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Article

Novel 2-Acetamido-2-ylidene-4-imidazole Derivatives (El-Saghier Reaction): Green Synthesis, Biological Assessment, and Molecular Docking

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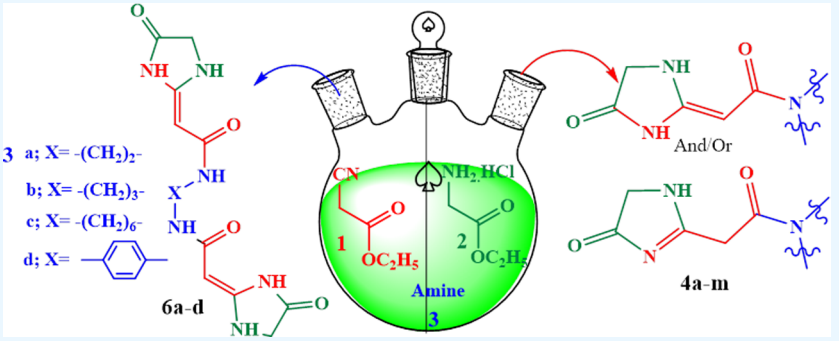

ABSTRACT: El-Saghier reaction is the novel, general, and green reaction of various amines with ethyl cyanoacetate and ethyl glycinate hydrochloride. A new series of imidazolidin-4-ones and bis-*N*-(alkyl/aryl) imidazolidin-4-ones was synthesized in a sequential, one-pot procedure under neat conditions for 2 h at 70 °C. Excellent high yields (90−98%) were achieved in a short period of time while avoiding issues related to the hazardous solvents utilized (cost, safety, and pollution). The spectrum analyses and elemental data of the newly synthesized compounds helped us to clarify their structures. The obtained compounds were tested for antibacterial activity in vitro and compared to the standard antibiotic chloramphenicol as the standard, measuring the inhibition zone (nm) and activity index (%). With an antibacterial percentage value of 80.0 against *Escherichia coli*, *N*,*N*′-(propane-1,3-diyl) bis(2-(4-oxo-4,5-dihydro-1*H*-imidazole-2-yl) acetamide) proved to be the most effective. Antimicrobial activity was confirmed by a molecular docking investigation to investigate how chemicals bind to the bacterial *FabH*−*CoA* complex in *E. coli* (PDB ID: 1HNJ).

1. INTRODUCTION

Substituted imidazoles are important moieties constituted in pharmaceuticals, pesticides, and bioactive compounds.[1,2] Many imidazoles with a single heterocyclic substituent in the 2-position serve as key intermediates in the synthesis of pharmaceutically active compounds.[3] It is vitally necessary to find novel compounds with robust antibacterial capabilities since many clinically relevant illnesses are now resistant to well-known families of antimicrobial reagents. The G protein-coupled receptor antagonist,[4] anticancer agents,[5] antibacterial activity,[6,7] as well as antifungal properties may all be produced chemically by altering the imidazolidine-4-one scaffold.[8,9] Antibiotic activity is one of these applications and one of the main areas of study for imidazolidine derivatives.[10,11] They were unsuitable for clinical usage due to their mild antibiotic action, though.

The described imidazolidin-4-ones, which are made from primaquine's amino acid derivatives, have strong gametocytocidal effects on *P. berghei*. As a result, imidazolidin-4-ones (**A**) are a unique class of 8-aminoquinoline antimalarials.[12] Additionally, several imidazolidinone derivatives with the pharmacophore di-aryl sulfonylurea were created and tested for their anticancer efficacy against a variety of human solid tumors. Due to the absence of methemoglobinemia or hypoglycemia after treatment, imidazolidine-2,4-diones (**B**) had greater cytotoxic activity than sulfur (**C**), indicating a distinct metabolic destiny. The chemotherapeutic efficacy of imidazole-4-one derivatives (**D**) as prospective anticancer medicines has received a lot of attention.[13] On the other hand, imidazole-5(4*H*)-one (**E**) reacted with active methylene reagents and was predicted to be more effective as an

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antibacterial agent[14] because these compounds have a pyrazole moiety (Figure 1).

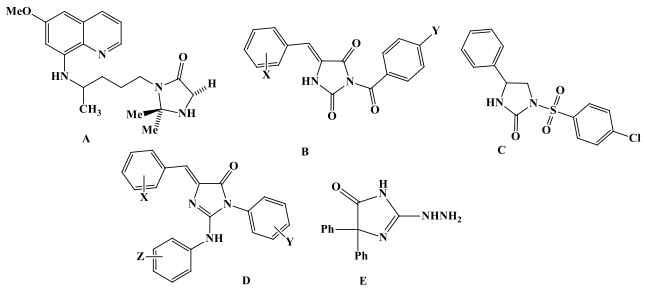


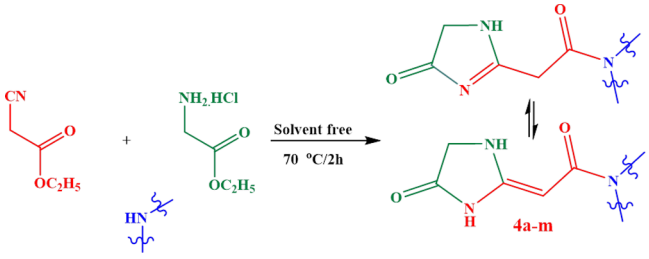
Figure 1. Structures of imidazolidin-4-one and imidazole-4-one literature biological activity analogues (**A**–**E**).

It has occasionally been attempted to develop libraries of imidazolidine-4-one and their derivatives due to their great synthetic relevance and diverse spectrum of bioactivities. Numerous synthetic techniques have been developed and improved to manufacture products with high yields, desired quality, and purity.[15,16] Considering these findings, the current framework was designed to discover a highly efficient, novel, and one-pot methodology toward the synthesis of imidazolidine-4-ones. The formation of pathogenic bacterial and fungal strains has been tested for by both generated compounds in a preliminary in vitro antimicrobial screening.

2. RESULTS AND DISCUSSION

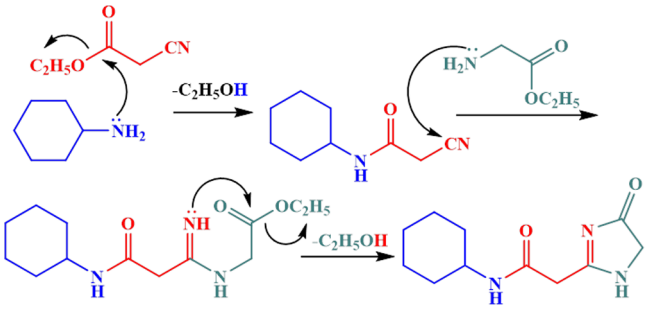
2.1. Chemistry. In keeping with our earlier efforts on the creation of a straightforward, universal technique for heterocyclic chemical synthesis to afford new derivatives,[17−22] we report here a fresh approach to the synthesis of imidazole-4-one and/or imidazolidin-4-one derivatives **4a**−**m** through the reaction of different amines with ethylcyanoacetate and ethylglycinate hydrochloride in a sequential, one-pot, procedure under neat condition for 2 h at 70 °C (Scheme 1).

Scheme 1. Synthesis of Imidazole-4-one and/or Imidazolidin-4-one Derivatives 4a−m in a Solvent-Free, Sequential One-Pot Method



The reaction mechanism involves a nucleophilic attack of the amine group of amines on the carbonyl group of ethylcyanoacetate with subsequent elimination of ethyl alcohol molecules to afford the corresponding cyanoacetamido derivatives **I**, after which comes the inclusion of the amino group of ethylglycinate hydrochloride on the cyano group (due to delocalization of the lone pair of nitrogen) to afford new intermediate **II** containing two active methylene groups, ester and imino groups. The active imino group had the opportunity to make another nucleophilic attack into the carbonyl carbon of ester and subsequent ring closure with elimination of another alcohol molecule to afford the desired products (Scheme 2).

