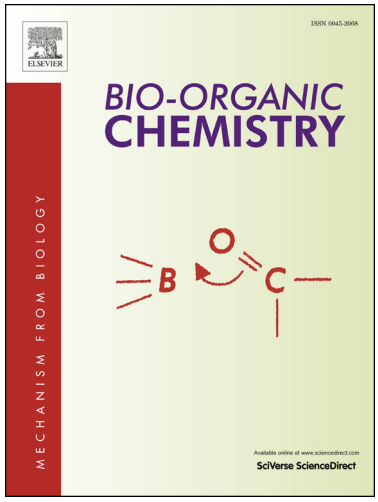


Synthesis, *in vitro* evaluation and molecular docking studies of thiazole derivatives as new inhibitors of α-glucosidase

Fazal Rahim, Hayat Ullah, Muhammad Tariq Javid, Abdul Wadood, Muhammad Taha, Muhammad Ashraf, Ayesha Shaukat, Muhammad Junaid, Shafqat Hussain, Wajid Rehman, Rashad Mehmood, Muhammad Sajid, Muhammad Naseem Khan, Khalid Mohammed Khan

PII: S0045-2068(15)30002-X
DOI: http://dx.doi.org/10.1016/j.bioorg.2015.06.006
Reference: YBIOO 1826

To appear in: *Bioorganic Chemistry*

Received Date: 23 April 2015
Revised Date: 15 June 2015
Accepted Date: 26 June 2015

Please cite this article as: F. Rahim, H. Ullah, M.T. Javid, A. Wadood, M. Taha, M. Ashraf, A. Shaukat, M. Junaid, S. Hussain, W. Rehman, R. Mehmood, M. Sajid, M.N. Khan, K.M. Khan, Synthesis, *in vitro* evaluation and molecular docking studies of thiazole derivatives as new inhibitors of α-glucosidase, *Bioorganic Chemistry* (2015), doi: http://dx.doi.org/10.1016/j.bioorg.2015.06.006

Synthesis, *in vitro* evaluation and molecular docking studies of thiazole derivatives as new inhibitors of α-glucosidase

Fazal Rahim,[a*] Hayat Ullah,[a] Muhammad Tariq Javid,[a] Abdul Wadood,[b] Muhammad Taha,[c,d] Muhammad Ashraf,[e] Ayesha Shaukat,[e] Muhammad Junaid,[b] Shafqat Hussain,[f] Wajid Rehman,[a] Rashad Mehmood,[g] Muhammad Sajid,[h] Muhammad Naseem Khan,[a] and Khalid Mohammed Khan[f]

[a]Depatment of Chemistry, Hazara University, Mansehra-21120, Pakistan
[b]Department of Biohemistry, Abdul Wali Khan University Mardan, Mardan-23200, Pakistan.
[c] Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA , Puncak Alam Campus,
[d] Faculty of Applied Science Universiti Teknologi MARA, 40450 Shah Alam, Selangor D. E. Malaysia,
[e]Department of Biochemistry and Biotechnology, The Islamia University of Bahawalpur, Bahawalpur 63100. Pakistan
[f]H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi-75270, Pakistan
[g]Depatment of Conservation Studies, Hazara University, Mansehra-21120, Pakistan
[h]Department of Biochemistry, Hazara University, Mansehra-21120, Pakistan.

Abstract

A series of thiazole derivatives **1-21** were prepared, characterized by EI-MS and ^{1}HNMR and evaluated for α-glucosidase inhibitory potential. All twenty one derivatives showed good α-glucosidase inhibitory activity with IC_{50} value ranging between 18.23±0.03 to 424.41 ± 0.94 μM when compared with the standard acarbose (IC_{50}, 38.25 ± 0.12 μM). Compound (**8**) (IC_{50}, 18.23 ± 0.03 μM) and compound (**7**) (IC_{50} = 36.75 ± 0.05 μM) exhibited outstanding inhibitory potential much better than the standard acarbose (IC_{50}, 38.25 ± 0.12 μM). All other analogs also showed good to moderate enzyme inhibition. Molecular docking studies were carried out in order to find the binding affinity of thiazole derivatives with enzyme. Studies showed these thiazole analogs as a new class of α-glucosidase inhibitors.

Keywords: Thiazole, Synthesis, Molecular docking, α-Glucosidase inhibition.

*Corresponding Author: fazalstar@gmail.com, Tel.: 0092-335-9528343;

1. Introdcution

α-Glucosidase (EC. 3.2.1.20) is a membrane-bound enzyme located at the epithelium of the small intestine [1]. It specifically hydrolyzed the *α*-glucopyranoside bond, thus releasing a/an *α*-D-glucose from the non-reducing end of the sugar [2]. It plays role in carbohydrates digestion and glycoprotein processing. Its inhibitors are be used to treat diabetics, HIV and cancers [3,4]. Clinical trials showed that the α-glucosidase inhibitors improved long-term glycemic control as measured by decreased hemoglobin A1c (HbA1c) in patients with type II diabetes and delayed the development of type II diabetes in patients with impaired glucose tolerance [5]. Recently, there had been widespread interest in α-glucosidase inhibitors, partly because of their potential as therapeutic targets, especially the inhibition of these enzymes had been found to help control postprandial blood glucose levels in diabetic patients [6,7], and can have profound effects on maturation, transport, and secretion of glycoproteins and can alter cell-cell recognition processes [8-10].

Several sugar α-glucosidase inhibitors, including acarbose, voglibose, and miglitol are clinically used in the effective treatment of type-2 diabetes mellitus [11]. However, such inhibitors, which are of great structural diversity, require tedious multi-steps for preparation. Amongst the various types of glucosidase inhibitors, also non-sugar derivatives have drawn considerable attention. Indeed, there is great structural diversity amongst glucosidase inhibitors, which are not based on a sugar scaffold [12-14].

In addition, α-glucosidase inhibitors may serve as a viable tool for better understanding of some biochemical processes in which α-glucosidase functions [15].

The thiazole and its derivatives are very much important in nature because they are present in thiamine that acts as a coenzyme for the oxidative decarboxylation of α-keto acids. It is also present in the skeleton of penicillin which is the most significant and the first one of the broad spectrum antibiotics [16]. Thiazole containing molecules such as sulfathiazole is used as an antimicrobial drug, ritonavir as antiretroviral drug, abafungin as antifungal drug, bleomycine and thiazofurin as antineoplastic drugs [17,18]. Thiazole containing compounds such as nizatidine is used as antihistaminic, niridazole as schistosomicidal and nitazoxanide as antiprotozoal [19].

Our research group is in struggle to discovered new biologically important scaffold which are simple molecules, easy to synthesize, high yielding and have no boring chemistry. In a continued effort in search for biologically active molecules [20-27], here we are reporting synthesis of thiazole derivatives and their α-glucosidase inhibition activity not published earlier.

2.0. Result Discussion

2.1. Chemistry

The synthesis of thiazole derivatives **1-21** (Scheme 1) was carried out by two-step reactions. In the first step, different substituted benzaldehyde/acetophenone (1 mmol) was mixed with thiosemicarbazide (1 mmol) in methanol in the presence of few drops of glacial acetic acid and refluxed for 3-5 hours. Completion of reaction was checked by periodic TLC. After completion of reaction, it was filtered and washed with methanol to obtained pure product in poor yield to good yield 0.175g to 0.300g depending on different attached substituents.

