Comparative Conventional and Microwave Assisted Synthesis of Heterocyclic Oxadiazole Analogues Having Enzymatic Inhibition Potential

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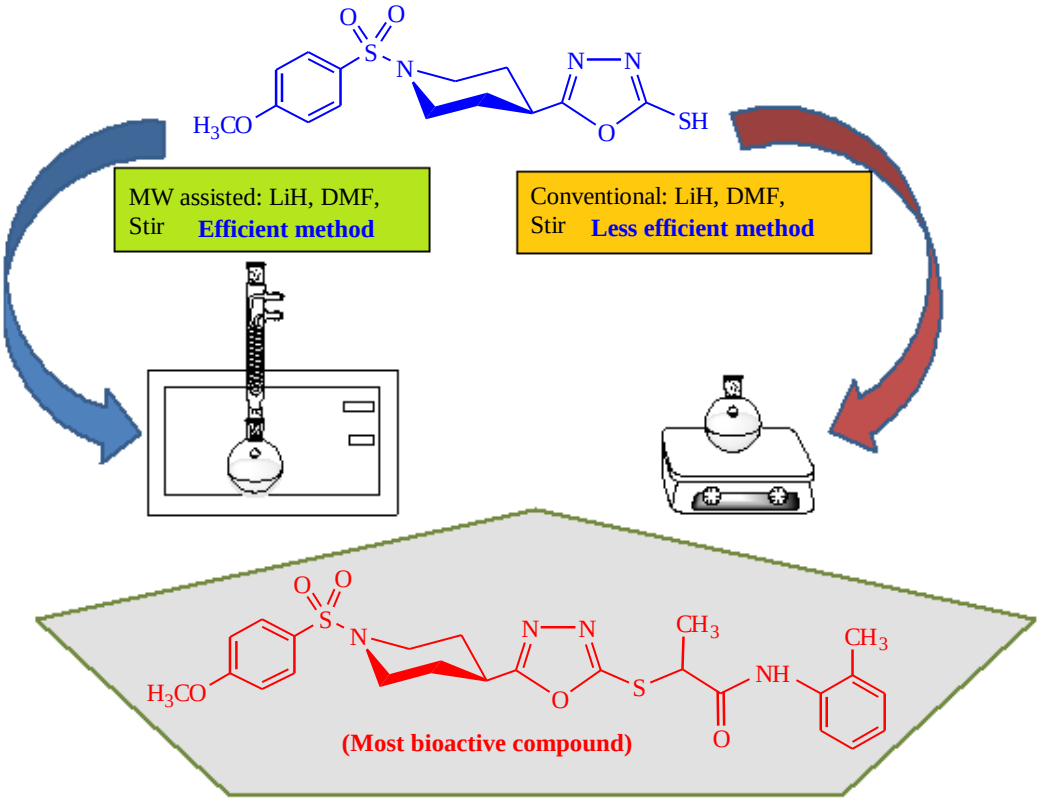
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4150



A comparative microwave assisted and conventional synthetic strategies were applied to synthesize heterocyclic 1,3,4-oxadiazole analogues as active anti-enzymatic agents. Green synthesis of compound **1** was achieved by stirring 4-methoxybenzenesulfonyl chloride (**a**) and ethyl piperidine-4-carboxylate (**b**). Compound **1** was converted into respective hydrazide (**2**) by hydrazine and then into 1,3,4-oxadiazole (**3**) by CS_2 on reflux. The electrophiles, *N*-alkyl/aralkyl/aryl-2-bromopropanamides (**6a-p**) were synthesized and converted to *N*-alkyl/aralkyl/aryl-2-propanamide derivatives (**7a-p**) by reaction with **3** under green chemistry. Microwave assisted method was found to be effective relative to conventional method. ^{13}C-NMR, ^{1}H-NMR and IR techniques were availed to corroborate structures of synthesized compounds and then subjected to screening against lipoxygenase (LOX), α-glucosidase, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes. A number of compounds presented better potential against these enzymes. The most active compounds against LOX and α-glucosidase enzymes were subjected to molecular docking study to explore their interactions with the active sites of the enzymes.

Keywords: 1,3,4-oxadiazole, piperidine, propanamides, enzyme inhibition

INTRODUCTION

Under the current pandemic situation, there exist many threatening diseases which demand thought-provoking resolution. The resistive behavior of pathogens against available drugs candidates is an alarming situation and need to be addressed in terms of introduction of new active multifunctional drugs candidates. The literature studies confirmed that the heterocyclic compounds could be able to behave actively to inhibit the action of a variety of enzymes and pathogens. The active behavior of heterocyclic compounds could be made specific and broad by changing the variety of attached functionalities with the main core of the designed molecules as in the case of current synthesis.[1]

Oxadiazole analogues have gained attention of chemists due to their dynamic potential for biological activities.[2] They have become important candidate for drug formulation.[3] Oxadiaozle and their derivatives have therapeutic importance as anti-enzymatic,[4] antibacterial,[5] insecticidal,[6] anti-inflammatory,[7] anticancer,[8] anti-HIV,[9] anti-depressant,[10] anti-convulsing,[11] muscle relaxant,[12] anti-mitotic[13] and ulcerogenic.[14] Lipoxygenase enzyme inhibitors are used in drugs in order to treat different disorders like autoimmune diseases, inflammation, cancer and bronchial asthma.[15] α-Glucosidase is responsible for its enzymatic activity to release D-glucose from dietary carbohydrates and cause hyperglycemia resulting in a disease called diabetes mellitus (type-2). Anti-α-glucosidase drugs candidates reduce conversion of carbohydrates into D-glucose which results in delayed glucose absorption and ultimately hyperglycemia is reduced, so such drugs can be used as anti-diabetic drug.[16] Cholinesterase enzymes (AChE and BChE) are serine hydrolases and are responsible for the termination of neurotransmitter acetylcholine through hydrolysis at cholinergic synapses leading to cholinergic brain synapses and neuromuscular junctions.[17]

The current research involved the synthesis of *N*-substituted propanamide derivatives of 1,3,4-oxadiazole through comparative conventional and microwave assisted protocols. Among followed methodologies, microwave assisted synthesis was more efficient with respect to saving a lot of time with better yield for synthesis of library of oxadiazole analogues.[18] The potent biological applications of the designed drugs might be due to the combination of three bioactive moieties, that is, oxadiazole, piperidine (azinane) and propanamides in one unit.

RESULTS AND DISCUSSION

Both conventional and microwave assisted methods were followed to design the most efficient and economical method to synthesize library of novel *N*-substituted propanamide analogues of 1,3,4-oxadiazole, **7a-p**. The protocol for synthesis of compounds, **7a-p**, has been elaborated in Scheme 1. Table 1 represents the different varying substituents in the target compounds. The synthesis of the main core **3** involved three reaction sub-steps corresponding to the synthesis of compound **1** by ethyl isonepecotate (**b**) and 4-methoxybenzenesulfonyl chloride (**a**) followed by the synthesis of compound **2** through the reaction of compound **1** and hydrazine. Compound **3** was synthesized by the reflux reaction of compound **2** with CS_2 and KOH. The electrophiles, **6a-p**, were prepared by reacting aryl amines (**4a-p**) with 2-bromopropionyl bromide (**5**) in aqueous basic medium. The terminal step involved the synthesis of analogues of 1,3,4-oxadiazole, **7a-p**, through coupling of **3** and **6a-p** by following microwave assisted and conventional techniques. Synthesis of target compounds, **7a-p**, by microwave assisted method resulted into high yield within 32-74 seconds as compared to conventional method which took 13-31 hours (Table 2).

Chemistry. Comprehensive discussion to justify the synthetic purity and molecular structure has been given for compound **7k**. Compound **7k** was obtained in the form of brown precipitates having melting point of 209-212 ºC. IR spectra partially helped to characterize its structure and confirmed the formation of oxadiazole ring. Characteristic stretching absorption band appeared at 3331 (N-H), 3037 (aromatic C-H), 1654 (amide C=O), 1332 (S=O), 1517 (aromatic C=C), 1565 (C=N) and 1244 & 1086 (C-O-C). The available different protons and their positions were confirmed by ^{1}H-NMR spectral details (Figure 1 and Figure 2). A singlet appearing at δ 10.13 confirmed the presence of NH of propanamide. Four protons of sulfonyl moiety appeared at δ 7.70 (d, J = 8.9 Hz, 2H, H-2" & H-6") and 7.17 (d, J = 8.9 Hz, 2H, H-3" & H-5") confirming the presence of aromatic ring with sulfonyl group. The four protons of an aromatic ring attached to nitrogen to propanamide were justified by the presence of two signal appearing at δ 7.42 (d, J = 9.1 Hz, 2H, H-2''' & H-6'''), and 6.89 (d, J = 9.1 Hz, 2H, H-3''' & H-5'''). The four protons of propanamide functionality were confirmed by two signals appearing at δ 3.62 (q, J = 6.8 Hz, 1H, H-2'''') and 1.42 (d, J = 7.0 Hz, 3H, H-3''''). The ethylene protons of ethoxy group attached to aromatic ring was justified by a quartet signal appearing at δ 3.96 (q, J = 6.9 Hz, 2H, H-7'''). Similarly the methyl of this ethoxy group was justified by a triplet signal appearing at δ 1.30 (t, J = 6.8 Hz, 3H, H-8'''). Three proton of methoxy group attached the aromatic ring of sulfonyl was

confirmed by the singlet signal appearing at δ 3.86 ppm. The piperidine ring having nine protons was justified by the signals resonating at 3.57-3.55 (m, 2H, H*e*-2' & H*e*-6'), 2.94-2.89 (m, 1H, H-4'), 2.51-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.07-2.04 (m, 2H, H*e*-3' & H*e*-5') and 1.76-1.70 (m, 2H, H*a*-3' & H*a*-5'). The available numbers of carbons in the back bone of compound **7k** were confirmed by spectra of ^{13}C-NMR as given in Figure 3. The one quaternary carbon of carbonyl of amide, two of 1,3,4-oxadiazole ring and four of two aromatic rings appeared at δ 163.11 (C-1''''), 162.68 (C-5), 160.94 (C-2), 159.85 (C-4''), 153.45 (C-4'''), 131.96 (C-1'') and 126.95 (C-1'''). The methine carbons of aromatic ring of sulfonyl group was justified by the carbon signals appearing at δ 129.63 (C-2'' & C-6'') and 114.53 (C-3'' & C-5''). The methine carbons of aromatic ring of propanamide was justified by the carbon signals appearing at δ 118.33 (C-2''' & C-6''') and 114.58 (C-3''' & C-5'''). Similarly the carbons of piperidne ring appeared at δ 44.94 (C-2' & C-6'), 30.98 (C-4') and 28.03 (C-3' & C-5'). The two aliphatic carbons of propanamide functionality resonated at δ 32.28 (C-2'''') and 18.94 (C-3''''). Figure 4 and Figure 5 has also been given to understand the NMR data of compound **7k** in a better way. With the aid of various spectroscopic techniques including ^{1}H-NMR, ^{13}C-NMR and IR, the compound **7k** was structurally corroborated to be *N*-(4-ethoxyphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide. Likewise the structures of all the synthesized compounds, **7a-p**, were structurally confirmed following the similar scheme of studies made during the discussion of compound **7k**.