Scheme 2. Reaction Mechanism for the Synthesis of *N*-Cyclohexyl-2-(4-oxo-4,5-dihydro-1*H*-imidazole-2-yl) Acetamide (4f)



To optimize the reaction conditions for the synthesis of imidazolidinones, the utilized catalyst was screened together with the reaction conditions, including the reaction medium, heating method, and reaction time, Table 1. Synthesis of *N*-

Table 1. Optimization of the Reaction Conditions for the Synthesis of Compound 4f

entry	heating mode/solvent	(one-pot)/reaction time (h)	additive	yield (%)
1	reflux/ethanol	4	no	25
2	80°C/1,4-dioxane	4	no	18
3	reflux/acetonitrile	4	no	20
4	70°C/1,4-dioxane	4	AcOH	19
5	reflux/1,4-dioxane	4	CAN	21
6	reflux/AcOH	4	no	50
7	120°C/neat	2	no	traces
8	100°C/neat	2	no	45
9	70°C/neat	2	LiBr	80
10	**70 °C/neat**	**2**	**no**	**90**

cyclohexyl-2-(4-oxo-4,5-dihydro-1*H*-imidazole-2-yl)acetamide (**4f**) was selected as a model reaction for this study and a sequential, consecutive reaction procedure was adopted. Cyclohexylamine was reacted with ethylcyanoacetate and then ethylglycinate hydrochloride was added (after treating with drops of triethylamine) in ethanol under reflux conditions for 4 h. Only 25% of the output included the intended product **4f**. We observed both procedures using nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectroscopy and thin-layer chromatography (TLC) to comprehend why the yield of **4f** was so low. In the TLC studies, cyclohexylamine was injected into an equimolar mixture of ethyl cyanoacetate and ethyl glycinate hydrochloride, and a yellow spot appeared 5 min later. The reaction mixture was characterized by ^{1}H NMR after the reaction had taken place for 1 h. The ^{1}H NMR and ^{13}C NMR spectra revealed that cyclohexylamine was entirely consumed but that ethyl glycinate hydrochloride did not completely react. Every hour, the combination of the reaction was described, and it was discovered that the rate at which the imidazole product formed was slower than expected. Impurities began to show up when the reaction time exceeded 2 h; however, cyclohexylamine was only totally consumed at a reaction time of 4 h. Considering this information, we propose that the inefficient nucleophilic substitution of the primary

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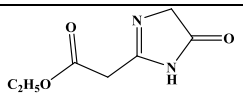
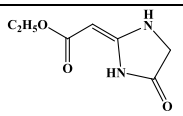
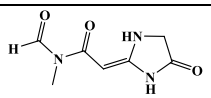
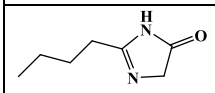
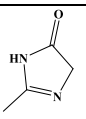
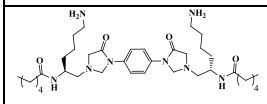
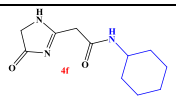
Table 2. Comparison between the Present Method with Respect to Other Methods in the Literature

Entry	Reaction conditions	Catalyst	solvent	Yield %	Ref.
	Condensation of ethyl glycinate and α,β-amino-carboxylic esters	Aminoacetic acid and cyanoacetic ester;	-	40	[23]
	Condensation of glycine ethyl ester and carbethoxyacetimidide ethyl ester at 0 °c, kept at R.T. for 24 h to afford the expected compounds	Magnesium sulphate	-	24	[24]
	Aqueous solution of 6-methyl-3H-imidazo[1,2-c]-pyrimidinium-2,7(6H)-dione p-toluene sulphonate stirred with sodium hydroxide at 0 °C	Aqueous Sodium hydroxide (0.2N)	H_2O	92	[25]
	To a solution of NaOH in MeOH at 0 °C was added methyl amino acetate hydrochloride in one portion at -11 °C.	Alcoholic Sodium hydroxide	MeOH; toluene	95	[26]
	A mixture of imidazole and oxidant (chloramine-B) in presence of aqueous perchloric acid was stirred at 30°C for 8-10 h.	Aqueous perchloric acid	H_2O	91.6	[27]
	Paraformaldehyde and K_2CO_3 were used to form the imidazolidine-4-one ring according to the methodintroduced previously [11].	Paraformaldehyde, K_2CO_3	TFA, DCM	20	[28]
	Cyclohexylamine was reacted with ethyl cyanoacetate then adding ethyl glycinate hydrochloride at 70°C	-	-	90	Our work

amine for the ethyl cyanoacetate is a factor in the reaction's lower yield. We attempted using 1,4-dioxane or acetonitrile as the solvent in this step to increase its effectiveness, but the reaction times remained lengthy, and the yield did not improve. To improve the amine's nucleophilicity, acids like AcOH or Lewis acids like CAN were added, but the yield remained poor. Lastly, we completed this stage under neat conditions at different temperatures since it was proposed that this would be able to give effective heating. Surprisingly, at 70 °C, cyclohexylamine was totally consumed in 2 h, no side products formed, and the yield of **4f** was greatly enhanced to 90%.

The mentioned examples use partial data from a published report of imidazolidine-4-one moieties.[23−28] Here, the authors discuss and illustrate the design, reaction conditions, solvent, catalyst, yield, and interpretation of a method-comparison study in the literature related to our new method as shown in Table 2. This comparison revealed that this article describes a new and creative class of dimer compounds that combine basic substrates with an advanced structure. The majority of these "monomers" are also fresh substances. Methods from the field of so-called "green chemistry" were applied to their synthesis.

Then, if possible, we wanted to streamline the process and do without the solvent. As a result, we performed the reaction at a variety of temperatures and neat conditions, and the outcomes were quite positive. When LiBr was added, the yield did not increase any further. Finally, it was discovered that the reaction was also extremely effective when carried out in conditions free of solvent. As can be seen in Table 3, several imidazole-4-one and/or imidazolidin-4-one derivatives were synthesized under the ideal conditions. Four different secondary amines (including dimethylamine, diethylamine, piperidine, and morpholine), three different primary aliphatic amines (such as ethanolamine, cyclohexylamine, and benzyl amine), six different primary aromatic amines (such as aniline, 1-napthyl amine, *o*-toluidine, *p*-methoxyaniline, *p*-chloroaniline, and *p*-nitroaniline were used, and the imidazolidine-4-ones were all prepared with a variety of yields. We note the yield increase in the case of the aliphatic primary amine being more than that of the secondary one followed by the aromatic amines. Also, in the case of aromatic amines, the yield was increased by the presence of a donating group in the aromatic ring than a withdrawing group.

