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Research Article

Synthesis, Antimicrobial Studies, and Molecular Docking Simulation of Novel Pyran, Pyrazole, and Pyranopyrazole Derivatives

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A group of compounds containing pyran, pyrazole, and pyranopyrazole were synthesized (**2**–**4**) using a facile and convenient protocol. The structure of the synthesized compounds was elucidated by spectroscopic and elemental analysis. *In vitro* antimicrobial evaluation was also performed for all synthesized derivatives against human pathogenic bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Bacillus subtilis* using chloramphenicol as a reference. It was depicted that compounds **3d**, **4b** displayed a high degree of inhibition against *Bacillus subtilis* and *Staphylococcus aureus*. Compounds **2d**, **4f** and **2d**, **4e**, **4f**, and **4e** had high inhibition effects against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively. The molecular docking study was performed against *S. aureus* bacteria to rationalize the binding affinities and the feasible modes of interaction with the active site of tyrosyl-tRNA synthetase. It was found that the synthesized compounds were well fit into the binding site of tyrosyl-tRNA synthetase. The obtained results were in good accordance with the experimental data. The data obtained were promising candidates for further development of novel heterocyclic scaffolds as therapeutics with high efficacy biomedical precursors.

1. Introduction

Infectious diseases remain one of the main causes of death in the world today [1, 2]. Nowadays, one of the major challenges that researchers face is developing new compounds to control a vast majority of diseases. Heterocyclic chemistry plays a leading role in the construction of antimicrobial, anti-inflammatory, and analgesic therapeutic agents. Pyrazole nucleus is one of the major heterocycles, which exhibits a diverse array of biological properties due to its similarity to different basic building blocks of the body. The first pyrazole pharmaceutical discovered phenazone was proven to possess antipyretic properties. This gave impetus for diversification of pyrazole derivatives with considerable medicinal interests and biological and industrial applications (Figure 1) [3, 4]. There are several FDA-approved drugs containing the pyrazole scaffold [5, 6]. Recently, new synthetic protocols have been developed to synthesize structurally diverse pyrazole derivatives [7, 8].

On the other hand, pyran derivatives have been extensively employed as medicine intermediates due to their useful biological and pharmacological potential such as diuretic, antibacterial, anticoagulant, spasmolytic, anticancer, hypnotic, and insecticide [9–11]. Furthermore, pyranopyrazoles are privileged heterocyclic scaffolds, which exhibit various important biological properties. Many pyranopyrazoles derivatives have been reported [12–14] for their diverse pharmacological activities [14–16] such as

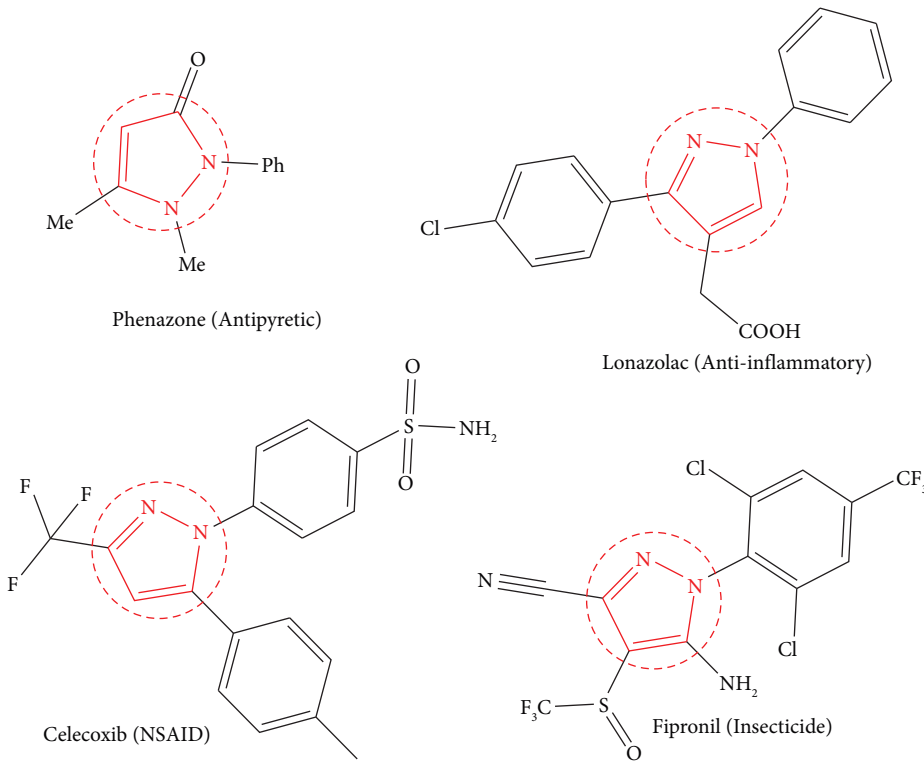


Figure 1: Different reported drugs bearing pyrazole scaffold.

antitumor [17], anticancer [18], antioxidant [19], and anti-inflammatory [20]. They also serve as potential inhibitors of human Chk1 kinase [21]. The innumerable applications of pyran, pyrazole, and pyranopyrazole analogs have stimulated researchers to develop new synthetic routes to prepare structurally diverse derivatives [8, 12, 15, 22, 23].

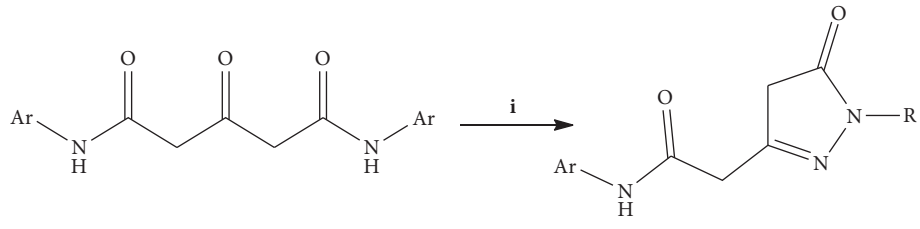
The approach of the present study combines the formation of substituted pyran and pyrazole rings with a variety of functional groups and a wide substrate scope. Meanwhile, the utilization of the synthesized derivatives for the construction of a series of new pyranopyrazole assemblies was performed, employing simple synthesis methods as well as the common one-pot multicomponent methodology [24].

2. Results and Discussion

2.1. Synthesis and Structure Elucidation. Compounds 3-oxo-N^1,N^5-diarylpentanediamides (**1a**, **b**) [25] were synthesized, characterized, and utilized as a key intermediate to achieve the required derivatives cited in the present study (Section 3). Thus, the reaction of compounds (**1a**, **b**) with hydrazine hydrate or phenyl hydrazine afforded pyrazole derivatives (**2a**–**d**). These reactions were carried out under reflux conditions using absolute ethanol and glacial acetic acid as solvents (Scheme 1). The structure of the produced pyrazole derivatives was proved using elemental data and spectroscopic studies (Section 3).