LOX inhibition studies. All synthesized compounds, **7a-p**, were studied for their inhibitory potential against LOX enzyme and results are given in Table 3. Quercetin was used as standard drug. All compounds were screened at 0.25 mM concentration. The trend of synthesized compounds, **7a-p**, was found the least with respect to the standard. Three compounds, **7b**, **7d** and **7h**, had comparable inhibition potential against LOX with inhibition (%) of 89.54 ± 0.65, 85.34 ± 0.73 and 87.26 ± 0.82, respectively, with respect to the standard having inhibition (%) of 89.25 ± 0.62. The best potential of compound **7b** might be due to the presence of two methyl groups at *ortho* and *meta* positions of phenyl ring attached to nitrogen of amide functionality, for **7d** due to two methyl groups at two *ortho* positions and for **7h** due to one methyl group at *ortho* position. The three compounds, **7e**, **7n** and **7p**, exhibited low activity but it was higher than the 50 % inhibition. Compounds, **7j** was found the least active against LOX among the whole series of compounds. The least activity of compound **7j** might be due to its least interactive structure as

given in the Table 1. Out of sixteen synthesized compounds, ten showed inhibition potential less than 50 %. Among the compounds, **7a-f**, bearing dimethyl phenyl group, **7b** (2,3-dimethylphenyl) and **7d** (2,6-dimethylphenyl) were the most active ones. The presence of phenyl ring (**7g**) and cyclohexyl group (**7m**) rendered no difference in activity but a decrease in activity was observed in case of benzyl group (**7o**). It means that the aliphatic carbons between phenyl ring and nitrogen of amide functionality has negative effect on bioactivity. Compound **7h** (2-methylphenyl) was found to be more active as compared to **7i** (4-methylphenyl), **7j** (2-ethylphenyl) and **7n** (2-methoxyphenyl). This comparison illustrates that *ortho* substitution by small alkyl group has positive effect but substitution at *para* position or at *ortho* by large alkyl/alkoxy group has negative effect. Compound **7i** (4-methylphenyl) possessed the least activity as compared to **7k** (4-ethoxyphenyl) and **7p** (4-methyl-2-methoxycarbonylphenyl). The substitution of large alkoxy group at *para* position only or at *ortho* position also increased the activity. Compound **7j** (2-ethylphenyl) possessed the least activity as compared to **7l** (2-ethyl-6-methylphenyl). All this discussion explicates that the substitution by small alkyl group like methyl at *ortho* position of phenyl ring presented higher bioactivity against lipoxygenase enzyme. By changing the substitution groups, LOX inhibition potential can be enhanced.

α-Glucosidase inhibition studies. All newly synthesized compounds were also screened for their enzyme inhibition potential against α-glucosidase enzyme. Acarbose was used as standard drug. Results are summarized in Table 3. Two compounds, **7c** and **7h** among the synthesized ones, were found the most active with percent inhibition of 67.16 ± 1.65 and 72.13 ± 1.59, respectively, as compared to the acarbose used as standard with percent inhibition of 65.73 ± 1.93 at 0.5 mM concentration. Compound **7h** showed the highest inhibition potential even more than that of standard drug. The highest potential against α-glucosidase enzyme might be due to the presence of one methyl group at *ortho* position that might be able to block the active site of α-glucosidase enzyme. All the other fourteen compounds presented inhibition potential less than 50 %. Compound **7f** was found the least active among all the screened compounds which explains its least interactive structure. Among the compounds, **7a-f**, bearing dimethyl phenyl group, **7c** (2,5-dimethylphenyl) was the most active one. The presence of phenyl ring (**7g**) was found more active than cyclohexyl group (**7m**) and benzyl group (**7o**) in this case. It means that the aliphatic carbons on direct attachment to nitrogen of amide functionality have negative effect on bioactivity just like to LOX. Compound **7h** (2-methylphenyl) was found to be more active as

compared to **7i** (4-methylphenyl), **7j** (2-ethylphenyl) and **7n** (2-methoxyphenyl). This comparison illustrates that *ortho* substitution by small alkyl group has positive effect but substitution at *para* position or at *ortho* by large alkyl/alkoxy group has negative effect (as in case of LOX). Compound **7i** (4-methylphenyl) was more active than **7k** (4-ethoxyphenyl) but less active than **7p** (4-methyl-2-methoxycarbonylphenyl). The substitution of large alkoxy group at *para* position had negative effect but at *ortho* position had positive effect. Compound **7j** (2-ethylphenyl) possessed higher activity as compared to **7l** (2-ethyl-6-methylphenyl). All this discussion also favors the best activity of the compounds bearing small alkyl group like methyl at *ortho* position of phenyl ring. So, the best α-glucosidase enzyme inhibition potential can be achieved by changing the substitution groups.

AChE inhibition studies. All the newly synthesized compounds were also studied against AChE enzyme inhibition. Eserine was used as standard drug. Results are shown in Table 3. Compounds **7d**, **7m** and **7p** were the most active having percentage inhibition values of 79.35±0.76, 71.24±0.79 and 81.15±0.63 respectively, at screening concentration of 0.25 mM. The best may be attributed due to the presence of 2,6-dimethylphenyl (**7d**), cyclohexyl (**7m**) and 4-methyl-2-methoxycarbonylphenyl (**7p**) as varying groups directly attached to the nitrogen of amide functionality. Eight compounds exhibited inhibition against this enzyme between 40-60 % and five compounds with inhibition below 40 %. Among di-substituted compounds, **7a-f**, bearing dimethyl phenyl group, **7d** (2,6-dimethylphenyl) was the most active one. The cyclohexyl group (**7m**) was found to be more active than phenyl ring (**7g**) and benzyl group (**7o**). It means that the aliphatic ring structure attached nitrogen of amide functionality has positive effect on bioactivity. Compound **7n** (2-methoxyphenyl) was found to be more active than **7h** (2-methylphenyl), **7i** (4-methylphenyl) and **7j** (2-ethylphenyl). Among mono-substituted varying groups, small alkyl group at *para* position and alkoxy group at *ortho* position executed better activity. Compound **7p** (4-methyl-2-methoxycarbonylphenyl) remained more active than **7i** (4-methylphenyl) and **7k** (4-ethoxyphenyl). The substitution of large alkoxy group at *ortho* position increased the bioactivity. All this discussion also explicates the *ortho* substitution of phenyl ring by small alkyl/alkoxy group and cycloalkyl group remained more active against AChE enzyme. The few structural modifications might be able to secure comparable results with standard.

BChE inhibition studies. All the newly synthesized compounds were also studied against BChE enzyme with Eserine as standard drug. Results are given in Table 3. Compounds **7c**, **7d**, **7j**

and **7p** were the most active with percent inhibition of 59.32±0.73, 61.45±0.61, 71.84±0.78 and 72.13±0.51, respectively. The best activity of these compounds may be due to 2,5-dimethylphenyl (**7c**), 2,6-dimethylphenyl (**7d**), 2-ethylphenyl (**7j**) and 4-methyl-2-methoxycarbonylphenyl (**7p**) group. The common in all of these compounds is substitution at *ortho* position. Remaining twelve compounds of the series showed inhibition potential less than 50 %. Among the compounds, **7a-f**, bearing dimethyl phenyl group, **7c** (2,5-dimethylphenyl) and **7d** (2,6-dimethylphenyl) were the most active ones. The cyclohexyl group (**7m**) was found to be more active than phenyl ring (**7g**) and benzyl group (**7o**). It means that the aliphatic ring structure attached nitrogen of amide functionality has positive effect on inhibitory activity (just like AChE). Compound **7j** (2-ethylphenyl) was found to be more active as compared to **7h** (2-methylphenyl), **7i** (4-methylphenyl) and **7n** (2-methoxyphenyl). The *ortho* substitution by large alkyl group has positive effect but substitution by small alkyl/alkoxy groups at *para*/*ortho* positions has negative effect. Compound **7p** (4-methyl-2-methoxycarbonylphenyl) remained more active than **7i** (4-methylphenyl) and **7k** (4-ethoxyphenyl). The substitution of large alkoxy group at *ortho* position increased the activity (just like AChE). Compound **7j** (2-ethylphenyl) possessed higher activity as compared to **7l** (2-ethyl-6-methylphenyl). All this discussion concludes the *ortho* substitution of phenyl ring by large alkyl group and cycloalkyl group remained more active against BChE enzyme. The few structural modifications might be able to secure comparable results with standard against BChE.

Molecular docking for LOX enzyme. Molecular docking was performed to evaluate protein binding of receptor protein with compounds, **7b** and **7h**. Docking results given in Table 4 were used to calculate inhibitory constant and binding affinity. Docking of LOX enzyme with compound **7b** (Figure 6) depicted binding interactions with TRP_{144} (interaction with methyl and oxygen of methoxy group of 4-methoxyphenylsulfonyl moiety), ALA_{119} (interaction with one methyl group of 2,3-dimethylphenyl moiety and π-π interaction with benzene ring of 2,3-dimethylphenyl moiety), ARG_{132} (interaction with one methyl group of 2,3-dimethylphenyl moiety), ARG_{131} (interaction with one methyl group of 2,3-dimethylphenyl moiety), LYS_{128} (interaction with one methyl group of 2,3-dimethylphenyl moiety), PRO_{503} (π-π interaction with benzene ring of 2,3-dimethylphenyl moiety), ARG_{384} (π-π interaction with benzene ring of 4-methoxyphenylsulfonyl moiety), GLU_{504} (π-π interaction with benzene ring of 2,3-dimethylphenyl moiety) and GLN_{139} (polar interaction with nitrogen of 1,3,4-oxadiazole ring).

Docking of compound **7h** (Figure 7) revealed binding with residues TYR_{383} (hydrogen bonding interaction with nitrogen of amide functionality), GLU_{622} (π-π interaction with 1,3,4-oxadiazole ring), SER_{14} (polar interaction with oxygen of sulfonyl functionality), TYR_{81} (polar interaction with sulfur of thio ether), LEU_{615} (π-π interaction with benzene ring of 4-methoxyphenylsulfonyl moiety), PRO_{621} (π-π interaction with benzene ring of 4-methoxyphenylsulfonyl moiety), ARG_{401} (π-π interaction with 1,3,4-oxadiazole ring), ARG_{101} (interaction with methyl group and π-π interaction with benzene ring of 2-methylphenyl moiety), HIS_{624} (interaction with methyl group of 2-methylphenyl moiety), PHE_{393} (interaction with methyl group of 2-methylphenyl moiety) and VAL_{397} (interaction with methyl group of 2-methylphenyl moiety). Docking study of standard quercetin showed binding (Figure 8) with residues THR_{545} (interaction with hydrogen of hydroxyl group of dihydroxyphenyl moiety), LEU_{448} (interaction with hydrogen of hydroxyl group of dihydroxyphenyl moiety), VAL_{243} (π-π interaction with benzene ring of chromen-4-one moiety and interaction with heterocyclic ring of chromen-4-one moiety), ALA_{453} (π-π interaction with benzene ring of dihydroxyphenyl moiety) and ARG_{370} (interaction with heterocyclic ring of chromen-4-one moiety).

Molecular docking for α-Glucosidase enzyme. Current work demonstrates the binding of human α-glucosidase (receptor protein) with standard drug, acarbose (ligand) which is anti-diabetic drug. Molecular docking was performed to evaluate protein binding of receptor protein with compound **7h**. Docking results given in Table 4 were used to calculate inhibitory constant and binding affinity. Binding observed after docking of compound **7h** (Figure 9) was with residues ALA_{820} (interacting with methyl group of 4-methoxyphenylsulfonyl group), GLU_{852} (π-π interaction with 1,3,4-oxadiazole ring), ARG_{881} (interacting with methyl group of 2-methylphenyl group and π-π interaction with 1,3,4-oxadiazole ring), LEU_{879} (interacting with piperidine ring and π-π interaction with 1,3,4-oxadiazole ring), ARG_{854} (interacting with piperidine ring) and VAL_{886} (π-π interaction with benzene ring of 2-methylphenyl group). Molecular docking study of standard acarbose (Figure 10) has also depicted binding with residues SER_{864} (hydrogen bonding with hydrogen of hydroxyl group), TYR_{360} (hydrogen bonding with hydrogen of hydroxyl group), ARG_{608} (hydrogen bonding with hydrogen of one hydroxyl group and oxygen of other hydroxyl group), HIS_{717} (hydrogen bonding with hydrogen of hydroxyl group), HIS_{584} (interaction with methyl group) and LEU_{355} (interaction with methylene group).

The results based on computational study and laboratory work were also compared and analyzed. The percent inhibition values are greatly affected by inhibitory constant which further influence the mode of action of drug inside the body. Smaller Ki value means the highest percent inhibition and greater activity of drug.[19] Type of bond is indicated by value of bond length. Bond length greater than 3.0 Å represents weak electrostatic attraction while bond length smaller than 3.0 Å indicates hydrogen bond. It is evident from Ki values that compound **7b** and **7h** showed better LOX activity as compared to standard drug quercetin and has potential to replace it. Small inhibitory constant means that inhibitor is bound strongly and enzyme-inhibitor complex do not tend to fall apart thus inhibitory effect is strong.

