Synthesis, antimicrobial evaluation and *in silico* studies of novel 3,4-disubstituted pyrrolidinesulfonamides

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3,4-Disubstituted pyrrolidinesulfonamides were synthesized and screened for their antimicrobial activity. Title compounds were established as potent antibacterial and antifungal agents. Noteworthy antimicrobial activity was found for the title compounds against the tested microorganisms. They exhibit comparable results with standard drugs. Besides the *in vitro* antimicrobial activity, the synthesized compounds were evaluated for their *in silico* inhibitory activity on active site of β-glucosidase enzyme. *In silico* studies were done by GOLD docking method against β-glucosidase 3VKK (PDB Id). In silico studies were conducted to evaluate the ability of synthesized compounds to inhibit the β-glucosidase enzyme. The results revealed that 3,4-disubstitutedpyrrolidinesulfonamides are the potent β-glucosidase inhibitors by binding at the active site. A sensible inhibition against β-glucosidases was observed for the compound with 13,4-oxadizole ring has higher β-glucosidase inhibition activity than the other compounds. The free energy of binding and inhibition constant (K_i) of the docked compounds were evaluated and presented.

Keywords: pyrrolidinesulfonamides; synthesis; *in silico* studies; β-glucosidase; antimicrobial activity.

Жаңа 3,4-алмастырылған пирролидинсульфонамидтердің синтезі, микробтарға қарсы қабілетін бағалау және *in silico* зерттеулері

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Жұмыста 3,4-алмастырылған пирролидинсульфонамидтері синтезделді және олардың микробтарға қарсы белсенділігі тексерілді. Бұл қосылыстар бактерияларға қарсы және антифунгицидті күшті агенттер екендігі анықталды. Қосылыстардың алынған микроорганизмдерге қарсы жоғары белсенділігі анықталды. Олар стандартты дәрілермен салыстырылатын нәтижелерді көрсетеді. *In vitro* антимикробтық белсенділігімен қатар, олардың β-глюкозидаза ферментінің белсенді орнына *in silico* ингибиторлық белсенділігі бағаланды. In silico зерттеулерді GOLD қондыру әдісі арқылы β-глюкозидазаға 3VKK (PDB Id) қарсы жүргізілді. *In silico* зерттеулер синтезделген қосылыстардың β-глюкозидаза ферментін ингибирлеу қабілетін бағалау үшін жүргізілді. Нәтижелер 3,4-алмастырылған пирролидинсульфонамидтер ферменттің активті орындарында байланысатын β-глюкозидазаның күшті ингибиторлары екенін көрсетті. 13,4-оксадизол сақинасы бар қосылыс үшін β-глюкозидазалардың айтарлықтай ингибирлеуі байқалды, ол басқа қосылыстарға қарағанда β-глюкозидазаға қатысты ингибирлеу жоғары белсенділігін көрсетеді. Жұмыста қосылыстардың бос байланыстырушы энергиясы мен ингибирлеу тұрақтылықтары (K_i) бағаланды.

Түйін сөздер: пирролидинсульфонамидтері; синтез; *in silico* зерттеулері; β-глюкозидаза; антимикробтық белсенділік.

Синтез, антимикробная оценка и *in silico* исследования новых 3,4-дизамещенных пирролидинсульфонамидов

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В работе синтезированы 3,4-дизамещенные пирролидинсульфонамиды с последующей проверкой их антимикробной активности. Установлено, что данные соединения являются сильными антибактериальными и противогрибковыми агентами. Обнаружена высокая антимикробная активность данных соединений против выбранных микроорганизмов. Они показывают сопоставимые результаты со стандартными препаратами. Помимо антимикробной активности *in vitro*, оценивали их ингибирующую активность *in silico* на активном участке фермента β-глюкозидазы. Исследования *in silico* проводили методом стыковки GOLD против β-глюкозидазы 3VKK (PDB Id). Исследования in silico проводили для оценки способности синтезированных соединений ингибировать фермент β-глюкозидазу. Результаты показали, что 3,4-дизамещенные пирролидинсульфонамиды являются мощными ингибиторами β-глюкозидазы, связываясь в активном центре. Заметное ингибирование β-глюкозидаз наблюдалось для соединения с 13,4-оксадизольным кольцом, которое обладает более высокой активностью ингибирования β-глюкозидазы, чем другие соединения. В работе также оценены свободные энергии связывания и константы ингибирования (K_i) присоединенных соединений.

Ключевые слова: пирролидинсульфонамиды; синтез; исследования *in silico*; β-глюкозидаза; антимикробная активность.

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1. Introduction

In the field of medicinal chemistry, chiral 3,4-disubstituted pyrrolidines derived from tartaric acid are widely used. Most of these pyrrolidine rings are found in biological compounds as their frameworks. These frameworks were successfully mutated into receptor molecules, amino-sugar derivatives as glycosidase inhibitors as well as sugar simulate in nucleoside analog. Besides kinases, pyrrolidines are also suitable substitutes for inhibitor design to recognize the specificity pockets of the corresponding enzymes in proteases [1,2]. Proline based pyrrolidines are used as drug candidates in the treatment of hepatitis C [3]. The solid-phase construction of a guanidine based bis-cyclic pyrrolidine exhibited marked bactericidal activity against known human pathogens, it may represent a newfangled category of antimicrobial therapeutics [4]. Pyrrolidineoxadiazole and pyrrolidine thiadiazole derivatives are useful in the treatment and prevention of oxytocin mediated disease states like preterm labor, premature birth and dysmenorrheal because of their markable oxytocin receptor antagonist activity [5], pyrrolidine and piperidine as antidiabetic agents [6].

Sulfonamides are promising antibacterial/antibiotic agents for over several years. In addition to their commercialized utilization as antibacterial/antibiotic agents, several sulfonamides are reported to inhibit enzymes such as carbonic anhydrase [7], cysteine protease [8], HIV protease [9] and cyclo-oxygenase [10]. Besides these potential applications, various other therapeutic applications, in cancer chemotherapy [11], diuretics [12], hypoglycemia [13] and the anti-impotence agent [14] and in metabolic syndrome treatment [15] are also reported for sulfonamides.

Glucosidases catalyze the cleavage of glycosidic bonds in oligosaccharides or glycoconjugates. The arrangement of hydroxyl groups in a sugar molecule influences the enzymatic action of several glucosidases. Accordingly, α- and β-glucosidases are able to catalyze the cleavage of glycosidic bonds bearing terminal glucose linked at the site of cleavage, respectively, through α- or β-linkages at the anomeric center [16]. The activity of glucosidases is fundamental to several biochemical operations like degradations of diet polysaccharides to furnish monosaccharide units, lysosomal glycoconjugate catabolism and glycoprotein processing and biosynthesis of oligosaccharide units in glycoproteins or glycolipids [17]. These multidimensional biochemical activities of glucosidases cater to the needs for developing new and potential therapeutic inhibitors to be used in diabetes [18], obesity [17], glycosphingolipid lysosomal storage disease [19], HIV infections [20] and tumors in general [21].

