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S-substituted derivatives of 1,2,4-triazol-3-thiol as new drug candidates for type II diabetes

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Abstract: The therapeutic applications of 1,2,4-triazoles motivated us to synthesize some new derivatives. Two series of S-substituted derivatives (**8a**–**8j**, **12a**–**12i**) of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4H-1,2,4-triazol-3-thiol (**6**) have been synthesized and evaluated for their biological potential. Using 4-chlorobenzene sulfonyl chloride (**1**) and ethyl piperidine-3-carboxylate (**2**), ethyl 1-[(4-chlorophenyl)sulfonyl]piperidine-3-carboxylate (**3**) was synthesized and converted into 3,4,5-trisubstituted 1,2,4-triazole (**6**) through formation of the corresponding carbohydrazide (**4**) and hydrazinecarbothioamide (**5**). Compound **6** was transformed into **8a**–**8j** by alkyl halides (**7a**–**7j**) and into **12a**–**12i** by N-aralkyl/aryl-2-bromoacetamides (**11a**–**11i**) in an aprotic solvent. The electrophiles, **11a**–**11i**, were synthesized by gearing up N-substituted aralkyl/aryl amines (**10a**–**10i**) with 2-bromoacetyl bromide (**9**) under dynamic pH control by aqueous sodium carbonate. Structures were elucidated through the spectral techniques of IR, EIMS, ^{1}H NMR, and ^{13}C NMR. Most of the synthesized derivatives were found to be potent inhibitors of α-glucosidase enzyme and even better than acarbose. Acarbose is a reference standard and is a commercially available α-glucosidase inhibitor to treat patients with type II diabetes. The low hemolytic activity also emphasized the potential of the synthesized compounds as new drug candidates.

Key words: 1,2,4-Triazole, sulfonamides, anti-α-glucosidase, hemolytic activity

1. Introduction

Triazole is an aromatic heterocyclic class of compounds containing two carbon atoms and three nitrogen atoms. There are two types of triazoles on the basis of arrangements of nitrogen atoms in five-member heterocyclic rings, 1,2,3-triazole and 1,2,4-triazole. Triazoles are well known for their biological activities and are excessively used as building blocks for the synthesis of a variety of organic compounds.[1] Triazoles are reported as good ligands for chelating polymers that are used for the removal of heavy metals from waste water.[2] Triazoles are well-known pharmacological agents[3] due to a range of bioactivities including anticancer,[4] antimicrobial,[5–7] antidiabetic,[3–5,8–10] and antiobesity[10] ones. Different chromanochalcones bearing 1,2,3-triazole,[4] fluorinated

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1,2,4-triazoles,[5] carbohydrate conjugated 1,2,3-triazoles,[8] and benzothiazoles bearing 1,2,3-triazole[9] were found to be active antidiabetic agents.

$\alpha-$Glucosidase (EC 3.2.1.20) is a glucosidase that works on 1,4-alpha bonds.[11] Mammalian α-glucosidase anchored in the mucosal brush border of the small intestine catalyzes the end-step digestion of starch and sucrose, which are abundant carbohydrates in the human diet.[12] α-Glucosidase inhibitors delay the breakdown of carbohydrate in the small intestine and diminish the postprandial blood glucose excursion in diabetic subjects.[13] Thus, these have a lowering effect on postprandial blood glucose and insulin levels. Commercially available α-glucosidase inhibitors such as acarbose, miglitol, and voglibose are widely used to treat patients with type II diabetes.[3−5,8−10,14]

Some series of sulfonamides were previously synthesized by our group and found to possess inhibition potential against the α-glucosidase enzyme.[15−17] These compounds previously synthesized by our group and a literature review[3−5,8−10] of triazoles prompted us to synthesize some series of compounds bearing these active functionalities. In search of new biologically potent molecules with the least toxicity, two new series of *S*-substituted derivatives of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-thiol were synthesized. A variety of functional moieties have been grouped together as a single unit to enhance their pharmaceutical potential. All the derivatives were screened for α-glucosidase inhibition and hemolytic activity. Most of the derivatives revealed moderate to good α-glucosidase inhibition potential. The most potent molecules might be further processed for the control of type II diabetes.

2. Result and discussion

The synthetic route for the title compounds (**8a**–**8j**, **12a**–**12i**) is described in the Scheme. The structures of all synthesized derivatives were elucidated by spectroscopic data analysis. The screening against the α-glucosidase enzyme revealed most of the synthesized compounds as good inhibiting agents that might be used for the treatment of type II diabetes. Two compounds, **8a** and **8j**, were found inactive. The results for α-glucosidase enzyme inhibition and hemolytic activity are given in Table 1. The molecular docking interactions are listed in Table 2.

2.1. Chemistry

Ethyl 1-[(4-chlorophenyl)sulfonyl] piperidine-3-carboxylate (**3**) was synthesized from ethyl nipecotate (**2**) and 4-chlorophenylsulfonyl chloride (**1**) and then refluxed with hydrated hydrazine in methanol. The resultant hydrazide was refluxed with phenyl isothiocyanate and subsequently the product obtained was cyclized on reflux in the presence of 10% NaOH to get compound **6**. A series of *N*-aralkyl/aryl-2-bromoacetamides (**11a**–**11i**) was prepared from *N*-aralkyl/aryl amines (**10a**–**10i**). Target compounds (**8a**–**8j**, **12a**–**12i**) were synthesized by gearing up compound **6** with a series of alkyl halides (**7a**–**7j**) and a series of *N*-aralkyl/aryl-2-bromoacetamides (**11a**–**11i**).

The molecular formulae of the synthesized compounds were established through their EIMS spectral data and the integration curves of protons in their ^{1}H NMR spectra. In the IR spectra, the C = N and C - N peaks were obtained in the range of 1550–1570 cm^{-1} and 1230–1260 cm^{-1}, respectively. Among the other characteristic signals, the SO_2 group of sulfonamide linkage and C - Cl stretching appeared around 1360–1395 cm^{-1} and 810–850 cm^{-1}, respectively. The characteristic signal of carbonyl stretching of acetamide moiety **(12a**–**12i)** appeared around 1660–1680 cm^{-1}. In the ^{1}H NMR spectra, relatively deshielded signals of ring C (Scheme) gave a pattern of two doublets, indicating a 1,4-disubstituted phenyl ring, each doublet with integration

Table 1. Hemolytic and anti α-glucosidase activity of all synthesized derivatives.

Compound	% Hemolysis	$\alpha-$Glucosidase	
		Inhibition (%) at 0.5 mM	IC_{50} (μM)
8a	8.2	15.41 ± 0.13	-
8b	11.6	78.12 ± 0.18	225.14 ± 0.12
8c	7.0	95.17 ± 0.13	21.23 ± 0.05
8d	7.5	82.13 ± 0.19	197.42 ± 0.12
8e	7.2	78.34 ± 0.16	225.15 ± 0.14
8f	8.6	94.19 ± 0.14	53.42 ± 0.03
8g	7.2	95.83 ± 0.12	35.28 ± 0.02
8h	5.5	67.12 ± 0.19	279.32 ± 0.15
8i	8.5	91.52 ± 0.12	83.54 ± 0.09
8j	11.5	43.12 ± 0.12	-
12a	8.3	51.36 ± 0.14	> 500
12b	8.7	91.27 ± 0.19	72.42 ± 0.13
12c	10.3	91.29 ± 0.15	41.16 ± 0.12
12d	12.4	92.17 ± 0.13	34.27 ± 0.11
12e	8.0	89.73 ± 0.18	194.21 ± 0.14
12f	12.0	92.27 ± 0.12	31.23 ± 0.08
12g	8.8	92.25 ± 0.17	35.24 ± 0.12
12h	6.0	91.29 ± 0.16	45.28 ± 0.12
12i	6.3	92.18 ± 0.19	31.24 ± 0.13
Triton X-100	99.27		
PBS	0.12		
Acarbose		92.23 ± 0.16	37.38 ± 0.12

of two protons in the aromatic region at δ 7.60–7.65 ppm and 7.47–7.52 ppm. Ring B (Scheme) revealed splitting of axial and equatorial protons of different positions of the piperidine ring in the aliphatic region of ^{1}H NMR spectra. Ring D (Scheme) revealed one doublet for two protons and a triplet for three protons around δ 7.28–7.20 ppm and δ 7.64–7.57 ppm, respectively, indicating the presence of a monosubstituted phenyl ring. Two characteristic doublets at δ 4.05–3.88 ppm and 4.00–3.83 ppm with J-coupling 14.2 Hz were attributed to methylene protons of the acetamide moiety of **12a**–**12i**. Different alkyl/aralkyl/aryl substituents gave their characteristic splitting patterns separately. In ^{13}C NMR spectra the two quaternary carbons of the triazole ring appeared around δ 157.1–155.0 ppm and 153.3–151.0 ppm, with most deshielded signals due to attached heteroatoms and delocalized electrons, while two quaternary carbons of ring C appeared around δ 140.4–139.0 ppm and 138.5–133.5 ppm due to the electron-withdrawing sulfonyl group and electronegative inductive effect of the attached chlorine atom while four methine carbons of ring C appeared around δ 130.0–131.9 ppm and 130.9–129.0 ppm, each for two tertiary carbons. Ring B carbons gave signals around δ 49.9–24.0 ppm. A single quaternary carbon of ring D appeared around δ 131.5–133.5 ppm. Ffive methine carbons were observed at δ 130.9–128.0, 129.9–128.0, and 127.9–126.0 ppm. In **12a**–**12i** the most deshielded signal at δ 168.9–165.0 ppm was attributed to the carbonyl carbon of acetamide moiety while the methylene carbon of acetamide moiety

Table 2. Molecular docking studies.

Compound	$\alpha-$Glucosidase		
	Interactions	Functionality	Bond distance, Å
8c	Acidic	Lys422 : NH - O : SO_2	2.25
	Arene - Cation	Arg404 with phenyl of triazole ring	3.44
	Arene - Arene	Trp271 with triazole ring	3.78
8g	Acidic	Lys422 : NH - O : SO_2	2.41
	Arene - Cation	Arg404 with phenyl of triazole ring	3.48
12d	Acidic	Lys422 : NH - O : SO_2	2.54
	Arene - Cation	Lys422 with 4-chlorophenyl ring	3.06
		Lys422 with phenyl of triazole ring	3.31
12f	Acidic	Arg404 : NH - O : SO_2	2.74
	Arene - Cation	Lys422 with phenyl of triazole ring	3.14
12g	Acidic	Lys422 : NH - O : SO_2	2.32
	Arene - Cation	Lys422 with phenyl of triazole ring	3.88
		Arg404 with triazole ring	2.68
12i	Acidic	Lys422 : NH - O : SO_2	2.71
		Arg404 with triazole ring	2.06
	Arene - Cation	Lys422 with 4-chlorophenyl ring	3.86

