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Synthesis of benzothiazole derivatives as a potent α-glucosidase inhibitor

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ABSTRACT

Diabetes is one of the pre-dominant metabolic disorders all over the world. It is the prime reason of mortality and morbidity due to hyperglycemia which is link with numerus obstacles. Delaying absorption and digestion of carbohydrate has great therapeutic impact for governing postprandial hyperglycemia. Consequently, alpha glucosidase is one of the potential therapeutic approaches that reduce absorption of glucose and delay carbohydrate digestion hence maintaining blood glucose level. In this regard we have synthesized benzothiazole based oxadiazole in search of potent anti-diabetic agent as α-glucosidase Inhibitors. Benzothiazole based oxadiazole derivatives **1–23** have been synthesized, characterized by ^{1}HNMR, ^{13}CNMR, and MS and evaluated for α-glucosidase Inhibition. All analogs exhibited a varying degree of α-glucosidase inhibitory activity with IC_{50} values ranging in between 0.5 ± 0.01–30.90 ± 0.70 μM when compared with the standard acarbose (IC_{50} = 866.30 ± 3.20 μM). Structure activity relationship has been established for all compounds. Molecular docking studies were performed to predict the binding interaction of the compounds with the active site of enzyme.

1. Introduction

α-Glucosidase (EC 3.2.1.20) as a catabolic enzyme hydrolyzes carbohydrates to produce energy metabolic sugars essential for normal physiological functions [1]. α-Glucosidase providing energy sources to maintain healthy functioning. In contrast, glucose absorption in patients with type-2 diabetes can cause clinically serious problems because high activity of this enzyme increases plasma mellitus glucose levels. Numerous reports address the relevance of α-glucosidase inhibition and the regulation of glucose levels in type-2diabetes mellitus by α-glucosidase inhibitors [2–4]. Several types of α-glucosidase inhibitors have been clinically applied to inhibit α-glucosidase for medicinal purposes including acarbose, voglibose and miglitol [5–6]. Inhibitors of this enzyme are designed to be orally taken, acting as an anti-diabetic drug by preventing the digestion of carbohydrates and by delaying the absorption of sugar. This allows plasma glucose to be maintained at a steady level. However due to numerous side effects of these drugs, medicinal chemists are continuously in struggles to discover new alpha glucosidase inhibitors. In this regard we have synthesized benzothiazole based oxadiazole derivatives (see-Fig. 1.).

The benzothiazoles are heterocyclic compounds with diverse range of biologically activity [7,8]. It shows numerous activities such as antimicrobial, antitumor, anti-inflammatory, antilieshmanial and antifungal [9,10], anticancer [11], antidiabetic [12], anticonvulsant [13], antiviral [14], antitubercular [15], antimalarial [16], antihelmintic [17], analgesic [18] and fungicidal activities [19]. Recently, benzothiazole derivatives have been evaluated as potential amyloid-binding diagnostic agents in neurodegenerative disease [20]. The1,3,4-oxadiazole constitute an important class of compounds in medicinal and pharmaceutical chemistry. The compounds containing 1,3,4-oxadiazole nucleus possess a vast spectrum of biological activities [21]. Recently, differently substituted 1,3,4-oxadiazoles have been reported for their biological activities, such as antibacterial [22], antifungal [23], insecticidal [24] antiviral [25] inflammatory [26] antitubercular [27] antitumoral [28], anticancer [29] and analgesic activity [30] (see-Fig. 2.).

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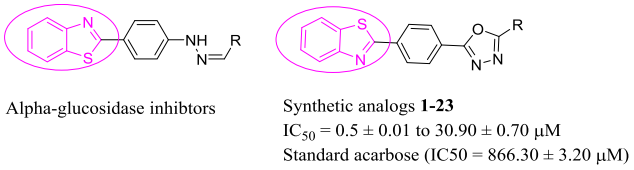

Fig. 1. Rational of the current study.

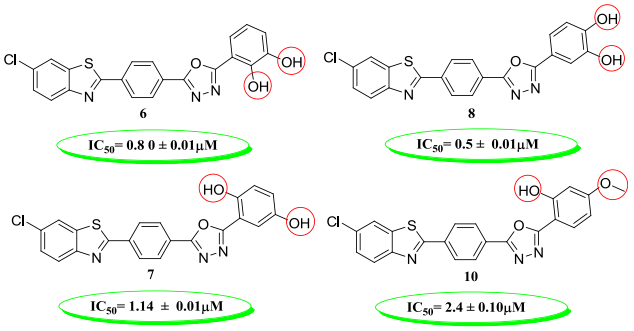

Fig. 2. Most potent analogs.

Our group has synthesized and screened benzothiazole esters and hydrazide for α-glucosidase potential. These analogs were found to have best activity [31]. Based on that, we have decided to synthesize benzothiazole linked oxadiazole derivatives **1–23** for α-glucosidase inhibition.

2. Experimental

2.1. Material and methods

Avance Bruker 500 MHz has been used for performing nuclear magnetic resonance experiments. Carlo Erba Strumentazion-Mod = 1106, Italy used for perofrming the lemental analysis. Finnigan MAT-311A, Germany was used for recording Electron impact mass spectra (EI-MS). Pre-coated silica gel aluminum plates (Kieselgel 60, 254, E. Merck, Germany) were used for performing Thin layer chromatography (TLC). UV at 254 and 365 nm were used for visualizing Chromatograms (see-Table 1.).

2.2. General procedure

Methyl 4-formylbenzoate (41 mmol) and sodium metabisulfite (41 mmol) was mixed in methanol and refluxed for 6 h at room temperature to give us sodium hydroxy (4-(methoxycarbonyl)phenyl) methane sulfonate intermediate (I). Then reaction mixture was poured into ice water and the solid product was filtered. The progress of reaction completion was checked by TLC. Compound (I) was then reacted with 2-amino-5-chlorobenzothiol in DMF (40 mL) and refluxed for 12 h to give us methyl 4-(6-chlorobenzo[*d*]thiazol-2-yl) benzoate (II) which was further mixed with hydrazine hydrate in methanol to form 4-(6-chlorobenzo[*d*]thiazol-2-yl)benzo hydrazide (III). Compound (III) was then reacted with different substituted aromatic carboxylic acids in POCl3 to give us the desired benzothiazole based oxadiazole derivatives 1–23 in good yields. The synthetic compounds were fully characterized by spectroscopy methods including 1H NMR, 13C NMR, HREI-MS.

2.2.1. 4-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)phenol

Yield: 81%;^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.92(d, J = 7.8 Hz, 2H, H-2″/6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.68 (d, J = 7.5 Hz, 1H, H-4, Ar), 7.54 (d,J = 7.6 Hz, 1H, H-5, Ar), 6.84 (d, J = 6.9 Hz, 2H, H-3″/5″, Ar), 5.34 (s, 1H, –OH); ^{13}C NMR (125 MHz, DMSO-d_6):δ 168.5, 164.1, 164.1, 158.0, 152.1, 142.7, 136.7, 129.3, 129.1, 127.8, 127.8, 127.8, 127.8, 125.8, 125.4, 122.9, 120.6, 116.1, 116.1, 116.0, 116.0; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_2S$, $[M]^+$405.1438; Found 405.1436.

