Original Article

In-vitro antimicrobial screening and molecular docking studies of synthesized 2-chloro-N-(4-phenylthiazol-2-yl)acetamide derivatives

Abstract

Introduction: Glucosamine-6-phosphate (GlcN6P) synthase biosynthetic pathway has been identified as potential targets for the development of new antimicrobial agents. Aim: A series of 2-chloro-N-(42-phenylthiazol-25-yl)acetamide derivatives (3a-r) was synthesized and evaluated their antimicrobial activity. **Materials and Methods:** The 2-chloro-N-(Para substituted phenylthiazol-25-yl) acetamide (2a-c) were synthesized by stirring intermediates (1a-c) with 2-chloroacetylchloride in dichloromethane in the presence of K2CO3. The intermediate (2a-c) were further reacted with different secondary amine such as pyrrolidine, N-methyl piperazine, N-ethyl piperazine, thiomorpholine, morpholine, piperidine etc in ethanol in presence of TEA Triethylamine (TEA) to get desired compounds (3a-r). Compounds were characterized by a spectroscopic technique such as Fourier transform infraredFTIR, ^{1}H-NMR, ^{13}C-NMR, and mass spectrometry. The synthesized thiazole derivatives (3a-r) were screened for anti-bacterial and anti-fungal activity against *Escherichia coli*, *Staphylococcus aureus* NCTC 6571, *Pseudomonas aeruginosa* NCTC 10662, *CandidaC. albicans* (MTCC-183), *AspergillusA. niger* (MTCC 281) NCTC 10418 and *AspergillusA. flavus* (MTCC 277). **Result and Conclusion:** The results of anti-bacterial screening revealed that among all the screened compounds, eight compounds *viz.* 3b, 3c, 3d, 3e, 3i, 3j, 3k, and 3p showed moderate to good anti-bacterial and antifungal activity having minimum inhibitory concentration (MIC) between 6.25- and 25 µg/ml. While compound 3d showed the most promising antibacterial activity against *E. coli* and *S. aureus*, while the compound 3j showed promising antifungal activity with MIC value 6.25 µg/ml against *C. albicans*, *A. niger* and *A. flavus*. In addition, all these eight potential molecules were also examined for possible binding on enzyme GlcN6Pglucosamine-6-phosphate synthase by molecular docking studies on (PDB ID 1JXA).

Key words:
Acetamide, antibacterial, antifungal, docking, thiazoles

Introduction

The advent of clinically significant species of multi-drug resistance strains of bacteria and fungi such as methicilin resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* and *Candida* species have made the treatment of infectious diseases a tenacious problem and turning into as an important global health delinquent.[1-4] To mitigate the situation, there will continually be a vibrant need to discover new chemotherapeutic agents to prevent the development of resistance and that preferably shorten the duration of therapy.

Glutamine-dependent amidotransferases play a central role in cellular metabolism; it is responsible for utilization of the amide nitrogen of glutamine in a variety of biosynthetic reactions. There structural elucidation and mechanism of action deliver a significant insinuations for the discovery of new therapeutic agents.[5,6] Trivial enzyme viz. glucosamine-6-phosphate

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(GlcN6P) synthase (GlmS, L-glutamine: D-fructose-6P amidotransferase, EC2.6.1.16) involve in hexosamine metabolism, which is isomerizes fructose 6-phosphate into GlcN6P in the presence of glutamine and finally form an N-acetylglucosamine, which is found in all class of organisms, but in bacteria and fungi it is necessary for cell wall formations such as peptidoglycan in bacteria and chitin, mannoproteins in fungi. In human beings, N-acetylglucosamine is used for biosynthesis of glycoproteins and mucopolysaccharides. Fact is that in all kind of cells the GlcN6P synthase is present.[7] In the prokaryotic cell, the inactivation of GlcN6P synthase even for a short time is lethal. But, due to the longer lifespan of mammalian cells, the depletion of amino sugar pool for a short time is not lethal.[8] This difference in the metabolism of the enzyme has enabled GlcN6P synthase an important target for drug discovery.

In the recent years, heterocyclic compounds containing thiazole ring system have fascinated medicinal chemists because of their diverse biological activities such as antibacterial,[9] anti-inflammatory,[10] antitumor,[11] schizophrenia,[12] antifungal,[13] anti-HIV,[14] antitubercular,[15] antiprotozoal,[16] antiallergic,[17] hypertension,[18] antimalarial,[19] etc. The thiazole derivatives [Figure 1a-c] having potent antimicrobial activity were reported by Sarojini *et al*.[20] with minimum inhibitory concentration (MIC) 6.25 μg/ml and their docking study on GlcN6P synthase (PDB Id: 1JXA) predicted that as a plausible inhibitor of the enzyme. Their study showed that compounds having a number of interactions with various active site residues of GlcN6P synthase. Similarly thiazole derivative [Figure 1d] was synthesized and evaluated by Gahtori *et al*.[21] and reported as a most potent antimicrobial agent, more potent than streptomycin having MIC 3.125 μg/ml. Another thiazole compound [Figure 1e] having MIC 1.56 μg/ml against *Escherichia coli* was synthesized and reported by Jing *et al*.[22] Likewise, Karegoudar *et al*.[23] reported the antimicrobial activity of thiazole derivative [Figure 1f] against various bacterial strain having MIC 6.25 μg/ml.

Keeping in view the assessment of this fertile nucleus, we hereby reported the synthesis of novel 2-chloro-N-(2-phenylthiazol-5-yl) acetamide derivatives and evaluated for their *in-vitro* antibacterial and antifungal activity coupled with molecular docking studies.

Results and Discussion

Chemistry

The different para-substituted phenylthiazol-5-amines were synthesized as per the scheme outlined in Figure 2. Various acetophenone and thiourea were reacted in the presence of iodine to give 2-amino-4-phenylthiazole (1a-c).[24] For cyclization purpose, any of the halogens can be used but in this reaction we used iodine because it is easy to handle.[25] The 2-chloro-N-(Para substituted phenylthiazol-2-yl) acetamide (2a-c) were synthesized by stirring intermediates (1a-c) with 2-chloroacetylchloride in dichloromethane in the presence of K_2CO_3.[26,27] The intermediate (2a-c) were further reacted with different secondary amine such as pyrrolidine, N-methyl piperazine, N-ethyl piperazine, thiomorpholine, morpholine, piperidine etc in ethanol in presence of Triethylamine (TEA) to get desired compounds (3a-r).