In addition, the reaction of compounds **1a**, **b** with 2-(4-chlorobenzylidene) malononitrile using piperidine afforded new pyran compounds **3a**, **b**, while the replacement of piperidine by ammonium acetate or aniline in an analogous manner successfully produced pyridine derivatives **3c**, **d** (Scheme 2). The microanalysis and spectroscopic data confirmed the structure of compounds **3a**–**d**. The IR spectra of **3a**–**d** revealed the disappearance of the characteristic ketonic carbonyl group, which was observed in the IR spectrum of **1a**, **b**, with the appearance of new NH_2 absorption bands at 3210–3293 cm^{-1} and sharp -CN absorption bands at 2202–2213 cm^{-1}. Furthermore, the ^{1}HNMR spectrum of compound **3a** showed the existence of a singlet signal at δ_{ppm} 10.31 (1H, NH D_2O exchangeable), singlet at δ 10.13 (1H, NH D_2O exchangeable) along with a multiplet at δ 7.63–7.00 (14H, Ar-) due to the aromatic protons, singlet signal at δ 6.93 (2H, NH_2 D_2O exchangeable), singlet at δ 4.70 (1H, -CH), and doublet of doublet at δ 3.71–3.61 (J = 15.9, 15.9 Hz, 2H, -CH_2), which may be due to H-transfer and the formation of diastereomeric pairs [26].

Pyrazoles **2a**–**d** were used as precursors to synthesize the fused pyranopyrazole derivatives **4a**–**f** (Scheme 3). A green one-pot multicomponent protocol was adopted for the synthesis of pyranopyrazole derivatives **4a**–**d** via the reaction of **2a**–**d** with malononitrile and p-chlorobenzaldehyde in water containing a catalytic amount of glycine, whereas **4e**, **f** were assembled by refluxing **2a**, **b** with ethyl cyanoacetate in ethanol as a solvent. The structure of the isolated compounds was established on the basis of spectroscopic and elemental analyses. The IR spectrum of compound **4a** as a representative example revealed the presence of a characteristic -CN absorption band at 2183 cm^{-1}, in addition to strong absorption bands at 3324, beside 3266 cm^{-1} (NH_2), 3131 cm^{-1} (NH), and 1646 cm^{-1} (CONH). Its ^{1}HNMR spectrum showed the existence of a singlet signal at δ_{ppm} 12.33 (1H,



1a,b

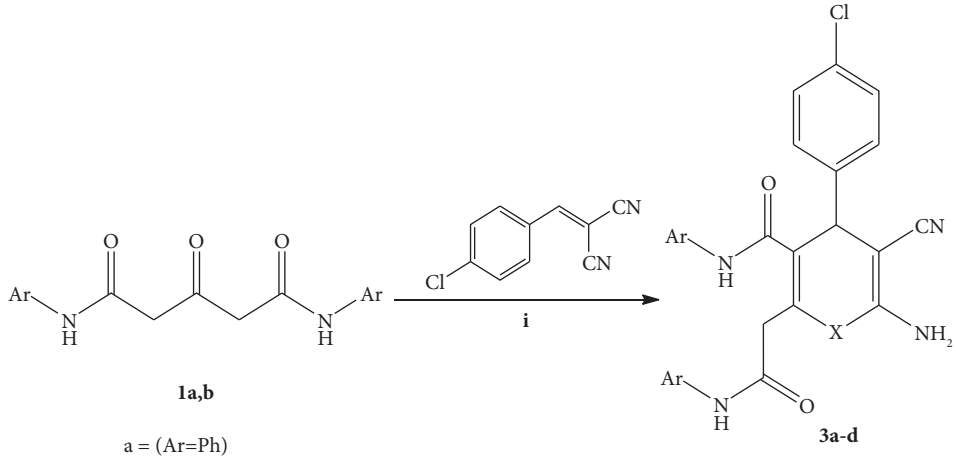
a = (Ar=Ph)
b = (Ar= 2-Cl-Ph)

2a-d

a = (Ar=Ph, R=H)
b = (Ar=Ph, R=Ph)
c = (Ar=2-Cl-Ph, R=H)
d = (Ar=2-Cl-Ph, R=Ph)

Reagents and conditions: (i) (a) hydrazine hydrate, EtOH, Reflux, 6 h; (b) phenyl hydrazine, acetic acid, Reflux, 6 h.

Scheme 1: Synthesis of pyrazole derivatives **2a**–**d**.



1a,b

a = (Ar=Ph)
b = (Ar= 2-Cl-Ph)

3a-d

a = (Ar=Ph, X=O)
b = (Ar= 2-Cl-Ph, X=O)
c = (Ar=Ph, X=NH)
d = (Ar=Ph, X=N-Ph)

Reagents and conditions: (i)EtOH, piperidine or ammonium acetate or aniline, Reflux, 1 h.

Scheme 2: Synthesis of pyran derivatives (**3a**–**d**).

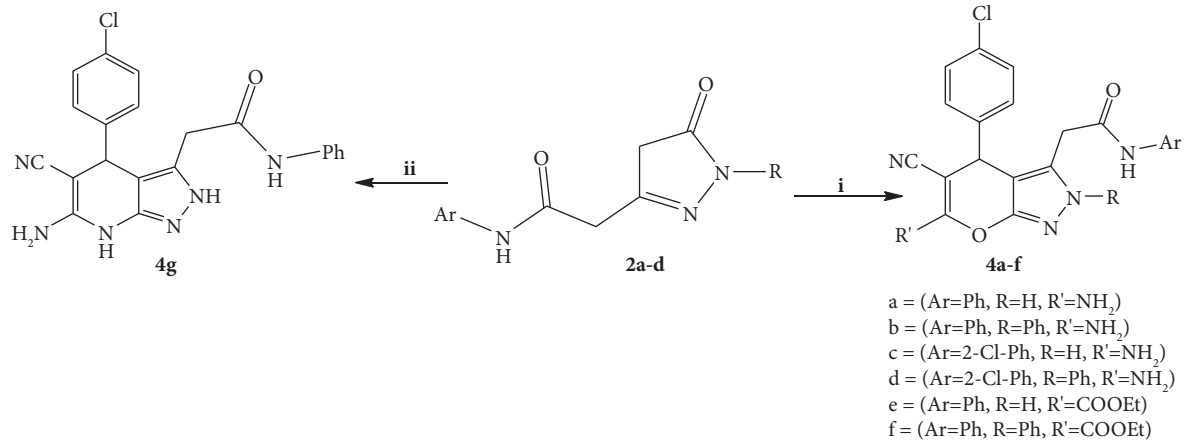
NH D_2O exchangeable), a singlet at δ 9.85 (1H, NH, D_2O exchangeable), a multiplet at δ 7.46–7.05 (9H, Ar-) related to the aromatic protons, a singlet signal at δ 6.95 (2H, NH_2 D_2O exchangeable), singlet at δ 4.65 (1H, CH), and doublet of doublet at δ 3.45–3.20 (J = 16.7 Hz, 16.6 Hz, 2H, -CH_2) [26].

Compound **2a** was further manipulated for the synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-4,7-dihydro-2*H*-pyrazolo[3,4-*b*]pyridine-3-yl)-*N*-phenylacetamide (**4g**) through the reaction with 2-(4-chlorobenzylidene)malononitrile and ammonium acetate in ethanol (Scheme 3). Moreover, the treatment of pyranopyrazole **4b** with p-anisidine in DMF under reflux afforded new pyridopyrazole compound (**4h**) (Scheme 4).

The structure of compound **4h** was confirmed by elemental analysis and spectroscopic data (Section 3).

