Heliyon 8 (2022) e11332

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Synthesis, characterization, molecular docking and biological evaluation of Schiff Base derivatives of cefpodoxime

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ARTICLE INFO

Keywords:
Cefpodoxime
Corona virus class
Antiviral
Schiff bases
FTIR
NMR (^{1}H and ^{13}C)

ABSTRACT

Synthesis of new Cefpodoxime derivatives via Schiff Bases mechanism and the efficiency of their antimicrobial and antiviral activities were addressed. They were analyzed for structural validation by using spectroscopic techniques using FTIR, ^{1}HNMR, and ^{13}CNMR. Molecular docking against IBV Virus papain-like protease (PLPro) was done with Auto dock tools against compounds having excellent IC_{50} values against IBV (Corona Class) virus. All derivatives showed strong zone of inhibition ranges from (55 ± 2.0 to 70 ± 0.8 mm) against *E. coli*. Compounds 1,2,4 and 6 derivatives showed remarkable activity against *Stenotrophomonas maltophilia* and *Serratia marcescens*. But For most the newly synthesized derivatives **C^{1}** (64 ± 1.60), **C^{3}** (32 ± 0.80), and **C^{8}** (64 ± 1.60) showed potential IC_{50} values against two variants of Corona class viruses i.e. *Avian Influenza (H9)* and *Avian corona (IBV) viruses*. The current study revealed that newly synthesized Schiff Bases possessed strong anti-viral potential. Further studies may make a breakthrough in medical sciences to tackle latest challenges such as Corona Virus Diseases.

1. Introduction

Schiff Base was initially synthesized by the Italian Scientist Hugo Schiff [1] in 1864. The condensation reaction of aldehydes/ketones with aromatic amines leads to the discovery of compounds that were later called Schiff Bases. Carbon nitrogen double bond ($R_1R_2C = NR_3$) was the functional group in compounds that indicates Schiff Bases. R_1 and R_2 indicate a side chain of organic origin while R_3 binding with nitrogen may be aryl or alkyl group [2].

The condensation of aldehydes (acetaldehyde, benzaldehyde, valeraldehyde, and cinnamon aldehyde) with aromatic amine (aniline) leads to the discovery of Schiff Base first time in the 18th century [3]. Schiff Bases have significant biological activities that are, the presence of unique electron donating and electron accepting functional moieties. Schiff bases possessed many potential biological activities as the compound having Schiff bases have both electrons-accepting and electron-donating groups.

Schiff bases have significant biological activities reported that include Antimicrobial activity antidepressant activity [4], Antidyslipidemic activity [5], Anthelmintic activity [6], Antitubercular activity [7], Anticonvulsant activity [8], Anti-inflammatory activity, analgesic activity and non-ulcerogenic activity [9], Antitumor activity [10], Antioxidant activity [11], Antiviral activity [12], Anti-hypertensive activity [13] and Antidiabetic and antiglycation activities. The current study encompasses the antiviral potential of newly synthesized novel compounds (C-1 to C-9) against *Avian Influenza* (H9) and *Avian corona* (IBV) viruses.

Avian Influenza (H9) viruses are viruses that contain a segmented, RNA genome encoding possessing negative-sense, 10 core proteins, and various proteins belong to the "*Orthomyxoviridae*" family. Different subtypes were formed as the result of the combination of hemagglutinin (HA), surface proteins, and neuraminidase (NA), for example, H_9N_2, H_1N_1, and H5N2 [14].

Avian corona (IBV) virus belongs to the coronavirus class (order *Nidovirales*, family *Corona-viridae*, genus *Corona-virus*) [15] that cause

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https://doi.org/10.1016/j.heliyon.2022.e11332
Received 8 February 2022; Received in revised form 6 April 2022; Accepted 24 October 2022

infection in the respiratory tract, kidney, gut, and reproduction of chicken. IBV is an enveloped coronavirus having un-segmented, single-stranded with a positive-sense genome of RNA Corona-viruses class contain the largest RNA virus genomes.

2. Statistical analysis

2.1. Anti-microbial activity

Anti-microbial activity that is newly synthesized Schiff-Bases was evaluated against four different bacterial strains *Bacillus subtilis* (BS), *Stenotrophomonas melophilia* (SM), *Serratia marcescens,* (SM) & *Escherichia coli.* (EC) by using *Agar Well* Diffusion *Method* [16]. Different dilutions (200 μg/ml, 300 μg/ml, and 400 μg/ml) of newly synthesized compounds that were dissolved in (DMSO) and samples were evaluated for analysis. The prepared Petri plates having agar medium were incubated at 37 °C in the incubator for 24-h and the result was documented to measure the zone of inhibition (mm) [17].

2.2. Antiviral activity of novel compounds

2.2.1. Inoculation of poultry viruses in chicken embryonated eggs

Seven to Eleven days old Chicken embryonated eggs were purchased from the local hatchery and utilized in antiviral studies by using the inoculation method. The candling of the eggs was done before inoculation. The susceptible viruses were inoculated in the chorioallantoic fluid of the eggs. The broader ends of the candled eggs were drilled with a sterile needle for inoculation. After inoculation, the hole was blocked