In second step, the product obtained in the first step (1 mmol) was mixed and refluxed with chloro or methoxy phencyl bromide (1 mmol) for 3-5 hours. Completion of reaction was monitored by periodic TLC. After completion of reaction, the reaction mixture was filtered and washed with hexane; pure product was obtained in good yield. The structures of all derivatives **(1-21)** were confirmed by different spectroscopic techniques, such as ^{1}H NMR and EI-MS.

Insert Scheme-1 here

Insert Table 1 here

2.2. *α*-Glucosidase inhibition

Compounds **1-21** showed a variable degree of α-glucosidase inhibition with IC_{50} value ranging between 18.23 ± 0.03 to 424.41 ± 0.94 μM when compared with standard acarbose (IC_{50} = 38.25 ± 0.12 μM).

Out of these **21** analogues, two compounds exhibited potent *α*-glucosidase inhibition. Compound **8** (IC_{50} = 18.23 ± 0.03 μM) and **7** (IC_{50} = 36.75 ± 0.05 μM) exhibited outstanding activity better than the standard acarbose.

Compounds **2**, **21**, **18**, **9** and **16** also showed good inhibition with IC_{50} value 43.26 ± 0.07, 46.39±0.05, 55.43 ± 0.08, 68.52 ± 0.08 and 99.16 ± 0.51 μM respectively. All other derivatives also showed good to moderate activities. The order of increase IC_{50} values of remaining compounds is as 17 < 14 <6 <20 <11 <13 <15 <5 <1 <19 <3 <10 <4 <12.

The most active analog among the series is **8** having 4-OH at R^1 and 4-Cl at R^3. The second most active compound is **7** having 4-benzyloxy group at R^1 and 4-Cl at R^3. From this study it was observed that by changing substituents at R^1 and R^3 greatly influence the potential of compounds.

The molecular docking studies were performed in order to know the mechanism of enzyme inhibition and binding interaction of these thiazole analog inside the binding pocket of α-glucosidase.

2.3. Molecular modeling and docking studies

The resulting anti-α-glucosidase activity of the tested compounds, especially compound 8 along with control acarbose prompted us to perform molecular docking study to understand the ligand-protein interactions in detail. The compound **8** and acarbose were docked into the active site of α-glucosidase (Asp214, Glu276, Asp 349 and Arg439) [28]. In general, the most active compound **8** formed three strong hydrogen bonds with active site residues (one with Glu276 and two with Arg439). As the number of hydrogen bond increased, it contributes toward the total strength of hydrogen bonding network. In case of compound **8**, along with the important residues in the pocket, one additional hydrogen bond is formed with pocket residue Asn347 (**Figure-1**). As the total number of hydrogen bonds become four hence compound **8** exhibited good fitting inside the pocket site with docking score -11.4139.

Insert Figure-1 here

The control, Acarbose, make three hydrogen bonds with the active site residues Asp214, Glu276 and Asp349.The strength of hydrogen bonds made by acarbose is relatively strong as compared to compound **8** but due to its bulky size it has some clashes with Arg439, Phe158 and leu218. Therefore, these clashes reduce its activity as compared to compound **8**. These results were also confirmed by the docking score. The control,

acarbose, due to its clashes didn't fit well in the pocket and hence have a docking score -9.177 while compound **8** has a good docking score -11.4139 **Figure-2.**

Insert Figure-2 here

The compound **12** is the least active and did not form hydrogen bonds with pocket residues (**Figure-3**).

Insert Figure-3 here

2.4. *α*-Glucosidase Assay

The α-glucosidase inhibition activity was performed with slight modifications as given by Pierre *et al*. 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.) in the buffer. The contents were mixed, pre-incubated for 10 min at 37 ºC 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 37ºC, absorbance of *p*-nitrophenol released was measured using Synergy HT 96-well plate reader, BioTek, USA. Acarbose was used as positive control. 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 EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA) [30]

3.0. Conclusion

Thiazole compounds (**1-21**) have been synthesized and evaluated for their *α*-glucosidase inhibitory potential. All compounds showed varying degree inhibitory potential. Compound **7** and **8** were found potent among the series with IC_{50} value 36.75±0.05 and 18.23±0.03 μM respectively, as compared to standard acarbose (IC_{50}, 38.25±0.12 μM). Consequently *in silico* studies were performed to recognize the binding mode of these compounds. The structures of all derivatives **(1-21)** were confirmed by different spectroscopic techniques such as ^{1}H NMR and EI-MS.

4. Materials and methods

NMR spectra were obtained with AVANCE AV 300 MHZ spectrometers. NMR spectra were recorded by using DMSO and acetone as solvent. TMS was used as internal standard. Finnegan MAT-311A spectrometer was used for electron impact mass spectra (EI-MS) analysis. Cesium iodide was used as an internal standard for mass measurement. All the above characterizations were performed at H.E.J Research Institute of Chemistry, Karachi University Pakistan. Column chromatography was performed on silica gel (E. Merck, type 60, 70-230 mesh). Pre-coated silica gel aluminum plates (Kieselgel 60, 20×20 and 0.5 mm thick, E. Merck, Germany) were used for TLC analysis. Light of wavelength 254 and 365 nm were used to visualize the chromatogram.

4.1. Computational Methods

The three dimensional structure of α-glucosidase for *Saccharomyces cerevisiae* has not been solved up to yet. However, only a few homology models have been reported for this enzyme previously [31-33]. The three dimensional coordinates of none of these model are publically available. So an attempt was made to construct a 3D model of α-glucosidase by homology modeling using the same protocol as described by Burke *et al* based on the crystal structure of *Saccrhromyces cerevisiae isomaltase* (3AJ7.pdb) [33]. The amino acid sequence of α-glucosidase from *Saccharomyces cerevisiae* was retrieved from UniProt protein resource data bank (http://www.uniprot.org/) under the access code P53341. 3D structure was built using homology modeling tools implemented in MOE 2013. The constructed model was subjected to energy minimization upto 0.05 RMS garadient using AMBER99 force field in order to get stable bond energies. The final refine structure was then used for docking purpose. All the synthesized compounds were sketched using Builder program implemented in MOE 2013 and were converted into their respective 3D structure. Subsequently, the energy of compounds was minimized up to 0.05 gradients using the MMFF94x force field. All compounds were docked into active pocket of *α*-glucosidase using the Triangular Matching docking method and 30 conformations of each compound were generated with docking score. Each complex was analyzed for interactions and their 3D images were taken.

4.2. General procedure for synthesis of thiazole derivatives

The synthesis of thiazole derivatives **1-21** (Scheme 1) was carried out by two-step reactions. In the first step, different substituted benzaldehyde/acetophenone (1 mmol) was mixed with thiosemicarbazide (1 mmol) in methanol in the presence of few drops of glacial acetic acid and refluxed for 3-5 hours. Completion of reaction was checked by periodic TLC. After completion of reaction, it was filtered and washed with methanol to obtained pure product in poor yield to good yield 0.175g to 0.300g depending on different attached substituents.

In second step, the product obtained in the first step (1 mmol) was mixed and refluxed with chloro or methoxy phencyl bromide (1 mmol) for 3-5 hours. Completion of reaction was monitored by periodic TLC. After completion of reaction, the reaction mixture was filtered and washed with hexane; pure product was obtained in good yield. The structures of all derivatives **(1-21)** were confirmed by different spectroscopic techniques, such as ^{1}H NMR and EI-MS.

