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Synthesis, characterization and molecular docking of N-aryl amides of pyrido[1,2-*a*]pyrimidin-2-ones as potential antibacterial agents

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Nitrogen-containing heterocyclic compounds play the most key role in the discovery of new drugs. Among all, pyrimidine possesses a wide spectrum because of its positive pharmacological and biological properties. Some novel amides of pyrido[1,2-*a*]pyrimidine-2-one acetic acids were synthesized, and the structure of the products was confirmed by FTIR, Mass, ^{1}H NMR, and ^{13}C NMR spectral analysis. The compounds synthesized were evaluated for their *in vitro* antibacterial activity against *Bacillus subtilis* and *Escherichia coli* by the disc diffusion method. All the compounds showed moderate antibacterial activity. Out of the all synthesized compounds(*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide and (2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)-*N*-phenylacetamide showed high sensitivity to the bacteria *Bacillus subtilis.* While in case of *Escherichia coli* compound *N*-(4-methoxyphenyl)-2-(2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide showed higher activity. Further the newly synthesized compounds docking studies were performed against the active site of 1T9U and 3UZ0 protein.

The compound (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)ylidene)acetamide possess great binding affinity towards 3UZ0 and 1T9U bacterial protein targets and possess bioavailability. Based on the docking result, we claim that (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide could serve as an effective antimicrobial compound to treat bacterial infections.

Keywords: Pyridopyrimidine, amides, pyrido[1,2-*a*]pyrimidine-2-one acetic acids, antibacterial activity, molecular docking, 3UZ0 and 1T9U protein.

Introduction

The heterocyclic compounds are the important scaffolds in the discovery of new drugs. The study of these compounds is of great significance in both theoretical and practical aspects[1]. Medicinal chemists are interested in nitrogen-containing heterocyclic compounds, because they are the fundamental building blocks for the development of novel compounds with biological properties. Organic compounds with nitrogen show better biological activity than non-nitrogen compounds. One such *N*-heterocyclic compounds exhibiting significant pharmacological activities is pyrimidines. Pyrimidines are essential constituent present in all living matter[2]. A broad spectrum of biological activities possessed by pyrimidine like including antibacterial, antifungal, antiviral, antitubercular, anti-inflammatory, anticancer, antimalarial, anti-HIV activity[3].

Serious challenges to physicians towards drug-resistant bacterial strains pose because they cause numerous recurrent infections in humans. *Pseudomonas aeruginosa* (*P. aeruginosa*), *Escherichia coli* (*E. coli*), *Streptococcus pyogenes* (*S. pyogenes*) such bacterial strains gained attention because of their ability to cause Cystic fibrosis, chronic lung infection in humans. Therefore, a novel compound has to be identified to avoid the detrimental effects on drug-resistant bacterial strains. This article describes the use of N-aryl amides of pyrido[1,2-*a*]pyrimidin-2-ones as a potential antimicrobial agent targeting *Escherichia coli* (*E. coli*) and *Bacillus subtilis* (*B. subtilis*) subcellular proteins[4].

The experimental binding modes and affinities of small molecules within the particular receptor target binding site can be predicted using docking methodology. Presently it is used as a standard computational tool in drug design for

ineffective screening studies and direct compound optimization to find new biologically active molecules[5]. Autodock is a suite of free, open-source software and it has been extensively used in drug discovery[6]. Compared with the molecular docking software Autodock vina has approximately two orders of magnitude speed-up in comparison with other docking softwares[7].

In this article, we confirm the antibacterial nature of synthesized *N*-aryl amides of pyrido[1,2-*a*]pyrimidin-2-ones by molecular docking studies. These study findings indicate bioavailability and supportive molecular interaction with amino acids present on selected bacterial subcellular proteins active site[4].

Materials and methods

Melting points were recorded using Biochem melting point and are uncorrected. The infrared (IR) spectrum was recorded in the KBr pellet technique using Perkin-Elmer spectrophotometer**.** Absorption frequencies were quoted in reciprocal centimeters. Nuclear Magnetic Resonance (^{1}H NMR and ^{13}C NMR) spectrum were determined by Bruker modern 400 MHz NMR instrument in $CDCl_3$ solvent, with tetramethylsilane as the internal reference. Chemical shifts were quoted in parts per million (ppm). Mass experiments were performed on GC (T 8000 TOP CE) and combined with a mass spectrometer (Md 800 FIS ONS). Reagent grade solvents and reagents used for the synthesis and standard methods were carried out for purification. Chromatographic columns packed with silica gel were used for purification of the crude products.