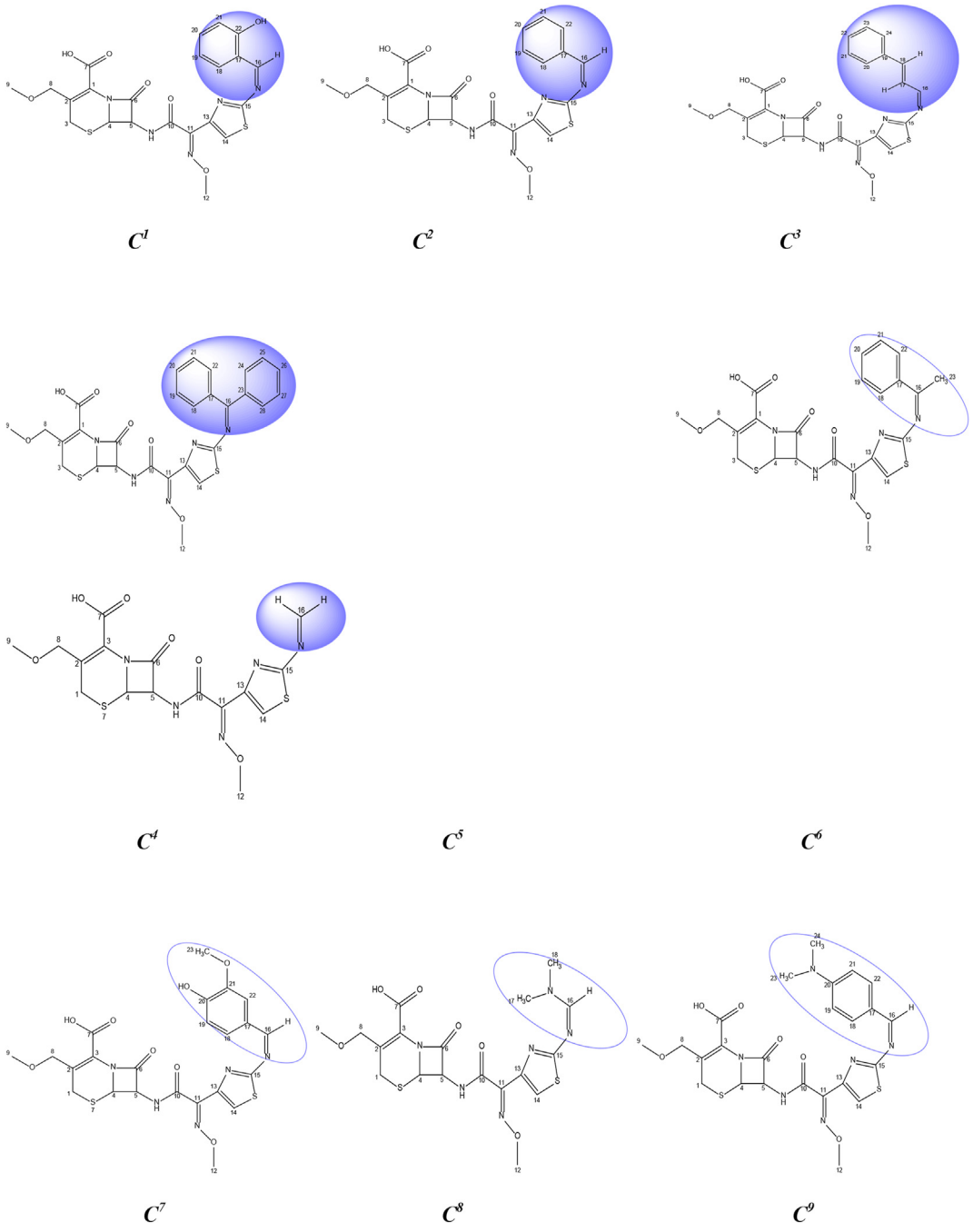


Figure 1. Highlighted substituted aldehydes and Ketones were showed of Synthesized Schiff Bases C^1–C^9.

with the help of molten wax, and eggs were incubated at 37 °C. The allantoic fluid was collected after 48 h of inoculation subjected to the Hemagglutination (HA) test for antiviral studies [18].

2.2.2. Hemagglutination test

In the Hemagglutination test, Chicken Blood was collected in freshly prepared *Alsevior* Solution and centrifugation was done for 5 min at 4000 rpm. The supernatant solution was discarded and RBCs (Red Blood Cells) were washed with *phosphate-buffered saline* (PBS) solution and pH was maintained at 7.2. The following step was repeated *three* times. 1 % suspension was prepared such that 10 µl of packed cells were mixed in 1 ml *phosphate-buffered saline* (PBS) solution with pH 7.2. After that, the prepared cells were used in performing the standard HA test [19].

3. Molecular modeling

3.1. Protein preparation

The crystal structure of enzymes IBV-PLpro [20], (PDB ID: 4x2z), was obtained from RCSB PDB. All water molecules were removed from the crystallographic structure and polar hydrogen atoms were added utilizing Autodock tools (ADT) version 1.5.6. ADT saved the prepared file in PDBQT format. In case of IBV-PLpro, the grid box was centered on the conserved catalytic triad and surrounding amino acid residues composing ubiquitin Binding Domain and amino acid residues composing subsites 1, 2 and 3. The grid dimensions were 50 × 50 × 50 Å with points separated by 0.5 Å for IBV-PLpro and 40 × 40 × 40 Å with points separated by 0.5 Å.

4. Results

4.1. Chemistry and characterization

The new derivatives were synthesized as shown in Figure 1, and characterization was done followed by the qualitative and quantitative analysis. Physical characteristics including Color, Odor, Melting Point, and Physical state were studied as shown in Table 1. The Schiff Base formation was verified by the FTIR-spectra of Schiff-Bases. The presence of Schiff Base (–C═N) carbon-nitrogen bond peaks at 1692, 1660, 1661, 1667, 1677, 1622, 1633, 1647 and 1669 cm^{-1} found. The characteristic peaks ensured the formation of the Schiff Base and the absence of peaks of carbonyl and amine groups authenticated the completion of the reaction [21]. The solubility of all the synthesized Schiff Base derivatives was tested in different solvents that included Methanol, Ethanol, Water, Chloroform, and DMSO. The sample ligands were frequently soluble in hydrophilic solvents.

Table 1. Physical characteristic of schiff-bases.

Code	Molecular formula	Molecular weight	Appearance	Yield %	Melting point °C
C	$C_{15}H_{17}N_5O_6S_2$	427	Amorphous white powder	100	88
C^1	$C_{22}H_{21}N_5O_7S_2$	531	Brown crystals	78	103–105
C^2	$C_{22}H_{21}N_5O_6S_2$	515	Yellowish brown crystals	77	113–115
C^3	$C_{24}H_{23}N_5O_6S_2$	541	Yellowish brown semi-solid	71	70
C^4	$C_{28}H_{25}N_5O_6S_2$	591	Yellowish brown crystals	75	91–93
C^5	$C_{23}H_{23}N_5O_6S_2$	529	Red semi-solid	77	60
C^6	$C_{16}H_{17}N_5O_6S_2$	439	Light brick crystals	79	86
C^7	$C_{23}H_{23}N_5O_8S_2$	561	Brown amorphous powder	74	96
C^8	$C_{18}H_{22}N_6O_6S_2$	482	Yellowish brown crystals	78	102–106
C^9	$C_{24}H_{26}N_6O_6S_2$	558	Brown crystals	79	130

4.2. Anti-microbial assay

Anti-bacterial assay of newly synthesized Schiff Bases ***C^1–C^9*** (Figure 1) was performed to evaluate the susceptibility. The analytical activity was done on present gram-positive *Bacillus subtilis* (BS), *Stenotrophomonas maltophilia* (SM), *Serratia marcescens* (SM) & *Escherichia Coli* (EC). Results of antibacterial activity were shown in graphical form as shown in Table 3.

In this assay, Antimicrobial-activity was done by the well diffusion method. In this activity, the Cefpodoxime drug was labeled as a standard drug for an antimicrobial relative study concerning all derived moieties. Four different bacterial strains were selected, and activity was checked by using three different concentrations (A), (B), and (C). 1 ml of DMSO as solvent was taken and 5 mg sample/standard dissolved and took 20 µl marked as A, 40 µl marked as B and 60 µl marked a C.

4.3. Anti-viral activity

1 mg of Nine Novel compounds ***C^1 to C^9*** (Figure 1) and parent drug C (Cefpodoxime) were dissolved in 1 ml DMSO solution separately by using Eppendorf tubes to prepare the stock solution. Later 100 µl solutions of each novel compound with an equal volume of viral inoculums were mixed and injected in 7–11 days old chicken embryonated eggs according to the described method.