The structures of varied 2-substituted-N-(*P*-substituted phenylthiazol-2-yl)acetamide derivatives were elucidated by combined use of infrared (IR), ^{1}H and ^{13}C-NMR and mass spectral (MS) data. The presence of the thiazole ring in compounds (1a-c) was supported by the appearance of two quaternary signals of (C-2, C-4) at δ value 151.8 and

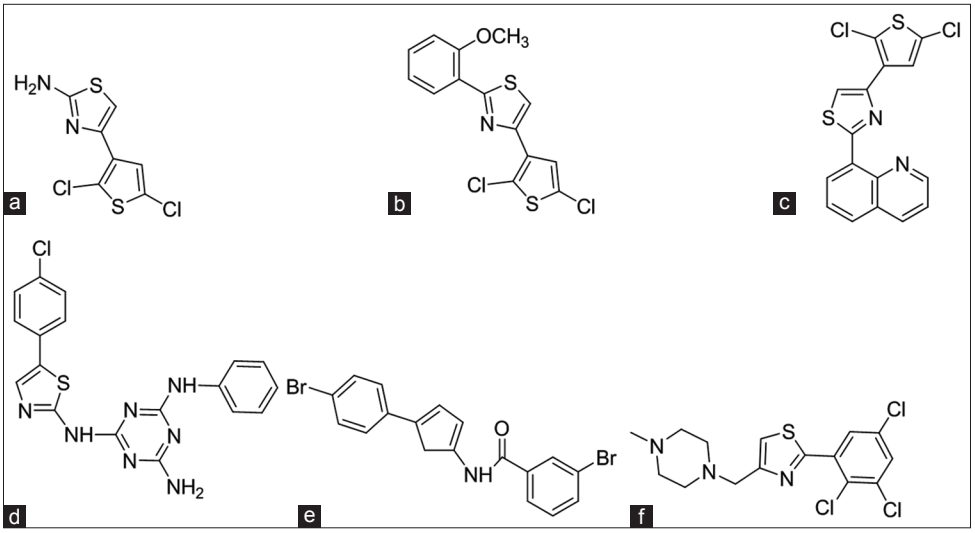

Figure 1: (a-f) Structures of various thiazole derivatives having potent antimicrobial activity

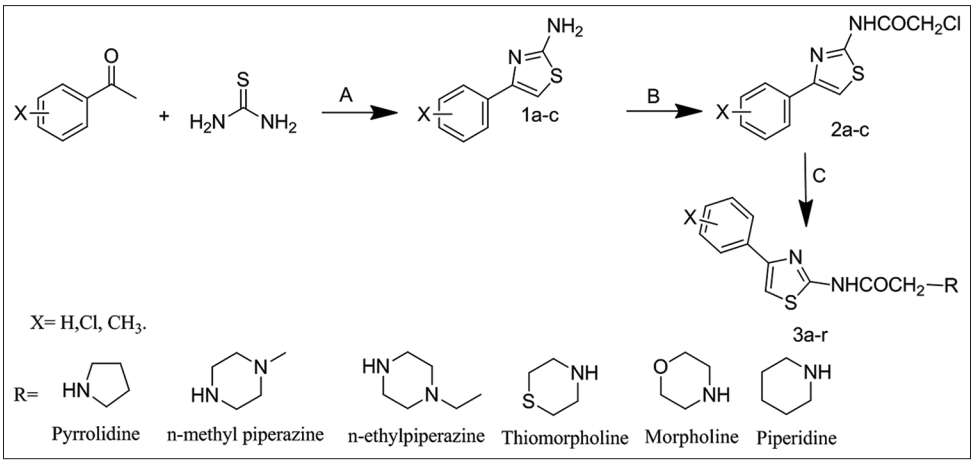

Figure 2: Route of synthesis of 2-substituted-N-(Para substituted phenylthiazol-2-yl)acetamide derivatives (3a-r). Reagent and conditions: (A) Iodine, abs. EtOH, refluxes (B) 2-chloroacetylchloride, pyridine, stirring then reflux. (C) TEA. Ethanol, reflux

169.7 ppm in ^{13}C-NMR spectrum of compound 1a. This was further supported by a mass spectrum of compound 1a (m/z 177.19). The formation of acetamide derivatives for compound 2c were established by locating characteristics peak of $COCH_2Cl$ group, which was observed at δ value 4.37 ppm integrating for two protons in ^{1}H-NMR. In ^{13}C-NMR this particular function was observed at δ value 43.1 and 165.4 ppm for CH_2 and CO group respectively for compound 2c. In IR spectra the characteristics absorption band of the compound appeared in the region 3167 for -NH- stretching, 1666 and 1632 for C=O and C=N stretching band for compound (2c). The characteristic IR band of representative compound (3a-c) were observed in the region 3160–3190/cm for -NH- stretching, 1650–1680/cm for the C=O and 1630–1650 for C=N cm^{-1} stretching. Synthesis of compound (3a-r) was identify -NHCO- group by ^{1}H-NMR observed at δ value 9–11 ppm (D_2O exchangeable), while the H-3 proton in thiazole ring was observed at δ 6.8–7.0 ppm as singlet. The synthesis was further confirmed by mass spectrometry in which molecular ion peak was registered at m/z 288.19 (M+) and M + 2 peaks at 290.19 for compound 3a. The synthesis of compounds was established by identifying the characteristics -CH_2CO- peak in NMR. In ^{1}H-NMR spectra of compounds (3a-r) the signal due methylene proton of -CH_2CO- group was resonated at δ value 3.30–3.42 ppm integrating for two protons. While in ^{13}C-NMR, the methylene carbon was located at δ value 63.8 for compound 3a. All these observations confirm successful synthesis of compounds.