General procedure:

A blend of 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid (0.1 mole) and purified thionyl chloride (0.20 mole) was stirred at room temperature under exclusion of moisture till the solution was complete. The thionyl chloride excess was distilled off under reduced pressure. The residue was recovered by using anhydrous ether (25 ml) and gradually added to a well cooled and stirred mixture of aniline (0.02 mole) in dry ether (25 ml). After the addition, it was set aside for a few minutes and ice water poured into it. The precipitated solid was filtered, dried, and purified by column chromatography.

Physical properties and spectral data:

*2-Oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-phenylacetamide (**A**):*

2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid: 2.04 g; thionyl chloride: 7 ml; aniline: 2.5 g; ether: 50 ml; yield 3 g (66%); m.p. 228–230°C; IR $(\gamma)_{max}$, cm^{-1}: 3010 (-NH), 1722 (-CO), 1690 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$, γ, ppm): 4.5 (2H, s, $-CH_2$), 6.3 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.1 (1H, s(b), -NH); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 174.9 (C=O), 168.5 (amide C=O), ArC (115.2, 119.2, 122.4, 126.6, 126.7, 127.6, 128.4, 128.47, 128.6, 129.2, 132.7, 134.8), 141.1 (CH), 95.3 (CH_2); GC-MS: *m/z* 280 (M+1).

*(Z)-2-(2-Oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-(p-tolyl)acetamide (**B**):*

2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid: 2.04 g; thionyl chloride: 7 ml; *p*-toludine: 2.7 g; ether: 50 ml; yield 2.8 g (59%); m.p. 249–251°C; IR $(\gamma)_{max}$, cm^{-1}: 3016 (-NH), 1728 (-CO), 1688 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.5 (2H, s, $-CH_2$), 6.8 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.1 (1H, s(b), -NH), 2.0 (3H, s, $-CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 169.2 (C=O), 166.0 (amide C=O), ArC (103.8, 121.5, 122.4, 129.2, 134.6, 135.7, 136.8, 147.2, 157.6, 161.6), 141 (CH), 49.6 (CH_2), 21.3 (CH_3); GC-MS: *m/z* 292 (M+1).

*N-(4-Methoxyphenyl)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)ylidene)acetamide (**C**):*

2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid: 2.04 g; thionyl chloride: 7 ml; *p*-anisidine: 3.1 g; ether: 50 ml; yield 3.1 g (62%); m.p. 245–246°C; IR $(\gamma)_{max}$, cm^{-1}: 3018 (-NH), 1730 (-CO), 1691 (-CO); ^{1}H NMR (400 MHz, $CDCl_3$, γ, ppm): 4.2 (2H, s, $-4CH_2$), 6.5 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.2 (1H, s(b), -NH), 3.8 (3H, s, $-OCH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 171.2 (C=O), 167.4 (amide C=O), ArC (103.9, 134.6, 147.1, 121.5, 162.4, 157.2, 122.6, 129.9, 114.5, 158.9), 139.4 (CH), 47.3 (CH_2), 55.8 (CH_3); GC-MS: *m/z* 308 (M+1).

*N-(4-Chlorophenyl)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)ylidene)acetamide (**D**):*

2-Oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic

acid: 2.04 g; thionyl chloride: 7 ml; *p*-chloroaniline: 3.2 g; ether: 50 ml; yield 3.5 g (67%); m.p. 257–258°C; IR $(\gamma)_{max}$, cm^{-1}: 3110 (-NH), 1758 (-CO), 1672 (-CO); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.6 (2H, s, $-CH_2$), 6.8 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.0 (1H, s(b), -NH); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 171.8 (C=O), 165.2 (amide C=O), ArC (104.3, 134.5, 146.01, 159.1, 120.9, 156.2, 135.7,121.7, 129, 133.3), 139.4 (CH), 53.2 (CH_2); GC-MS: *m/z* 313 (M+1).