4.2.1. (E)-4-(4-Chlorophenyl)-2-(2-(3-nitrobenzylidene)hydrazinyl)thiazole (1)

Yield: 33%; Solid m.p. 257 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.4 (s, 1H, NH), 8.4 (br. s, 1H, H-2), 8.2 (dd, $J_{4,6}$ = 1.2, $J_{4,5}$ = 8.1 Hz , 1H, H-4), 8.1 (s, 1H, HC=N), 8.0 (d, $J_{6,5}$ = 7.8 Hz , 1H, H-6), 7.8 (d, $J_{3'',2''/5'',6''}$ = 8.4 Hz , 2H, H-3″/5″), 7.7 (t, $J_{5/4,6}$ = 8.1 Hz, 1H, H-5), 7.4 (m, 3H, H-5′/2″/6″); ^{13}C NMR (75 MHz, DMSO-d_6): 171.4, 150.3, 148.4, 143.1, 134.5, 134.1, 132.1, 131.0, 129.7, 129.1, 129.1, 128.6, 128.6, 126.0, 121.3, 105.2; EI-MS: *m/z* (rel. int. %): 358 (M^{+}, 51), 210 (100), 174 (43), 168 (52), 102 (15); MS: as calculated 358.0291 and found 358.0286.

4.2.2.(E)-2-(2-(1-(2-Bromo-4-nitrophenyl)ethylidene)hydrazinyl)-4-(4-chlorophenyl)thiazole

(2)

yield: 50%; Solid m.p. 262 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.8 (s, 1H, NH), 8.2 (m, 2H, H-3/5), 8.1 (d, $J_{3'',2''/5'',6''}$ = 6.3Hz , 2H, H-3″/5″), 8.0 (m, 1H, H-6), 8.1 (d, $J_{2'',3''/6'',5''}$ = 8.7Hz , 2H, H-2″/6″), 7.5 (s, 1H, H-5′), 3.3 (s, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.4, 168.4, 152.2, 150.0, 141.5, 134.1, 132.2, 131.0, 129.1, 129.1, 128.6,

128.6, 126.5, 123.1, 122.4, 105.1, 16.2; EI-MS: *m/z* (rel. int. %): 449 (M^+, 18), 221 (17), 149 (15), 137 (31), 83 (100); MS: as calculated 449.9553 and found 449.9545.

4.2.3. (E)-4-(4-Chlorophenyl)-2-(2-(2-nitrobenzylidene)hydrazinyl)thiazole (3)

Yield: 50%; Solid m.p. 260 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.5 (s, 1H, NH), 8.4 (s, 1H, HC=N), 8.0 (d, $J_{3'',2''/5'',6''}$ = 8.1 Hz , 2H, H-3″/5″), 8.0 (d, $J_{3,4/6,5}$ = 8.4 Hz , 2H, H-3/6), 7.7 (t, $J_{4/3,5}$ = 7.5 Hz, 1H, H-4), 7.6 (t, $J_{5/4,6}$ = 7.2 Hz, 1H, H-5), 7.4 (m, 3H, H-5′/2″/6″); ^{13}C NMR (75 MHz, DMSO-d_6): 171.4, 150.1, 147.6, 143.1, 134.6, 134.1, 131.7, 131.0, 130.2, 129.1, 129.1, 128.6, 128.6, 128.2, 124.1, 105.2; EI-MS: *m/z* (rel. int. %): 358 (M^+, 54), 210 (100), 168 (91), 83 (68), 44 (56); MS: as calculated 358.0291 and found 358.0295.

4.2.4. (E)-4-(4-Chlorophenyl)-2-(2-(1-(4-(piperidin-1-yl)phenyl)ethylidene)hydrazinyl)thiazole (4)

Yield: 43%; Solid m.p. 280 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.9 (m, 4H, H-3″/5″/2/6), 7.4 (m, 4H, H-2″/6″/3/5), 7.2 (s, 1H, H-5′), 3.3 (s, 3H, Me), 3.0 (s, 10H, H-2‴/3‴/4‴/5‴/6‴); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 168.7, 151.8, 150.1, 134.2, 131.0, 130.0, 130.0, 129.1, 129.1, 128.7, 128.7, 127.0, 111.8, 111.8, 105.1, 54.7, 54.7, 25.4, 25.4, 24.3, 17.1; EI-MS: *m/z* (rel. int. %): 410 (M^+, 54), 375 (20), 299 (29), 210 (100), 168 (91), 83 (68), 44 (56); MS: as calculated 410.1332 and found 410.1327.

4.2.5. (E)-4-((2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)methyl)-N,N-dimethylaniline (5)

Yield: 38%; Solid m.p. 270 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 8.0 (s, 1H, HC=N), 7.8 (d, $J_{3'',2''/5'',6''}$ = 6.3 Hz , 2H, H-3″/5″), 7.6 (m, 2H, H-2/6), 7.4 (d, $J_{2'',3''/6'',5''}$ = 6.6 Hz , 2H, H-2″/6″), 7.3 (d, $J_{3,2}$ = 6.3 Hz , 1H, H-3), 7.2 (d, $J_{5,6}$ = 6.3 Hz , 1H, H-5), 7.2 (s, 1H, H-5′), 3.0 (s, 6H, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.5, 153.2, 150.1, 143.2, 134.2, 131.0, 129.1, 129.1, 128.8, 128.8, 128.1, 128.1, 123.1, 111.8, 111.8, 105.0, 41.2, 41.2; EI-MS: *m/z* (rel. int. %): 356 (M^+, 3), 210 (100), 168 (39), 147 (46), 43 (87); MS: as calculated 356.0862 and found 356.0854.

4.2.6. (E)-4-(4-Chlorophenyl)-2-(2-(naphthalene-2-yl-methylene)hydrazinyl)thiazole (6)

Yield: 32%; Solid m.p. 276 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 8.3 (s, 1H, HC=N, 8.0 (d, $J_{3'', 2''/5'',6''}$ = 8.4 Hz , 2H, H-3″/5″), 7.9 (m, 5H, H-2/3/4/5/8), 7.5 (m, 2H, H-7/6), 7.4 (d, $J_{2'',3''/6'',5''}$ = 8.4 Hz , 2H, H-2″/6″), 7.2 (s, 1H, H-5′); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 150.1, 143.2, 134.2, 136.0, 133.8, 131.0, 129.1, 128.6, 128.6, 128.4, 128.0, 127.9, 127.9, 127.1, 126.8, 126.1, 126.1, 105.1; EI-MS: *m/z* (rel. int. %): 363 (M^+, 18), 210 (87), 168 (35), 153 (100), 127 (33); MS: as calculated 363.0597 and found 363.0590.