All the protocols followed in this study were approved by the departmental biosafety committee of The Islamia University of Bahawalpur, Pakistan.

5. Structure-activity relationship studies

The newly synthesized derivatives of cefpodoxime indicated that the substitution of aromatic aldehydes and ketones showed that **C^1** (IC_{50} ± SEM (µM) = 8.29 ± 0.92) substituted with the hydroxyl group on benzene ring and **C^7** (IC_{50} ± SEM (µM) = 6.26 ± 0.62). The results are shown in Table 2 having substituted methoxy group showed active results.

6. Docking

The crystal structure of enzymes IBV-PLpro, (PDB ID: 4x2z), was obtained from RCSB PDB. All water molecules were removed from the crystallographic structure and polar hydrogen atoms were added utilizing Autodock tools (ADT) version 1.5.6. ADT saved the prepared file in PDBQT format. In case of IBV-PLpro, the grid box was centered on the conserved catalytic triad and surrounding amino acid residues composing ubiquitin Binding Domain was centered on catalytic dyad (HIS41 and CYS143) and amino acid residues composing subsites 1, 2 and 3. The grid dimensions were 50 × 50 × 50 Å with points separated by 0.5 Å for IBV-PLpro and 40 × 40 × 40 Å with points separated by 0.5 Å. The docking studies of ***C^1, C^3, C^4, C^5, C^8*** and ***C^9 in*** 2D and 3D figures were shown below in Figure 2 binding energies, residues, types of interactions, hydrophobic interactions, and electrostatic interactions of C^1–C^9 newly synthesized compounds during docking studies against IBV Papain like protease protein (PLpro) shown in Table 4.

7. Material and method

All chemicals with a grade of analytical standard utilized in this current research work were purchased from the following distributors. Cefpodoxime was obtained from Mega Pharmaceutical Pvt. Ltd. Lahore. Its percentage purity was 97%.

7.1. General procedure

All the materials, different solvents, and chemicals were purchased from Sigma-Aldrich and Merck international. All list was of analytical

Table 2. Antiviral potential of Novel compounds as HA Titer against H9 and IBV Viruses.

Sr. No.	Ligands	R_1	R_2	H_9		IBV	
				HA titer	IC_{50}	HA titer	IC_{50}
1	C^1	H	HO–C_6H_5	0.00 ± 0.00	16 ± 3.90	0.00 ± 0.00	64 ± 1.60
2	C^2	H	–C_6H_5	2.00 ± 0.90	-	4.00 ± 0.90	-
3	C^3	H	-CH = CH–C_6H_5	8.00 ± 1.80	-	0.00 ± 0.00	32 ± 0.80
4	C^4	–CH_3	–C_6H_5	2.00 ± 0.90	64 ± 1.60	0.00 ± 0.00	16 ± 0.40
5	C^5	–C_6H_5	–C_6H_5	0.00 ± 0.00	–	0.00 ± 0.00	16 ± 0.40
6	C^6	H	H	0.00 ± 0.00		2.00 ± 0.00	–
7	C^7	H	$C_8H_{10}O_2$	16.0 ± 1.80	16 ± 0.40	2.00 ± 0.90	–
8	C^8	H	$C_3H_9O_2$	0.00 ± 0.00	32 ± 0.80	0.00 ± 0.00	64 ± 1.60
9	C^9	H	$C_9H_{13}N_2$	4.00 ± 0.24	–	0.00 ± 0.00	16 ± 0.40
10	C	H	HO–C_6H_5	2.00 ± 0.00	–	16.0 ± 1.80	–
11	Negative Control	Normal Saline		1024 ± 0.00	–	1024 ± 0.00	–
12	Virus Control	H_9 and IBV		1024 ± 0.00	–	1024 ± 0.00	–
13	Solvent Control	DMSO		1024 ± 0.00	–	1024 ± 0.00	–
14	Amantadine	Standard H_9 Drug		2.80 ± 0.00	65.00 ± 1.50	–	–
15	Ribavirin	Standard IBV Drug		-	-	6.90 ± 1.8	139 ± 1.50

grade and utilized without any purification. Thin-layer chromatography (TLC) was done on *Merck precoated* silica gel, aluminum plates (*Kieselgel*) for purification. Later, TLC was visualized using a UV lamp, with wavelength of light fixed at 245nm. Melting points were measured by Gallen Kamp melting point apparatus. IR (Infrared) spectra were recorded on FTIR. ^{1}H NMR proton spectra were obtained using NMR spectrophotometer (100 MHz), and ^{13}C NMR spectra were obtained at NMR spectrophotometer (400 MHz).

7.2. Synthesis

Equimolar solution of available aldehydes/ketones and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h as shown in Scheme 1. at controlled temperature in the water bath, cooled at room temperature and filtration was performed [22]. R_1 and R_2 of synthesized Schiff Bases were shown in Table 5 The solvent evaporation was performed by a rotary evaporator; the solid by-product was collected and dried at room temperature. Recrystallization done was performed with alcohol (ethanol). Physical Characterization was done by using different physio-chemical procedures.

7.2.1. Synthesis of 7-((E)-2-(2-((Z)-(2-hydroxybenzylidene) amino) thiazol-4-yl)-2-(methoxyimino) acetamido)-3-(methoxy methyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^1)

Equimolar mixture of Salicylaldehyde and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml). Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask. The reaction mixture was refluxed for 3 h at solvent boiling point in the water bath, cooled at room temperature and filtration was performed. Brown crystals: Yield (78%), m. p. 103–105 °C, Mol. Wt. 531.56, Elemental Analysis: (Calculated) for $C_{22}H_{21}N_5O_7S_2$: C, 49.70; H, 3.99; N, 13.28; (Found): C, 47.25; H, 3.78; N,12.99; FTIR (cm^{-1}), 3312, 3439, 3565 ν(NH), 2808, 2881, 2978ν(CH), 1652,1684 ν(C=N), 1608 ν(CH = CH), 1228,1271 ν(C–N), 1162 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.33–9.44s(2H), 4.79–4.81d(1H), 4.84–5.20d(1H), (CH), 3.21s(3H), 3.84s(2H), (−CH_2), 3.53s(3H), 3.83s(3H); (−CH_3), 7.11s

Table 3. Zone of inhibition of all ligands.