*(Z)-N-(Naphthalene-2-yl)-2-(2-oxo-7-methyl-2H-pyrido [1,2-a]pyrimidin-3(4H)-ylidene)acetamide (**E**):*

2-Oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3 (4*H*)-ylidene acetic acid: 2.18 g; thionyl chloride: 7 ml; naphthylamine 2.6 g; ether: 50 ml; yield 3 g (62%); m.p. 274–275°C; IR $(\gamma)_{max}$, cm^{-1}: 3110 (-NH), 1742 (-CO), 1678 (-CO); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.3 (2H, s, $-CH_2$), 6.5 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.0 (1H, s(b), -NH), 2.12 (3H, s, $-CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 168.9 (C=O), 165.7 (amide C=O), ArC (120.5, 119.6, 142.9, 122.2, 160.7, 157.4, 135.4, 119.9, 116.7, 129, 133.7, 126.8, 126.5, 124.6, 125.3, 121.4), 140.2 (CH), 48.9 (CH_2), 22.3 (CH_3); GC-MS: *m/z* 342 (M+1).

*(Z)-2-(7-Methyl-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)-N-(p-tolyl)acetamide (**F**):*

2-Oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3 (4*H*)-ylidene acetic acid: 2.18 g; thionyl chloride: 7 ml; *p*-toludine: 2.7 g; ether: 50 ml; yield 3 g (61%); m.p. 252–253°C; IR $(\gamma)_{max}$, cm^{-1}: 3110 (-NH), 1769 (-CO), 1668 (-CO); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.5 (2H, s, $-CH_2$), 6.8 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.1 (1H, s(b), -NH), 2.1 (3H, s, $-CH_3$), 2.3 (3H, s, $-CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 169.2 (C=O), 166.0 (amide C=O), ArC (119.4, 120.0, 121.5, 122.4, 129.2, 134.6, 136.8, 142.7, 157.6, 161.6), 141 (CH), 49.6 (CH_2), CH_3 (17.8, 21.3); GC-MS: *m/z* 306 (M+1).

*N-(4-Methoxyphenyl)-2-(2-oxo7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide (**G**):*

2-Oxo-7-methyl-2*H*-pyrido[1, 2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid: 2.18 g; thionyl chloride: 7 ml; *p*-anisidine: 3.1 g; ether: 50 ml; yield 3.2 g (60%); m.p. 248–250°C; IR $(\gamma)_{max}$, cm^{-1}: 3020 (-NH), 1734 (-CO), 1691 (-CO); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.2 (2H, s, $-CH_2$), 6.5 (1H, d, -CH), 2.1 (3H, s, $-CH_3$), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.2 (1H, s(b), -NH), 3.8 (3H, s, $-OCH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 171.2 (C=O), 167.4 (amide C=O), ArC (120.6, 118.5, 142.3, 121.5, 162.4, 157.2, 122.6, 129.9, 114.5, 158.9), 139.4 (CH), 47.3 (CH_2), 19.7, 55.8 (CH_3); GC-MS: *m/z* 322 (M+1).

*N-(4-Chlorophenyl)-2-(2-oxo-7-methyl-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetamide (**H**):*

2-Oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acid: 2.18 g; thionyl chloride: 7 ml; *p*-chloroaniline: 3.2 g; ether: 50 ml; yield 3.6 g (67%), m.p. 262– 263°C; IR $(\gamma)_{max}$, cm^{-1}: 3014 (-NH), 1741 (-CO), 1684 (-CO); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 4.6 (2H, s, $-CH_2$), 6.8 (1H, d, -CH), aromatic and pyridine ring 7–8 (8H, m, =CH), 9.0 (1H, s(b), -NH), 2.1 (3H, s, $-CH_3$); ^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm): 171.8 (C=O), 165.2 (amide C=O), ArC (104.3, 134.5, 146.01, 159.1, 120.9, 156.2, 135.7, 121.7, 129, 133.3), 139.4 (CH), 53.2 (CH_2) 21.2 (CH_3); GC-MS: *m/z* 327 (M+1).

