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SYNTHESIS, ENZYME INHIBITION AND DOCKING STUDIES OF 1,2,4-TRIAZOLES DERIVED FROM ALIPHATIC ESTERS

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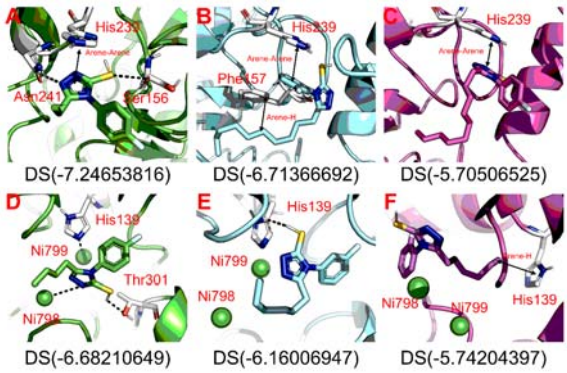
New structural type inhibitors of glucosidase and urease, i.e. substituted 1, 2, 4-triazole-3-thiones 4(a-o) were synthesized in two steps from carboxylic acid hydrazides and aryl isothiocyanates. The hydrazides in turn were synthesized from aliphatic esters. Triazoles series 4(a-o) were evaluated for α-glucosidase and urease activities. The compounds (4i,4j,4k,4o) with respective IC_{50} values of 95.91±0.22, 88.24±0.22, 66.47±0.26, 94.21±0.15 [μM] showed good α-glucosidase inhibition, when compared to the standard acarbose having an IC_{50} =51.23 [μM]. Similarly, 4a, 4b, 4c, 4f, 4k with an IC_{50} values 50.3±0.21, 42.41±0.923, 47.04±0.58, 40.03±1.305, 32.26±1.070 [μM] respectively showed good urease inhibition results when compared to the standard thiourea having IC_{50} = 24.14 [μM]. These results were also supported by docking studies.



INTRODUCTION

From the viewpoint of synthetic organic chemistry, thiosemicarbazides (TSC) are interesting molecules as they can take part in numerous organic transformations. The family of compounds like 1,2,4- triazoles have such building blocks like (TSC) containing multifunctional groups in their structures.[1] A wide range of drugs comprising triazoles as a basic heterocyclic structural constituent show pharmacological significance such as anticonvulsant,[2] antitumor, antiviral,[3] antimalarial,[4] antiproliferative,[5] antioxidants, analgesics,[6] anticancer,[7] antifungal,[8] antiplasmodial,[9] antibacterial,[10] immunostimulants,[11] antidiabetic,[12] urease inhibitors,[13] and α-glycosidase inhibitors.[14] These diverse characteristics of the triazoles nucleus have motivated the researchers to develop unique triazoles derivatives with favorable biological activities. Triazoles have been observed as structural type inhibitors of urease. Serwar *et al.* have pointed out that 1,2,4-triazole-3-thiones due to having structural similarity with the natural substrate of urease, *i.e.* urea.[15] Recently reported data about fluorine incorporated 1,2,3-triazoles derivatives revealed

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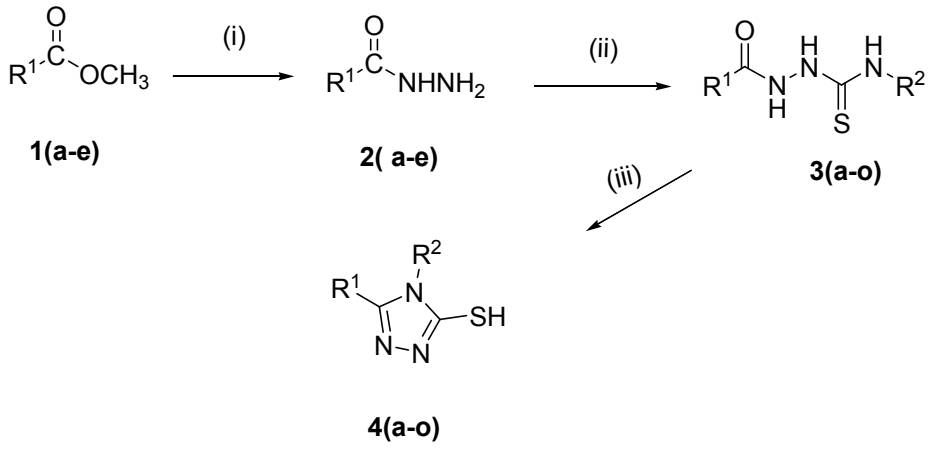
that such compounds significantly influence the properties of organic molecules. Limited data has been reported till now about fluorinated heterocycles. Due to this fact, efforts have been made to develop new methodologies for the synthesis and biological evaluations of such compounds. 1,2,3-triazoles derivatives like fluoro substituted phenyl ring containing triazoles exhibit potent α-glucosidase inhibition activities.[16] Recently a series of triazoles derivatives were synthesized which showed potent α-glucosidase inhibition activities.[17] Taha and co-workers reported some triazoles compounds having fluoro substituted phenyl rings with potent urease inhibition activities. Esters with aliphatic chain like heptyl, octyl etc were evaluated for urease inhibition and it was observed that compounds having heteroatoms and straight long chain showed good results than compounds having heteroatoms with branched chains.[18] Keeping in view the recent applications of five-membered heterocycles for enzyme inhibition we synthesized novel 1,2,4-triazoles from aliphatic esters and evaluated them for enzyme inhibition.