Schiff Base Ligands	Zone of inhibition of organisms (mm)							
	Bacillus subtilis (BS)		*Stenotrophomonas maltophilia* (SM)		*Serratia marcescens* (SM)		*E. coli* (EC)	
C^1	A	3 ± 0.9	A	20 ± 1.1	A	50 ± 0.4	A	25 ± 1.1
	B	5 ± 1.1	B	28 ± 1.9	B	50 ± 0.3	B	30 ± 2.1
	C	7 ± 1.3	C	30 ± 0.3	C	65 ± 0.5	C	68 ± 0.9
C^2	A	1 ± 0.9	A	35 ± 2.1	A	20 ± 1.9	A	45 ± 1.9
	B	2 ± 1.9	B	38 ± 1.8	B	25 ± 2.0	B	60 ± 2.0
	C	3 ± 2.0	C	60 ± 1.8	C	30 ± 2.0	C	65 ± 2.0
C^3	A	–	A	–	A	–	A	0
	B	–	B	–	B	–	B	0
	C	–	C	–	C	–	C	40 ± 1.5
C^4	A	–	A	6 ± 1.5	A	8 ± 2.0	A	40 ± 1.5
	B	–	B	20 ± 1.5	B	19 ± 1.5	B	50 ± 2.0
	C	–	C	35 ± 2.0	C	30 ± 1.5	C	60 ± 2.0
C^5	A	–	A	–	A	–	A	–
	B	–	B	–	B	–	B	35 ± 1.5
	C	–	C	–	C	–	C	56 ± 2.0
C^6	A	–	A	20 ± 2.0	A	25 ± 1.8	A	55 ± 1.5
	B	–	B	25 ± 1.5	B	30 ± 2.0	B	60 ± 2.0
	C	–	C	33 ± 2.0	C	50 ± 1.5	C	70 ± 0.8
C^7	A	–	A	–	A	–	A	23 ± 1.0
	B	–	B	–	B	–	B	50 ± 1.5
	C	–	C	–	C	–	C	56 ± 2.0
C^8	A	–	A	–	A	–	A	22 ± 2.0
	B	–	B	–	B	–	B	49 ± 1.5
	C	–	C	–	C	–	C	55 ± 2.0
C^9	A	–	A	–	A	–	A	23 ± 1.5
	B	–	B	–	B	–	B	50 ± 2.0
	C	–	C	–	C	–	C	56 ± 1.8

– = No activity.

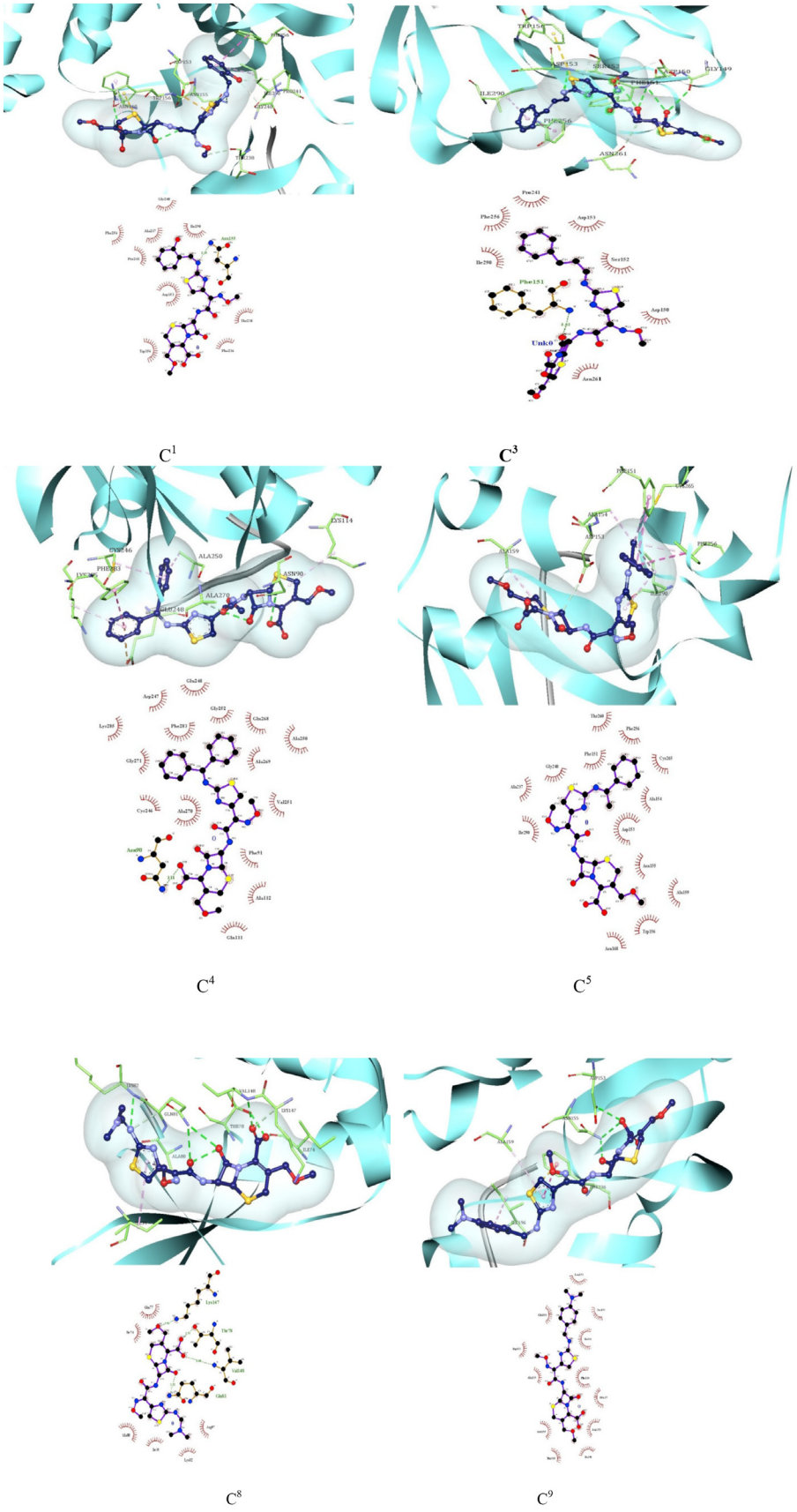


Figure 2. 2D and 3D structure of Molecular docking of C^1, C^3, C^4, C^5, C^8 and C^9 of IBV-PLpro.

Table 4. Representing binding energies, residues, types of interactions, hydrophobic interactions, and electrostatic interactions of C^1–C^9 newly synthesized compounds during docking studies against IBV Papain like protease protein (PLpro).

