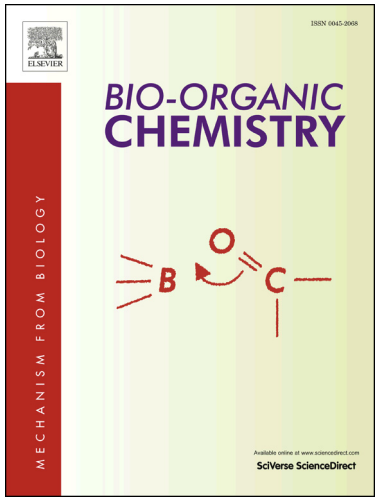

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Synthesis, *In Vitro* α-Glucosidase Inhibitory Activity and Molecular Docking Studies of New Thiazole Derivatives

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[b]*Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA (UiTM), Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor D. E., Malaysia*
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Abstract

Current study based on the synthesis of new thiazole derivatives *via* "one pot" multicomponent reaction, evaluation of their *in vitro* α-glucosidase inhibitory activities, and *in silico* studies. All synthetic compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR and EIMS. CHN analysis was also performed. These newly synthesized compounds showed activities in the range of IC_{50} = 9.06 ± 0.10-82.50 ± 1.70 μM as compared to standard acarbose (IC_{50} = 38.25 ± 0.12 μM). It is worth mentioning that most of the compounds such as **1** (IC_{50} = 23.60 ± 0.39 μM), **2** (IC_{50} = 22.70 ± 0.60 μM), **3** (IC_{50} = 22.40 ± 0.32 μM), **4** (IC_{50} = 26.5 ± 0.40 μM), **6** (IC_{50} = 34.60 ± 0.60 μM), **7** (IC_{50} = 26.20 ± 0.43 μM), **8** (IC_{50} = 14.06 ± 0.18 μM), **9** (IC_{50} = 17.60 ± 0.28 μM), **10** (IC_{50} = 27.16 ± 0.41 μM), **11** (IC_{50} = 19.16 ± 0.19 μM), **12** (IC_{50} = 9.06 ± 0.10 μM), **13** (IC_{50} = 12.80 ± 0.21 μM), **14** (IC_{50} = 11.94 ± 0.18 μM), **15** (IC_{50} = 16.90 ± 0.20 μM), **16** (IC_{50} = 12.60 ± 0.14 μM), **17** (IC_{50} = 16.30 ± 0.29 μM), and **18** (IC_{50} = 32.60 ± 0.61 μM) exhibited potent inhibitory potential. Molecular docking study was performed in order to understand the molecular interactions between the molecule and enzyme. Newly identified α-glucosidase inhibitors except few were found to be completely non-toxic.

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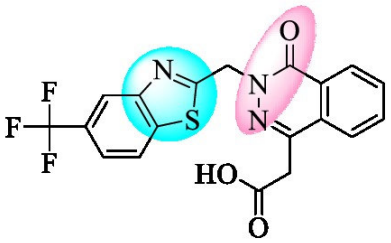
Keywords: Synthesis; thiazole; *in vitro* α-glucosidase; structure-activity relationship; *in silico* study

Introduction

Thiazole or 1,3-thiazole is a five membered azole heterocyclic organic compound [1-2], considered to be aromatic as it follows the Huckel rule [3]. Thiazole and its derivatives emerged as active pharmaceutical ingredients in several drugs for their potential as antiinflammatory [4], anticonvulsant [5], insecticidal [6], antioxidant, antitumour, antihyperlipidemic, antihypertensive, and pesticidal [7]. Thiazole ring has privileged to have industrial applications such as polymers, liquid crystals, photo nucleases, [8] and as fluorescent dyes [9].Diabetes is epidemic disease worldwide and world health organization (WHO) has alarmed that if no proper action will be taken by 2030 there will be at least 350 million people in the world who will suffer with type-2 diabetes mellitus (T2DM) [10]. α-Glucosidase is the key enzyme which catalyzes the final step in the digestion of carbohydrates. The inhibitors of α-glucosidase retard the secretion of D-glucose from the carbohydrate and slower down the absorption of glucose level. Hence, ultimately results in the suppression of postprandial hyperglycemia [11]. Acarbose, voglibose, and miglitol are mainly used for the treatment of type-2 diabetes mellitus. Regrettably, these drugs are 50% less effective than other antidiabetic agents such as metformin and sulfonylurea as well as some side effects are also associated with them such as diarrhea, flatulence and abdominal discomfort (AG, 1994). Therefore, it is restrictive aspect to use the drug alone and often use in combination with other antidiabetic drugs to improve the efficacy. So it is upmost task to develop safer medication for diabetes [12].

Medicinally important molecule Zopolrestat® having thiazole moiety in its core structure is now on clinical use for its effectiveness in diabetic complications [13]. Similarly *N*-(6-substituted-1,3-benzothiazol-2-yl) benzenesulfonamides illustrate promising antidiabetic potential *in vivo* system in a NIDDM (non-insulin-dependent diabetes mellitus) rat model [14] (Figure-1).

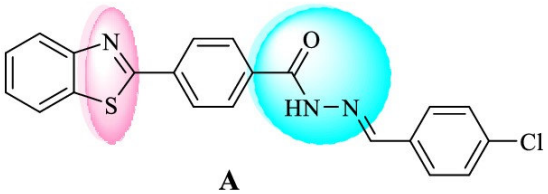


Zopolrestat

N-(6-Substituted-1, 3-benzothiazol-2-yl) benzenesulfonamide

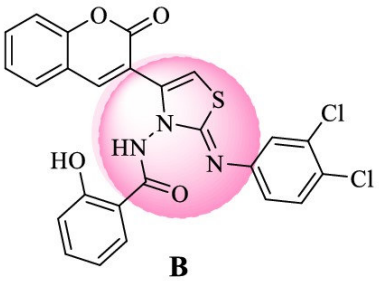
Figure-1: Rationale of the Current Study

Our research aim is mostly dedicated to the syntheses of diverse heterocycles and evaluation of their biological potentials [15-21]. We have evaluated thiazole scaffold (**A** and **B**) as potential *α*-glucosidase inhibitors (Figure-2) [22-24]. For current study, it was thought that new thiazole derivatives with diverse functionalities may produce better *in vitro α*-glucosidase inhibitory effects, therefore a library of new thiazole based molecules **1-24** was synthesized *via* "one pot" two step reaction and screened for *in vitro α*-glucosidase inhibition. To the best of our knowledge, the synthesized compounds are never reported previously.



A

IC_{50} = 5.31 ± 0.03 μM



B

IC_{50} = 0.12 ± 0.01 μM)

Synthetic Derivatives 1-24 (IC_{50} = 9.06 ± 0.10-82.50 ± 1.70 μM)

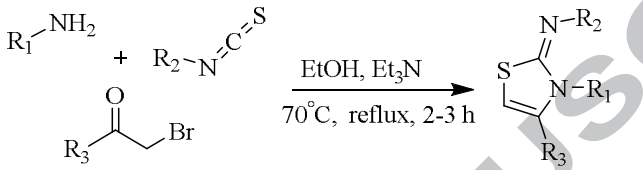
Figure-2: Rationale of the current study

Results and Discussion

Chemistry

New thiazole derivatives **1-24** were synthesized *via* "one pot" multicomponent reaction in

which a variety of aryl hydrazide/phenyl hydrazine/benzophenone hydrazone reacted with aryl isothiocyanate in ethanol to get thiosemicarbazide intermediate within 30 minutes. Triethylamine was used as base. After that phenacyl bromide derivative was added into the same pot to afford new thiazole derivative. Completion of reaction was checked by periodic TLC. Precipitates were obtained into the reaction mixture which were filtered and washed with cold ethanol to obtained pure products in good yield (Scheme-1). The structures of all derivatives **1-24** were confirmed by different spectroscopic techniques such as ^{1}H-NMR, ^{13}C-NMR and EIMS. CHN analysis was also performed.



Scheme-1: Synthetic route for the compounds **1-24**

Table-1: α-Glucosidase inhibitory activities of thiazole derivatives **1-24**

Comp. No.	R_1	R_2	R_3	(IC_{50} ± SEM)[a]
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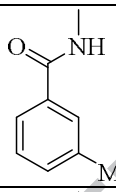
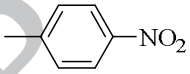
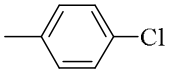
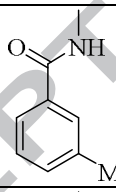
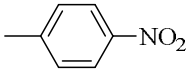
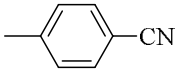
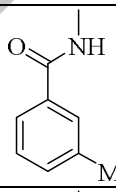
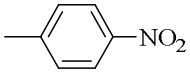
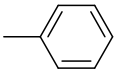
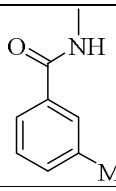
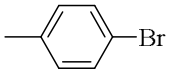
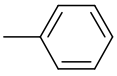
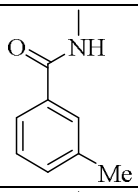
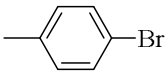
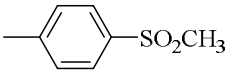
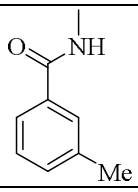
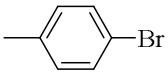
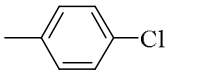
1				23.60 ± 0.39
2				22.70 ± 0.60
3				22.40 ± 0.32
4				26.5 ± 0.40