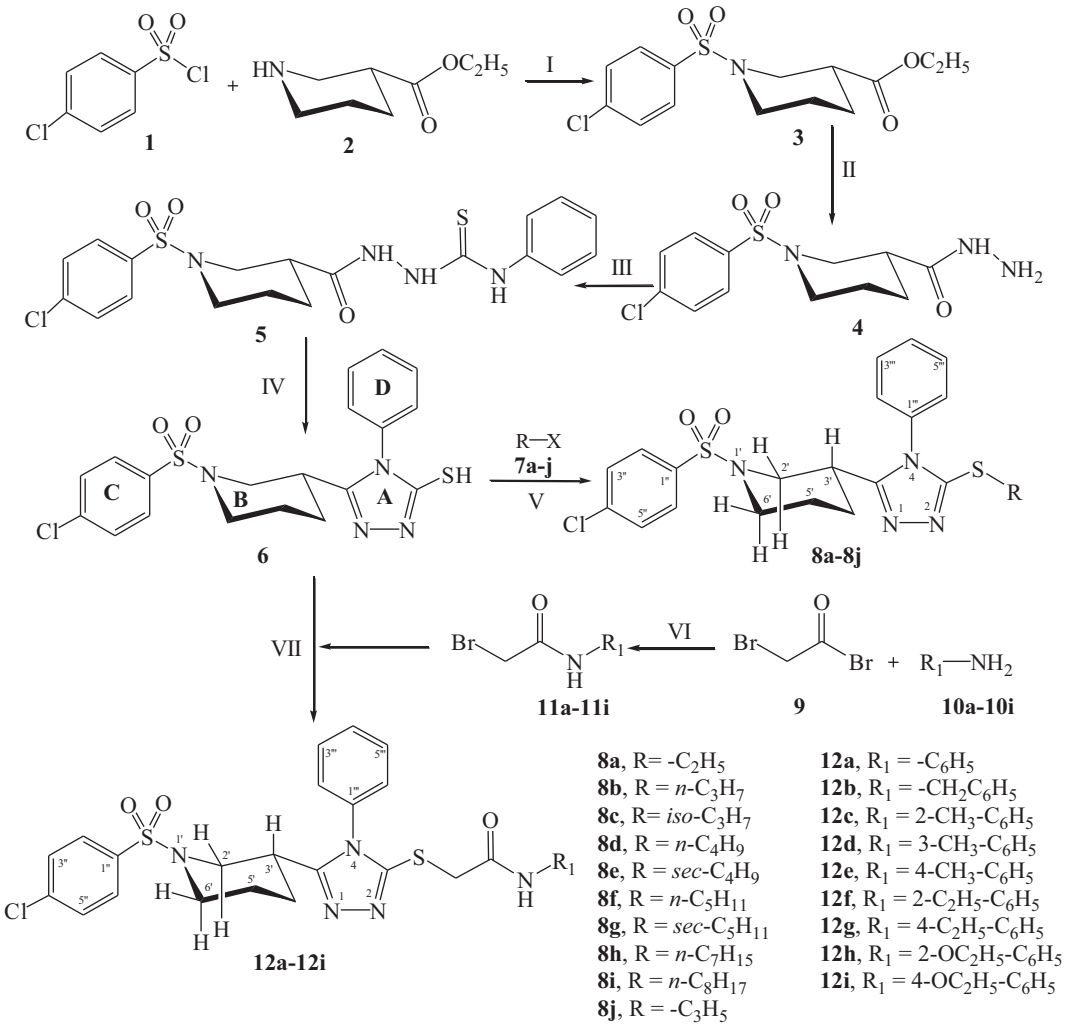
was recorded at δ 33.5–32.0 ppm. Alkyl/aralkyl/aryl substituents showed their characteristic signals at their corresponding δ values. EIMS spectra showed the characteristic splitting pattern by signals at m/z 284, 258, 175, and 111. A base peak corresponding to p-chlorophenyl sulfonyl moiety appeared at $m/z = 175$. In **12a**–**12i**, sometimes the moiety formed by the fragmentation of aralkyl/aryl amine appeared as a base peak. EIMS spectra confirmed the M^+ peaks for all derivatives. On the basis of all these spectroscopic data, the structures of all synthesized derivatives were corroborated.

2.2. Hemolytic activity

All derivatives (**8a**–**8j**, **12a**–**12i**) were screened for hemolytic activity. The % lysis values are described in Table 1 for each derivative. Phosphate-buffered saline (PBS) was used as a negative control while Triton X-100 was the positive control. Compounds **8b**, **8j**, **12d**, and **12f** were reported to possess the highest % lysis at 11.6, 11.5, 12.4, and 12, respectively. The lowest % lysis was recorded for compound **8h** as 5.5, probably because of the S-substituted straight-chain heptyl group exhibiting an electron-donating effect. Compounds **12h** and **12i** also exhibited low % lysis potential at 6 and 6.3, respectively, probably due to the ethoxy-substituted phenyl ring, which exhibited an electron-donating effect. The low % lysis of the derivatives rendered them the least cytotoxic.

2.3. α-Glucosidase inhibition and molecular docking

All derivatives **8a**–**8j** and **12a**–**12i** were screened for α-glucosidase inhibitory potential and found to exhibit excellent to moderate inhibitory action. Acarbose was used as a positive control. The % inhibition and IC_{50} values are presented in Table 1. To study the interactions responsible for the α-glucosidase inhibitory potential



Scheme. Outline for the synthesis of *S*-substituted derivatives of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazole-3-thiol (**8a**–**8j**, **12a**–**12i**). Reagents & conditions: (I) 5% Na_2CO_3 soln. / H_2O / pH 9–10 / stirring for 3–4 h. (II) N_2H_4 / MeOH / refluxing for 5–6 h. (III) Phenyl isothiocyanate / MeOH / refluxing for 3–4 h. (IV) 10% NaOH / refluxing for 2–3 h. (V) DMF / NaH / stirring for 2–3 h. (VI) Aq. 5% Na_2CO_3 / stirring for 30 min. (VII) DMF / NaH / stirring for 2–3 h.

of the target compounds, molecular docking studies were carried out. The different molecular interactions of the most active compounds are listed in Table 2. Some of the derivatives revealed excellent IC_{50} values, even better than those of the positive control, acarbose. Compounds **8c**, **8g**, **12d**, **12f**, **12g**, and **12i** revealed excellent IC_{50} (μM) values of 21.23 ± 0.05, 35.28 ± 0.02, 34.27 ± 0.11, 31.23 ± 0.08, 35.24 ± 0.12, and 31.24 ± 0.13, respectively, as compared to that of acarbose, 37.38 ± 0.12. These six compounds exhibited better inhibition potential than that of acarbose. The excellent inhibitory potential of **8c** and **8g** may be credited to the presence of isopropyl and 2-pentyl groups attached to the triazole ring through sulfur, respectively. Among all the aliphatic groups, the branched ones remained more efficient and those are also propyl and pentyl groups. Among the remaining compounds, **8f** bearing a 1-pentyl group showed moderate activity, having an IC_{50} value of 53.42 ± 0.03 μM. Compounds **8a** and **8j**, bearing ethyl and allyl groups, respectively, were

found to be inactive. Molecular docking studies revealed that compound **8c** exhibited acidic, arene-cation, and arene-arene interactions among Lys422, Arg404, and Trp271 of the α-glucosidase enzyme with bond lengths (Å) of 2.25, 3.44, and 3.78, respectively. A strong hydrogen bond interaction was observed with Lys422 of the glucosidase enzyme by the oxygen of the sulfonyl group. These strong interactions and the three-dimensional orientation of compound **8c** might be responsible for its excellent α-glucosidase inhibitory potential (Figure 1). Compound **8g** exhibited one acidic and one arene-cation interaction with Lys422 and Arg404 of the glucosidase enzyme with bond lengths (Å) of 2.41 and 3.48, respectively. The acidic interaction was shown by the sulfonyl group with Lys422 and arene-cation interaction by the phenyl ring attached to the triazole moiety with Arg404 of the glucosidase enzyme. These strong interactions with short bond distances and 3D-orientation adopted by the *sec*-pentyl-substituted compound might be responsible for α-glucosidase inhibitory potential (Figure 2). The excellent inhibitory potential of **12d**, **12f**, **12g**, and **12i** may be attributed to the presence of 3-methylphenyl, 2-ethylphenyl, 4-ethylphenyl, and 4-ethoxyphenyl groups, respectively, attached to the nitrogen of amide functionality. The ethyl substitution was rendered more potent at both the *ortho* and *para* positions of the phenyl ring, but the substitution of methyl and ethoxy groups remained effective only at the *meta* and *para* positions, respectively. Among the remaining compounds, **12c** and **12h**, bearing 2-methylphenyl and 2-ethoxyphenyl, respectively, showed moderate activity, having IC_{50} values of 41.16 $\pm$ 0.12 and 45.28 $\pm$ 0.12 μM. Molecular docking studies revealed that Lys422 of the α-glucosidase enzyme showed one acidic and two arene-cation interactions with the sulfonyl oxygen, 4-chloro phenyl ring, and phenyl ring attached to the triazole moiety of ligand **12d** indicating bond lengths (Å) of 2.54, 3.06, and 3.31, respectively. These strong acidic and arene-cation interactions might be responsible for the better inhibitory potential of compound **12d** than that of the reference, acarbose (Figure 3). Compound **12f** exhibited strong acidic and arene-cation interactions with Arg404 and Lys422 of the glucosidase enzyme with bond lengths (Å) of 2.74 and 3.56, respectively (Figure 4). Compound **12g** developed very strong acidic and arene-cation interactions with Lys422 through bond distances (Å) of 2.32 and 3.88. Another arene-cation binding with Arg404 through bond distance (Å) of 2.68 was also observed (Figure 5). Compound **12i** developed two acidic interactions with Lys422 through the sulfonyl oxygen of sulfamoyl moiety and Arg404 through the triazole ring, and one arene-cation interaction with Lys422 through 4-chlorophenyl moiety. The bond lengths (Å) were found to be 2.71, 3.86, and 2.06, respectively (Figure 6).

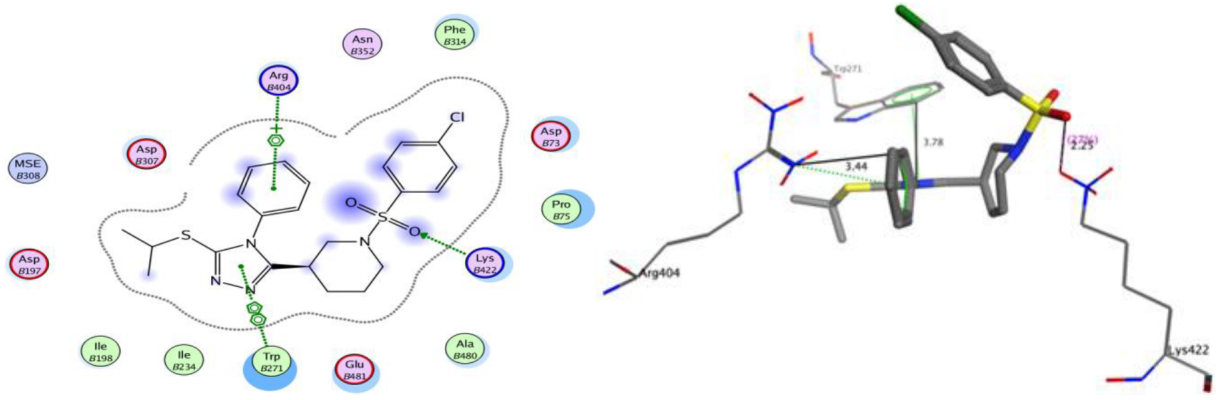


Figure 1. Molecular docking interactions of compound **8c** (2D & 3D).