Target	Compound	Binding energy (kcal/mol)	Residues forming H bonds	Type of Interaction	Distance between H bonds (Å)	Residues participating in Hydrophobic interactions	Type of Interaction	Distance between hydrophobic interactions (Å)	Residues participating in Electrostatic interactions	Type of Interaction	Distance between Electrostatic interactions (Å)
IBV Plpro	C^1	−7.8	ASN 155	Conventional	3.2	TRP 156	π-CH	4.26	ASP 153	π-anion	3.18
			ASN 160	Conventional	3.32		π-S	3.85	–	–	–
			THR 238	C–H	3.57	ILE 290	π-CH	5.47	–	–	–
			GLY 240	C–H	3.52	PHE 256	Π–π	4.43	–	–	–
			PRO 241	C–H	3.61	–	–	–	–	–	–
	C^3	−7.9	GLY 149	Conventional	3.24	SER 152	π donor	4.2	–	–	–
			ASP 150	Conventional	3.36	TRP 156	π-S	5.38	–	–	–
				C–H	3.7	PHE 256	π–π	3.8	–	–	–
			PHE 151	Conventional	3.02	ILE 290	π-CH	5.24	–	–	–
				Conventional	3.31	–	–	–	–	–	–
			ASP 153	Conventional	3.33	–	–	–	–	–	–
			ASN 261	C—H	3.75	–	–	–	–	–	–
	C^4	−8.5	ASN 90	Conventional	3.11	LYS 114	π-CH	4.97	GLU 248	π-anion	4.28
			ALA 270	C–H	2.91	CYS 246	π-CH	4.95	–	–	–
			–	–	–	ALA 250	π-CH	4.92	–	–	–
			–	–	–	PHE 283	π–π	4.71	–	–	–
			–	–	–	LYS 285	π-CH	4.9	–	–	–
	C^5	−7.3	ASP 153	C–H	3.1	PHE 151	π-CH	4.94	–	–	–
			–	–	–		π–π	5.28	–	–	–
			–	–	–	ALA 154	CH–CH	4.46	–	–	–
			–	–	–	ALA 159	π-CH	5.05	–	–	–
			–	–	–	PHE 256	π-CH	4.69	–	–	–
			–	–	–		π–π	5.08	–	–	–
			–	–	–	CYS 265	CH–CH	4.71	–	–	–
			–	–	–	ILE 290	CH–CH	4.79	–	–	–
			–	–	–		π-CH	5.21	–	–	–
	C^8	−6.8	ILE 74	Conventional	3.3	ILE 39	π-CH	4.99	–	–	–
			THR 78	Conventional	2.7	ALA 80	π-CH	4.42	–	–	–
			GLN 81	C–H	3.46	–	–	–	–	–	–
				Conventional	3.23	–	–	–	–	–	–
			LYS 82	Conventional	3.37	–	–	–	–	–	–
			LYS 147	Conventional	3.17	–	–	–	–	–	–
			VAL 148	Conventional	3	–	–	–	–	–	–
	C^9	−7.6	ASP 153	Conventional	2.97	ALA 159	π-CH	4.7	–	–	–
			ASP 155	Conventional	3.08	ILE 196	π-CH	4.89	–	–	–
			ILE 196	C–H	3.58	PHE 236	π–π	5.11	–	–	–
			–	–	–		π-S	5.08	–	–	–

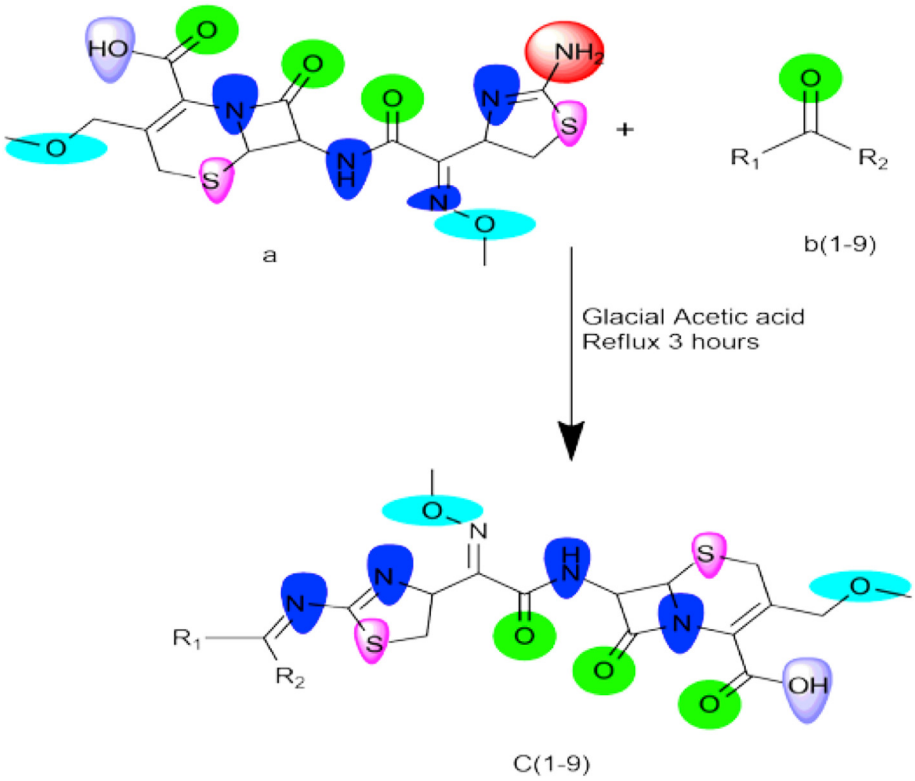
(1H), (−NH−), 4.82s(2H), (-NH_2), 9.51s,(1H) (OH),^{13}C NMR (DMSO−d6, 400 ppm), δ 25.8 (C-1), 129.5 (C-2), 123.6 (C-3), 61.8 (C-4), 58.8 (C-5), 163.7 (C-6), 159.5 (C-7), 69.7 (C-8), 57.8 (C-9), 162.9 (C-10), 151.7 (C-11), 61.8 (C-12), 149.0 (C-13), 123.6 (C-14), 168.3 (C-15), 160.3 (C-16), 119.4 (C-17), 131.2 (C-18), 122.2 (C-19). 135.1 (C-20). 117.2 (C-21), 160.6 (C-22).

7.2.2. Synthesis of 7-((E)-2-(2-((Z)-benzylidene amino) thiazol-4-yl)-2-(methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylicacid (C^2)

Equimolar mixture of Benzaldehyde and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Yellowish brown crystals: Yield (77%), m. p. 113–115 °C, Mol. Wt. 515.09, Elemental Analysis: (Calculated) for $C_{22}H_{21}N_5O_6S_2$: C, 51.25; H, 4.11; N, 13.58; (Found): C, 50.25; H, 4.01; N, 13.30; FTIR (cm^{-1}), 3309, 3447 ν(NH), 2817, 2886 ν(CH), 1710,1762 ν(C=N), 1660 ν(CH = CH), 1374 ν(C–N), 1274 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 10.02 s (1H), 5.20d (1H), 4.80–4.81d (2H), (CH), 3.204s–3.208s (2H), 3.831–3.839s (2H), (−CH_2), 3.84–3.85s (2H), 3.91s (3H); (−CH_3), 7.47–7.49s (2H), (−NH−), 4.811–4.819s (2H), (-NH_2), 7.93–7.95s, (4H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 25.7 (C-1), 129.0 (C-2), 123.6 (C-3), 61.8 (C-4), 58.8 (C-5), 163.9 (C-6), 159.5 (C-7), 69.7 (C-8), 57.8 (C-9), 162.9 (C-10), 151.8 (C-11), 61.8 (C-12), 148.9(C-13), 123.6 (C-14), 168.3 (C-15), 159.5 (C-16), 129.1 (C-17), 130.8 (C-18), 128.7 (C-19), 130.8 (C-20), 128.9 (C-21), 129.3 (C-22).