EXPERIMENTAL

Chemicals used to synthesize new compounds were taken from national suppliers of brand Alfa Aesar and Sigma Aldrich. Thin layer chromatography (TLC) was used to check completion of reactions and purity of synthesized compounds. Pre-coated aluminum plates were used with ethyl acetate and n-hexane as a solvent system. UV lamp (254 nm) was used for visualization of spots. Open capillary method was used to take melting points on George and Griffin melting point apparatus. KBr pellet method was employed to record IR spectra by using Jasca-320-A spectrophotometer. Bruker spectrometers were used to record ^{13}C-NMR and ^{1}HNMR in $CDCl_3$ solvent against TMS reference standard. Values of chemical shift were recorded in ppm unit.

Synthesis of ethyl 1-[(4-methoxyphenyl)sulfonyl]piperidin-4-carboxylate (1). Compound **1** was synthesized by reaction of equimolar 4-methoxybenzenesulfonyl chloride (**a**) with ethyl piperidin-4-carboxylate (**b**) at room temperature stirring in aqueous medium. Na_2CO_3 (5 %) solution was used as buffer to maintain pH at 9-10. Progress of reaction was monitored by using TLC. On completion of reaction, product was neutralized by using dilute HCl. White precipitates were filtered, washed with distilled water and dried at room temperature.

Synthesis of 1-[(4-methoxyphenyl)sulfonyl]piperidin-4-carbohydrazide (2). Conversion of compound **1** into **2** was achieved by refluxing compound **1** with equimolar hydrazine in methanol for two hours. Reaction progress was checked by using TLC. Excess solvent was evaporated at completion of reaction. Reaction mixture was cooled at room temperature to acquire title product.

Synthesis of 5-[1-(4-methoxyphenyl)sulfonyl)piperidin-4-yl]-1,3,4-oxadiazol-2-thiol (3). Compound **2** (0.01 mol) was refluxed with CS_2 (0.015) in presence of KOH (0.01 mol) for 2 hours using methanol as solvent. TLC was performed to view the progress of reaction. At reaction completion, the contents of reaction mixture were acidified at pH 4-5 with dilute HCl. Compound **3** was obtained in the form of white precipitate which was filtered, washed with distilled water and dried for further utilization.

General procedure for synthesis of *N*-substituted-2-bromopropanamide (6a-p). Vigorous stirring of equimolar alkyl/aralkyl/aryl amines (**4a-p**) with 2-bromopropionyl bromide (**5**) in aqueous medium for 1 hour using 5 % Na_2CO_3 solution to maintain pH 9-10, resulted into formation of *N*-alkyl/aralkyl/aryl-2-bromopropanamide (**6a-p**). Solvent extraction was used to get liquid product while precipitates obtained were filtered and dried.

General procedure for synthesis of *N*-alkyl/aralkyl/aryl propanamide derivatives of 3 (7a-p).

Conventional synthesis: Compound **3** was dissolved in DMF followed by equimolar LiH. The mixture was stirred for half an hour. Equimolar electrophiles, **6a-p**, were added and mixture was stirred at room temperature for 17-31 hours to acquire title compounds, **7a-p**. Thin layer chromatography was utilized to monitor the reaction conditions and progress. Precipitates were filtered, washed with distilled water and dried at room temperature.

Microwave assisted synthesis: Compound **3** was dissolved in DMF followed by equimolar LiH. The mixture was stirred for half an hour. Equimolar electrophiles, **6a-p**, were added and mixture was stirred in microwave irradiation for 32-74 seconds to acquire title compounds, **7a-p**. Thin layer chromatography was utilized to monitor the reaction conditions and progress. Precipitates were filtered, washed with distilled water and dried at room temperature.

5-{1-[(4-Methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-thiol (3). White crystalline solid; yield: 92 %; m.p.: 165-169 ºC; molecular formula: $C_{14}H_{17}N_3O_4S_2$; molecular weight: 355.43 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3039 (C-H stretching of aromatic ring), 2258 (S-H stretching), 1599 (C=N stretching), 1518 (C=C aromatic stretching), 1321 (-SO_2 stretching), 1233 & 1079 (C-O-C bond stretching); ^{1}HNMR (600 MHz, $CDCl_3$, δ/ppm): 11.06 (s, 1H, SH), 7.72 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"), 7.02 (d, *J* = 8.9 Hz, 2H, H-3" & H-5"), 3.90 (s, 3H, H-7"), 3.73-3.71 (m, 2H, H*e*-2' & H*e*-6'), 2.72-2.68 (m, 1H, H-4'), 2.56-2.52 (m, 2H, H*a*-2' & H*a*-6'), 2.14-2.11 (m, 2H, H*e*-3' & H*e*-5'), 1.96-1.90 (m, 2H, H*a*-3' & H*a*-5'); ^{13}C-NMR (150 MHz,

$CDCl_3$, *δ*/ppm): 163.20 (C-5), 159.92 (C-2), 160.40 (C-4"), 129.77 (C-2" & C-6"), 127.43 (C-1"), 114.39 (C-3" & C-5"), 55.67 (C-7"), 45.01 (C-2' & C-6'), 32.67 (C-4'), 27.66 (C-3' & C-5').

***N*-(2,4-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7a).** Off white solid; yield: 93 %; m.p.: 150-152 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3342 (N-H stretching), 3049 (C-H), 1668 (C=O), 1340 (-SO_2 stretching), 1529 (C=C stretching), 1561 (C=N stretching), 1239 & 1082 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, *δ*/ppm): 7.71 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"), 7.55 (d, *J* = 8.1 Hz, 1H, H-6'"), 7.05-7.00 (m, 4H, H-3", H-5", H-3'" & H-5'"), 3.89 (s, 3H, H-7"), 3.69-3.67 (m, 2H, H*e*-2' & H*e*-6'), 3.61 (q, *J* = 6.8 Hz, 1H, H-2""), 2.82-2.79 (m, 1H, H-4'), 2.60-2.56 (m, 2H, H*a*-2' & H*a*-6'), 2.31 (s, 3H, H-8'"), 2.29 (s, 3H, H-7'"), 2.13-2.10 (m, 2H, H*e*-3' & H*e*-5'), 2.03-1.95 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3""); ^{13}C-NMR (150 MHz, $CDCl_3$, *δ*/ppm): 163.10 (C-1""), 161.54 (C-5), 160.89 (C-2), 160.50 (C-4"), 134.15 (C-4'"), 132.94 (C-1"), 131.49 (C-2'"), 129.73 (C-2" & C-6"), 127.65 (C-1'"), 127.60 (C-3'"), 120.01 (C-5'"), 114.70 (C-6'"), 114.32 (C-3" & C-5"), 55.63 (C-7"), 45.13 (C-2' & C-6'), 32.31 (C-2""), 30.92 (C-4'), 28.32 (C-3' & C-5'), 20.74 (C-8'"), 18.42 (C-3""), 17.69 (C-7'").

***N*-(2,3-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7b).** Light pink solid; yield: 96 %; m.p.: 170-172 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3348 (N-H stretching), 3045 (C-H), 1668 (C=O), 1349 (-SO_2 stretching), 1522 (C=C stretching), 1565 (C=N stretching), 1234 & 1087 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, *δ*/ppm): 7.71 (d, *J* = 8.6 Hz, 2H, H-2" & H-6"), 7.48 (d, *J* = 8.0 Hz, 1H, H-6'"), 7.13 (t, *J* = 7.9 Hz, 1H, H-5'"), 6.99-7.02 (m, 3H, H-3", H-5" & H-4'"), 3.89 (s, 3H, H-7"), 3.70-3.68 (m, 2H, H*e*-2' & H*e*-6'), 3.61 (q, *J* = 6.8 Hz, 1H, H-2""), 2.33 (s, 3H, H-8'"), 2.82-2.79 (m, 1H, H-4'), 2.59-2.55 (m, 2H, H*a*-2' & H*a*-6'), 2.18 (s, 3H, H-7'"), 2.13-2.10 (m, 2H, H*e*-3' & H*e*-5'), 2.03-1.94 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3""); ^{13}C-NMR (150 MHz, $CDCl_3$, *δ*/ppm): 163.10 (C-1""), 161.54 (C-5), 160.88 (C-2) 160.50 (C-4"), 137.84 (C-1'"), 135.28 (C-3'"), 132.64 (C-1"), 129.74 (C-2" & C-6"), 127.64 (C-2'"), 126.66 (C-4'"), 126.31 (C-5'"), 118.52 (C-6'"), 114.32 (C-3" & C-5"), 55.63 (C-7"), 45.13 (C-2' & C-6'), 32.34 (C-2""), 30.92 (C-4'), 28.30 (C-3' & C-5'), 20.63 (C-8'"), 18.42 (C-3""), 13.62 (C-7'").

***N*-(2,5-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7c).** Grey solid; yield: 88 %; m.p.: 151-153 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3351 (N-H stretching), 3056 (C-H), 1679 (C = O), 1351 (-SO_2 stretching), 1533 (C = C stretching), 1572 (C = N stretching), 1245 & 1087 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, δ/ppm): 7.71 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"), 7.64 (s, 1H, H-6'"), 7.07 (d, *J* = 7.6 Hz, 1H, H-3'"), 7.01 (d, *J* = 8.9 Hz, 2H, H-3" & H-5"), 6.85 (d, *J* = 7.5 Hz, 1H, H-4'"), 3.89 (s, 3H, H-7"), 3.69-3.67 (m, 2H, H*e*-2' & H*e*-6'), 3.62 (q, *J* = 6.8 Hz, 1H, H-2'""), 2.84-2.81 (m, 1H, H-4'), 2.62-2.58 (m, 2H, H*a*-2' & H*a*-6'), 2.34 (s, 3H, H-8'"), 2.24 (s, 3H, H-7'"), 2.14-2.11 (m, 2H, H*e*-3' & H*e*-5'), 2.02-1.96 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.9 Hz, 3H, H-3'""); ^{13}C-NMR (150 MHz, $CDCl_3$, δ/ppm): 163.09 (C-1'""), 161.68 (C-5), 160.89 (C-2), 160.34 (C-4"), 137.13 (C-1'"), 132.54 (C-1"), 135.45 (C-5'"), 129.74 (C-2" & C-6"), 127.65 (C-3'"), 124.66 (C-2'"), 123.39 (C-4'"), 119.70 (C-6'"), 114.32 (C-3" & C-5"), 55.63 (C-7"), 45.13 (C-2' & C-6'), 32.26 (C-2'""), 30.92 (C-4'), 28.36 (C-3' & C-5'), 21.28 (C-8'"), 18.42 (C-3'""), 17.21 (C-7'").

***N*-(2,6-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7d).** Off white solid; yield: 89 %; m.p.: 198-200 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3331 (N-H stretching), 3034 (C-H), 1659 (C=O), 1337 (-SO_2 stretching), 1536 (C=C stretching), 1573 (C=N stretching), 1248 & 1094 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, δ/ppm): 7.69 (d, *J* = 8.8 Hz, 2H, H-2" & H-6"), 7.16 (t, *J* = 6.4 Hz, 1H, H-4'"), 7.11 (d, *J* = 7.4 Hz, 2H, H-3'" & H-5'"), 7.00 (d, *J* = 8.8 Hz, 2H, H-3" & H-5"), 3.89 (s, 3H, H-7"), 3.69-3.67 (m, 2H, H*e*-2' & H*e*-6'), 3.61 (q, *J* = 6.8 Hz, 1H, H-2'""), 2.74-2.70 (m, 1H, H-4'), 2.53-2.49 (m, 2H, H*a*-2' & H*a*-6'), 2.27 (s, 6H, H-7'" & H-8'"), 2.11-2.03 (m, 2H, H*e*-3' & H*e*-5'), 1.94-1.88 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.7 Hz, 3H, H-3'""); ^{13}C-NMR (150 MHz, $CDCl_3$, δ/ppm): 163.11 (C-1'""), 161.68 (C-5), 160.88 (C-2), 160.34 (C-4"), 135.26 (C-1'"), 133.33 (C-1"), 135.45 (C-4'"), 129.73 (C-2" & C-6"), 128.75 (C-2'" & C-6'"), 127.83 (C-3'" & C-5'"), 114.31 (C-3" & C-5"), 55.63 (C-7"), 45.08 (C-2' & C-6'), 32.43 (C-2'""), 30.92 (C-4'), 28.14 (C-3' & C-5'), 18.36 (C-7'" & C-8'"), 18.42 (C-3'"").