5				82.50 ± 1.70
6				34.60 ± 0.60
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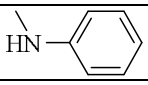
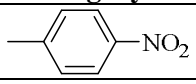
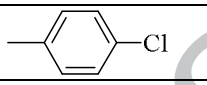
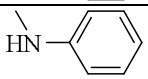
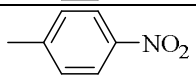
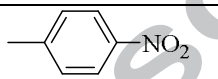
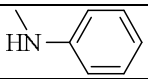
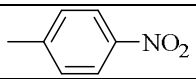
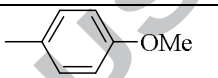
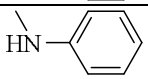
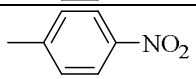
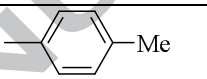
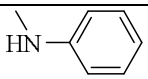
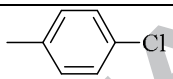
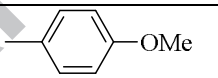
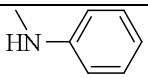
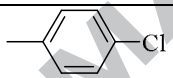
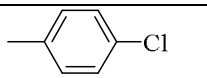
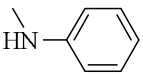
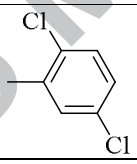
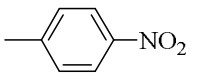
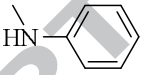
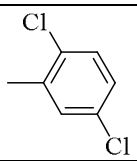
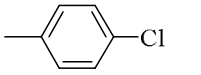
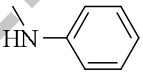
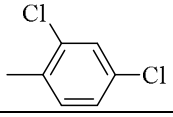
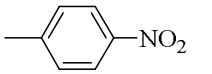
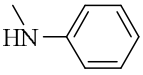
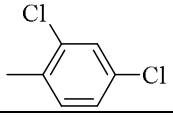
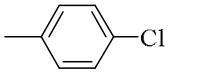
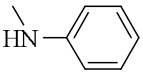
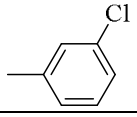
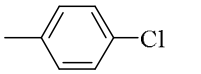
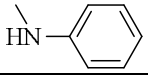
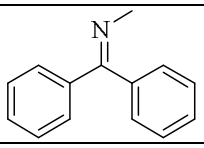
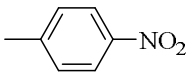
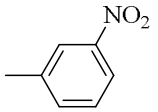
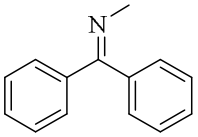
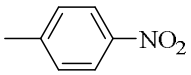
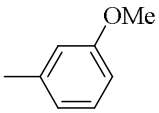
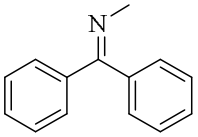
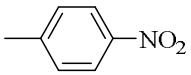
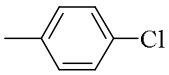
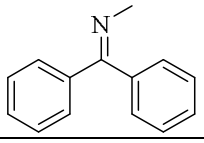
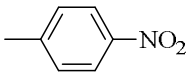
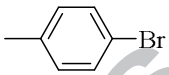
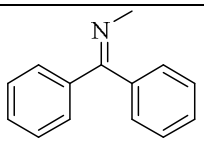
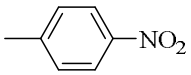
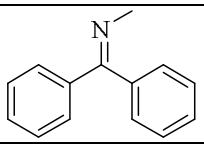
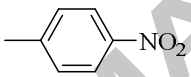
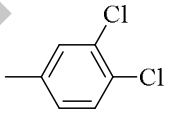
7				26.20 ± 0.43
8				14.06 ± 0.18
9				17.60 ± 0.28
10				27.16 ± 0.41
11				19.16 ± 0.19
12				9.46 ± 0.10
13				12.80 ± 0.21
14				11.94 ± 0.18
15				16.90 ± 0.20
16				12.60 ± 0.14
17				16.30 ± 0.29
18				32.60 ± 0.61
Category "C"				

19				48.80 ± 0.60
20				50.10 ± 0.71
21				72.10 ± 1.01
22				72.40 ± 1.19
23				46.50 ± 0.50
24				49.50 ± 0.59
Standard = Acarbose[b]				38.25 ± 0.12

SEM[a]: standard error of mean; Acarbose[b]: Standard Inhibitor for α-Glucosidase.

Stereochemical assignment of iminic double bond by NOESY

***Z*-Isomer** ***E*-Isomer**

Figure-3: Possible isomers of products

There is possibility of two isomers either (*Z*) or (*E*) (Figure-3) in the result of reaction but ^{1}H-NMR spectra of all synthetic compounds displayed the formation of single isomer. However, nuclear Overhauser enhancement spectroscopy (NOESY) was performed on one of the synthesized compounds (compound **2**) for confirming the stereochemistry of the iminic double bond. Out of many NOESY interactions, some confirmed the (*Z*) stereochemistry of the iminic bond. Strong NOESY interactions between H-5′ and H-6′ with H-5 showed that these rings of the molecule are close in space. Whereas, absence of any distinctive NOESY interaction of H-2″and H-3″ with H-2‴ and 3‴showed that these two rings are not close

enough to show NOESY interactions. These evidences showed the *Z* stereochemistry of the iminic double bond in compounds (Figure-3a).

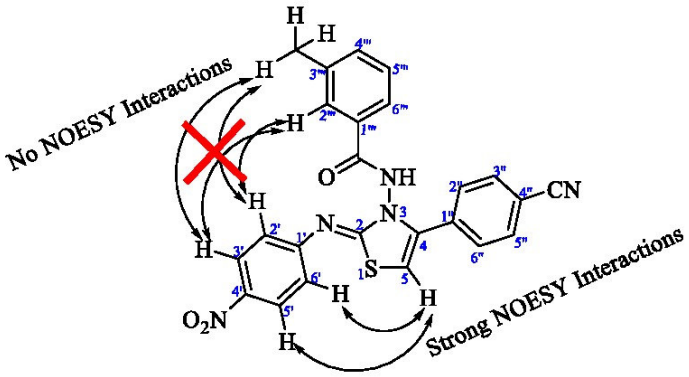


Figure-3a: NOESY interactions between protons of compound 9

Furthermore, the formation of *E* isomer is not favorable as rings R_1 and R_2 are much closed to create steric hindrance which brings out the instability in the molecule. However, in case of *Z*-isomer, rings R_1 and R_2 are very far apart and free from any steric hindrance. Figure-3b clearly showed that the formation of stable *Z*-isomer is more favorable as compare to unstable *E*-isomer.

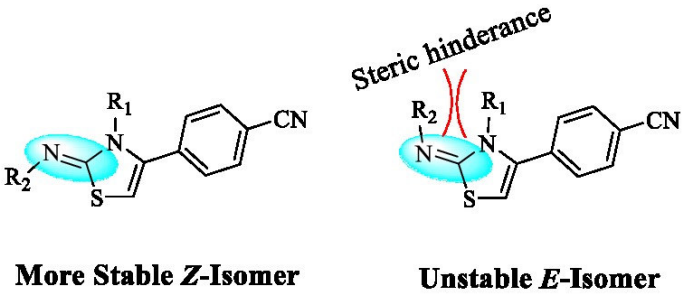


Figure-3b: Comparison of stability of E- and Z-isomer

α-Glucosidase inhibitory activity

All synthetic compounds were evaluated for their *in vitro* *α*-glucosidase inhibitory activities. Activity results (Table-1) showed that all derivatives found to have activity in the range of IC_{50} = 9.06 ± 0.10-82.50 ± 1.70 *μ*M as compared to standard acarbose (IC_{50} = 38.25 ± 0.12 *μ*M). It is worth mentioning that except compounds **5**, **19**, **20**, **21**, **22**, **23** and **24**, all

derivatives were showed superior activities than standard acarbose. All structural feature such as thiazole ring, amide linkage, amine linkage and arene moieties are seemingly played a crucial role in exhibiting the activity. However, limited structure-activity relationship (SAR) was established by looking at the substitution pattern at R_1, R_2 and R_3. For that purpose, all compounds were divided into three categories "A", "B" and "C". Category "A" comprised of compounds having benzamide group as R_1, category "B" having aniline moiety as R_1 and category "C" consist of molecules having diphenyl methanimine group as R_1.

Compound **12** (IC_{50} = 9.06 ± 0.10 μM) belongs to category "B" and has *para* chloro substitutions at R_2 and R_3, respectively. It was found to be the most potent analog of this series and fourfold more active than the standard acarbose. Comparison of its activity with its structurally similar compounds revealed that compound **17** (IC_{50} = 16.30 ± 0.29 μM) which has *meta* chloro substitution at R_2 instead of *para*, a slight decline in the activity observed. Similarly, compounds having three chloro substitutions such as **14** (IC_{50} = 11.94 ± 0.18 μM) and **16** (IC_{50} = 12.60 ± 0.14 μM) also showed excellent activity like compounds having two chloro substituents in structure as shown in figure-4. Another compound **13** (IC_{50} = 12.80 ± 0.21 μM) which has *para* nitro group instead of chloro at R_3, showed lesser activity than **14**. Similar pattern was observed in case of **15** (IC_{50} = 16.90 ± 0.20 μM) which also has distinctly similar structure as **16** but only nitro group instead of chloro at R_3, a decline in the activity was noticed. Activity of compound **11** (IC_{50} = 19.16 ± 0.19 μM), having *para* methoxy group instead of chloro, can compare with the most active compound **12** almost twice decline in the inhibitory activity experienced (Figure-4). The above activity pattern showed that chloro group is playing a crucial role in the activity.

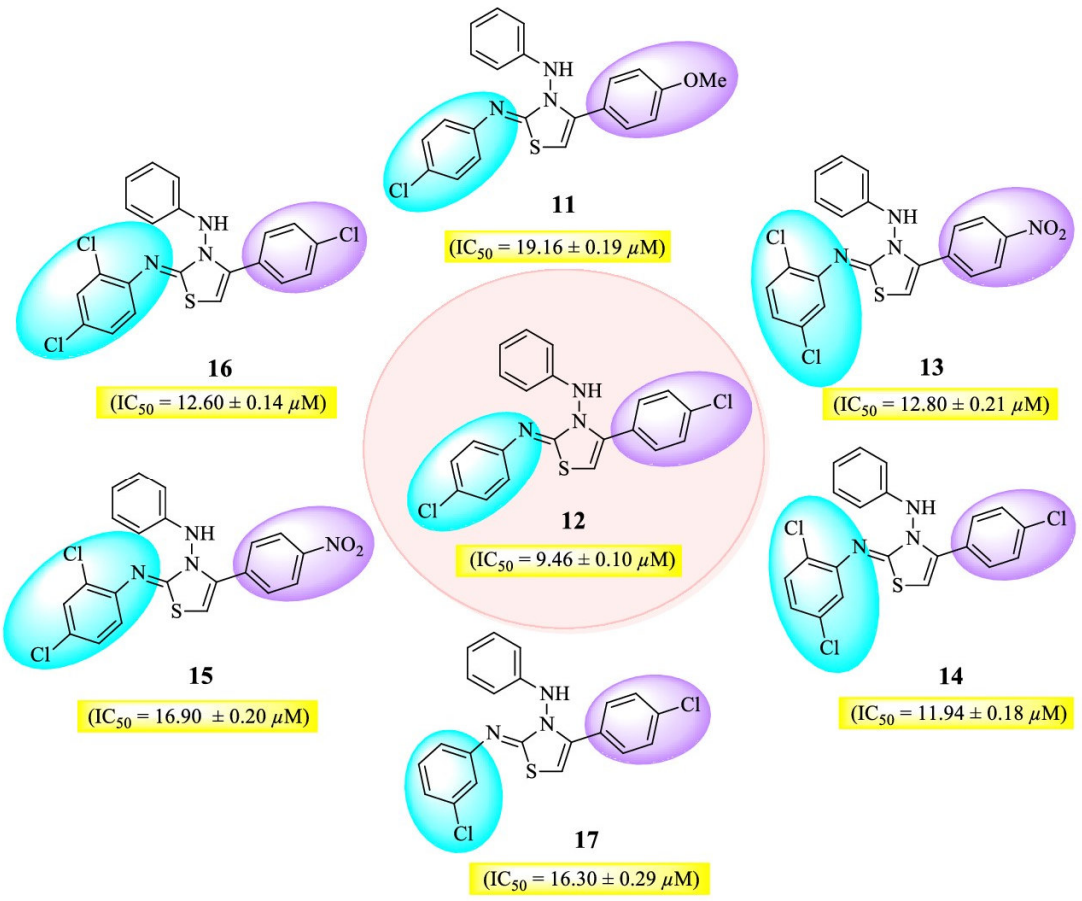


Figure-4: Comparison of structure-activity relationship of compound **12** with **11** and **13**-**17**.