RESULTS AND DISCUSSION

Chemistry

Aliphatic esters **1(a-e)** were converted to their respective hydrazides **2(a-e)**. The hydrazides were treated with different isothiocyanates and afforded thiosemicarbazides **3(a-o).** 1,2,4-triazoles **4(a-o)** were synthesized from thiosemicarbazides **3(a-o)** by cyclodehydration under basic conditions.[18] The synthesis of thiosemicarbazides and triazoles were confirmed by observing different spectroscopic results like IR,^{1}H NMR, and EI-MS. Spectral values for thiosemicarbazides in IR spectra showed broadband for (NH) groups stretching in the region of 3326-3116 cm^{-1} aliphatic (-CH) stretching in the region of 2972-2818 cm^{-1} and aromatic (-CH) stretching in the region of 3060-3009 $cm.^{-1}$A (C=S) transmittance at 1285-1201cm^{-1} and C-F at 793-716cm^{-1}. Similarly, for triazoles aliphatic (-CH) stretching appears in the region of 2956-2896 cm^{-1}, and for C=N at 1661-1590 cm^{-1}, C=C at 1530-1480 cm^{-1} and C-F at 747-706 cm^{-1}. Product formation was also confirmed by ^{1}H-NMR spectra. As for thiosemicarbazides spectra showed triplets and multiplets for aliphatic chains in the region of δ = 2.18- 0.7ppm, doublets, triplets or multiplets for aromatic protons in the region of δ = 7.99-6.87ppm, three broad downfield assimilating to one proton each assigned to the three NH protons, in the region of 10.40-8.91ppm. For triazoles, spectra show triplets, multiples for aliphatic chain in the region of 2.69-0.77ppm, doublets, triplets or multiples for aromatic protons in region of 7.70-7.21ppm and singlet for SH protons in the region of 13.83-12.18ppm. In EI-MS spectra product formation for thiosemicarbazides and triazoles was confirmed by the presence of molecular ion peaks in the respective spectra with intensities of 5-8% for few thiosemicarbazides and 98-100% for almost all triazoles. These above spectral results were strong evidence for the formation of thiosemicarbazides and triazoles. The synthetic pathway is given in Scheme 1.



(i) ethanol,hydrazine hydrate (80%),reflux, (ii) RNCS, ethanol,reflux, (iii) 5% NaOH.

Scheme 1 – Synthesis of Triazole derivatives.

Table 1

Different substituents of synthesized triazoles

	R^1	R^2	S.No	R^1	R^2
4a	Butyl	2F-C_6H_4	**4i**	Nonyl	3F-C_6H_4
4b	Hexyl	2F-C_6H_4	**4j**	Decyl	3F-C_6H_4
4c	Heptyl	2F-C_6H_4	**4k**	Butyl	4F-C_6H_4
4d	Nonyl	2F-C_6H_4	**4l**	Hexyl	4F-C_6H_4
4e	Decyl	2F-C_6H_4	**4m**	Heptyl	4F-C_6H_4
4f	Butyl	3F-C_6H_4	**4n**	Nonyl	4F-C_6H_4
4g	Hexyl	3F-C_6H_4	**4o**	Decyl	4F-C_6H_4
4h	Heptyl	3F-C_6H_4			

Biological Activity

α-Glucosidase inhibition studies

In vitro ***α***-glucosidase inhibition activities at 1 μM concentration was determined by using the previously reported method.[19] α- glucosidase inhibition activities were determined for synthesized compounds of 4(a-o) series by taking acarbose as standard inhibitor having IC_{50} value of 51.23 μM. The α-glucosidase inhibition activities were determined according to the literature protocols and results are shown in Table-1.2. The tested compounds showed varying degree of inhibition. As compared to standard, compounds (4i, 4j, 4k, 4o) with IC50 values of 95.91±0.22, 88.24±0.22, 66.47±0.26, 94.21±0.15 [μM] respectively showed good inhibition near to standard. It was observed here that triazoles with para-fluorinated benzene and shorter alkyl chains or triazoles with meta-fluorinated benzene and longer alkyl chains showed good *α*-glucosidase inhibition. Compounds 4a, 4b, 4f 4h, 4m, 4n exhibited moderate activity with respective IC_{50} values of 181.56±0.13, 145.72±0.18, 174.80±0.14, 177.41±0.17, 122.03±0.25, 195.73±0.17 [μM] It was observed here that triazoles with ortho and meta fluorinated benzene with shorter chains but para fluorinated benzene with longer chains were found moderately active,. Compounds 4c, 4d, 4e, 4g, 4l exhibited weak activity with IC_{50} values of 203.19±0.12, 207.60±0.13, 209.74±0.11, 298.09±0.08, 247.36±0.15, [μM]. It was also observed here that triazoles with ortho and para fluorinated benzene with longer chains were found less active.

Urease inhibition studies

In vitro urease inhibition activities at 1[μM] concentration was determined by previously reported method as BioVision's Urease Activity Assay Kit (Colorimetric) using manufacturer's protocol (K378-100). Urease inhibition activities were determined for synthesized compounds of 4(a-o) series by taking thiourea as standard inhibitor having an IC_{50} value of 24.14 [μM]. The urease inhibition activities were determined according to the literature protocols and results are summarized in Table-1.2. The tested compounds showed broad range of activity. As compared to standard, the compounds 4a, 4b, 4c, 4f, 4k with an IC_{50} values 50.3±0.21, 42.41±0.923, 47.04±0.58, 40.03±1.305, 32.26±1.070 [μM] respectively showed good urease inhibition results as compared to the standard.

But 4d, 4g, 4h 4i, 4j 4m, 4o exhibited moderate activity with respective IC_{50}values of 133.55± 0.61, 154.45±1.10, 193.34±1.82, 176.29±1.76, 161.73±1.91,132.64±0.81, 151.08±0.64[μM] and 4e, 4l, 4n exhibited weak activity with IC_{50} values of 224.62±1.54, 215.75±1.11, 247.09±1.14, [μM]. Here activity could not be associated to some specific factor or combinations however it was observed that triazoles with shorter alkyl chain generally showed good urease inhibition and others with longer alkyl chains showed moderate to week results usually.