Table 1
Benzothiazole based oxadiazole analogs (1–23).

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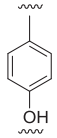
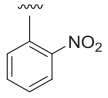
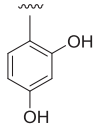
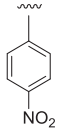
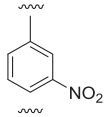
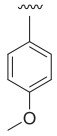
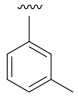
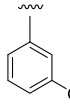
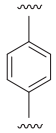
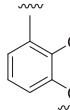
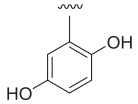
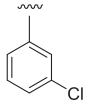
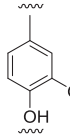
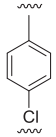
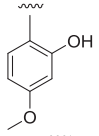
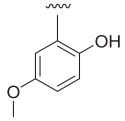
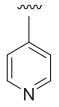
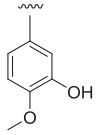
1		13	
2		14	
3		15	
4		16	
5		17	
6		18	
7		19	
8		20	
9		21	
10		22	
11		23	
12			

2.2.2. 4-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,3-diol

Yield: 84%;^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.68 (d, J = 7.5 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.43 (d,J = 7.6 Hz, 1H, H-6″, Ar),

6.40 (d, J = 6.1 Hz, 1H, H-5″Ar), 6.30 (s, 1H, H-3″, Ar), 5.34 (s, 2H, –OH);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 167.1, 164.2, 159.5, 156.4, 152.4, 143.1, 137.0, 130.1, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 1210, 108.9, 105.4, 100.4; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_3S$, $[M]^+$421.1459; Found 421.1457.

2.2.3. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole

Yield: 78%;^{1}H NMR (500 MHz, DMSO-d_6):δ 8.63 (s, 1H, H-2″, Ar), 8.42(d, J = 8.8 Hz, 1H, H-6″, Ar), 8.18 (d, J = 7.8, 1H, H-4″, Ar), 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.74 (t, 1H, H-5″, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.7, 164.2, 164.2, 152.3, 148.5, 143.1, 137.0, 133.5, 130.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.9, 126.0, 125.6, 123.7, 122.9, 122.6, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}ClN_4O_3S$, $[M]^+$434.0448; Found 434.0445.

2.2.4. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole

Yield: 75%;^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 8.00(d, J = 7.8, 2H, H-2″/6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.02 (d, J = 7.3, 2H, H-3″/5″, Ar), 3.80 (s, 3H, –CH_3);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 164.2, 164.2, 160.4, 152.3, 143.1, 137.0, 129.6, 128.8, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 115.7, 115.7, 114.6, 114.6, 55.6; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3O_2S$, $[M]^+$419.0149; Found 419.0147.

2.2.5. 3-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)phenol

Yield: 85%;^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H,H-4, Ar), 7.59 (d, J = 7.6 Hz, 1H, H-6″, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.31 (t, 1H, H-5″, Ar), 7.30 (s, 1H, H-2″, Ar), 6.89 (d, J = 7.1 Hz, 1H, H-4″, Ar), 5.34 (s, 1H, –OH);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.8, 164.4, 164.4, 157.2, 152.3, 143.1, 137.0, 130.4, 129.6, 127.8, 127.8, 127.8, 127.8, 127.3, 126.0, 125.6, 122.9, 121.0, 120.0, 115.7, 112.8; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_2S$, $[M]^+$405.1134; Found 405.1133.

2.2.6. 3-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2-diol

Yield: 86%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.14 (d, J = 7.3 Hz, 1H, H-6″, Ar), 6.89 (t, 1H, H-5″, Ar), 6.70 (d, J = 7.1 Hz, 1H, H-4″, Ar), 5.34 (s, 2H, –OH);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.7, 167.1, 164.3, 152.3, 145.4, 143.8, 143.1, 137.0, 130.5, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 123.0, 122.9, 121.0, 117.1, 113.2; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_3S$, $[M]^+$421.0241; Found 421.0240.

2.2.7. 2-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,4-diol

Yield: 85%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.11 (s, 1H, H-6″, Ar), 6.87 (d, J = 6.9 Hz, 1H, H-4″, Ar), 6.70 (d, J = 6.8 Hz, 1H, H-3″, Ar), 5.34 (s, 2H, –OH);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 167.1, 164.2, 152.3, 150.0, 149.9, 143.1, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 117.6, 117.1, 114.1, 113.3; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_3S$, $[M]^+$421.1309; Found 421.1310.

2.2.8. 4-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)benzene-1,2-diol

Yield: 82%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.50 (d, J = 7.2 Hz, 1H, H-6″, Ar), 7.11 (s, 1H, H-2″, Ar), 6.81 (d, J = 6.9 Hz, 1H, H-5″, Ar), 5.34 (s, 2H, –OH);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.2, 164.3, 152.3, 147.1, 145.7, 143.1, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 120.0, 116.0, 114.1, 108.7; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_3S$, $[M]^+$421.0135; Found 421.0132.

2.2.9. 2-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)-5-methoxyphenol

Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.48 (d, J = 7.5 Hz, 1H, H-6″, Ar), 6.57 (d, J = 6.8 Hz, 1H, H-5″, Ar), 6.56 (s, 1H, H-3″, Ar), 5.34 (s, 1H, –OH), 3.80 (s, 3H, –CH_3);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 167.1, 164.2, 161.8, 156.0, 152.3, 143.1, 137.0, 129.7, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 107.2, 104.0, 100.1, 55.6; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3O_3S$, $[M]^+$435.1034; Found 435.1032.

2.2.10. 2-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)-4-methoxyphenol

Yield: 76%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.15 (s, 1H, H-6″, Ar), 6.76 (d, J = 6.8 Hz, 1H, H-3″, Ar), 6.75 (d, J = 6.8 Hz, 1H, H-4″, Ar), 5.34 (s, 1H, –OH), 3.80 (s, 3H, –OCH_3);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.5, 167.2, 164.3, 153.5, 152.3, 149.5, 143.1, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 117.2, 115.5, 113.0, 112.5, 55.6; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3O_3S$, $[M]^+$435.1034; Found 435.1033.

2.2.11. 5-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)-2-methoxyphenol

Yield: 74%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.56 (d, J = 7.5 Hz, 1H, H-6″, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.18 (s, 1H, H-2″, Ar), 6.85 (d, J = 7.0 Hz, 1H, H-5″, Ar), 5.34 (s, 1H, –OH), 3.80 (s, 3H, –OCH_3);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.7, 164.2, 164.2, 152.3, 147.3, 147.2, 143.1, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.0, 120.0, 114.1, 111.2, 108.3, 55.8; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3O_3S$, $[M]^+$ 435.0137; Found 435.0139.