Considering the vitality of pyrrolidine and sulfonamides in view, a new series of N,N'-(pyrrolidine-3,4-diyl)sulfonamide derivatives containing 1,3,4-oxadiazole/azetidinone/thiazolidinone were synthesized and examined for their antimicrobial activity and inhibitory activity against human β-glucosidase enzyme.

2. Experiment

2.1 Materials and Methods

All chemicals and reagents were procured from Merck India Ltd. X-6 digital display binocular microscope (uncorrected) was used to determine the melting points. Nicolet nexus 470 FT-IR spectrometer (USA) using deploying KBr crystal or KBr plate was used to record the IR spectra of the synthesized compounds. ^{1}H NMR (400 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker Avance (Switzerland) spectrometer. The elemental analysis was carried on Vario Micro Cube Elementar (Germany) instrument. The reaction progress was

monitored by TLC with a mixture of cyclohexane and ethylacetate (9:1) as an elutent. A 300 mesh silica gel was used to perform flash column chromatography. The yields were calculated by the last step reaction.

The standard bacterial and fungal strains were procured from National Centre for Cell Science (Pune, India). The antimicrobial activity was expressed in terms of minimum inhibitory concentration (MIC). The MIC was found by the agar cup plate method for antibacterial activity and disc diffusion method for antifungal activity. Streptomycin and clotrimazole were used as standards (20 μg/mL) for antibacterial studies and antifungal studies respectively.

2.2 Docking method

A genetic algorithm (GA) based software namely GOLD (Genetic Optimization of Ligand Docking, Cambridge Crystallographic Data Centre, Cambridge, UK) was used to carry out the docking studies. GOLD version 3.0.1 program was used to perform the molecular docking method for studying the binding affinities of synthesized molecules into the active site of the β-glucosidase protein. The location and measurement of the protein pockets and cavities were done automatically by a program named CASTP server (Cambridge Crystallographic Data Centre, Cambridge, UK), which is used for active site identification [22].

2.3 General Procedures

*2.3.1 Synthesis of ethyl 2-((3S,4S)-3,4-bis(N-cyclopropylthiophene-2-sulfonamido)pyrrolidin-1-yl)acetate **(2)***

To the solution of ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulfonamido)pyrrolidin-1-yl)acetate **(1)** (1.3 g, 2.71 mmol) in acetonitrile (12 mL), potassium carbonate (1.39 g, 10.03 mmol), cyclopropyl bromide (0.33 g, 2.71 mmol) and few crystals of KI were added and refluxed for 20 h. The residue obtained after the removal of the solvent was poured into water under reduced pressure and extracted with CH_2Cl_2 (3x10 mL). The combined organic layer was dried over anhydrous Na_2SO_4. A crude solid was obtained on filtration and concentration of the organic layer under reduced pressure, which was then purified by column chromatography using 60-120 mesh silica gel as an adsorbent and dichloromethane and methanol (10:1) mixture as an eluent [23,24]. The spectral and physical characterization data of compound **2** are shown in Table 1.

*2.3.2 Synthesis of N,N'-((3S,4S)-1-(2-hydrazinyl-2-oxoethyl) pyrrolidine-3,4-diyl)bis(N-cyclopropylthiophene-2-sulfonamide) **(3)***

A solution of compound **2** (1.1 g, 1.9 mmol) and hydrazine hydrate in ethanol (85%, 3.8 mmol) was refluxed for 5 h. The crude product obtained on evaporation of the reaction mixture under reduced pressure was purified by recrystallization from the proper absolute alcohol. The spectral and physical characterization data of compound **3** are shown in Table 1.

*2.3.3 Synthesis of N,N'-((3S,4S)-1-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)pyrrolidine-3,4-diyl)bis(N-cyclopropyl thiophene-2-sulfonamide) **(4a)***

A mixture of benzoic acid (0.122 g, 1.0 mmol) and compound-3 (0.55 g, 1.0 mmol) in phosphoryl chloride (5 mL) was refluxed over a steam bath for 5-6 h. The cooled reaction mixture was poured on to crushed ice (~300 g) under continuous stirring. The separated solid mass was neutralized using sodium bicarbonate solution (10% w/v), collected by filtration, washed with cold water and dried in vacuum. The resulting solid thus obtained was recrystallized from absolute ethanol (95%) to obtain the desired product **4a**.

Compounds **4b-4f** were prepared from compound **3** and the appropriate 4-substituted benzoic acid by using a procedure similar to that described for the synthesis of **4a**.

The IR (KBr) spectrum of compound **4a** showed peaks (cm^{-1}) around 3135 (Ar-H), 1645 & 1232 (characteristic peaks for oxadiazole), 1322 & 1182 (asymmetric & symmetric stretching of O=S=O), 1140 & 1125 (C-N exo) respectively. The ^{1}H NMR (400 MHz, $^\delta$ppm) spectrum exhibits the signals 8.02-7.62 (m, 5H, Ar-H), 7.59-7.17 (m, 6H, thiophene), 3.64 (s, 2H, N-CH_2-), 3.28 (m, 2H, -SO_2-N-CH-), 3.07 (m, 2H, H_a protons of pyrrolidine), 2.69 (m, 2H, cyclopropyl C-H attached to N), 2.28 (m, 2H, H_b protons of pyrrolidine), 0.51&0.39(m, 8H, -CH_2 of cyclopropane). The ^{13}C NMR (75 MHz, $^\delta$ppm) spectrum has the peaks at 144.4 & 131.8 (thiophene), 170.4 & 162.9 (oxadiazole), 116.4, 142.7, 128.8 & 131.3 (Ar). The spectral and physical characterization data of compounds **4a-4f** are shown in Table 1.

*2.3.4 General procedure for the synthesis of N,N'-((3S,4S)-1-(2-((E)-2-(4-substitutedbenzylidene hydrazinyl)-2-oxoethyl) pyrrolidine-3,4-diyl)bis(N-cyclopropylthiophene-2-sulfonamide) **(5a-f)***

To an equimolar methanolic solution of compound **3** (0.83 g, 1.52 mmol) and benzaldehyde (0.16 g, 1.52 mmol) mixture, few drops of glacial acetic acid were added. The mixture was then refluxed on a water bath for 5 h, allowed to cool, poured into crushed ice and filtered. 60-120 mesh silica gel and cyclohexane-ethylacetate (9:1) solvent mixture as an eluent were used to purify the crude mass by column chromatography.

Compounds **5b-5f** were prepared from compound-**3** and the appropriate 4-substituted benzaldehyde by using a procedure similar to that described for the synthesis of **5a**.