Table 2

Urease and α-glucosidase inhibition activities of Triazoles 4(a-o)

Compound	**IC_{50} (μM) + *SEM***	
	Urease	**α-glucosidase**
4a	50.3±0.21	181.56±0.13
4b	42.41±0.923	145.72±0.18
4c	47.04±0.58	203.19±0.12

Table 2 (continued)

4d	133.55±0.61	207.60±0.13
4e	224.62±1.54	209.74±0.11
4f	40.03±1.305	174.80±0.14
4g	154.45±1.10	298.09±0.08
4h	193.34±1.82	177.41±0.17
4i	176.29±1.76	95.91±0.22
4j	161.73±1.91	88.24±0.22
4k	32.26±1.070	66.47±0.26
4l	215.75±1.11	247.36±0.15
4m	132.64±0.81	122.03± 0.25
4n	247.09±1.14	195.73±0.17
4o	151.08±0.64	94.21±0.15
Standards	**Thiourea= 24.14**	**Acarbose= 51.23**

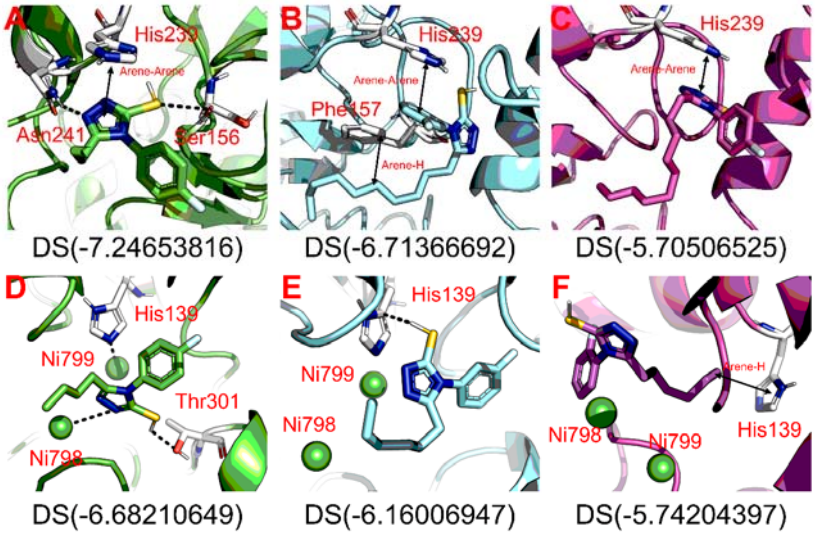


Fig. 1 – The protein-ligand interaction (PLI) profile for synthesized compounds against the α-Glucosidase enzyme. (**A**) The 3D binding mode of most active compound **4k**, (**B**) for compound **4j** and (**D**) for **4o**. The PLI profile for synthesized compounds against urease enzyme using PDB code **4UBP**. **(A).** The PLI profile for the most active compound **4k**, **(B)** for 4f, and **(C)** for **4b**. The docking score (DS) labeled for each compound in each panel.

Molecular Docking

Molecular docking study was carried out using the MOE package[20] to illustrate the binding mode of synthesized compound enlisted in the current study against both urease and α-glucosidase enzyme. The docking results of the synthesized compounds against α-glucosidase enzyme revealed fit-well binding mode in the active site of the enzyme with various potential and also showed different PLI profile. All the enlisted compounds showed different PLI profile and enzymatic activity, and it might be due to attachment of fluorine at different position, i.e., *-ortho*, *-para*, *-meta*, and might be due to the different attached 4-(3-fluorophenyl)-5-methyl-4H-1,2,4-triazole-3-thiol moiety. In case of high potent compound 4k in the series adopt various interactions with critical residues; Ser156, His239 and some additional hydrophobic interaction, i.e., Phe157 (Fig. 1A). The ranked 2nd (4j) and 3rd (4o) compound in the series shared similar PLI profile (Fig. 1B and 1C). The only difference among the PLI profile of both compounds is; compound 4j interact with hydrophobic residue, *i.e.*, Phe157 where compound 4o lack this interaction respectively.

In case of the molecular docking result of synthesized compounds against urease enzyme

revealed a similar observation of best-fit well binding mode in the catalytic site of urease enzyme. The two embedded Ni ions (Ni198 & 799) conjointly participated in a significant role in the enhancement of the enzymatic potential by linking the criticalresidues and the active moiety of the compounds. The most promising docked conformation of most active compound 4k in the series revealed most favorable interactions with the essential active site residues, including His139, Thr301, additionally the two embedded Ni ions were found in conjugate with; His139-Ni799 and HS-Ni-798 of the compound (Fig. 1D). In the case of the PLI profile for ranked 2nd (4f) and 3rd (4b), revealed a similar profile. Both the compound adopted critical interaction with His139, but with a different active moiety of the compounds, and this might be one of the reasons for showing various activities against this enzyme (Fig. 1E and 1F). We could not observe any metallic interaction with Ni.

Overall the molecular docking results delineated that all the compounds showed good inhibitory potential against both the targets. The variation in the activity might be due to the attached fluorine atom at a different position. Interestingly, the fluorine at *-para* position act as an activating group, hence, showed high potency, while at other position (*-ortho and -meta*) act as a deactivating group based on the common mechanism of electrophilic aromatic directing groups and hence showed less potency comparatively.

EXPERIMENTAL

Materials

Physical constants and spectroanalytical techniques were applied for the characterization of synthesized compounds. Aluminum sheets precoated silica gel $60F_{254}$ (Merck, Germany) were used for performing thin layer chromatography (TLC). For melting point determination Stuart digital melting point apparatus (SMP10) with open capillaries was used, FT-IR spectrophotometer 8400 shimadzu was used to record Infrared (IR) spectra. Mass VG autspec geifab and a Hewlett packard MS engine thermo spray and ionization by electron impact at 70 eV was used to record Mass spectra. NMR spectrophotometer Bruker biospin (Germany) at 300MHz was used to record H^1 NMR spectra. Aliphatic esters were purchased from Alpha aesar. All the reagents and solvents with high purity grade were used.

General procedure for the synthesis of Thiosemicarbazides 3(a-o)

A (6.53 mmol) solution of respective isothiocyanates in absolute MeOH (20 mL) was mixed with a (6.53 mmol) solution of carboxylic acid hydrazide in absolute MeOH (30 mL) with constant stirring and then reaction mixture was reflux for 2–3 h. Completion of the reaction was monitored through TLC. On completion, the resulting product was purified by filtration and recrystallization with EtOH/water to get pure thiosemicarbazides **3(a-o).** [15]

The products were confirmed through IR, ^{1}H-NMR and Mass analysis.