4.2.7. (E)-2-(2-(4-(Benzyloxy)benzylidene)hydrazinyl)-4-(4-chlorophenyl)thiazole (7)

Yield: 81%; Solid m.p. 278 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 8.0 (s, 1H, HC=N), 7.8 (d, $J_{3'',2''/5'',6''}$ = 6.3 Hz , 2H, H-3″/5″), 7.6 (d, $J_{2'',3''/6'',5''}$ = 6.3 Hz , 2H, H-2″/6″), 7.4 (d, $J_{2,3/6,5}$ = 5.4 Hz , 2H, H-2/6), 7.3 (m, 5H, H-2‴/3‴/4‴/5‴/6‴), 7.2 (s, 1H, H-5′), 7.0 (d, $J_{3,2/5,6}$ = 6.6 Hz , 2H, H-3/5), 5.1 (s, 2H, OCH_2); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 161.2, 150.1, 143.2, 136.5, 134.2, 131.0, 130.1, 130.1, 129.1, 129.1, 128.7, 128.7, 128.7, 128.7, 127.5, 127.0, 127.0, 126.1, 114.2, 114.2, 105.1, 70.7; EI-MS: *m/z* (rel. int. %): 429 (M^+, 17), 214 (53), 91 (100), 65 (22); MS: as calculated 419.0859 and found 419.0848.

4.2.8. (E)-2,6-Di-t-butyl-4-((2-(4-(4-Chlorophenyl)thiazole-2-yl)hydrazono)methyl)-phenol (8)

Yield: 100%; Solid m.p. 287 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.9 (s, 1H, HC=N), 7.7 (d, $J_{3'',2''/5'',6''}$ = 6.3 Hz , 2H, H-3″/5″), 7.4 (s, 2H, H-2/6), 7.0 (s, 1H, H-5′), 6.9 (d, $J_{2'',3''/6'',5''}$ = 6.6 Hz , 2H, H-2″/6″), 3.7 (s, 3H, OMe), 1.3 (s, 18H, 6Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 150.1, 156.8, 143.2, 136.1, 136.1, 134.2, 131.0, 129.1, 129.1, 128.7, 128.7, 125.4, 123.6, 123.6, 105.1, 36.4, 36.1, 36.1, 36.1, 34.2, 34.2, 31.4, 31.4; EI-MS: *m/z* (rel. int. %): 441 (M^+, 18), 216 (35), 210 (100), 174 (37), 168 (59); MS: as calculated 441.1642 and found 441.1650.

4.2.9. 1-((E)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl)-3-((Z)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl)benzene (9)

Yield: 85%; Solid m.p. 278 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.2 (s, 2H, 2xNH), 8.0 (s, 2H, 2xHC=N), 7.8 (d, $J_{3'',2''/5'',6''}$ = 8.4 Hz , 4H, 2xH-3″/5″), 7.6 (s, 2H, 2xH -5′), 7.4 (m, 8H, H-2/3/5/6, 2xH-2″/6″); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 171.6, 150.1, 150.1, 143.1, 143.1, 136.1, 136.1, 134.2, 134.2, 133.7, 133.7, 131.4, 131.3, 129.2, 129.2, 129.2, 129.2, 128.7, 128.7, 128.7, 128.7, 128.6, 128.2, 105.1, 105.1; EI-MS: *m/z* (rel. int.

%): 549 (M^+, 18), 338 (22), 210 (100), 168 (59), 82 (13); MS: as calculated 549.4973 and found 549.4964.

4.2.10. 5-(4-chlorophenyl)-2-((E)-2-(4-((E)-(2-(4-(4-chlorophenyl)thiazol-2-yl)hydrazono)methyl)benzylidene)hydrazinyl)thiazole (10)

Yield: 86%; Solid m.p. 290 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 10.4 (s, 2H, 2xNH), 8.2 (m, 4H, 2xHC=N, H-3″/5″), 7.8 (m, 6H, 2xH-2″/6″, H-3″/5″), 7.4 (m, 4H, H-2/4/5/6), 7.2 (s, 2H, 2x H-5′); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 171.6, 150.1, 150.1, 143.2, 143.2, 134.2, 134.2, 133.7, 133.7, 131.3, 131.3; 131.0, 131.0, 129.1, 129.1, 129.1, 129.1, 128.7, 128.7, 128.7, 128.7, 128.3, 128.3, 105.1, 105.1; EI-MS: *m/z* (rel. int. %): 549 (M^+, 20), 338 (17), 210 (100), 168 (38), 128 (36); MS: as calculated 549.4973 and found 549.4964.

4.2.11. (E)-5-((2-(4-(4-Chlorophenyl)thiazole-2-yl)hydrazono)methyl)-2-methoxy-phenol (11)

Yield: 52%; Solid m.p. 281 °C; ^{1}H-NMR: (DMSO-d_6, 400 MHz): δ 8.1 (s, 1H, HC=N), 7.8 (d, $J_{3″,2″/5″,6″}$ = 6.3 Hz , 2H, H-3″/5″), 7.4 (d, $J_{2″,3″/6″,5″}$ = 6.3 Hz , 2H, H-2″/6″), 7.3 (m, 2H, H-2/5), 7.1 (dd, $J_{6,2}$ = 1.8, $J_{6,5}$ = 6.3 Hz , 1H, H-6), 7.0 (s, 1H, H-5′); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 152.1, 150.1, 147.1, 143.1, 134.2, 131.0, 130.1, 129.1, 129.1, 128.7, 128.7, 122.7, 115.8, 112.2, 105.1, 56.0; EI-MS: *m/z* (rel. int. %): 359 (M^+, 18), 210 (60), 101 (32), 59 (81), 43 (100); MS: as calculated 359.0495 and found 359.0486.

4.2.12. (E)-4-(4-Methoxyphenyl)-2-(2-(1-(3- nitrophenyl)ethylidene)hydrazinyl)thia-zole (12)

Yield: 74%; Solid m.p. 290 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 8.5 (s, 1H, H-2), 8.2 (t, $J_{4/5,6\ 6/5,4}$ = 7.8 Hz, 2H, H-4/6), 7.8 (d, $J_{2″,3″/6″,5″}$ = 8.7 Hz , 2H, H-2″/6″), 7.7 (t, $J_{5/6,4}$ = 8.1 Hz, 1H, H-5), 7.1 (s, 1H, H-5′), 6.9 (d, $J_{3″,2″/5″,6″}$ = 8.7 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe), 2.4 (s, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 168.6, 160.4, 150.1, 134.8, 134.2, 131.7, 131.7, 128.4, 128.4, 126.0, 126.4, 125.2, 114.7, 114.7, 105.1, 55.7, 17.0; EI-MS: *m/z* (rel. int. %): 368 (M^+, 100), 205 (77), 164 (93), 149 (26), 82 (46); MS: as calculated 368.4096 and found 368.4096.

4.2.13. (E)-2-(2-(Anthracen-9-ylmethylene)hydrazinyl)-4-(4-methoxyphenyl)thiazole (13)

Yield: 73%; Solid m.p. 277 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.3 (s, 1H, NH), 9.2 (s, 1H, HC=N), 8.6 (m, 3H, H-2/6/10), 8.1 (d, $J_{5,4/7,8}$ = 8.1 Hz , 2H, H-5/7), 7.8 (d, $J_{2'',3''/6'',5''}$ = 8.4 Hz , 2H, H-2″/6″), 7.6 (m, 4H, H-3/4/8/9), 7.1 (s, 1H, H-5′), 6.9 (d, $J_{3'',2''/5'',6''}$ = 8.7 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 160.5, 150.1, 143.2, 131.7, 131.7, 128.7, 128.7, 128.7, 128.4, 128.4, 128.0, 128.0, 128.0, 128.0, 125.4, 125.4, 125.4, 125.4, 125.1, 123.8, 114.7, 114.7, 105.1, 55.7; EI-MS: *m/z* (rel. int. %): 409 (M^+, 45), 203 (100), 191(21), 176 (26), 101 (15), 88 (25); MS: as calculated 409.5029 and found 409.5020.