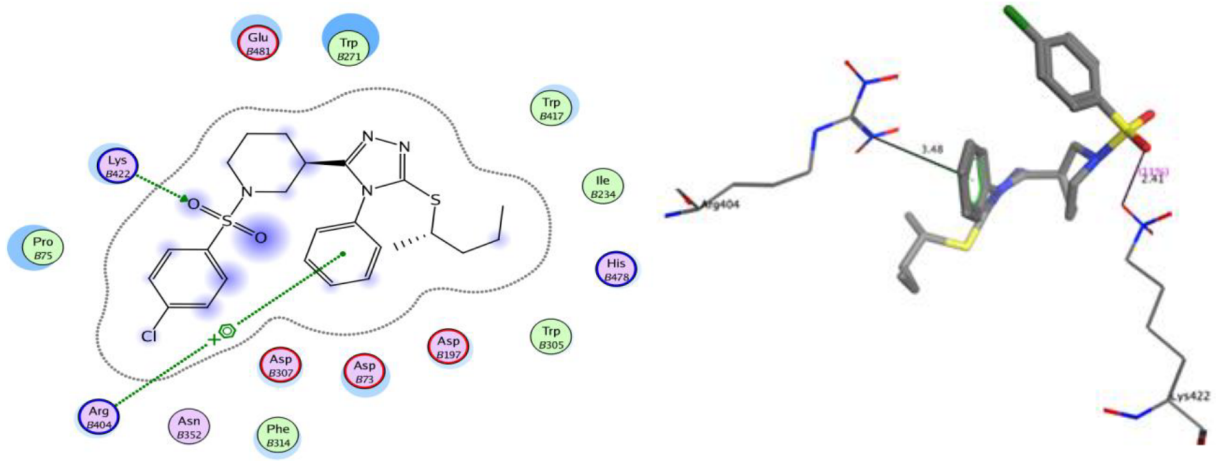


Figure 2. Molecular docking interactions of compound **8g** (2D & 3D).

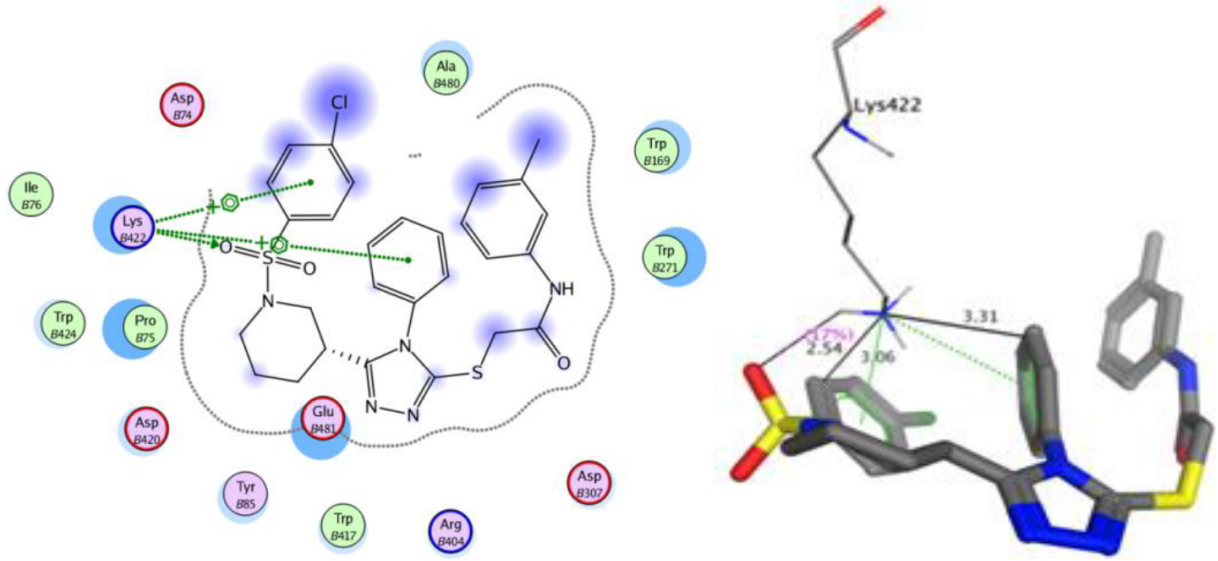


Figure 3. Molecular docking interactions of compound **12d** (2D & 3D).

2.4. Conclusions

The synthesized compounds were structurally elucidated by spectroscopic analysis. The bioactivity results in Table 1 and Table 2 show that the series of synthesized compounds presented notable inhibitory action against the α-glucosidase enzyme. The subtle variation in structure has greatly affected the bioactivity results. The most active molecules might be considered for drug development programs to treat type II diabetes.

3. Experimental

3.1. General

The chemicals required to carry out the presented research project were from Merck and Sigma-Aldrich and purchased from local suppliers. A Gallenkamp digital melting point apparatus was used to record the melting points of all synthesized derivatives by open capillary tube and were uncorrected. Purity of all derivatives was confirmed by TLC using EtOAc and n-hexane as the mobile phase. A UV lamp operating at 254 nm was

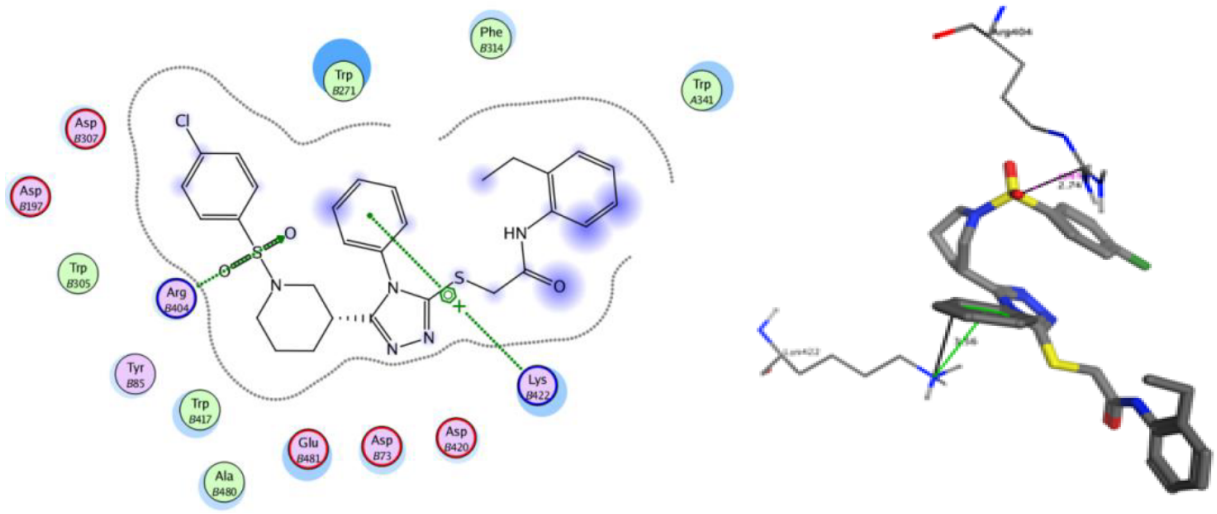


Figure 4. Molecular docking interactions of compound **12f** (2D & 3D).

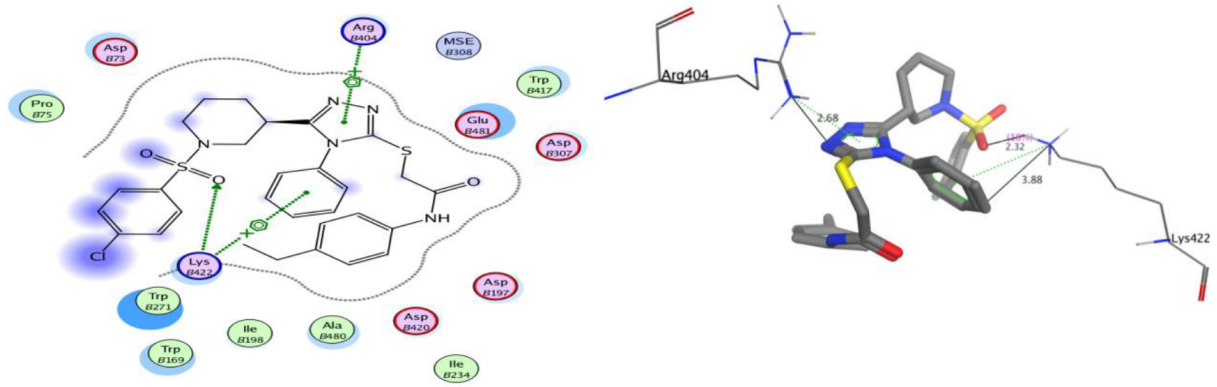


Figure 5. Molecular docking interactions of compound **12g** (2D & 3D).

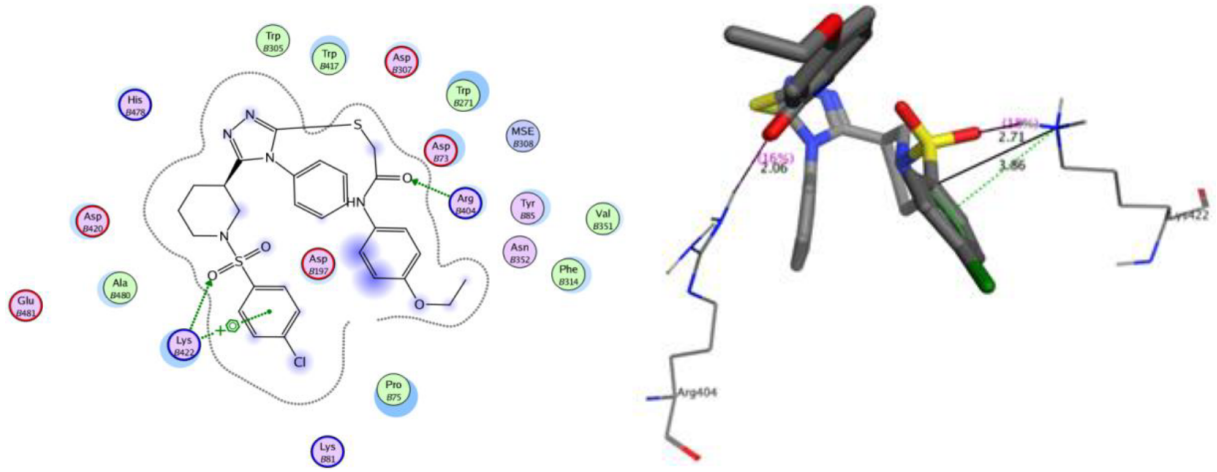


Figure 6. Molecular docking interactions of compound **12i** (2D & 3D).

used to observe the developed TLC. A Jasco FTIR spectrometer was used to record IR spectra through the KBr pellet method. ^{1}H NMR and ^{13}C NMR were recorded on Bruker spectrometers operating at 500 and 600 MHz and at 125 and 150 MHz, respectively, using chloroform-d_1 as solvent and TMS as reference standard. A JMS-HX 110 spectrometer was used to record EIMS spectra.

3.2. Synthesis of ethyl 1-[(4-chlorophenyl)sulfonyl]piperidine-3-carboxylate (3)

Ethyl piperidine-3-carboxylate (**2**; 0.05 mol) was suspended in an aqueous medium under controlled pH of 10–11. pH was controlled by drops of aqueous 5% Na_2CO_3 solution. 4-Chlorobenzenesulfonyl chloride (**1**; 0.05 mol) was added gradually and the mixture was stirred for 3–4 h. Reaction completion was confirmed by TLC. To quench the precipitates, cold distilled water was added and precipitates were filtered, washed, and dried.