Antibacterial activity

The varied 2-Substituted-N-(Para substituted phenylthiazol-2-yl)acetamide derivatives were tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains viz. *E. coli* NCTC 10418, *S. aureus* NCTC 65710, *Pseudomonas aeruginosa* NCTC 10662 by disc diffusion method at a concentration range of 6.25, 12.5, 25, 50, 100 and 200 μg/ml.[28] The results of the antibacterial activity are represented as MIC the concentration at which no visible growth was observed (zone of inhibition in mm) shown in Table 1. The compound N-(2-phenylthiazol-5-yl)-2-thiomorpholino acetamide 3d showed the most promising antibacterial activity among all the screened compounds having MIC of 6.25 μg/ml against the *E. coli* and *S. aureus*, bacterial strains respectively. The compounds 3b, 3c, 3e, 3i, 3j, 3k, and 3p showed moderate activity having MIC in between 12.5 and 25 μg/ml. The least potent compound were 3a, 3f, 3g, 3h, 3m, 3n, 3o, 3q and 3r. The overall result indicated that un-substituted phenyl ring containing thiazole derivative were the most potent followed by the chloro substituted phenyl derivatives. The antibacterial results of unsubstituted phenyl ring containing thiazole derivative indicate that thiomorpholine and morpholine rings possess best antibacterial activity, followed by the 4-methyl and 4-ethylpiperazine derivatives. The pyrrolidine and piperidine derivative 3a and 3f gives least antibacterial activity among them.

Antifungal activity

The varied 2-substituted-N-(*P*-substituted phenylthiazol-2-yl)acetamide derivatives were also screened for antifungal activity[29,30] against three fungal strains viz. *C. albican*, *Aspergillus flavus*, *Aspergillus niger* serial plate dilution method at a concentration range of 6.25, 12.5, 25, 50, and 100 μg/ml. The results of the antifungal activity are represented as MIC the concentration at which no visible growth was observed (zone of inhibition in mm) shown in Table 1. The compound N-(2-(4-chlorophenyl)thiazol-5-yl)-2-thiomorpholinoacetamide 3j showed the most promising antifungal activity among all the screened compounds at MIC 6.25 μg/ml having zone of the inhibition of 9.0, 9.5, and 8.5 mm against the *Candida albicans, A. niger* and *A. flavus* fungal strains, respectively. The compound 3d, 3e, 3i, and 3k showed moderate activity between 12.5 and 25 μg/ml concentration and the remaining test compound showed least potent against the *C. albicans,*

Table 1: Antimicrobial activity data of synthesized compounds (3a-r)

Compound number	X	R	MIC (zone of inhibition in mm)					
			Antibacterial activity			Antifungal activity		
			Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Candida albicans*	*Aspergillus flavus*	*Aspergillus niger*
3a	H	Pyrrolidine	50 (6.5)	100 (6.0)	100 (6.5)	200 (7.0)	100 (6.0)	100 (6.5)
3b	H	4-methylpiperazin	25 (6.5)	50 (6.0)	50 (6.5)	200 (7.5)	100 (7.5)	100 (6.5)
3c	H	4-ethylpiperazin	50 (6.5)	50 (6.0)	50 (6.0)	100 (7.5)	50 (7.0)	50 (7.5)
3d	H	Thiomorpholine	6.25 (8.5)	12.5 (7.5)	6.25 (8.0)	50 (6.5)	25 (6.0)	25 (6.5)
3e	H	Morpholine	25 (5.5)	25 (5.5)	25 (6.0)	50 (6.0)	50 (6.0)	50 (6.0)
3f	H	Piperidine	100 (6.5)	100 (6.0)	100 (6.0)	100 (6.5)	100 (6.0)	100 (6.5)
3g	Cl	Pyrrolidine	100 (6.5)	200 (6.5)	100 (6.0)	200 (6.5)	200 (7.0)	200 (6.5)
3h	Cl	4-methylpiperazin	100 (6.5)	100 (6.0)	100 (6.5)	100 (6.5)	50 (6.0)	100 (6.0)
3i	Cl	4-ethylpiperazin	50 (6.5)	50 (6.0)	50 (6.0)	50 (6.5)	50 (6.0)	100 (6.5)
3j	Cl	Thiomorpholine	25 (6.5)	50 (6.0)	25 (6.0)	6.25 (9.0)	6.25 (9.5)	6.25 (8.5)
3k	Cl	Morpholine	25 (6.5)	50 (6.0)	50 (6.0)	50 (6.0)	25 (6.5)	50 (7.5)
3l	Cl	Piperidine	50 (7.5)	100 (7.0)	100 (7.5)	100 (6.5)	50 (6.0)	50 (6.5)
3m	CH_3	pyrrolidine	200 (7.0)	100 (6.0)	100 (6.5)	200 (6.5)	200 (7.0)	200 (6.5)
3n	CH_3	4-methylpiperazin	100 (6.0)	100 (6.5)	100 (6.5)	200 (6.5)	100 (6.0)	100 (6.0)
3o	CH_3	4-ethylpiperazin	100 (7.5)	200 (6.5)	100 (7.5)	200 (7.0)	100 (6.5)	200 (6.5)
3p	CH_3	Thiomorpholine	25 (6.0)	50 (6.0)	25 (6.5)	100 (6.0)	100 (6.0)	100 (6.0)
3q	CH_3	Morpholine	100 (6.0)	100 (6.0)	100 (6.5)	100 (6.0)	200 (6.5)	200 (7.0)
3r	CH_3	Piperidine	200 (7.5)	200 (6.0)	100 (6.5)	100 (6.0)	200 (6.0)	200 (6.0)
Cefixime			6.25 (9.0)	6.25 (8.0)	6.25 (8.5)	NT	NT	NT
Fluconazole			NT	NT	NT	6.25 (9.5)	6.25 (10.5)	6.25 (9.5)
DMSO			00	00	00	00	00	00

NT – Not tested; MIC – Minimum inhibitory concentration; DMSO – Dimethyl sulfoxide

A. niger and *A. flavus* fungal strains. The antifungal results of chloro-substituted phenyl ring containing thiazole derivative indicate that thiomorpholine possesses best antifungal activity, followed by the morpholine, 4-ethylpiperazine and unsubstituted phenyl ring containing thiomorpholine and morpholine derivatives. Overall chloro-substituted phenyl ring containing thiazole derivative indicates that thiomorpholine possesses best antifungal activity due to the chloro-substitution, which may increases the lipophilicity in a fungal cell wall.