4-(2-Fluorophenyl)-1-pentanoylthiosemicarbazide **(3a).**

Yield: 75%; m.p.126°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3220, 3020,2818, 1643, 1533, 1352,729; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 9.93 (brs, 1H, NH), 9.73 (s, 1H, NH), 9.59 (s, 1H, NH), 7.98-7.16 (m, 4H, ArH), 2.18 (t, *J* = 7.4Hz, 2H, CH_2), 1.68-1.54 (m, 2H, CH_2), 1.46-1.27 (m, 2H, CH_2), 0.97(t, *J* = 6.6Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 186 (5), 155 (7), 154 (8), 153 (100), 133 (5),111 (18), 95 (28),75 (10).

4-(2-fluorophenyl)-1-heptanoylthiosemicarbazide **(3b).**

Yield: 68%; m.p.125°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$3253, 3116, 3055, 2967, 2857, 1715, 1685,1554, 1480, 1285,793, 682; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 9.84 (brs, 1H, NH), 9.69 (s, 1H, NH), 9.49 (s, 1H, NH), 7.58 -7.06 (m, 4H, ArH), 2.16 (t, *J*=7.4 Hz, 2H, CH_2) 1.57-1.46 (m, 2H, CH_2), 1.36-1.14 (m, 6H, $3CH_2$), 0.86 (t, *J* = 6.5 Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 155 (4), 154 (8), 153 (100), 113 (6), 111 (11) , 95 (32) ,75 (10), 74 (5).

4-(2-fluorophenyl)-1-octanoylthiosemicarbazide **(3c).**

Yield: 94%; m.p. 122°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3321, 3260, 3039, 2969, 2828, 1714, 1543, 1482, 1392, 1262, 1091, 793 ,719, 499; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.88 (s, 1H, NH), 9.75 (s,1H, NH), 9.53 (s, 1H, NH), 7.88-6.97 (m, 4H, ArH), 2.15 (t, *J* = 7.52 Hz, 2H, CH_2), 1.76-1.42 (m, 2H, CH_2) 1.35-1.00 (m, 8H, $4CH_2$), 0.91-0.83 (m, 3H,CH_3); EI-MS m/z (rel. int.%): 193 (5), 167 (7), 155 (5), 154 (12), 153 (100), 127 (8), 111 (35), 109 (8), 95 (20), 75 (8), 57 (9).

4-(2-fluorophenyl)-1-decanoylthiosemicarbazide **(3d).**

Yield: 91%; m.p.120°C; IR (ATR, cm^{-1}) $\bar{\upsilon}_{max}$ 3246, 3140, 3060, 2899, 1653, 1433, 1302, 1201, 1151, 1020, 860, 679, 579; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.87 (brs, 1H, NH), 9.69 (s, 1H, NH), 9.32 (br s, 1H, NH), 7.34-7.15 (m, 4H, ArH), 2.15 (t, *J* = 7.6Hz, 2H, CH_2) 1.54-1.49 (m, 2H, CH_2), 1.29-1.25 (m, 12H, $6CH_2$), 0.86 (t, *J* = 6.4Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 321 (8), 155 (8), 154 (6), 153 (100), 121 (7), 111 (12), 95 (34), 84 (5) ,75 (10).

4-(2-fluorophenyl)-1-undecanoylthiosemicarbazide **(3e).**

Yield: 97%; m.p.121°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3257, 3190, 3029, 2928, 2849, 1683, 1523, 1472, 1382, 1231, 1040, 679; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.98 (s, 1H, NH), 9.63 (brs, 1H, NH), 9.28 (s, 1H, NH), 7.58-7.04 (m, 4H, ArH), 2.14 (t, *J* = 7.5Hz, 2H, CH_2), 1.68-1.46 (m, 2H, CH_2), 1.31-1.18 (m, 14H, $7CH_2$), 0.85 (t, *J* = 6.6Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 185 (5), 155 (7), 154 (6), 15 (100), 126 (9), 111 (12), 109 (8), 95 (31), 84 (5), 75 (9).

4-(3-fluorophenyl)-1-pentanoylthiosemicarbazide **(3f).**

Yield:82%; m.p.110°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3218, 3009, 2821, 1641, 1535, 1355, 733; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.89 (brs 1H, NH), 9.69 (s, 1H, NH), 9.58 (s, 1H, NH), 7.99-7.13 (m, 4H, ArH), 2.16 (t, *J* = 7.5Hz, 2H, CH_2) 1.65-

1.51 (m, 2H, CH_2), 1.43-1.25 (m, 2H, CH_2), 0.96 (t, J = 6.7 Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 193 (5), 169 (5), 155 (8), 154 (12), 153 (100), 111 (10), 95 (28), 85 (7), 75 (10) .

4-(3-fluorophenyl)-1-heptanoylthiosemicarbazide **(3g).** Yield: 92%; m.p. 90°C; IR (ATR,cm^{1}): □$_{max}$ 3250, 3119, 3030, 2969, 2859, 1714, 1683, 1553, 1482, 1282, 790, 679; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.84 (br s, 1H, NH), 9.66 (br s, 1H, NH) 9.13 (brs, 1H, NH), 7.52-7.49 (m, 1H, ArH), 7.39-7.33 (m, 1H, ArH), 7.27 (d, J = 8.0Hz, 1H, ArH) 6.98 (t, J = 8.8Hz, 1H, ArH), 2.18 (t, J = 7.6Hz, 2H, CH_2), 1.57-1.46 (m, 2H, CH_2), 1.33-1.23 (m, 6H, 3CH_2), 0.87 (t, J = 6.4 Hz, 3H, CH_3). EI-MS m/z (rel. int. %): 193 (5), 155 (5), 154 (10), 153 (100), 111 (13), 96 (7), 95 (35), 85 (5), 75 (12).