Another compound **8** (IC_{50} = 14.06 ± 0.18 μM) from category "B" having *para* nitro group at R_2 and R_3, also found to be potent analog. On comparison of its activity with compounds such as **9**, **7** and **10** those have methoxy, chloro and methyl groups at R_3, respectively, decline in the activity from nitro to methoxy, methoxy to chloro and chloro to methyl group was observed (Figure-5). But still these are potent analogs with much better activity than the standard.

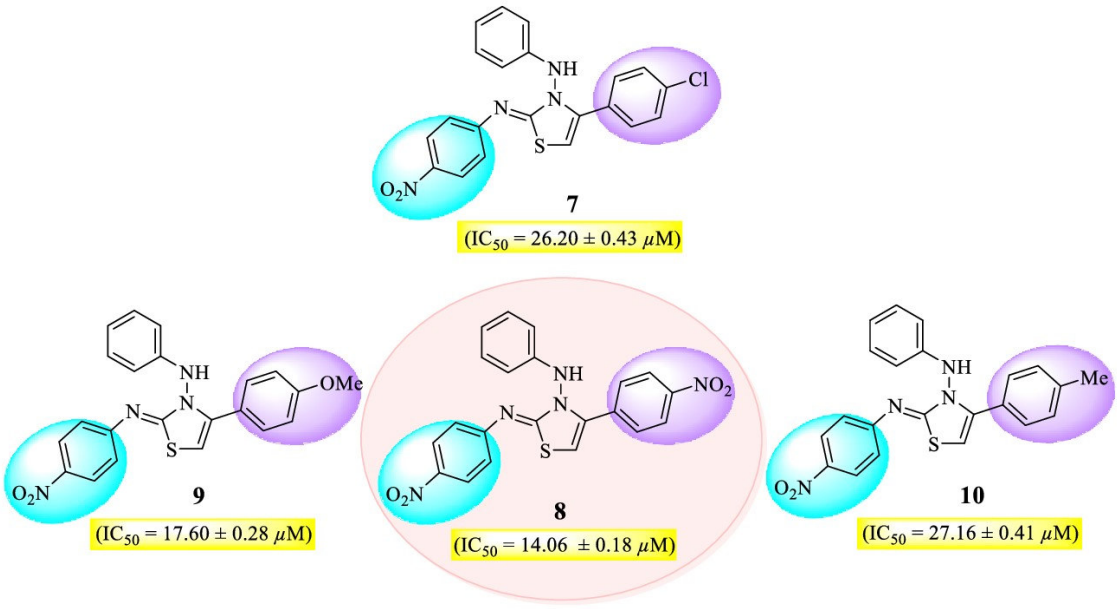


Figure-5: Comparison of structure-activity relationship of compound **8** with **7**, **9**, and **10**.

In case of category "A", compounds **1** (IC_{50} = 23.60 ± 0.39 μM) having *para* chloro group, **2** (IC_{50} = 22.70 ± 0.60 μM) having *para* cyano group and **3** (IC_{50} = 22.40 ± 0.32 μM) has no substitution at R_3, although rest of the structure is same. Interestingly, all thee derivatives showed almost similar activity (Figure-6).

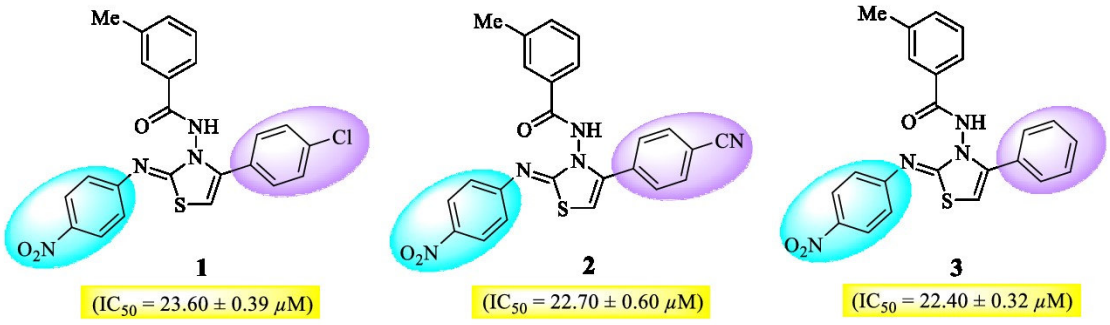


Figure-6: Comparison of structure-activity relationship of compounds **1**, **2**, and **3**.

Activity of other three derivatives such as **4** (IC_{50} = 26.5 ± 0.40μM), **5** (IC_{50} = 82.50 ± 1.70 μM) and **6** (IC_{50} = 34.60 ± 0.60 μM) was different from each other. However, the structure of all three is very similar to each other but only differ at R_3. Compounds **4** have no substitution at R_3, while **5** and **6** have *para* methane sulphonyl and *para* chloro group, respectively. Comparison of activity pattern of all three derivatives revealed that methane sulphonyl group in compound **5** caused major decline in the activity (Figure-7).

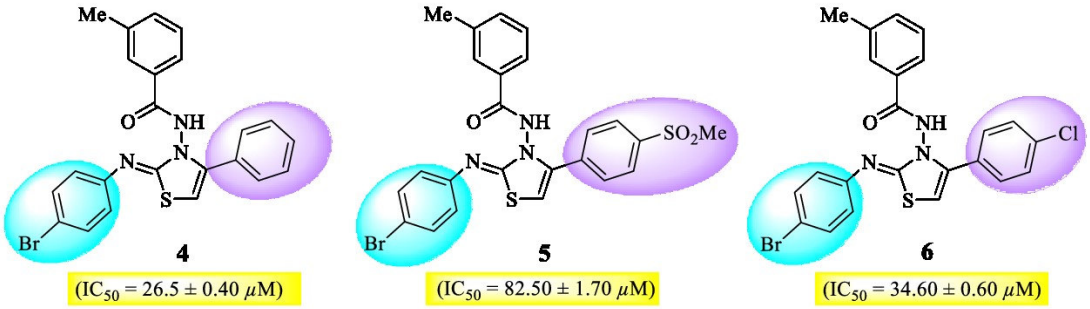


Figure-7: Comparison of structure-activity relationship of compounds **4**, **5**, and **6**.

Activity pattern of category "C" which has diphenyl methanimine group as R_1 showed that this category demonstrated comparatively decreased activity than category "A" and "B". Amongst compound **19**-**24**, compound **20** which differ with rest of the derivatives only by the substitution at R_3, where it has *para* methoxy group (Figure-8).

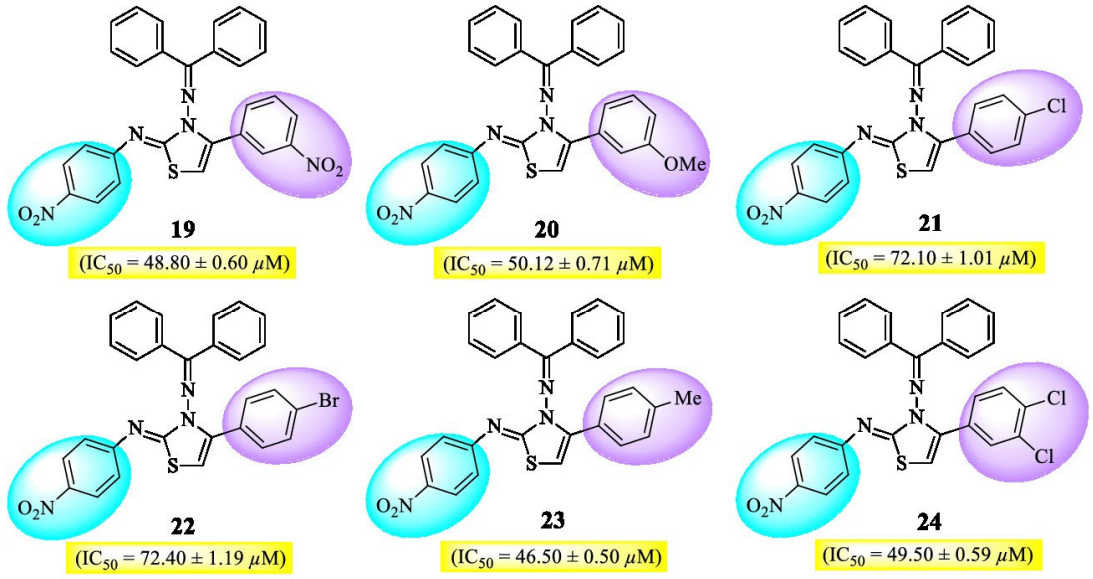


Figure-8: Comparison of structure-activity relationship of compounds **19-24**.

In order to get insights regarding the molecular interaction of these derivatives with the active site of the enzyme, molecular docking study was performed. A plausible demonstration is given below.

Molecular docking

Docking study was carried out by using MOE (Molecular Operating Environment) software package. The docking results showed that all compounds were well accommodated in the binding pocket of *α*-glucosidase. The docking conformation of most active compound **12** (IC_{50} = 9.06 ± 0.10 *μ*M) with chlorine group at *para* position of phenyl ring showed good

interaction network as well as good docking score (-11.8617). Compound **12** made two π-interactions at the binding pocket. Phe157 made arene-arene interaction with aniline moiety and Phe300 with chlorobenzene group (**Figure-9a**). When chlorine group present at *meta* position of the phenyl ring in compound **17** (IC_{50} = 16.30 ± 0.29 μM) showed less biological activity as well as low docking score (-9.9130). The docking conformation of compound **17** showed an arene-arene and arene-cation interaction between the chloro benzene rings of compound with Phe157 and Arg312 of the enzyme (**Figure-9b**). Compound **16** (IC_{50} = 12.60 ± 0.14 μM) having an extra chlorine group at *ortho* position as compared to the compound **12**, showed two arene-arene interaction between chlorophenyl and dichlorophenyl ring of the compound with His239 and Phe157 of the enzyme, respectively (**Figure-9c**). These three chlorobenzene containing compounds with different positions and numbers showed almost similar behavior regarding interactions but their docking scores showed their fitness in the binding pocket of enzyme, well correlated with their biological activities. In case of compound **7** (IC_{50} = 26.20 ± 0.43 μM), where one chlorine group is replaced with nitro (NO_2) group as compared to compound **12** and **17**, established an arene-cation interaction between chlorobenzene ring of the compound with Arg312 of the enzyme (**Figure-9d**). The substitution of nitro (NO_2) group resulted in decreased docking score (-9.8135) and binding interactions along with IC_{50} value as compared to compounds **16**, **12**, and **17**. This reduced inhibition potency might be due to the deactivating nature of nitro group by electron withdrawing inductive effect and resonance.