2.2.12. 2-(5-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-yl)phenol

Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.60 (d, J = 7.7 Hz, 1H, H-6″, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.21 (t, 1H, H-4″, Ar), 7.04 (m, 1H, H-5″, Ar), 7.00 (d, J = 6.8 Hz, 1H, H-3″, Ar), 5.34 (s, 1H, –OH);^{13}C NMR (125 MHz, DMSO-d_6):δ 168.6, 167.2, 164.2, 157.2, 152.3, 143.1, 137.0, 130.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.1, 126.0, 125.6, 122.9, 121.6, 121.0, 117.6, 107.8; HR-EI-MS: m/z calcd for $C_{21}H_{12}ClN_3O_2S$, $[M]^+$405.0236; Found 405.0235.

2.2.13. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(2-nitrophenyl)-1,3,4-oxadiazole

Yield: 76%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar), 8.02 (d, J = 8.2 Hz, 1H, H-6″, Ar), 8.00 (d, J = 8.1, 1H, H-3″, Ar), 7.88 (m, 1H, H-5″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.65 (m, 1H, H-4″, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.3, 164.3, 152.3, 146.7, 143.1, 137.0, 135.1, 131.4, 129.6, 129.3, 128.2, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 124.1, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}ClN_4O_3S$, $[M]^+$434.0447; Found 434.0446.

2.2.14. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole

Yield: 81%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 8.30 (d, J = 8.4 Hz, 2H, H-3″/5″, Ar), 8.20 (d, J = 8.1, 2H, H-2″/6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar),7.65 (m, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.6, 164.1, 164.1, 152.3, 147.6, 143.1, 137.0, 132.0, 130.6, 130.6, 129.6, 128.6, 128.6, 127.8, 127.8, 127.8, 127.8, 126.9, 125.6, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}ClN_4O_3S$, $[M]^+$434.0448; Found 434.0446.

2.2.15. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-o-tolyl-1,3,4-oxadiazole

Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d_6):δ 8.10 (s, 1H, H-7, Ar), 7.82(d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-6″, Ar), 7.65 (d, J = 7.4 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.30 (t, 1H, H-5″, Ar), 7.27 (t, 2H, H-3″/4″, Ar), 2.56 (s, 3H, –CH_3);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.2, 164.2, 152.3, 143.1, 137.0, 137.0, 136.7, 129.6, 129.3, 128.3, 127.8, 127.8, 127.8, 127.8, 127.2, 126.1, 126.0, 125.6, 122.9, 121.0, 18.5; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3OS$, $[M]^+$403.0136; Found 403.0135.

2.2.16. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-m-tolyl-1,3,4-oxadiazole

Yield: 75%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar), 7.78 (s, 1H, H-2″, Ar), 7.84 (d, J = 7.9 Hz, 1H, H-6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.37 (t, 1H, H-5″, Ar), 7.16 (d, J = 7.2 Hz, 1H, H-3″, Ar), 2.32 (s, 3H, –CH_3);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.1, 164.1, 152.3, 143.1, 138.6, 137.0, 130.2, 129.6, 128.9, 128.8, 127.8, 127.8, 127.8, 127.8, 126.0, 125.8, 125.6, 124.2, 122.9, 121.0, 21.4; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3OS$, $[M]^+$403.01435; Found 403.01439.

2.2.17. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-p-tolyl-1,3,4-oxadiazole

Yield: 76%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar),7.92 (d, J = 7.9 Hz, 2H, H-2″/6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.26 (d, J = 7.3 Hz, 2H, H-3″/5″, Ar), 2.32 (s, 3H, –CH_3);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.4, 164.2, 164.2, 152.3, 143.1, 142.0, 137.0, 131.5, 129.6, 127.8, 127.8, 127.8, 127.8, 127.2, 127.2, 126.1, 126.1, 126.0, 125.6, 122.9, 121.0, 21.1; HR-EI-MS: m/z calcd for $C_{22}H_{14}ClN_3OS$, $[M]^+$403.0137; Found 403.0136.

2.2.18. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(2-chlorophenyl)-1,3,4-oxadiazole

Yield: 72%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.70 (d, J = 7.8 Hz, 1H, H-6″, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.52 (d, J = 7.5 Hz, 1H, H-3″, Ar), 7.37 (t, 1H, H-5″, Ar), 7.33 (t, 1H, H-4″, Ar);^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.2, 164.2, 152.3, 143.1, 137.0, 136.8, 132.0. 130.0, 129.6,129.1, 128.8, 127.8, 127.8, 127.8, 127.8, 127.1, 126.0, 125.6, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}Cl_2N_3OS$, $[M]^+$423.0143; Found 423.0142.

2.2.19. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(3-chlorophenyl)-1,3,4-oxadiazole

Yield: 74%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar), 8.00 (s, 1H, H-2″, Ar), 7.90 (d, J = 8.0 Hz, 1H, H-6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.42 (t, 2H, H-4″/5″, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.1, 164.1, 152.3, 143.1, 137.0, 134.6, 129.6,129.4, 128.6, 127.8, 127.8, 127.8, 127.8, 127.3, 127.2, 126.0, 125.6, 125.4, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}Cl_2N_3OS$, $[M]^+$423.0122; Found 423.0120.

2.2.20. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(4-chlorophenyl)-1,3,4-oxadiazole

Yield: 75%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.70 (d, J = 7.8 Hz, 2H, H-2″/6″, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.52 (d, J = 7.6 Hz, 2H, H-3″/5″, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.6, 164.2, 164.2, 152.3, 143.1, 137.0, 134.1, 129.6,129.0, 129.0, 128.7, 128.7, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 124.0, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{21}H_{11}Cl_2N_3OS$, $[M]^+$423.0241; Found 423.0240.

2.2.21. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(pyridin-3-yl)-1,3,4-oxadiazole

Yield: 77%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.21 (s, 1H, H-2″, Ar), 8.40 (d, J = 8.5 Hz, 1H, H-6″, Ar), 8.68 (d, J = 8.8 Hz, 1H, H-4″, Ar), 8.10 (s, 1H, H-7, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.55 (t, 1H, H-5″, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.6, 164.1, 164.1, 152.5, 152.3, 147.6, 143.1, 137.0, 133.8, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 124.1, 123.8, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{20}H_{11}ClN_4OS$, $[M]^+$390.0140; Found 390.0138.

2.2.22. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(pyridin-4-yl)-1,3,4-oxadiazole

Yield: 78%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.71 (d, J = 8.8 Hz, 2H, H-3″/5″, Ar), 8.10 (s, 1H, H-7, Ar), 7.97 (d, J = 8.1 Hz, 2H, H-2″/6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 164.2, 164.2,152.3, 149.5, 149.5, 143.4, 143.1, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 122.9, 121.1, 121.1, 121.0; HR-EI-MS: m/z calcd for $C_{20}H_{11}ClN_4OS$, $[M]^+$390.0142; Found 390.0141.