Computational studies

To understand the mechanism of action underlying activity of most active compound 3d and 3j, we proceeded to examine the interaction of compound 3d and 3j with microbial glucosamine-6-phosphate synthase (PDB code: 1JXA).[31] All docking runs were carried out as per Glide XP Docking protocol in Schrodinger 9.4.[32,33] The XP Glide score obtained for compound 3d and 3j was found to be −7.56 and −7.82 respectively. The three-dimensional and two-dimensional interaction diagram of most potent compounds are shown in Figures 3, 4, 5 and 6 . The compound 3d having the most potent antibacterial activity among all the synthesized compounds showed interaction with the key amino acid residues GLH488, LEU601, GLU58, ALA602, VAL399, SER401, GLY350, GLU351, SER347, CYS-300, THR352, SER303, THR352, VAL605 and LEU484. The C=O group and NH group of acetamide of compound 3d formed H-bond network with the amino acid residue VAL605 and Val399 at 1.65 and 1.90 Å respectively. Similarly compound 3j having potent antifungal activity showed hydrophobic interactions with amino acid GLH488, LEU484, TRP74, SER604, VAL399, GLY350, VAL605, GLN348, SER349, SER303, THR302, CYS300 and LYS487 located in the binding pocket and played vital roles in the interaction of compound 3j with the enzyme. The C=O and N from thiomorpholine of compound 3j formed H-bond network with the amino acid SER604 and VAL605 at 1.77 and 2.01 Å respectively.

The absorption, distribution, metabolism and excretion (ADME) properties are crucial determinants for the successful development of new drugs. Unfavorable ADME properties can lead to rejection of a drug in the later stages of drug process.[34] The most promising compounds were further analyzed for ADME, Lipinski's "rule of 5" and Jorgensen's "rule of 3" using QikProp tool of Schrodinger which is built using experimental details of 710 compounds including 500 drugs and heterocyclic compounds. The QikProp properties[35] of these compounds are listed in Table 2. QikProp calculates properties like molecular weight, molecular volume, number of H-bond donors, number of H-bond acceptors, polar surface area, QPlogPo/w (Predicted octanol/water partition coefficient), percentage of human oral absorption and violations related to Lipinski's "rule of 5"[36] and Jorgensen's "rule of 3"[37] to filter out compounds with clear-cut undesirable properties. Compounds that

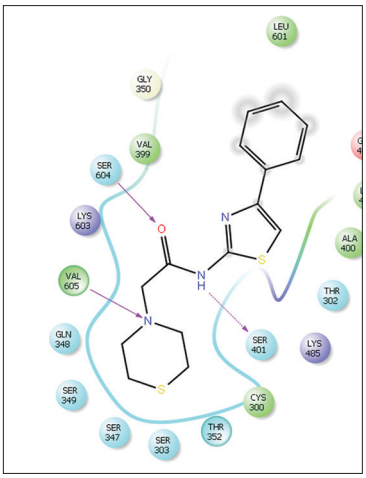

Figure 3: Two-dimensional diagram showing hydrogen bonding interaction of compound 3d for antibacterial with active sites of enzyme glucosamine-6-phosphate synthase (PDB ID:1JXA)

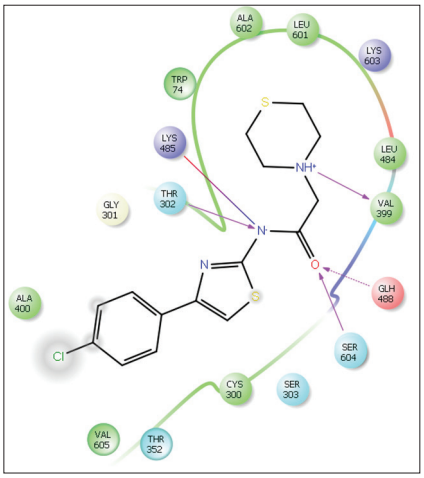

Figure 5: Two-dimensional diagram showing hydrogen bonding interaction of compound 3j for antifungal with active sites of enzyme glucosamine-6-phosphate synthase (PDB ID:1JXA)

satisfy Lipinski's "rule of 5" and Jorgensen's "rule of 3," are considered drug-like and these compounds are more likely to be orally available. All these promising compounds showed excellent ADME properties and passed Lipinski's "rule of 5" and Jorgensen's "rule of 3," having no violations and also showed that they have potential of >75% orally bioavailable. The excellent ADME property of these hits makes them promising candidates for future development as antimicrobial and antifungal agents.

Materials and Methods

Chemistry

All chemicals and reagents were obtained from various manufacturers and used without of further purification. The reactions were monitored and the purity of the compounds was checked by thin layer chromatography

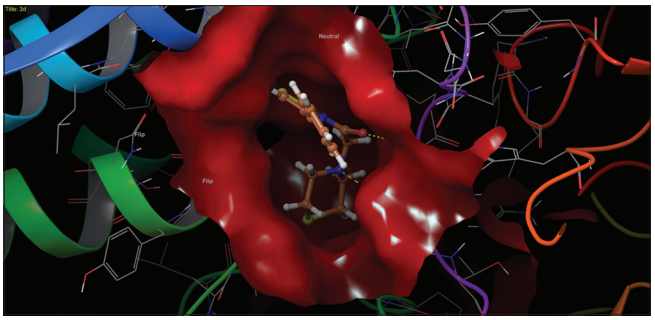

Figure 4: Three-dimensional diagram showing hydrogen bonding interaction of compound 3d for antibacterial with active sites of enzyme glucosamine-6-phosphate synthase (PDB ID:1JXA)

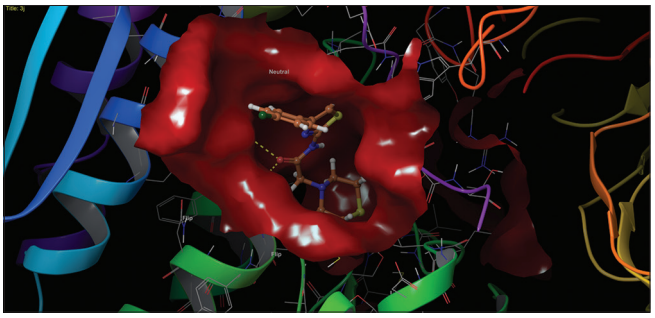

Figure 6: Three-dimensional diagram showing hydrogen bonding interaction of compound 3j for antifungal with active sites of enzyme glucosamine-6-phosphate synthase (PDB ID:1JXA)

