267.

*4-(5-Bromo-1H-benzo[d]imidazol-2-yl)-2-methoxyphenyl acetate (**24**)*

Yield: 63 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 7.93 (d, 1H, $J_{4,6} = 2$ Hz, H-4), 7.79 (m, 2H, H-2′, H-6′), 7.57 (d, 1H, $J_{7,6} = 8.4$ Hz, H-7), 7.37 (dd, 1H, $J_{6,4} = 2$, $J_{6,7} = 8.4$ Hz, H-6), 7.23 (d, 1H, $J_{5',6'} = 8$ Hz, H-5′), 3.94 (s, 3H, O=C-CH_3), 2.27 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 169.1 (C, O=C), 152.7 (C, C-2), 151.3 (C, C-3′), 141.7 (C, C-4′), 141.2 (C, C-8), 140.6, (C, C-9), 128.3 (C, C-1′), 126.1 (CH, C-6), 123.0 (CH, C-5′), 122.2 (CH, C-6′), 118.6 (CH, C-4), 117.6 (C, C-5), 117.4 (CH, C-7), 126.2 (CH, C-6), 111.6 (CH, C-2′), 55.9 (CH_3, O=C-CH_3), 20.2 (CH_3, OCH_3); EIMS: *m/z* (rel. abund. %), 360 (M^+, 9), 362 (M+2, 12), 318 (100), 305 (5), 290 (7), 275 (9), 239 (6), 196 (5); HRMS (EI) calcd. for $C_{16}H_{13}BrN_2O_3$: $m/z = 360.0110$, found 360.0117.

*2-Bromo-6-(5-bromo-1H-benzo[d]imidazol-2-yl)-4-chlorophenol (**25**)*

yield: 72 %; ^{1}H-NMR: (400 MHz, DMSO-d_6): δ 10.33 (s, 1H, NH), 7.88 (m, 2H, H-4, H-6′), 7.62 (d, 1H, $J_{7,6} = 8.8$

Hz, H-7), 7.38 (d, 1H, $J_{6,7} = 8.4$ Hz, H-6), 6.50 (s, 1H, H-4′), 6.48 (s, 1H, OH); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 152.9 (C, C-2), 152.7 (C, C-2′), 141.3 (C, C-8), 140.6 (C, C-9), 133.7 (CH, C-4′), 129.5 (C, C-5′), 127.7 (CH, C-6′), 126.3 (CH, C-6), 121.8 (C, C-1′), 118.6 (CH, C-4), 117.5 (C, C-5), 117.3 (CH, C-7), 115.6 (C, C-3′); EIMS: *m/z* (rel. abund. %), 400 (M^+, 74), 402 (M+2, 76), 385 (100), 357 (54), 345 (25), 329 (11); HRMS (EI) calcd. for $C_{13}H_7Br_2ClN_2O$: $m/z = 399.8614$, found 399.8610.

Acknowledgments The authors are thankful to the Higher Education Commission (HEC) Pakistan, for their financial support to Research Project No. 20-2073 under National Research Program for Universities.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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