***N*-(3,4-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7e).** White solid; yield: 92 %; m.p.: 199-201 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3348 (N-H

stretching), 3032 (C-H), 1666 (C=O), 1349 (-SO_2 stretching), 1520 (C=C stretching), 1568 (C=N stretching), 1247& 1094 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, δ/ppm): 10.17 (s, 1H, NH), 7.69 (d, *J* = 7.7 Hz, 2H, H-2" & H-6"), 7.25-7.21 (m, 2H, H-5"' & H-6"'), 7.17 (d, *J* = 7.7 Hz, 2H, H-3" & H-5"), 7.06 (s, 1H, H-2"'), 3.86 (s, 3H, H-7"), 3.62 (q, *J* = 6.8 Hz, 1H, H-2""), 3.56-3.54 (m, 2H, H*e*-2' & H*e*-6'), 2.94-2.90 (m, 1H, H-4'), 2.52-2.48 (m, 2H, H*a*-2' & H*a*-6'), 2.19 (s, 3H, H-8"'), 2.15 (s, 3H, H-7"'), 2.07-2.05 (m, 2H, H*e*-3' & H*e*-5'), 1.76-1.71 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3""); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 162.68 (C-1""), 161.03 (C-5), 160.89 (C-2), 159.70 (C-4"), 136.57 (C-1"'), 132.54 (C-1"), 136.50 (C-3"'), 129.82 (C-2" & C-6"), 129.63 (C-4"'), 129.24 (C-5"'), 126.96 (C-2"'), 118.04 (C-6"'), 114.53 (C-3" & C-5"), 55.68 (C-7"), 44.92 (C-2' & C-6'), 32.22 (C-2""), 30.95 (C-4'), 28.02 (C-3' & C-5'), 19.66 (C-8"'), 18.58 (C-7"'), 18.42 (C-3"").

***N*-(3,5-Dimethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7f).** Off white solid; yield: 90 %; m.p.: 198-200 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3349 (N-H stretching), 3053 (C-H), 1661 (C=O), 1347 (-SO_2 stretching), 1532 (C=C stretching), 1560 (C=N stretching), 1246 & 1094 (C-O-C bond stretching); ^{1}H-NMR (600MHz, DMSO, δ/ppm): 10.22 (s, 1H, NH), 7.70 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"), 7.18-7.15 (m, 4H, H-3", H-5", H-2"' & H-6"'), 6.61 (s, 1H, H-4"'), 3.86 (s, 3H, H-7"), 3.61 (q, *J* = 6.8 Hz, 1H, H-2""), 3.56-3.54 (m, 2H, H*e*-2' & H*e*-6'), 2.95-2.89 (m, 1H, H-4'), 2.51-2.47 (m, 2H, H*a*-2' & H*a*-6'), 2.23 (s, 6H, H-7"' & H-8"'), 2.15-2.05 (m, 2H, H*e*-3' & H*e*-5'), 1.77-1.71 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.9 Hz, 3H, H-3""); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 162.68 (C-1""), 162.25 (C-5), 160.89 (C-2), 159.60 (C-4"), 138.62 (C-1"'), 132.54 (C-1"), 137.98 (C-3"' & C-5"'), 129.63 (C-2" & C-6"), 126.96 (C-4"'), 123.24 (C-2"' & C-6"'), 114.54 (C-3" & C-5"), 55.67 (C-7"), 44.91 (C-2' & C-6'), 32.24 (C-2""), 30.93 (C-4'), 28.02 (C-3' & C-5'), 21.13 (C-7"' & C-8"'), 18.42 (C-3"").

2-[(5-{1-[(4-Methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]-*N*-phenylpropanamide (7g). Off white solid; yield: 90 %; m.p.: 245-247 ºC; molecular formula: $C_{25}H_{26}N_4O_5S_2$; molecular weight: 502.61 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3355 (N-H stretching), 3059 (C-H), 1677 (C=O), 1346 (-SO_2 stretching), 1531 (C=C stretching), 1569 (C=N stretching), 1240 & 1088 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, δ/ppm): 10.38 (s, 1H, NH), 7.70 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"),7.53-7.52 (m, 2H, H-2"' & H-6"'), 7.32 (t, *J* = 8.5 Hz, 2H, H-3"' & H-5"'), 7.17 (d, *J* = 8.9 Hz, 2H, H-3" & H-5"), 6.97 (t, *J* = 7.3 Hz, 1H, H-4"'), 3.86 (s,

3H, H-7''), 3.62 (q, *J* = 6.7 Hz, 1H, H-2'''), 3.57-3.55 (m, 2H, H*e*-2' & H*e*-6'), 2.96-2.90 (m, 1H, H-4'), 2.50-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.08-2.06 (m, 2H, H*e*-3' & H*e*-5'), 1.78-1.71 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.9 Hz, 3H, H-3'''), ^{13}C-NMR (150 MHz, DMSO, *δ*/ppm): 162.68 (C-1'''), 161.21 (C-5), 160.89 (C-2), 159.59 (C-4''), 138.75 (C-1'''), 132.54 (C-1''), 129.64 (C-2'' & C-6''), 128.97 (C-3''' & C-5'''), 126.95 (C-4'''), 116.77 (C-2''' & C-6'''), 114.54 (C-3'' & C-5''), 55.68 (C-7''), 44.93 (C-2' & C-6'), 32.24 (C-2'''), 30.97 (C-4'), 28.01 (C-3' & C-5'), 18.42 (C-3''').

2-[(5-{1-[(4-Methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]-*N*-(2-methylphenyl)propanamide (7h). White solid; yield: 93 %; m.p.: 152-154 ºC; molecular formula: $C_{24}H_{28}N_4O_5S_2$; molecular weight: 516.63 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3351 (N-H stretching), 3047 (C-H), 1652 (C=O), 1339 (-SO_2 stretching), 1527 (C=C stretching), 1571 (C=N stretching), 1233 & 1093 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, *δ* / ppm): 7.75-7.70 (m, 3H, H-2'', H-6'' & H-3'''), 7.25 (d, *J* = 8.0 Hz, 1H, H-6'''), 7.21 (t, *J* = 7.4 Hz, 1H, H-5'''), 7.07 (t, *J* = 7.4 Hz, 1H, H-4'''), 7.01 (d, *J* = 8.9 Hz, 2H, H-3'' & H-5''), 3.89 (s, 3H, H-7''), 3.70-3.68 (m, 2H, H*e*-2' & H*e*-6'), 3.61 (q, *J* = 6.8 Hz, 1H, H-2'''), 2.84-2.81 (m, 1H, H-4'), 2.60-2.57 (m, 2H, H*a*-2' & H*a*-6'), 2.34 (s, 3H, H-7'''), 2.14-2.11 (m, 2H, H*e*-3' & H*e*-5'), 2.02-1.96 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.9 Hz, 3H, H-3'''); ^{13}C-NMR (150 MHz, $CDCl_3$, *δ*/ppm): 163.11 (C-1'''), 161.64 (C-5), 160.89 (C-2), 160.13 (C-4''), 135.47 (C-1'''), 130.80 (C-1''), 129.74 (C-2'' & C-6''), 127.63 (C-2'''), 127.25 (C-3'''), 127.06 (C-4'''), 124.27 (C-5'''), 119.38 (C-6'''), 114.33 (C-3'' & C-5''), 55.63 (C-7''), 45.12 (C-2' & C-6'), 30.92 (C-4'), 32.32 (C-2'''), 28.32 (C-3' & C-5'), 18.42 (C-3'''), 17.75 (C-7''').

2-[(5-{1-[(4-Methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]-*N*-(4-methylphenyl)propanamide (7i). Off white solid; yield: 96 %; m.p.: 207-209 ºC; molecular formula: $C_{24}H_{28}N_4O_5S_2$; molecular weight: 516.63 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3330 (N-H stretching), 3035 (C-H), 1654 (C=O), 1347 (-SO_2 stretching), 1538 (C=C stretching), 1564 (C=N stretching), 1248 & 1089 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, *δ*/ppm): 10.26 (s, 1H, NH), 7.70 (d, *J* = 8.8 Hz, 2H, H-2'' & H-6''), 7.41 (d, *J* = 8.5 Hz, 2H, H-3'' & H-5''), 7.17 (d, *J* = 8.9 Hz, 2H, H-2''' & H-6'''), 7.12 (d, *J* = 8.2 Hz, 2H, H-3''' & H-5'''), 3.86 (s, 3H, H-7''), 3.62 (q, *J* = 6.8 Hz, 1H, H-2'''), 3.57-3.55 (m, 2H, H*e*-2' & H*e*-6'), 2.94-2.91 (m, 1H, H-4'), 2.50-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.24 (s, 3H, H-7'''), 2.08-2.05 (m, 2H, H*e*-3' & H*e*-5'), 1.77-1.70 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3'''); ^{13}C-NMR (150 MHz, DMSO, *δ*/ppm):

162.68 (C-1""), 161.07 (C-5), 160.89 (C-2) 159.69 (C-4"), 136.28 (C-4"'), 130.39 (C-1"), 129.63 (C-2" & C-6"), 129.34 (C-3"' & C-5"'), 126.95 (C-1'"), 116.81 (C-2"' & C-6"'), 114.53 (C-3" & C-5"), 55.68 (C-7"), 44.93 (C-2' & C-6'), 32.29 (C-2""), 30.96 (C-4'), 28.02 (C-3' & C-5'), 20.24 (C-7"'), 18.42 (C-3"").

***N*-(2-Ethylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7j).** Light brown solid; yield: 89 %; m.p.: 136-138 ºC; molecular formula: $C_{25}H_{30}N_4O_5S_2$; molecular weight: 530.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3359 (N-H stretching), 3061 (C-H), 1677 (C=O), 1349 (-SO_2 stretching), 1523 (C=C stretching), 1565 (C=N stretching), 1247 & 1094 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, δ/ppm): 9.36 (s, 1H, NH), 7.71-7.67 (m, 3H, H-2", H-6" & H-6"'),7.22-7.16 (m, 4H, H-3", H-5", H-3"' & H-5"'), 7.05 (t, *J* = 7.4 Hz, 1H, H-4"'), 3.86 (s, 3H, H-7"), 3.62 (q, *J* = 6.8 Hz, 2H, H-2""), 3.57-3.55 (m, 2H, H*e*-2' & H*e*-6'), 2.93-2.89 (m, 1H, H-4'), 2.65 (q, *J* = 7.5 Hz, 2H, H-7"'), 2.52-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.08-2.05 (m, 2H, H*e*-3' & H*e*-5'), 1.77-1.70 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3""), 1.05 (t, *J* = 7.5 Hz, 2H, H-8"'); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 162.68 (C-1""), 161.47 (C-5), 160.88 (C-2), 159.06 (C-4"), 136.14 (C-1'"), 131.80 (C-1"), 129.63 (C-2"'), 129.59 (C-2" & C-6"), 126.97 (C-4"'), 126.20 (C-5"'), 125.74 (C-3"'), 123.93 (C-6"'), 114.52 (C-3" & C-5"), 55.67 (C-7"), 45.29 (C-2' & C-6'), 32.23 (C-2""), 31.06 (C-4'), 28.03 (C-3' & C-5'), 23.35 (C-7"'), 18.42 (C-3""), 14.28 (C-8"').