(TLC) and spot being located under iodine vapors or UV-light. Melting points were determined by the open capillary method with electrical melting point apparatus and are uncorrected. IR spectra were recorded as KBr (pellet) on bio rad Fourier transform-IR spectrophotometer and ^{1}H and ^{13}C-NMR spectra were recorded on Bruker DP×300 MHz spectrophotometer using dimethyl sulfoxide (DMSO)-d_6 or $CDCl_3$ as a NMR solvent. Mass spectra (MS-ESI) were recorded on a JEOL-AccuTOF JMS-T100 LS mass spectrometer and elemental analysis were performed on a Vario-EL III CHNOS- Elemental analyzer and were within ±0.4% of the theoretical values.

Synthesis of 2-amino-4-substituetedphenylthiazole (1a-c)

2-Amino-4-phenylthiazole derivatives (1a-c) were synthesized by reported method[24,25] mixture containing of (10 mmol) of substituted acetophenone and (20 mmol) of thiourea in previously dissolved iodine in anhydrous ethanol taken in a round bottom flask and refluxed overnight. This crude reaction mixture was cooled and extracted with ether to remove unreacted substituted acetophenone and iodine. This residue was then dissolved in boiling water and filtered to remove sulfur. Then the solution was cooled somewhat and made basic with ammonium hydroxide. The aminothiazole was separated and recrystallized with alcohol, Yield: 78–85%.

Table 2: QikProp properties of all the compounds (3b, 3c, 3d, 3e, 3i, 3j, 3k, and 3p) calculated from QikProp tool of Schrodinger

Molecule	Molecule MW	WPSA	Volume	Donor HB	Accept HB	QPlog Po/w	PSA	Percentage of human oral absorption	Rule of five	Rule of three
3b	316.42	25.519	1059.247	1	8	1.46	58.263	73.873	0	0
3c	330.447	25.522	1115.967	1	8	1.829	57.728	76.641	0	0
3d	319.439	73.386	1015.355	1	6.5	2.558	52.429	91.964	0	0
3e	303.378	25.596	969.033	1	7.7	1.608	61.668	86.35	0	0
3i	353.884	145.058	1059.535	1	6.5	3.045	52.428	94.818	0	0
3j	350.865	97.192	1103.395	1	8	1.944	58.262	76.704	0	0
3k	364.892	97.196	1160.063	1	8	2.315	57.728	79.48	0	0
3p	344.474	25.526	1176.008	1	8	2.129	57.729	78.4	0	0

MW – Molecular weight; HB – Hydrogen bonding; PSA – Polar surface area; WPSA – Weakly-polar surface area

Synthesis of 2-chloro-N-(P-substituted phenylthiazol-5-yl)acetamide (2a-c)

2-chloro-N-(para substituted phenylthiazol-5-yl)acetamide (2a-c) was synthesized by reported method.[26,27] A mixture of 1a-c (10.0 mmol) in pyridine (10.0 ml), and dropwise chloroacetyl chloride (12.0 mmol) was added with continuous stirring slowly. The course of addition was 20 min. The solution mixture was heated on a boiling water bath up to reaction is completed. The mixture was kept to attain room temperature and then poured onto crushed ice. The separated solid was filtered off, washed repeatedly with water, dried and recrystallized from ethanol to give 2a-c, Yield: 80–84%.

Synthesis of 2-Substituted-N-(P-substituted phenylthiazol-2-yl)acetamide derivatives (3a-r)

A mixture of 2-chloro-N-(*P*-substituted phenylthiazol-5-yl)acetamide (2a-c) (5.0 mmol) with different heterocyclic amines and K_2CO_3 (10.0 mmol) in acetone taken in a round bottom flask and refluxed for 6–8 h. The reaction was monitored on TLC. After the reaction completion, the solvent was removed by vacuum distillation and the residue was treated with sodium bicarbonate (5% w/v) to remove acid impurities. The residue was washed with water, dry and recrystallize with ethanol to give 2-substituted-N-(para substituted phenylthiazol-2-yl) acetamide derivatives (3a-r).

N-(4-Phenylthiazol-2-yl)-2-(pyrrolidin-1-yl)acetamide 3a

Yield: 67%; m.p.: 142–144°C; IR (KBr) cm^{-1}: 3160 (N-H), 1668 (C=O), 1638 (C=N), 1556 (C=C), 1024 (C-N).^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.74–1.79 (m, 4H, 2×CH_2), 2.61–2.68 (m, 4H, 2×CH_2), 3.40 (s, 2H, CH_2), 6.90 (s, 1H, thiazole), 7.49 (s, 1H, Ar-H), 7.98 (d, 2H, Ar-H *J* = 7.5 Hz), 8.21 (d, 2H, Ar-H *J* = 7.1 Hz), 10.32 (bs, 1H, CONH, D_2O exchangeable). ^{13}C-NMR (75 MHz, DMSO-d_6); δ 23.14, 59.92, 63.85, 129.22, 129.65, 143.38, 143.82, 151.61, 169.24 (C=O). ESI-MS: m/z 288.19, (M+). Anal. calcd for $C_{15}H_{17}N_3OS$: C 62.69, H, 5.96, N 14.62. Found: C 62.76, H 5.98, N 14.66%.

2-(4-Methylpiperazin-1-yl)-N-(4-phenylthiazol-2-yl) acetamide 3b

Yield: 67%; m.p.: 168–170°C; IR (KBr) cm^{-1}: 3168 (N-H), 1669 (C=O), 1632 (C=N), 1540 (C=C), 1028 (C-N).^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.26 (s, 3H, CH_3 piperizine), 2.39–2.44 (m, 4H, 2×CH_2), 2.43–2.47 (m, 4H, 2×CH_2), 3.36 (s, 2H, CH_2), 6.92 (s, 1H, thiazole), 7.47 (s, 1H, Ar-H), 7.59 (d, 2H, Ar-H *J* = 7.5 Hz), 8.46 (d, 2H, Ar-H *J* = 7.1 Hz), 10.39 (bs, 1H, CONH, D_2O exchangeable). ESI-MS: m/z 317.18 (M+), anal. calcd for $C_{16}H_{20}N_4OS$: C 60.73, H 6.37, N 17.71. Found: C 60.81, H 6.39, N 17.74%.