*2.3.5 Synthesis of 2-((3S,4S)-3,4-bis(N-cyclopropylthiophene-2-sulfonamido)pyrrolidin-1-yl)-N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)acetamide **(6a)***

A solution of **5a** (0.64 g, 1.0 mmol) in dioxane (8 mL) was added to a well stirred mixture of chloroacetylchloride (0.24 g, 2.0 mmol) and triethylamine (0.2 g, 2.0 mmol) in dioxane (10 mL) at 0-5°C. The reaction mixture was then stirred for 8 h, kept at room temperature for 2 days and then washed with cold water. The obtained solid was filtered, washed with water and recrystallized from methanol to yield the desired product **6a**.

Compounds **6b-6f** were prepared from **5a** by using a procedure adopted for the synthesis of **6a**.

The IR (KBr) spectrum of compound **6a** showed peaks (cm^{-1}) around 3490 (N-H), 3135 (Ar-H), 1689 (C=O of azitidinone), 1322 & 1182 (asymmetric and symmetric stretching), 1215(C-N of azitidinone), 810 (C-Cl). The ^{1}H NMR (400 MHz, $^\delta$ppm) spectrum exhibits the signals 9.35 (s, 1H, -CO-NH), 7.65-7.25 (m, 6H, thiophene), 7.47-7.32(m, 5H, Ar-H), 5.51 (d, 1H, Cl-C-H of

Table 1 – The spectral and physical characterization data

Com No.	Molecular Formula	M.P., °C	Yield, %	IR (KBr, cm^{-1})	^{1}H NMR (DMSO-d_6, 400 MHz, δppm)	^{13}C NMR (DMSO-d_6, 75MHz, δppm)	Results of elemental analysis
2	$C_{22}H_{29}N_3O_6S_4$	162-164	70	3496&3424 (asym.& sym.NH_2),3221(N-H), 1698(C=O), 1125 (C-N), 1100 (pyrrolidine C-N), 1322&1182 (sym.&assym. O=S=O),1388 (thiophene C-S)	7.68-7.18(m,6H), 4.55(m,2H,), 3.4(q, 2H, J=7.2 Hz), 3.33(s,2H), 3.14&2.25(m,4H)*, 2.70(m,2H), 1.3(t, 3H, J=5.2 Hz), 0.70-0.30(m,8H,)	171.5 (C=O)144.4 & 131.8 (thiophene), 64.3(O-CH_3), 15.6(CH_3), 5.2&25.0 (cyclopropyl)	C, 47.29 (47.22); H, 5.28 (5.24); N, 7.57 (7.55)
3	$C_{20}H_{27}N_5O_5S_4$	174-176	65	3430 & 3370 (asym.&sym -NH_2), 1739 (C=O), 1125 (exo C-N), 1100 (pyrrolidine C-N), 1388 (thiophene C-S), 1322 & 1182 (asym.& sym. O=S=O)	8.03 (s, H), 7.59-7.15(m,6H), 4.23(m,2H), 3.17(s,2H), 3.12&2.35 (m,4H), 2.74(m,2H), 2.0 (s, 2H), 0.51&0.39(m,8H)	170.7 (C=O), 144.4 & 131.8 (thiophene), 5.2&25.0 (Cyclopropyl)	C, 44.09 (44.02); H, 4.92 (4.99); N, 12.87 (12.83)
4a	$C_{27}H_{29}N_5O_5S_4$	182-184	70	3135 (Ar-H), 1645 & 1232 (characteristic peaks for oxadiazole), 1322 & 1182 (asymmetric and symmetric stretching O=S=O), 1140 & 1125 (two C-Nexo)	8.02-7.62(m,5H), 7.62(m,3H), 7.59-7.17 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 2.69 (m,2H), 3.07&2.28 (m,4H), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophene), 170.4 & 162.9(oxadiazole), 116.4, 142.7, 128.8 & 131.3(Ar)	C, 51.37 (51.33); H, 4.59 (4.63); N, 11.13 (11.08)
4b	$C_{28}H_{31}N_5O_5S_4$	156-158	70	3135(Ar-H), 1649 & 1233(Characteristic peaks for oxadiazole), 1327 & 1185(asymmetric and symmetric stretching O=S=O), 1142 & 1126(two C-Nexo)	7.97-7.26 (m,4H), 7.59-7.17 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 3.07&2.28 (m,4H), 2.69 (m,2H,), 2.34 (s,3H), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophene), 170.4 & 162.9(oxadiazole), 117.1, 129.1, 131.2 & 139.1(phenyl), 23.1(CH_3)	C, 52.12 (52.07); H, 4.86(4.84); N, 10.89(10.84)
4c	$C_{28}H_{31}N_5O_6S_4$	138-140	70	3139(Ar-H), 1651 & 1234(Characteristic peaks for oxadiazole), 1329 & 1188(asymmetric and symmetric stretching O=S=O), 1144 & 1128(two C-Nexo)	8.02-7.03 (m,4H), 7.59-7.17 (m, 6H), 3.81(s,3H), 3.64 (s,2H), 3.28(m,2H), 3.07 &2.28 (m,4H), 2.69 (m,2H), (m,2H), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophen), 170.4 & 162.9(oxadiazole), 117.7, 129.6, 115.5 & 163.4(phenyl), 57.0(-OCH_3)	C, 50.89(50.81); H, 4.79(4.72); N, 10.63(10.58)
4d	$C_{27}H_{28}ClN_5O_5S_4$	172-174	70	3141(Ar-H), 1653 & 1237(Characteristic peaks for oxadiazole) , 1331 & 1189(asymmetric and symmetric stretching O=S=O), 1145 & 1129(two C-Nexo)	7.58-7.53(m,4H), 7.70-7.22 (m, 6H), 3.63 (s,2H), 4.11 (m,2H), 3.32 & 2.17 (m,4H), 2.69 (m,2H), 2.17 (m,2H,), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophen), 170.4 & 162.9(oxadiazole), 117.7, 131.7, 129.6 & 131.3(phenyl)	C, 48.71(48.67); H, 4.29(4.24); N, 10.59(10.51)
4e	$C_{27}H_{28}N_6O_7S_4$	166-168	75	3140(Ar-H), 1651 & 1233(Characteristic peaks for oxadiazole), 1329 & 1185(asymmetric and symmetric stretching O=S=O), 1143 & 1126(two C-Nexo)	7.29-7.09(m,4H), 7.70-7.22(m, 6H), 3.63(s,2H), 4.11 (m,2H), 3.32 & 2.17 (m,4H), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophene), 170.4 & 162.9(oxadiazole), 116.8, 127.7, 128.4 & 136.7(phenyl)	C, 45.69(45.63); H, 3.893.97); N, 9.81(9.85)
4f	$C_{27}H_{28}N_6O_7S_4$	202-204	75	3148(Ar-H), 1656& 1237(asymmetric and symmetric stretching O=S=O), 1335&1189(asymmetric and symmetric stretching O=S=O) 1147&1129(two C-Nexo)	7.95-7.4(m,4H), 7.59-7.17 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 3.07 & 2.28 (m,2H), 2.69 (m,2H), 0.51&0.39(m,8H)	144.4 & 131.8 (thiophene), 170.4 & 162.9(oxadiazole), 116.4, 127.0, 124.1 & 150.5(phenyl)	C, 47.93(47.91); H, 4.21(4.17); N, 12.35(12.42)
5a	$C_{27}H_{31}N_5O_5S$	166-168	75	3135(Ar-H), 1620(C=N), 1388(thiophene),1322 & 1182(asymmetric and symmetric stretching O=S=O), 1125 & 1100 (two C-Nexo)	11.07(s,1H), 8.53(s,1H), 7.93-7.58(m,5H), 7.59-7.15 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 3.23 & 2.58 (m,4H), 2.69 (m,2H), 0.51&0.26 (m,8H)	171.3(C=O)145.1 & 132.3(thiophen), 144.1 (C=N), 133.1,131.2 & 129 (phenyl)	C, 51.11(51.16); H, 4.96(4.93); N, 11.10(11.05)
5b	$C_{28}H_{33}N_5O_5S_4$	134-136	65	3134(Ar-H), 1615(C=N),1387(thiophene),1322&& 1181(asymmetric and symmetric stretching O=S=O), 1127 & 1102(two C-Nexo)	11.07(s,1H), 8.53(s,1H), 7.91-7.40(m,4H), 7.61-7.17 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 3.07 & 2.28 (m,4H), 2.69 (m,2H), 2.28 (m,2H), 2.41(s,3H), 0.51&0.26 (m,8H)	171.3(C=O), 145.1 & 132.3(thiophen), 144.4(C=N), 142, 131, 129 & 126 (phenyl), 21.3(CH_3)	C, 51.88(51.91); H, 5.10(5.13); N, 10.77(10.71)