2.2.23. 2-(4-(6-chlorobenzo[d]thiazol-2-yl)phenyl)-5-(pyridin-2-yl)-1,3,4-oxadiazole

Yield: 76%; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (d, J = 8.6 Hz, 1H, H-3″, Ar), 8.10 (s, 1H, H-7, Ar), 8.00 (d, J = 8.2 Hz, 1H, H-6″, Ar), 7.82 (d, J = 7.7 Hz, 4H, H-2′/3′/5′/6′, Ar), 7.81 (d, J = 7.6 Hz, 1H, H-5″, Ar), 7.67 (d, J = 7.8 Hz, 1H, H-4, Ar), 7.54 (d, J = 7.6 Hz, 1H, H-5, Ar), 7.34 (t, 1H, H-4″, Ar); ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.6, 164.1, 164.1, 157.2, 152.3, 149.0, 143.1, 137.0, 137.0, 129.6, 127.8, 127.8, 127.8, 127.8, 126.0, 125.6, 124.0, 123.2, 122.9, 121.0; HR-EI-MS: m/z calcd for $C_{20}H_{11}ClN_4OS$, $[M]^+$390.0122; Found 390.0121.

2.3. α-Glucosidase inhibition assay

Total volume of 100 µL reaction mixture contained 70 µL 50 mM phosphate buffer pH 6.8, 10 µL test compound (0.5 mM in methanol) followed by the addition of 10 µL enzyme solution (0.057 units, Sigma Inc; "α-Glucosidase from Saccharomyces cerevisiae") in the buffer. The contents were mixed, pre-incubated for 10 min at 37 °C and pre-read at 400 nm. The reaction was initiated by the addition of 10 µL of 0.5 mM substrate (*p*-nitrophenyl glucopyranoside, Sigma Inc.). After 30 min of incubation at 37 °C, absorbance of *p*-nitrophenol released was measured using Synergy HT 96-well plate reader, BioTek, USA. Acarbose was used as positive control [32,33]. All experiments were carried out in triplicates. The percent inhibition was calculated by the following equation:

$$\text{Inhibition}(\%) = (\text{Abs of Control - Abs of Test/Abs of Control}) \times 100$$

Active compound solutions were suitably diluted, and their inhibition studies were determined. Data obtained was used for the determination of IC50 values (concentration at which there is 50% enzyme inhibition) using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA).

2.4. Molecular docking

To understand the binding interactions of the newly synthesized Benzothiazole derivatives in the active site ofα-glucosidase, molecular docking was performed using MOE-Dock program. The crystal structure of α-glucosidase is not available yet, so, we used homology model as described by Taha M *et al* [32]. The energy of the modelled protein molecule was minimized after the 3D protonation using the default parameters of MOE energy minimization algorithm (gradient: 0.05, Force Field: Amber99). The three-dimensional coordinates of the Benzothiazole derivatives were constructed using MOE. Then, the molecule was energy minimized using the default parameters of MOE energy minimization algorithm (gradient: 0.05, Force Field: Amber99). The minimized molecule was saved in the mdb file format as input file. The binding pocket of the enzyme was selected by the site finder, implemented in MOE software. The compound was docked into the binding pocket of α-glucosidase enzyme using default parameters of MOE-Dock. The top ranked pose of each compound was selected on the basis of docking score (S) for further analysis.

3. Results and discussion

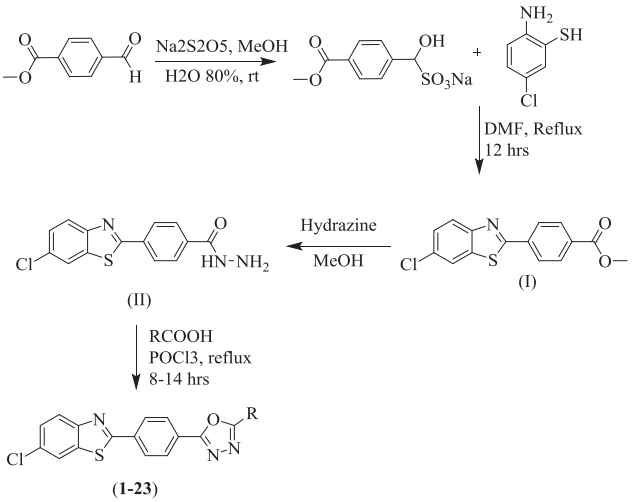
3.1. Chemistry

The synthesis of intermediate compounds II was carried out as reported [12] from compound I. Compound **II** was then reacted with diverse aromatic carboxylic acids in $POCl_3$ to synthesize benzothiazole derivatives **1–23** in good yields [32]. The synthetic compounds were fully characterized by spectroscopy methods including ^1H NMR, ^{13}C NMR, HR MS, of the synthesized compounds Scheme 1.

Basic Skeleton of Benzothiazole based Oxadiazole

3.2. α-Glucosidase inhibitory potential

To continue our research works on enzyme inhibition [34–41]. We have synthesized benzothiazole based oxadiazole analogs (**1–23**) and screened for α-Glucosidase inhibitory activity. All analogs have varied degree of α-glucosidase inhibition with IC_{50} values ranging in between 0.5 ± 0.01–36.50 ± 0.50 μM when compared with the standard acarbose (IC_{50} = 866.30 ± 3.20 μM) (Table 2.). All Compounds **1–20** showed



Scheme 1. Synthesis of novel benzothiazole derivatives 1–23.

Table 2
α-Glucosidase inhibitory potential of Benzothiazole Based oxadiazole.

S.No.	IC_{50} ± SEM[a]	S. No.	IC_{50} ± SEM[a]
1	5.3 ± 0.01	13	8.50 ± 0.3
2	3.30 ± 0.01	14	15.50 ± 0.6
3	27.5 ± 0.5	15	12.20 ± 0.30
4	12.80 ± 0.1	16	36.50 ± 0.50
5	3.8 ± 0.05	17	18.40 ± 0.40
6	0.8 0 ± 0.01	18	8.80 ± 0.2
7	1.14 ± 0.01	19	16.90 ± 0.3
8	0.5 ± 0.01	20	9.80 ± 0.20
9	3.6 ± 0.10	21	30.90 ± 0.70
10	2.4 ± 0.10	22	26.2 ± 0.5
11	2.6 ± 0.10	23	12.10 ± 0.2
12	6.50 ± 0.3	Acarbose	866.30 ± 3.20

SEM[a] = standard mean error.

outstanding inhibitory potential with IC_{50} values **1**(5.3 ± 0.01), **2**(3.30 ± 0.01), **3**(27.5 ± 0.5), **4**(12.80 ± 0.1), **5**(3.8 ± 0.05), **6**(0.8 0 ± 0.01), **7**(1.14 ± 0.01), **8**(0.5 ± 0.01), **9**(3.6 ± 0.10), **10**(2.4 ± 0.10), **11**(2.6 ± 0.10), **12**(6.50 ± 0.3), **13**(8.50 ± 0.3), **14**(15.50 ± 0.6), **15**(12.20 ± 0.30), **16**(36.50 ± 0.50), **17**(18.40 ± 0.40), **18**(8.80 ± 0.2), **19**(16.90 ± 0.3), **20**(9.80 ± 0.20), **21**(30.90 ± 0.70), **22**(26.2 ± 0.5) and **23**(12.10 ± 0.2) μM, respectively when compared with the standard acarbose.