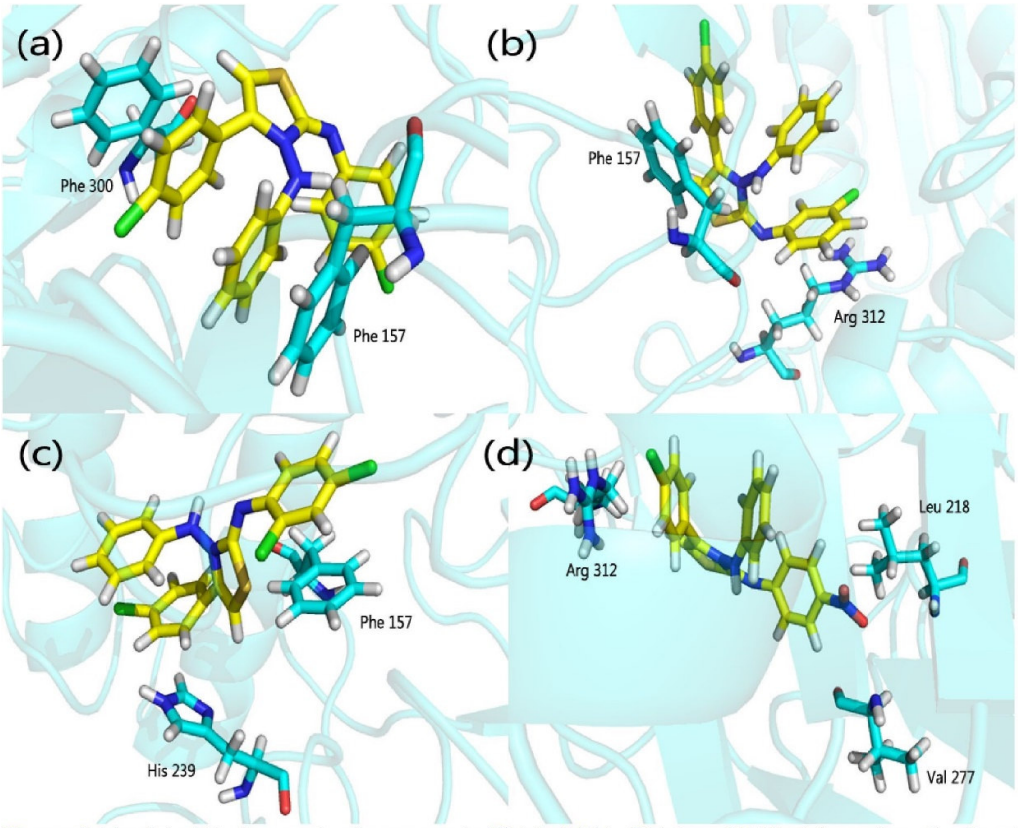


Figure-9: Predicted binding mode of compounds **12** (a), **17** (b), **16** (c), and **7** (d) at the active site of *α*-glucosidase.

In case of compounds containing methyl substituted benzamide ring **1**-**6**, the docking conformation of compound **1** (IC_{50} = 23.60 ± 0.39 μM) with a docking score (-12.5054) established good interactions with the active side residues Asn241, His279, and Phe157. Asn241 was observed to make hydrogen bond with the oxygen atom of 3-methyl benzamide moiety of the compound **1**, while His-279 and Phe-157 makes arene-cation and arene-arene interactions with the methyl and chlorobenzene moieties of the compound, respectively (**Figure**-**10a**). Compounds **3** and **4** also showed almost similar mode. In case of compound **5** (IC_{50} = 82.50 ± 1.70 μM) with a docking score of -9.9758 displayed only one arene-arene interaction between His239 and chloro substituted phenyl ring of the compound (**Figure**-**10b**). In this series of methyl substituted benzamide ring containing compounds which has an electron donating inductive effect by methyl group, it was observed that compounds **1**-**4** and **6**, in which inductively electron withdrawing groups (NO_2, CN, Br, Cl) at the two ends of the molecule were presents, showed good and almost similar docking results. Moreover, their biological activities were also found in close range. Whereas in compound **5**, addition of electron rich species methane sulfonyl group at one end of the molecule resulted in reduced docking score and interactions.

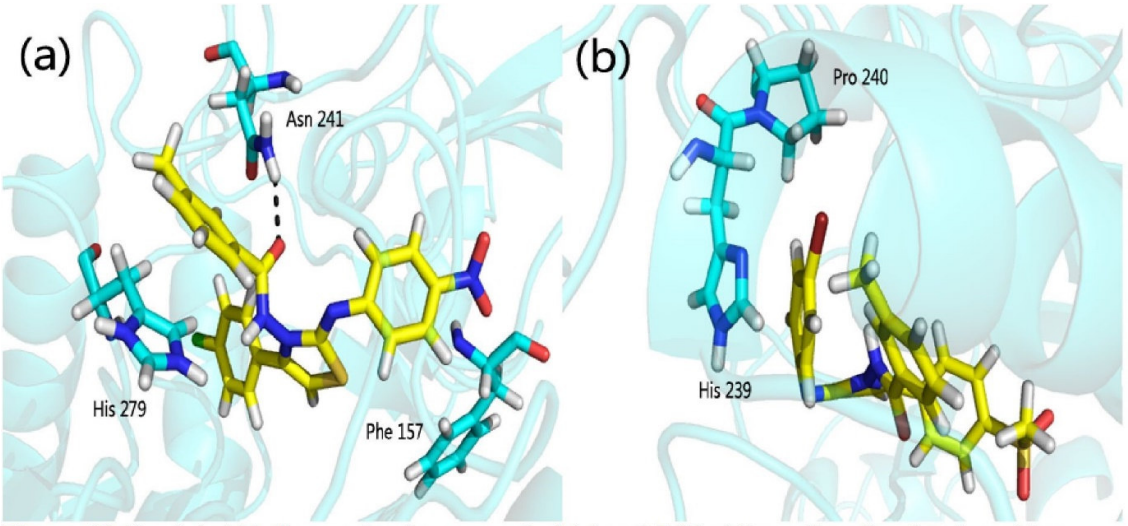


Figure-10: Predicted binding mode of compounds **1** (a) and **5** (b) at the active site of *α*-glucosidase.

In case of diphenyl methanimine containing compounds **19**-**24**, it was observed that halogen containing compounds showed somewhat poor computational inhibition. In case of compound **20** (IC_{50} = 42.90 ± 0.71 μM) with a docking score (-13.6348) showed a hydrogen bond interaction between the oxygen atom of methoxy group with Tyr313 and arene-cation interaction of Arg312 with the benzene moiety of the compound (**Figure-11a**). Whereas, in case of compound **22** (IC_{50} = 72.40 ± 1.19 μM) with a docking score (-12.303) was observed to show a single arene-cation interaction (**Figure-11b**)

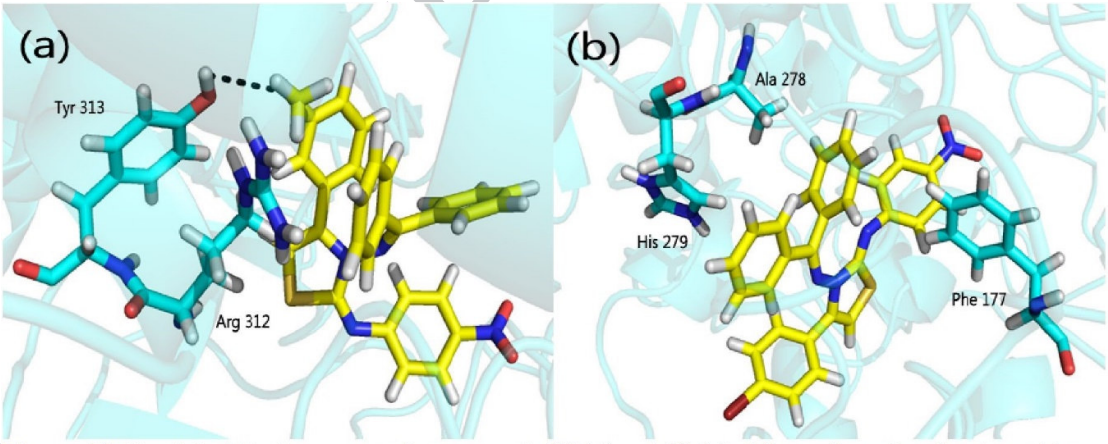


Figure-11: Predicted binding mode of compounds **20** (a) and **22** (b) at the active site of *α*-glucosidase.

In Vitro Cytotoxicity

Finally, thiazoles derivatives with *α*-glucosidase inhibitory activities were subjected for cytotoxicity evaluation. Compound **2**, **8**, and **19** showed a moderate toxicity towards 3T3 mouse fibroblast cell line. All other compounds were found to be non-toxic.

Table-2: *In Vitro* cytotoxicity of thiazole derivatives **1-24**

Comp. No.	(IC_{50} ± SEM)[a]	Comp. No.	(IC_{50} ± SEM)[a]	Comp. No.	(IC_{50} ± SEM)[a]
1	NT[c]	**9**	NT[c]	**17**	NT[c]
2	30.55 ± 0.09	**10**	NT[c]	**18**	NT[c]
3	NT[c]	**11**	NT[c]	**19**	23.82 ± 0.43
4	NT[c]	**12**	NT[c]	**20**	NT[c]
5	NT[c]	**13**	NT[c]	**21**	NT[c]
6	NT[c]	**14**	NT[c]	**22**	NT[c]
7	NT[c]	**15**	>30	**23**	NT[c]
8	27.03 ± 0.14	**16**	NT[c]	**24**	NT[c]
Cycloheximide[c]				0.26 ± 0.1 μM	

Non Toxic (NT[c]); Cycloheximide[c] (Standard inhibitor for cytotoxicity)

Conclusion

Newly synthesized thiazoles were showed *in vitro* α-glucosidase inhibitory activities in the range of IC_{50} = 9.06 ± 0.10-82.50 ± 1.70 μM compared to standard acarbose (IC_{50} = 38.25 ± 0.12 μM). Except compounds **5**, **19**, **20**, **21**, **22**, **23** and **24**, all compounds were found to be potent. Molecular docking studies were carried out in order to understand the binding interactions of all compounds. From this study compounds **1**-**4** and **6**-**18** were identified as lead molecules. Further research on these non-toxic molecules may result powerful α-glucosidase inhibitors.

Experimental

Materials and Methods

Analytical grade reagents and solvents were purchased from Sigma-Aldrich and used as received. Thin layer chromatography was performed on pre-coated 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 spectrometer. The ^{1}H- and ^{13}C-NMR were recorded on Bruker AM spectrometer, operating at 300, 400 and 500 MHz instruments. The chemical shift values are presented in ppm (δ), relative to tetramethylsilane (TMS) as an internal standard and the coupling constant (J) are in Hz. CHN analysis was performed on a Carlo Erba Strumentazion-Mod-1106, Italy.