3.3. Synthesis of 1-[(4-chlorophenyl)sulfonyl]piperidine-3-carbohydrazide (4)

Compound **3** (0.04 mol) and hydrazine hydrate (0.04 mol) were allowed to reflux in methanol (40 mL) for 5–6 h. Reaction completion was confirmed by TLC. Excess methanol was distilled off and cold water was used to obtain the precipitates. The formed precipitates were filtered, washed, and dried.

3.4. Synthesis of 2-({1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}carbonyl)-*N*-phenyl-1-hydrazinecarbothioamide (5)

Compound **4** (0.03 mol) was refluxed with phenyl isothiocyanate (0.03 mol) in the presence of methanol (100 mL) in a 250-mL round bottom flask for 3–4 h. Reaction was monitored by TLC. On completion of the reaction, methanol was distilled off and distilled water was added to separate out the precipitates. The product was filtered, washed, and dried.

3.5. Synthesis of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-thiol (6)

Compound **5** (0.02 mol) was refluxed in a basic aqueous medium of 10% NaOH solution for 2–3 h. Upon reaction completion, confirmed by TLC, the reaction mixture was allowed to cool to room temperature. Reaction contents were acidified by dil. HCl up to pH 4–5. White precipitates were collected, washed, and dried.

3.6. Synthesis of *N*-aralkyl/aryl-2-bromoacetamides (11a–11i)

N-substituted aralkyl/aryl amines (**10a**–**10i**, 5 mmol) were suspended in 5% Na_2CO_3 solution and distilled water (15 mL), and dynamic pH was controlled at about 9–10. 2-Bromoacetyl bromide (**9**, 5 mmol) was introduced to the reaction flask slowly with vigorous shaking and set to stir for 30 min. Reaction completion and product purity were confirmed by TLC. The precipitates of *N*-aralkyl/aryl-2-bromoacetamides (**11a**–**11i**) were filtered, washed, and dried for the final step of reaction.

3.7. Synthesis of *S*-substituted derivatives of 5-{1-[(4-chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-thiol (8a–8j, 12a–12i)

Compound **6** (0.2 g, 0.46 mmol) was stirred with NaH for 30 min in DMF (15 mL). Equimolar alkyl halides (**7a**–**7j**, 0.46 mmol) and *N*-aralkyl/aryl-2-bromoacetamides (**11a**–**11i**, 0.46 mmol) were added and stirred for

2–3 h. To collect the precipitates, distilled water was added to reaction contents followed by filtration, washing, and drying.

3.7.1. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl ethyl sulfide (8a)

Light yellow, sticky; yield: 81%; molecular formula: $C_{21}H_{23}ClN_4O_2S_2$; molecular mass: 463.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3051 (Ar - H), 1563 (C = N), 1548 (Ar C = C), 1363 (-SO_2), 1230 (C - N), 818 (C - Cl); ^{1}H NMR ($CDCl_3$, 500 MHz, δ/ ppm): 7.65 (d, J = 8.0 Hz, 2H, H - 2″ & H - 6″), 7.62–7.61 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.26–7.24 (m, 2H, H - 2‴ & H - 6‴), 3.93 (d, J = 9.6 Hz, 1H, H_e - 2′), 3.78 (d, J = 11.6 Hz, 1H, H_a - 2′), 3.22 (q, J = 6.1 Hz, 2H, H - 1⁗), 2.81 - 2.78 (m, 1H, H - 3′), 2.74 (t, J = 11.1 Hz, 1H, H_e - 6′), 2.31 (dt, J = 12.0, 2.6 Hz, 1H, H_a - 6′), 1.88–1.86 (m, 1H, H_e - 4′), 1.80–1.76 (m, 1H, H_e - 5′), 1.68–1.60 (m, 1H, H_a - 5′), 1.58–1.49 (m, 1H, H_a - 4′), 1.40 (t, J = 7.3 Hz, 3H, H - 2⁗); ^{13}C NMR ($CDCl_3$, 125 MHz, δ/ ppm): 155.9 (C - 5), 152.1 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.7 (C - 1‴), 130.5 (C - 4‴), 130.3 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.1 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 32.9 (C - 3′), 29.1 (C - 4′), 26.9 (C - 1⁗), 24.3 (C - 5′), 14.7 (C - 2⁗); EIMS (m/z): 465 $[M + 2]^+$, 463 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 29 $[C_2H_5]^+$.

3.7.2. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl propan-1-yl sulfide (8b)

White, sticky; yield: 83%; molecular formula: $C_{22}H_{25}ClN_4O_2S_2$; molecular mass: 477.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3057 (Ar - H), 1565 (C = N), 1541 (Ar C = C), 1366 (-SO_2), 1238 (C - N), 812 (C - Cl); ^{1}H NMR ($CDCl_3$, 500 MHz, δ/ ppm): 7.65 (d, J = 8.4 Hz, 2H, H - 2″ & H - 6″), 7.63–7.61 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.26–7.24 (m, 2H, H - 2‴ & H - 6‴), 3.92 (d, J = 9.6 Hz, 1H, H_e - 2′), 3.78 (d, J = 11.6 Hz, 1H, H_a - 2′), 3.18 (t, J = 7.1 Hz, 2H, H - 1⁗), 2.81–2.76 (m, 1H, H - 3′), 2.74 (br.t, J = 11.0 Hz, 1H, H_e - 6′), 2.30 (td, J = 11.7, 2.4 Hz, 1H, H_a - 6′), 1.88–1.85 (m, 1H, H_e - 4′), 1.80–1.76 (m, 1H, H_e - 5′), 1.74 (qui, J = 7.2 Hz, 2H, H - 2⁗), 1.68–1.60 (m, 1H, H_a - 5′), 1.58–1.48 (m, 1H, H_a - 4′), 1.00 (t, J = 7.3 Hz, 3H, H - 3⁗); ^{13}C NMR ($CDCl_3$, 125 MHz, δ/ppm): 155.9 (C - 5), 152.4 (C - 3), 139.4 (C - 1″), 134.9 (C - 4″), 132.7 (C - 1‴), 130.5 (C - 4‴), 130.3 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.1 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 34.4 (C - 3′), 32.9 (C - 1⁗), 29.1 (C - 4′), 24.3 (C - 5′), 22.7 (C - 2⁗), 13.2 (C - 3⁗); EIMS (m/z): 479 $[M + 2]^+$, 477 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 43 $[C_3H_7]^+$.

3.7.3. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl isopropyl sulfide (8c)

Light yellow, sticky; yield: 79%; molecular formula: $C_{22}H_{25}ClN_4O_2S_2$; molecular mass: 477.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3041 (Ar - H), 1553 (C = N), 1541 (Ar C = C), 1373 (-SO_2), 1240 (C - N), 828 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.64 (d, J = 8.4 Hz, 2H, H - 2″ & H - 6″), 7.61–7.60 (m, 3H, H - 3‴

to H - 5‴), 7.50 (d, J = 8.2 Hz, 2H, H - 3″ & H - 5″), 7.24–7.22 (m, 2H, H - 2‴ & H - 6‴), 3.93 (d, J = 9.8 Hz, 1H, H_e - 2′), 3.87 (sep, J = 6.7 Hz, 1H, H - 1⁗), 3.78 (br.d, J = 11.5 Hz, 1H, H_a - 2′), 2.80–2.76 (m, 1H, H - 3′), 2.74 (t, J = 10.9 Hz, 1H, H_e - 6′), 2.30 (td, J = 11.9, 2.2 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.78–1.76 (m, 1H, H_e - 5′), 1.65–1.59 (m, 1H, H_a - 5′), 1.56–1.48 (m, 1H, H_a - 4′), 1.38 (d, J = 6.7 Hz, 6H, H - 2⁗ & H - 3⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.8 (C - 5), 151.7 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.8 (C - 1‴), 130.4 (C - 4‴), 130.2 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.2 (C - 2‴ & C - 6‴), 49.3 (C - 2′), 46.0 (C - 6′), 38.7 (C - 3′), 33.0 (C - 1⁗), 29.1 (C - 4′), 24.3 (C - 5′), 23.4 (C - 2⁗ & C - 3⁗); EIMS (m/z): 479 $[M + 2]^+$, 477 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 43 $[C_3H_7]^+$.

3.7.4. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl butan-1-yl sulfide (8d)

Light yellow, sticky; yield: 77%; molecular formula: $C_{23}H_{27}ClN_4O_2S_2$; molecular mass: 491.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3047 (Ar - H), 1556 (C = N), 1545 (Ar C = C), 1378 (-SO_2), 1242 (C - N), 832 (C - Cl); ^{1}H NMR ($CDCl_3$, 500 MHz, δ/ppm): 7.64 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.61–7.60 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.25–7.24 (m, 2H, H - 2‴ & H - 6‴), 3.92 (br.d, J = 10.1 Hz, 1H, H_e - 2′), 3.78 (br.d, J = 11.5 Hz, 1H, H_a - 2′), 3.19 (t, J = 7.3 Hz, 2H, H - 1⁗), 2.78–2.75 (m, 1H, H - 3′), 2.72 (br.t, J = 11.1 Hz, 1H, H_e - 6′), 2.30 (td, J = 11.9, 2.6 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.79–1.74 (m, 1H, H_e - 5′), 1.71 (qui, J = 7.5 Hz, 2H, H - 2⁗), 1.63–1.56 (m, 1H, H_a - 5′), 1.54–1.50 (m, 1H, H_a - 4′), 1.42 (sex, J = 7.5 Hz, 2H, H - 3⁗), 0.91 (t, J = 7.4 Hz, 3H, H - 4⁗); ^{13}C NMR ($CDCl_3$, 125 MHz, δ/ppm): 155.9 (C - 5), 152.3 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.8 (C - 1‴), 130.4 (C - 4‴), 130.2 (C - 2″ & C - 6″), 129.4 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.1 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 32.9 (C - 3′), 32.2 (C - 2⁗), 31.3 (C - 4′), 29.1 (C - 1⁗), 24.3 (C - 5′), 21.7 (C - 3⁗), 13.5 (C - 4⁗); EIMS (m/z): 493 $[M + 2]^+$, 491 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 57 $[C_4H_9]^+$.

3.7.5. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl 1-methylpropan-1-yl sulfide (8e)

Light yellow, crystalline; yield: 79%; mp: 70–72 °C; molecular formula: $C_{23}H_{27}ClN_4O_2S_2$; molecular mass: 491.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3049 (Ar - H), 1558 (C = N), 1547 (Ar C = C), 1374 (-SO_2), 1245 (C - N), 835 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.65 (d, J = 8.4 Hz, 2H, H - 2″ & H - 6″), 7.62–7.61 (m, 3H, H - 3‴ to H - 5‴), 7.51 (d, J = 8.4 Hz, 2H, H - 3″ & H - 5″), 7.24–7.23 (m, 2H, H - 2‴ & H - 6‴), 3.93 (br.d, J = 10.3 Hz, 1H, H_e - 2′), 3.78 (br.d, J = 11.4 Hz, 1H, H_a - 2′), 3.73–3.69 (m, 1H, H - 1⁗), 2.80–2.76 (m, 1H, H - 3′), 2.74 (br.t, J = 11.1 Hz, 1H, H_e - 6′), 2.30 (td, J = 11.8, 2.4 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.78–1.76 (m, 1H, H_e - 5′), 1.73 (qui, J = 7.1 Hz, 2H, H - 2⁗), 1.66–1.61 (m, 1H, H_a - 5′), 1.54–1.51 (m, 1H, H_a - 4′), 1.40 (d, J = 7.2 Hz, 3H, H - 4⁗), 0.95 (t, J = 7.3 Hz, 3H, H - 3⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.8 (C - 5), 151.8 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.9 (C - 1‴), 130.3 (C - 4‴), 130.2 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.2 (C

- 2‴ & C - 6‴), 49.4 (C - 2′), 46.1 (C - 6′), 45.1 (C - 3′), 33.0 (C - 1⁗), 29.7 (C - 4′), 29.1 (C - 2⁗), 24.3 (C - 5′), 20.9 (C - 4⁗), 11.2 (C - 3⁗); EIMS (m/z): 493 $[M + 2]^+$, 491 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 57 $[C_4H_9]^+$.