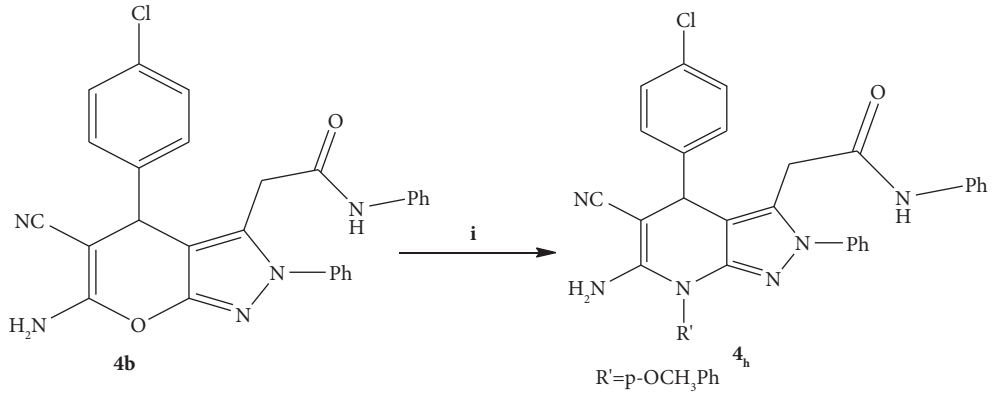
2.2. Antimicrobial Activity. The mentioned compounds were assessed against human pathogenic strains, and the results are represented in Table 1.

New derivatives of pyrazole, pyran, and pyranopyrazole were prepared and selected to screen their *in vitro* antimicrobial activity against Gram-positive bacteria such as *Bacillus subtilis* and *Staphylococcus aureus* and Gram-negative bacteria such as *Escherichia coli* and *Pseudomonas aeruginosa*. The organisms were assessed against the activity of 50 mg/mL solutions of each compound and using the diameter of the inhibition zone (IZ) in mm as the standard for the antimicrobial activity. The bactericide chloramphenicol was utilized as a reference to evaluate the efficacy of the tested compounds under the same conditions. The results in Table 1 depicted that compounds **3d**, **4b**



Reagents and conditions: (i) malononitrile or Et-cyanoacetate, 4-chlorobenzaldehyde, glycine, H2O, stirring, 30 min; (ii) 2-(4-chlorobenzylidene) malononitrile, ammonium acetate, Reflux, 10-12 h.

Scheme 3: Synthesis of pyranopyrazole derivatives (**4a**–**g**).



Reagents and conditions: (i) p-anisidine, DMF, Reflux, 5 h.

Scheme 4: Synthesis of pyranopyrazole derivatives (**4h**).

displayed a high degree of inhibition against *Bacillus subtilis* and *Staphylococcus aureus*. Compounds **2d**, **4f** and **2d**, **4e** had high inhibition effects against *Escherichia coli* and *Pseudomonas aeruginosa,* respectively. Compounds **2a**–**d**, **3a**, **b**, **d**, **4a**, **c**, **d**, **e**, **f**, **g**, **h** and **2a**–**d**, **3a**–**c**, **4a**, **c**, **d**, **e**, **f**, **g**, **h** also exhibited moderate inhibition effects against *Bacillus subtilis* and *Staphylococcus aureus*, respectively. Compounds **2a**–**c**, **3a**–**d**, **4a**–**e**, **g**, **h** and **2c**, **3a**–**d**, **4b**–**d**, **f**–**h** showed mild inhibition effects against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively. Compounds **3a**–**b**, **4a** were reflecting the lack of growth inhibition against *Pseudomonas aeruginosa*.

2.3. Molecular Docking Results. The molecular docking study indicated that these compounds may have moderate to high activity against *S. aureus* bacteria (Table 2). This activity may be strongly related to the interactions of the amino acids of *S. aureus* tyrosyl-tRNA synthetase in the binding site with these compounds. To explain the observed antibacterial activities of the prepared compounds, a molecular docking study was performed to determine their binding affinities into the binding site by calculating their estimated free binding energies, the number of the intermolecular hydrogen bonds along with the number, and the type of interactions that may be formed with the amino acids of tyrosyl-tRNA synthetase into its binding site (Table 2).

The synthesized compounds fit well into the binding site of tyrosyl-tRNA synthetase. The resulting complexes were found stable and showed negative binding energies in the range of −5 to −11 kcal/mol (Table 2). The negative binding energies indicated that the inhibition of tyrosyl-tRNA synthetase by these compounds was thermodynamically favorable. The synthesized compounds formed subsets. In the first subset, each compound was derived from another by the chlorine substation of the aromatic ring. The first subset was **2b/2d**, **2a/2c**, **4b/4d**, **3a/3b**, and **4a/4c**. In the second subset, the amine was substituted by the phenyl/methoxyphenyl moieties. The second subset was **3c/3d**, **4e/4f**, and **4g/4h**. For the first subset, it was observed that the chlorine

Table 1: *In vitro* antimicrobial activity of compounds **2a**–**d**, **3a**–**d**, and **4a**–**h** (inhibition zone in mm)[a].

Compounds		Antimicrobial activity							
		Bacterial species (G^+)				Bacterial species (G^-)			
		Bacillus subtilis		*Staphylococcus aureus*		*Escherichia coli*		*Pseudomonas aeruginosa*	
		IZ	RA%	IZ	RA%	IZ	RA%	IZ	RA%
Control: DMSO		0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Standard	Chloramphenicol	25	100	40	100	29	100	30	100
2a		21	84	16	40	15	51.7	—	—
2b		19	76	38	95	20	68.9	—	—
2c		21	84	12	30	29	100	25	83.3
2d		29	116	30	75	33	113.8	35	116.7
3a		27	108	30	75	29	100	29	96.7
3b		16	64	35	87.5	31	106.9	27	90
3c		15	60	30	75	28	96.6	29	96.7
3d		32	128	40	100	30	103.4	30	100
4a		25	100	30	75	15	51.7	—	—
4b		33	132	46	115	27	93.1	30	100
4c		28	112	35	87.5	21	72.4	27	90
4d		25	100	32	80	20	68.9	30	100
4e		20	80	32	80	29	100	32	106.7
4f		25	100	26	65	32	110.3	30	100
4g		21	84	31	77.5	30	103.4	30	100
4h		30	120	30	75	25	86.2	25	83.3

[a]G^+ = Gram positive; G^- = Gram negative; R.A. = relative activity; RA = $(IZ\ of\ sample\ compound/IZ\ of\ antibiotic) \times 100$; IZ: inhibition zone diameter (mm/mg sample).

Table 2: Binding free energies, hydrogen bonds, number of interactions of the closest residues and the docked synthesized compounds into the binding site of tyrosyl-tRNA synthetase.