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Table 1 – The spectral and physical characterization data (continued)

Com No.	Molecular Formula	M.P., °C	Yield, %	IR (KBr, cm^{-1})	^{1}H NMR (DMSO-d_6, 400 MHz, δppm)	^{13}C NMR (DMSO-d_6, 75MHz, δppm)	Results of elemental analysis
5c	$C_{28}H_{33}N_5O_6S_4$	148-150	70	3135(Ar-H), 1617(C=N), 1388(thiophene),1321&& 1182(asymmetric and symmetric stretching O=S=O), 1129 & 1101(two C-Nexo)	11.07(s,1H), 8.53(s,1H), 8.02-7.03(m,4H), 7.59-7.17 (m, 6H), 3.81(s,3H), 3.64 (s,2H), 3.28(m,2H), 3.07 & 2.28 (m,2H), 2.69 (m,2H), 2.28 (m,2H), 0.51&0.26 (m,8H)	171.3(C=O), 145.1 & 132.3(thiophen), 144.4(C=N), 162.6, 131.0, 126.3 & 114.9(phenyl), 56.0(-OCH_3)	C, 50.59(50.66); H, 4.95(5.01); N, 10.51(10.55)
5d	$C_{27}H_{30}ClN_5O_5S_4$	154-156	75	3136(Ar-H), 1625(C=N) , 1387(thiophene),1322&& 1182(asymmetric and symmetric stretching O=S=O), 1125 & 1100	11.07(s,1H), 8.53(s,1H), 7.58-7.53(m,4H), 7.70-7.22 (m, 6H), 3.63 (s,2H), 4.11 (m,2H), 3.32&2.17 (m,2H), 2.69 (m,2H), 2.17 (m,2H), 0.51&0.26 (m,8H)	171.0(C=O), 145.1 & 132.3(thiophen), 144.3(C=N), 136.6, 131.5, 130.3 & 129.0(phenyl)	C, 48.49(48.53); H, 4.49(4.52); N, 10.45(10.48)
5e	$C_{27}H_{30}BrN_5O_5S_4$	174-176	75	3135(Ar-H), 1622(C=N), 1388(thiophene),1322&& 1182(two C-Nexo)	11.07(s,1H), 8.53(s,1H), 7.29-7.09(m,4H), 7.70-7.22(m, 6H), 3.63(s,2H), 4.11 (m,2H), 3.32&2.17(m,2H), 2.69(m,2H), 0.51&0.26 (m,8H)	171.0(C=O), 145.1 & 132.3(thiophen), 144.3(C=N), 137.1,132.9, 131.5 & 128.4(phenyl)	C, 45.52(45.50); H, 4.29(4.24); N, 9.89(9.83)
5f	$C_{27}H_{30}N_6O_7S_4$	185-187	70	3135(Ar-H), 1626(C=N), 1389(thiophene),1322&& 1182(asymmetric and symmetric stretching O=S=O), 1125 & 1100(two C-Nexo)	11.07(s,1H), 8.53(s,1H), 8.03-7.62(m,4H), 7.59-7.17 (m, 6H), 3.64 (s,2H), 3.28 (m,2H), 3.07&2.28(m,2H), 2.69 (m,2H), 0.51&0.26 (m,8H)	171.0(C=O), 145.1 & 132.3(thiophen), 144.3(C=N), 150.1, 140.2 & 124.5 (phenyl)	C, 47.79(47.77); H, 4.42(4.45); N, 12.34(12.38)
6a	$C_{29}H_{32}ClN_5O_6S_4$	142-143	70	3490(N-H), 3135 (Ar-H), 1689 (C=O of Azitidinone), 1322 & 1182 (asymmetric and symmetric stretching O=S=O),1215(C-N of Azitidinone), 810 (C-Cl)	9.35(s,1H), 7.65-7.25 (m, 6H),7.47-7.32(m,5H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.21(s,2H), 3.52 (m,2H), 3.16&2.18 (m,4H), 2.69 (m,2H), 0.51&0.26 (m,8H)	144.4 & 131.8(thiophen), 142.7, 128.1, 129.2 & 130.3 (phenyl)	C, 49.09(49.04); H, 4.62(4.54); N, 9.79(9.86)
6b	$C_{30}H_{34}ClN_5O_6S_4$	158-159	65	3485(N-H), 3137(Ar-H), 1686(C=O of Azitidinone), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1212(C-N of Azitidinone), 808(C-Cl)	9.35(s,1H), 7.65-7.25 (m, 6H),7.19-7.09(m,4H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.21(s,2H), 3.52(m,2H), 3.16&2.18(m,4H), 2.69 (m,2H), 2.18 (m,2H), 2.19(s,3H), 0.51&0.26 (m,8H)	144.4 & 131.8(carbons of thiophen), 131.1, 130.0, 129.7 & 133.7 (phenyl), 21.1(CH_3)	C, 49.73(49.79); H, 4.79(4.73); N, 9.63(9.67)
6c	$C_{30}H_{34}ClN_5O_7S_4$	171-172	70	3480(N-H), 3135(Ar-H), 1683(C=O of Azitidinone), 1322 & 1182(asym.&sym. SO_2) (asymmetric and symmetric stretching O=S=O),1210(C-N of Azitidinone), 806(C-Cl)	9.42(s,1H), 7.65-7.28 (m, 6H), 7.22-6.88 (m,4H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.45(s,2H), 3.28 (m,2H), 3.07&2.28 (m,4H), 2.69 (m,2H), 0.51-0.26 (m,8H)	144.4 & 131.8(thiophen), 132.6, 128.0, 125.6 & 132.3 (phenyl), 57.0 (OCH_3)	C, 48.61(48.67); H, 4.69(4.63); N, 9.51(9.46)
6d	$C_{29}H_{31}C_{l2}N_5O_6S_4$	138-139	75	3495(N-H), 3143(Ar-H), 1692(C=O of Azitidinone), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1218(C-N of Azitidinone), 814(C-Cl)	9.33(s,1H), 7.66-7.18 (m, 6H),7.49(m,4H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.45(s,2H), 3.28 (m,2H, -), 3.07&2.28 (m,4H), 2.69 (m,2H), 0.51&0.26 (m,8H)	144.4 & 131.8(thiophen), 139.4, 128.1, 127.3 & 135.7 (phenyl)	C, 46.71(46.77); H, 4.23(4.20); N, 9.46(9.40)
6e	$C_{29}H_{31}BrClN_5O_6S_4$	166-167	77	3493(N-H), 3142(Ar-H), 1690(C=O of Azitidinone), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1216(C-N of Azitidinone), 812(C-Cl)	9.30(s,1H), 7.6-7.18 (m, 6H), 7.78-7.18 (m,4H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.45(s,2H), 3.28 (m,2H), 3.07&2.28 (m,4H), 2.69 (m,2H), 0.51&0.26 (m,8H)	144.4 & 131.8(thiophen), 135.7, 127.3, 128.1 & 139.4 (phenyl)	C, 44.19(44.13); H, 4.05(3.96); N, 8.91(8.87)
6f	$C_{29}H_{31}ClN_6O_8S_4$	187-188	80	3493(N-H), 3142(Ar-H), 1694(C=O of Azitidinone), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1223(C-N of Azitidinone), 817(C-Cl)	9.34(s,1H), 7.59-7.15 (m, 6H), 8.18-7.55(m,4H), 5.51(d,1H, J=4.7Hz), 3.97(d,1H, J=9.11Hz), 3.45(s,2H), 3.28 (m,2H), 3.07&2.28 (m,2H, 2.69 (m,2H), 0.51&0.26 (m,8H)	144.4 & 131.8(thiophen), 147.3, 126.5, 130.0 & 139.5 (phenyl)	C, 46.23(46.12); H, 4.16(4.14); N, 11.23(11.13)