Besides the imidazolidine-4-ones, symmetrical bis-*N*-(alkyl/aryl) imidazolidine-4-ones could also be obtained easily. 1 equiv of the aliphatic and aromatic compound has two amino groups (such as 1,2-diaminoethane, 1,3-diaminopropane, 1,6-diaminohexane, and 1,4-phenylenediamine), 2 equiv of ethyl cyanoacetate, and 2 equiv of ethylglycinate hydrochloric acid, which were mixed and subjected to heat at 70 °C for 2 h, and high yields of the desired products were produced (Scheme 3), and Table 4. Also, we noted that the reaction was completed after 2 h and triturated with cold water, and the yield was improved in the case of the reaction being left overnight and then separated. The method described here offers a good option for the manufacture of these kinds of compounds

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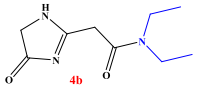
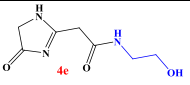
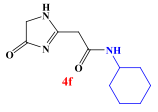
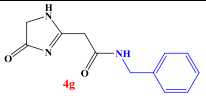
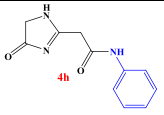
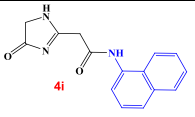
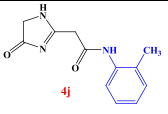
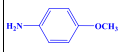
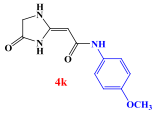
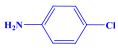
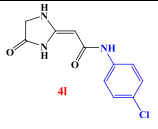
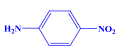
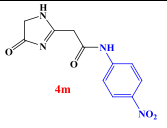
Table 3. Synthesis of Imidazole-4-one and/or Imidazolidin-4-one Derivatives 4a−m from Simple Amines in a Sequential, One-Pot Procedure

Entry	Amine (**3a-m**)	Product (**4a-m**)	m.p./ °C	Yield (%)
1			150	92
2			122	98
3			160	90
4			148	88
5			234	82
6			174	90
7			154	85
8			231	77
9			218	74
10			210	80
11			275	67
12			244	74
13			253	61

because it is extremely effective, user- and environment-friendly, and cost-effective.

There is another optimization in this reaction depending on the molar ration of the reactants, where we find that excellent yields were isolated when we used 1.0 mol of amine, 1.0 mol ethyl cyanoacetate, and 1.20 mole ethylglycinate hydrochloric acid as shown in Table 5.

Spectral and elemental analyses of the newly produced chemicals validated their structures. The IR spectra of the obtained compounds showed characteristic bands belong to two C═O group bands, one of amidic group and the other for imidazoline moieties were observed at 1629−1655 and 1652−1712 cm^{-1}, whereas the ^{1}H NMR spectra of imidazoline moieties were observed at 3.56−4.33 ppm as singlet signal belong to methylene group, at 7.63−9.48 ppm as singlet signal belong to NH proton disappeared by D_2O. In the ^{13}C NMR spectra of the compounds, C=O group of imidazolines was observed at 170.14−177.44 ppm, the C═N group at 151.55−161.30 ppm, and -CH_2 group of imidazoline moieties at 48.64−66.57 ppm. The accuracy range of the data from the elemental analysis was 0.04% (see, Supporting Information Figures S1−S39).

2.2. Antimicrobial Activity. Pathogenic bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*as Gram-negative bacteria and *Staphylococcus aureus*, and *Bacillus cereusas* Gram-positive bacteria, as well as fungi such as *Aspergillus flavus*, *Trichophyton rubrum*, and *Candida albicans*, have been tested using the well diffusion method.[29−31] The antimicrobial experiment was performed with DMSO as a solvent and the results were recorded as the inhibition zone diameter (IZ, mm) at 100 ppm,[32,33] Table 6.

The activity index (%) was determined by comparing the synthesized compounds' biological activity to that of the gold standard for antibiotics, chloramphenicol, Table 6. Biological activity data show that the produced compounds are effective against the bacteria and fungi studied, Table 6. **6b** showed strong action against all the designated bacteria and fungi. The activity index of the named compounds also varied widely from 42.1% for **6c** (against *Staphylococcus aureus*, as Gram-positive bacteria) to 80.0% (against *Escherichia coli*, as Gram-negative bacteria) in the range of tested bacteria.

In addition, when compared to the gold standard for antibiotics, chloramphenicol and the synthesized compounds had impressive antibacterial/antifungal efficacy, Table 6.

2.3. Molecular Docking. Molecular docking research was carried out to determine the interactions and orientations of the synthesized compounds with the active site of the target protein.[34−36] Molecular operating environment (MOE) was used to conduct molecular docking on the *E. coli FabH−CoA* complex (PDB ID: 1HNJ) in this research.[37,38] Targeting the fatty acid synthesis receptor FabH allows researchers to assess the drugs' efficacy against bacteria. The crystal structure of the *E. coli FabH−CoA* complex was obtained from the Protein Data Bank database (PDB ID: 1HNJ; URL: http://www.rcsb.org).[39,40] The binding mechanisms of the named medicines to docking score (*S*, kcal/mol) and interactions with hydrogen bonds were used to evaluate the target receptor, Figure 2, and Table 7.

The subject substrates' extensive hydrogen bonds and hydrophobic interactions with the target receptor are the cause of the subject substrates' high negative docking scores (*S*), as shown in Figure 2 and Table 7. This demonstrates how docked substrates are located relatively near to the receptor's active site.[41−43] The inhibitory action in 1HNJ was arranged as follows: **6b** > **6a** > **4g** > **4f** > **4m** > **6d** > **4h** > **4d** > **4b** > **4k** >

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Scheme 3. Synthesis of bis-*N*-(Alkyl/Aryl) Acetamido-2-ylidene-4-imidazole Derivatives 6a−d

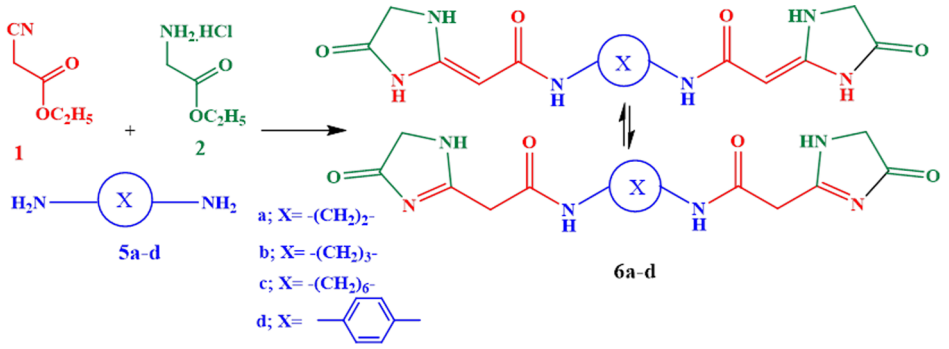


Table 4. Formation of Symmetrical Compound (6a−d) under the One-Pot Condition

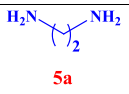
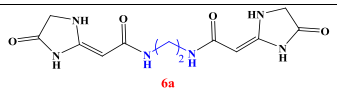
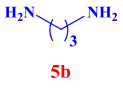
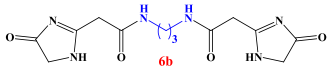
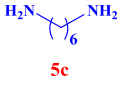
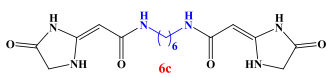
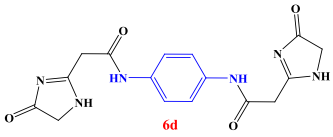
Entry	1°Amine (**5a-d**)	Product (**6a-d**)	m.p. (°C)	Yield(%)
14	 5a	 6a	202	96
15	 5b	 6b	233	92
16	 5c	 6c	215	94
17	 5d	 6d	266	89

Table 5. Optimization of the Reaction Molar Ratio for the Synthesis of Compound 4f

entry	cyclohexylamine	ethyl cyanoacetate	ethylglycinate hydrochloride	yield (%)
1	1	1	1	75
2	1	1	1.2	90
3	1.2	1	1.2	80
4	1	1.2	1.2	80
5	1	1	1.5	85

4c > **6c** > **4i** > **4j** > **4e** > **4a**. Compound **6b** is the most active of the compounds according to the docking studies.