Compound	Estimated free binding energy (kcal/mol)	H-bonds (HBs)	Number of interactions between the amino acids and the docked compounds into the binding site
2b	−8.05	5	10
2d	−8.43	5	10
2a	−6.63	4	9
2c	−6.86	4	8
4b	−9.28	2	15
4d	−7.71	3	15
3a	−9.93	1	10
3b	−10.31	2	12
4a	−9.76	7	12
4c	−9.94	7	13
3c	−9.51	2	10
3d	−10.28	3	17
4e	−8.88	4	12
4f	−9.34	4	12
4g	−9.26	5	11
4h	−5.79	4	15

substitution increased the antibacterial activity. For instance, the difference between **4a** and **4c** is the presence of chlorine substitution (Figure 2). The substituted chlorine atom interacted with ASP A195, which increased the stability of **4c**-tyrosyl-tRNA synthetase compared with that of **4a**-tyrosyl-tRNA. Thus, the increased antimicrobial activity of **4c** compared to that of **4a** is represented in Figure 2. For the second subsets, the amine substitution increased the antibacterial activity and led to the stability of the formed complex into the binding site of tyrosyl-tRNA synthetase. For instance, **3d** incorporated an aromatic group on imine functionality compared with **3c** (Figure 2). The aromatic ring interacted with LEU A70 and THR A75 through π-alkyl and π-donor hydrogen bonds, which increased the stability of the **3d**-tyrosyl-tRNA synthetase complex compared to that of the **3c**-tyrosyl-tRNA synthetase complex. Furthermore, in

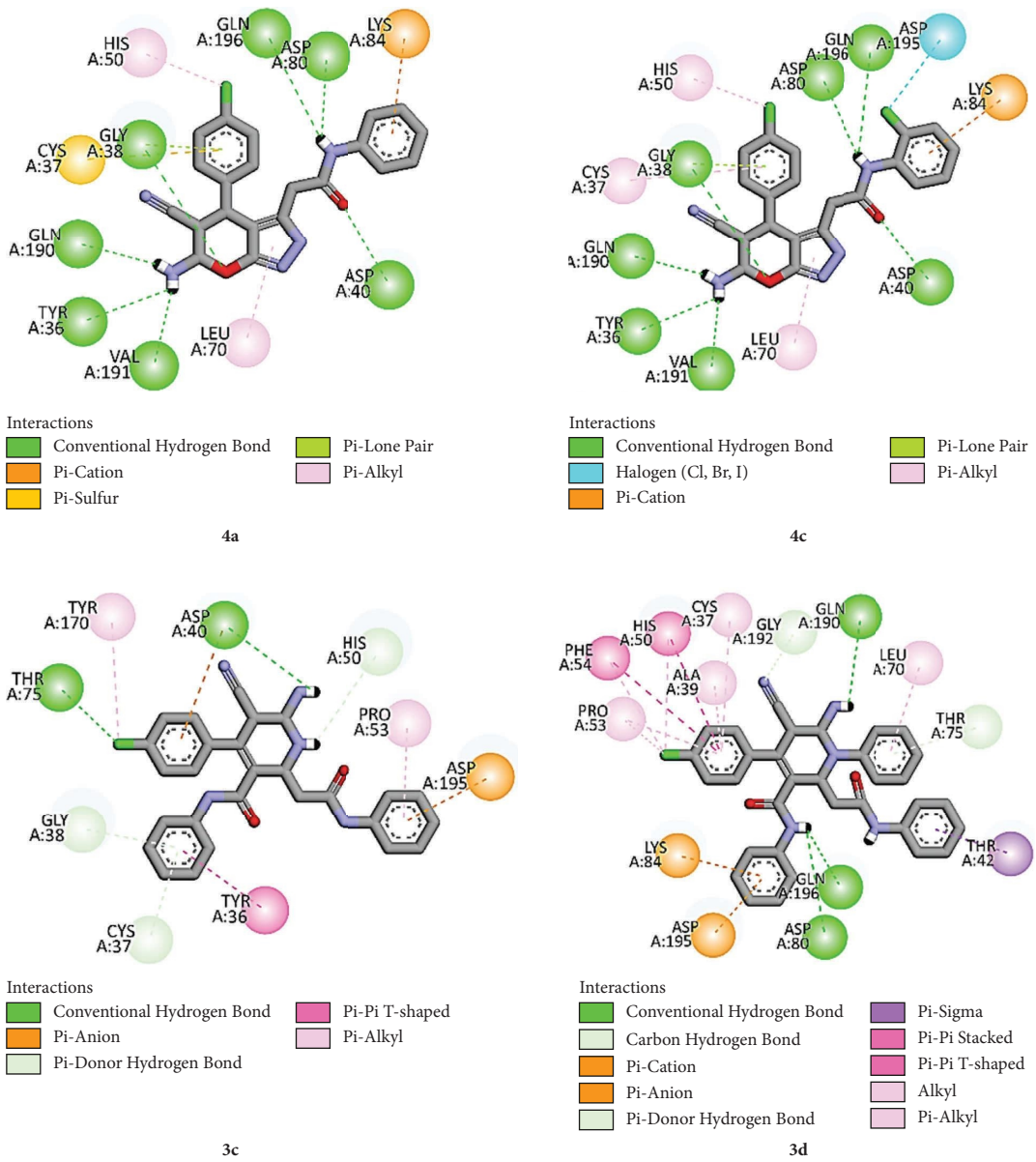


Figure 2: 2D closest interactions between active site residues of tyrosyl-tRNA synthetase and synthesized compounds **4a**, **4c**, **3c**, and **3d**.

the **3d**-tyrosyl-tRNA synthetase complex, the number of intermolecular interactions between **3d** and the active amino acids of tyrosyl-tRNA synthetase increased significantly, which may be due to the change in its geometry (Figure 2).

3. Materials and Methods

The melting points were determined with an electrothermal melting point device and were uncorrected. Pye-Unicam IR spectrophotometer SP 2000 was used to record the IR (KBr) spectra (Faculty of Science, Fayoum University). At the Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University, Nasr City, Cairo, mass spectroscopy was performed on a Direct Inlet part to mass analyzer in Thermo Scientific GCMS model ISQ. The purity of the compounds was verified using mass spectrometry, which was also utilized to investigate the distinctive fragmentation and the anticipated molecular weight. Mass spectroscopy was performed in electron impact mode. Nuclear magnetic resonance (NMR) spectra were measured in DMSO-d_6 (TMS, ^{1}H $\delta = 0$; DMSO-d_6, ^{1}H $\delta = 2.50$, ^{13}C $\delta = 39.52$) on a BRUKER AVANCE III (^{1}H at 400-MHz, ^{13}C at 100 MHz) magnetic resonance spectrometer at NMR unit, Faculty of Pharmacy, Beni-Suef University, Egypt. Chemical shifts (δ) and coupling constants (J) were recorded in parts per million (ppm) and Hertz (Hz), respectively.

The charts of ^{1}HNMR, IR, etc., from which we analyzed the synthesized compounds are available as a supplementary data file. The values were presented in the manuscript, and the charts were added for comparing the numbers and data in the manuscript with the analysis charts.

3.1. Synthesis

3.1.1. Synthesis of 3-Oxo-N^1,N^5-diphenylpentanediamide (1a). Diethyl-3-oxopentanedioate (20.2 mL, 0.1 mol) was refluxed with aniline (9.12 mL, 0.1 mol) in 30 mL pyridine for 4 h. The reaction mixture was cooled and poured over ice/HCl solution. The solid precipitate was filtered out, dried, and recrystallized from ethanol to give **1a** [25].

Compound 1a: off-white crystals; mp 138–140°C (Lit. [25] mp = 155°C); yield (23.68 mg, 80%).

3.1.2. Synthesis of N^1,N^5-bis(2-chlorophenyl)-3-oxopentanediamide (1b). Diethyl-3-oxopentanedioate (18.15 mL, 0.1 mol) was refluxed with 2-chloroaniline (10.54 mL, 0.1 mol) in 30 mL pyridine for 4 h. The reaction mixture was cooled and poured over ice/HCl solution. The solid precipitate was filtered out, dried, and recrystallized from ethanol to give **1b**.