Molecular docking:

Molecular docking studies are used to predict binding modes of the synthesized compounds with proteins, binding affinity and strength of the protein-ligand complexes. All the newly synthesized compounds were docked individually using Autodock Vina 1.5.6 software. After receiving the modeled three-dimensional structure of bacterial multidrug efflux transporter AcrB (PDB ID: 1T9U) and SpoIIIAH-SpoIIQ complex protein (PDB ID: 3UZ0) to Autodock Vina 1.5.6, it was optimized structurally through adding hydrogen to a protein selected by Kollaman charges. After adding hydrogen the model was saved in PDBQT format. Ligands were prepared for docking studies by adjusting the torsion angles and were saved in PDBQT format. Using PDBSUM, proteins potential binding sites were selected. A grid was generated around the binding site of the protein to identify the XYZ coordinates. Lamarckian Genetic Algorithm (LGA) was selected for docking, freezing, and default parameters used in Autodock Vina 1.5.6. By performing docking studies the binding modes of protein and their binding energies of ligands were estimated. Using SPDBV, the XYZ coordinates of PDB were selected. The interaction of ligand with the 1T9U and 3UZ0 protein

and ligand poses were analyzed and studied based on H-bonding poses to the receptor molecule and van der Waals interaction between the poses and receptor molecule. The unwanted co-factors, chains, and water molecules were removed.

Biological evaluation:

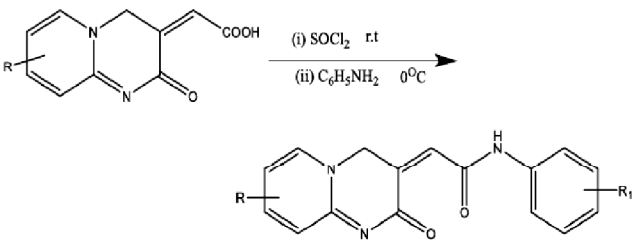
The *in vitro* antibacterial activity screened for the synthesized compounds against *Bacillus subtilis,* and *Escherichia coli* bacterial strains by disc diffusion method against the standard drug Ciprofloxacin (10 μg/disc). Each Petri dish was divided into four quadrants, in 3 quadrants, extract discs such as I (100 mcg), II (200 mcg), III (300 mcg) discs (discs are soaked overnight in extract solution). One quadrant for Standard Ciprofloxacin 5 mcg was placed in each quadrant with the help of sterile forceps. In the refrigerator at 40°C or at room temperature, Petri dishes were set for 1 h for diffusion. Incubate at 370°C for 24 h. The zone of inhibition was observed for different antibiotics. Measured it using a scale or divider or vernier calipers and recorded the average of two diameters of each zone of inhibition.

Results and discussion

The series of *N*-aryl amides of 2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene acetic acids were prepared usind standard procedure. The amides were prepared in two steps viz.

(i) Conversion of acid to acid chloride using thionylchloride.

(ii) Treatment of acid chloride with various amines to afford *N*-arylamides with moderate yields (Scheme 1).



R = H and 5-Me; R_1 = aniline, *p*-toludine, *p*-chloroaniline, *p*-anisidine, naphthylamine

Scheme 1

The synthesized compounds **A-H** were characterized by IR, ^{1}H, and ^{13}C NMR spectral measurements. IR displayed characteristic -NH band at 3243 cm^{-1} and at 1734 cm^{-1}, 1630 cm^{-1} for the two carbonyls. The ^{1}H NMR of the spectrum of the compound **A** exhibited peaks at δ 4.5 and 6.3 corresponding to H4 and H32, respectively. A multiplet at δ 7.0–8.0 was due to the pyridine and benzene nucleus of amine fragment. ^{13}C registered 16 signals, and the mass spectrum displayed M^+ peak at *m/z* 280, confirming the suggested structure.