4-(3-fluorophenyl)-1-octanoylthiosemicarbazide **(3h).** Yield: 52%; m.p.121°C; IR (ATR,cm^{-1}): $\bar{\upsilon}_{max}$ 3263, 3033, 2972, 2826, 1714, 1548, 1486, 1394, 1262,1094, 936, 716, 497; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.93 (s,1H, NH), 9.74 (s,1H, NH), 9.27 (brs, 1H, NH), 7.57-7.49 (m, 1H, ArH), 7.45-7.34 (m, 1H, ArH) 7.32-7.19 (m, 1H, ArH), 6.94 (t, J = 7.5Hz, 1H, ArH), 2.12 (t, J = 7.5Hz, 2H, CH_2), 1.78-1.39 (m, 2H, CH_2), 1.27-0.98 (m, 8H, 4CH_2), 0.91-0.71 (m, 3H, CH_3); EI-MS m/z (rel. int.%): 311 (M^+, 5), 222 (5), 155 (8), 154 (10), 153 (100), 127 (7), 111 (34), 109 (10), 95 (18), 75 (10), 57 (8).

4-(3-fluorophenyl)-1-decanoylthiosemicarbazide **(3i).** Yield: 90%; m.p.100°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3226, 3011, 2939, 2824, 1648, 1537, 1362, 8020, 736, 609; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.92-9.76 (m, 1H, NH), 9.75-9.53 (m, 1H, NH), 8.91 (s,1H, NH), 7.57-7.46 (m, 1H, ArH), 7.42-7.32 (m, 1H, ArH), 7.31-7.22 (m,1H, ArH), 6.99 (t, J = 7.43Hz, 1H, ArH), 2.18 (t, J = 7.4Hz, 2H, CH_2), 1.61-1.42 (m, 2H, CH_2), 1.38-1.13 (m, 12H, 6CH_2), 0.87 (t, J = 6.4Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 339 (M^+, 8), 155 (5), 154 (8), 153 (100), 121 (8), 111 (13), 95 (35), 75 (12), 71 (8).

4-(3-fluorophenyl)-1-undecanoylthiosemicarbazide **(3j).** Yield:86%; m.p.105°C; IR(ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3187, 3036, 2925, 2846, 1688, 1527, 1479, 1386, 1235, 1046, 676; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.99 (s, 1H, NH), 9.67 (brs, 1H, NH), 9.22 (s, 1H, NH), 7.67-7.31 (m, 2H, ArH), 7.31-7.21 (m,1H, ArH), 7.08-6.87 (m, 1H, ArH), 2.17 (t, J = 7.4Hz, 2H, CH_2), 1.64-1.41 (m, 2H,CH_2), 1.34-1.14 (m, 14H, 7CH_2), 0.86 (t, J = 6.51 Hz, 3H,CH_3); EI-MS m/z (rel. int.%): 185 (7), 169 (5), 155 (5), 154 (8), 153 (100), 126 (7), 111 (10), 109 (7), 95 (33), 75 (11), 57 (5).

4-(4-Fluorophenyl)-1-pentanoylthiosemicarbazide **(3k).** Yield:75%; m.p.112°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3223, 2822, 1646, 1535, 1357, 728; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.16 (s, 1H, NH), 9.97 (s, 1H, NH), 9.71 (s, 1H, NH), 7.59-7.39 (m, 2H, ArH), 7.36-7.17 (m, 2H, ArH), 2.18 (t, J = 7.5Hz, 2H, CH_2), 1.69-1.52 (m, 2H, CH_2), 1.43-1.24 (m, 2H, CH_2,), 0.91 (t, J = 6.7Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 218 (5), 155 (9), 154 (7), 153 (100), 133 (7), 109 (8), 95 (31), 75 (9), 57 (8).

4-(4-Fluorophenyl)-1-Heptanoylthiosemicarbazide **(3l).** Yield:70%; m.p.93°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3248, 3118, 2966, 2858, 1716, 1681, 1556, 1484, 1278, 791, 677; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.12 (s, 1H, NH), 9.96 (s, 1H, NH) 9.68 (s, 1H, NH), 7.56-7.36 (m, 2H, ArH), 7.33-7.14 (m, 2H, ArH,), 2.15 (t, J = 7.52Hz, 2H, CH_2) 1.67-1.39 (m, 2H, CH_2), 1.43-1.08 (m, 6H, 3CH_2), 0.85 (t, J = 6.62Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 186 (5), 155 (8), 154 (12), 153 (100), 113 (8), 111 (16), 95 (37), 85 (5), 75 (11), 57 (5).

4-(4-Fluorophenyl)-1-Octanoylthiosemicarbazide **(3m).** Yield: 85%; m.p.120°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3326, 3265, 3022, 2967, 2834, 2849, 1718, 1546, 1484, 1396, 1269,1091, 930, 724, 579; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 10.90 (s, 1H, NH), 9.89 (s, 1H, NH), 9.69 (s, 1H, NH), 7.54-7.35 (m, 2H, ArH), 7.29-7.11 (m, 2H, ArH), 2.09 (t, J = 7.5 Hz, 2H, CH_2), 1.82-1.37 (m, 2H, CH_2), 1.21-0.93 (m, 8H, 4CH_2), 0.94-0.73 (m, 3H, CH_3); EI-MS m/z (rel. int.%): 209 (8), 193 (5), 155 (7), 154 (15), 153 (100) 127 (10), 111 (37), 109 (12), 95 (22), 75 (13), 57 (10).

4-(4-fluorophenyl)-1-decanoylthiosemicarbazide **(3n).** Yield: 75%; m.p.96°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3228, 3015, 2821, 1658, 1306, 1101 , 508, 496; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.40 (s, 1H, NH), 9.87 (s, 1H, NH), 9.65 (s, 1H, NH), 7.52-7.33 (m, 2H, ArH), 7.26-7.09 (m, 2H, ArH), 2.18 (t, J = 7.4Hz, 2H, CH_2), 1.67-1.38 (m, 2H, CH_2), 1.43-1.09 (m,12H, 6CH_2), 0.89 (t, J = 6.3Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 321 (8), 185 (8), 155 (4), 154 (10), 153 (100), 111 (10), 95 (37), 75 (15), 57 (7), 43 (5).