General Experimental Procedure for the Syntheses of Thiazole derivatives 1-24

Benzohydrazide derivative/phenyl hydrazine/benzophenone hydrazone (1 mmol), phenyl isothiocyanate derivative (1 mmol) were taken in ethanol (10 mL) into a 100 mL round-bottomed flask and refluxed for half an hour. Than phenacyl bromide derivatives (1 mmol)

and trimethylamine (1 mmol) were added into above mixture and further refluxed for 3 h. TLC was taken in order to check the reaction progress. Precipitates were formed which were filtered and washed with cold ethanol (10 mL) to afford pure products in high yields.

***In Vitro* α-Glucosidase Inhibition Assay**

The inhibitory activities of all the thiazole derivatives were measured by using the methods similar to those described previously [25-27]. Typically, α-glucosidase activity was assayed in 50 mM phosphate buffer (pH 6.8) containing 5% v/v dimethyl sulfoxide and PNP glycoside was used as a substrate. The inhibitors were pre-incubated with enzyme at 37 $^{\circ}$C for 0.5 h. The substrate was then added and enzymatic reaction was carried out at 37 $^{\circ}$C for 60 min. The reaction was monitored spectrophotometrically by measuring the absorbance at 400 nm. All experiments were carried out in triplicates. The percent inhibition was calculated by the following equation:

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

Active compound solutions were suitably diluted and their inhibition studies were determined. Data obtained was used for the determination of IC_{50} values (concentration at which there is 50% enzyme inhibition) using Microsoft Excel word (2010) (Figure-12).

Representative graph for calculating IC_{50} values

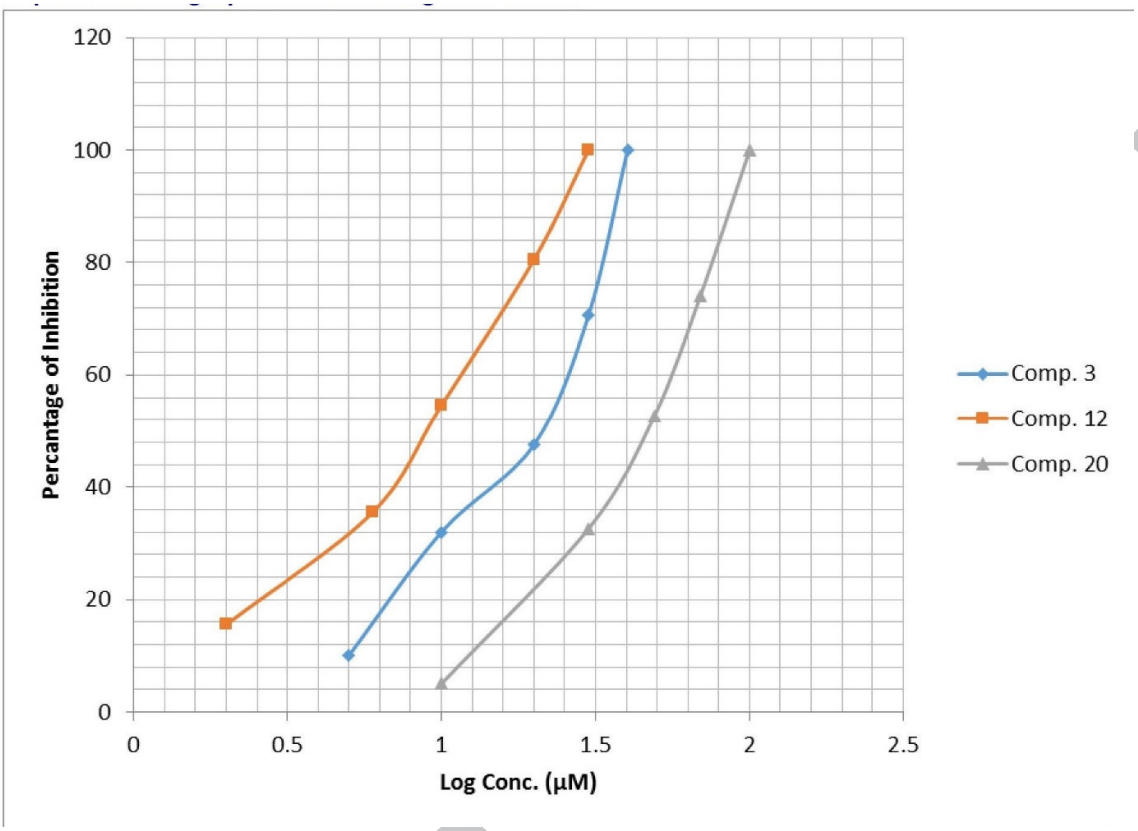


Figure-12: α-Glucosidase inhibitory effect of compound **3**, **12**, and **20**

Molecular Docking

Protein-ligand docking study on thiazole analogs was carried out against the active site of α-glucosidase enzyme to understand the ligand-enzyme interactions using molecular operating environment (MOE) software, version 2011. The X-ray crystal structures of a few bacterial α-glucosidase have been reported. However, the 3D structure of α-glucosidase used in biological assays from yeast has never been reported [28]. To find a proper structural template for homology modeling, we searched for the protein data bank (PDB) from the protein sequence data bank (http://www.ncbi.nlm.nih.gov/protein/). The crystallographic structure of *Saccharomyces cerevisiae* isomaltase (PDB code 3AJ7; Resolution 1.30 Å) with 72.4% of sequence identity with the target was selected as a template [29]. The 3D structure of α-glucosidase for *Saccharomyces cerevisiae* was predicted using MOE homology modeling tools. The predicted model was then subjected to energy minimization up to 0.05 gradients. The 3D structures of these newly synthesized compounds were built using MOE-builder module program implemented in MOE and save as a (mdb) file for molecular

docking. Subsequently, the energy of all compounds was minimized up to 0.05 gradient using MMFF 94x force field. Energy minimization of all compounds was followed by the preparation of protein for docking purposes. All the synthesized compounds was docked into the active site of protein using the triangular matching docking method. The complex was analyzed for interactions and their 3D images were taken by using visualizing tool PyMol.

3T3 Cell based (mouse Fibroblast) cytotoxicity assay

Standard MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-dimethyltetrazolium bromide) colorimetric assay was used to evaluate the cytotoxicity of thiazoles derivatives with α-glucosidase inhibitory activities, in 96-well flat-bottomed microplates. 3T3 Cells (mouse fibroblasts) in Dulbecco's modified eagle's medium was cultured for this purpose, supplemented with streptomycin, penicillin, and 5% fetal bovine serum (FBS) by using a flask placed in a 5% CO_2 incubator at 37 ^{0}C. The growth of cells was harvested exponentially by using hemocytometer, the harvested cells was counted and in a particular medium was diluted. Cell cultures was prepared with a required concentration and plated onto 96-well plates. After overnight incubation, medium was removed and fresh medium was added with different concentrations of the compound. After 72 h, MTT was added to each well and incubation was continued for 4 h. Subsequently, 100 μL of DMSO was added to each well to solubilize formazan-MTT adduct, formed by the action of enzyme mitochondrial dehydrogenase. The extent of MTT reduction to formazan within cells was calculated by measuring the absorbance at 540 nm by using a microplate ELISA reader [30].

***N*-(4-(4-Chlorophenyl)-2-((4-nitrophenyl)imino)thiazol-3(2*H*)-yl)-3-methylbenzamide (1)**

Yield: 89%; M.P.: 220-222 $^{\circ}$C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.54 (s, 1H, NH), 8.31 (d, $J_{6''',5'''}$ = 9.3 Hz, 1H, H-6‴), 8.27 (d, $J_{3',2'} = J_{5',6'}$ = 8.7 Hz, 1H, H-3′, H-5′), 7.83 (m, 3H, H-2‴, H-5‴, H-6‴), 7.57 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.18 (d, $J_{2',3'} = J_{6',5'}$ = 9.0 Hz, 2H, H-2′, H-6′), 6.72 (s, 1H, H-5), 2.34 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ165.7, 156.1, 138.2, 138.1, 134.0, 133.2, 131.9, 131.1, 129.4, 129.4, 128.7, 128.7, 128.6, 127.9, 127.9, 125. 5, 125.5, 124.5, 121.5, 121.5, 116.8, 96.2, 20.8; EI MS: *m/z* (rel. abund. %) 464 (M^+,77), 466 (M^++2, 32), 296 (100); Anal. Calcd for $C_{23}H_{17}ClN_4O_3S$, C = 59.42, H = 3.69, N = 12.05; Found C = 59.45, H = 3.67, N = 12.08; IR (KBr, cm^{-1}): 3590 (amidic-NH), 1670 (C=O), 1620, 1590, 1565 (C=C, Aromatic), 1545, 1395 (NO_2).

***N*-(4-(4-Cyanophenyl)-2-(4-nitrophenylimino)thiazol-3(2*H*)-yl)-3-methylbenzamide (2)**

Yield: 69%; M.P.: 230-232 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.18 (m, 3H, H-3′, H-5′, H-2″), 8.06 (d, $J_{6'',5''}$ = 8.4Hz, 1H, H-6″), 7.94 (m, 4H, H-3‴, H-5‴, H-4′), 7.57 (m, 2H, H-5, H-5″), 7.32 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 8.1Hz, 2H, H-2‴, H-6‴), 7.10 (d, $J_{2',3'} = J_{6',5'}$ = 9Hz, 2H, H-2′, H-6′), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.7, 161.8, 158.4, 155.2, 146.5, 138.7, 138.6, 134.2, 132.5, 132.0, 132.0, 131.5, 128.0, 127.2, 127.2, 125.3, 125.3, 124.7, 123.0, 123.0, 111.7, 108.4, 21.2; EI MS: *m/z* (rel. abund. %)) 455 (M^+, 2), 296 (95), 159 (100); Anal. Calcd for $C_{24}H_{17}N_5O_3S$, C = 63.29, H = 3.76, N = 15.38; Found C = 63.26, H = 3.73, N = 15.40; IR (KBr, cm^{-1}): 3605 (amidic-NH), 2255 (CN), 1670 (C=O), 1634, 1596, 1575 (C=C, Aromatic), 1557, 1418 (NO_2).