4.2.14. (E)-4-((2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)methyl)-N,N-dimethylaniline (14)

Yield: 38%; Solid m.p. 264 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.9 (s, 1H, HC=N), 7.7 (d, $J_{2,3/6,5}$ = 8.7 Hz , 2H, H-2/6), 7.4 (d, $J_{2'',3''/6'',5''}$ = 8.7 Hz , 2H, H-2″/6″), 7.0 (s, 1H, H-5′), 6.9 (d, $J_{3,2/5,6}$ = 8.7 Hz , 2H, H-3/5), 6.7 (d, $J_{3'',2''/5'',6''}$ = 9.6 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe), 2.9 (s, 6H, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 160.5, 153.2, 150.1, 143.2, 128.4, 128.4, 128.1, 128.1, 125.2, 123.1, 114.7, 114.7, 111.7, 111.7, 105.1, 55.7, 41.0, 41.0; EI-MS: *m/z* (rel. int. %): 352 (M^+, 100), 206(100), 191 (91), 164 (65), 147 (67); MS: as calculated 352.1358 and found 352.1350.

4.2.15. (E)-4-(4-Methoxyphenyl)-2-(2-(naphthalen-2-yl-methylene)hydrazinyl)thiazole (15)

Yield: 32%; Solid m.p. 291 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 12.2 (s, 1H, NH), 8.1 (s, 1H, HC=N), 8.0 (s, 1H, H-8), 7.9 (m, 4H, H-/3/4/5/8), 7.8 (d, $J_{2'',3''/6'',5''}$ = 6.6 Hz , 2H, H-2″/6″), 7.5 (m, 2H, H-6/7), 7.1 (s, 1H, H-5′), 6.9 (d, $J_{3'',2''/5'',6''}$ = 6.6 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe); EI-MS: *m/z* (rel. int. %): 359 (M^+, 48), 206 (100), 191 (22), 164 (33), 153 (79); MS: as calculated 359.1092 and found 359.1099.

4.2.16. (E)-2-(2-(4-(Benzyloxy)benzylidene)hydrainyl)-4-(4-methoxyphenyl)thiazole (16)

Yield: 81%; Solid m.p. 310 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.9 (s, 1H, HC=N), 8.0 (d, $J_{2,3/6,5}$ = 6.6 Hz , 2H, H-2/6), 7.5 (d, $J_{2''',3'''/6''',5'''}$ = 6.3 Hz , 2H, H-2‴/6‴), 7.4 (d, $J_{2'',3''/6'',5''}$ = 5.4 Hz , 2H, H-2″/6″), 7.3 (m, 2H, H-3‴/5‴), 7.2 (t, $J_{4'''/3''',5'''}$ = 6 Hz, 1H, H-4‴), 7.1 (s, 1H, H-5′), 7.0 (d, $J_{3,2/5,6}$ = 6.6 Hz , 2H, H-3/5), 6.9 (d, $J_{3'',2''/5'',6''}$ = 6.3 Hz , 2H,

H-3″/5″), 5.1 (s, 2H, OCH_2), 3.7 (s, 3H, OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 128.7, 127.5, 128.7, 127.0, 127.0, 136.5, 114.3, 161.2, 144.2, 70.5, 130.1, 126.0, 130.3, 143.1, 171.6, 128.4, 114.7, 105.1, 128.4, 114.7, 125.2, 150.1, 160.4, 55.6; EI-MS: *m/z* (rel. int. %): 415 (M^+, 10), 206 (88), 191 (17), 149 (18), 91 (100); MS: as calculated 415.1354 and found 415.1349.

4.2.17. (E)-2,6-Di-tert-butyl-4-((2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)-methyl)phenol (17)

Yield: 99%; Solid m.p. 282 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.9 (s, 1H, HC=N), 7.7 (d, $J_{2'',3''/6'',5''}$ = 6.3 Hz , 2H, H-2″/6″), 7.4 (s, 2H, H-2/6), 7.0 (s, 1H, H-5′), 6.9 (d, $J_{3'',2''/5'',6''}$ = 6.6 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe), 1.3 (s, 18H, 6Me); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 160.5, 156.8, 150.1, 143.2, 136.1, 136.1, 128.4, 128.4, 125.2, 125.4, 123.6, 123.6, 114.7, 114.7, 105.1, 55.8, 34.3, 34.3, 31.4, 31.4, 31.4, 31.4, 31.4, 31.4; EI-MS: *m/z* (rel. int. %): 437 (M^+, 22), 261 (32), 206 (100), 191 (30), 164 (61); MS: as calculated 437.2137 and found 437.2130.

4.2.18. 1-((E)-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)methyl)-3-((Z)-(2-(4-(4-methoxy phenyl)thiazol-2-yl)hydrazono)methyl)benzene (18)

Yield: 86%; Solid m.p. 279 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 11.5 (s, 2H, NH), 8.2 (s, 1H, H-2), 8.0 (s, 2H, 2xHC=N), 7.9 (s, 2H, 2xH-5′), 7.7 (d, $J_{2'',3''/6'',5''}$ = 8.7 Hz , 4H, 2xH-2″/6″), 7.6 (d, $J_{4,5/6,5}$ = 7.5 Hz , 2H, H-4/6), 7.5 (m, 1H, H-5), 6.9 (d, $J_{3'',2''/5'',6''}$ = 8.7 Hz , 4H, 2xH-3″/5″), 3.7 (s, 6H, 2-OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 171.6, 160.4, 160.4, 150.1, 150.1, 143.2, 143.2, 133.7, 133.7, 131.4, 131.1, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 125.2, 125.2, 124.8, 124.6, 114.6, 114.6, 105.1, 105.1, 55.7, 55.7; ESI/MS; calculated for and found EI-MS: *m/z* (rel. int. %): 540 (M^+, 59), 309 (66), 206 (100), 191 (42), 149 (46), 128 (37); MS: as calculated 540.1402 and found 540.1410.

4.2.19. 5-(4-methoxyphenyl)-2-((E)-2-(4-((E)-(2-(4-(4-methoxyphenyl)thiazol-2-yl)hydrazono)methyl)benzylidene)hydrazinyl)thiazole (19)

Yield: 85%; Solid m.p. 284 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 11.5 (s, 1H, NH), 8.0 (s, 2H, 2xHC=N), 7.9 (s, 2H, 2xH-5′), 7.7 (d, $J_{2'',3''/6'',5''}$ = 8.7 Hz , 4H, 2xH-2″/6″), 7.6 (d, $J_{2,3/6,5}$ = 7.5 Hz , 2H, H-2/6), 7.6 (d, $J_{3,2/5,6}$ = 7.5 Hz , 2H, H-3/5), 6.9 (d, $J_{3'',2''/5'',6''}$ = 8.7

Hz , 4H, 2xH-3″/5″), 3.7 (s, 6H, 2OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 160.4, 160.4, 150.1, 150.1, 143.2, 143.2, 133.7, 133.7, 131.2, 131.2, 128.4, 128.4, 128.4, 128.4, 128.3, 128.3, 125.2, 125.2, 125.1, 125.1, 114.6, 114.6, 105.1, 105.1, 55.7, 55.7; EI-MS: *m/z* (rel. int. %): 540 (M^+, 29), 390 (54), 206 (100), 191 (37), 149 (35); MS: as calculated 540.1402 and found 540.1415.