Antibacterial activity:

By considering Ciprofloxacin (10 μg/disc) as a standard drug, the *in vitro* antibacterial studies of newly synthesized compounds were screened against *Bacillus subtilis* and *Escherichia coli* by disc diffusion method. The study revealed that the tested compounds (**A**-**H**) possess potential antibacterial activity against *Bacillus subtilis* and *Escherichia coli*. The zones of inhibition exhibited by the compounds ranged from 11–13 mm disc (Table 1). The relative susceptibility of

Table 1. Antibacterial activity of synthesised compounds (**A**-**H**) against *Bacillus subtilis* and *Escherichia coli* tested by disc diffusion assay

Compound	Zone of inhibition *Bacillus subtilis*			Standard Ciprofloxacin	Zone of inhibition *Escherichia coli*		
	50 μg/disc	100 μg/disc	150 μg/disc	(10 μg/disc) (mm)	50 μg/disc	100 μg/disc	150 μg/disc
A	11	12	13	25	10	11	12
B	10	11	11		11	12	12
C	12	11	11		13	13	17
D	10	11	11		10	11	12
E	11	12	13		12	11	11
F	11	11	13		11	12	12
G	10	12	12		12	14	12
H	09	10	11		10	11	11

the test microorganisms to a particular antimicrobe were indicated by the diameter of the inhibition zone.

The inhibition results at three concentrations viz. 50 μg, 100 μg, and 150 μg showed that the compounds are sensitive to bacteria at higher concentrations, the sensitivity decreases at lower concentrations. The compound **A** and **E** showed increased sensitivity to the bacteria *Bacillus subtilis,* while *Escherichia coli* compound **C** showed higher activity. The least activity was recorded for compound **B** for both the bacterial strains. The compounds from **A**-**H**, to inhibit bacterial species growth, indicate the compounds' broad-spectrum antibacterial potentials, which makes the synthesized compounds for bioprospecting for antibiotic drugs.

Docking studies:

Molecular docking studies are widely used for the computation of protein-ligand interactions. Docking studies were performed to find the binding affinities and key interactions between the active site of 1T9U and 3UZ0 protein and the newly synthesized compounds, using AutoDock Vina 1.5.6 software. The docking run generated nine different poses for each compound, and the corresponding binding energy scores were generated. The results of all the synthesized compounds and proteins with higher binding energy scores were summarized in Table 2. The compound's stability of the best-docked pose was evaluated by determining the protein's hydrogen-bonding interactions with compounds. Based on

Table 2. Docking results of the designed compounds (**A**-**H**) towards 1T9U and 3UZ0

Compound	PDB	Binding energy Δ*G* (kcal/mol)	PDB	Binding energy Δ*G* (kcal/mol)	Grid X-Y-Z coordinates
A	3UZ0	–10.4	1T9U	–10.7	40, 40, 40
B	3UZ0	–8.8	1T9U	–8.1	40, 40, 40
C	3UZ0	–9.3	1T9U	–9.2	40, 40, 40
D	3UZ0	–9	1T9U	–8.4	40, 40, 40
E	3UZ0	–8.9	1T9U	–8.6	40, 40, 40
F	3UZ0	–9	1T9U	–8.7	40, 40, 40
G	3UZ0	–9	1T9U	–8.5	40, 40, 40
H	3UZ0	–9.3	1T9U	–9.1	40, 40, 40