Table 7 displays that the subject compounds showed a strong docking score of −5.40 (**4a**) to −8.72 (**6b**) kcal/mol toward the *E. coli FabH−CoA* complex. A high docking score (−8.72 kcal/mol) suggests that **6b** is the most energetic. **6b** found five hydrogen bond interactions: N5 with MET 207, O9 with CYS 112, O9 with ASN 274, O17 with LEU 191, and O24 with ASN. When evaluating a molecule for its potential as a hit and lead or therapy candidate, the inhibition constant (K_i value) is an important factor. For a molecule to be called a hit or lead compound, its K_i value must be low, typically in the micromolar (μM) range, because a low K_i value is often indicative of high potency.[44−46] 1HNJ domain Ki values for the synthesized compounds ranged from 0.41 (**6b**) to 79.51, making them all candidates for hits and leads (**4b**). It appears that **6b**, which had the second-lowest K_i value among the produced compounds, could be a potential therapeutic option, Table 7.

3. MATERIALS AND METHODS

3.1. Chemistry. At El-Gomhouria Company for Drugs in Egypt, all the chemicals were readily available for purchase, and they were all used without additional purification. The uncorrected melting points were all determined in open-glass capillaries using a Griffin melting point equipment. On a Perkin Elmer 1430 infrared spectrophotometer, IR spectra were captured. At Sohag University in Egypt, ^{1}H NMR and ^{13}C NMR spectra were recorded using a Jeol-400 MHz NMR-spectrometer (DMSO-d_6) and $CDCl_3$ (see the Supporting Information). Tetramethylsilane (TMS) is used as an internal standard, and the chemical shifts are presented in ppm downfield. The Vario El Fab-Nr elemental analyzer underwent micro studies. A Hewlett Packard 5988 spectrometer was used to record the mass spectra (Microanalysis Center, Cairo University, Egypt). It was done by using TLC to monitor the reactions.

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Table 6. Antimicrobial Data of the Studied Compounds

	bacteria								fungi					
	Gram-negative bacteria				Gram-positive bacteria				*Aspergillusflavus*		*Trichophytonru-brum*		*Candida albicans*	
	Pseudomonas aeruginosa		*Escherichia coli*		*Staphylococcus aureus*		*Bacillus cereus*		IZ, nm	%	IZ, nm	%	IZ, nm	%
	IZ, nm	%	IZ, nm	%	IZ, nm	%	IZ, nm	%						
6b	14	66.7	16	80.0	10	52.6	12	60.0	12	66.7	13	68.4	12	60.0
4b	12	57.1	14	70.0	12	63.2	13	65.0	15	83.3	15	78.9	13	65.0
4f	14	66.7	12	60.0	13	68.4	14	70.0	14	77.8	15	78.9	14	70.0
4g	11	52.4	14	70.0	12	63.2	13	65.0	15	83.3	14	73.7	13	65.0
4m	10	47.6	12	60.0	10	52.6	11	55.0	13	72.2	13	68.4	11	55.0
4d	12	57.1	12	60.0	12	63.2	12	60.0	13	72.2	12	63.2	12	60.0
4c	13	61.9	15	75.0	13	68.4	14	70.0	13	72.2	14	73.7	14	70.0
6a	11	52.4	11	55.0	9	47.4	10	50.0	11	61.1	12	63.2	10	50.0
4k	10	47.6	10	50.0	8	42.1	11	55.0	10	55.6	11	57.9	10	50.0
4j	11	52.4	13	65.0	11	57.9	12	60.0	14	77.8	14	73.7	12	60.0
4h	12	57.1	11	55.0	9	47.4	10	50.0	11	61.1	12	63.2	10	50.0
6c	9	42.9	10	50.0	8	42.1	10	50.0	10	55.6	11	57.9	9	45.0
4e	9	42.9	9	45.0	7	36.8	10	50.0	9	50.0	10	52.6	9	45.0
4a	13	61.9	13	65.0	11	57.9	12	60.0	14	77.8	13	68.4	12	60.0
6d	10	47.6	10	50.0	8	42.1	10	50.0	10	55.6	11	57.9	9	45.0
4i	11	52.4	12	60.0	10	52.6	12	60.0	12	66.7	13	68.4	12	60.0
chloramphenicol	21		20		19		20		18		19		20	

3.2. General Procedure for the Synthesis of 4-Imidazolinone and/or 4-Imidazolidinone Derivatives 4a−m. An equimolar mixture of amines **3a−m** (0.001 mol) and ethylcyanoacetate **1** (0.001 mol) was fused together for 15 min and then 0.0012 mol of ethyl glycinate hydrochloride **2** (treated with an equimolar amount of triethylamine before addition to activate the amino group) was added and the reaction time of 2 h was completed at 70 °C to obtain the equivalent imidazole-4-one/imidazolidine-4-one **4a−m**. The precipitates were recovered by filtration, extensively washed with water, and recrystallized from ethanol.

*3.2.1. N,N-Dimethyl-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (**4a**).* Yield (92%), pale yellow needles, mp 150 °C, anal. data: ($C_7H_{11}N_3O_2$, 169.18), Calcd: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.64; H, 6.60; N, 24.85. IR (ν_{max}, cm^{-1}): 3387 (NH), 2982 (CH_{aliph}), 1722 (CO), 1662 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.21 (s, 6H, $2CH_3$), 3.41 (s, 2H, CH_2−CO), 3.76 (s, 2H, $CH_{2imidazole}$), 9.15 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 30.15, 41.95, 55.12, 161.23, 166.47, 185.47.

3.2.2. N,N-Diethyl-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (4b). Yield (98%), pale yellow needles, mp 122 °C, Anal. data: ($C_9H_{15}N_3O_2$, 197.23), Calcd: C, 54.81; H, 7.67; N, 21.30. Found: C, 54.73; H, 7.85; N, 21.20. IR (ν_{max}, cm^{-1}): 3402 (NH), 2975 (CH_{aliph}), 1745 (CO), 1640 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 1.21 (t, 6H, J = *7.20 Hz*, $2CH_3$), 3.41 (s, 2H, CH_2−CO), 3.76 (s, 2H, $CH_{2imidazole}$), 4.20 (q, 4H, J = *7.14 Hz*, $2CH_2$), 8.54 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 14.40, 45.45, 57.23, 62.00, 158.32, 167.12, 173.55.

*3.2.3. (E)-2-(2-Oxo-2-(piperidin-1-yl)ethylidene)-imidazolidin-4-one (**4c**).* Yield (90%), pale yellow needles, mp 160 °C, Anal. data: ($C_{10}H_{15}N_3O_2$, 209.24), Calcd: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.33; H, 7.27; N, 20.11. IR (n_{max}, cm^{-1}): 3240 (NH), 2989 (CH_{aliph}), 1713 (CO), 1653 (CO). ^{1}H NMR ($CDCl_3$): δ ppm 1.19−1.22 (m, 4H, $2CH_{2pip}$), 1.52−1.55 (m, 2H, CH_{2pip}), 3.86 (s, 2H, $CH_{2imidazole}$), 4.06−4.16 (m, 4H, $2CH_2$-N_{pip}), 5.05 (s, 1H, =CH), 8.86 (s, 1H, NH, exchangeable by D_2O), 10.53 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR ($CDCl_3$): δ ppm 13.75, 26.08, 31.05, 60.19, 88.77, 155.35, 166.93, 172.16.

*3.2.4. (E)-2-(4-Hydroxy-1H-imidazole-2(3H)-ylidene)-1-morpholinoethanone (**4d**).* Yield (74%), pale yellow needles, mp 148 °C, Anal. data: ($C_9H_{13}N_3O_3$, 211.22), Calcd: C, 51.18; H, 6.20; N, 19.89. Found: C, 51.11; H, 6.23; N, 19.93. IR (n_{max}, cm^{-1}): 3238 (NH), 2991 (CH_{aliph}), 1713 (CO), 1653 (CO). 1H NMR ($CDCl_3$): δ ppm 3.73 (s, 1H, OH, exchangeable by D_2O), 3.77 (m, 4H, $2CH_2$−N), 4.21 (m, 4H, $2CH_2$−O), 5.14 (s, 1H, CH=C−NH), 5.63 (s, 1H, CH=$_{imidazole}$C−OH), 9.48 (s, 1H, NH, exchangeable by D_2O), 10.64 (s, 1H, NH, exchangeable by D_2O). ^{13}C MR ($CDCl_3$): δ ppm 14.27, 31.44, 60.17, 89.14, 155.34, 167.37, 172.18.