The structure activity relationship has been also established. The SAR was mainly based upon by bringing about difference of substituents on phenyl ring. The compound **8,** a 3,4-dihydroxy analog was found to be the most potent among the series with (IC_{50} value 0.5 ± 0.01 μM). If we compare it with other dihydroxy analogs like compound **6** a 2,3-dihydroxy analog (IC_{50} value 0.80 ± 0.01 μM) and **7**, a 2,5-dihydroxy analog (IC_{50} value 1.14 ± 0.01 μM), and **2**, a 2,4-dihydroxy analog (IC_{50} value 3.30 ± 0.01 μM), the analog **8** is superior. The little bit difference in their potential is seems to be due to the difference in the position of hydroxyl groups on phenyl ring. Similarly, if we compare mono-hydroxy analogs like **1** (IC_{50} = 5.3 ± 0.01 μM) **5** (IC_{50} = 3.8 ± 0.05 μM) and **12** (IC_{50} = 6.50 ± 0.3 μM), analog **5** was found to be more superior. This higher potential indicates that hydroxyl group at *meta* position is more favorable for inhibition. Comparing the hydroxyl methoxy analogs **9** (IC_{50} = 3.6 ± 0.10 μM), **10** (IC_{50} = 2.4 ± 0.10 μM), and **11** (IC_{50} = 2.6 ± 0.10 μM), analog **10** was found more potent. This higher inhibition is attributed to the position of hydroxyl and methoxy group at *ortho* and *meta* position.

By comparing analog *o*-methyl **15** (IC_{50} = 12.20 ± 0.30 μM) with **16**, a *m*-methyl analog (IC_{50} = 36.50 ± 0.50 μM) and **17,** a *p*-methyl (IC_{50} = 18.40 ± 0.40 μM), the analog **15** is superior. The reason for greater potential is might be due position of methyl group on phenyl ring. Comparing the chloro analogs **18** (IC_{50} = 8.80 ± 0.2 μM), **19** (IC_{50} = 16.90 ± 0.3 μM) and **20** (IC_{50} = 9.80 ± 0.20 μM), analog **18** was found more superior. This greater potential indicate that chloro at ortho position is more ideal for inhibition. Similar pattern was observed by comparing analog **21**, **22** and **23** having nitrogen is present at *meta, para* and *ortho* position. It was concluded from this study that either EWG or EDG on phenyl part showed potential but the slight difference in potential was mainly affected by the position of the substituent as well as in some cases the number of substituent also play a role. To understand the binding interaction of the most active analogs molecular docking study was performed.

3.3. Molecular docking

MOE-Dock module implemented in MOE program was utilized to explore the binding conformations of the compounds within the active site of α-glucosidase enzyme. The default parameters of MOE-Dock program were used in the docking protocol. At the end of docking

experiment, the best conformations based on docking score were analyzed for hydrogen bonding/arene-arene/arene-cation interactions. From the docking calculation study, it was observed that the top ranked conformations of almost all compounds were well accommodated inside the active site of α-glucosidase enzyme and were involved in various type of interactions with the active site residues of α-glucosidase enzyme. *i.e.,* Lys 155, Leu 237, Glu 276, Phe 300, Phe 310, Asp 347, Asp 349, Arg 439, etc. The detail of docking scores and interactions for all compounds are listed in Table 3. The structural features observed in this group for the active nature of compounds are the presence of electron donating groups like –OH. Fig. 3 displays the interaction modes of some most active compounds among these docked

Table 3
Docking scores and report of predicted interactions of docked conformations.

Compounds	Docking score	Interaction Report
1	-7.0065	**Ligand Receptor Interaction Distance E (kcal/mol)**
		S9 12 O TRP 154 H-donor 3.82 -1.7
		S9 12 O LYS 155 H-donor 2.66 10.3
		C15 21 O LYS 155 H-donor 3.31 -0.6
		6-ring CG LYS 155 pi-H 3.77 -0.2
		6-ring CD ARG 312 pi-H 3.94 -0.2
		6-ring 6-ring PHE 300 pi-pi 3.75 -0.0
2	-7.8112	S9 12 OE1 GLU 304 H-donor 3.21 0.3
		C15 21 OE1 GLU 304 H-donor 3.32 -0.4
		CL21 28 OH TYR 344 H-donor 3.40 -0.6
		O28 38 O PRO 309 H-donor 2.62 -2.6
		N18 25 ND2 ASN 153 H-acceptor 3.04 -4.1
		N18 25 N PHE 157 H-acceptor 3.53 -0.7
		CL21 28 ND2 ASN 347 H-acceptor 3.46 -0.3
		6-ring CG LYS 155 pi-H 4.10 -0.4
		6-ring CG LYS 155 pi-H 5.01 -0.2
		6-ring CE LYS 155 pi-H 3.54 -0.3
		6-ring CD2 LEU 237 pi-H 4.16 -0.2
		6-ring N ARG 312 pi-H 4.23 -1.1
		5-ring CD ARG 312 pi-H 3.47 -0.6
3	-5.5623	S9 12 OE2 GLU 276 H-donor 3.96 -0.1
		CL21 28 OD1 ASN 347 H-donor 4.28 -0.0
		CL21 28 ND2 ASN 347 H-acceptor 4.33 -0.2

(*continued on next page*)

Table 3 (*continued*)

		O29 40 CB GLN 238 H-acceptor 3.30 -0.2 O30 41 CB ASN 153 H-acceptor 2.57 0.5 O30 41 N GLN 238 H-acceptor 3.09 -1.1 6-ring CA LYS 155 pi-H 4.05 -0.2 6-ring CG LYS 155 pi-H 4.24 -0.3 5-ring CE LYS 155 pi-H 4.62 -1.7 6-ring CD ARG 312 pi-H 4.24 -0.9 5-ring CD ARG 312 pi-H 4.53 -0.5
4	-6.1002	C6 8 OD1 ASN 153 H-donor 3.25 -0.4 S9 12 O TRP 154 H-donor 3.59 -0.5 C12 16 OE1 GLU 304 H-donor 3.30 -0.5 CL21 28 O SER 235 H-donor 3.02 0.2 5-ring ND2 ASN 153 pi-H 4.88 -0.3 6-ring CG LYS 155 pi-H 4.00 -0.7 6-ring CE LYS 233 pi-H 3.94 -0.2 5-ring CA PHE 311 pi-H 4.06 -0.2 6-ring CD2 PHE 311 pi-H 4.73 -0.3 5-ring CD2 PHE 311 pi-H 3.60 -0.4 6-ring N ARG 312 pi-H 4.35 -0.4
5	-7.6914	C14 19 OE1 GLU 304 H-donor 3.27 -0.3 O28 39 OD2 ASP 349 H-donor 2.62 -1.9 N18 25 NH1 ARG 312 H-acceptor 2.96 -3.8 C6 8 5-ring HIS 239 H-pi 4.29 -0.2 5-ring CG LYS 155 pi-H 4.35 -1.0 6-ring CE LYS 155 pi-H 3.93 -0.2 5-ring CD2 LEU 237 pi-H 4.38 -0.6