***N*-(4-Ethoxyphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7k).** Brown solid; yield: 84 %; m.p.: 209-211 ºC; molecular formula: $C_{25}H_{30}N_4O_6S_2$; molecular weight: 546.66 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3331 (N-H stretching), 3037 (C-H), 1654 (C=O), 1332 (-SO_2 stretching), 1517 (C=C stretching), 1565 (C=N stretching), 1244 & 1086 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, δ/ppm): 10.13 (s, 1H, NH-1), 7.70 (d, *J* = 8.9 Hz, 2H, H-2" & H-6"), 7.42 (d, *J* = 9.1 Hz, 2H, H-2"' & H-6"'), 7.17 (d, *J* = 8.9 Hz, 2H, H-3" & H-5"), 6.89 (d, *J* = 9.1 Hz, 2H, H-3"' & H-5"'), 3.96 (q, *J* = 6.9 Hz, 2H, H-7"'), 3.86 (s, 3H, H-7"), 3.62 (q, *J* = 6.8 Hz, 1H, H-2""), 3.57-3.55 (m, 2H, H*e*-2' & H*e*-6'), 2.94-2.89 (m, 1H, H-4'), 2.51-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.07-2.04 (m, 2H, H*e*-3' & H*e*-5'), 1.76-1.70 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 7.0 Hz, 3H, H-3""), 1.30 (t, *J* = 6.8 Hz, 3H, H-8"'); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 163.11 (C-1""), 162.68 (C-5), 160.94 (C-2), 159.85 (C-4"), 153.45 (C-4"'), 131.96 (C-1"), 129.63 (C-2" & C-6"), 126.95 (C-1'"), 118.33 (C-

2''' & C-6'''), 114.58 (C-3''' & C-5'''), 114.53 (C-3'' & C-5''), 63.11 (C-7'''), 55.67 (C-7''), 44.94 (C-2' & C-6'), 32.28 (C-2''''), 30.98 (C-4'), 28.03 (C-3' & C-5'), 18.94 (C-3''''), 14.67 (C-8''').

***N*-(2-Ethyl-6-methylphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7l).** Off white solid; yield: 91 %; m.p.: 128-130 ºC; molecular formula: $C_{26}H_{32}N_4O_5S_2$; molecular weight: 544.69 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3347 (N-H stretching), 3042 (C-H), 1661 (C=O), 1344 (-SO_2 stretching), 1519 (C=C stretching), 1577 (C=N stretching), 1230 & 1081 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, δ/ppm): 7.68 (d, *J* = 8.9 Hz,2H, H-2'' & H-6''), 7.67 (d, *J* = 8.9 Hz, 1H, H-3'''), 7.22-7.18 (m, 1H, H-4'''), 7.05 (d, *J* = 8.9 Hz, 1H, H-5'''), 7.00 (d, *J* = 8.9 Hz, 2H, H-3'' & H-5''), 3.88 (s, 3H, H-7''), 3.68-3.66 (m, 2H, H*e*-2' & H*e*-6'), 3.62 (q, *J* = 6.8 Hz, 1H, H-2''''), 2.94-2.89 (m, 1H, H-4'), 2.61 (q, *J* = 6.9 Hz, 2H, H-8'''), 2.50-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.23 (s, 1H, H-7'''), 2.07-2.04 (m, 2H, H*e*-3' & H*e*-5'), 1.76-1.70 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 7.0 Hz, 3H, H-3''''), 1.25 (t, *J* = 6.8 Hz, 3H, H-9'''); ^{13}C-NMR (150 MHz, $CDCl_3$, δ/ppm): 163.09 (C-1''''), 162.98 (C-5), 160.88 (C-2), 159.59 (C-4''), 135.77 (C-1'''), 132.20 (C-1''), 129.75 (C-2'' & C-6''), 129.72 (C-2'''), 129.47 (C-6'''), 127.88 (C-5'''), 126.88 (C-4'''), 126.53 (C-3'''), 114.29 (C-3'' & C-5''), 55.69 (C-7''), 45.13 (C-2' & C-6'), 32.41 (C-2''''), 30.41 (C-4'), 28.21 (C-3' & C-5'), 24.14 (C-8'''), 18.31 (C-3''''), 17.62 (C-7'''), 14.62 (C-9''').

***N*-Cyclohexyl-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7m).** Off white solid; yield: 91 %; m.p.: 151-153 ºC; molecular formula: $C_{23}H_{32}N_4O_5S_2$; molecular weight: 508.65 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3338 (N-H stretching), 3041 (C-H), 1658 (C=O), 1343 (-SO_2 stretching), 1513 (C=C stretching), 1560 (C=N stretching), 1233 & 1084 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, DMSO, δ/ppm): 10.10 (s, 1H, NH), 7.68 (d, *J* = 8.9 Hz, 2H, H-2'' & H-6''), 7.01 (d, *J* = 7.0 Hz, 2H, H-3'' & H-5''), 3.86 (s, 3H, H-7''), 3.68-3.66 (m, 2H, H*e*-2' & H*e*-6'), 3.62 (q, *J* = 6.8 Hz, 1H, H-2''''), 3.54 (m, 1H, H-1'''), 2.94-2.89 (m, 1H, H-4'), 2.50-2.46 (m, 2H, H*a*-2' & H*a*-6'), 2.13-2.10 (m, 2H, H*e*-3' & H*e*-5'), 2.03-1.94 (m, 2H, H*a*-3' & H*a*-5'), 1.74-1.72 (m, 2H, H*e*-2''' & H*e*-6'''), 1.51-1.50 (m, 1H, H*e*-4'''), 1.49-1.48 (m, 2H, H*a*-2''' & H*a*-6'''), 1.47-1.45 (m, 1H, H*a*-4'''), 1.42 (d, *J* = 7.0 Hz, 3H, H-3''''), 1.21-1.19 (m, 2H, H*e*-3''' & H*e*-5'''), 1.13-1.11 (m, 2H, H*a*-3''' & H*a*-5'''); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 162.72 (C-1''''), 162.66 (C-5), 160.88 (C-2), 160.57 (C-4''), 132.20 (C-1''), 129.61 (C-2'' & C-6''), 114.45 (C-3'' & C-5''), 55.70 (C-7''), 51.59 (C-1'''), 45.90 (C-2' & C-6'),

38.80 (C-2''' & C-6'''), 32.26 (C-2''''), 30.20 (C-4'), 28.05 (C-3' & C-5'), 25.46 (C-4'''), 24.75 (C-3''' & C-5'''), 18.94 (C-3'''').

***N*-(2-Methoxyphenyl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7n).** Brown solid; yield: 94 %; m.p.: 82-84 ºC; molecular formula: $C_{24}H_{28}N_4O_6S_2$; molecular weight: 532.63 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3345 (N-H stretching), 3044 (C-H), 1667 (C=O), 1341 (-SO_2 stretching), 1530 (C=C stretching), 1565 (C=N stretching), 1237 & 1088 (C-O-C bond stretching); ^{1}H-NMR (600MHz, DMSO, δ/ppm): 9.41 (s, 1H, NH), 7.90 (d, *J* = 7.9 Hz, 1H, H-6'''), 7.70 (d, *J* = 8.9 Hz, 2H, H-2'' & H-6''), 7.17 (d, *J* = 8.9 Hz, 2H, H-3'' & H-5''), 7.04-6.99 (m, 2H, H-3''' & H-5'''), 6.95 (t, *J* = 8.0 Hz, 1H, H-4'''), 3.84 (s, 3H, H-7''), 3.82 (s, 3H, H-7'''), 3.62 (q, *J* = 6.8 Hz, 1H, H-2''''), 3.56-3.54 (m, 2H, H*e*-2' & H*e*-6'), 2.94-2.89 (m, 1H, H-4'), 2.51-2.47 (m, 2H, H*a*-2'& H*a*-6'), 2.07-2.05 (m, 2H, H*e*-3' & H*e*-5'), 1.77-1.70 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3''''); ^{13}C-NMR (150 MHz, DMSO, δ/ppm): 162.67 (C-1''''), 161.46 (C-5), 160.88 (C-2), 160.18 (C-4''), 148.59 (C-2'''), 132.80 (C-1''), 129.62 (C-2'' & C-6''), 127.57 (C-4'''), 127.00 (C-1'''), 120.51 (C-5'''), 118.52 (C-6'''), 114.53 (C-3'' & C-5''), 111.18 (C-3'''), 55.67 (C-7'' & C-7'''), 44.89 (C-2' & C-6'), 32.28 (C-2''''), 30.98 (C-4'), 28.00 (C-3' & C-5'), 18.42 (C-3'''').

***N*-Benzyl-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (7o).** Off white solid; yield: 81 %; m.p.: 131-133 ºC; molecular formula: $C_{24}H_{28}N_4O_5S_2$; molecular weight: 516.63 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3340 (N-H stretching), 3031 (C-H), 1657 (C=O), 1332 (-SO_2 stretching), 1522 (C=C stretching), 1565 (C=N stretching), 1238 & 1080 (C-O-C bond stretching); NMR (600 MHz, $CDCl_3$, δ/ppm): 8.04 (s, 1H, NH), 7.71 (d, *J* = 8.9 Hz, 2H, H-2'' & H-6''), 7.33 (t, *J* = 8.8 Hz, 2H, H-3''' & H-5'''), 7.26 (t, *J* = 8.7 Hz, 2H, H-4'''), 7.23 (d, *J* = 8.9 Hz, 2H, H-2''' & H-6'''), 7.01 (d, *J* = 8.9 Hz, 2H, H-3'' & H-5''), 4.40 (s, 2H, H-7'''), 3.89 (s, 3H, H-7''), 3.69-3.67 (m, 2H, H*e*-2' & H*e*-6'), 3.62 (q, *J* = 6.8 Hz, 1H, H-2''''), 2.93-2.89 (s, 1H, H-4'), 2.51-2.48 (m, 2H, H*a*-2' & H*a*-6'), 2.14-2.11 (m, 2H, H*e*-3' & H*e*-5'), 2.02-1.94 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3''''); ^{13}C-NMR (150 MHz, $CDCl_3$, δ/ppm): 163.11 (C-1''''), 162.98 (C-5), 160.88 (C-2), 159.59 (C-4''), 137.90 (C-1'''), 132.20 (C-1''), 129.77 (C-2''' & C-6'''), 129.73 (C-2'' & C-6''), 114.34 (C-3'' & C-5''), 114.32 (C-4'''), 114.18 (C-3''' & C-5'''), 55.64 (C-7''), 45.24 (C-2' & C-6'), 36.55 (C-7'''), 32.71 (C-2''''), 30.71 (C-4'), 28.49 (C-3' & C-5'), 18.42 (C-3'''').

Methyl 2-({2-[(5-{1-[(4-methoxyphenyl)sulfonyl]-4-piperidinyl}-1,3,4-oxadiazol-2-yl)thio]propanoyl}amino)-5-methylbenzoate (7p). Off white solid; yield: 87 %; m.p.: 108-110 ºC; molecular formula: $C_{26}H_{30}N_4O_7S_2$; molecular weight: 574.67 g mol^{-1}; IR (KBr, υ_{max}, cm^{-1}): 3353 (N-H stretching), 3041 (C-H), 1665 (C=O), 1342 (-SO_2 stretching), 1520 (C=C stretching), 1566 (C=N stretching), 1240 & 1071 (C-O-C bond stretching); ^{1}H-NMR (600 MHz, $CDCl_3$, δ /ppm): 7.74 (s, 1H, H-3'''), 7.71 (d, *J* = 8.9 Hz, 2H, H-2'' & H-6''), 7.42 (d, *J* = 8.8 Hz, 1H, H-5'''), 7.06 (d, *J* = 8.0 Hz, 1H, H-6'''), 7.02 (d, *J* = 8.9 Hz, 2H, H-3'' & H-5''), 3.89 (s, 3H, H-7''), 3.87 (s, 3H, H-8'''), 3.69-3.67 (m, 2H, H*e*-2' & H*e*-6'), 3.62 (q, *J* = 6.8 Hz, 1H, H-2''''), 2.93-2.89 (s, 1H, H-4'), 2.51-2.48 (m, 2H, H*a*-2' & H*a*-6'), 2.34 (s, 3H, H-7'''), 2.14-2.11 (m, 2H, H*e*-3' & H*e*-5'), 2.02-1.94 (m, 2H, H*a*-3' & H*a*-5'), 1.42 (d, *J* = 6.8 Hz, 3H, H-3''''); ^{13}C-NMR (150 MHz, $CDCl_3$, δ/ppm): 163.15 (C-1''''), 161.46 (C-5), 160.88 (C-2), 160.18 (C-4''), 136.10 (C-1'''), 132.80 (C-1''), 129.73 (C-2'' & C-6''), 128.94 (C-4'''), 128.55 (C-6'''), 128.30 (C-3'''), 127.60 (C-5'''), 114.35 (C-2'''), 114.22 (C-3'' & C-5''), 55.64 (C-7''), 47.61 (C-8'''), 45.49 (C-2' & C-6'), 32.28 (C-2''''), 30.92 (C-4'), 28.03 (C-3' & C-5'), 21.30 (C-7'''), 19.56 (C-3'''').