Table 1 – The spectral and physical characterization data (continued)

Com No.	Molecular Formula	M.P., °C	Yield, %	IR (KBr, cm^{-1})	^{1}H NMR (DMSO-d_6, 400 MHz, δppm)	^{13}C NMR (DMSO-d_6, 75MHz, δppm)	Results of elemental analysis
7a	$C_{29}H_{33}N_5O_6S_5$	162-164	73	3482(N-H), 3135 (Ar-H), 1712 (C=O of thiazolidine), 1322 & 1182 (asymmetric and symmetric stretching O=S=O),1215(C-N of thiazolidine)	8.38(s,1H), 7.65-7.15(m, 6H),7.36-7.23(m,5H), 6.14(s,1H), 4.25(m,2H), 3.79(s,2H),3.31(s,2H), 3.10&2.88 (m,4H), 3.24(m,2H), 0.51& 0.26 (m,8H)	144.4 &131.8(thiophene), 140.7, 127.1, 128.2 & 129.3 (phenyl)	C, 49.26(49.20); H, 4.79(4.70); N, 9.96(9.89)
7b	$C_{30}H_{35}N_5O_6S_5$	168-170	75	3478(N-H), 3135(Ar-H), 1710(C=O of thiazolidine), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1245(C-N of thiazolidine)	8.38(s,1H), 7.65-7.15(m, 6H),7.26-7.10(m,4H), 6.14(s,1H), 3.31(s,2H), 4.25(m,2H), 3.79(s,2H),3.10&2.88 (m,4H), 3.24(m,2H), 2.19(s,3H), 0.51&0.26 (m,8H)	144.4 &131.8(thiophen), 137.5, 128.1, 129.2 & 138.1 (phenyl), 21.1 (-CH_3)	C, 49.86(49.91); H, 4.96(4.89); N, 9.79(9.70)
7c	$C_{30}H_{35}N_5O_7S_5$	162-164	68	3476(N-H), 3135(Ar-H), 1708(C=O of thiazolidine), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1243(C-N of thiazolidine)	8.39(s,1H), 7.65-7.15(m, 6H), 7.22-6.88(m,4H), 6.14(s,1H), 4.25(m,2H), 3.81(s,3H), 3.79(s,2H), 3.31(s,2H), 3.24(m,2H), 3.10&2.88 (m,4H), , 0.51&0.26 (m,8H)	144.4 &131.8(thiophen), 130.0, 129.0, 113.6 & 160.0(phenyl), 56.0 (-OCH_3)	C, 48.87(48.83); H, 4.71(4.78); N, 9.42(9.49)
7d	$C_{29}H_{32}ClN_5O_6S_5$	158-160	71	3487(N-H), 3135(Ar-H), 1715(C=O of thiazolidine), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1253(C-N of thiazolidine)	8.39(s,1H), 7.65-7.15(m, 6H), 7.37-7.23(m,4H), 6.14(s,1H), 3.31(s,2H), 4.25(m,2H), 3.79(s,2H),3.10&2.88 (m,4H), 3.24(m,2H), 2.19(s,3H), 0.51&0.26 (m,8H)	144.4 &131.8(thiophene), 138.6, 129.1, 128.0 & 133.3 (phenyl)	C, 46.99(46.92); H, 4.40(4.34); N, 9.42(9.49)
7e	$C_{29}H_{32}BrN_5O_6S_5$	170-172	73	3485(N-H), 3135(Ar-H), 1712(C=O of thiazolidine), 1322 & 1182(asymmetric and symmetric stretching O=S=O),1250(C-N of thiazolidine)	8.37(s,1H), 7.65-7.15(m, 6H), 7.78-7.33(m,4H), 6.14(s,1H), 3.31(s,2H), 4.25(m,2H),3.79(s,2H),3.10&2.88(m,4H), 3.24(m,2H), 2.19(s,3H), 0.51&0.26 (m,8H)	144.4 &131.8(thiophen), 138.5, 130.0, 131.0 & 121.3 (phenyl)	C, 44.39(44.27); H, 4.19(4.10); N, 8.99(8.90)
7f	$C_{29}H_{32}N_6O_8S_5$	178-180	65	3489(N-H), 3135(Ar-H), 1720(C=O of thiazolidine), 1322 & 1182) (asymmetric and symmetric stretching O=S=O),1256(C-N of thiazolidine)	8.41(s,1H), 7.65-7.15(m, 6H), 8.20-7.71 (m,4H), 6.14(s,1H), 3.31(s,2H), 4.25(m,2H), 3.79(s,2H),3.10&2.88 (m,4H), 3.24(m,2H), 2.19(s,3H, 0.51&0.26 (m,8H)	144.4 &131.8(thiophen), 146.9, 127.7, 124.0 & 148.4 (phenyl)	C, 46.35(46.26); H, 4.35(4.28); N, 11.22(11.16)