(*continued on next page*)

Table 3 (*continued*)

		6-ring CD2 LEU 237 pi-H 4.14 -0.6 5-ring CG GLU 304 pi-H 3.54 -0.5 6-ring CA PRO 309 pi-H 4.09 -0.2 6-ring CD ARG 312 pi-H 4.44 -0.2
6	-8.4590	O28 38 OD2 ASP 349 H-acceptor 1.62 -4.0 O28 38 OD2 ASP 349 H-donor 3.22 -3.0 N18 25 NH1 ARG 312 H-acceptor 2.05 -6.3 O NH LYS 155 H-donor 3.13 -0.3 5-ring CA LYS 155 pi-H 4.43 -0.3 5-ring CG LYS 155 pi-H 4.04 -0.3 5-ring CD1 LEU 237 pi-H 4.38 -0.4 5-ring CD2 LEU 237 pi-H 4.17 -0.4 6-ring CD2 LEU 237 pi-H 4.30 -0.2 6-ring CD ARG 312 pi-H 4.57 -0.3
7	-8.3401	O29 40 OE2 GLU 276 H-donor 1.56 -3.6 N18 25 NH1 ARG 312 H-acceptor 2.10 -6.7 O28 38 OD2 ASP 439 H-donor 3.51 -6.0 O29 40 NH LYS 155 H-acceptor 2.61 -0.3 5-ring CA LYS 155 pi-H 4.29 -0.3 5-ring CG LYS 155 pi-H 3.87 -0.7 6-ring CA LEU 237 pi-H 4.40 -0.2 5-ring CD2 LEU 237 pi-H 4.21 -0.4
8	-8.7654	O28 38 OD2 ASP 349 H-donor 1.21 -6.0 O29 40 OD2 ASP 349 H-donor 1.61 -1.2 N18 25 NH1 ARG 312 H-acceptor 2.00 -2.3 O28 38 ND2 ASN 347 H-acceptor 2.03 -1.3

(*continued on next page*)

Table 3 (*continued*)

		O29 40 NH LYS 155 H-acceptor 3.41 -0.3 5-ring CA LYS 155 pi-H 4.16 -0.2 5-ring CG LYS 155 pi-H 3.86 -0.7 6-ring CG LYS 155 pi-H 4.92 -0.2 6-ring CA LEU 237 pi-H 4.30 -0.4 5-ring CD2 LEU 237 pi-H 3.90 -0.3 6-ring CD2 LEU 237 pi-H 4.11 -0.3 6-ring CB PHE 300 pi-H 4.33 -0.3 6-ring 6-ring PHE 310 pi-pi 3.71 0.1 6-ring N ARG 312 pi-H 4.48 -0.8
9	-7.7645	S9 12 O PHE 310 H-donor 3.64 0.1 C25 34 OE2 GLU 276 H-donor 3.20 -0.3 O28 38 OE2 GLU 276 H-donor 2.53 -2.9 N7 10 CA LYS 155 H-acceptor 3.76 -0.4 6-ring CG LYS 155 pi-H 4.20 -0.3 6-ring CB ASP 349 pi-H 3.69 -0.4
10	-8.0001	O29 40 NH LYS 155 H-acceptor 3.51 -0.3 6-ring CG LYS 155 pi-H 4.20 -0.6 5-ring CB PHE 300 pi-H 4.51 -0.4 N18 25 NH1 ARG 312 H-acceptor 3.60 -6.7 5-ring CD ARG 312 pi-H 3.96 -0.7 6-ring CD ARG 312 pi-H 4.40 -0.2 5-ring NH1 ARG 312 pi-cation 4.12 -2.1 6-ring 6-ring PHE 300 pi-pi 3.39 -0.0
11	-7.8832	S9 12 O TRP 154 H-donor 3.28 -0.1 C22 29 OE1 GLU 304 H-donor 3.31 -0.8

(*continued on next page*)

Table 3 (*continued*)

		C22 29 OE2 GLU 304 H-donor 3.11 -0.4 O29 39 OE2 GLU 276 H-donor 2.81 -3.4 5-ring CD2 LEU 237 pi-H 3.78 -0.8 6-ring CA PHE 311 pi-H 4.13 -0.9 6-ring N ARG 312 pi-H 4.68 -0.4 5-ring CB ARG 312 pi-H 3.53 -0.4
12	-6.6783	C3 4 OE2 GLU 304 H-donor 3.18 1.5 N17 24 CD2 PHE 311 H-acceptor 2.80 67.3 N18 25 ND2 ASN 153 H-acceptor 2.38 23.1 6-ring CG LYS 155 pi-H 3.93 -1.0 6-ring CE LYS 155 pi-H 4.64 -0.6 6-ring CA LEU 237 pi-H 4.87 -0.2 6-ring CA PHE 311 pi-H 4.48 -0.6 6-ring N ARG 312 pi-H 3.94 -2.1 6-ring CB ARG 312 pi-H 4.27 -0.2 5-ring CB ARG 312 pi-H 4.22 -0.2
13	-6.5534	C3 4 OE2 GLU 304 H-donor 3.19 1.3 N17 24 CD2 PHE 311 H-acceptor 2.77 77.9 N18 25 ND2 ASN 153 H-acceptor 2.37 25.2 O29 40 CG LYS 155 H-acceptor 2.68 354.1 6-ring CG LYS 155 pi-H 3.93 -1.0 6-ring CE LYS 155 pi-H 4.66 -0.6 6-ring CA LEU 237 pi-H 4.88 -0.2 6-ring CA PHE 311 pi-H 4.49 -0.6 6-ring N ARG 312 pi-H 3.94 -2.1 6-ring CB ARG 312 pi-H 4.27 -0.2

(*continued on next page*)

Table 3 (*continued*)

		5-ring CB ARG 312 pi-H 4.21 -0.2
14	-6.2599	S9 12 O TRP 154 H-donor 2.97 1.6 C15 21 O LYS 155 H-donor 2.91 -1.0 C22 29 OE1 GLU 304 H-donor 2.90 -1.5 O29 40 CG GLN 350 H-acceptor 2.81 -0.4 5-ring CA LYS 155 pi-H 3.65 -0.3 6-ring CA LYS 155 pi-H 4.13 -0.2 6-ring CA PHE 311 pi-H 3.88 -0.5 6-ring N ARG 312 pi-H 3.82 -0.5 5-ring CB ARG 312 pi-H 3.99 -0.3 5-ring CD ARG 312 pi-H 3.74 -0.2
15	-6.3409	S9 12 OE1 GLU 304 H-donor 2.04 141.7 S9 12 OE2 GLU 304 H-donor 1.71 485.0 C22 29 O PHE 310 H-donor 2.03 634.5 N7 10 CE LYS 155 H-acceptor 3.38 -0.3 C24 33 6-ring PHE 157 H-pi 4.64 -0.2 6-ring 6-ring PHE 311 pi-pi 3.65 -0.0
16	-4.8923	S9 12 O TRP 154 H-donor 2.75 6.7 S9 12 O LYS 155 H-donor 2.41 31.1 C28 39 OE2 GLU 304 H-donor 1.90 17226. C12 16 6-ring TYR 313 H-pi 4.50 -0.2 6-ring CA SER 156 pi-H 4.12 -0.3 6-ring CB PHE 157 pi-H 4.69 -0.3 5-ring CB PHE 157 pi-H 4.30 -0.9 6-ring CD2 PHE 300 pi-H 4.56 -0.3 5-ring CD ARG 312 pi-H 3.58 -1.3