*3.2.5. (E)-N-(2-Hydroxyethyl)-2-(4-oxoimidazolidin-2-ylidene)acetamide (**4e**).* Yield (77%), white needles, mp 234 °C, Anal. data: ($C_7H_{11}N_3O_3$, 185.23), Calcd: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.33; H, 7.27; N, 20.11. IR (ν_{max}, cm^{-1}): 3238 (OH), 3175 (NH), 2989 (CH_{aliph}), 1712 (CO), 1692 (CO). ^{1}H NMR ($CDCl_3$): δ ppm 3.63 (s, 1H, OH, exchangeable by D_2O), 3.86 (s, 2H, $CH_{2imidazole}$), 4.06−4.16 (m, 4H, $2CH_2$), 5.05 (s, 1H, CH), 5.50 (s, 1H, NH, exchangeable by D_2O), 8.70 (s, 1H, NH, exchangeable by D_2O), 10.54 (s, 1H, NH, exchangeable by D_2O).

*3.2.6. N-Cyclohexyl-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (**4f**).* Yield (90%), pale yellow needles, mp 174 °C, Anal. data: ($C_{11}H_{17}N_3O_2$, 223.23), Calcd: C, 59.17; H, 7.67; N, 18.82. Found: C, 59.19; H, 7.69; N, 18.78. IR (ν_{max}, cm^{-1}): 3445, 3282 (2NH), 2936 (CH_{aliph}), 1712 (CO), 1631 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 1.12−1.76 (m, 10H, $5CH_{2cyclo}$), 2.09 (s, 1H, NH, exchangeable by D_2O), 3.28 (s, 2H, CH_2−CO), 3.51 (m, 1H, CH−NH), 3.56 (s, 2H, $CH_{2imidazole}$), 8.07 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 24.77, 25.56, 25.81, 31.22, 32.55, 48.64, 161.40, 163.83, 171.03.

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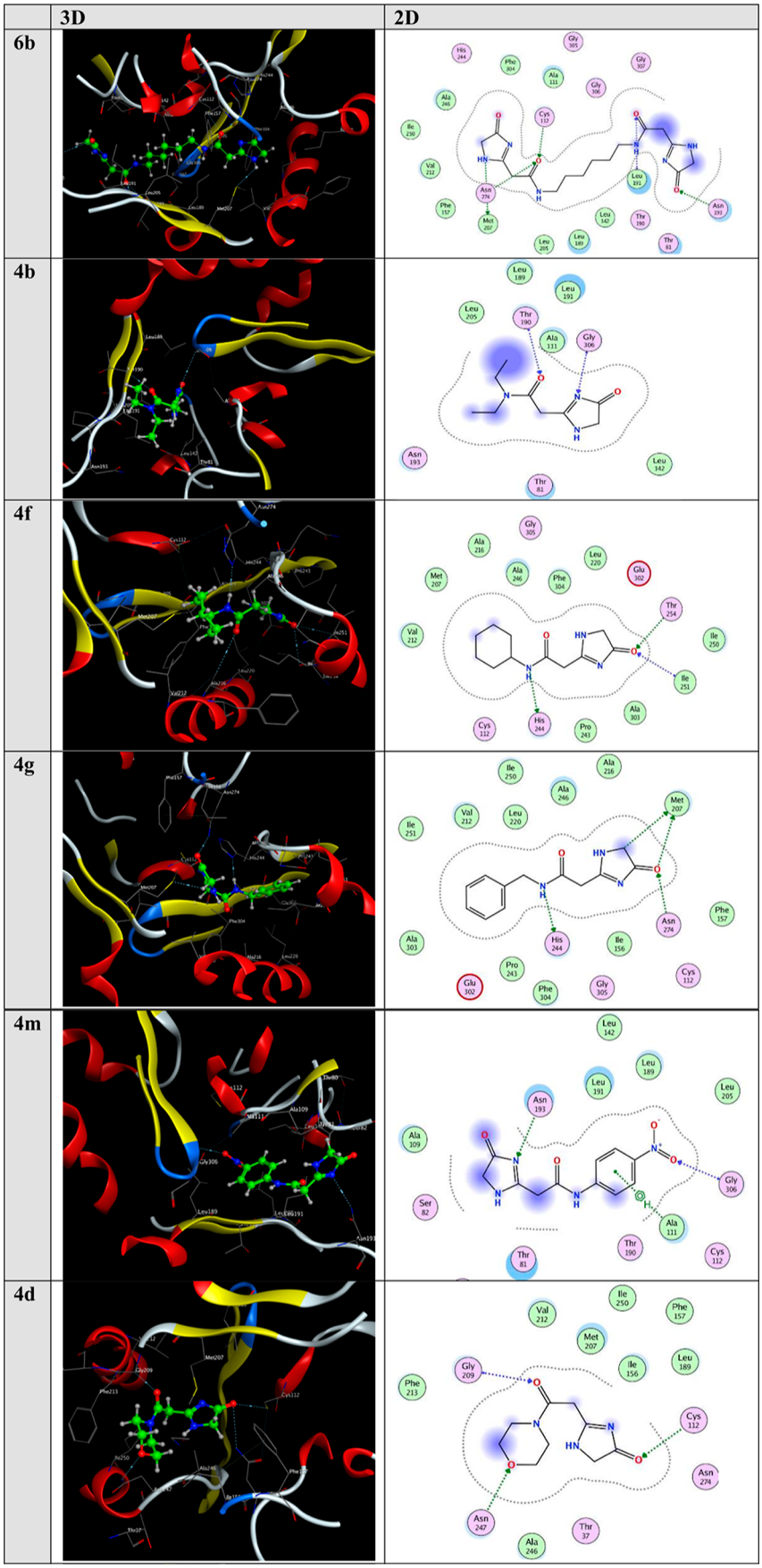