4-(4-fluorophenyl)-1-undecanoylthiosemicarbazide **(3o).** Yield: 77%; m.p.103°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3252, 3193, 3010, 2923, 2844, 1684, 1525, 1474, 1383, 1233, 1049, 672; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.93 (br s, 1H, NH), 9.79 (br s, 1H, NH), 9.54 (br s, 1H, NH), 7.42-7.40 (m, 2H, ArH), 7.16 (t, J = 8.8Hz, 2H, ArH), 2.16 (t, J = 7.2Hz, 2H, CH_2), 1.54-1.50 (m, 2H CH_2), 1.29-1.25 (m, 14H, 7CH_2), 0.8 6(t, J = 6.4Hz, 3H, CH_3). EI-MS m/z (rel. int.%): 222 (5), 169 (7), 155 (5), 154 (8), 153 (100), 121 (5), 111 (13), 95 (30), 84 (7), 75 (10), 57 (7), 43 (5).

General procedure for the synthesis of 1,2,4-triazoles 4(a-o)

The respective thiosemicarbazide **3(a-o)** (1.113 mmol) was mixed portion-wise with a stirred solution of NaOH (5%, 30 mL) and was reflux for 3-4h. On cooling, filtered the reaction mixture and then acidified the filtrate with 6N HCl to pH 2–3. The precipitated product was separated by filtration, then washed thoroughly with water, and purified by recrystallization with EtOH/water.[15]

5-butyl-4-(2-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol **(4a).** Yield: 78%; m.p.128°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3137, 2976, 2706, 1912, 1581, 1329,1178, 696, ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.76 (s, 1H, SH), 7.70-7.57 (m, 3H, ArH), 7.52-7.34 (m,1H, ArH), 2.69 (t, J=7.4Hz, 2H, CH_2), 1.43-1.28 (quin, J = 7.37Hz, 2H, CH_2), 1.26-1.06 (m, 2H, CH_2), 0.85 (t, J = 6.7Hz, 3H, CH_3): EI-MS m/z (rel. int.%): 253 (M+2, 5.6), 251 (M^+, 100), 250 (7), 209 (65), 191 (9), 190 (17), 189 (7), 83 (3), 41 (2).

4-(2-fluorophenyl)-5-hexyl-4H-1, 2, 4-triazole-3-thiol **(4b).** Yield: 80%; m.p.126°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$3237, 3032, 2827, 1667, 1511, 1461, 701; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.79 (s, 1H, SH), 7.67-7.49 (m, 3H, ArH), 7.42 (t, J = 7.6Hz, 1H, ArH), 2.45-2.31 (m, 2H, CH_2), 1.44 (quin, J = 7.2Hz, 2H, CH_2), 1.28-1.11 (m, 6H, 3CH_2), 0.80 (t, J = 6.4Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 281 (M+2, 8),

279 (M^+, 100), 278 (9), 236 (12), 208 (12), 191 (4), 190 (20), 189 (5), 167 (4), 136 (8), 55 (3).

4-(2-fluorophenyl)-5-heptyl-4H-1, 2, 4-triazole-3-thiol

(4c). Yield: 88%; m.p.138°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3159, 2876, 1500, 1491, 1319, 1268, 1072, 998,767, 696, 554; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.80 (s,1H, SH), 7.68-7.57 (m, 3H, ArH), 7.52-7.41 (m, 1H, ArH), 2.42-2.21 (m, 2H, CH_2), 1.44 (quin, J = 7.2Hz, 2H, CH_2), 1.25-1.08 (m, 8H, $4CH_2$), 0.77 (t, J = 6.84 Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 295 (M+2, 6),293 (M^+, 100), 278 (17), 250 (5), 150 (5), 115 (12), 109 (9), 95 (5), 83 (3), 74 (4), 55 (4), 41 (6).

4-(2-fluorophenyl)-5-nonyl-4H-1, 2, 4-triazole-3-thiol

(4d). Yield: 84%; m.p.134°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3188, 2936, 2765, 1640,1500, 727;^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.83 (s, 1H, SH), 7.67-7.61 (m, 1H, ArH), 7.58-7.48 (m, 2H, ArH), 7.42 (t, J = 7.6H, ArH), 2.45-2.32 (m, 2H, CH_2), 1.44 (quin, J = 7.2Hz, 2H, CH_2), 1.27-1.15 (m, 12H, $6CH_2$), 0.84 (t, J = 6.4Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 323 (M+2, 8), 321 (M^+, 100), 320 (18), 306 (15), 264 (18), 236 (17), 223 (15), 222 (92), 209 (62), 208 (8), 190 (18), 189 (8), 55 (5), 41 (7).

5-decyl-4-(2-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol

(4e). Yield: 81%; m.p.124°C; IR (ATR,cm^{-1}): $\bar{\upsilon}_{max}$2926, 2866, 1661, 1550, 1490, 1158, 777, 628; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.81 (s,1H, SH), 7.72-7.60 (m, 1H, ArH), 7.59-7.46 (m, 2H, ArH), 7.45-7.37 (m, 1H, ArH), 2.48-2.26 (m, 2H,CH_2), 1.43 (quin, J = 7.2 Hz, 2H, CH_2), 1.29-1.11 (m, 14H, $7CH_2$), 0.85 (t, J = 6.7Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 337 (M+2, 8), 335 (M^+, 98), 334 (18), 306 (18), 292 (15), 250 (5), 236 (12), 223 (19), 222 (100), 209 (75), 19 (8), 150 (3), 115 (15), 95 (4), 55 (5).

5-butyl-4-(3-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol

(4f). Yield: 81%; m.p. 128°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3117, 2906, 2775, 1992, 1620,1259, 887, 566; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 13.83 (s, 1H, SH), 7.62-7.48 (m, 3H, ArH), 7.38 (d, J = 7.9Hz, 1H, ArH), 2.49 (t, J = 7.6Hz, 2H, CH_2), 1.47 (quin, J = 7.5Hz, 2H, CH_2), 1.37-1.08 (m, 2H, CH_2) ,0.84 (t, J = 6.9Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 253 (M+2, 5), 251 (M^+, 100), 208 (35), 190 (15), 167 (3), 136 (8), 109 (10), 95 (5), 83 (4), 75 (4).