4.2.20. (E)-2-Methoxy-5-((2-(4-(4-methoxyphenyl)thiazol-2- yl)hydrazono)methyl)-phenol (20)

Yield: 52%; Solid m.p. 270 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.8 (s, 1H, HC=N), 7.7(d, $J_{2'',3''/6'',5''}$ = 6.6 Hz , 2H, H-2″/6″), 7.2 (d, $J_{2,6}$ = 0.9 Hz , 1H, H-2), 7.1 (s, 1H, H-5′), 6.9 (m, 4H, H-3″/5″/5/6), 3.7 (s, 6H, 2OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 171.6, 160.4, 152.1, 150.0, 147.0, 143.1, 131.2, 128.2, 128.2, 125.1, 122.6, 115.8, 114.7, 114.7, 112.2, 105.1, 56.2, 55.7; EI-MS: *m/z* (rel. int. %): 355 (M^+, 30), 206 (100), 191 (27), 164 (54), 149 (43); MS: as calculated 355.0991and found 355.0999.

4.2.21. (E)-4-((2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)methyl)benzene-1,2-diol (21)

Yield: 86%; Solid m.p. 287 °C; ^{1}H-NMR: (DMSO-d_6, 300 MHz): δ 7.8 (s, 1H, HC=N), 7.7 (d, $J_{5,6}$ = 6.6 Hz , 1H, H-5), 7.2 (d, $J_{6,5}$ = 6.6 Hz , 1H, H-6), 7.1(d, $J_{2,6}$ = 1.5 Hz , 1H, H-2), 7.0 (s, 1H, H-5′), 6.9 (d, $J_{2'',3''/6'',5''}$ = 6.6 Hz , 2H, H-2″/6″), 6.7 (d, $J_{3'',2''/5'',6''}$ = 6 Hz , 2H, H-3″/5″), 3.7 (s, 3H, OMe); ^{13}C NMR (75 MHz, DMSO-d_6): 171.5, 150.1, 149.4, 146.0, 143.2, 133.1, 131.1, 129.1, 129.1, 128.6, 127.4, 127.4, 123.1, 117.2, 116.2, 105.1, 46.5; EI-MS: *m/z* (rel. int. %): 341 (M^+, 30), 217 (100), 191 (27), 164 (54), 149 (43); MS: as calculated 341.0834 and found 341.0823.

Acknowledgments

The authors are thankful to Higher Education Commission of Pakistan.

References

1. A.J. Hirsh, S.Y. Yao, J.D. Young, C.I. Cheeseman, Gastroenterology, 113 (1997) 205.
2. J.B. Torrelles, A.K. Azad, L.S. Schlesinger, J. Immunol. 177 (2006) 1805.
3. E. Gallienne, T. Gefflaut, M. Lemaire, J. Org. Chem. 71 (2006) 894.
4. J. E. Groopman, Rev. Infect. Dis. 12 (1990) 908.
5. B. Brazdova, N.S. Tan, N.M. Samoshina, V. V. Samoshin, Carbohydr. Res. 344 (2009) 311.
6. N. Zitzmann, A.S. Mehta, S. Carrouee, T.D. Butters, F.M. Platt, J. McCauley, B.S. Blumberg, R.A. Dwek, T.M. Block, Proc. Natl. Acad. Sci. USA. 96 (1999) 11878.
7. R.A. Dwek, T.D. Butters, F.M. Platt, N. Zitzmann, Nat. Rev. Drug Discov. 1 (2002) 65.
8. G. Long, M. Westenberg, H. Wang, J.M. Vlak, Z. Hu, J. Gen. Virol. 87 (2006) 839.
9. S. Nadanaka, H. Yoshida, F. Kano, M. Murata, K. Mori, Mol. Biol. Cell. 15 (2004) 253.
10. A. Goffard, N. Callens, B. Bartosch, C. Wychowski, F.L. Cosset, C. Montpellier, J. Dubuisson, J. Virol. 79 (2005) 8400.
11. B.D. Walker, M. Kowalski, W.C. Goh, K. Kozarsky, M. Krieger, C. Rosen, L. Rohrschneider, W.A. Haseltine, J. Sodroski, J. Pro. Natl. Acad. Sci. USA. 84 (1987) 8120.
12. H. Takahashi, S. Sou, R. Yamasaki, M. Sodeoka, Y. Hashimoto, Chem. Pharm. Bull. 48 (2000) 1494.
13. S. Sou, S. Mayumi, H. Takahashi, R. Yamasaki, S. Kadoya, M. Sodeoka, Y. Hashimoto, Bioorg. Med. Chem. Lett. 10 (2000) 1081.
14. L. J. Scott, C.M. Spencer, Drugs. 59 (2000) 521.
15. K.M. Khan F. Rahim, A. Wadood, N. Kosar, M. Taha, A. Khan, M. I. Fakhri, M. Junaid, W. Rehman, M. Khan, S. Perveen, O. Abid, B. Mohammad, M. Sajid, M. I. Choudhary, Eur J Med Chem. 81 (2014) 245.
16. A. D. Baron, Diabetes Res. Clin. Pr. 40 (1998) 51.
17. J.V. Metzger, The chemistry of heterocyclic compounds, in: Thiazole and Its Derivatives, A Series of Monographs. 34 (1979). Wiley, Chichester.
18. J. Quiroga, P. Hernandez, B. Insuasty, R. Abonia, J. Cobo, A. Sanchez, M. Nogueras, J. N. Low, J. Chem. Soc. Perkin Trans1. 4 (2002)555.
19. I. Hutchinson, S. A. Jennings, B. R. Vishnuvajjala, A. D. Westwell, M.F.G. Stevens, J. Med. Chem. 45 (2002) 744.
20. K.M. Khan, F. Rahim, A. Wadood, N. Kosar, M. Taha, S. Lalani, A. Khan, M.I. Fakhri, M. Junaid, W. Rehman, M. Khan, S. Perveen, M. Sajid, M.I. Choudhary, Eur J Med Chem. 81 (2014) 245
21. S. Imran; M. Taha; N.H. Ismail; K. M. Khan; F. Naz; M. Hussain; S. Tauseef, *Molecules* 19, 2014, 11722.
22. M. Taha, N.H. Ismail, S. Imran, K.M. Khan, 4-[5-(2-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]benzohydrazide. Molbank (2014) M826.
23. W. Jamil, S. Perveen, S.A.A. Shah, M. Taha, N.H. Ismail, S. Perveen, N. Ambreen, K. M. Khan M.I. Choudhary, Molecules 19 (2014) 8788.