Figure 2. continued

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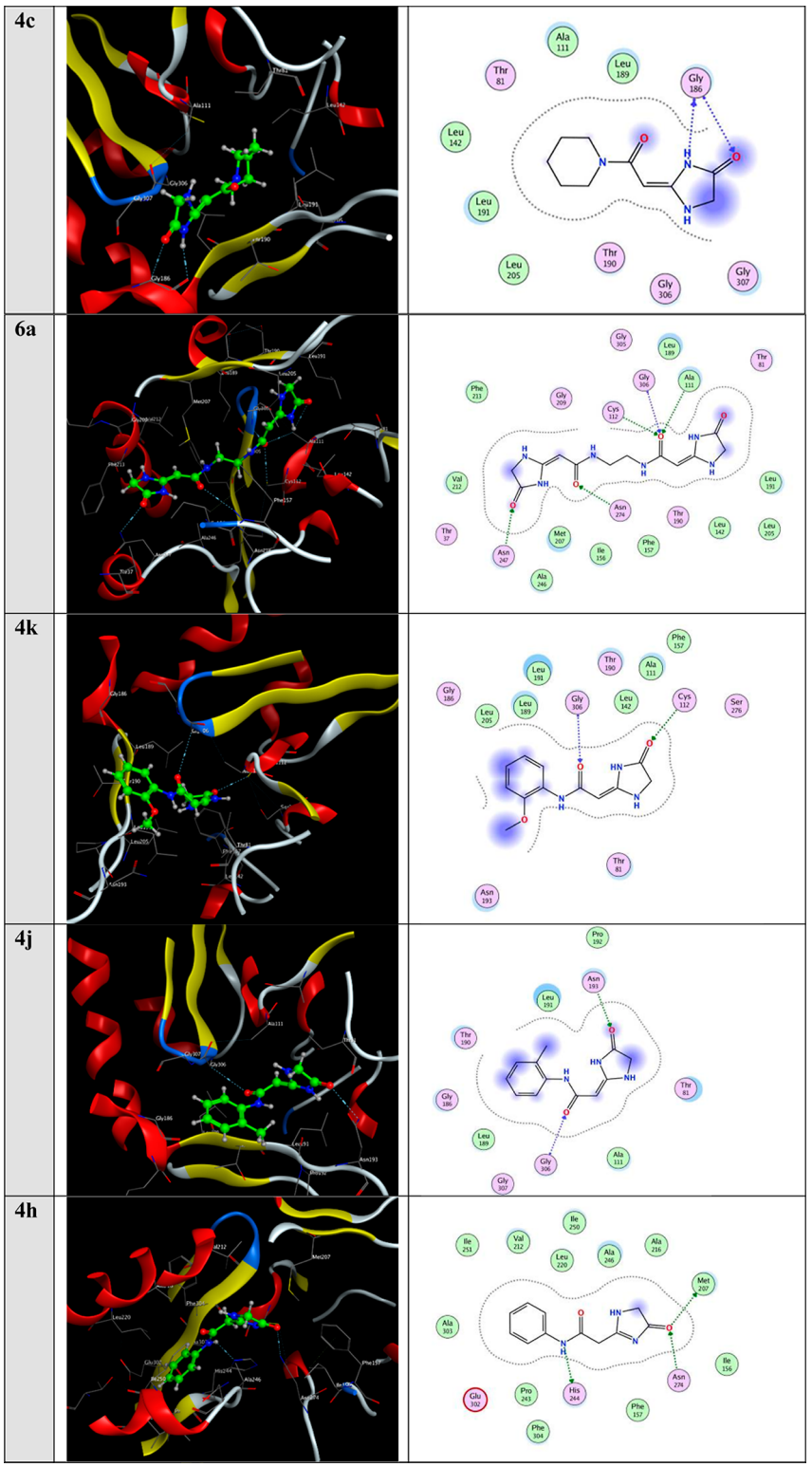

Figure 2. continued

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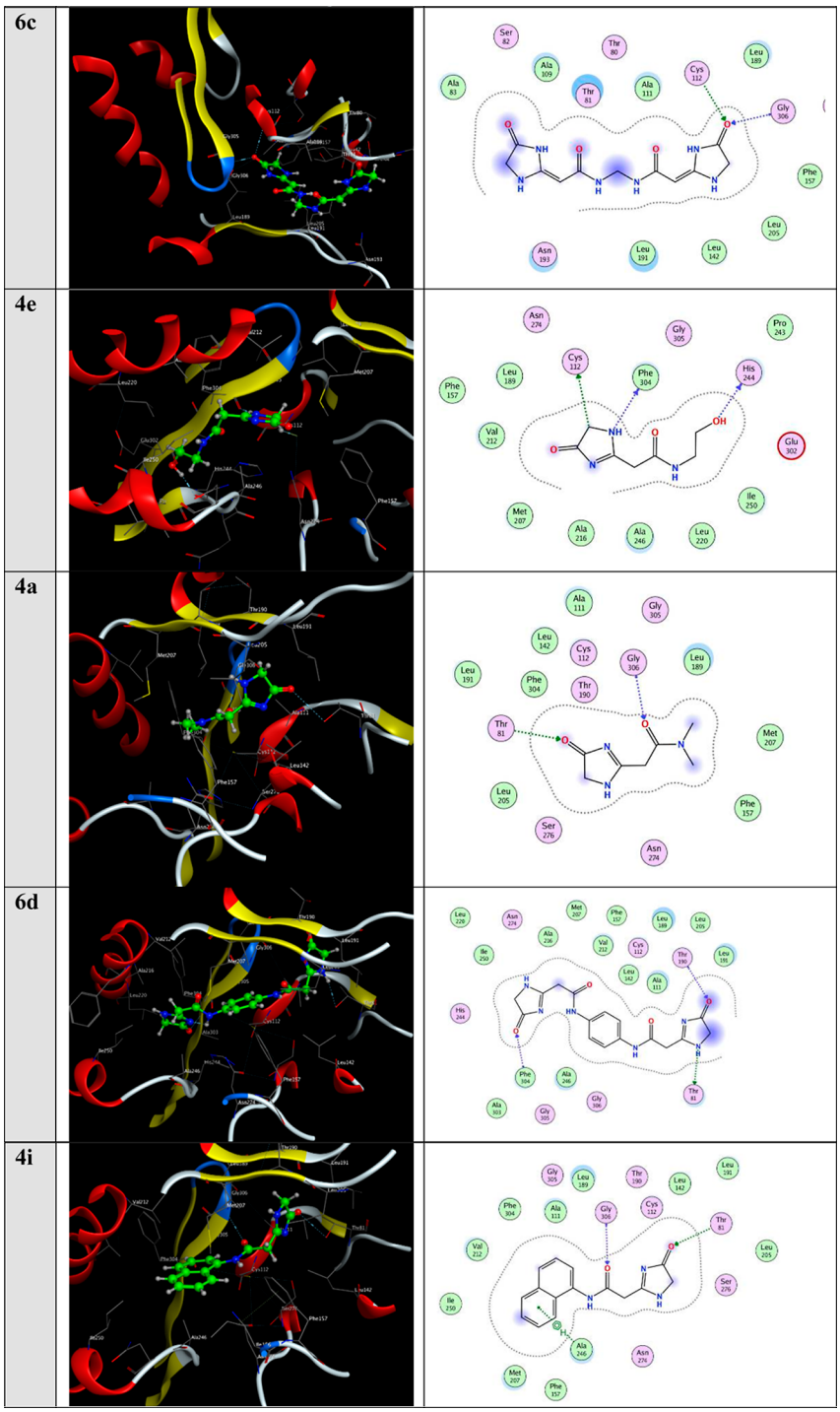

Figure 2. 3D and 2D interaction of docked compounds through the 1HNJ active site.

*3.2.7. N-Benzyl-2-(5-oxo-4,5-dihydro-1H-imidazole-2-yl)-acetamide (**4g**).* Yield (85%), pale yellow needles, mp 154 °C, Anal. data: ($C_{21}H_{13}N_3O_2$, 231.25), Calcd: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.25; H, 5.71; N, 18.21. IR (n_{max}, cm^{-1}): 3268, 3205 (2NH), 3053 (CH_{arom}), 2977 (CH_{aliph}), 1747 (CO), 1669 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.81 (s, 2H, CH_2−CO), 3.98 (s, 2H, $CH_{2imidazole}$), 4.27 (s, 2H, CH_2−NH), 7.09−7.62 (m, 5H, CH of Ar), 8.47 (s, 1H, NH, exchangeable by D_2O), 10.61 (s, 1H, NH, exchangeable by D_2O). ^{13}CNMR (DMSO-d_6): δ ppm 41.22, 43.26, 55.02, 126.71, 126.92, 126.99, 128.06, 166.81, 166.94, 182.36.

*3.2.8. 2-(4-Oxo-4,5-dihydro-1H-imidazole-2-yl)-N-phenyl-acetamide (**4h**).* Yield (80%), pale yellow needles, mp 169 °C, Anal. data: ($C_{11}H_{11}N_3O_2$, 217.22), Calcd: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.82; H, 5.15; N, 19.29. IR (n_{max}, cm^{-1}): 3311, 3162 (2NH), 3051 (CH_{arom}), 2989 (CH_{aliph}), 1693 (CO), 1627 (CO). 1H NMR (DMSO-d_6): δ ppm 3.41 (s, 2H, CH_2−CO), 4.09 (s, 2H, $CH_{2imidazole}$), 7.23−7.70 (m, 5H, CH of Ar), 8.72 (s, 1H, NH, exchangeable by D_2O), 10.69 (s, 1H, NH, exchangeable by D_2O). ^{13}C NMR (DMSO-d_6): δ ppm 27.06, 42.22, 116.36, 119.77, 124.34, 129.31, 138.87, 161.43, 163.05.