3-Methyl-*N*-(2-(4-nitrophenylimino)-4-phenylthiazol-3(2*H*)-yl)benzamide (3)

Yield: 74%; M.P.: 285-287 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.53 (s, 1H, NH), 8.29 (d, $J_{3',2'} = J_{5',6'} = J_{2'',3''} = J_{6'',5''}$ = 9.3 Hz, 4H, H-3′, H-5′, H-2″, H-6″), 7.82 (d, $J_{2',3'} = J_{6',5'} = J_{6''',5'''}$ = 9.3 Hz, 3H, H-2′, H-6′, H-6‴), 7.73 (m, 3H, H-5, H-2‴, H-4‴), 7.49 (t, $J_{3'',2''/3'',4''} = J_{5'',6''/5'',4''}$ = 7.5 Hz, 2H, H-3″, H-5″), 7.41 (t, $J_{4'',3''/4'',5''} = J_{5''',4'''/5''',6'''}$ = 7.5 Hz, 2H, H-4″, H-5‴), 2.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.9, 161.7, 158.5, 155.0, 146.5, 138.4, 134.2, 134.0, 132.3, 131.5, 128.7, 128.7, 128.4, 128.4, 128.2, 127.7, 125.0, 125.0, 124.6, 123.3, 123.3, 108.4, 21.4; EI MS: *m/z* (rel. abund. %) 430 (M^+, 2), 296 (100), 159 (92); Anal. Calcd for $C_{23}H_{18}N_4O_3S$, C = 64.17, H = 4.21, N = 13.02; Found C = 64.15, H = 4.24, N = 13.05.

***N*-(2-(4-Bromophenylimino)-4-phenylthiazol-3(2*H*)-yl)-3-methylbenzamide (4)**

Yield: 78%; M.P.: 265-267 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.84 (s, 1H, NH), 7.71 (s, 1H, H-2‴), 7.69 (d, $J_{2'',3''} = J_{6'',5''}$ = 7.5 Hz, 2H, H-2″, H-6″), 7.59 (m, 5H, H-2′, H-3′, H-5′, H-6′, H-5‴), 7.48 (t, $J_{3'',2''/3'',4''} = J_{5'',4''/5'',6''} = J_{4'',3''/4'',5''}$ = 7.5 Hz, 3H, H-3″, H-4″, H-5″), 7.39 (m, 2H, H-4‴, H-6‴), 2.39 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.7, 161.9, 160.6, 158.5, 148.1, 138.3, 135.3, 134.0, 132.7, 132.7, 132.5, 131.5, 129.7, 128.2, 124.6, 122.7, 122.7, 121.5, 120.5, 113.6, 110.6, 108.2, 55.6, 21.4; EI MS: *m/z* (rel. abund. %) 329 (69), 194 (28), 159 (100); Anal. Calcd for $C_{24}H_{20}BrN_3O_2S$, C = 58.30, H = 4.08, N = 8.50; Found C = 58.33, H = 4.05, N = 8.52.

_N_-(2-(4-Bromophenylimino)-4-(4-(methylsulfonyl)phenyl)thiazol-3(2_H_)-yl)-3-methylbenzamide (5)

Yield: 85%; M.P.: 235-237 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.17 (s, 1H, NH), 8.00 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.59 (s, 1H, H-2‴), 7.56 (d, $J_{6‴,5‴}$ = 7.2 Hz, 1H, H-6‴), 7.48 (d, $J_{3′,2′/5′,6′}$ = 8.7 Hz, 2H, H-3′, H-5′), 7.33 (m, 2H, H-4‴, H-5‴), 7.21 (s, 1H, H-5), 6.85 (d, $J_{2′,3′} = J_{6′,5′}$ = 9.0 Hz, 2H, H-2′, H-6′), 3.21 (s, 3H, $SO_2\underline{CH_3}$), 2.29 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ164.7, 161.8, 158.4, 148.1, 140.3, 139.3, 138.6, 134.0, 132.7, 132.7, 132.3, 131.5, 128.3, 128.3, 128.2, 127.5, 127.5, 124.6, 122.9, 122.9, 121.5, 108.4, 47.8, 21.2; EI MS: *m/z* (rel. abund. %) 541 (M^+, 1.8), 543 (M^++2, 2), 331 (100), 183 (100); Anal. Calcd for $C_{24}H_{20}BrN_3O_3S_2$, C = 53.14, H = 3.72, N = 7.75; Found C = 53.16, H = 3.75, N = 7.72.

_N_-(2-(4-Bromophenylimino)-4-(4-chlorophenyl)thiazol-3(2_H_)-yl)-3-methylbenzamide (6)

Yield: 81%; M.P.: 200-202 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.71 (d, $J_{3″,2″} = J_{5″,6″}$ = 8.4 Hz, 2H, H-3″, H-5″), 7.55 (s, 1H, H-2‴), 7.52 (d, $J_{6‴,5‴}$ = 7.5 Hz, 1H, H-6‴), 7.45 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.31 (m, 2H, H-4‴, H-5‴), 7.00 (s, 1H, H-5), 6.82 (d, $J_{2″,3″} = J_{6″,5″}$ = 8.7 Hz, 2H, H-2″, H-6″), 2.27 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ155.6, 152.5, 148.1, 147.1, 143.8, 143.0, 140.0, 128.7, 128.7, 127.6, 127.6, 127.0, 126.4, 126.4, 124.8, 124.8, 123.9, 123.9, 122.2, 122.2, 23.1; EI MS: *m/z* (rel. abund. %) 497 (M^+, 1.3), 499 (M^++2, 1.4), 329 (100), 331 (100); Anal. Calcd for $C_{23}H_{17}BrClN_3OS$, C = 55.38, H = 3.44, N = 8.42; Found C = 55.36, H = 3.42, N = 8.44.

4-(4-Chlorophenyl)-2-(4-nitrophenylimino)-_N_-phenylthiazol-3(2_H_)-amine (7)

Yield: 79%; M.P.: 190-192 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, $J_{3′,2′} = J_{5′,6′}$ = 8.7 Hz, 2H, H-3′, H-5′), 7.91 (d, $J_{2′,3′} = J_{6′,5′}$ = 8.7 Hz, 2H, H-2′, H-6′), 7.64 (d, $J_{3″,2″} = J_{5″,6″}$ = 7.5 Hz, 2H, H-3″, H-5″), 7.57 (d, $J_{2″,3″} = J_{6″,5″}$ = 8.4 Hz, 2H, H-2″, H-6″), 7.48 (t, $J_{3‴,2‴/3‴,4‴} = J_{5‴,4‴/5‴,6‴}$ = 7.5 Hz, 2H, H-3‴, H-5‴), 7.33 (m, 2H, H-4‴, H-5), 7.03 (d, $J_{2‴,3‴} = J_{6‴,5‴}$ = 9.0 Hz, 2H, H-2‴, H-6‴), 4.29 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 158.2, 155.0, 147.0, 146.5, 133.6, 132.4, 129.4, 129.4, 128.8, 128.8, 125.3, 125.3, 123.1, 123.1, 122.9, 120.4, 120.4, 113.3, 113.3, 108.2l; EI MS: *m/z* (rel. abund. %) 422 (M^+, 1), 137 (72), 105 (100); Anal. Calcd for $C_{21}H_{15}ClN_4O_2S$, C = 59.65, H = 3.58, N = 13.25; Found C = 59.63, H = 3.60, N = 13.23; IR (KBr, cm^{-1}): 3586 (amidic-NH), 1675 (C=O), 1632, 1587, 1570 (C=C, Aromatic), 1561, 1402 (NO_2).

4-(4-Nitrophenyl)-2-(4-nitrophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (8)

Yield: 84%; M.P.: 200-202 °C; ^{1}H NMR (300M Hz, DMSO-d_6): δ 8.33 (d, $J_{3'',2''} = J_{5'',6''} = 8.7$ Hz, 2H, H-3″, H-5″), 8.18 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.66 (d, $J_{2''',3'''} = J_{6''',5'''} = 7.5$ Hz, 2H, H-2‴, H-6‴), 7.51 (t, $J_{3''',2'''} = J_{5''',6'''} = 7.5$ Hz, 2H, H-3‴, H-5‴), 7.36 (m, 2H, H-4‴, H-5), 7.05 (d, $J_{2'',3''} = J_{6'',5''} = 9$ Hz, 2H, H-2″, H-6″), 4.33 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 155.0, 147.2, 147.1, 146.3, 140.1, 129.3, 129.3, 126.7, 126.7, 125.1, 125.1, 123.4, 123.4, 123.3, 123.3, 122.7, 113.1, 113.1, 108.1; EI MS: *m/z* (rel. abund. %) 433 (M^+, 8), 285 (24), 105 (100); Anal. Calcd for $C_{21}H_{15}N_5O_4S$, C = 58.19, H = 3.49, N = 16.16; Found C = 58.17, H = 3.46, N = 16.18.

4-(4-Methoxyphenyl)-2-(4-nitrophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (9)

Yield: 73%; M.P.: 187-189 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, $J_{3',2'} = J_{5',6'} = 9$ Hz, 2H, H-3′, H-5′), 7.49 (d, $J_{2',3'} = J_{6',5'} = 8.7$ Hz, 2H, H-2′, H-6′), 7.18 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''} = 8.1$ Hz, 2H, H-3‴, H-5‴), 7.07 (d, $J_{2'',3''} = J_{6'',5''} = 9.0$ Hz, 2H, H-2″, H-6″), 6.95 (d, $J_{3'',2''} = J_{5'',6''} = 9.0$ Hz, 2H, H-3″, H-5″), 6.77 (t, $J_{4''',3'''} = J_{4''',5'''} = 7.5$ Hz, 1H, H-4‴), 6.59 (m, 3H, H-2‴, H-6‴, H-5), 3.74 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.6, 156.7, 150.7, 147.3, 139.8, 129.3, 129.3, 129.2, 129.2, 128.8, 128.8, 122.8, 122.6, 120.7, 120.7, 119.3, 113.6, 113.6, 112.2, 112.2, 91.9, 55.1; EI MS: *m/z* (rel. abund. %) 416 (M^+, 97), 418 (M^++2, 100), 386 (28), 133 (44); Anal. Calcd for $C_{22}H_{18}N_4O_3S$, C = 63.14, H = 4.34, N = 13.39; Found C = 63.12, H = 4.36, N = 13.36.

2-(4-Nitrophenylimino)-*N*-phenyl-4-*p*-tolylthiazol-3(2*H*)-amine (10)

Yield: 79%; M.P.: 180-182 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, $J_{3',2'} = J_{5',6'} = 9.0$ Hz, 2H, H-3′, H-5′), 7.79 (d, $J_{2',3'} = J_{6',5'} = 8.1$ Hz, 2H, H-2′, H-6′), 7.65 (d, $J_{2''',3'''} = J_{6''',5'''} = 7.5$ Hz, 2H, H-2‴, H-6‴), 7.48 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''} = 7.5$ Hz, 2H, H-3‴, H-5‴), 7.31 (m, 3H, H-2″, H-6″, H-4‴), 7.03 (d, $J_{3'',2''/5'',6''} = 9.0$ Hz, 3H, H-3″, H-5″, H-5), 4.21 (s, 1H, NH), 2.35 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 158.4, 155.2, 147.2, 146.3, 137.7, 131.0, 129.3, 129.3, 129.1, 129.1, 128.7, 128.7, 125.1, 125.1, 123.3, 123.3, 122.6, 113.3, 113.3, 108.2; EI MS: *m/z* (rel. abund. %) 402 (M^+, 24), 222 (79), 117 (100); Anal. Calcd for $C_{22}H_{18}N_4O_2S$, C = 65.65, H = 4.51, N = 13.92; Found C = 65.63, H = 4.54, N = 13.95.