3.7.6. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl pentan-1-yl sulfide (8f)

Light yellow, sticky; yield: 76%; molecular formula: $C_{24}H_{29}ClN_4O_2S_2$; molecular mass: 505.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3042 (Ar - H), 1551 (C = N), 1540 (Ar C = C), 1371 (-SO_2), 1237 (C - N), 834 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.64 (d, J = 8.4 Hz, 2H, H - 2″ & H - 6″), 7.60–7.59 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.4 Hz, 2H, H - 3″ & H - 5″), 7.24–7.23 (m, 2H, H - 2‴ & H - 6‴), 3.91 (br.d, J = 11.0 Hz, 1H, H_e - 2′), 3.77 (br.d, J = 11.5 Hz, 1H, H_a - 2′), 3.18 (t, J = 7.2 Hz, 2H, H - 1⁗), 2.79–2.74 (m, 1H, H - 3′), 2.71 (br.t, J = 11.1 Hz, 1H, H_e - 6′), 2.29 (td, J = 11.7, 2.3 Hz, 1H, H_a - 6′), 1.95–1.93 (m, 1H, H_e - 4′), 1.89–1.86 (m, 1H, H_e - 5′), 1.72 (qui, J = 7.2 Hz, 2H, H - 2⁗), 1.64–1.59 (m, 1H, H_a - 5′), 1.58–1.49 (m, 1H, H_a - 4′), 1.36 (sex, J = 7.9 Hz, 2H, H - 4⁗), 1.32 (qui, J = 7.4 Hz, 2H, H - 3⁗), 0.88 (t, J = 6.9 Hz, 3H, H - 5⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.9 (C - 5), 152.3 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 133.8 (C - 1‴), 130.4 (C - 4‴), 130.2 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.8 (C - 3‴ & C - 5‴), 127.1 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 32.9 (C - 3′), 32.5 (C - 2⁗), 30.7 (C - 3⁗), 29.1 (C - 4′), 29.0 (C - 1⁗), 24.3 (C - 5′), 22.1 (C - 4⁗), 13.8 (C - 5⁗); EIMS (m/z): 507 $[M + 2]^+$, 505 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 71 $[C_5H_{11}]^+$.

3.7.7. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl 1-methylbutan-1-yl sulfide (8g)

Light yellow, sticky; yield: 72%; molecular formula: $C_{24}H_{29}ClN_4O_2S_2$; molecular mass: 505.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3048 (Ar - H), 1554 (C = N), 1546 (Ar C = C), 1377 (-SO_2), 1243 (C - N), 833 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.65 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.62–7.58 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.25–7.23 (m, 2H, H - 2‴ & H - 6‴), 3.93 (br.d, J = 11.1 Hz, 1H, H_e - 2′), 3.78 (br.d, J = 13.8 Hz, 1H, H_a - 2′), 3.76–3.72 (m, 2H, H - 1⁗), 2.79–2.76 (m, 1H, H - 3′), 2.74 (br.t, J = 11.2 Hz, 1H, H_e - 6′), 2.28 (td, J = 11.5, 1.9 Hz, 1H, H_a - 6′), 1.89–1.86 (m, 1H, H_e - 4′), 1.79–1.75 (m, 1H, H_a - 5′), 1.72–1.70 (m, 1H, H_e - 5′), 1.68–1.61 (m, 1H, H_a - 4′), 1.56–1.48 (m, 2H, H - 3⁗), 1.41 (q, J = 8.4 Hz, 2H, H - 2⁗), 1.37 (d, J = 6.7 Hz, 3H, H - 5⁗), 0.88 (t, J = 7.3 Hz, 3H, H - 4⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.8 (C - 5), 151.7 (C - 3), 139.5 (C - 1″), 134.8 (C - 4″), 132.9 (C - 1‴), 130.3 (C - 2″ & C - 6″), 130.1 (C - 3″ & C - 5″), 129.5 (C - 3‴ & C - 5‴), 128.9 (C - 4‴), 127.2 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 43.3 (C - 2⁗), 38.8 (C - 3′), 33.0 (C - 1⁗), 29.1 (C - 4′), 24.3 (C - 5′), 21.5 (C - 5⁗), 21.5 (C - 3⁗), 13.7 (C - 4⁗); EIMS (m/z): 507 $[M + 2]^+$, 505 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 71 $[C_5H_{11}]^+$.

3.7.8. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl heptan-1-yl sulfide (8h)

Off-white, sticky; yield: 85%; molecular formula: $C_{26}H_{33}ClN_4O_2S_2$; molecular mass: 533.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3050 (Ar - H), 1559 (C = N), 1548 (Ar C = C), 1381 (-SO_2), 1245 (C - N), 835 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.65 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.61–7.60 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.25–7.23 (m, 2H, H - 2‴ & H - 6‴), 3.92 (td, J = 11.4, 1.5 Hz, 1H, H_e - 2′), 3.77 (br.d, J = 11.7 Hz, 1H, H_a - 2′), 3.18 (td, J = 7.2, 3.2 Hz, 2H, H - 1⁗), 2.79–2.75 (m, 1H, H - 3′), 2.70 (br.t, J = 11.2 Hz, 1H, H_e - 6′), 2.29 (td, J = 11.7, 2.5 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.78–1.75 (m, 1H, H_e - 5′), 1.73 (qui, J = 7.4 Hz, 2H, H - 2⁗), 1.64–1.59 (m, 1H, H_a - 5′), 1.58–1.52 (m, 1H, H_a - 4′), 1.37 (qui, J = 7.3 Hz, 2H, H - 3⁗), 1.31–1.22 (m, 6H, H - 4⁗ & H - 6⁗), 0.87 (t, J = 7.2 Hz, 3H, H - 7⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.9 (C - 5), 152.3 (C - 3), 139.4 (C - 1″), 134.7 (C - 4″), 132.8 (C - 1‴), 130.4 (C - 2″ & C - 6″), 130.2 (C - 3″ & C - 5″), 129.5 (C - 3‴ & C - 5‴), 128.9 (C - 2‴ & C - 6‴), 127.1 (C - 4‴), 49.4 (C - 2′), 46.0 (C - 6′), 32.9 (C - 3′), 32.5 (C - 5⁗), 31.6 (C - 3⁗), 29.3 (C - 4′), 29.1 (C - 4⁗), 28.7 (C - 2⁗), 28.6 (C - 1⁗), 24.3 (C - 5′), 22.5 (C - 6⁗), 14.0 (C - 7⁗); EIMS (m/z): 535 $[M + 2]^+$, 533 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 99 $[C_7H_{15}]^+$, 111 $[C_6H_4Cl]^+$, 43 $[C_3H_7]^+$.

3.7.9. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl octan-1-yl sulfide (8i)

Yellow, sticky; yield: 83%; molecular formula: $C_{27}H_{35}ClN_4O_2S_2$; molecular mass: 547.0 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3052 (Ar - H), 1561 (C = N), 1550 (Ar C = C), 1383 (-SO_2), 1247 (C - N), 837 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.64 (d, J = 8.4 Hz, 2H, H - 2″ & H - 6″), 7.61–7.60 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.4 Hz, 2H, H - 3″ & H - 5″), 7.25–7.24 (m, 2H, H - 2‴ & H - 6‴), 3.92 (br.d, J = 11.0 Hz, 1H, H_e - 2′), 3.78 (br.d, J = 11.7 Hz, 1H, H_a - 2′), 3.18 (td, J = 7.1, 2.5 Hz, 2H, H - 1⁗), 2.79–2.75 (m, 1H, H - 3′), 2.72 (br.t, J = 11.1 Hz, 1H, H_e - 6′), 2.30 (td, J = 11.8, 2.4 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.78–1.76 (m, 1H, H_e - 5′), 1.70 (qui, J = 7.5 Hz, 2H, H - 2⁗), 1.65–1.58 (m, 1H, H_a - 5′), 1.56–1.49 (m, 1H, H_a - 4′), 1.36 (qui, J = 7.5 Hz, 2H, H - 3⁗), 1.30–1.26 (m, 8H, H - 4⁗ to H - 7⁗), 0.88 (t, J = 7.1 Hz, 3H, H - 8⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 155.9 (C - 5), 152.2 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.8 (C - 1‴), 130.4 (C - 4‴), 130.2 (C - 2″ & C - 6″), 129.4 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 127.1 (C - 2‴ & C - 6‴), 49.4 (C - 2′), 46.0 (C - 6′), 32.9 (C - 3′), 32.5 (C - 6⁗), 31.7 (C - 4⁗), 29.3 (C - 5⁗), 29.1 (C - 3⁗), 29.1 (C - 4′), 28.9 (C - 2⁗), 28.6 (C - 1⁗), 24.3 (C - 5′), 22.5 (C - 7⁗), 14.0 (C - 8⁗); EIMS (m/z): 549 $[M + 2]^+$, 547 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 113 $[C_8H_{17}]^+$, 111 $[C_6H_4Cl]^+$, 43 $[C_3H_7]^+$.

3.7.10. 5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl allyl sulfide (8j)

Dark brown, sticky; yield: 83%; molecular formula: $C_{22}H_{23}ClN_4O_2S_2$; molecular mass: 475.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3070 (Ar - H), 1569 (C = N), 1568 (Ar C = C), 1391 (-SO_2), 1257 (C - N), 845 (C - Cl); ^{1}H

NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.67 (d, J = 9.9 Hz, 2H, H - 2″ & H - 6″), 7.64–7.61 (m, 3H, H - 3‴ to H - 5‴), 7.51 (d, J = 8.0 Hz, 2H, H - 3″ & H - 5″), 7.25–7.24 (m, 2H, H - 2‴ & H - 6‴), 6.00–5.88 (m, 1H, H - 2⁗), 5.25 (d, J = 16.9 Hz, 1H, H_a - 3⁗), 5.14 (d, J = 9.9 Hz, 1H, H_b - 3⁗), 3.87 (br.d, J = 8.4 Hz, 1H, H_e - 2′), 3.81 (d, J = 6.7 Hz, 1H, H - 1⁗), 3.79 (d, J = 10.8 Hz, 1H, H_a - 2′), 2.82–2.80 (m, 1H, H - 3′), 2.72 (br.t, J = 11.2 Hz, 1H, H_e - 6′), 2.30 (br.t, J = 11.8 Hz, 1H, H_a - 6′), 1.87–1.85 (m, 1H, H_e - 4′), 1.78–1.76 (m, 1H, H_e - 5′), 1.64–1.59 (m, 1H, H_a - 5′), 1.57–1.50 (m, 1H, H_a - 4′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 156.1 (C - 5), 151.4 (C - 3), 139.4 (C - 1″), 134.7 (C - 4″), 132.7 (C - 1‴), 132.5 (C - 2″ & C - 6″), 130.4 (C - 3″ & C - 5″), 130.2 (C - 3‴ & C - 5‴), 129.5 (C - 4‴), 128.9 (C - 2⁗), 127.1 (C - 2‴ & C - 6‴), 119.0 (C - 3⁗), 49.4 (C - 2′), 46.0 (C - 6′), 35.3 (C - 3′), 32.9 (C - 1⁗), 29.1 (C - 4′), 24.3 (C - 5′); EIMS (m/z): 477 $[M + 2]^+$, 475 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 111 $[C_6H_4Cl]^+$, 41 $[C_3H_5]^+$.