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Table 7. Molecular Docking Data

	ligand	receptor	interaction	distance	*E* (kcal/mol)	*S* (kcal/mol)	inhibition constant (Ki) (μM)
6b	N 5	MET 207	H-donor	3.02	−1.50	−8.72	0.41
	O 9	CYS 112	H-acceptor	2.82	−0.10		
	O 9	ASN 274	H-acceptor	2.71	−0.80		
	O 17	LEU 191	H-acceptor	3.06	−2.50		
	O 24	ASN 193	H-acceptor	3.25	−1.00		
4b	N 3	GLY 306	H-acceptor	3.74	−0.70	−6.81	2.23
	O 8	THR 190	H-acceptor	3.51	−0.90		
4f	N 1	HIS 244	H-donor	3.44	−0.80	−7.41	3.76
	O 10	ILE 251	H-acceptor	3.61	−0.70		
	O 10	THR 254	H-acceptor	3.29	−0.70		
4g	N 1	HIS 244	H-donor	3.42	−2.30	−7.72	3.89
	C 8	MET 207	H-donor	3.54	−0.90		
	O 10	MET 207	H-donor	3.37	−0.20		
	O 10	ASN 274	H-acceptor	3.27	−1.20		
4m	N 6	ASN 193	H-acceptor	3.25	−1.50	−7.39	7.77
	O 19	GLY 306	H-acceptor	3.34	−0.90		
	6-ring	ALA 111	pi-H	3.89	−0.60		
4d	O 4	ASN 247	H-acceptor	3.45	−1.20	−6.98	10.34
	O 9	GLY 209	H-acceptor	3.52	−0.80		
4c	O 15	CYS 112	H-acceptor	3.64	−0.70	−6.34	
	N 5	GLY 186	H-donor	3.39	−2.30		
	O 9	GLY 186	H-acceptor	3.70	−0.70		
6a	O 3	ALA 111	H-acceptor	3.63	−0.70	−7.77	2.05
	O 3	CYS 112	H-acceptor	3.07	−1.00		
	O 3	GLY 306	H-acceptor	3.32	−2.00		
	O 16	ASN 274	H-acceptor	3.14	−1.00		
	O 22	ASN 247	H-acceptor	3.11	−1.80		
4k	O 4	GLY 306	H-acceptor	3.81	−0.70	−6.42	19.96
	O 10	CYS 112	H-acceptor	2.98	−0.80		
4j	O 4	GLY 306	H-acceptor	3.68	−0.80	−6.09	34.81
	O 10	ASN 193	H-acceptor	3.13	−2.50		
4h	N 1	HIS 244	H-donor	3.00	−1.20	−7.05	6.90
	O 10	MET 207	H-donor	3.31	−0.30		
	O 10	ASN 274	H-acceptor	3.37	−0.70		
6c	O 20	CYS 112	H-acceptor	3.17	−0.90	−6.19	29.41
	O 20	GLY 306	H-acceptor	2.94	−3.30		
4e	O 7	HIS 244	H-donor	2.72	−2.20	−5.74	62.80
	C 11	CYS 112	H-donor	3.73	−0.80		
	N 12	PHE 304	H-donor	2.96	−3.20		
4a	O 6	GLY 306	H-acceptor	3.03	−2.50	−5.60	79.51
	O 12	THR 81	H-acceptor	3.27	−1.20		
6d	N 20	THR 81	H-donor	3.46	−0.90	−7.12	6.13
	O 25	PHE 304	H-acceptor	3.10	−0.90		
	O 26	THR 190	H-acceptor	3.65	−0.60		
4i	O 4	GLY 306	H-acceptor	3.46	−0.90	−6.12	33.10
	O 10	THR 81	H-acceptor	3.40	−0.80		
	6-ring	ALA 246	pi-H	3.84	−0.60		

*3.2.9. N-(Naphthalen-1-yl)-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (**4i**).* Yield (74%), pale yellow needles, mp 218 °C, Anal. data: ($C_{15}H_{13}N_3O_2$, 267.28), Calcd: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.42; H, 4.94; N, 15.66. IR (n_{max}, cm^{-1}): 3464, 3313 (2NH), 3051 (CH_{arom}), 2989 (CH_{aliph}), 1686 (CO), 1630 (CO). 1H NMR (DMSO-d_6): δ ppm 3.74 (s, 2H, CH_2−CO), 3.91 (s, 2H, $CH_{2imidazole}$), 6.89−7.56 (m, 8H, CH of Ar + NH exchanged by D_2O), 7.95 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 56.34, 61.08, 120.88, 121.47, 122.02, 125.20, 126.57, 128.63, 129.37, 129.75, 131.08, 132.91, 142.29, 148.70, 158.46, 166.37.

*3.2.10. (E)-2-(4-Oxoimidazolidin-2-ylidene)-N-(o-tolyl)-acetamide (**4j**).* Yield (80%), pale yellow needles, mp 210 °C, Anal. data: ($C_{12}H_{13}N_3O_2$, 231.25), Calcd: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.30; H, 5.64; N, 18.23. IR (n_{max}, cm^{-1}): 3311, 3162 (2NH), 3051 (CH_{arom}), 2989 (CH_{aliph}), 1693 (CO), 1627 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.63 (s, 3H, CH_3), 4.29 (s, 2H, $CH_{2imidazole}$), 5.68 (s, 1H, =CH), 7.23−7.70 (m, 4H, CH of Ar), 8.12 (s, 2H, 2 NH, exchangeable by D_2O), 11.19 (s, 1H, NH, exchangeable by D_2O).

*3.2.11. (E)-N-(2-Methoxyphenyl)-2-(4-oxoimidazolidin-2-ylidene)acetamide (**4k**).* Yield (67%), pale yellow needles,

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mp 275 °C, Anal. data: ($C_{12}H_{13}N_3O_3$, 247.25), Calcd: C, 58.29; H, 5.30; N, 16.99. Found: C, 58.31; H, 5.36; N, 16.91. IR (n_{max}, cm^{-1}): 3302, 3112 (2NH), 3065 (CH_{arom}), 2960 (CH_{aliph}), 1712 (CO), 1643 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.32 (s, 2H, $CH_{2imidazole}$), 4.02 (s, 3H, OCH3), 4.80 (s, 1H, =CH), 7.34 (s, 2H, 2NH, exchangeable by D_2O), 7.55−7.63 (m, 4H, CH of Ar), 10.13 (s, 1H, NH, exchangeable by D_2O).

*3.2.12. N-(4-Chlorophenyl)-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (**4l**).* Yield (74%), pale yellow needles, mp 244 °C, Anal. data: ($C_{11}H_{10}N_4O_4$, 262.22), Calcd: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.41; H, 3.78; N, 21.40. IR (n_{max}, cm^{-1}): 3452, 3312 (2NH), 3087 (CH_{arom}), 2974 (CH_{aliph}), 1704 (CO), 1663 (CO). 1H NMR (DMSO-d_6): δppm 3.72 (s, 2H, CH_2−CO), 4.12 (s, 2H, $CH_{2imidazole}$), 7.15−7.58 (m, 4H, CH of Ar), 7.37 (s, 1H, NH, exchangeable by D_2O), 8.14 (s, 1H, NH, exchangeable by D_2O).