2-(4-Chlorophenylimino)-4-(4-methoxyphenyl)-*N*-phenylthiazol-3(2*H*)-amine (11)

Yield: 75%; M.P.: 160-162 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.57 (m, 2H, H-3′, H-5′), 7.30 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.4 Hz, 3H, H-2″, H-6″, H-5) ,7.06 (t, $J_{3''',2'''/3''',4'''} = J_{5''',3'''/5''',4'''}$ = 6.6 Hz, 2H, H-3‴, H-5‴), 6.86 (m, 6H, H-2′, H-6′, H-3″, H-5″, H-2‴, H-6‴), 6.64 (m, 1H, H-4‴), 3.71 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 159.8, 146.8, 142.0, 140.1, 129.5, 129.5, 129.0, 129.0, 125.5, 125.5, 121.9, 121.4, 121.4, 119.8, 113.7, 113.7, 112.2, 112.2, 94.0, 55.1; EI MS: *m/z* (rel. abund. %) 407 (M^+,29), 409 (M^++2, 10), 135 (100); Anal. Calcd for $C_{22}H_{18}ClN_3OS$, C = 64.78, H = 4.45, N = 10.30; Found C = 64.75, H = 4.47, N = 10.32.

4-(4-Chlorophenyl)-2-(4-chlorophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (12)

Yield: 72%; M.P.: 175-177 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.58 (m, 2H, H-3′, H-5′), 7.38 (m, 2H, H-2‴, H-6‴), 7.31 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.4 Hz, 2H, H-3″, H-5″), 7.12 (m, 3H, H-3‴, H-5‴, H-5), 6.85 (m, 2H, H-2′, H-6′), 6.81 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.4 Hz, 2H, H-2″, H-6″), 6.67 (m, 1H, H-4‴); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 147.3, 147.0, 133.6, 132.7, 132.4, 130.2, 130.2, 129.4, 129.4, 128.8, 128.8, 122.7, 122.3, 122.3, 120.3, 120.3, 113.1, 113.1, 108.2; EI MS: *m/z* (rel. abund. %) 409 (M^+, 8), 411 (M^++2, 20), 413 (M^++4, 11), 139 (100); Anal. Calcd for $C_{21}H_{15}Cl_2N_3S$, C = 61.17; H = 3.67, N = 10.19; Found C = 61.15; H = 3.69, N = 10.16.

2-(2,5-Dichlorophenylimino)-4-(4-nitrophenyl)-*N*-phenylthiazol-3(2*H*)-amine (13)

Yield: 80%; M.P.: 195-197 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 10.61 (s, 1H, NH), 7.92 (m, 4H, H-3″, H-5″, H-2‴, H-6‴), 7.80 (s, 1H, H-6′), 7.76 (m, 2H, H-3′, H-4′), 7.67 (m, 4H, H-2″, H-6″, H-3‴, H-5‴), 7.57 (m, 2H, H-4‴, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 147.3, 147.2, 147.0, 140.2, 132.7, 130.2, 130.2, 129.3, 129.3, 126.5, 126.5, 123.2, 123.2, 122.6, 122.5, 122.5, 113.3, 113.3, 108.1; EI MS: *m/z* (rel. abund. %) 262 (40), 286 (100); Anal. Calcd for $C_{21}H_{14}Cl_2N_4O_2S$, C = 55.15, H = 3.09, N = 12.25; Found C = 55.13, H = 3.07, N = 12.28.

4-(4-Chlorophenyl)-2-(2,5-dichlorophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (14)

Yield: 76%; M.P.: 185-187 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.92 (d, $J_{6',5'}$ = 2.4 Hz, 1H, H-6′), 7.88 (d, $J_{2''',3'''/6''',5'''} = J_{3',4'}$ = 7.8 Hz, 3H, H-2‴, H-6‴, H-3′), 7.83 (d, $J_{2'',3''} = J_{6'',5'}$ = 8.7 Hz, 2H, H-2″, H-6″), 7.75 (dd, $J_{3'',2''} = J_{5'',6''}$ = 8.7 Hz, $J_{3'',5''} = J_{5'',3''}$ = 2.4 Hz, 2H, H-3″, H-

5″), 7.67 (m, 3H, H-3‴, H-5‴, H-4′), 7.57 (m, 2H, H-4‴, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 158.2, 147.2, 133.6, 132.2, 132.1, 131.4, 129.0, 129.0, 128.9, 128.9, 128.6, 125.8, 124.1, 122.7, 120.1, 120.1, 113.3, 113.3, 110.6, 108.0; EI MS: *m/z* (rel. abund. %) 321 (14), 286 (85), 77 (100); Anal. Calcd for $C_{21}H_{14}Cl_3N_3S$, C = 56.46, H = 3.16, N = 9.41; Found C = 56.43, H = 3.18, N = 9.39.

2-(2,4-Dichlorophenylimino)-4-(4-nitrophenyl)-*N*-phenylthiazol-3(2*H*)-amine (15)

Yield: 58%; M.P.: 194-196 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 9.14 (s, 1H, NH), 8.25 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.4 Hz, 2H, H-3″, H-5″), 7.85 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 8.7 Hz, 2H, H-2‴, H-6‴), 7.55 (d, $J_{3',5'}$ = 2.1, 1H, H-3′), 7.36 (dd, $J_{5',6'}$ = 8.4 Hz, $J_{5',3'}$ = 2.1 Hz, 1H, H-5′), 7.17 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''}$ = 7.8 Hz, 2H, H-3‴, H-5‴), 6.98 (d, $J_{6',5'}$ = 8.7 Hz, 1H, H-6′), 6.87 (s, 1H, H-5), 6.77 (t, $J_{4''',3'''} = J_{4''',5'''}$ =7.5 Hz, 1H, H-4‴), 6.62 (d, $J_{2'',3''} = J_{6'',5''}$ =8.1 Hz, H-2″, H-6″); ^{13}C NMR (75 MHz, DMSO-d_6): δ161.8, 158.2, 147.3, 147.2, 140.4, 137.3, 134.3, 131.6, 129.5, 129.5, 129.4, 128.1, 126.7, 126.5, 125.0, 123.4, 123.4, 122.7, 113.2, 113.2, 108.1; EI MS: *m/z* (rel. abund. %) 454 (M^+, 30), 456 (M^++2, 40), 330 (70); Anal. Calcd for $C_{21}H_{14}Cl_2N_4O_2S$, C = 55.15, H = 3.09, N = 12.25; Found C = 55.12, H = 3.07, N = 12.22.

4-(4-Chlorophenyl)-2-(2,4-dichlorophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (16)

Yield: 59%; M.P.: 187-189 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 9.03 (s, 1H, NH), 7.58 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.4 Hz, 2H, H-3″, H-5″), 7.53 (d, $J_{3',5'}$ = 2.4 Hz, 1H, H-3′), 7.47 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.7 Hz, 2H, H-2″, H-6″), 7.34 (dd, $J_{5',3'}$ = 2.1 Hz, $J_{5',6'}$ = 8.4 Hz, 1H, H-5′), 7.17 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''}$ = 8.1 Hz, 2H, H-3‴, H-5‴), 6.97 (d, $J_{6',5'}$ = 8.4 Hz, 1H, H-6′), 6.77 (t, $J_{4''',3'''} = J_{4''',5'''}$ = 7.5 Hz, 1H, H-4‴), 6.60 (m, 3H, H-2‴, H-6‴, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 158.4, 147.3, 137.2, 134.1, 133.6, 132.4, 131.6, 129.3, 129.1, 129.1, 128.5, 128.5, 128.3, 125.2, 122.7, 120.3, 120.3, 113.3, 113.3, 108.2; EI MS: *m/z* (rel. abund. %) 445 (M^+,100), 447 (M^++2, 97), 410 (31); Anal. Calcd for $C_{21}H_{14}Cl_3N_3S$, C = 56.46, H = 3.16, N = 9.41; Found C = 56.44, H = 3.18, N = 9.44.

4-(4-Chlorophenyl)-2-(3-chlorophenylimino)-*N*-phenylthiazol-3(2*H*)-amine (17)

Yield: 73%; M.P.: 174-176 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.57 (d, $J_{3'',2''} = J_{5'',6''}$ = 8.4 Hz, 2H, H-3″, H-5″), 7.47 (d, , $J_{2'',3''} = J_{6'',5''}$ = 8.7 Hz, 2H, H-2″, H-6″), 7.33 (t, $J_{5',4'} = J_{5',6'}$ = 8.1 Hz, 1H, H-5′), 7.19 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''}$ = 8.1 Hz, 2H, H-3‴, H-5‴), 7.05 (d, $J_{4',5'}$ =7.2 Hz, 1H, H-4′), 6.80 (m, 3H, H-2′, H-6′, H-4‴) 6.59 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 8.7 Hz, 2H, H-2‴, H-6‴), 6.56 (s, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ161.6, 158.2, 150.3, 147.2,

134.1, 133.4, 132.2, 131.3, 129.4, 129.4, 128.8, 128.8, 127.2, 122.7, 122.5, 120.5, 120.3, 120.3, 113.3, 113.3, 108.1; EI MS: *m/z* (rel. abund. %) 411 (M^+, 100), 413 (M^++2, 91) 320 (25); Anal. Calcd for $C_{21}H_{15}Cl_2N_3S$, C = 61.17, H = 3.67, N = 10.19; Found C = 61.15, H = 3.69, N = 10.16.

4-(4-Methoxyphenyl)-*N*-phenyl-2-(phenylimino)thiazol-3(2*H*)-amine (18)

Yield: 74%; M.P.: 145-147 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.45 (d, $J_{2'',3''} = J_{6'',5''}$ = 8.7 Hz, 2H, H-2″, H-6″), 7.27 (t, $J_{3',2'/3',4'} = J_{5',6'/5',4'}$ = 7.8 Hz, 2H, H-3′, H-5′), 7.15 (t, $J_{3''',2'''/3''',4'''} = J_{5''',6'''/5''',4'''}$ = 8.1 Hz, 2H, H-3‴, H-5‴), 6.97 (t, $J_{4',3'} = J_{4',5'}$ = 7.2 Hz, 1H, H-4′), 6.90 (d, $J_{2',3'} = J_{6',5'}$ = 7.2 Hz, 2H, H-2′, H-6′), 6.79 (d, $J_{2''',3'''} = J_{6''',5'''}$ = 7.2 Hz, 2H, H-2‴, H-6‴), 6.73 (t, $J_{4''',3'''} = J_{4''',5'''}$ = 7.2 Hz, 1H, H-4‴), 6.57 (d, $J_{3'',2''} = J_{5'',6''}$ = 7.8 Hz, 2H, H-3″, H-5″), 6.27 (s, 1H, H-5), 3.70 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 159.6, 158.2, 149.2, 147.2, 130.1, 130.1, 129.6, 129.6, 129.1, 129.1, 127.3, 122.7, 126.4, 122.4, 122.4, 121.2, 121.2, 113.3, 113.3, 108.1, 55.7; EI MS: *m/z* (rel. abund. %) 373 (M^+, 100) , 150 (62), 132 (86); Anal. Calcd for $C_{22}H_{19}N_3OS$, C = 70.75, H = 5.13, N = 11.25; Found C = 70.73, H = 5.16, N = 11.22.