Compound 1b: white crystals; mp 194–196°C; yield (27.36 mg, 75%); IR (KBr) ν/cm^{-1}: 3282 (2 NH), 1731 (C=O), 1658 (CONH); ^{1}HNMR (DMSO-d_6): δ 9.94 (s, 2H, 2 NH D_2O exchangeable), 7.39–6.88 (m, 8H, Ar-), 3.51 (s, 4H, $2CH_2$); ^{13}C-NMR (DMSO-d_6): δ 197.40, 169.12, 136.70, 129.55, 128.54, 127.21, 126.18, 121.18, 48.89. Ms m/z (%): 365 (M^+, 24.20), 128 (55.50), 77 (100). Anal. Calcd. For $C_{17}H_{16}N_2O_3$: (C, 55.91; H, 3.86; Cl, 19.41; N, 7.67%). Found (C, 55.70; H, 3.56; Cl, 19.12; N, 7.45%).

3.1.3. Synthesis of 2-(5-hydroxy-1H-pyrazol-3-yl)-N-phenylacetamide (2a). Hydrazine hydrate (0.5 mL, 0.01 mol) was added to a solution of 3-oxo-N^1,N^5-phenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) in 20 mL ethanol, and the mixture was refluxed for 2 h. The solid product was filtered off, washed with cold ethanol, and recrystallized from ethanol to give **2a** [25]. Compound 2a: white crystals; mp 240–242°C (Lit. [25] mp = 246°C); yield (2 gm, 95%).

3.1.4. Synthesis of 2-(5-hydroxy-1-phenyl-1H-pyrazol-3-yl)-N-phenylacetamide (2b). A solution of 3-oxo-N^1,N^5-diphenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) in 20 mL of glacial acetic acid was refluxed with phenylhydrazine (0.98 mL, 0.01 mol) for 3 h. The mixture was diluted with water and left overnight; the obtained solid was separated by filtration, washed with cold ethanol, and crystallized from ethanol to yield **2b** [25].

3.1.5. Another Method for the Synthesis of Compound 2b. Compound 3-Oxo-N^1,N^5-diphenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) and phenylhydrazine (0.98 mL, 0.01 mol) were taken in an agate mortar, and 2 mL of acetic acid was added. The mixture was vigorously ground by using a pestle until a pasty mass was obtained (30 min). The reaction mixture was triturated with ethanol and recrystallized from ethanol to yield **2b**.

Compound 2b: orange crystals; mp 184–186°C (Lit. [25] mp = 192°C); yield (2.63 gm, 90%).

3.1.6. Synthesis of N-(2-chlorophenyl)-2-(5-hydroxy-1H-pyrazol-3-yl)acetamide (2c). Hydrazine hydrate (0.5 mL, 0.01 mol) was added to a solution of N^1,N^5-bis(2-chlorophenyl)-3-oxopentanediamide **(1b)** (3.65 gm, 0.01 mol) in 20 mL ethanol and refluxed for 2 h. The resulting solid was filtered off, washed with cold ethanol, and recrystallized from ethanol to give **2c**. Compound 2c: white crystals; mp 270–272°C; yield (2.08 gm, 83%); IR (KBr) ν/cm^{-1}: 3247 (NH), 3104 (NH), 1658 (2CO); ^{1}HNMR (DMSO-d_6): δ 11.40 (s, 1H, OH D_2O exchangeable), 10.08 (s, 1H, NH D_2O exchangeable), 9.45 (s, 1H, NH D_2O exchangeable), 7.59–7.01 (m, 4H, Ar-), 5.38 (s, 1H, CH), 3.54 (s, 2H, CH_2). Anal. Calcd. For $C_{11}H_{10}ClN_3O_2$: (C, 52.50; H, 4.01; Cl, 14.09; N, 16.70%). Found (C, 52.36; H, 3.87; Cl, 13.90; N, 16.45%).

3.1.7. Synthesis of N-(2-chlorophenyl)-2-(5-hydroxy-1-phenyl-1H-pyrazol-3-yl)acetamide (2d). A solution of N^1,N^5-bis(2-chlorophenyl)-3-oxopentanediamide **(1b)** (3.65 gm, 0.01 mol) in 20 mL glacial acetic acid was refluxed with phenylhydrazine (0.98 mL, 0.01 mol) for 3 h. The mixture was diluted with water and left overnight; the obtained solid was separated by filtration, washed with cold ethanol, and crystallized from ethanol to yield **2d**.

Compound 2d: yellow crystals; mp 218–220°C; yield (2.87 gm, 88%); IR (KBr) ν/cm^{-1}: 3243 (NH), 1658 (2CO); ^{1}HNMR (DMSO-d_6): δ 11.64 (s, 1H, OH D_2O exchangeable), 10.29 (s, 1H, NH D_2O exchangeable), 7.76 - 7.24 (m, 9H, Ar-), 5.55 (s, 1H, CH), 3.57 (s, 2H, CH_2); ^{13}C-NMR (DMSO-d_6): δ 170.76, 168.68, 149.90, 138.55, 133.97, 128.54, 127.69, 127.21, 126.57, 126.18, 125.61, 121.18, 120.25, 46.18, 43.18. Anal. Calcd. For $C_{17}H_{14}ClN_3O_2$: (C, 62.30; H, 4.31; Cl, 10.82; N, 12.82%). Found (C, 62.15; H, 4.20; Cl, 10.56; N, 12.62%).

3.1.8. Synthesis of 6-Amino-4-(4-chlorophenyl)-5-cyano-2-(2-oxo-2-(phenylamino)ethyl)-N-phenyl-4H-pyran-3-carboxamide (3a). Compound 3-Oxo-N^1,N^5-diphenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) was dissolved in 50 mL of absolute ethanol; later, 2-(4-chlorobenzylidene) malononitrile (1.9 gm, 0.01 mol) was added with a few droplets of piperidine. The reaction mixture was refluxed for 1 h. The obtained solid was precipitated, filtered out after cooling, washed with cold ethanol, dried, and recrystallized from acetic acid to yield **3a**.

Compound 3a: white crystals; mp 248–250°C; yield (4.11 gm, 85%); IR (KBr) ν/cm^{-1}: 3471 (NH_2), 3293 (NH), 3189 (NH), 2202 (CN), 1693 (CO); ^{1}HNMR (DMSO-d_6): δ 10.31 (s, 1H, NH D_2O exchangeable), 10.13 (s, 1H, NH D_2O exchangeable), 7.63–7.00 (m, 14H, Ar-), 6.93 (s, 2H, NH_2, D_2O exchangeable), 4.70 (s, 1H, -CH), 3.71–3.61 (dd, J = 15.9, 15.9 Hz, 2H, -CH_2); ^{13}C-NMR (DMSO-d_6): δ 169.12, 165.13, 157.90, 155.47, 142.39, 139.91, 138.55, 131.14, 129.55, 128.54, 128.07, 127.21, 123.33, 122.47, 120.48, 120.25, 118.95, 103.89, 53.55, 46.05, 43.18. Ms m/z (%): 484 (M^+, 20.42), 365 (20.47), 81 (100). Anal. Calcd. For $C_{27}H_{21}ClN_4O_3$: (C, 66.87; H, 4.37; Cl, 7.31; N, 11.55). Found (C, 66.46; H, 4.23; Cl, 7.11; N, 11.23).