2-(4-Ethylpiperazin-1-yl)-N-(4-phenylthiazol-2-yl) acetamide 3c

Yield: 72%; m.p.: 208–210°C; IR (KBr) cm^{-1}: 3210 (N-H), 1671 (C=O), 1642 (C=N), 1562 (C=C), 1032 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ1.32 (t, 3H, CH_2CH_3 piperazin), 2.44 (q, 2H, CH_2CH_3 piperazin), 2.43–2.47 (m, 8H, 4×CH_2), 3.39 (s, 2H, CH_2), 7.12 (s, 1H, thiazole), 7.51 (s, 1H, Ar-H), 7.66 (d, 2H, Ar-H *J* = 7.6 Hz), 8.23 (d, 2H, Ar-H *J* = 7.1 Hz), 10.92 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{17}H_{22}N_4OS$: C 61.79, H 6.71, N 16.95. Found: C 61.84, H 6.73, N 16.98%.

N-(4-Phenylthiazol-2-yl)-2-thiomorpholino acetamide 3d

Yield: 69%; m.p.: 130–132°C; IR (KBr) cm^{-1}: 3189 (N-H), 1659 (C=O), 1622 (C=N), 1552 (C=C), 1028 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.59–2.63 (m, 4H, 2×CH_2), 2.82–2.87 (m, 4H, 2×CH_2), 3.37 (s, 2H, CH_2), 6.99 (s, 1H, thiazole), 7.54 (s, 1H, Ar-H), 7.77 (d, 2H, Ar-H *J* = 7.5 Hz), 8.24 (d, 2H, Ar-H *J* = 7.1 Hz), 11.00 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{15}H_{17}N_3OS_2$: C 56.40, H 5.36, N 13.15. Found: C 56.48, H 5.39, N 13.18%.

2-Morpholino-N-(4-phenylthiazol-2-yl)acetamide 3e

Yield: 58%; m.p.: 118–120°C; IR (KBr) cm^{-1}: 3178 (N-H), 1668 (C=O), 1633 (C=N), 1542 (C=C), 1024 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.71–2.78 (m, 4H, 2×CH_2), 3.82–3.89 (m, 4H, 2×CH_2), 3.41 (s, 2H, CH_2), 6.92 (s, 1H, thiazole), 7.49 (s, 1H, Ar-H), 7.68 (d, 2H, Ar-H *J* = 7.52 Hz),

8.11 (d, 2H, Ar-H *J* = 7.1 Hz), 11.12 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{15}H_{17}N_3O_2S$: C 59.38, H 5.65, N 13.85. Found: C 59.46, H 5.67, N 13.88%.

N-(4-Phenylthiazol-2-yl)-2-(piperidin-1-yl)acetamide 3f

Yield: 67%; m.p.: 152–154°C; IR (KBr) cm^{-1}: 3166 (N-H), 1668 (C=O), 1645 (C=N), 1550 (C=C), 1036 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.63–1.76 (m, 6H, 3×CH_2), 2.49–2.53 (m, 4H, 2×CH_2), 3.38 (s, 2H, CH_2), 6.88 (s, 1H, thiazole), 7.51 (s, 1H, Ar-H), 7.69 (d, 2H, Ar-H *J* = 7.5 Hz), 8.22 (d, 2H, Ar-H *J* = 7.1 Hz), 10.89 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{16}H_{19}N_3OS$: C 63.76, H 6.35, N 13.94. Found: C 63.81, H 6.36, N 13.99%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(pyrrolidin-1-yl) acetamide 3 g

Yield: 74%; m.p.: 166–168°C; IR (KBr) cm^{-1}: 3172 (N-H), 1656 (C=O), 1642 (C=N), 1539 (C=C), 1024 (C-N). 752 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.65–1.74 (m, 4H, 2×CH_2), 2.56–2.61 (m, 4H, 2×CH_2), 3.41 (s, 2H, CH_2), 6.91 (s, 1H, thiazole), 7.61 (d, 2H, Ar-H *J* = 7.5 Hz), 8.06 (d, 2H, Ar-H *J* = 7.1 Hz), 9.89 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{15}H_{16}ClN_3OS$: C 55.98, H 5.01, N 13.06. Found: C 56.10, H 5.04, N 13.10%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(4-methylpiperazin-1-yl)acetamide 3 h

Yield: 79%; m.p.: 186–188°C; IR (KBr) cm^{-1}: 3169 (N-H), 1656 (C=O), 1638 (C=N), 1555 (C=C), 1030(C-N). 760 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.31 (s, 3H, CH_3 piperazine), 2.41–2.49 (m, 8H, 2×CH_2), 3.31 (s, 2H, CH_2), 6.90 (s, 1H, thiazole), 7.61 (d, 2H, Ar-H *J* = 7.6 Hz), 8.12 (d, 2H, Ar-H *J* = 7.1 Hz), 10.44 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{16}H_{19}ClN_4OS$: C 54.77, H 5.46, N 15.97. Found: C 54.81, H 5.48, N 15.99%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide 3i

Yield: 80%; m.p.: 228–230°C; IR (KBr) cm^{-1}: 3172 (N-H), 1677 (C=O), 1632 (C=N), 1542 (C=C), 1028 (C-N). 754 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ1.26(t, 3H,CH_2CH_3 piperazin), 2.46 (q, 2H, CH_2CH_3 piperazin), 2.42–2.49 (m, 8H, 4×CH_2), 3.43 (s, 2H, CH_2), 6.89 (s, 1H, thiazole), 7.69 (d, 2H, Ar-H *J* = 7.5 Hz), 8.22 (d, 2H, Ar-H *J* = 7.1 Hz), 10.89 (bs, 1H, CONH, D_2O exchangeable). ESI-MS: m/z 365.11(M+), 367.11(M + 2). Anal. calcd for $C_{17}H_{21}ClN_4OS$: C 55.96, H 5.80, N 15.35. Found: C 55.99, H 5.83, N 15.38%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-thiomorpholinoacetamide 3j.