3.7.11. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-phenylacetamide (12a)

White amorphous solid; yield: 79%; mp: 87–89 °C; molecular formula: $C_{27}H_{26}ClN_5O_3S_2$; molecular mass: 568.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3041 (Ar - H), 1673 (C = O), 1553 (C = N), 1537 (Ar C = C), 1362 (-SO_2), 1247 (C - N), 828 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 10.2 (s, 1H, -NH), 7.65 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.64–7.61 (m, 3H, H - 3‴ to H - 5‴), 7.60 (d, J = 7.2 Hz, 2H, H - 2⁗ & H - 6⁗), 7.49 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.31 (t, J = 7.4 Hz, 1H, H - 3⁗ & H - 5⁗), 7.25 (d, J = 7.9 Hz, 2H, H - 2‴ & H - 6‴), 7.09 (t, J = 7.4 Hz, 1H, H - 4⁗), 3.93 (d, J= 8.5 Hz, 1H, H_e - 2′), 3.91 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 3.83 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.78 (br.d, J= 11.8 Hz, 1H, H_a - 2′), 2.82–2.78 (m, 1H, H - 3′), 2.69 (br.t, J= 11.4 Hz, 1H, H_e - 6′), 2.31 (dt, J= 11.9, 2.7 Hz, 1H, H_a - 6′), 1.89–1.87 (m, 1H, H_e - 5′), 1.80–1.77 (m, 1H, H_e - 4′), 1.62–1.52 (m, 2H, H_a - 4′ & H_a - 5′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 166.5 (C - 1⁗), 156.6 (C - 5), 152.9 (C - 3), 139.5 (C - 1″), 138.2 (C - 4″), 134.8 (C - 1⁗), 131.9 (C - 1‴), 131.0 (C - 2″ & C - 6″), 130.6 (C - 3″ & C - 5″), 129.5 (C - 3‴ & C - 5‴), 128.9 (C - 4‴, C - 3⁗ & C - 5⁗), 126.8 (C - 2‴ & C - 6‴), 124.2 (C - 4⁗), 119.7 (C - 2⁗ & C - 6⁗), 49.3 (C - 2′), 46.0 (C - 6′), 36.1 (C - 3′), 32.9 (C - 2⁗), 29.1 (C - 4′), 24.3 (C - 5′); EIMS (m/z): 570 $[M + 2]^+$, 568 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 120 $[C_7H_6NO]^+$, 111 $[C_6H_4Cl]^+$, 92 $[C_6H_6N]^+$.

3.7.12. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-benzylacetamide (12b)

Light yellow amorphous solid; yield: 82%; mp: 104–106 °C; molecular formula: $C_{28}H_{28}ClN_5O_3S_2$; molecular mass: 582.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3043 (Ar - H), 1674 (C = O), 1555 (C = N), 1544 (Ar C = C), 1375 (-SO_2), 1245 (C - N), 823 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 7.63 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.62–7.58 (m, 3H, H - 3‴ to H - 5‴), 7.48 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.31 (t, J = 6.7 Hz, 1H, H - 4⁗), 7.28 (d, J 7.6 Hz, 2H, H - 2‴ & H - 6‴), 7.24 (t, J = 6.8 Hz, 2H, H - 3⁗ & H - 5⁗), 7.21 (d, J = 6.1 Hz, 2H, H - 2⁗ & H - 6⁗), 4.44 ($t_{(two\ d\ merged)}$, J = 4.3 Hz, 2H, H - 2⁗), 3.89 (td, J= 11.8, 1.9 Hz, 1H, H_e - 2′), 3.81 (s, 2H, H - 7⁗), 3.76 (br.d, J= 12.4 Hz, 1H, H_a - 2′), 2.78–2.75 (m,

1H, H - 3′), 2.66 (br.t, J= 11.3 Hz, 1H, H_e - 6′), 2.29 (dt, J= 11.7, 2.7 Hz, 1H, H_a - 6′), 1.85–1.83 (m, 1H, H_e - 5′), 1.78–1.75 (m, 1H, H_e - 4′), 1.56–1.51 (m, 2H, H_a - 4′ & H_a - 5′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 168.3 (C - 1′′′′), 156.4 (C - 5), 152.3 (C - 3), 139.5 (C - 1′′), 138.2 (C - 4′′), 134.9 (C - 1′′′′′), 132.0 (C - 1′′′), 130.8 (C - 2′′ & C - 6′′), 130.5 (C - 3′′ & C - 5′′), 129.5 (C - 3′′′ & C - 5′′′), 128.8 (C - 3′′′′ & C - 5′′′′), 128.5 (C - 4′′′), 127.4 (C - 2′′′′ & C - 6′′′′), 127.2 (C - 4′′′′), 126.9 (C - 2′′′ & C - 6′′′), 49.2 (C - 2′), 46.0 (C - 6′), 43.6 (C - 7′′′′), 35.0 (C - 3′), 32.9 (C - 2′′′′), 29.1 (C - 4′), 24.3 (C - 5′); EIMS (m/z): 584 $[M + 2]^+$, 582 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 111 $[C_6H_4Cl]^+$, 106 $[C_7H_8N]^+$.

3.7.13. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(2-methylphenyl)acetamide (12c)

White amorphous solid; yield: 77%; mp: 89–91 °C; molecular formula: $C_{28}H_{28}ClN_5O_3S_2$; molecular mass: 582.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3047 (Ar - H), 1670 (C = O), 1557 (C = N), 1542 (Ar C = C), 1371 (-SO_2), 1247 (C - N), 827 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 9.63 (s, 1H, -NH), 7.93 (d, J = 8.5 Hz, 1H, H - 6′′′′), 7.64 (d, J = 8.5 Hz, 2H, H - 2′′ & H - 6′′), 7.63–7.60 (m, 3H, H - 3′′′ to H - 5′′′), 7.48 (d, J = 8.5 Hz, 2H, H - 3′′ & H - 5′′), 7.26–7.25 (m, 2H, H - 2′′′ & H - 6′′′), 7.20 (t, J = 7.5 Hz, 1H, H - 4′′′′), 7.17 (d, J = 7.5 Hz, 1H, H - 3′′′′), 7.05 (dt, J = 7.4, 1.2 Hz, 1H, H - 5′′′′), 3.99 (d, J = 14.2 Hz, 1H, H_a - 2′′′′), 3.91 (d, J = 14.2 Hz, 1H, H_b - 2′′′′), 3.88 (br.d, J= 11.3 Hz, 1H, H_e - 2′), 3.77 (br.d, J= 11.8 Hz, 1H, H_a - 2′), 2.80–2.76 (m,1H, H - 3′), 2.68 (br.t, J= 10.8 Hz, 1H, H_e - 6′), 2.33 (dt, J= 12.8, 2.5 Hz, 1H, H_a - 6′), 2.31 (s, 3H, CH_3 - 2′′′′), 1.88–1.86 (m, 1H, H_e - 5′), 1.79–1.76 (m, 1H, H_e - 4′), 1.62–1.51 (m, 2H, H_a - 4′ & H_a - 5′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 166.8 (C - 1′′′), 156.7 (C - 5), 152.7 (C - 3), 139.5 (C - 1′′), 136.1 (C - 4′′), 134.9 (C - 1′′′′′), 131.9 (C - 1′′′), 131.0 (C - 2′′′′), 130.6 (C - 2′′ & C - 6′′), 130.4 (C - 3′′′′), 129.5 (C - 3′′ & C - 5′′), 129.2 (C - 4′′′), 128.8 (C - 3′′′ & C - 5′′′), 126.8 (C - 2′′′ & C - 6′′′), 126.5 (C - 5′′′′), 124.9 (C - 4′′′′), 122.4 (C - 6′′′′), 49.3 (C - 2′), 46.0 (C - 6′), 35.7 (C - 3′), 32.9 (C - 2′′′′), 29.1 (C - 4′), 24.3 (C - 5′), 18.2 (CH_3 - 2′′′′); EIMS (m/z): 584 $[M + 2]^+$, 582 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 111 $[C_6H_4Cl]^+$, 106 $[C_7H_8N]^+$.

3.7.14. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(3-methylphenyl)acetamide (12d)

White amorphous solid; yield: 74%; mp: 97–99 °C; molecular formula: $C_{28}H_{28}ClN_5O_3S_2$; molecular mass: 582.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3049 (Ar - H), 1666 (C = O), 1555 (C = N), 1544 (Ar C = C), 1373 (-SO_2), 1243 (C - N), 825 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 10.0 (s, 1H, -NH), 7.64 (d, J = 8.5 Hz, 2H, H - 2′′ & H - 6′′), 7.63–7.59 (m, 3H, H - 3′′′ to H - 5′′′), 7.49 (d, J = 8.5 Hz, 2H, H - 3′′ & H - 5′′), 7.43 (s, 1H, H - 2′′′′), 7.38 (d, J = 7.9 Hz, 1H, H - 6′′′′), 7.26 (d, J = 7.3 Hz, 2H, H - 2′′′ & H - 6′′′), 7.19 (t, J = 7.7 Hz, 1H, H - 5′′′′), 6.91 (d, J = 7.5 Hz, 1H, H - 4′′′′), 3.92 (br.d, J= 11.3 Hz, 1H, H_e - 2′), 3.90 (d, J = 14.2 Hz, 1H, H_a - 2′′′′), 3.83 (d, J = 14.2 Hz, 1H, H_b - 2′′′′), 3.78 (br.d, J= 11.8 Hz, 1H, H_a - 2′), 2.82–2.77 (m,1H, H - 3′), 2.69 (br.t, J= 11.4 Hz, 1H, H_e - 6′), 2.33 (s, 3H, CH_3 - 3′′′′), 2.31 (dt, J= 12.3, 3.2 Hz, 1H, H_a - 6′), 1.90–1.87 (m, 1H, H_e - 5′), 1.80–1.77 (m, 1H, H_e - 4′), 1.62–1.51 (m, 2H, H_a - 4′

& H_a - 5′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 166.4 (C - 1‴′), 156.6 (C - 5), 152.9 (C - 3), 139.5 (C - 1″), 138.8 (C - 4″), 138.0 (C - 2⁗), 134.8 (C - 1⁗), 131.9 (C - 1‴), 131.0 (C - 3⁗), 130.6 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 128.9 (C - 3‴ & C - 5‴), 128.7 (C - 4‴), 126.8 (C - 2‴ & C - 6‴), 125.0 (C - 5⁗), 120.3 (C - 4⁗), 116.9 (C - 6⁗), 49.3 (C - 2′), 46.0 (C - 6′), 36.1 (C - 3′), 32.9 (C - 2⁗), 29.1 (C - 4′), 24.3 (C - 5′), 21.4 (CH_3 - 3⁗); EIMS (m/z): 584 $[M + 2]^+$, 582 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 111 $[C_6H_4Cl]^+$, 106 $[C_7H_8N]^+$.