3.1.9. Synthesis of 6-Amino-N-(2-chlorophenyl)-4-(4-chlorophenyl)-2-(2-((2-chlorophenyl)amino)-2-oxoethyl)-5-cyano-4H-pyran-3-carboxamide (3b). N^1,N^5-bis(2-chlorophenyl)-3-oxopentanediamide **(1b)** (3.65 gm, 0.01 mol) was dissolved in 50 mL of absolute ethanol; later, 2-(4-chlorobenzylidene) malononitrile (1.9 gm, 0.01 mol) was added with a few droplets of piperidine. The reaction mixture was refluxed for 1 h; the solid precipitate was filtered out after cooling, washed with cold ethanol, dried, and recrystallized from acetic acid to yield **3b**.

Compound 3b: brown crystals; mp 120–122°C; yield (4.42 gm, 80%); IR (KBr) ν/cm^{-1}: 3266 (NH_2), 3193 (NH), 3124 (NH), 2183 (CN), 1658 (CO); ^{1}HNMR (DMSO-d_6): δ 10.08 (s, 1H, NH D_2O exchangeable), 9.09 (s, 1H, NH D_2O exchangeable), 7.63–7.00 (m, 12H, Ar-), 6.93 (s, 2H, NH_2 D_2O exchangeable), 4.91 (s, 1H, CH), 3.71–3.61 (dd, J = 15.9 Hz, 2H, CH_2). Anal. Calcd. For $C_{27}H_{19}Cl_3N_4O_3$: (C, 58.56; H, 3.46; Cl, 19.20; N, 10.12). Found (C, 58.32; H, 3.24; Cl, 19.01; N, 9.91).

3.1.10. Synthesis of 6-Amino-4-(4-chlorophenyl)-5-cyano-2-(2-oxo-2-(phenylamino)ethyl)-N-phenyl-1,4-dihydropyridine-3-carboxamide (3c). To an alcoholic solution of 3-oxo-N^1,N^5-diphenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) and 2-(4-chlorobenzylidene) malononitrile (1.9 gm, 0.01 mol), ammonium acetate (2.31 gm, 0.03 mol) was added. The reaction mixture was refluxed for 6 h, cooled, and added to ice/HCl. The precipitate product was filtered off, washed with water, dried, and recrystallized with an appropriate solvent.

Compound 3c: orange crystals; mp 184–186°C (ethanol); yield (2.94 gm, 61%); IR (KBr) ν/cm^{-1}: 3259 (NH_2), 3197 (NH), 3135 (NH), 2198 (CN), 1662 (CO); ^{1}HNMR (DMSO-d_6): δ 10.31 (s, 1H, NH D_2O exchangeable), 10.13 (s, 1H, NH D_2O exchangeable), 9.46 (s, 1H, NH D_2O exchangeable), 7.63–7.00 (m, 14H, Ar-), 6.56 (s, 2H, NH_2 D_2O exchangeable), 4.70 (s, 1H, CH), 3.71–3.61 (dd, J = 15.9 Hz, 2H, CH_2); ^{13}C-NMR (DMSO-d_6): δ 168.68, 165.36, 153.81, 148.52, 141.33, 139.58, 137.81, 131.14, 129.55, 128.07, 127.21, 124.35, 123.33, 120.25, 119.41, 118.95, 96.51, 57.20, 36.09, 33.92. Anal. Calcd. For $C_{27}H_{22}ClN_5O_2$: (C, 67.01; H, 4.58; Cl, 7.33; N, 14.47). Found (C, 66.86; H, 4.34; Cl, 7.09; N, 14.12).

3.1.11. Synthesis of 6-Amino-4-(4-chlorophenyl)-5-cyano-2-(2-oxo-2-(phenylamino)ethyl)-N,1-diphenyl-1,4-dihydropyridine-3-carboxamide (3d). To an alcoholic solution of 3-oxo-N^1,N^5-diphenylpentanediamide **(1a)** (2.96 gm, 0.01 mol) and 2-(4-chlorobenzylidene) malononitrile (1.9 gm, 0.01 mol), aniline (3.72 mL, 0.01 mol) was added. The reaction mixture was refluxed for 6 h, cooled, and added to ice/HCl. The precipitate product was filtered off, washed with water, dried, and recrystallized with an appropriate solvent.

Compound 3d: yellow crystals; mp 260–262°C (acetic acid); yield (2.96 gm, 53%); IR (KBr) ν/cm^{-1}: 3309 (NH_2), 3193 (NH), 2213 (CN), 1658 (CO); ^{1}HNMR (DMSO-d_6): δ 10.47 (s, 1H, NH D_2O exchangeable), 9.57 (s, 1H, NH D_2O exchangeable), 7.81–7.04 (m, 19H, Ar-), 6.44 (s, 2H, NH_2 D_2O exchangeable), 5.36 (s, 1H, CH), 4.09–3.90 (dd, J = 15.6 Hz, 2H, CH_2). Anal. Calcd. For $C_{33}H_{26}ClN_5O_2$: (C, 70.77; H, 4.68; Cl, 6.33; N, 12.51). Found (C, 70.56; H, 4.46; Cl, 6.12; N, 12.23).

3.1.12. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-2,4-dihydropyrano[2,3-c]pyrazol-3-yl)-N-phenylacetamide (4a). Compound 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(2a)** (2.17 gm, 0.01 mol) was added to a mixture of malononitrile (0.66 gm, 0.01 mol), 4-chlorobenzaldehyde (1.41 gm, 0.01 mol), and (2 mol%) glycine in 25 mL of water [27]. The reaction mixture was stirred vigorously for 30 min at 25°C. The solid obtained was separated by filtration, washed with cold ethanol, dried, and recrystallized with a suitable solvent.

Compound 4a: white crystals; mp 240–242°C (DMF/water); yield (3.64 gm, 90%); IR (KBr) ν/cm^{-1}: 3324 (NH_2), 3266 (NH), 3131 (NH), 2183 (CN), 1646 (CO); ^{1}HNMR (DMSO-d_6): δ 12.33 (s, 1H, NH D_2O exchangeable), 9.85 (s, 1H, NH D_2O exchangeable), 7.46–7.05 (m, 9H, Ar-), 6.95 (s, 2H, NH_2D_2O exchangeable), 4.65 (s, 1H, -CH), 3.45 - 3.20 (dd, J = 16.7 Hz, 16.6 Hz, 2H, -CH_2); ^{13}C-NMR (DMSO-d_6): δ 172.40, 162.63, 151.87, 139.58, 138.55, 134.84, 131.14, 128.54, 127.69, 127.21, 123.80, 121.18, 120.25, 105.32, 62.66, 36.48, 33.92. Ms m/z (%): 405 (M^+, 22.42), 285 (19.47), 195 (100). Anal. Calcd. For $C_{21}H_{16}ClN_5O_2$: (C, 62.15; H, 3.97; Cl, 8.73; N, 17.26). Found (C, 61.79; H, 3.43; Cl, 8.41; N, 16.88).