LOX inhibition assay. Reported method with few modifications was used to perform LOX inhibition activity.[15] LOX was soybean LOX, 15-LOX. Briefly, mixture containing 200 µL total volume with 10 µL of test compound, 15 µL of lipoxygenase enzyme, and 150 µL of sodium phosphate buffer (pH 8, 10mM) was prepared. All ingredients were mixed thoroughly and were pre-read at 234 nm wavelength. Pre-incubation of mixture was done at 25 °C for 10 minutes. 25 µL of substrate solution was added to initiate the reaction. Absorbance change was measured at 234 nm after 6 minutes. Synergy HTX 96-well plate reader was used in all experiments. The percentage inhibition was measured by following equation 1. Control is the absorbance without test sample while test is in the presence of test sample.

$$\text{Inhibition (\%)} = \frac{\text{Control}-\text{Test}}{\text{Control}} \times 100 \qquad \text{Equation 1}$$

α-Glucosidase inhibition assay. Pierre's protocol with slight changes was used in order to perform α-glucosidase assay.[16] Alpha-Glucosidase was from yeast. Reaction mixture containing 10 µL of purified enzyme (α-glucosidase) was taken in buffer phosphate (6.8 pH) and 10 µL of test substance was incubated at 37 °C for time duration of 10 minutes. Initial absorbance was recorded at 400 nm. Then final reading of absorbance was taken after incubation of 20 minutes at 37 °C and absorbance change was recorded at 400 nm. Acarbose was used as positive control

and experiments were performed in triplicate. Equation 1 was also used to calculate percentage inhibition.

AChE inhibition assay. Pre-reported method was used to perform AChE assay with necessary modifications.[1,16] AChE was from electric eel. Total volume of 100 µL of reaction mixture was prepared by adding 10 µL of enzyme (0.005 per unit well), 60 µL of Na_2PO_4 buffer solution (50 mM, 7.7 pH) and 10 µL of test compound (0.5 mM per well). After mixing of contents, absorption at 405 nm was recorded. Pre-incubation of content was done at 37 °C for 10 minutes. In order to start the reaction, 10 µL of substrate, acetylcholine iodide (0.5 Mm $well^{-1}$) was added and then 10 µL DTNB having 0.5 mM per well concentration. Absorbance at 405 nm was measured after incubation of 15 minutes at 37 °C with the help of plate reader. Eserine was used as standard drug. Percent inhibition was calculated as given in equation 1.

BChE inhibition assay. BChE activity was performed by using reported method.[20] BChE was from equine. Briefly, 100 µL of reaction mixture having 60 µL of buffer solution (Na_2PO_4) with 7.7 pH and 50 mM concentration, 10 µL test compound (0.5 mM per well) and 10 µL of butyryl cholinesterase enzyme. All contents were mixed and absorption was recorded at 405 nm. Contents were pre-incubated at 37 °C for 10 minutes. Reaction was started by addition of 10 µL of butyryl choline chloride (0.5 mM per well) and 10 µL DTNB (0.5 mM). After incubation of 15 minutes at 37 °C, absorbance was recorded at 405 nm. Drug used as positive control was Eserine (0.5 mM per well). Percent inhibition was calculated through equation 1.

Statistical analysis. All the calculations were made in triplicate and the triplicate data was subjected to statistical analysis by Microsoft Excel 2010. Results were presented as mean ± SEM.

Molecular Docking. In the field of drug formulation and analysis, computational biology has attracted the attention of scientists because it is economic and quick process for designing of drugs. Molecular docking helps us to find out biological activity of molecule by indicating binding affinity, drug action site and other interacting factors. So drug designing become more convenient. Three dimensional structures of receptor proteins for lipoxygenase and α-glucosidase were taken from data bank. Resolution was 2.4 Å and PDB ID were 3O8Y and 5NN4 respectively.[21] Accelrys discovery studio visualizers were used in order to remove water molecules and other entities.[22] Chemdraw was used to draw ligand compounds, **7b** and **7h**.[23] Molfile or sdf form of ligands was downloaded. Discovery studio visualizer was used to convert

them into pdb form by applying geometrical optimization and force field. In order to study ligand actions on targeted protein and their comparison, docking was performed. Vina dock and autodock were used to perform docking. Results were further analyzed with the help of discovery studio in order to get 2d and 3d images. Addition of charges was made to both the receptor protein and ligands by using autodock. Addition of Kollman charges to receptor protein and gasteiger partial charges to ligands was made. Tortions were reduced from all the ligands. In receptor protein, grid designed was 30×40×40 Å having 1.0Å separation. Autodock was used to convert all ligands to pdbqt file and then vina autodock was used to perform automated docking of ligand protein.[24,25]

CONCLUSION

Comparative conventional and microwave assisted methods were used to synthesize the library of 1,3,4-oxadiazole analogues and their structures were confirmed by spectral data. In terms of high percent yield within few seconds made the sense that microwave assisted method is more efficient and well built. Anti-enzymatic study showed that synthesized compounds possessed inhibition potential ranging from poor to excellent. Three compounds presented comparable potential to the standard quercetin against lipoxygenase. Two compounds possessed more inhibition potential than that of standard drug acarbose against α-glucosidase enzyme. Molecular docking indicated binding modes of synthesized compounds against various target enzymes. The most potent compounds might be useful addition in pharmaceutical research and drug formulation against various enzymes after further studies.

Acknowledgements. Authors are thankful to Higher Education Commission (HEC), Pakistan for funding Prof. Dr. Muhammad Ashraf NRPU research grant (No. 4950).

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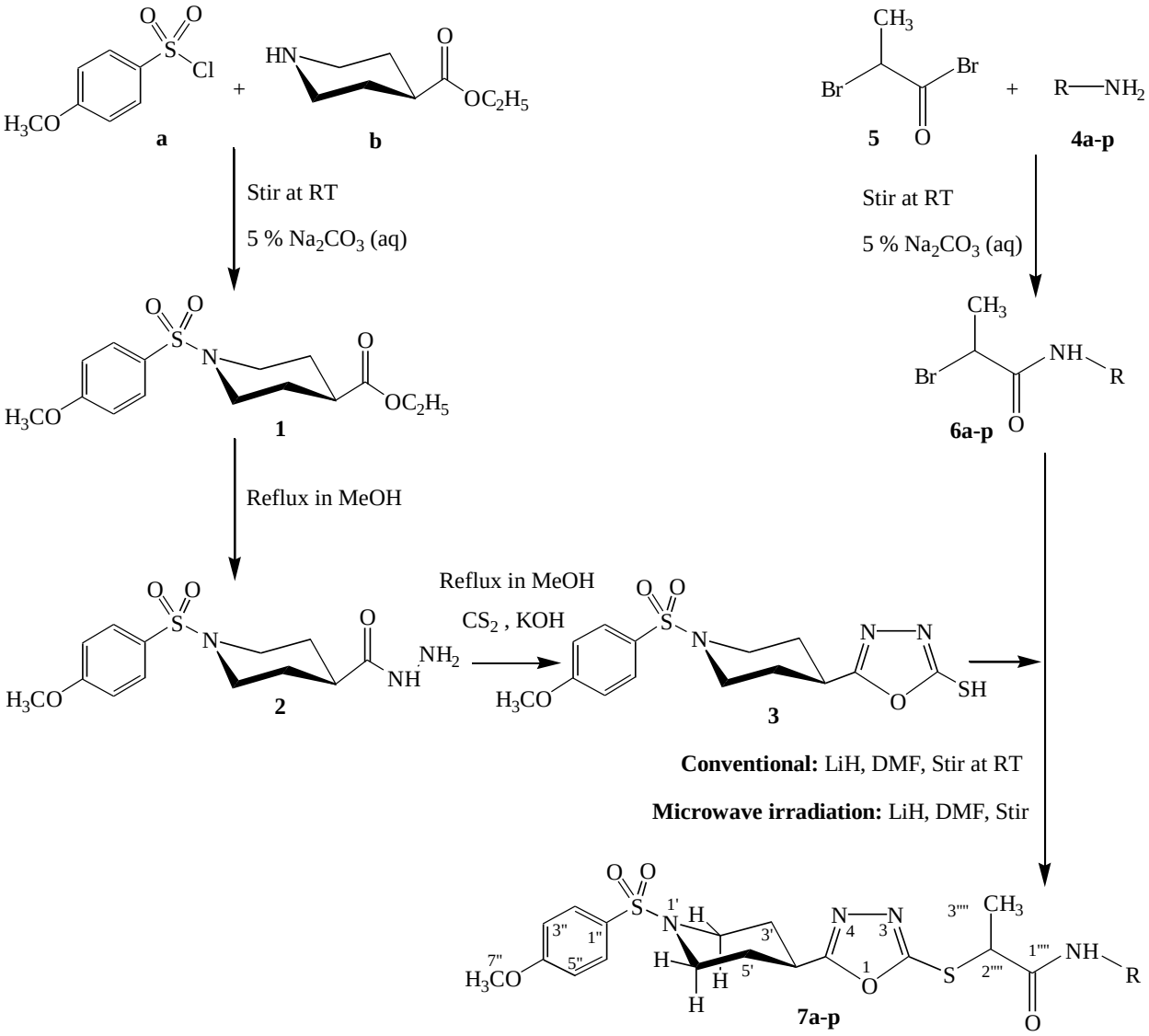
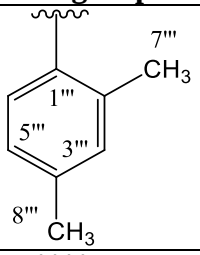
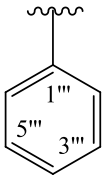
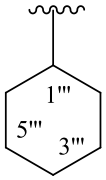
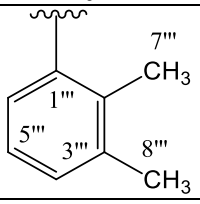
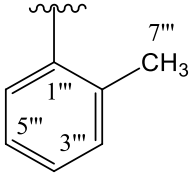
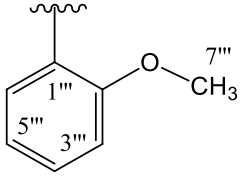
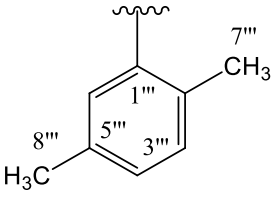
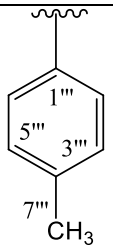
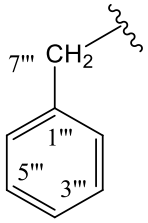
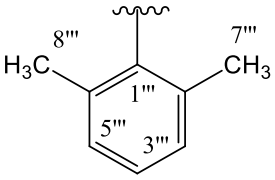
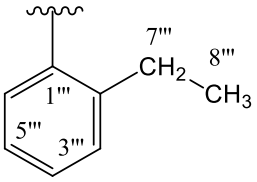
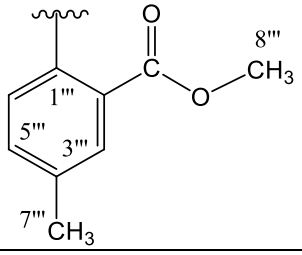
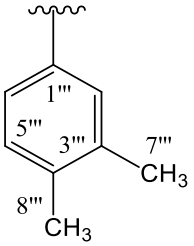
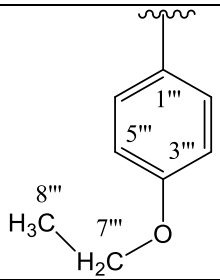
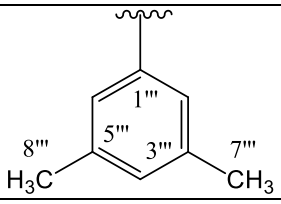
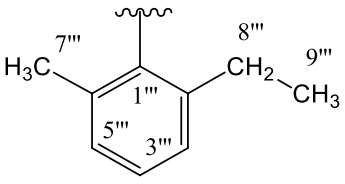


Scheme 1: Synthesis of *N*-(alkyl/aralkyl/aryl)-2-[(5-{1-[(4-methoxyphenyl)sulfonyl]piperidin-4-yl}-1,3,4-oxadiazol-2-yl)thio]propanamide (**7a-p**)