24. M. Taha, N.H. Ismail, W. Jamil, H. Rashwan, S.M. Kashif, A.A. Sain, M.I. Adenan, E.H. Anouar, M. Ali, F. Rahim, K.M. Khan. Eur J Med Chem. 84 **(**2014) 731.
25. Z.S. Saify, A. Kamil, S. Akhtar, M. Taha, A. Khan, K.M. Khan, S. Jahan, F. Rahim, S. Perveen, M.I. Choudhary, Med. Chem. Res., 23 (2014) 4447.
26. K.M. Khan, M. Khan, M. Saleem, M. Taha, S. Perveen, M.I. Choudhary, J. Pak. Chem Soc. 35 (2013) 901.
27. M. Taha, N.H. Ismail, S. Lalani, M.Q. Fatmi, Atia-tul-Wahab, S. Siddiqui, K.M Khan, S. Imran, M.I. Choudhary, *Eur J. Med. Chem*. 92 (2015) 387**.**
28. S. B. Ferreira, A.C.R. Sodero, M.F.C. Cardoso, E.S. Lima, C. R. Kaiser, F. P. Silva, V. F. Ferreira, J. Med. Chem. 53 (2010) 2364.
29. a) F. Rahim, K. Ullah, H. Ullah, A. Wadood, M. Taha, A.U. Rehman, M. Ashraf, A. Shaukat, W. Rehman, S. Hussain, K.M. Khan, Bioorg. Chem. 58 (2015) 81; b) F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, M.T. Javid, M. Taha, W. Rehman, A. Rehman, K.M. Khan. *Bioorg. Chem.* **2015**, *60*, 42-48; c) M. Taha, N.H. Ismail, M.S. Baharudin, S. Lalani S. Mehboob, K.M. Khan, S. yousuf, S. Siddiqui F. Rahim M.I. Choudhary. Med. Chem. Res. 24 (2015) 1310.
30. L.R. Guerreiro, E.P. Carriero, L. Fernandes, T.A. Cardote, R. Moreira, A.T. Caldeira, R. C. Guedes, A. J. Burke, Bioorg. Med. Chem. 21 (2013) 1911.
31. J. H. Park, S. Ko, H. Park, Bull. Korean Chem. Soc. 29 (2008) 921.
32. A. Roujeinikova, C. Raasch, S. Sedelnikova, W. Liebl, W. Rice, J. Mol. Biol. 321 (2002) 149.
33. K. Yamamoto, H. Miyake, M. Kusunoki, S. Osaki, FEBS. J. 277 (2010) 4205.

Scheme, Table and Figures captions

Scheme-1; Synthesis of thiazole derivatives **1-21**

Table-1; α-Glucosidase inhibitory potential of thiazole derivatives **1-21**

Figure-1; The recognized binding modes and molecular interactions of the thiazole analog **8** in the active site of α-glucosidase.

Figure-2: The recognized binding modes and molecular interactions of the control, Acarbose in the active site of α-glucosidase.

.

Figure-3: The recognized binding modes and molecular interactions of thiazole analog **12** in the active site of α-glucosidase.

Scheme-1

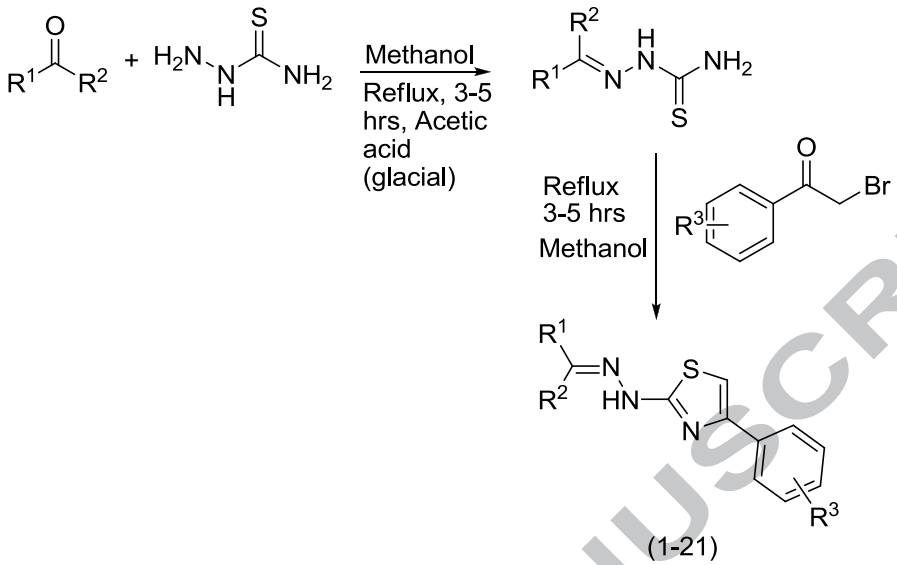


Figure-1:

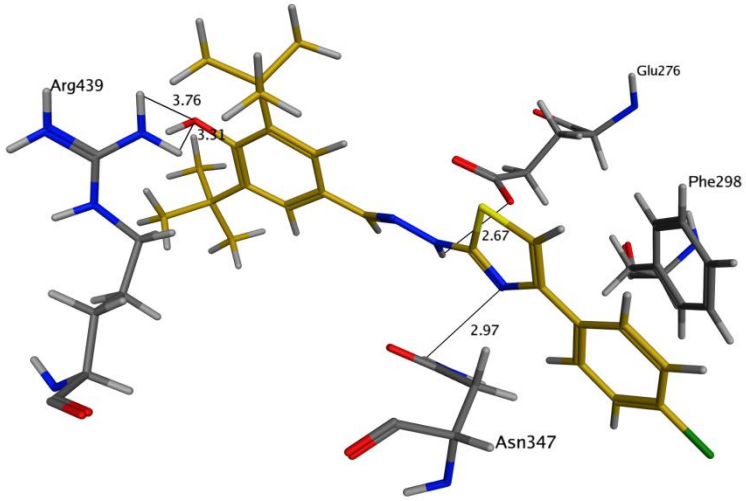


Figure-2:

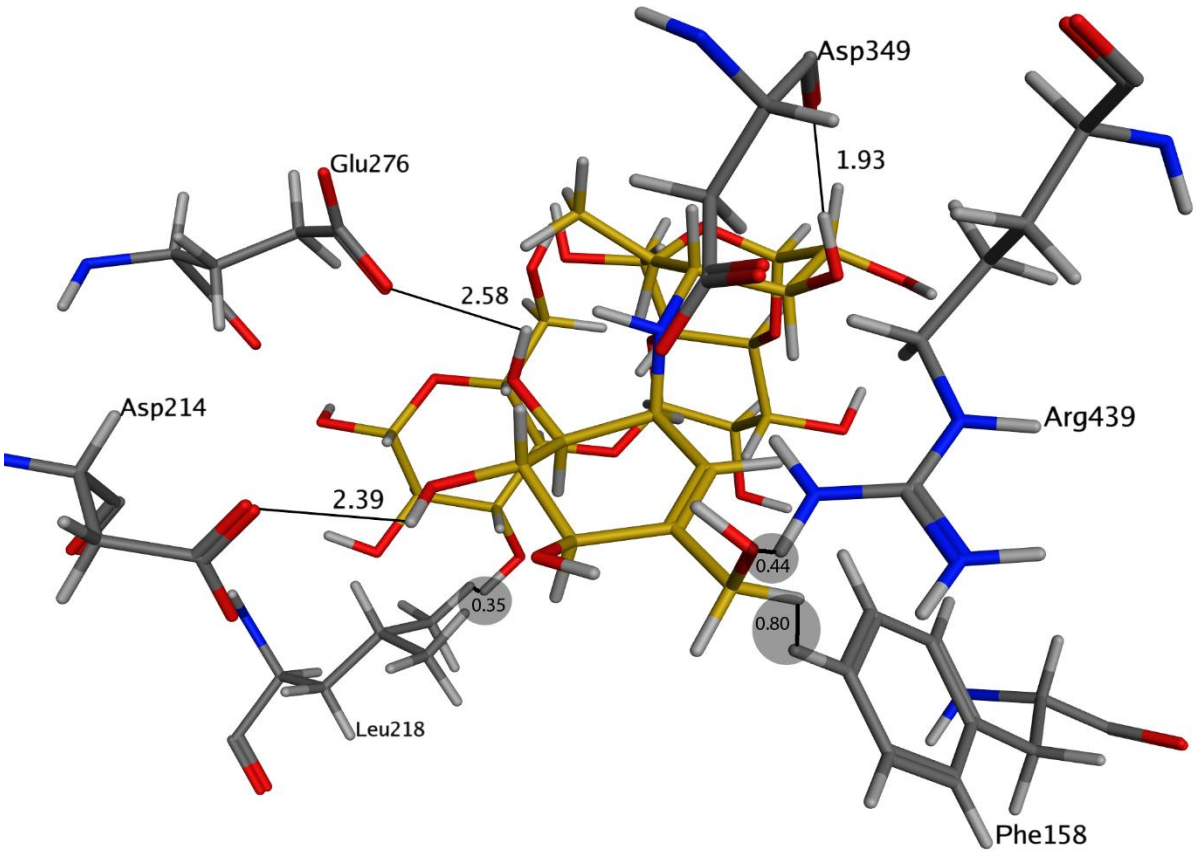


Figure-3:

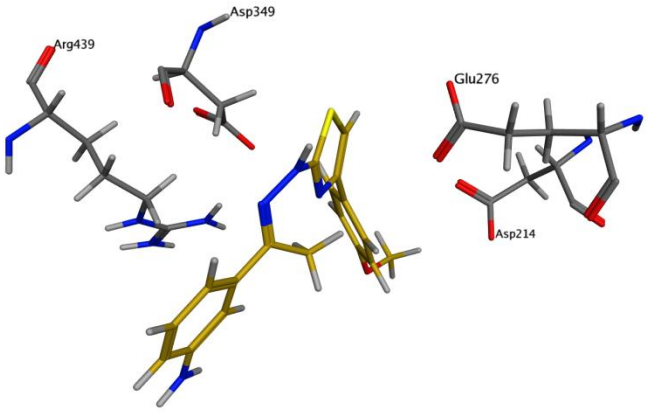
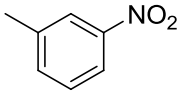
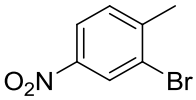
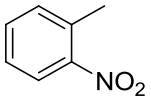
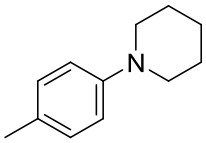
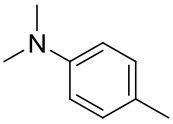
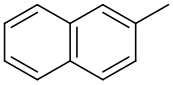
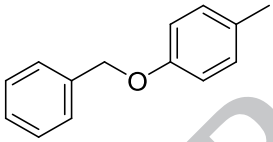
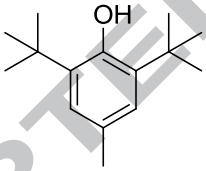
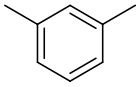
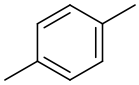
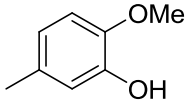
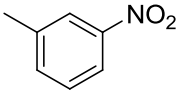
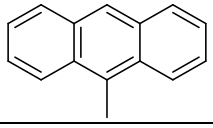
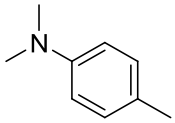
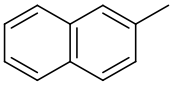
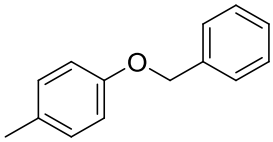
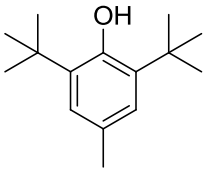
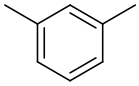
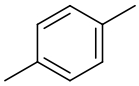
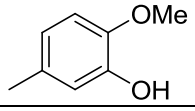
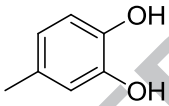
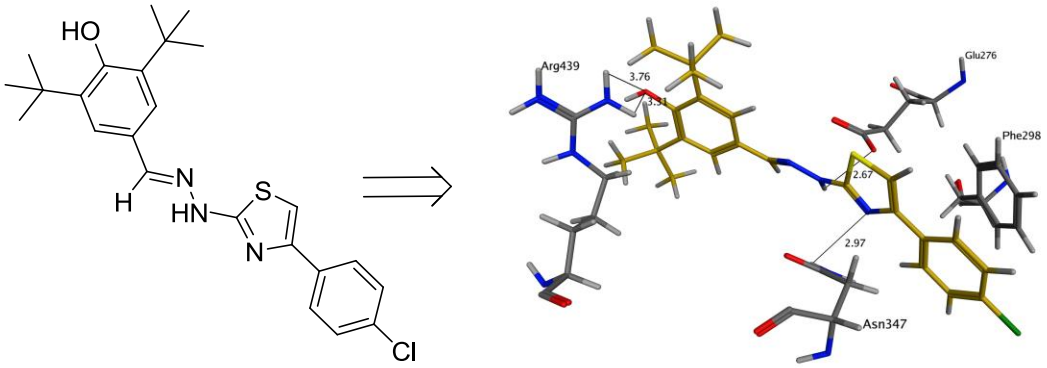


Table-1:

S. No.	R^1	R^2	R^3	IC_{50} ± SEM[a] (μM)
1		H	4-Cl	219.85±1.12
2		CH_3	4-Cl	43.26 ± 0.07
3		H	4-Cl	239.18±1.08
4		CH_3	4-Cl	387.52±1.13
5		H	4-Cl	205.46±1.17
6		H	4-Cl	175.25±0.97
7		H	4-Cl	36.7 5±0.05
8		H	4-Cl	18.23±0.03
9		H	4-Cl	68.52±0.08
10		H	4-Cl	341.91±1.15
11		H	4-Cl	176.43±1.12
12		CH_3	4-OMe	424.41±0.94
13		H	4-OMe	191.72±0.73

14		H	4-OMe	145.81±0.26
15		H	4-OMe	193.55±0.41
16		H	4-OMe	99.16±0.51
17		H	4-OMe	123.32±0.83
18		H	4-OMe	55.43±0.08
19		H	4-OMe	226.32±0.95
20		H	4-OMe	175.72±0.84
21		H	4-OMe	46.39±0.05
Acarbose	-	-	-	38.25±0.12

Graphical abstract



(Compound 8)

(IC_{50}, 18.23 ± 0.03 μM)

Potent Inhibitors of α-glucosidase

Highlights:

- Synthesis of Thiazole Derivatives
- *In vitro α-glucosidase* inhibitory activity
- Identification of a novel class of α-glucosidase inhibitors
- Structure-activity Relationship established
- Molecular docking