Yield: 78%; m.p.: 148–150°C; IR (KBr) cm^{-1}: 3188 (N-H), 1678 (C=O), 1628 (C=N), 1556 (C=C), 1024 (C-N). 750 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.51–2.59 (m, 4H, 2×CH_2), 2.82–2.89 (m, 4H, 2×CH_2), 3.43 (s, 2H, CH_2), 6.78 (s, 1H, thiazole), 7.61 (d, 2H, Ar-H *J* = 7.5 Hz), 8.10 (d, 2H, Ar-H *J* = 7.1 Hz), 10.58 (bs, 1H, CONH, D_2O exchangeable). ESI-MS: m/z 354.10 (M+), 356.10 (M + 2). Anal. calcd for $C_{15}H_{16}ClN_3OS_2$: C 50.91, H 4.56, N 11.87. Found: C 50.99, H 4.58, N 11.90%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-morpholinoacetamide 3k

Yield: 76%; m.p.: 136–138°C; IR (KBr) cm^{-1}: 3211 (N-H), 1660 (C=O), 1645 (C=N), 1560 (C=C), 1030 (C-N). 762 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.47–2.53 (m, 4H, 2×CH_2), 3.43 (s, 2H, CH_2), 3.71–3.79 (m, 4H, 2×CH_2), 6.89 (s, 1H, thiazole), 7.61 (d, 2H, Ar-H *J* = 7.5 Hz), 8.06 (d, 2H, Ar-H *J* = 7.0 Hz), 9.98 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{15}H_{16}ClN_3O_2S$: C 53.33, H 4.77, N 12.44. Found: C 53.38, H 4.79, N 12.47%.

N-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(piperidin-1-yl) acetamide 3l

Yield: 69%; m.p.: 178–180°C; IR (KBr) cm^{-1}: 3212 (N-H), 1662 (C=O), 1638 (C=N), 1560 (C=C), 1034 (C-N). 755 (C-Cl). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.63–1.74 (m, 6H, 3×CH_2), 2.47–2.51 (m, 4H, 2×CH_2), 3.34 (s, 2H, CH_2), 6.93 (s, 1H, thiazole), 7.63 (d, 2H, Ar-H *J* = 7.4 Hz), 8.08 (d, 2H, Ar-H *J* = 7.0 Hz), 9.82 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{16}H_{18}ClN_3OS$: C 57.22, H 5.40, N 12.51. Found: C 57.29, H 5.43, N 12.54%.

2-(Pyrrolidin-1-yl)-N-(4-p-tolylthiazol-2-yl)acetamide 3 m

Yield: 66%; m.p.: 148–150°C; IR (KBr) cm^{-1}: 3176 (N-H), 1663 (C=O), 1638 (C=N), 1560 (C=C), 1030 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.74–1.81 (m, 4H, 2×CH_2), 2.41(s, 3H, Ar-CH_3) 2.59–2.61 (m, 4H, 2×CH_2), 3.38 (s, 2H, CH_2), 6.89 (s, 1H, thiazole), 7.35 (d, 2H, Ar-H *J* = 7.5 Hz), 7.73 (d, 2H, Ar-H *J* = 7.0 Hz), 9.97 (bs, 1H, CONH, D_2O exchangeable). Anal. calcd for $C_{16}H_{19}N_3OS$: C 63.76, H 6.35, N 13.94. Found C 63.82, H 6.37, N 13.95%.

2-(4-Methylpiperazin-1-yl)-N-(4-p-tolylthiazol-2-yl) acetamide 3n

Yield: 64%; m.p.: 172–174°C; IR (KBr) cm^{-1}: 3168 (N-H), 1664 (C=O), 1637 (C=N), 1562 (C=C), 1024 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.31 (s, 3H, CH_3 piperazin), 2.39 (s, 3H, Ar-CH_3) 2.41–2.46 (m, 4H, 2×CH_2), 2.47–2.51 (m, 4H, 2×CH_2), 3.38 (s, 2H, CH_2), 6.89 (s, 1H, thiazole), 7.41 (d, 2H, Ar-H *J* = 7.4 Hz), 7.76 (d, 2H, Ar-H *J* = 7.0 Hz), 9.82 (bs, 1H, CONH, D_2O exchangeable). ESI-MS: m/z331.14 (M+). Anal. calcd for $C_{17}H_{22}N_4OS$: C 61.79, H 6.71, N 16.95. Found: C 61.83, H 6.73, N 16.98%.

2-(4-Ethylpiperazin-1-yl)-N-(4-p-tolylthiazol-2-yl) acetamide 3o

Yield: 60%; m.p.: 214–216°C; IR (KBr) cm^{-1}: 3178 (N-H), 1656 (C=O), 1640 (C=N), 1538 (C=C), 1024(C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.22 (t, 3H, CH_2CH_3 piperazin), 2.38 (s, 3H Ar-CH_3) 2.41 (q, 2H,CH_2CH_3 piperazin), 2.43–2.48 (m, 8H, 4×CH_2), 3.32 (s, 2H, CH_2), 6.91 (s, 1H, thiazole),

7.33 (d, 2H, Ar-H *J* = 7.5 Hz), 7.72 (d, 2H, Ar-H *J* = 7.0 Hz), 10.28 (bs, 1H, CONH D_2O exchangeable). Anal. calcd for $C_{18}H_{24}N_4OS$: C 62.76, H 7.02, N 16.26. Found: C, 62.77, H 7.04, N 16.25%.

2-Thiomorpholino-N-(4-p-tolylthiazol-2-yl)acetamide 3p

Yield: 64%; m.p.: 142–144°C; IR (KBr) cm^{-1}: 3178 (N-H), 1658 (C=O), 1634 (C=N), 1553 (C=C), 1022 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.41 (s, 3H, Ar-CH_3), 2.59–2.63 (m, 4H, 2×CH_2), 2.78–2.86 (m, 4H, 2×CH_2), 3.39 (s, 2H, CH_2), 6.89 (s, 1H, thiazole), 7.41 (d, 2H, Ar-H *J* = 7.4 Hz), 7.82 (d, 2H, Ar-H *J* = 7.1 Hz), 9.88 (bs, 1H, CONH D_2O exchangeable). Anal. calcd for $C_{16}H_{19}N_3OS_2$:C 57.63, H 5.74 N, 12.60. Found: C 57.67, H 5.76, N,12.63%.