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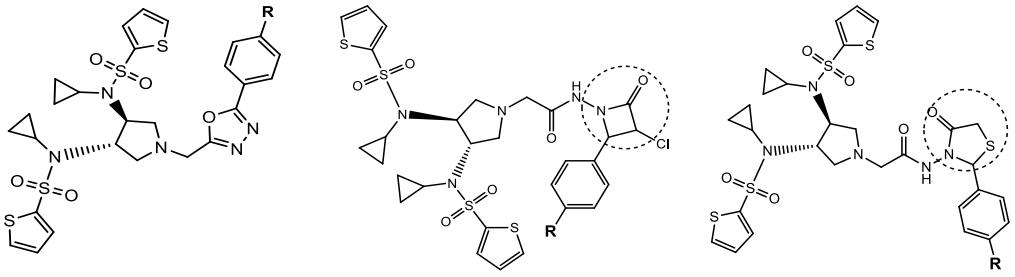


4a-f **6a-f** **7a-f**

R = -H, -CH_3, -OCH_3, -Cl, -Br, -NO_2

azetidine), 3.97 (d, 1H, C-H of azetidine), 3.21 (s, 2H, N-CH_2-), 3.52 (m, 2H, -SO2-N-CH-), 3.16 (m, 2H, H_a protons of pyrrolidine), 2.69 (m, 2H, cyclopropyl C-H attached to N), 2.18 (m, 2H, H_b protons of pyrrolidine), 0.51&0.26 (m, 8H, -CH_2- of cyclopropyl ring). The ^{13}C NMR (75 MHz, $^{\delta}$ppm) spectrum has the peaks at 144.4 & 131.8 (thiophene), 142.7, 128.1, 129.2 & 130.3 (phenyl). The spectral and physical characterization data of compounds **6a-6f** are shown in Table 1.

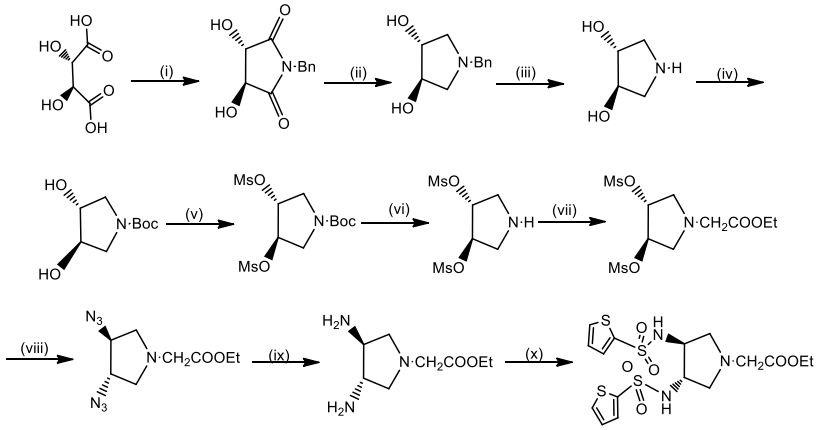
*2.3.6 Synthesis of 2-((3S,4S)-3,4-bis(N-cyclopropylthiophene-2-sulfonamido)pyrrolidin-1-yl)-N-(4-oxo-2-(4-substituted)phenylthiazolidin-3-yl)acetamide **(7a)***

A mixture of **5a** (0.64 g, 1.0 mmol) and mercaptoacetic acid (0.18 g, 2.0 mmol) was heated in an oil bath at 120-125°C for 12 h, cooled and treated with 10% sodium bicarbonate solution. The product was isolated and recrystallized from methanol-dioxane (4:1) mixture to give the desired compound. Compounds **7b-7f** were prepared from **7a** by using a procedure similar to that described for the synthesis of **7a**.

The IR (KBr) spectrum of compound **7a** showed peaks (cm^{-1}) around 3482 (N-H), 3135 (Ar-H), 1712 (C=O of thiazolidine), 1322 & 1182 (asymmetric and symmetric stretching), 1215 (C-N of thiazolidine). The ^{1}H NMR (300 MHz, $^{\delta}$ppm) spectrum shows the signals at 8.38, 1H, -CO-NH), 7.65-7.15 (m, 6H, thiophene), 7.36-7.23 (m, 5H, Ar-H), 6.14 (s, 1H, thiazolidine-N-CH-S-), 4.25 (m, 2H, -SO_2-N-CH-), 3.79 (s, 2H, -CO-CH-S- of thiazolidine), 3.31 (s, 2H, N-CH_2-), 3.10 (m, 2H, H_a protons of pyrrolidine), 3.24 (m, 2H, cyclopropyl C-H attached to N), 2.88 (m, 2H, H_b protons of pyrrolidine), 0.51&0.26 (m, 8H, -CH_2- of cyclopropyl ring. The ^{13}C NMR (75 MHz, $^{\delta}$ppm) spectrum has the peaks at 144.4 &131.8 (thiophene), 140.7, 127.1, 128.2 & 129.3 (phenyl). The spectral and physical characterization data of compounds **7a-f** are shown in Table 1.

3. Results and discussion

The strategy starts with the synthesis of starting material *ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulfonamido)pyrrolidin-1-yl)acetate* **(1)** from L-tartaric acid as shown in Figure 1 [25,26].