4-(3-fluorophenyl)-5-hexyl-4H-1, 2, 4-triazole-3-thiol

(4g). Yield: 75%; m.p.126°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3257, 3111, 2964, 2896, 1686 ,1491, 808; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.72 (s, 1H, SH), 7.65- 7.59 (m, 1H, ArH), 7.46-7.39 (m, 2H, ArH), 7.30 (d, J = 8.0Hz, 1H, ArH), 2.43 (t, J = 7.6Hz, 2H, CH_2), 1.44 (quin, J = 7.2Hz, 2H, CH_2), 1.25-1.12 (m, 6H, $3CH_2$), 0.80 (t, J = 6.4Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 281 (M+2, 8), 279 (M^+, 100), 78 (14), 250 (7), 222 (50), 209 (42), 191 (4), 150 (4), 136 (12), 109 (8), 83 (4), 55 (3), 41(2).

4-(3-fluorophenyl)-5-heptyl-4H-1, 2, 4-triazole-3-thiol

(4h). Yield: 86%; m.p.122°C;IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$3156, 2879, 1432, 1364, 1100, 1048,627; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 13.68 (s, 1H, SH), 7.59-7.49 (m, 3H, ArH), 7.30 (d, J = 7.8Hz, 1H, ArH), 2.42 (t, J = 7.4Hz, 2H, CH_2), 1.44 (quin, J = 7.5Hz, 2H, CH_2), 1.36-1.07 (m, 8H, $4CH_2$), 0.77 (t, J = 6.8Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 295 (M+2, 6), 293 (M^+, 100), 292 (10), 236 (13), 208 (18), 167 (4), 136 (6), 115 (4), 109 (5), 95 (8), 75 (4).

4-(3-fluorophenyl)-5-nonyl-4H-1, 2, 4-triazole-3-thiol

(4i). Yield: 81%; m.p.132°C; IR(ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3318, 3117, 2856, 1540, 1470, 817; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 12.18 (s, 1H, SH), 7.62 (d, J = 7.8 Hz, 1H, ArH), 7.50-7.38 (m, 2H, ArH), 7.30 (d, J = 7.7Hz, 1H, ArH), 2.43 (t, J = 7.4Hz, 2H, CH_2), 2.18 (t, J = 7.3Hz, 2H, CH_2), 1.53-1.37 (m, 2H, CH_2), 1.32-1.08 (m, 10H, $5CH_2$), 0.89-0.78 (m, 3H, CH_3); EI-MS m/z (rel. int.%): 323 (M+2, 10), 321 (M^+, 100), 320 (12), 288 (9), 278 (9), 264 (9), 250 (5), 236 (12), 223 (18), 222 (62), 209 (47), 191 (4), 167 (4), 150 (4), 115 (8), 95 (5), 73 (3).

5-decyl-4-(3-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol

(4j). Yield: 80%; m.p.124°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3104, 2926, 2826, 1620, 1520, 1420, 1249,717, 626; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.62 (s, 1H, SH), 7.70-7.56 (m, 1H, ArH), 7.47-7.36 (m, 2H, ArH), 7.30 (d, J = 7.7Hz, 1H, ArH), 2.43 (t, J = 7.5Hz, 2H, CH_2), 1.52-1.35 (m, 2H, CH_2), 1.30-1.10 (m, 14H, $7CH_2$), 0.85 (t, J = 6.8Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 337 (M+2, 8), 335 (M^+, 100), 334 (22), 320 (15), 95 (8), 55 (8), 43 (5).

5-butyl-4-(4-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol

(4k). Yield: 75%; m.p.128°C; IR (ATR,cm^{-1}): $\bar{\upsilon}_{max}$ 3104, 2936, 2703, 2313, 1711, 1109, 807; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 13.73 (s, 1H, SH), 7.64-7.45 (m, 1H, ArH), 7.68-7.49 (m, 2H, ArH), 7.31(d, J = 7.9Hz, 1H, ArH), 2.44 (t, J = 7.6Hz, 2H, CH_2), 1.47 (quin, J = 7.5Hz, 2H, CH_2), 1.38-1.09 (m, 2H, CH_2), 0.80 (t, J = 6.9Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 253 (M+2, 5), 251 (M^+, 100), 250 (5), 209 (75), 191 (7), 177.1 (5), 136 (12), 95 (8), 83 (4), 75 (5), 55 (6).

4-(4-fluorophenyl)-5-hexyl-4H-1, 2, 4-triazole-3-thiol

(4l). Yield:82%; m.p.126°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3208, 2935, 2301, 1578, 1130, 671; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.64 (s, 1H, SH), 7.54-7.41 (m, 1H, ArH), 7.43-7.36 (m, 2H, ArH), 7.21 (d, J = 7.8Hz, 1H, ArH), 2.37 (t, J = 7.5Hz, 2H, CH_2), 1.44 (quin, J = 7.4Hz, 2H,CH_2), 1.36-1.06 (m, 6H, $3CH_2$), 0.77 (t, J = 6.8Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 281 (M+2, 5), 279 (M^+, 100), 260 (15), 222 (45), 208 (12), 190 (25), 189 (5), 149 (4), 122.0 (4), 41(2).

4-(4-fluorophenyl)-5-heptyl-4H-1, 2, 4-triazole-3-thiol

(4m). Yield: 80%; m.p.138◦C; IR (ATR,cm-1): $\bar{\upsilon}_{max}$ 3163, 2873, 1410, 1319, 1023, 977, 536; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.61 (s, 1H, SH), 7.51-7.36 (m, 1H, ArH), 7.39-7.28 (m, 2H, ArH), 7.21 (d, J = 7.7Hz, 1H, ArH), 2.34 (t, J = 7.5Hz, 2H, CH_2), 1.44 (quin, J = 7.3Hz, 2H, CH_2), 1.32-1.08 (m, 8H, $4CH_2$), 0.74 (t, J = 6.9Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 295 (M+2, 6), 293 (M^+, 100), 278 (15), 250 (3), 236 (15), 208 (20), 190 (15), 177 (7), 167 (3), 136 (8), 109 (10), 95 (5), 75 (4).