(*continued on next page*)

Table 3 (*continued*)

		5-ring 6-ring PHE 311 pi-pi 3.20 -0.0
17	-6.0010	S9 12 O TRP 154 H-donor 2.60 13.1 S9 12 O LYS 155 H-donor 2.61 12.6 C12 16 6-ring TYR 313 H-pi 4.56 -0.2 6-ring CA SER 156 pi-H 4.12 -0.2 6-ring CB PHE 157 pi-H 4.77 -0.2 5-ring CB PHE 157 pi-H 4.20 -0.7 5-ring CD ARG 312 pi-H 3.63 -1.6 5-ring 6-ring PHE 311 pi-pi 3.27 -0.0 6-ring 6-ring PHE 311 pi-pi 3.99 -0.0
18	-8.6784	C3 4 OE1 GLU 304 H-donor 2.80 131.5 C3 4 OE2 GLU 304 H-donor 2.99 9.6 N17 24 CD2 PHE 311 H-acceptor 2.87 69.0 N18 25 ND2 ASN 153 H-acceptor 2.60 0.8 6-ring CG LYS 155 pi-H 3.67 -0.2 6-ring CE LYS 155 pi-H 4.16 -0.3 6-ring CA PHE 311 pi-H 4.79 -0.4 6-ring N ARG 312 pi-H 4.21 -0.2 5-ring CB ARG 312 pi-H 4.58 -0.3 6-ring CB ARG 312 pi-H 4.43 -0.5 5-ring CD ARG 312 pi-H 3.49 -0.2
19	-6.0112	S9 12 OE2 GLU 304 H-donor 1.67 556.0 C14 19 O PRO 309 H-donor 3.65 -0.2 CL21 28 OE1 GLN 350 H-donor 4.14 -0.1 N7 10 CE LYS 155 H-acceptor 2.78 -0.1 CL28 39 N PHE 157 H-acceptor 3.97 -0.2

(*continued on next page*)

Table 3 (*continued*)

		6-ring CD2 LEU 237 pi-H 4.40 -0.2
20	-7.9965	S9 12 O TRP 154 H-donor 3.14 0.2 C15 21 O LYS 155 H-donor 3.06 -1.0 C22 29 OE1 GLU 304 H-donor 3.04 -0.8 CL28 39 OD1 ASN 347 H-donor 4.17 -0.1 5-ring CA LYS 155 pi-H 3.69 -0.3 6-ring CA LYS 155 pi-H 4.12 -0.2 6-ring CA PHE 311 pi-H 3.98 -0.8 6-ring CD2 PHE 311 pi-H 4.41 -0.3 6-ring N ARG 312 pi-H 3.85 -0.7 5-ring CB ARG 312 pi-H 4.00 -0.2 5-ring NH1 ARG 312 pi-cation 4.68 -0.3
21	-5.3478	S9 12 OE1 GLU 304 H-donor 2.63 10.5 S9 12 OE2 GLU 304 H-donor 2.23 65.5 N7 10 CE LYS 155 H-acceptor 3.06 -0.8 N25 35 CB ASN 153 H-acceptor 3.23 -0.4 6-ring CE LYS 155 pi-H 4.18 -0.7
22	-5.8993	S9 12 O TRP 154 H-donor 3.24 0.6 S9 12 O LYS 155 H-donor 2.21 70.5 CL21 28 O SER 235 H-donor 2.87 1.0 N24 33 CG GLN 350 H-acceptor 3.32 -0.4 6-ring CG LYS 155 pi-H 4.16 -0.9 5-ring NZ LYS 155 pi-cation 3.83 -2.2 6-ring N ARG 312 pi-H 4.43 -0.7 6-ring CB ARG 312 pi-H 3.97 -0.2 5-ring 6-ring PHE 311 pi-pi 3.30 -0.0

(*continued on next page*)

Table 3 (*continued*)

23	-6.4578	S9	12	O	TRP 154	H-donor	3.22	-1.7
		S9	12	O	LYS 155	H-donor	2.73	7.3
		C15	21	O	LYS 155	H-donor	3.15	-0.9
		6-ring		CE	LYS 155	pi-H	4.44	-0.6
		6-ring		CA	PHE 311	pi-H	4.57	-0.4
		6-ring		N	ARG 312	pi-H	4.05	-0.8
		6-ring		CB	ARG 312	pi-H	4.46	-0.3
		5-ring		CB	ARG 312	pi-H	4.34	-0.3
		5-ring		CD	ARG 312	pi-H	3.42	-0.3
Standard Acarbose	-5.2311	O	29	ND2	ASN 412	H-acceptor	2.94	-2.6
		O	67	NZ	LYS 155	H-acceptor	2.94	-1.7
		N	58	OE1	GLU 276	ionic	2.71	-6.7
		O	67	O	ASP 349	H-donor	2.76	-2.9
		O	84	NH1	ARG 439	H-acceptor	2.75	0.4

conformations. The docking conformation of the most active compound (compound **8**) showed five hydrogen bonds and several hydrophobic interactions with active site residues of the enzyme (Fig. 3**A and** Table 3). The oxygen atoms of the hydroxyl moieties attached to the phenyl ring of the compounds formed three hydrogen bonds with active site residues Lys155, Arg312, Asn347 and Asp349 at distance of 3.4 Å, 2.0 Å, 2.0 Å, 1.2 Å and 1.6 Å respectively. Whereas the Glu276 and Arg312 formed hydrogen bonds with the oxygen and nitrogen atoms of the oxadiazole moiety of the compound at distance 3.4 Å and 2.0 Å respectively. In case of second most active compound (compound **6**), four hydrogen bonds with active residues Lys155, Arg312 and Asp349 were observed (Fig. 3**B and** Table 3). Lys155 established hydrogen bond with the oxygen atom and Arg312 formed hydrogen bond with nitrogen atom of oxadiazole moiety and oxygen atom of hydroxyl moiety of the compound at distances 3.1 Å, 2.0 Å and 3.2 Å respectively. Whereas Asp349 formed hydrogen bond with oxygen atom of hydroxyl moiety of compound with distance of 1.6 Å. In case of compound **7**, the third most active compound in the series, four hydrogen bonds at distances 2.4, 1.6, 2.0 and 1.5 with active site residues Lys155, Glu276, Arg312 and Asp349 respectively were observed (Fig. 3**C** and Table 3). The docking conformation of compound **10**, which is the fourth most active compound in the series, showed only two hydrogen bonds with active site residues (Fig. 3**D** and Table 3). In case of least active compounds of the series (compound **16**, **21** and **22**), the docking results showed that these compounds showed poor interaction with the active site residues as compare to the most active compounds (compound **6**, **7**, **8** and **10**). As in shown in Table 3, the distances polar interactions as well as bonding energies of least active compounds are more as compare to the most active compounds (Table 3). This poor interaction might be one of the reasons for least active compounds to show less activities. In case of reference compound (**Acarbose**), the docking results showed that the bonding distances of this compound are more as compare to the most active compounds (Table 3). The reference compound also showed less number of interactions as compare to the interactions of the most active compounds. The larger bonding distances and less number of interactions with the active site residues showed by the refence compound might be the reasons for less activity showed by this compound. Overall the docking results showed that compounds having more hydroxyl moieties showed good biological activities and good interaction with active site residues as compare to the compounds having less hydroxyl moieties. Furthermore, not only the number but also the position of hydroxyl moieties might play a role in the biological activities as well as binding mode of these compounds. The correlation coefficient graph (Fig. 4) showed that a good correlation between the docking scores and biological activities of compounds exist.