7.2.3. Synthesis of 7-((E)-2-(methoxyimino)-2-(2-((Z)-((E)-3-phenyl alkylidene) amino) thiazol-4-yl) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^3)

Equimolar mixture of Cinnamonaldehyde and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also



Scheme 1. Synthesis of Schiff's bases of Cefpodoxime

dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Yellowish brown semi-solid: Yield (71%), Mol. Wt. 541.60, Elemental Analysis: (Calculated) for $C_{24}H_{23}N_5O_6S_2$: C, 53.22; H, 4.28; N, 12.93; (Found): C, 53.25; H, 4.78; N, 12.97; FT-IR (cm^{-1}), 3301ν(NH), 2824, 2896 ν(CH), 1621–1661 ν(C=N), 1446, 1515 ν(CH = CH), 1012-1035ν (C–N), 1066 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.68-9-69d (1H), 7.71–7.74t (4H), 4.79–4.93s (1H), (CH), 3.21–3.22t (3H), 3.84s (1H), (−CH_2), 3.71s (2H), 3.84s (3H); (−CH_3), 7.71–7.74t (4H), (−NH−), 4.14s (2H), (-NH_2), 9.59–9.60d, (2H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 21.2 (C-1), 130.1 (C-2), 119.2 (C-3), 56.9 (C-4), 56.9 (C-5), 152.8 (C-6), 152.4 (C-7), 143.8 (C-8), 56.9 (C-9), 141.9 (C-10), 152.4 (C-11), 72.5 (C-12), 143.8 (C-13), 119.2 (C-14), 152.8 (C-15), 152.4 (C-16), 119.2 (C-17), 134.1 (C-18), 134.1 (C-19), 128.8 (C-20), 128.6 (C-21), 127.5 (C-22), 128.6 (C-23), 128.8 (C-24).

7.2.4. Synthesis of (E)-7-(2-(2-((diphenyl methylene) amino) thiazol-4-yl)-2 (methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^4)

Equimolar mixture of Benzophenone and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Yellowish brown crystals: Yield (71%), m. p. 91–93 °C, Mol. Wt. 591.66, Elemental Analysis: (Calculated) for $C_{28}H_{25}N_5O_6S_2$: C, 56.80; H, 4.22; N, 11.87; (Found): C, 57.05; H, 4.09; N, 12.30; FT-IR (cm^{-1}), 3273, 3352 ν(NH), 2932,2968ν(CH), 1757ν(C=N), 1667 ν(CH = CH), 1370 ν(C–N), 1268 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 7.72–7.74s (5H), 7.66–7.69s (5H), 4.79–4.81d (1H), (CH), 3.83–3.86s (2H), 3.88–3.93s (2H), (−CH_2), 3.51s (3H), 3.83s (3H); (−CH_3), 7.55s (1H), (−NH−), 4.15s (2H), (-NH_2), 7.74s, (1H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), 21.2 (C-1), 129.4 (C-2), 128.5 (C-3), 69.7 (C-4), 57.4 (C-5), 151.7 (C-6), 151.7 (C-7), 69.7 (C-8), 57.4 (C-9),151.7 (C-10), 151.7 (C-11), 57.4 (C-12), 137.1(C-13), 128.5 (C-14), 151.7 (C-15), 195.7 (C-16), 195.7 (C-17), 129.4 (C-18), 128.5 (C-19), 132.5 (C-20), 128.5 (C-21), (C-22), 129.4 (C-23), 129.4 (C-24), 128.5 (C-25), 132.5 (C-26), 128.5 (C-27), 129.4 (C-28).

7.2.5. Synthesis of 7-((E)-2-(methoxyimino)-2-(2-((Z)-(1-phenyl ethylidene) amino) thiazol-4-yl) acetamido)-3-(meth-oxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^5)

Equimolar mixture of Acetophenone and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Red semi solid: Yield (77%), Mol. Wt. 529.59, Elemental Analysis: (Calculated) for$C_{23}H_{23}N_5O_6S_2$: C, 52.15; H, 4.41; N, 14.38; (Found): C, 52.25; H, 4.30; N, 13.30; FT-IR (cm^{-1}), 3201, 3270 ν(NH), 2810, 2886 ν(CH), 1677 ν(C=N), 1528 ν(CH = CH), 1363 ν(C–N), 1266 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 7.94–7.95 d (5H), 4.800–4.808d (2H), 6.72–6.78d (1H), (CH), 3.15s (1H), 3.16s (2H), 3.84s (2H), (−CH_2), 3.25s (3H), 3.83s (3H); (−CH_3), 7.52s (1H),

Table 5. R_1 and R_2 of synthesized Schiff Bases of C.

Code	R_1	R_2
C^1	H	HO–C_6H_5
C^2	H	–C_6H_5
C^3	H	–CH=CH–C_6H_5
C^4	–C_6H_5	–C_6H_5
C^5	–CH_3	–C_6H_5
C^6	H	H
C^7	H	$C_8H_{10}O_2$
C^8	H	$C_3H_9O_2$
C^9	H	$C_9H_{13}N_2$

(−NH−), 4.80s (2H), (-NH_2), 9.51s, (1H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 25.4 (C-1), 133.0 (C-2), 123.6 (C-3), 61.8 (C-4), 58.8 (C-5), 163.9 (C-6), 159.6 (C-7), 69.7 (C-8), 57.8 (C-9),162.8 (C-10), 151.8 (C-11), 61.8 (C-12), 148.9(C-13), 123.6 (C-14), 168.3 (C-15), 25.4 (C-16), 168.3 (C-17), 136.9 (C-18), 128.0 (C-19), 128.6 (C-20), 133.0 (C-21), 128.6 (C-22), 128.0 (C-23).

7.2.6. Synthesis of (E)-7-(2-(methoxyimino)-2-(2-(methylene amino) thiazol-4-yl) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^6)

Equimolar mixture of Formaldehyde and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Light brick crystals: Yield (79%), m. p. 86 °C, Mol. Wt. 439.06, Elemental Analysis: (Calculated) for $C_{16}H_{17}N_5O_6S_2$: C, 41.15; H, 4.21; N, 16.38; (Found): C, 41.25; H, 4.11; N, 16.32; FT-IR (cm^{-1}), -3275, 3473 ν(NH), 2824, 2971ν(CH), 1666 ν(C=N), 1622 ν(CH = CH), 1097 ν(C–N), 1066 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.51 s (1H), 5.16–5.17d (1H), 5.2d (1H), (CH), 1.25–1.26s (2H), 1.49–1.50s (4H) (−CH_2), 1.03–1.24s (4H) (−CH_3), 7.10s (1H), (−NH−), 4.82s (2H), (-NH_2), 9.51s, (1H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 25.4 (C-1), 128.9 (C-2), 123.6 (C-3), 61.9 (C-4), 58.8 (C-5), 163.9 (C-6), 159.5 (C-7), 69.7 (C-8), 57.8 (C-9),162.8 (C-10), 151.9 (C-11), 61.9 (C-12), 148.9(C-13), 123.6 (C-14), 171.7 (C-15), 162.8(C-16).