3.1.13. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-2-phenyl-2,4-dihydropyrano[2,3-c]pyrazol-3-yl)-N-phenylacetamide (4b). Compound 2-(5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(2b)** (2.93 gm, 0.01 mol) was added to a mixture of malononitrile (0.66 gm, 0.01 mol), 4-chlorobenzaldehyde (1.41 gm, 0.01 mol), and (2 mol%) glycine in 25 mL water. The reaction mixture was stirred vigorously for 30 min at 25°C. The obtained solid was separated by filtration, washed with cold ethanol, dried, and recrystallized with a suitable solvent.

Compound 4b: yellow crystals; mp 182–184°C (ethanol); yield (4.09 gm, 85%); IR (KBr) ν/cm^{-1}: 3328 (NH_2), 3193 (NH), 2194 (CN), 1654 (CO); ^{1}HNMR (DMSO-d_6): δ 9.93 (s, 1H, NH D_2O exchangeable), 7.84–7.01 (m, 14H, Ar-), 6.58 (s, 2H, NH_2 D_2O exchangeable), 4.76 (s, 1H, -CH), 3.67–3.56 (dd, J = 16.5 Hz, 13.2 Hz, 2H, -CH_2); ^{13}C-NMR (DMSO-d_6): δ 171.43, 162.31, 151.87, 139.91, 138.55, 138.23, 136.70, 132.01, 129.55, 128.54, 128.07, 127.21, 126.18, 122.47, 121.81, 121.18, 120.25, 108.72, 61.76, 38.14, 35.02. Anal. Calcd. For $C_{27}H_{20}ClN_5O_2$: (C, 67.29; H, 4.18; Cl, 7.36; N, 14.53). Found (C, 66.86; H, 3.92; Cl, 7.12; N, 14.18).

3.1.14. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-2,4-dihydropyrano[2,3-c]pyrazol-3-yl)-N-(2-chlorophenyl) acetamide (4c). A mixture of *N*-(2-chlorophenyl)-2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)acetamide **(2c)** (2.52 gm, 0.01 mol), malononitrile (0.66 gm, 0.01 mol), 4-chlorobenzaldehyde (1.41 gm, 0.01 mol), and (2 mol%) glycine in 25 mL water was vigorously stirred for 30 min at

25°C. The produced solid was filtered out, washed with cold ethanol, dried, and purified by crystallization.

Compound 4c: orange crystals; mp 186–188°C (DMF/water); yield (3.62 gm, 82%); IR (KBr) ν/cm^{-1}: 3459 (NH_2), 3320 (NH), 3205 (NH), 2183 (CN), 1677 (CO); ^{1}HNMR (DMSO-d_6) δ 12.23 (s, 1H, NH D_2O exchangeable), 9.75 (s, 1H, NH D_2O exchangeable), 7.36–6.95 (m, 8H, Ar-), 6.72 (s, 2H, NH_2 D_2O exchangeable), 4.55 (s, 1H, CH), 3.35–3.10 (dd, J = 16.7 Hz, 16.6 Hz, 2H, CH_2); ^{13}C-NMR (DMSO-d_6): δ 170.76, 161.31, 152.44, 139.58, 136.01, 134.84, 131.14, 128.54, 128.07, 127.21, 127.12, 126.18, 125.61, 122.47, 120.25, 103.89, 61.76, 37.59, 35.02. Anal. Calcd. For $C_{21}H_{15}Cl_2N_5O_2$: (C, 57.29; H, 3.43; Cl, 16.10; N, 15.91%). Found (C, 57.05; H, 3.21; Cl, 15.89; N, 15.73%).

3.1.15. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-2-phenyl-2,4-dihydropyrano[2,3-c]pyrazol-3-yl)-N-(2-chlorophenyl)acetamide (4d). A mixture of 2-(5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(2d)** (3.28 gm, 0.01 mol), malononitrile (0.66 gm, 0.01 mol), 4-chlorobenzaldehyde (1.41 gm, 0.01 mol), and (2 mol%) glycine in 25 mL water was vigorously stirred for 30 min at 25°C. The produced solid was filtered out, washed with cold ethanol, dried, and purified by crystallization.

Compound 4d: yellow crystals; mp 210–212°C (ethanol); yield (4.09 gm, 79%); IR (KBr) ν/cm^{-1}: 3320 (NH_2), 3197 (NH), 2202 (CN), 1662 (CO); ^{1}HNMR (DMSO-d_6): δ 9.83 (s, 1H, NH D_2O exchangeable), 7.71–6.91 (m, 13H, Ar-), 6.48 (s, 2H, NH_2 D_2O exchangeable), 4.66 (s, 1H, CH), 3.57–3.46 (dd, J = 16.5 Hz, 13.2 Hz, 2H, CH_2); ^{13}C-NMR (DMSO-d_6): δ 172.66, 161.31, 150.94, 138.23, 137.61, 136.28, 136.01, 132.01, 128.07, 128.05, 127.21, 126.57, 126.18, 124.35, 123.33, 122.98, 121.81, 121.18, 119.41, 108.72, 62.30, 37.59, 36.48. Anal. Calcd. For $C_{27}H_{19}Cl_2N_5O_2$: (C, 62.80; H, 3.71; Cl, 13.73; N, 13.56%). Found (C, 62.56; H, 3.43; Cl, 13.65; N, 13.34%).

3.1.16. Synthesis of Ethyl 4-(4-chlorophenyl)-5-cyano-3-(2-oxo-2-(phenylamino)ethyl)-2,4-dihydropyrano[2,3-c]pyrazole-6-carboxylate (4e). Compound **4e** was yielded by refluxing 2-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide (**2a**) (2.17 gm, 0.01 mol), ethyl cyanoacetate (1.1 mL, 0.01 mol), and 4-chlorobenzaldehyde (1.41 gm, 0.01 mol) in 15 mL absolute ethanol for 2 h. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

Compound 4e: pale gray crystals; mp 268–270°C; yield (3.7 gm, 80%); IR (KBr) ν/cm^{-1}: 3320 (NH), 3209 (NH), 2244 (CN), 1747 (CO ester), 1666 (CO amide); ^{1}HNMR (DMSO-d_6): δ 12.33 (s, 1H, NH D_2O exchangeable), 9.85 (s, 1H, NH D_2O exchangeable), 7.49–7.00 (m, 9H, Ar-), 4.65 (s, 1H, CH), 4.03 (q, J = 16.9 Hz, 2H, CH_2), 3.45–3.20 (dd, J = 16.7 Hz, 16.6Hz, 2H, CH_2), 1.31 (t, J = 21.3 Hz, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 171.76, 163.02, 156.77, 149.18, 139.58, 138.55, 134.84, 133.04, 130.04, 129.55, 128.07, 123.33, 120.25, 116.35, 106.22, 103.94, 67.22, 36.48, 35.94, 17.85. Anal. Calcd. For $C_{24}H_{19}ClN_4O_4$: (C, 62.27; H, 4.14; Cl, 7.66; N, 12.10). Found (C, 62.02; H, 3.87; Cl, 7.45; N, 11.90).