Table 1: Different Alkyl/Aralkyl/Aryl groups

C #	R groups	C #	R groups	C #	R groups
7a		**7g**		**7m**	
7b		**7h**		**7n**	
7c		**7i**		**7o**	
7d		**7j**		**7p**	
7e		**7k**			
7f		**7l**			

Note: C # = Compound number

Table 2: Comparison of conventional and microwave assisted methods

Compounds	Reaction Yield (%)		Reaction time	
	Microwave	Conventional	Microwave (seconds)	Conventional (hours)
7a	93	71	44	22
7b	96	76	52	25
7c	88	81	69	21
7d	89	83	74	23
7e	92	79	32	29
7f	90	86	49	20
7g	90	67	35	28
7h	93	82	33	22
7i	96	87	67	17
7j	89	81	61	26
7k	84	79	58	18
7l	91	66	33	23
7m	91	61	45	19
7n	94	57	47	27
7o	81	61	34	31
7p	87	43	37	30

Table 3: Percentage inhibition for anti-enzymatic potential of synthesized compounds

Compound	Inhibition (%)			
	LOX at 0.25 mM	α-Glucosidase at 0.5 mM	AChE at 0.25 mM	BChE at 0.25 mM
7a	23.52±0.34	34.84±1.33	31.47±0.29	39.68±0.43
7b	89.54 ± 0.65	32.75±1.42	27.83±0.36	34.15±0.37
7c	28.42±0.42	67.16±1.65	34.19±0.31	59.32±0.73
7d	85.34±0.73	45.57±1.29	79.35±0.76	61.45±0.61
7e	55.43±0.68	27.45±1.57	47.26±0.38	29.83±.35
7f	39.27±0.55	23.79±1.76	45.17±0.24	33.21±0.46
7g	29.32±0.58	47.54±1.34	49.32±0.35	43.61±0.39
7h	87.26±0.82	72.13±1.59	40.16±0.19	30.41±0.27
7i	21.43±0.67	39.59±1.48	46.24±0.49	26.52±0.41
7j	15.22±0.54	46.86±0.13	41.63±0.52	71.84±0.78
7k	36.57±0.63	26.87±1.38	46.39±0.35	18.45±0.37
7l	35.23±0.45	34.62±1.24	35.12±0.26	34.91±0.31
7m	21.12±0.56	35.54±1.53	71.24±0.79	47.69±0.29
7n	71.35±0.82	23.87±1.35	57.31±0.86	26.47±0.34
7o	16.47±0.61	29.28±1.67	42.63±0.39	36.25±0.38
7p	67.16±0.78	45.56±1.59	81.15±0.63	72.13±0.51
Standard	**89.25±0.62[a]**	**65.73±1.93[b]**	**91.46±1.25[c]**	**83.75±1.16[c]**

Note: a = Quercetin, b = Acarbose, c = Eserine

Table 4: Binding affinity and inhibitory constant value of selected compounds

Protein	Compound	Binding affinity	K_i (nMol)
Lipoxygenase PDB ID: 3O8Y	**7b**	-8.8	0.349
	7h	-8.7	0.413
	Quercetin	-8.2	0.961
α-Glucosidase PDB ID: 5NN4	**7h**	-8.4	0.685
	Acarbose	-8.4	0.685

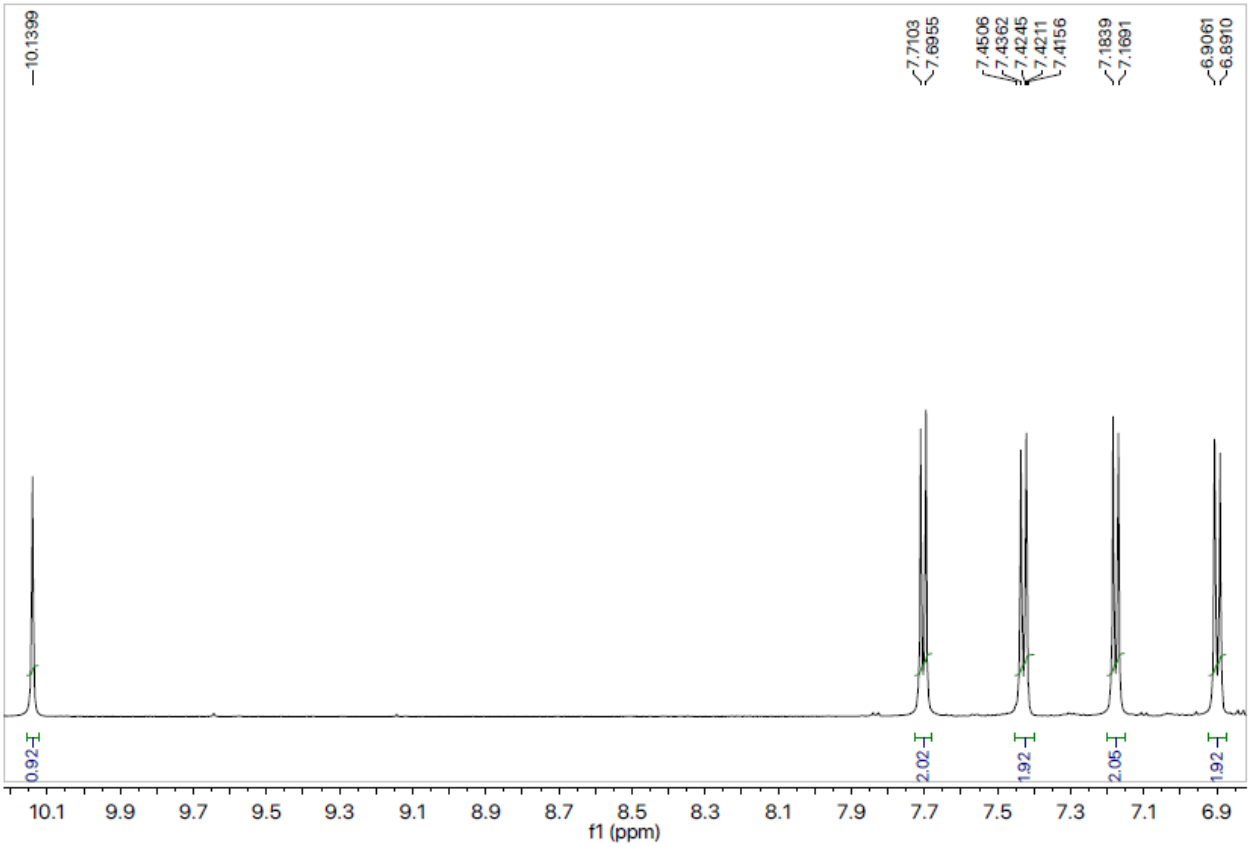


Figure 1: ^{1}H-NMR spectrum of compound **7k** (aromatic and NH)

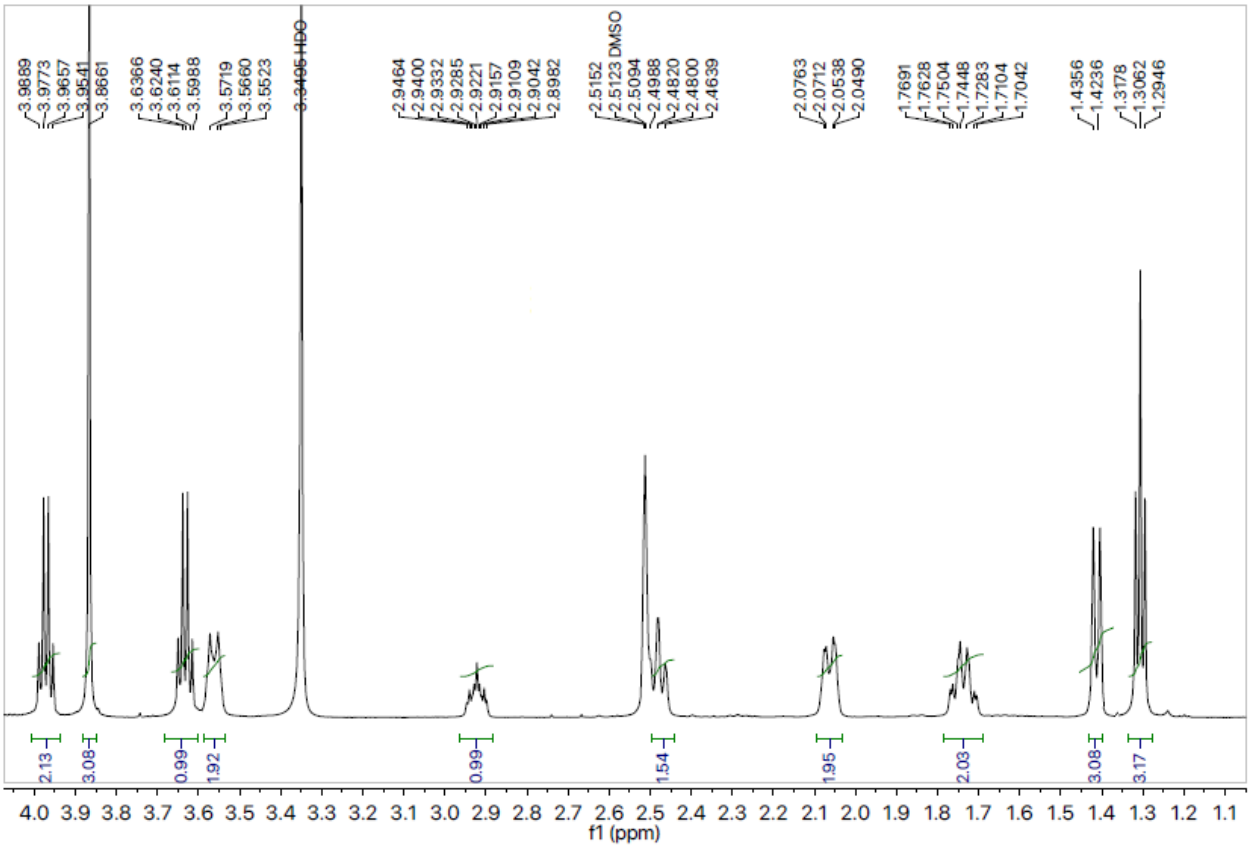


Figure 2: ^{1}H-NMR spectrum of compound **7k** (aliphatic)