4. Conclusion

Benzothiazole based oxadiazole derivatives (**1–23)** have been synthesized and evaluated for α-glucosidase inhibitory potential.All derivatives displayed potent α-glucosidase inhibitory potential ranging between0.5 ± 0.01–30.90 ± 0.70 μM as a compare to acarbose. The dihydroxy analogs were found to be the most potent among the series. Molecular docking revealed that the top ranked conformations of almost all compounds were well accommodated inside the active site of α-glucosidase enzyme and were involved in various types of interactions with the active site residues of α-glucosidase enzyme.

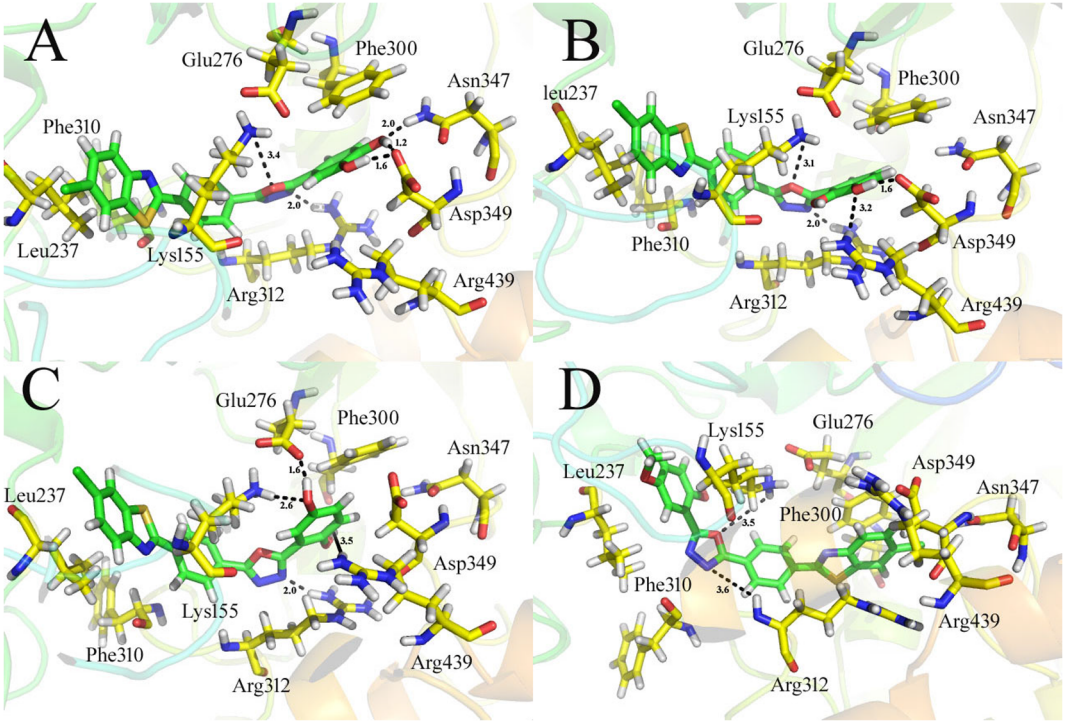


Fig. 3. Docking conformations of compounds onα-glucosidase enzyme. A. 3D binding mode of compound 8 as inhibitor of α-glucosidase enzyme. B. 3D binding mode of compound 6. C. 3Dbinding mode of compound 7. D. 3D binding mode of compound 10 in binding cavity of α-glucosidase enzyme. Ligands are shown green color.

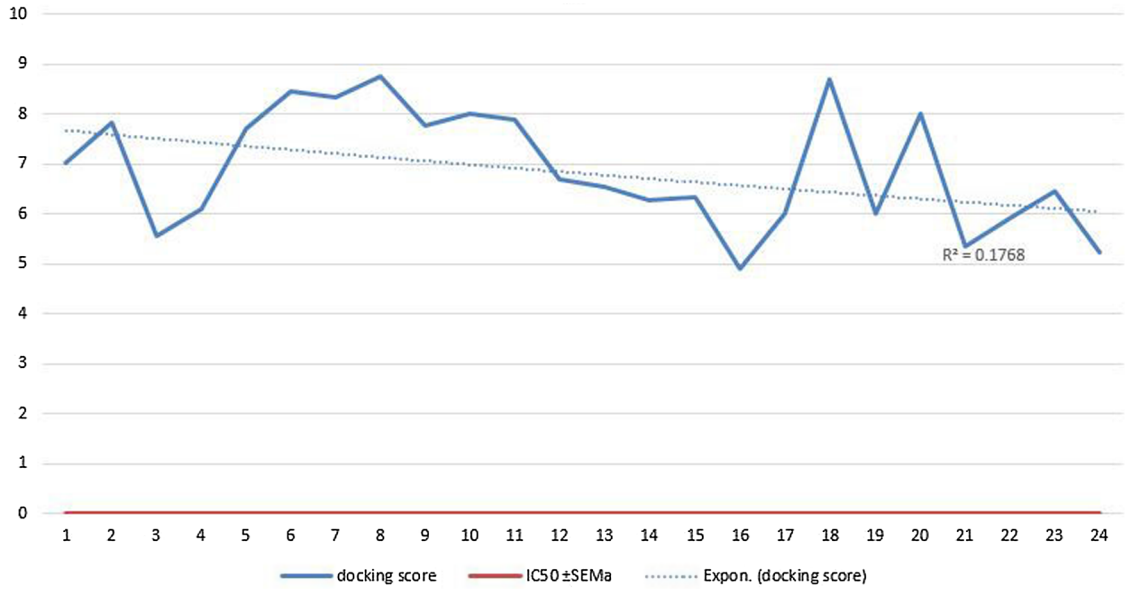


Fig. 4. A correlation graph for predicted docking score and IC_{50} values.

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