7.2.7. Synthesis of 7-((E)-2-(2-((Z)-(4-hydroxy-3-methoxybenzylidene) amino) thiazol-4-yl)-2-(methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^7)

Equimolar mixture of Vanillin and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Brownish amorphous powder: Yield (74%), m. p. 96 °C, Mol. Wt. 561.59, Elemental Analysis: (Calculated) for $C_{23}H_{23}N_5O_8S_2$: C, 49.19; H, 4.13; N, 12.47; (Found): C, 48.21; H, 4.31; N, 14.21; FT-IR (cm^{-1}), 3201, 3429 ν(NH), 2881 ν(CH), 1633 ν(C=N), 1540 ν(CH = CH), 1370 ν(C–N), 1239 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.77 s (1H), 7.39–7.42d (2H), 6.95–6.96d (2H), (CH), 3.15–3.21s (3H), 3.84s (2H), (−CH_2), 3.83s (3H), 3.83s (3H), 3.84s (3H); (−CH_3), 7.39s (1H), (−NH−), 3.79d (2H), (-NH_2), 9.77s, (1H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 25.4 (C-1), 128.8 (C-2), 123.8 (C-3), 62.0 (C-4), 57.4 (C-5), 153.7 (C-6), 153.0 (C-7), 69.7 (C-8), 57.4 (C-9),153.7 (C-10), 151.7 (C-11), 62.0 (C-12), 148.2 (C-13), 123.8 (C-14), 153.7 (C-15), 153.0 (C-16), 128.8 (C-17), 123.8 (C-18), 115.4 (C-19), 151.7 (C-20), 148.2 (C-21), 111.8 (C-22), 56.9 (C-23).

7.2.8. Synthesis of 7-((E)-2-(2-((Z)-((dimethyl amino) methylene) amino) thiazol-4-yl)-2-(methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^8)

Equimolar mixture of Dimethyl Formamide and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Yellowish brown crystals: Yield (78%), m. p. 102–106 °C, Mol. Wt. 482.53, Elemental Analysis: (Calculated) for $C_{18}H_{22}N_6O_6S_2$: C, 44.80; H, 4.60; N, 17.42; (Found): C, 46.20; H, 4.50; N, 18.21; FT-IR (cm^{-1}), 3380 ν(NH), 2911, 2977 ν(CH), 1647 ν(C=N), 1615 ν(CH=CH), 1374 ν(C–N), 1194 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.49–9.53 s (2H), 4.14–4.15d (4H), 5.19–5.20d (2H), (CH), 3.20s, 3.49s (2H), 3.84s (2H), (−CH_2), 3.84t (3H), 3.83s (3H); (−CH_3), 7.94s (1H), (−NH−), 4.08d (2H), (-NH_2), 9.49–9.53d, (1H) (OH), ^{13}C NMR (DMSO−d6, 400 MHz), δ 25.4 (C-1), 91.7 (C-2), 92.0 (C-3), 61.8 (C-4), 58.8 (C-5), 162.2 (C-6), 159.6 (C-7), 69.7 (C-8), 57.4 (C-9),162.2 (C-10), 151.7 (C-11), 61.8 (C-12), 92.0(C-13), 91.7 (C-14), 168.4 (C-15), 151.7 (C-16),35,7 (C-17), 35.7 (C-18).

7.2.9. Synthesis of 7-((E)-2-(2-((Z)-(4-(dimethyl amino) benzylidene) amino) thiazol-4-yl)-2-(methoxyimino) acetamido)-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid (C^9)

Equimolar mixture of Dimethylaminobenzaldehyde and Cefpodoxime drug were added in 250 ml capacity round bottom flask in ethanol (30 ml) used as a solvent. Few drops (Five to Six) of glacial acetic acid were also dropped in a round-bottom flask as the catalyst. The reaction mixture refluxing for 03 h at controlled temperature in the water bath, cooled at room temperature and filtration was performed. Brown crystals: Yield (79%), m. p. 130 °C, Mol. Wt. 558.63, Elemental Analysis: (Calculated) for $C_{24}H_{26}N_6O_6S_2$: C, 51.60; H, 4.69; N, 15.04; (Found): C, 51.25; H, 4.50; N, 15.30; FT-IR (cm^{-1}), 3308, ν(NH), 2969ν (CH), 1760 ν(C=N), 1669 ν(CH=CH), 1372 ν(C–N), 1271 ν(C–O), ^{1}H NMR (DMSO−d6, 400 MHz); δ 9.67s (1H), 9.50–9.54t (4H), 4.78–4.80d (4H), (CH), 3.20s–3.21s (2H), 3.84–3.85t (4H), (−CH_2), 3.84–3.85s (2H), 3.91s (3H); (−CH_3), 7.66–7.81s (4H), (−NH−), 4.78–4.80d (1H), (-NH_2), 8.27, (1H) (OH),^{13}C NMR (DMSO−d6, 400 MHz), 25.4 (C-1), 130.5 (C-2), 123.3 (C-3), 60.0 (C-4), 57.4 (C-5), 168.6 (C-6), 154.2 (C-7), 69.7 (C-8), 57.4 (C-9), 168.6 (C-10), 153.9 (C-11), 62.0 (C-12), 152.3(C-13), 123.3 (C-14), 168.6 (C-15), 154.2 (C-16), 130.5 (C-17), 131.4 (C-18), 124.6 (C-19), 130.5 (C-20), 124.6 (C-21), 124.6 (C-22), 49.7(C-23), 49.7(C-24).

8. Discussion

New novel compounds were synthesized by a condensation reaction, that is a single-step reaction in a drug having a primary amine carbon group was condensed with nine different aldehydes/ketones by reflux distillation method under controlled temperature. The obtained compounds C^1–C^9 were dried with the help of a rotary evaporator. The percentage yield was calculated by using weighing apparatus. The physical and chemical characteristics (color, odor, physical form, solubility, and melting point) were studied. Solubility was determined in Methanol, Ethanol, Chloroform, Water, DMSO, n-Hexane, and n-Butanol by using Sonicator. The melting point was determined by the Gallen Kamp apparatus.

Novel synthesized compounds ***C^1–C^9*** (Table No. 5), synthesis was confirmed by spectroscopic techniques such as FTIR (Fourier Transform Infrared spectroscopy), H^1-NMR (Proton Nuclear Magnetic spectroscopy), and C^{13} Nuclear Magnetic Spectroscopy.

Antibacterial studies against four bacterial strains (*Bacillus subtilis, Stenotrophomonas maltophilia, Serratia marcescens,* and *E. Coli*) were performed and compared with standard antibacterial drug Cefpodoxime i.e. the parent drug from which all nine-novel compounds were synthesized.

C^1 and ***C^2*** have average antibacterial activity against *Bacillus subtilis* as compared to the parent drug cefpodoxime.