3.7.15. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(4-methylphenyl)acetamide (12e)

White amorphous solid; yield: 78%; mp: 96–98 °C; molecular formula: $C_{28}H_{28}ClN_5O_3S_2$; molecular mass: 582.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3044 (Ar - H), 1672 (C = O), 1554 (C = N), 1545 (Ar C = C), 1375 (-SO_2), 1243 (C - N), 831 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 10.0 (s, 1H, -NH), 7.64 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.63–7.59 (m, 3H, H - 3‴ to H - 5‴), 7.49 (d, J = 8.6 Hz, 2H, H - 3″ & H - 5″), 7.47 (d, J = 8.4 Hz, 2H, H - 2⁗ & H - 6⁗), 7.25 (d, J = 7.2 Hz, 2H, H - 2‴ & H - 6‴), 7.11 (d, J = 8.1 Hz, 2H, H - 3⁗ & H - 5⁗), 3.92 (br.d, J= 11.5 Hz, 1H, H_e - 2′), 3.88 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 3.83 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.78 (br.d, J= 12.0 Hz, 1H, H_a - 2′), 2.82–2.77 (m, 1H, H - 3′), 2.69 (br.t, J= 11.4 Hz, 1H, H_e - 6′), 2.32 (dt, J= 15.0, 2.8 Hz, 1H, H_a - 6′), 2.30 (s, 3H, CH_3 - 4⁗), 1.89–1.87 (m, 1H, H_e - 5′), 1.80–1.76 (m, 1H, H_e - 4′), 1.64–1.52 (m, 2H, H_a - 4′ & H_a - 5′); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 166.3 (C - 1‴′), 156.6 (C - 5), 152.9 (C - 3), 139.5 (C - 1″), 135.6 (C - 4″), 134.9 (C - 1⁗), 133.8 (C - 4‴), 131.9 (C - 1‴), 130.9 (C - 4⁗), 130.5 (C - 2″ & C - 6″), 129.5 (C - 3″ & C - 5″), 129.3 (C - 3‴ & C - 5‴), 128.9 (C - 2‴ & C - 6‴), 126.8 (C - 3⁗ & C - 5⁗), 119.8 (C - 2⁗ & C - 6⁗), 49.3 (C - 2′), 46.0 (C - 6′), 36.1 (C - 3′), 32.9 (C - 2‴′), 29.1 (C - 4′), 24.3 (C - 5′), 20.8 (CH_3 - 4⁗); EIMS (m/z): 584 $[M + 2]^+$, 582 $[M]^+$, 435 $[C_{19}H_{18}ClN_4O_2S_2]^{\bullet+}$, 375 $[C_{18}H_{18}ClN_3O_2S]^{\bullet+}$, 361 $[C_{18}H_{18}ClN_2O_2S]^+$, 284 $[C_{12}H_{13}ClN_2O_2S]^{\bullet+}$, 258 $[C_{11}H_{13}ClNO_2S]^+$, 175 $[C_6H_4ClO_2S]^+$, 134 $[C_8H_8NO]^+$, 111 $[C_6H_4Cl]^+$, 106 $[C_7H_8N]^+$.

3.7.16. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(2-ethylphenyl)acetamide (12f)

Off-white amorphous solid; yield: 72%; mp: 81–83 °C; molecular formula: $C_{29}H_{30}ClN_5O_3S_2$; molecular mass: 596.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3039 (Ar - H), 1668 (C = O), 1551 (C = N), 1534 (Ar C = C), 1367 (-SO_2), 1243 (C - N), 821 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 9.61 (s, 1H, -NH), 7.87 (d, J = 8.0 Hz, 1H, H - 6⁗), 7.68–7.63 (m, 5H, H - 2″, H - 6″ & H - 3‴ to H - 5‴), 7.52 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.27 (d, J = 7.2 Hz, 2H, H - 2‴ & H - 6‴), 7.24 (t, J = 9.2 Hz, 1H, H - 4⁗), 7.21 (d, J = 9.2 Hz, 1H, H - 3⁗), 7.13 (t, J = 7.5 Hz, 1H, H - 5⁗), 4.03 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 3.96 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.92 (td, J= 11.6, 1.8 Hz, 1H, H_e - 2′), 3.80 (br.d, J= 12.0 Hz, 1H, H_a - 2′), 2.84–2.80 (m, 1H, H - 3′), 2.71 (br.t, J= 11.5 Hz, 1H, H_e - 6′), 2.65 (q, J = 7.5 Hz, 2H, $CH_3\underline{CH}_2$ - 2⁗), 2.34 (dt, J= 11.8, 2.6 Hz, 1H, H_a - 6′), 1.90–1.89 (m, 1H, H_e - 5′), 1.82–1.79 (m, 1H, H_e - 4′), 1.66–1.52 (m, 2H, H_a - 4′ & H_a - 5′), 1.17 (t, J = 7.3 Hz, 3H, $\underline{CH}_3CH_2$ - 2⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 167.0 (C - 1‴′), 156.8 (C - 5), 152.8 (C - 3), 139.5 (C - 1″), 135.5 (C - 1⁗), 135.2 (C - 4″), 134.8 (C - 1‴), 131.9 (C - 2″ & C - 6″),

131.0 (C - 3″ & C - 5″), 130.6 (C - 3‴ & C - 5‴), 129.5 (C - 4‴), 128.9 (C - 3⁗), 128.7 (C - 5⁗), 126.8 (C - 2⁗), 126.4 (C - 2‴ & C - 6‴), 125.4 (C - 4⁗), 123.5 (C - 6⁗), 49.3 (C - 2′), 46.0 (C - 6′), 35.5 (C - 3′), 32.9 (C - 2⁗), 29.1 (C - 4′), 24.6 (C - 5′), 24.3 (-$\underline{\mathrm{CH}}_2\mathrm{CH}_3$ - 2⁗), 14.1 (-$\mathrm{CH}_2\underline{\mathrm{CH}}_3$ - 2⁗); EIMS (m/z): 598 $[\mathrm{M}+2]^+$, 596 $[\mathrm{M}]^+$, 435 $[\mathrm{C_{19}H_{18}ClN_4O_2S_2}]^{\bullet+}$, 375 $[\mathrm{C_{18}H_{18}ClN_3O_2S}]^{\bullet+}$, 361 $[\mathrm{C_{18}H_{18}ClN_2O_2S}]^+$, 284 $[\mathrm{C_{12}H_{13}ClN_2O_2S}]^{\bullet+}$, 258 $[\mathrm{C_{11}H_{13}ClNO_2S}]^+$, 175 $[\mathrm{C_6H_4ClO_2S}]^+$, 148 $[\mathrm{C_9H_{10}NO}]^+$, 120 $[\mathrm{C_8H_{10}N}]^+$, 111 $[\mathrm{C_6H_4Cl}]^+$.

3.7.17. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(4-ethylphenyl)acetamide (12g)

Off-white amorphous solid; yield: 73%; mp: 94–96 °C; molecular formula: $\mathrm{C_{29}H_{30}ClN_5O_3S_2}$; molecular mass: 596.1 g mol^{-1}; IR (KBr, cm^{-1}) $\upsilon_{\max}$: 3043 (Ar - H), 1676 (C=O), 1557 (C = N), 1531 (Ar C = C), 1367 (-$\mathrm{SO_2}$), 1243 (C - N), 817 (C - Cl); ^{1}H NMR ($\mathrm{CDCl_3}$, 600 MHz, δ/ppm): 10.07 (s, 1H, -NH), 7.65 (d, J = 8.5 Hz, 2H, H - 2″, H - 6″), 7.64–7.59 (m, 3H, H - 3‴ to H - 5‴), 7.50 (d, J = 8.3 Hz, 2H, H - 3″ & H - 5″), 7.49 (d, J = 8.5 Hz, 2H, H - 2⁗ & H - 6⁗), 7.24 (d, J = 7.2 Hz, 2H, H - 2‴ & H - 6‴), 7.14 (d, J = 8.4 Hz, 2H, H - 3⁗ & H - 5⁗), 3.93 (br.d, J= 11.3 Hz, 1H, H_e - 2′), 3.91 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 3.83 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.78 (br.d, J= 11.8 Hz, 1H, H_a - 2′), 2.81–2.78 (m, 1H, H - 3′), 2.69 (br.t, J= 11.4 Hz, 1H, H_e - 6′), 2.60 (q, J = 7.5 Hz, 2H, $\mathrm{CH_3}\underline{\mathrm{CH}}_2$ - 4⁗), 2.30 (dt, J= 12.0, 2.8 Hz, 1H, H_a - 6′), 1.89–1.87 (m, 1H, H_e - 5′), 1.80–1.76 (m, 1H, H_e - 4′), 1.63–1.52 (m, 2H, H_a - 4′ & H_a - 5′), 1.20 (t, J = 7.5 Hz, 3H, $\underline{\mathrm{CH}}_3\mathrm{CH_2}$ - 4⁗); ^{13}C NMR ($\mathrm{CDCl_3}$, 150 MHz, δ/ppm): 166.3 (C - 1⁗), 156.6 (C - 5), 152.9 (C - 3), 140.3 (C - 4⁗), 139.5 (C - 1″), 135.8 (C - 4″), 131.9 (C - 1‴), 131.4 (C - 1⁗), 131.0 (C - 2″ & C - 6″), 130.5 (C - 3″ & C - 5″), 129.5 (C - 3‴ & C - 5‴), 128.9 (C - 4‴), 128.2 (C - 3⁗ & C - 5⁗), 126.8 (C - 2‴ & C - 6‴), 119.2 (C - 2⁗ & C - 6⁗), 49.3 (C - 2′), 46.0 (C - 6′), 36.0 (C - 3′), 32.9 (C - 2⁗), 29.1 (C - 4′), 28.3 (-$\underline{\mathrm{CH}}_2\mathrm{CH}_3$ - 4⁗), 24.3 (C - 5′), 15.7 (-$\mathrm{CH}_2\underline{\mathrm{CH}}_3$ - 4⁗); EIMS (m/z): 598 $[\mathrm{M}+2]^+$, 596 $[\mathrm{M}]^+$, 435 $[\mathrm{C_{19}H_{18}ClN_4O_2S_2}]^{\bullet+}$, 375 $[\mathrm{C_{18}H_{18}ClN_3O_2S}]^{\bullet+}$, 361 $[\mathrm{C_{18}H_{18}ClN_2O_2S}]^+$, 284 $[\mathrm{C_{12}H_{13}ClN_2O_2S}]^{\bullet+}$, 258 $[\mathrm{C_{11}H_{13}ClNO_2S}]^+$, 175 $[\mathrm{C_6H_4ClO_2S}]^+$, 148 $[\mathrm{C_9H_{10}NO}]^+$, 120 $[\mathrm{C_8H_{10}N}]^+$, 111 $[\mathrm{C_6H_4Cl}]^+$.