***N*-(Diphenylmethylene)-4-(3-nitrophenyl)-2-(4-nitrophenylimino)thiazol-3(2*H*)-amine (19)**

Yield: 89%; M.P.: 175-177 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 8.26 (d, $J_{6'',5''}$ = 9.0 Hz, 1H, H-6″), 8.14 (m, 5H, H-3′, H-5′, H-2″, H-4″, H-5″), 7.69 (m, 2H, H-4‴, H-4⁗), 7.56 (m, 4H, H-2‴, H-2⁗, H-6‴, H-6⁗), 7.46 (m, 4H, H-3‴, H-3⁗, H-5‴, H-5⁗), 7.27(m, 2H, H-2′, H-6′), 7.05 (s, 1H, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.4, 155.5, 155.2, 147.6, 146.5, 135.2, 134.3, 132.8, 132.8, 131.2, 131.2, 129.6, 129.0, 129.0, 129.0, 129.0, 128.7, 128.7, 128.7, 128.7, 125.1, 125.1, 123.3, 123.3, 123.2, 120.1, 108.2; EI MS: *m/z* (rel. abund. %) 521 (M^+,88), 180 (60), 165 (100); Anal. Calcd for $C_{28}H_{19}N_5O_4S$, C = 64.48, H = 3.67, N = 13.43; Found C = 64.45, H = 3.69, N = 13.45; IR (KBr, cm^{-1}): 3605 (amidic-NH), 1685 (C=O), 1607, 1586, 1570 (C=C, Aromatic), 1535, 1408 (NO_2).

***N*-(Diphenylmethylene)-4-(3-methoxyphenyl)-2-(4-nitrophenylimino)thiazol-3(2*H*)-amine (20)**

Yield: 95%; M.P.: 165-167 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.26 (d, $J_{2''',3'''}$ = 9.0 Hz, 1H, H-2‴), 8.01 (d, $J_{3',2'} = J_{5',6'}$ = 9 Hz, 2H, H-3′, H-5′), 7.69 (m, 1H, H-2⁗), 7.55 (m, 2H, H-6‴, H-6⁗), 7.40 (m, 8H, H-2′, H-6′, H-3‴, H-4‴, H-5‴, H-3⁗, H-4⁗, H-5⁗), 6.85 (dd,

$J_{4'',2''}$ = 1.8 Hz, $J_{4'',5''}$ = 6.6 Hz, 1H, H-4″), 6.80 (s, 1H, H-5), 6.76 (bd.s, 1H, H-2″), 6.70 (d, $J_{6'',5''}$ = 7.5 Hz, H-6″), 3.60 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.9, 158.9, 158.3, 145.3, 143.0, 138.2, 138.0, 135.2, 131.4, 129.8, 129.8, 129.6, 129.2, 129.0, 129.0, 128.2, 128.2, 128.1, 128.1, 127.8, 127.8, 127.3, 127.3, 123.2, 120.2, 114.4, 113.5, 103.6, 55.0; EI MS: *m/z* (rel. abund. %) 506 (M^+, 45), 166 (78), 165 (98), 77 (100); Anal. Calcd for $C_{29}H_{22}N_4O_3S$, C = 68.76, H = 4.38, N = 11.06; Found C = 68.74, H = 4.40, N = 11.04.

4-(4-Chlorophenyl)-*N*-(diphenylmethylene)-2-(4-nitrophenylimino)thiazol-3(2*H*)-amine (21)

Yield: 85%; M.P.: 177-179 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.92 (s, 1H, H-5), 7.87 (d, $J_{3',2'}$ = $J_{5',6'}$ = 9.3 Hz, 2H, H-3′, H-5′), 7.57 (m, 4H, H-2‴, H-2⁗, H-6‴, H-6⁗), 7.43 (m, 6H, H-3‴, H-3⁗, H-4‴, H-4⁗, H-5‴, H-5⁗), 7.37 (m, 4H, H-2′, H-6′, H-2″, H-6″), 7.27 (d, $J_{3'',2''}$ = $J_{5'',6''}$ = 7.5 Hz, 2H, H-3″, H-5″); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 155.7, 155.0, 146.3, 133.4, 132.7, 132.7, 132.2, 131.2, 131.2, 129.1, 129.1, 129.1, 129.1, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 125.3, 125.3, 123.1, 123.1, 120.3, 120.3, 108.2; EI MS: *m/z* (rel. abund. %) 510 (M^+, 1), 180 (100), 139 (95); Anal. Calcd for $C_{28}H_{19}ClN_4O_2S$, C = 65.81, H = 3.75, N = 10.96; Found C = 65.84, H = 3.72, N = 10.98.

4-(4-Bromophenyl)-*N*-(diphenylmethylene)-2-(4-nitrophenylimino)thiazol-3(2*H*)-amine (22)

Yield: 56%; M.P.: 179-181 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.92 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.57 (m, 2H, H-3″, H-5″), 7.47 (m, 10H, H-2‴, H-2⁗, H-3‴, H-3⁗, H-4‴, H-4⁗, H-5‴, H-5⁗, H-6‴, H-6⁗), 7.26 (d, $J_{2'',3''}$ = $J_{6'',5''}$ = 6.6 Hz, 3H, H-2″, H-6″, H-5); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.7, 158.4, 155.7, 155.2, 146.5, 133.3, 132.8, 132.8, 131.6, 131.6, 131.2, 131.2, 129.1, 129.1, 129.1, 129.1, 128.7, 128.7, 128.6, 128.6, 128.6, 128.6, 125.3, 125.3, 123.1, 123.1, 122.2, 108.2; EI MS: *m/z* (rel. abund. %) 554 (M^+, 2), 465 (59), 183 (79); Anal. Calcd for $C_{28}H_{19}BrN_4O_2S$, C = 60.55, H = 3.45, N = 10.09; Found C = 60.53, H = 3.43, N = 10.11.

***N*-(Diphenylmethylene)-2-(4-nitrophenylimino)-4-*p*-tolylthiazol-3(2*H*)-amine (23)**

Yield: 70%; M.P.: 160-162 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 7.85 (d, $J_{3',2'}$ = $J_{5',6'}$ = 9 Hz, 2H, H-3′, H-5′), 7.73 (s, 1H, H-5), 7.58 (m, 2H, H-2″, H-6″), 7.45 (m, 10H, H-2‴, H-2⁗, H-3‴, H-3⁗, H-4‴, H-4⁗, H-5‴, H-5⁗, H-6‴, H-6⁗), 7.27 (d, $J_{3'',2''}$ = $J_{5'',6''}$ = 6.3 Hz, 2H, H-

3″, H-5″), 7.10 (d, $J_{2',3'} = J_{6',5'} = 8.1$ Hz, 2H, H-2′, H-6′), 2.20 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 155.7, 155.2, 146.3, 137.5, 132.8, 132.8, 131.3, 131.2, 131.2, 129.3, 129.3, 129.3, 129.3, 129.1, 129.1, 128.8, 128.8, 128.7, 128.7, 128.7, 128.7, 125.5, 125.5, 123.3, 123.3, 108.2; EI MS: *m/z* (rel. abund. %) 490 (M^+, 5), 399 (50), 180 (100), 77 (100); Anal. Calcd for $C_{29}H_{22}N_4O_2S$, C = 71.00, H = 4.52, N = 11.42; Found C = 71.03, H = 4.54, N = 11.40.

4-(3,4-Dichlorophenyl)-*N*-(diphenylmethylene)-2-(4-nitrophenylimino)thiazol-3(2*H*)-amine (24)

Yield: 65%; M.P.: 180-182 °C; ^{1}H NMR (300 Hz, DMSO-d_6): δ 8.07 (s, 1H, H-5), 7.89 (d, $J_{3',2'} = J_{5',6'} = 9.3$ Hz, 2H, H-3′, H-5′), 7.78 (d, $J_{2'',6''} = 1.5$ Hz, 1H, H-2″), 7.57 (m, 12H, H-5″, H-6″, H-2‴, H-2⁗, H-3‴, H-3⁗, H-4‴, H-4⁗, H-5‴, H-5⁗, H-6‴, H-6⁗), 7.25 (d, $J_{2',3'} = J_{6',5'} = 6.3$ Hz, 2H, H-2′, H-6′); ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.8, 158.2, 155.7, 155.2, 146.3, 133.6, 133.4, 132.8, 132.8, 132.5, 131.2, 131.2, 130.2, 129.3, 129.3, 129.3, 129.3, 128.7, 128.7, 128.7, 128.7, 127.9, 125.1, 125.1, 123.3, 123.3, 118.4, 108.4; EI MS: *m/z* (rel. abund. %) 545 (M^+, 2), 452 (48), 180 (100); Anal. Calcd for $C_{28}H_{18}Cl_2N_4O_2S$, C = 61.66, H = 3.33, N = 10.27; Found C = 61.64, H = 3.31, N = 10.25.

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Synthesis, *In Vitro* α-Glucosidase Inhibitory Activity and Molecular Docking Studies of New Thiazole Derivatives

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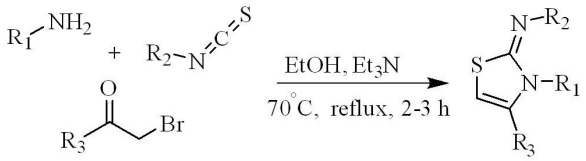
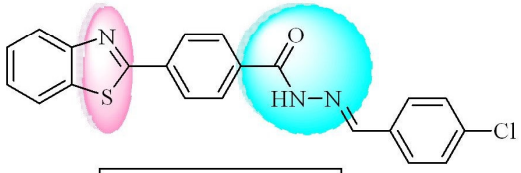
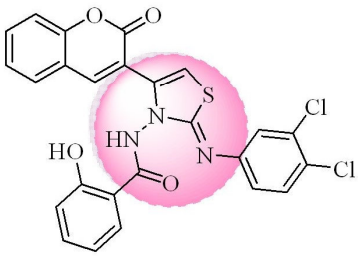


Scheme-1: Synthetic route for the compounds 1-24



IC_{50} = 5.31 ± 0.03 μM



IC_{50} = 0.12 ± 0.01 μM)

Synthetic Derivatives 1-24 (IC_{50} = 9.06 ± 0.10-82.50 ± 1.70 μM)

Standard Acarbose (IC_{50} = 38.25 ± 0.12 μM)

Research Highlights

- New thiazole derivatives were synthesized *via* "one pot" multicomponent reaction
- Synthetic compounds are hybrid of carbohydrazide and thiazole scaffolds
- Compounds demonstrated α-glucosidase inhibitory properties
- Molecular docking studies were carried out
- Compounds may serve as leads for future research