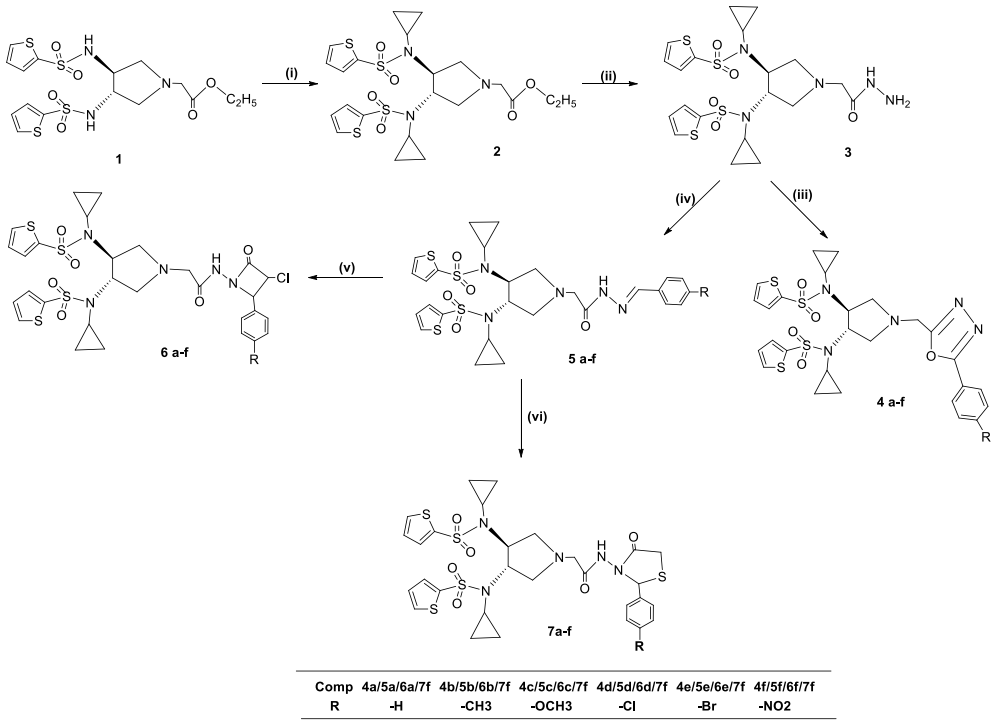


Reagents & Conditions: (i) Benzylamine, xylene, 190°C, 8h; (ii) I_2, $NaBH_4$, THF, r.t; (iii) Pd/C/H_2, MeOH, r.t.; (iv) Boc_2O, $NaHCO_3$, dioxane, r.t., 2h; EtOAc (v) MsCl, Et_3N, DCM (vi) CF_3COOH, H_2O; (vii) $ClCH_3COOC_2H_5$, K_2CO_3 (viii) NaN_3, DMF (ix) Pd/C/H_2, EtOAc; (x) RSO_2Cl, Py, reflux, 2h

Figure 1 – Synthesis of ethyl-3,4-bis(thiophene-2-sulfonamido)pyrrolidinylacetate

Initially *ethyl 2-((3S,4S)-3,4-bis(thiophene-2-sulfonamido) pyrrolidin-1-yl)acetate* **(1)** was alkylated with cyclopropyl bromide to get N-alkylated sulfonamide **(2)**. This on treatment with hydrazine produces respective hydrazide **(3)**, which on reaction with substituted benzoic acid in presence of $POCl_3$ gives 1,3,4-oxadiazole derivatives **(4a-f)**. Again, the hydrazide **(3)** on treatment with substituted aldehydes gives benzylidene derivative **(5a-f)**, which on reaction with chloroacetylchloride and mercaptoacetic acid produces azitidinones **(6a-f)** and thiazolidinones **(7a-f)** respectively. The synthesis of target compounds is depicted in Figure 2.

The compound **1** undergoes N-alkylation at sulfonamide group and further on treatment with hydrazine produces hydrazide **(3)**. This hydrazide can be converted to 1,3,4-oxadiazole **(4a-f)** and substituted benzylidene hydrazinyl derivatives **(5a-f)** on reaction with substituted benzoic acid in the presence of $POCl_3$ and substituted benzaldehyde respectively. Finally, the cyclization of the compounds **5a-f** takes place in presence of chloroacetylchloride and mercaptoacetic acid to produce azetidinone derivatives **(6a-f)** and thiazolidinone derivatives **(7a-f)** respectively.



Reagents & Conditions: (i) acetonitrile, potassium carbonate, cyclopropyl bromide, KI, reflux, 20h; (ii)) Hydrazine hydrate, ethanol, reflux, 5h; (iii) 4-substituted benzoic acid, phosphoryl chloride, reflux, 5-8h; (iv) 4-substituted benzaldehyde, Glacial aceticacid, reflux, 4-8h; (v) chloroacetylchloride, triethylamine, dioxane, 0-5^{o}C, 8h; (vi) Mercaptoaceticacid, 120-125^{o}C, 12h

Figure 2 – Synthesis of pyrrolidine-3,4-disubstitutedsulfonamides containing 1,3,4-oxadiazole, azetidinone and thiazolidinone

3.1 Antimicrobial studies

The antibacterial activities of titled compounds, **4a-f**, **6a-f** and **7a-f** have been conducted against gram positive *Staphylococcus aureus, Bacillus subtilis,* and gram negative *Escherichia coli, Proteus vulgaris*. The compounds belonging to 6a-f series are highly active against gram-positive and gram-negative bacteria showing the broad spectra of antibacterial activity. The activity of the rest of the compounds was found moderate to low against the tested microorganisms. This was expected because of the presence of ß-lactum ring in the **6a-f** series. The antibacterial activity of the tested compounds is shown in Table 2.

The antifungal activities of the series **4a-f**, **6a-f** and **7a-f** were tested against *Asperigillusflavus* and *Candida albicans*. The compounds **7a-f** exhibit privileged activity among the tested compounds and the others were found either moderately active or slightly active. 1,3,4-Oxadizole possessing pyrrolidine-3,4-diyl sulfonamide derivative bearing thiazolidin-4-one moiety **(4f)** showed moderate activity. The test results are presented in Table 2.

Table 2 – Antimicrobial activity

Comp (20 µg/mL)	Zone of inhibition (mm)*					
	Antibacterial activity				Antifungal activity	
	Gm + ve		Gm -ve			
	S. aureus	*B. subtilis*	*E. coli*	*P. vulgaris*	*Asperigillus flavus*	*Candida albicans*
4a	13	16	18	23	15	16
4b	14	15	16	19	13	15
4c	11	14	17	21	18	14
4d	18	19	22	25	16	19
4e	15	17	20	26	17	17
4f	19	21	23	29	20	21
6a	14	13	20	25	17	15
6b	16	14	24	20	15	13
6c	14	18	23	27	14	17
6d	18	17	19	21	18	16
6e	17	19	17	22	19	18
6f	20	21	25	29	23	21
7a	13	16	12	22	18	17
7b	15	14	14	25	16	19
7c	11	19	13	22	17	21
7d	17	17	16	23	19	22
7e	15	20	14	21	21	20
7f	18	21	19	27	23	24
Streptomycin	22	24	28	32	--	--
Clotrimazole	--	--	--	--	25-30	25-30

* indicate diameter of inhibition in mm.

3.2 In silico studies

It was already evident that β-glucosidase and related proteins are prime controllers of apoptosis or programmed cell death concerned with human disease including diabetes. N-substituted pyrrolidines exhibit glycosidase inhibitory activity [27,28]. The synthesized compounds were screened for antidiabetic activity by choosing human β-glucosidase as the target protein. In a view to assessing the potential of the synthesized compounds for the β-glucosidase inhibitory activity, they were docked into the active site of the receptor (3VKK).