3.1.17. Synthesis of Ethyl 4-(4-chlorophenyl)-5-cyano-3-(2-oxo-2-(phenylamino)ethyl)-2-phenyl-2,4-dihydropyrano[2,3-c]pyrazole-6-carboxylate (4f). Compound **4f** was yielded by refluxing 2-(5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)-*N*-phenylacetamide **(2b)** (2.93 gm, 0.01 mol), ethyl cyanoacetate (1.1 mL, 0.01 mol), and 4-chlorobenzaldehyde (1.41 gm, 0.01 mol) in 15 mL absolute ethanol for 2 h. The formed precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

Compound 4f: pale yellow crystals; mp 282–284°C; yield (4.09 gm, 76%); IR (KBr) ν/cm^{-1}: 3320 (NH), 2256 (CN), 1743 (CO ester), 1666 (CO amidic); ^{1}HNMR (DMSO-d6) δ 9.93 (s, 1H, NH D_2O exchangeable), 7.84–7.01 (m, 14H, Ar-), 4.76 (s, 1H, CH), 3.93 (q, J = 13.5 Hz, 2H, CH_2), 3.40–3.16 (dd, J = 15.8 Hz, 16.3Hz, 2H, CH_2), 1.06 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 172.00, 162.63, 160.45, 150.45, 139.91, 138.55, 138.23, 136.70, 132.01, 128.54, 128.19, 128.07, 127.21, 126.18, 123.33, 122.98, 120.25, 117.86, 108.72, 107.49, 61.76, 36.09, 35.02, 16.47. Anal. Calcd. For $C_{30}H_{23}ClN_4O_4$: (C, 66.85; H, 4.30; Cl, 6.58; N, 10.40). Found (C, 66.56; H, 4.17; Cl, 6.25; N, 10.16).

3.1.18. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-(2-phenyl) 4,7-dihydro-2H-pyrazolo[3,4-b]pyridin-3-yl)-N-phenylacetamide (4g). Compound **2a** (2.17 gm, 0.01 mol) and 2-(4-chlorobenzylidene) malononitrile (1.89 gm, 0.01 mol) were refluxed in 30 mL of absolute ethanol for 10–12 h in the presence of ammonium acetate (2.31 gm, 0.03 mol). The reaction mixture was left to cool. The obtained solid was filtered off, dried, and recrystallized from ethanol to give **4g**. Compound 4g: pale orange crystals; mp 120–122°C; yield (2.46 gm, 61%); IR (KBr) ν/cm^{-1}: 3282 (NH_2), 3143 (NH), 2121 (CN), 1650 (CO); ^{1}HNMR (DMSO-d6) δ 12.33 (s, 1H, NH D_2O exchangeable), 9.85 (s, 1H, NH D_2O exchangeable), 7.96 (s, 1H, NH D_2O exchangeable), 7.49–7.00 (m, 9H, Ar-), 5.97 (s, 2H, NH_2), 4.65 (s, 1H, CH), 3.45–3.20 (dd, J = 16.7 Hz, 16.6 Hz, 2H, CH_2); ^{13}C-NMR (DMSO-d_6): δ 170.76, 153.90, 144.16, 139.91, 138.55, 134.84, 132.01, 129.55, 128.54, 128.07, 123.33, 121.18, 120.25, 105.32, 59.06, 36.09, 34.06. Anal. Calcd. For $C_{21}H_{17}ClN_6O$: (C, 62.41; H, 4.36; Cl, 7.67; N, 15.16). Found (C, 62.16; H, 4.22; Cl, 7.34; N, 15.02).

3.1.19. Synthesis of 2-(6-amino-4-(4-chlorophenyl)-5-cyano-7-(4-methoxyphenyl)-2-phenyl-4,7-dihydro-2H-pyrazolo[3,4-b]pyridin-3-yl)-N-phenylacetamide (4h). Compound 2-(6-amino-4-(4-chlorophenyl)-5-cyano-2-phenyl-2,4-dihydropyrano[2,3-*c*]pyrazol-3-yl)-*N*-phenylacetamide **(4b)** (4.81 gm, 0.01 mol) was added to a solution of p-anisidine (1.15 mL, 0.01 mol) in 30 mL dimethylformamide and refluxed for 5 h. The reaction mixture was cooled and added to ice/H_2O. The produced solid precipitate was filtered out, washed with water, dried, and recrystallized from acetic acid to afford **4h**. Compound **4h**: dark brown crystals; mp 148–150°C; yield (4.39 gm, 75%); IR (KBr) ν/cm^{-1}: 3216 (NH_2), 3135 (NH), 2206 (CN), 1662 (CO); ^{1}HNMR (DMSO-d_6) δ 10.47 (s, 1H, NH D_2O exchangeable), 7.82–7.05 (m, 18H, Ar-), 6.15 (s, 2H, NH_2

D_2O exchangeable), 4.99 (s, 1H, CH), 4.09–3.90 (dd, $J = 15.6$ Hz, 2H, CH_2), 3.49 (s, 3H, CH_3); ^{13}C-NMR (DMSO-d_6): δ 171.43, 154.97, 149.18, 147.38, 142.39, 139.58, 138.55, 134.84, 132.01, 129.55, 128.54, 127.12, 126.18, 122.98, 122.75, 121.18, 120.10, 114.33, 105.32, 63.28, 54.85, 41.74, 35.02. Anal. Calcd. For $C_{34}H_{27}ClN_6O_2$: (C, 69.56; H, 4.64; Cl, 6.04; N, 14.32). Found (C, 69.24; H, 4.43; Cl, 5.83; N, 14.15).

3.2. Antimicrobial Test. The semiquantitative disk diffusion procedure was used to evaluate the antimicrobial activity of the prepared compounds. The diameter of the inhibition zone around each disk was estimated in millimeters. All the procedures were performed according to the standard protocol of the NCCLS disk diffusion susceptibility method [28]. All the above tests were conducted in triplicates.

3.3. Molecular Docking Study. To further understand the experimental antimicrobial activity of the synthesized compounds against *S. aureus*, the molecular docking study was performed, and their binding affinities into *S. aureus* tyrosyl-tRNA synthetase were determined. The target tyrosyl-tRNA synthetase was downloaded from the RCSB website (PDB code 1JIJ) [29]. The intermolecular interactions of the prepared compounds into the binding site of tyrosyl-tRNA synthetase have been explored using the AutoDock package [30].

4. Conclusion

In the present study, a series of pyran, pyrazole, and pyranopyrazole derivatives were synthesized and their structure was elucidated. The synthesized compounds were then screened for their antimicrobial activity against some human pathogenic bacterial strains such as *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas aeruginosa* using chloramphenicol as a reference. Compounds **3c**, **4b** and **3d**, **4b** exhibited a high degree of inhibition against *Bacillus subtilis* and *Staphylococcus aureus*, respectively. Compounds **2d**, **4f** and **2d**, **4e** had a high inhibition effect against *Escherichia coli* and *Pseudomonas aeruginosa*, respectively. The docking studies of the prepared compounds **4a**, **c** indicated that the substituted chlorine atom in **4c** interacted with ASP A195, which increased the stability of **4c**-tyrosyl-tRNA synthetase compared with that of **4a**-tyrosyl-tRNA. Thus, **4c** had a higher antibacterial activity than **4a**. The data obtained from the theoretical calculations were promising candidates for further development as therapeutic precursors with high efficacy.

Data Availability

The data used to support the findings of this study can be made available upon reasonable request to the corresponding author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Supplementary Materials

The supplementary file containing the original analysis charts (FTIR, ^{1}HNMR, ^{13}C-NMR, and mass spectra) is available. (*Supplementary Materials*)

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