4-(4-fluorophenyl)-5-nonyl-4H-1, 2, 4-triazole-3-thiol

(4n). Yield: 85%; m.p.126°C; IR (ATR,cm^{-1}): $\bar{\upsilon}_{max}$ 3056, 2856, 1 640, 1410, 1118, 666; ^{1}HNMR (400 MHz, DMSO-d_6) δ = 13.73 (s, 1H, SH), 7.56-7.48 (m, 2H, ArH), 7.48-7.33 (m, 2H, ArH), 2.43 (t, J = 7.6Hz, 2H, CH_2), 2.36 (brs, 2H, CH_2), 1.46 (quin, J = 7.1Hz, 2H, CH_2), 1.34-1.09 (m, 10H, $5CH_2$) 0.88 (t, J = 6.9Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 323

(M+2, 4), 321 (M^+, 100), 320 (22), 278 (17), 250 (5), 236 (17), 223 (20), 222 (80), 208 (8), 189 (8), 167 (3), 136 (8), 109 (10), 95 (8), 75 (4).

5-decyl-4-(4-fluorophenyl)-4H-1, 2, 4-triazole-3-thiol **(4o).** Yield: 69%; m.p.124°C; IR (ATR, cm^{-1}): $\bar{\upsilon}_{max}$ 3107, 2966, 2755, 1911, 1088, 1590, 1390, 847, 576; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.69 (s, 1H, SH), 7.53-7.46 (m, 2H, ArH), 7.45-7.36 (m, 2H, ArH), 2.40 (t, J = 7.5Hz, 2H, CH_2), 2.33 (brs 2H, CH_2), 1.43 (quin, J = 7.15Hz, 2H,CH_2), 1.30-1.07 (m, 12H, $6CH_2$), 0.85 (t, J = 6.8Hz, 3H, CH_3); EI-MS m/z (rel. int.%): 337 (M+2, 8), 335 (M^+, 100), 334 (12), 306 (12), 292 (12), 264 (15), 236 (10), 223 (18), 222 (90), 209 (60), 178 (4), 167 (3), 148 (2), 136 (5), 115 (8), 109 (10), 95 (5), 82 (2), 69 (2).

α-glucosidase Inhibition assay

α-glucosidase inhibitory activity of synthetic compounds were determined by previously reported method with slight modifications[19]. A mixture of 200 µL α- glucosidase and 50 µL phosphate buffer (100mM, pH 6.00) was preincubated with 20 µL of varying concentration of each compound and standard for 10min. Then 20 uL of 3 mM p-nitrophenyl glucopyranoside (pNPG) was added as substrate and incubated further at 20°C for 15 min. Then, 2 mL of 0.1 Na_2CO_3 was added to stop the reaction. The absorbance of *p*.nitrophenol released from pNPG was measured at 405 nm using Perkin Elmer lambda 25 double beam UV-Visible spectrophotometer. Acarbose was used as a standard. The percentage inhibition was calculated as concentrations of compounds resulting in 50% inhibition of enzyme activity (IC_{50}).

Urease Inhibition assay

Urease inhibitory activity against the selected series of compounds was determined by BioVision's Urease Activity Assay Kit (Colorimetric) using manufacturer's protocol (K378-100). 200 µl of urease enzyme (Sigma Aldrich) was mixed with 200 µL each compound and then 1.2 mL of 1X urea was added and incubated at 37°C for 20 min. After incubation 1 mL of ammonia reagent 1 (K378-100-2) and then ammonia reagent 2 (K378-100-3) and incubated at 37°C for 30 min. then absorbance was measured at 670 nm using Perkin Elmer lambda 25 double beam UV-Visible spectrophotometer. Thiourea was used as a standard. The percentage inhibition was calculated as concentrations of compounds resulting in 50% inhibition of enzyme activity (IC_{50}).

Molecular Docking

Molecular Operating Environment (MOE) package[20]was used to perform molecular docking study in order to explore the binding mode of the synthesized compounds within the active site of urease and α-glucosidase enzyme. The 3D structures of the synthesized compounds were generated using the builder module of MOE. Next, all the compounds were subjected to MOE for protonation, and energy minimization using the default parameters (gradient: 0.05, Force Field: MMFF94X). The structural coordinates of the targeted enzymes were retrieved from protein databank using PDB code 4UBP for urease enzyme, while due to the unavailability of the crystallographic structure of the corresponding enzyme, we used the homology model described by Taha Metal[21] for the α-glucosidase enzyme. Both the structures were prepared using the preparation module of MOE and were subjected for 3D protonation and finally were energy minimized to get a stable conformation of the targeted enzyme. The default parameters of MOEwere used for molecular docking purpose, *i.e.*, Placement: Triangle Matcher, Rescoring-1: London dG, Refinement: Force field, Rescoring-2: GBVI/WSA. For each ligand total, ten conformations were allowed to generate, and the top-ranked conformations based on docking score were selected for protein-ligand interaction (PLI) profile analysis.

CONCLUSION

Thiosemicarbazides were used as intermediates for the synthesis of 1,2,4-triazoles which were then subjected to spectroscopic analysis and evaluated for enzyme inhibitions like ***α***-glucosidase inhibition and urease inhibition. Compounds 4i, 4j, 4k, and 4o with IC_{50} values of 95.91±0.22, 88.24±0.22, 66.47±0.26, 94.21±0.15 [µM] respectively exhibited good *α*-glucosidase inhibition potential, and 4a, 4b, 4c, 4f, 4k with an IC_{50} values 50.3± 0.21, 42.41±0.923, 47.04±0.58, 40.03±1.305, 32.26±1.070 [µM] respectively exhibited good urease inhibition potential.

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