GOLD Score is a result of force field based scoring functions of protein-ligand hydrogen bond energy S(hb_ext), protein-ligand van der Waals energy S (vdw_ext), ligand internal van der Waals energy S(hb_int), ligand intramolecular hydrogen bond energy S(vdw_int). The total fitness score was computed by multiplying the external vdw score with 1.375, an empirical correction to encourage the hydrophobic protein-ligand contact. Ligand binding positions were predicted by optimizing the fitness function:

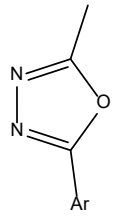
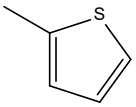
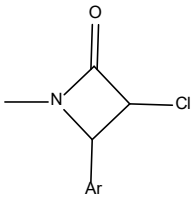
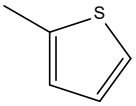
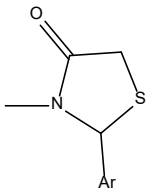
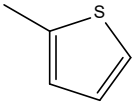
GOLD Score = S (hb_ext) + S (vdw_ext) + S (hb_int) + + S (vdw_int)

It was evident that the docking results show the amino acid residues Tyr 18, Arg 98, Val 145, Glu 152, Gly 101 of the enzyme were involved in hydrogen bonding interaction with the top poses of compounds. The inhibitory interactions translate into therapeutic efficiency to be established by traditional clinical studies. The β-glucosidase inhibitory activity of the model compounds from series **4**, **6** and **7** in terms of GOLD Score fitness and bonding interactions were shown in Table 3.

The title compounds under investigation exhibited remarkable inhibitory action against ß-glucosidases. The fitness score of 44.99 indicated that the presence of 1,3,4-oxadiazole containing pyrrolidine sulfonamides exhibit higher inhibitory activity against β-glucosidase.

The negative binding energy values represent the highest potential for the binding sites of the target protein to the title compounds. The low k_i values either in the micromolar or in nanomolar ranges of the title compounds are direct evidence

Table 3 – β-glucosidase inhibitory activity and hydrogen bonding interactions of compounds **4f**, **6f** and **7f**

Comp	G	Ar	R^1	Number of hydrogen bonds	Atoms		Bond length (A^O)	Fitness
					Protein	Comp		
4f		$C_6H_4NO_2$		5	Val 145	O27	2.226	44.99
					Glu 152	O39	2.052	
					Tyr 18	N9	1.485	
					Tyr 18	O7	2.513	
					Gly 101	O7	2.652	
6f		$C_6H_4NO_2$		3	Tyr 18	O19	2.217	37.12
					Tyr 21	O19	2.225	
					Arg 98	O26	2.310	
7f		$C_6H_4NO_2$		2	Val 148	O27	1.598	17.32
					Arg 98	O10	1.986	

for their high affinity interaction for the protein under investigation. The details are given in Table 4. The docking conformations of **4f**, **6f** and **7f** are shown in Figures 3-5 and represent the active site of the β-glucosidase protein.

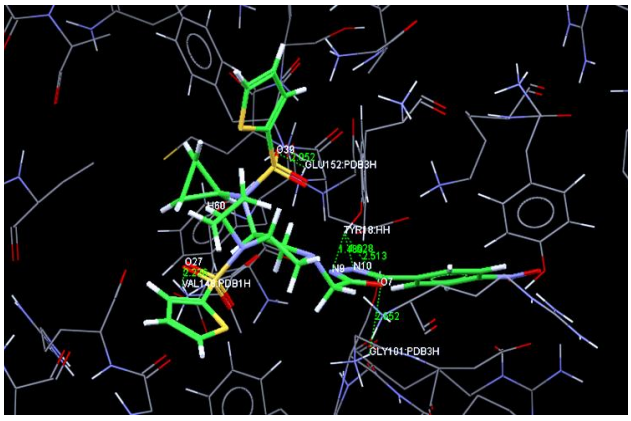


Figure 3 – Docking result of compound **4f**

Table 4 – Docking results and pharmacophore analysis of model compounds

Parameter	4f	6f	7f
Free energy of Binding (kcal/mol)	-9.22	-8.24	-7.92
Inhibition constant k_i at 298.15 K	835.12 nM	712.10 nM	691.12 nM
Total Intermolecular Energy (kcal/mol)	-11.23	-9.21	-10.12
vdW + Hbond + desolv Energy (kcal/mol)	-12.12	-11.11	-12.02
GPCR ligand	-0.07	-0.69	0.03
Ion channel modulator	-0.69	-1.56	-0.82
Kinase inhibitor	-0.49	-1.06	-0.46
Nuclear receptor ligand	-0.79	-0.59	-1.10
Protease inhibitor	0.39	0.42	-0.22
Enzyme inhibitor	-0.25	-1.21	-0.21
miLogP	-0.212	2.108	2.624
Clogp	-2.16	1.09	-0.51

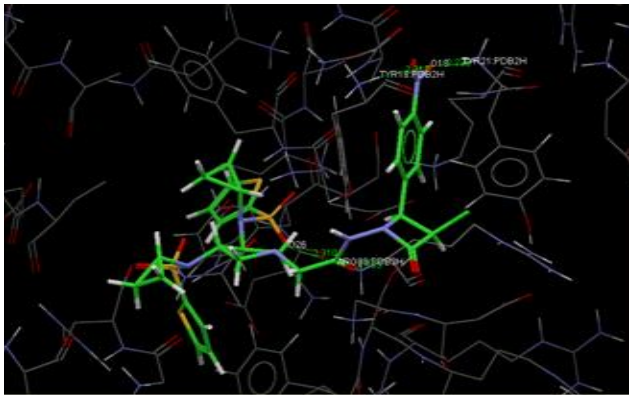


Figure 4 – Docking result of compound **6f**

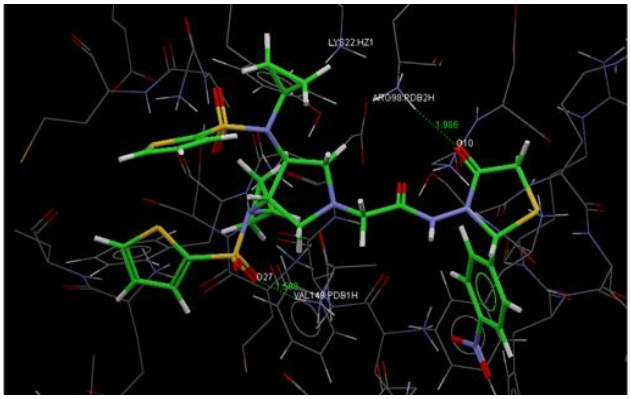


Figure 5 – Docking result of compound **7f**

4. Conclusions

Title compounds were established as potent antibacterial and antifungal active by exhibiting comparable results with standard drugs. A series of 3,4-disubstitutedpyrrolidine sulfonamide compounds were synthesized. The compounds exhibit moderate inhibition against the ß-glucosidases enzyme. The 3,4-disubstitutedpyrrolidinesulfonamides containing 1,3,4-oxadiazole moiety is a higher potent ß-glucosidase inhibitor than that of azetidinone and thiazolidinone moieties. Structure activity relation (SAR) proved that the inhibition activity against ß-glucosidase was favored by the introduction of thiophensulfonyl group at the 3 & 4 positions and a five membered oxadiazole ring at the N1 position of the pyrrolidine ring. These SAR results are in good compatible with docking studies.

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Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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