3.7.18. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(2-ethoxyphenyl)acetamide (12h)

White amorphous solid; yield: 82%; mp: 84–86 °C; molecular formula: $\mathrm{C_{29}H_{30}ClN_5O_4S_2}$; molecular mass: 612.1 g mol^{-1}; IR (KBr, cm^{-1}) $\upsilon_{\max}$: 3048 (Ar - H), 1674 (C = O), 1557 (C = N), 1543 (Ar C = C), 1375 (-$\mathrm{SO_2}$), 1247 (C - N), 825 (C - Cl); ^{1}H NMR ($\mathrm{CDCl_3}$, 600 MHz, δ/ppm): 9.48 (s, 1H, -NH), 8.31 (dd, J = 8.0, 1.6 Hz, 1H, H - 6⁗), 7.63 (d, J = 8.5 Hz, 2H, H - 2″ & H - 6″), 7.61–7.57 (m, 3H, H - 3‴ to H - 5‴), 7.48 (d, J = 8.5 Hz, 2H, H - 3″ & H - 5″), 7.26–7.24 (m, 2H, H - 2‴ & H - 6‴), 7.02 (dt, J = 7.7, 1.6 Hz, 1H, H - 4⁗), 6.92 (dt, J = 7.8, 1.3 Hz, 1H, H - 5⁗), 6.85 (dd, J = 8.2, 1.3 Hz, 1H, H - 3⁗), 4.10 (q, J = 7.0 Hz, 2H, $\mathrm{CH_3}\underline{\mathrm{CH}}_2\mathrm{O}$ - 2⁗), 4.03 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 4.00 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.89 (td, J= 11.5, 1.8 Hz, 1H, H_e - 2′), 3.77 (br.d, J= 11.9 Hz, 1H, H_a - 2′), 2.80–2.75 (m, 1H, H - 3′), 2.67 (br.t, J= 11.5 Hz, 1H, H_e - 6′), 2.30 (dt, J= 11.9, 2.8 Hz, 1H, H_a - 6′), 1.86–1.83 (m, 1H, H_e - 5′), 1.78–1.75 (m, 1H, H_e - 4′), 1.61–1.50 (m, 2H, H_a - 4′ & H_a - 5′), 1.45 (t, J = 7.0 Hz, 3H, $\underline{\mathrm{CH}}_3\mathrm{CH_2O}$ - 2⁗); ^{13}C NMR ($\mathrm{CDCl_3}$, 150 MHz, δ/ppm): 166.0 (C - 1⁗), 156.4 (C - 5), 151.8 (C - 2⁗), 147.8 (C - 3), 139.4 (C - 1″), 134.8 (C - 4″), 132.2 (C - 1‴), 130.7 (C - 2″ & C - 6″), 130.4 (C - 3″ & C - 5″), 129.4

(C - 3‴ & C - 5‴), 128.9 (C - 4‴), 127.7 (C - 1⁗), 126.9 (C - 2‴ & C - 6‴), 124.1 (C - 4⁗), 120.7 (C - 6⁗), 120.3 (C - 5⁗), 111.1 (C - 3⁗), 64.2 (-O<u>CH</u>$_2$CH$_3$ - 2⁗), 49.4 (C - 2′), 46.0 (C - 6′), 36.4 (C - 3′), 32.9 (C - 2⁗), 29.0 (C - 4′), 24.3 (C - 5′), 14.8 (-OCH$_2$<u>CH</u>$_3$ - 2⁗); EIMS (m/z): 614 [M + 2]$^+$, 612 [M]$^+$, 435 [$C_{19}H_{18}ClN_4O_2S_2$]$^{\bullet+}$, 375 [$C_{18}H_{18}ClN_3O_2S$]$^{\bullet+}$, 361 [$C_{18}H_{18}ClN_2O_2S$]$^+$, 284 [$C_{12}H_{13}ClN_2O_2S$]$^{\bullet+}$, 258 [$C_{11}H_{13}ClNO_2S$]$^+$, 175 [$C_6H_4ClO_2S$]$^+$, 164 [$C_9H_{10}NO_2$]$^+$, 136 [$C_8H_{10}NO$]$^+$, 111 [C_6H_4Cl]$^+$.

3.7.19. 2-[(5-{1-[(4-Chlorophenyl)sulfonyl]-3-piperidinyl}-4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-*N*-(4-ethoxyphenyl)acetamide (12i)

Light pink amorphous solid; yield: 81%; mp: 83–85 °C; molecular formula: $C_{29}H_{30}ClN_5O_4S_2$; molecular mass: 612.1 g mol^{-1}; IR (KBr, cm^{-1}) υ_{max}: 3046 (Ar - H), 1678 (C = O), 1558 (C = N), 1541 (Ar C = C), 1372 (-SO_2), 1248 (C - N), 826 (C - Cl); ^{1}H NMR ($CDCl_3$, 600 MHz, δ/ppm): 10.01 (s, 1H, -NH), 7.64 (d, J = 8.5 Hz, 2H, H - 2″, H - 6″), 7.63–7.60 (m, 3H, H - 3‴ to H - 5‴), 7.49 (d, J = 8.6 Hz, 2H, H - 3″ & H - 5″), 7.48 (d, J = 9.1 Hz, 2H, H - 2⁗ & H - 6⁗), 7.26–7.25 (m, 2H, H - 2‴ & H - 6‴), 6.83 (d, J = 9.0 Hz, 2H, H - 3⁗ & H - 5⁗), 4.00 (q, J = 7.0 Hz, 2H, CH_3<u>CH_2</u>O - 4⁗), 3.92 (td, J= 11.5, 2.1 Hz, 1H, H_e - 2′), 3.88 (d, J = 14.2 Hz, 1H, H_a - 2⁗), 3.82 (d, J = 14.2 Hz, 1H, H_b - 2⁗), 3.78 (br.d, J= 12.2 Hz, 1H, H_a - 2′), 2.82–2.78 (m, 1H, H - 3′), 2.69 (br.t, J= 11.4 Hz, 1H, H_e - 6′), 2.31–2.30 (m, 1H, H_a - 6′), 1.89–1.87 (m, 1H, H_e - 5′), 1.80–1.77 (m, 1H, H_e - 4′), 1.61–1.53 (m, 2H, H_a - 4′ & H_a - 5′), 1.39 (t, J = 7.0 Hz, 3H, <u>CH_3</u>CH_2O - 4⁗); ^{13}C NMR ($CDCl_3$, 150 MHz, δ/ppm): 166.1 (C - 1⁗), 156.6 (C - 5), 155.6 (C - 4⁗), 152.9 (C - 3), 139.5 (C - 1″), 134.8 (C - 4″), 132.0 (C - 1⁗), 131.3 (C - 1‴), 130.9 (C - 2″ & C - 6″), 130.5 (C - 3″ & C - 5″), 129.5 (C - 3‴ & C - 5‴), 128.9 (C - 4‴), 126.8 (C - 2‴ & C - 6‴), 121.3 (C - 2⁗ & C - 6⁗), 114.7 (C - 3⁗ & C - 5⁗), 63.7 (-O<u>CH</u>$_2$$CH_3$ - 4⁗), 49.3 (C - 2′), 46.0 (C - 6′), 36.0 (C - 3′), 32.9 (C - 2⁗), 29.1 (C - 4′), 24.3 (C - 5′), 14.8 (-OCH$_2$<u>CH</u>$_3$ - 4⁗); EIMS (m/z): 614 [M + 2]$^+$, 612 [M]$^+$, 435 [$C_{19}H_{18}ClN_4O_2S_2$]$^{\bullet+}$, 375 [$C_{18}H_{18}ClN_3O_2S$]$^{\bullet+}$, 361 [$C_{18}H_{18}ClN_2O_2S$]$^+$, 284 [$C_{12}H_{13}ClN_2O_2S$]$^{\bullet+}$, 258 [$C_{11}H_{13}ClNO_2S$]$^+$, 175 [$C_6H_4ClO_2S$]$^+$, 164 [$C_9H_{10}NO_2$]$^+$, 136 [$C_8H_{10}NO$]$^+$, 111 [C_6H_4Cl]$^+$.

3.8. Hemolytic activity

The protocol reported by Sharma et al. and Powell et al. was followed to screen all the derivatives for hemolytic activity.[18,19] Heparinized bovine blood (3 mL) was taken from bovines from the Department of Clinical Medicine and Surgery, University of Agriculture (Pakistan). Blood was centrifuged at 1000 $\times g$ for 5 min and plasma was discarded. Cells were washed with 5 mL of chilled sterile isotonic PBS three times at pH 7.4. Erythrocytes were maintained at 108 cells/mL for each assay and 100 μL of each compound was mixed with human erythrocytes (108 cells/mL) separately. Samples were incubated at 37 °C for 35 min and agitated after 10 min. The samples were placed on ice immediately after incubation for 5 min and centrifuged at 1000 $\times g$ for 5 min. Supernatant (100 μL) was taken from each tube and diluted 10 times with chilled (4 °C) PBS. Triton X-100 (0.1% v/v) was taken as a positive control and PBS was taken as a negative control and passed through the same process. The absorbance was noted at 576 nm using a UV spectrophotometer (BioTek, USA). The % RBC lysis for each sample was calculated.

3.9. α-Glucosidase assay

Anti-α-glucosidase activity was examined by the protocol reported by Brueggeman et al.[20] A reaction mixture of 100 μL was made up of 70 μL of phosphate buffer (50 mM, pH 6.8), 10 μL of enzyme, and 10 μL of test

compound (0.5 mM). The reaction contents were preincubated at 37 °C for 10 min and preabsorbance was measured at 400 nm. *p*-Nitrophenyl glucopyranoside (substrate) (10 μL, 0.5 mM) was added to initiate the reaction. Acarbose was used as a positive reference standard. The contents were incubated at 37 °C for 30 min and, using a Synergy HT microplate reader, absorbance was noted at 400 nm. Triplicate readings were taken. The percent inhibition was calculated by the following equation:

$$\text{Inhibition } (\%) = \frac{\text{Control} - \text{Test}}{\text{Control}} \times 100$$

Here, Control is absorbance in control and Test is absorbance in test sample. IC_{50} values of compounds were calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc., Amherst, NH, USA).

3.10. Statistical analysis

All measurements were done in triplicate and statistical analysis was performed with Microsoft Excel 2010. Results are presented as mean ± SEM.

3.11. Molecular docking

In an attempt to learn about the inhibitory interactions bioinformatically, nineteen different synthesized compounds were docked in the active pocket of α-glucosidase by using the default parameters of the MOE-Dock program. Chemical structures of these nineteen ligands were drawn with ChemDraw Ultra 12.0 software and then opened in MOE software (2009–2010). Energy minimization was preceded up to 0.05 gradients by using the MMFF94X force field through the default parameter of the MOE energy minimization algorithm. All these compounds were saved in a separate database in the mdb file format. The protein molecule of α-glucosidase (PDB Code; 3NO4) was downloaded from the Protein Data Bank. All the water molecules were removed from the receptor protein and 3D protonation was carried out using the Protonate 3D option. In the same way, the energy of the protein molecule was also minimized by the default parameters of MOE 2009–2010 energy minimization algorithms (gradient: 0.05, force field: MMFF94X). Finally, all these compounds were docked into the binding pocket of the enzyme. For validity confirmation, a redocking procedure was applied. After docking analysis of each compound with 30 conformations, the best 2D images were saved for their specific types of interactions and their 3D images were drawn along with their bond lengths.[21−23]

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