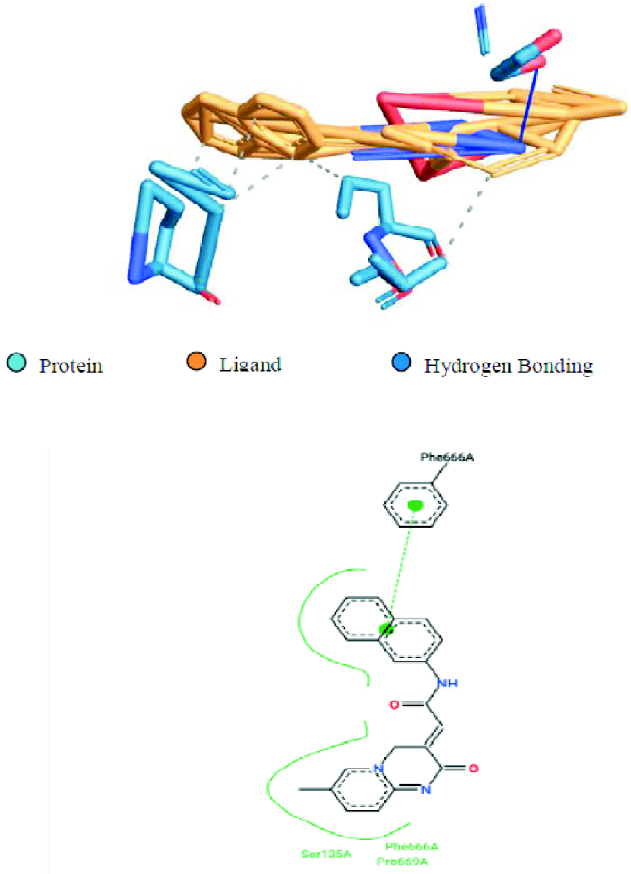


Fig. 1. 2D and 3D structure of (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide docked with protein 1T9U.

these factors, among all the compounds (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide shows the highest binding energy with 1T9U and 3UZ0 protein with binding energy Δ*G* –10.7 and –10.4 (kcal/mol) (Figs. 1 and 2). The docking score and H-bond interaction, van der Waal forces, were done for all the synthesized compounds. Binding energies were calculated; it consists of van der Waal forces, H-bonding, π-π interactions, cation-π interactions, etc. The hydrogen bonding distance for (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide with the proteins are 3 and 3.21 Å and donor angles are 134.72° and 114.91° respectively.

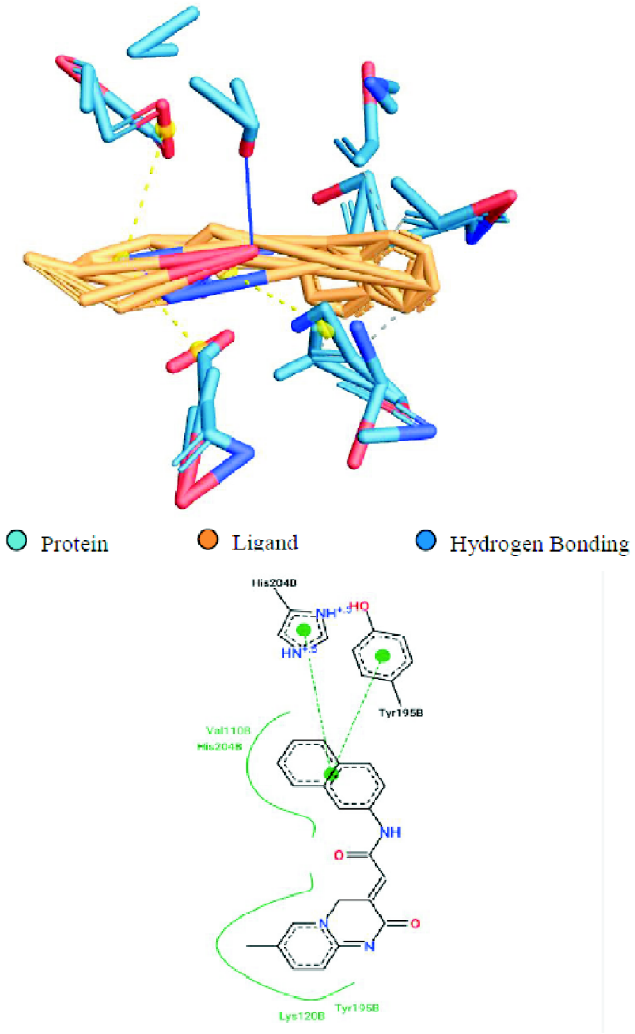


Fig. 2. 2D and 3D structure of (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide docked with protein 3UZ0.

Conclusion

In summary, a series of novel *N*-aryl amides of pyrido[1, 2-*a*]pyrimidin-2-ones were prepared and evaluated for their antibacterial activity against *Bacillus subtilis* and *Escherichia coli*, and Molecular docking studies also performed in which 3UZ0 and 1T9U as the target protein. Based on the result, we claim that (*Z*)-*N*-(naphthalene-2-yl)-2-(2-oxo-7-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetamide could serve as an effective antimicrobial compound to treat bacterial infections. We believe that this work on this unique moiety to explore its activities further helps humankind synthesize new drugs.

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