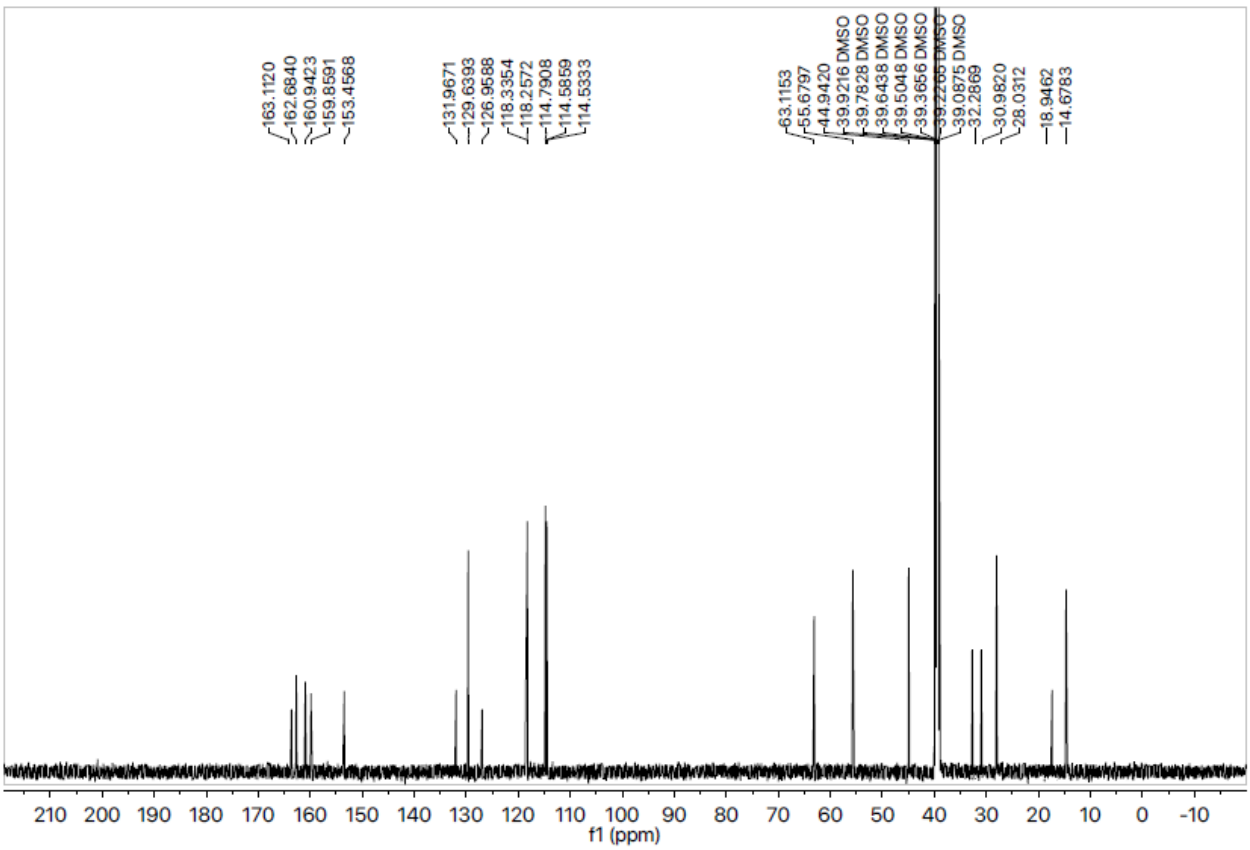


Figure 3: ^{13}C-NMR spectrum of compound **7k**

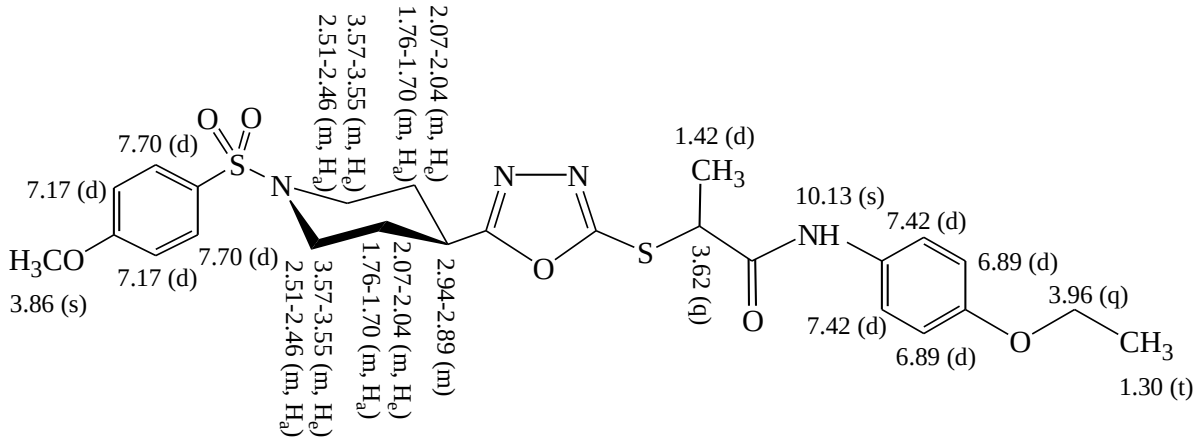


Figure 4: ^{1}H-NMR data of compound **7k**

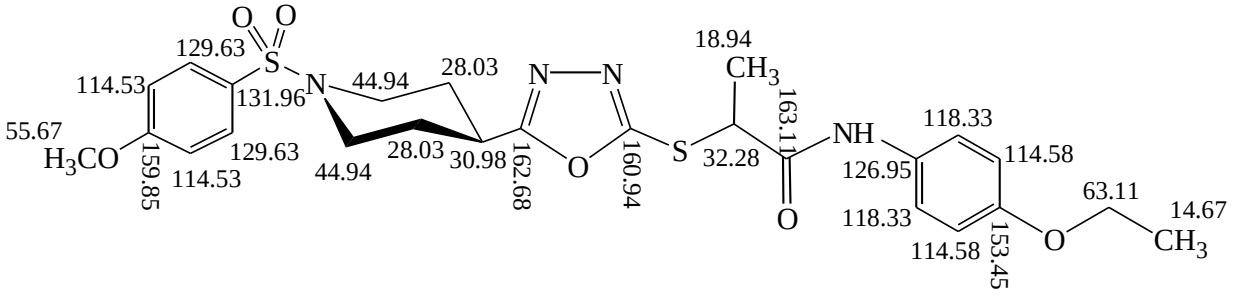


Figure 5: ^{13}C-NMR data of compound **7k**

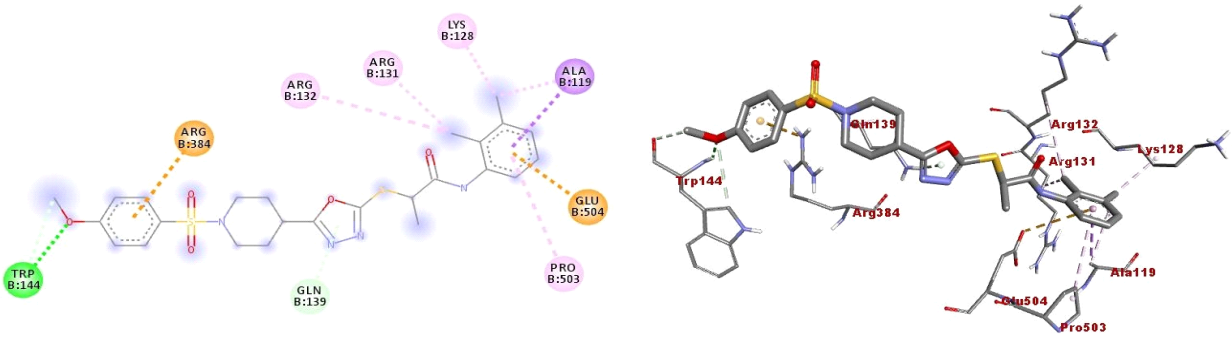


Figure 6 (2D & 3D): Binding mode of compound **7b** with lipoxygenase enzyme

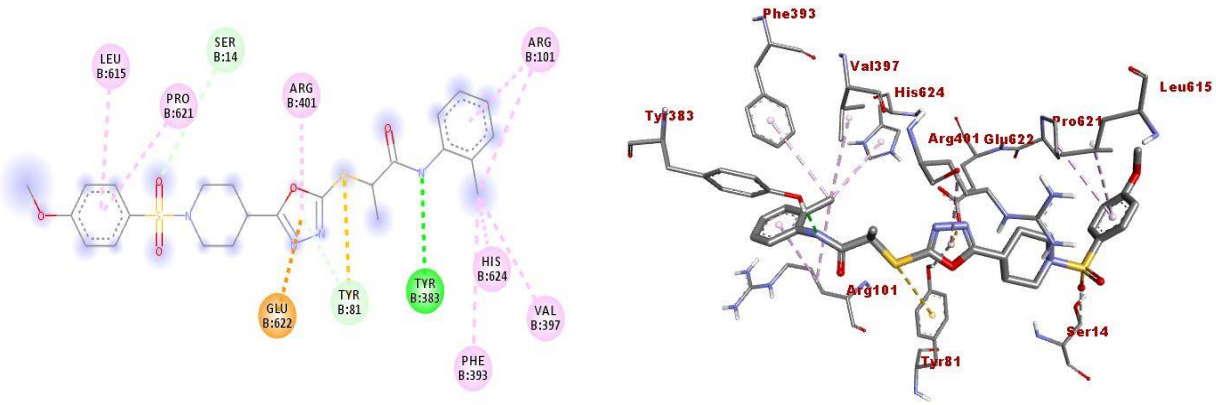


Figure 7 (2D & 3D): Binding mode of compound **7h** with lipoxygenase enzyme

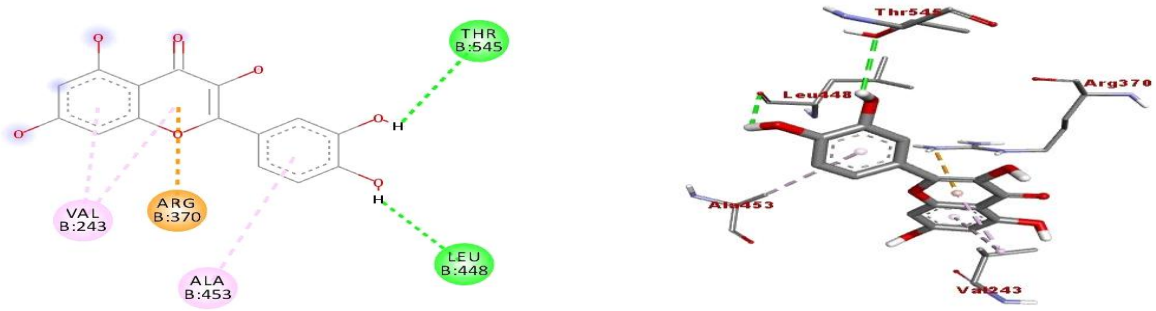


Figure 8 (2D & 3D): Binding mode of standard quercetin with lipoxygenase enzyme

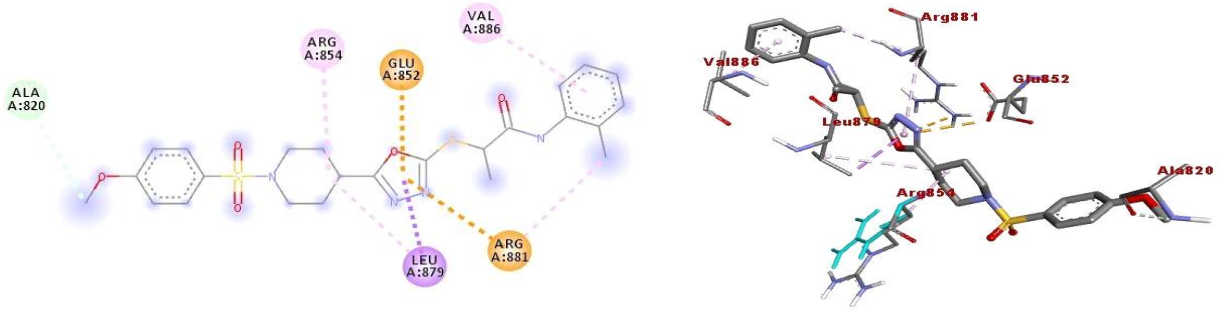


Figure 9 (2D & 3D): Binding mode of compound **7h** with α-glucosidase enzyme

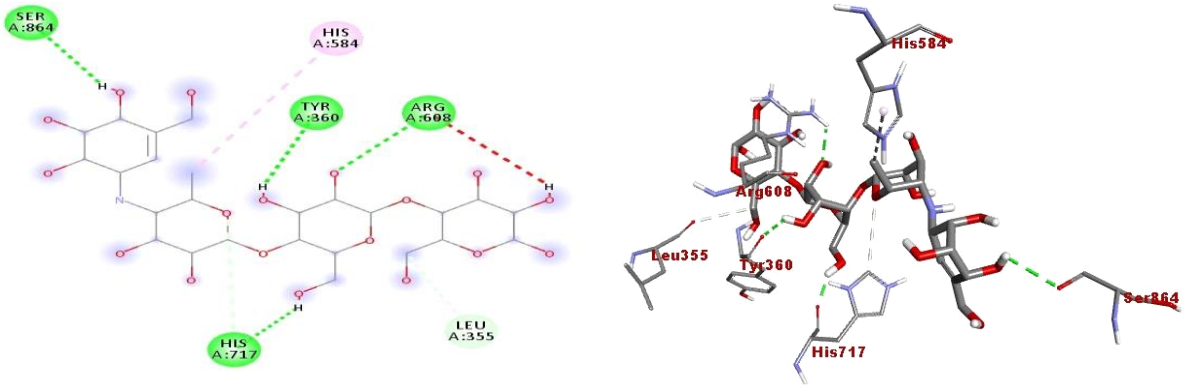


Figure 10 (2D & 3D): Binding mode of acarbose (standard drug) with α-glucosidase enzyme