*3.2.13. N-(4-Nitrophenyl)-2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide (**4m**).* Yield (61%), pale yellow needles, mp 253 °C, Anal. data: ($C_{11}H_{10}N_4O_4$, 262.22), Calcd: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.41; H, 3.78; N, 21.40. IR (n_{max}, cm^{-1}): 3302, 3112 (2NH), 3065 (CH_{arom}), 2960 (CH_{aliph}), 1712 (CO), 1643 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.69 (s, 2H, CH_2−CO), 4.33 (s, 2H, $CH_{2imidazole}$), 7.26−7.47 (m, 4H, CH of Ar), 7.37 (s, 1H, NH, exchangeable by D_2O), 8.67 (s, 1H, NH, exchangeable by D_2O).

3.3. General Procedure for Synthesis of bis-*N*-(alkyl/aryl) Acetamido-2-ylidene-4-imidazole (6a−d). A mixture of amines **5a−d** (0.001 mol) and ethylcyanoacetate **1** (0.002 mol) fused together for 15 min and then 0.0024 mol of ethyl glycinate hydrochloride **2** (treated with an equimolar amount of triethyl amine before addition to activate the amino group) was added and the reaction time of 2 h was completed at 70 °C to obtain the equivalent bis-*N*-(alkyl/aryl) acetamido-2-ylidene-4-imidazole. The precipitates were recovered by filtering, carefully washed with water, and recrystallized from ethanol.

*3.3.1. (2E,2′E)-N,N′-(Ethane-1,2-diyl)bis(2-(4-oxoimidazolidin-2-ylidene)acetamide) **6a**.* Yield (96%), pale yellow needles, mp 202 °C, Anal. data: ($C_{12}H_{16}N_6O_4$, 308.29), Calcd: C, 46.75; H, 5.23; N, 27.26. Found: C, 46.66; H, 5.28; N, 27.32. IR (n_{max}, cm^{-1}): 3238, 3162 (2NH), 2974 (CH_{aliph}), 1712 (CO), 1692 (CO). ^{1}H NMR ($CDCl_3$): δ ppm 3.14 (s, 4H, $2CH_2$−CO), 3.76 (s, 4H, $2CH_2$−NH), 4.19 (s, 4H, $2CH_{2imidazole}$), 9.17 (s, 2H, 2NH, exchangeable by D_2O), 10.62 (s, 2H, 2NH, exchangeable by D_2O). ^{13}CMR ($CDCl_3$): δ ppm 31.45, 60.17, 89.13, 155.15, 167.36, 172.23.

*3.3.2. N,N′-(Propane-1,3-diyl)bis(2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide) **6b**.* Yield (92%), pale yellow needles, mp 233 °C, Anal. data: ($C_{13}H_{18}N_6O_4$, 322.32), Calcd: C, 48.44; H, 5.63; N, 26.07. Found: C, 48.47; H, 5.57; N, 26.10. IR (ν_{max}, cm^{-1}): 3290, 3167 (2NH), 3065 (CH_{arom}), 2971 (CH_{aliph}), 1745 (CO), 1652 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 1.40 (m, 2H, CH_2), 3.06 (s, 4H, $2CH_2$−CO), 3.61 (s, 4H, $2CH_{2imidazole}$), 3.74 (m, 4H, CH_2), 8.02 (s, 1H, NH, exchangeable by D_2O), 8.32 (s, 2H, 2NH, exchangeable by D_2O), 8.88 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 25.67, 29.13, 45.86, 61.91, 154.87, 162.32, 168.30.

3.3.3. N,N′-(Hexane-1,6-diyl)bis(2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide)6c. Yield (94%), pale yellow needles, mp 215 °C, Anal. data: ($C_{16}H_{24}N_6O_4$, 364.40), Calcd: C, 52.74; H, 6.64; N, 23.06. Found: C, 52.71; H, 6.59; N, 23.14. IR (ν_{max}, cm^{-1}): 3448, 3290 (2NH), 3067 (CH_{arom}), 2940 (CH_{aliph}), 1725 (CO), 1651 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 1.26 (m, 4H, $2CH_2$), 1.34 (m, 4H, $2CH_2$), 3.11 (m, 4H, $2CH_2$), 3.30 (s, 4H, $2CH_2$−CO), 3.63 (s, 4H, $2CH_{2imidazole}$), 8.04 (s, 1H, NH, exchangeable by D_2O). 8.23 (s, 2H, 2NH, exchangeable by D_2O), 9.91 (s, 1H, NH, exchangeable by D_2O). ^{13}CMR (DMSO-d_6): δ ppm 25.84, 26.39, 29.13, 45.86, 61.91, 151.02, 162.32, 169.52.

*3.3.4. N,N′-(1,4-Phenylene)bis(2-(4-oxo-4,5-dihydro-1H-imidazole-2-yl)acetamide) **6d**.* Yield (89%), pale yellow needles, mp 266 °C, Anal. data: ($C_{16}H_{16}N_6O_4$, 356.34), Calcd: C, 53.93; H, 4.53; N, 23.58. Found: C, 53.85; H, 4.56; N, 23.63. IR (ν_{max}, cm^{-1}): 3463, 3312 (2NH), 3070 (CH_{arom}), 2979 (CH_{aliph}), 1684 (CO), 1630 (CO). ^{1}H NMR (DMSO-d_6): δ ppm 3.76 (s, 4H, $2CH_2$−CO), 3.98 (s, 4H, $2CH_{2imidazole}$), 6.89, 7.19 (s, 2H, 2NH, exchangeable by D_2O), 7.20−7.34 (m, 4H, CH_{arom}), 7.66 (s, 2H, 2NH), exchangeable by D_2O. ^{13}CMR (DMSO-d_6): δ ppm 56.37, 61.01, 126.44, 128.64, 133.07, 148.88, 158.29, 165.68.

3.4. Antimicrobial Activity. The antibacterial and antifungal activity of the produced compounds was measured using the agar well diffusion method,[47,48] wherein a volume of the microbial inoculum is dispersed evenly across the entire agar plate surface to inoculate it. Then, a sterile cork borer or tip is used to puncture a hole with a diameter of 6 to 8 mm, and 20 to 100 μL of the antimicrobial agent solution is injected into the well to achieve the necessary concentration. The plates were then kept at 37 °C for 24 h. The diameter of the zone of inhibition formed in the wells after incubation was used to determine antimicrobial efficacy.[49,50]

3.5. Molecular Docking. Possible binding mechanisms of the investigated drugs against the *E. coli FabH−CoA* complex receptor (PDB ID: 1HNJ) were investigated using molecular docking. The 3D structure of the receptor of interest was obtained from the Protein Data Bank (http://www.rcsb.org/). The MOE program was used for molecular docking research. Score function (*S*, kcal/mol) was used to rank the compounds' binding affinities toward the target receptor.[51]

4. CONCLUSIONS

2-Acetamido-2-ylidene-4-imidazole/bis-*N*-(alkyl/aryl) acetamido-2-ylidene-4-imidazoles were synthesized via the reaction of different amines with ethylcyanoacetate and ethylglycinate hydrochloric acid via the green reaction condition. Chemical and spectroscopic data allowed for the elucidation of the novel substances. Synthesized compounds were effective in combating the investigations on antibacterial action. The compounds showed an activity index that ranged from 42.1% for *N,N′*-(hexane-1,6-diyl)bis(2-(4-oxo-4,5-dihydro-1*H*-imidazole-2-yl)-acetamide) in the case of *S. aureus* (Gram positive) to 80.0% for, *N′*-(propane-1,3-diyl)bis(2-(4-oxo-4,5-dihydro-1*H*-imidazole-2-yl)acetamide) in the case of *E. coli* (Gram negative). Molecular docking simulations with the *E. coli FabH−CoA* complex (PDB ID: 1HNJ) were performed to explore the possible interactions of the enzyme with the synthesized compounds. According to the obtained results, the synthesized compounds seemed to be a promising candidate for the progress of antimicrobials.

■ ASSOCIATED CONTENT

Supporting Information

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All spectra data of IR, ^{1}H NMR, and ^{13}C NMR for the synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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