C^1, C^2, C^4, and ***C^6*** showed effective activity against *Stenotrophomonas maltophilia* in comparison to parent drug Cefpodoxime (C). Cefpodoxime as control showed average activity and ***C^3, C^5, C^6, C^7, C^8***, and ***C^9*** showed no activity on any concentration in comparison with Cefpodoxime.

C^1, C^2, C^4, and ***C^6*** showed effective activity against *Serratia marcescens* in comparison of Cefpodoxime (C), Cefpodoxime (C) as control showed average activity and ***C^3, C^5, C^6, C^7, C^8***, and ***C^9*** showed no activity on any concentration in comparison with Cefpodoxime.

C^1, C^2, C^3, C^5, C^6, C^8, and ***C^9*** showed effective activity against *E. coli*, whereas Cefpodoxime C as control showed average activity and ***C^7*** showed no activity on any concentration in comparison with Cefpodoxime.

All newly synthesized compounds ***C^1, C^2, C^3, C^4, C^5, C^6, C^7, C^8***, and ***C^9*** showed highly strong antiviral potential against Avian Influenza (H^9) and Avian corona (IBV) viruses.

The grid box was centered on the conserved catalytic triad and surrounding amino acid residues composing ubiquitin Binding Domain.

8.1. Docking interactions with IBV-PLpro

Most of the molecular interactions were localized in the thumb (residues 56–168), finger (residues 169–231), and palm (residues 232–310) domains of IBV PLPro. Significant interactions were also observed with residues composing the Ubiquitin Binding Domain of IBV PLPro.

C*^{1}** displayed binding energy of -7.8 kcal/mol. The carboxylate **–OH** (O28) donated **H to the carbonyl group of ASN160 producing only one H-bond. Further, three weak C–H interactions were formed with residues of the palm domain i.e.; –OH of the o-cresol functional group donated hydrogen to carbons **CD** of **PRO241** and CA of GLY240. Third, C–H linkage was established between the methoxamine group **(C24)** and THR238. One H-bond was donated by the **ND2** amino group of **ASN155** to a nitrogen atom (N21) linking the cresol group. The electron-deficient Thiazole ring system was stabilized by π-anion interaction with –OH of **ASP153**. The aromatic system of the o-cresol ring was stabilized by stacking with PHE 256 and the alkyl group of **ILE290.** The delocalized π-electron density of the indole ring of **TRP156** established hydrophobic linkages with Sulphur and carbon atoms of the β-lactam ring.

In the case of ***C*^{2}**, styrene linked Thiazole portion was deeply embedded in Ubiquitin Binding Domain. **PHE256** stabilized the aromatic styrene via π-stacking which was further strengthened by π-CH contact with **ILE 290**. H-bond was also established between the amino group of **ASP153** and nitrogen atom linking styrene to Thiazole ring. The π electron density of the indole ring of **TRP156** stabilized the conformation by hydrophobic contact with the sulfur atom of the Thiazole moiety. Further stability was achieved by donation of lone pair from **OH** hydroxyl group of **SER152** to electron-deficient aromatic Thiazole ring. The carboxylate **–OH (O28)** further anchored by forming two H-bonds with **ASP150** and adjacent residue GLY149. The amide of **PHE151** donated hydrogen to the carbonyl oxygen of the β-lactam ring. Weak C–H interactions were also observed between methoxamine carbon **(C24)** and **ASP150**; beta-lactam carbon and **ASN261.**

The Diphenylmethane moiety of ***C*^{4}** displayed hydrophobic interactions with Blocking Loop 1 (BL-1) composed of residues (**ASP245-VAL251**) linking finger and palm domains. Both rings of diphenylmethane established π-CH contacts with **ALA250**, **CYS246,** and **LYS285.** Further stability was achieved by an edge to face π-stacking with the aromatic ring of PHE283 and π-anion contact with **–OH (OE2)** of **GLU248**. the β-lactam ring was deeply embedded in the thumb domain with carboxylate **–OH (O28)** accepting H-bond from an amino group (ND2) of ASN90. Another hydrophobic contact was established between the π-electron of the thiazine ring and the alkyl group of **LYS114**.

The β-lactam ring system of ***C*^{5}** sustained only weak interactions like the C–H bond with –OH (OD2) of ASP153 and π-CH contact with **ALA159.** The alkyl group of ethylbenzene substituent **(C36)** firmly anchored the molecule in the thumb and UBD Domain by maintaining three alkyl-alkyl contacts with **ALA154**, **CYS265**, and **ILE290**. The aromatic ring systems of phenylalanine residues **151** and **256** stabilized the conformation simultaneously via stacking with π-electrons of the ethylbenzene ring and interacting with $–CH_3$ electrons. π-CH contact was also formed between the alkyl group of **ILE290** and the π-electron density of the Thiazole ring system.

***C*^{8}** displayed interactions with thumb domain amino acid residues. Two H-bonds were formed by β-lactam carboxylate **–OH (O28)** with **OG1 –OH** of **THR78** and the carbonyl oxygen of **ILE74.** β-lactam carbonyl O27 also accepted H-bond from the amino group of **VAL148** while also maintaining weak **C–H** interaction with CA of **LYS147**. Methoxy oxygen **O2** was also hydrogen loving from amino group **NZ** of **LYS147**. H-bond was established between **N21** nitrogen atom attached to dimethylamine substituent with **LYS82.** CA of GLN 81 formed a weak **C–H** bond with **N21**. **NE2** amino group of **GLN81** donated H-bond to **O14** of carbonyl group adjacent to the Thiazole ring system. π-electrons of Thiazole ring further interacted with **$–CH_3$** electrons to **ILE39** to stabilize the interaction.

***C*^{9}** constituted only two linkages in UBD Domain via H-bonding of residues **ASP153** and **ASN155** with carboxylate **–OH (O28)** attached to the thiazine ring system. The π-electron cloud of **PHE236** stabilized the Thiazole ring simultaneously via edge to face π-stacking and interacting with ring sulfur. Alkyl group electrons of **ALA159** further anchored Thiazole ring by π-CH interactions whilst alkyl group electrons of **ILE196** interacted with π-electrons of N, N-dimethylaniline substituent. **C29** of N, N-dimethylaniline substituent exhibited weak **C–H** interaction with **ILE296.**

9. Conclusion

Newly synthesized Schiff base derivatives showed potential antiviral potential against Corona class virus variant Avian Coronavirus (IBV) along with antibacterial potential against selective strains. The compounds also have hepatoprotective characteristics as compounds have significant antioxidant potential. Some of the compounds show significant anti-urease potential. Further clinical studies may lead to a breakthrough in medical sciences and the market will have potential drugs against complex infective diseases.

Declarations

Author contribution statement

Waqas Mahmood: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Mohsin Abbas Khan: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Irshad Ahmad: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Syed Adnan Ali Shah, Mirza Imran Shahzad, Muhammad Ashraf, Irfan Pervaiz, Muhammad Sajid-ur-Rehman and Umair Khurshid: Contributed reagents, materials, analysis tools or data.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

Data will be made available on request.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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