2-Morpholino-N-(4-p-tolylthiazol-2-yl)acetamide 3q

Yield: 64%; m.p.: 124–126°C; IR (KBr) cm^{-1}: 3176 (N-H), 1662 (C=O), 1632 (C=N), 1546 (C=C), 1026 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 2.40 (s, 3H, Ar-CH_3), 2.59–2.64 (m, 4H, 2×CH_2), 3.39 (s, 2H, CH_2), 3.69–3.74 (m, 4H, 2×CH_2), 6.91 (s, 1H, thiazole), 7.39 (d, 2H, Ar-H *J* = 7.4 Hz), 7.82 (d, 2H, Ar-H *J* = 7.1 Hz), 10.18 (bs, 1H, CONH D_2O exchangeable). ESI-MS: m/z 318.18(M+). Anal. calcd for $C_{16}H_{19}N_3O_2S$: C 60.54, H 6.03, N 13.24. Found: C 60.59, H 6.05, N 13.27%.

2-(Piperidin-1-yl)-N-(4-p-tolylthiazol-2-yl)acetamide 3r

Yield: 67%; m.p.: 154–156°C; IR (KBr) cm^{-1}: 3208 (N-H), 1668 (C= O), 1640 (C=N), 1563 (C=C), 1030 (C-N). ^{1}H-NMR (300 MHz, DMSO-d_6); δ 1.69–1.77 (m, 6H, 3×CH_2), 2.41 (s, 3H, Ar-CH_3), 2.49–2.54 (m, 4H, 2×CH_2), 3.34 (s, 2H, CH_2), 6.91 (s, 1H, thiazole), 7.39 (d, 2H, Ar-H *J* = 7.4 Hz), 7.82 (d, 2H, Ar-H *J* = 6.9 Hz), 10.10 (bs, 1H, CONH D_2O exchangeable).) ^{13}C-NMR (75 MHz, DMSO-d_6); δ 22.32, 25.18, 56.82, 64.17, 128.27, 142.33, 144.17, 152.13, 169.20 (C=O) ESI-MS: m/z316.10(M+). Anal. calcd for $C_{16}H_{21}N_3OS$: C 64.73, H 6.71, N 13.32. Found: C 64.76, H 6.73, N 13.36%.

Antibacterial activity

Antibacterial activity of newly synthesized compounds was evaluated by cup plate method against *E. coli* (NCTC, 10418), *S. aureus* (NCTC, 65710), *P. aeruginosa* (NCTC, 10662) strains. Nutrient agar was used as the culture medium. Tween 80 (0.01%) in normal saline was used for suspension of the bacterial spore for lawning purpose. 50 ml of liquid agar medium was poured into each Petri dish (15 cm diameter). Bacterial suspension was spread over the solid agar medium and plates were kept in anincubator at 37°C for 1 h for drying. Wells were completed on these seeded agar plates using an agar punch and DMSO was used as solvent for the preparation of test samples at conc. Range of 6.25, 12.5, 25.0, 50, 100 and 200 μg/ml were added into each well, labeled previously. DMSO was used as a control. This procedure was repetitive for each bacterial strain and the plates were incubated at 37°C for 24 h. The MIC was noted by seeing the lowest concentration of the test drug at which there was no visible growth. Antimicrobial activity of each compound (3a-r) was compared with standard cefixime and results have been summarized as MIC (average zone of inhibition of two reading in millimeter) in Table 1.

Antifungal activity

The synthesized compounds were evaluated for their *in-vitro* antifungal activity by serial plate dilution method. Suspension of corresponding species of fungal strain (3.0 ml) was transferred in normal saline water, for lawning. 20 ml of agar media was poured into each of the petri dish, excess of the suspension was decanted, and the plates were kept in an incubator at 37°C for 1 h for drying. Wells were completed on these seeded agar plates using an agar punch and DMSO was used as solvent for the preparation of test samples at concentration range of 6.25, 12.5, 25.0, 50, 100, and 200 μg/ml were added into each well labeled. DMSO was used as control. This procedure was repetitive for each bacterial strain and the plates were incubated at 37°C for 72–84 h. Antifungal activity was determined by measuring the diameter of the inhibition zone. The MIC was noted by seeing the lowest concentration of the test drug at which there was no visible growth. The activity of each compound (3a-r) was compared with standard fluconazole in DMSO and results have been summarized as MIC (average zone of inhibition of two reading in millimeter) in Table 1.

Computational studies

Docking studies were performed for synthesized molecule 3d and 3j using the Glide module in the Schrodinger 9.4 program. The crystal structures of the proteins complex (PDBId: 1JXA) were downloaded from the RCSB protein data bank (http://www.rcsb.org/pdb/home/home.do) and prepared with the protein preparation wizard module in Schrodinger 9.4. Binding site of the ligand was created by keeping the co-crystallized ligand at the center of a rectangular box drawn in the receptor. Binding site is also known as receptor grid generation. A 20 Å grid space was defined for the co-crystallized ligand using the Glide grid module of the software. For low-energy conformers and to correct the chirality of all the ligands the LigPrep module was used. Where by producing the ring conformations and penalizing the nonpolar amide bond conformations ligands were kept flexible, whereas the receptor was kept rigid during the course of the docking studies. All other parameters of the Glide module were set as default values.

Absorption, distribution, metabolism and excretion important parameter of physicochemical properties were predicted using QikProp3.6 (Schrodinger) which calculates the numerous parameter such as molecular weight, molecular volume, number of H-bond donors, number of H-bond acceptors, polar surface area, QPlogPo/w (Predicted octanol/water partition coefficient) percentage of human

oral absorption and violations related to Lipinski's "rule of 5" and Jorgensen's "rule of 3" to screen the compound to know the disagreeable properties. Before using the QikProp the compound was neutralized by using of LigPrep which were treated for calculation of ADME properties.

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