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Design, Synthesis of Novel Ethylene Bridged N-Acyl Homoserine Lactones as Inhibitors of Quorum Sensing Signaling in Pathogenic Bacteria to Prevent Biofilm Formation

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Abstract

Gram-negative bacteria such as Pseudomonas aeruginosa use N-acylated L-homoserine lactones (AHLs) as autoinducers (AIs) for quorum sensing (QS) signaling, a chief regulatory protein responsible for cell-to-cell communication system in bacteria. QS are responsible for social adaptation, virulence factor production, biofilm production and antibiotic resistance in bacteria. Inhibition of this communication signaling system could lead to an effective treatment of pathogenic bacterial infections. Hence, quorum sensing signaling proteins attracted greater attention and considered as novel targets to develop drugs acting against drug resistant bacterial infections. In view of this, the present investigation was directed towards the design of AHL analogues employing a rational drug design approach. Novel series of ethyl bridged N-acyl Homo serine lactones has been designed and synthesized.

Keywords

N-acyl Homo serine lactones, quorum sensing, *Chromobacterium Violaceum*

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INTRODUCTION:

Overuse of antibiotics for the treatment of gram positive and gram-negative bacterial infections led to the development of many antibiotic resistant strains. This would result in a tragedy in the antibiotics existence where no antibiotic would be effective to treat simple bacterial infections soon. Recently, research has prompted on to the development of novel strategies which would be helpful in treating the pathogenic infections caused by the antibiotic resistant strains with the minimal use of antibiotics. One of such novel approaches is to inhibit or interfere the quorum sensing mechanism in bacteria. Quorum sensing mechanism is the cell-cell signal communication process that depends on the optimum concentration of the signal molecules known as Acetyl homoserine lactone (AHL). The signaling molecule usually induced by a protein in the bacterial cell called LuxI and released from the bacterial cell into the external environment. Whenever, an optimum amount of signal molecules is available in the external environment surround the bacterial cell, diffuses through the cell, and activates LuxR receptors in the bacterial cell that promotes the gene transcription. This process led to the synthesis of proteins required for the pathogenesis, virulence, and biofilm development.

Recently few compounds have been reported to have QS inhibition and some of them act by preventing the binding of signal molecule Acyl

Homoserine Lactone (AHL) to the LuxR receptors present in the bacteria. The antagonistic properties can be incorporated into the agonist AHL either by increasing the chain length or by adding some aromatic or other ring systems to replace lactone ring. In view of the above observation, the present investigation was proposed to design and synthesize some novel N-acyl Homoserine lactone derivatives based on the existing inhibitory molecules to develop new quorum sensing inhibitors.

In the present investigation, N-acyl homoserine lactone derivatives were designed and synthesized. The synthesized compounds were characterized by the physical, spectral and elemental analysis data. The compounds were screened for the quorum sensing inhibitory activity on chromobacteriaum violaceum strain.

EXPERIMENTAL METHODS:

Designing of the proposed molecules:

The proposed molecules were designed to target mainly the LuxR receptors and antagonizing the action of AHL molecules and its binding. LuxR antagonist Chlorolactone was considered as the lead for the designing, the p-chloro phenyl group was replaced with various aromatic and hetero aromatic substitutions and a secondary amine group was added between the ethyl group and the terminal hetero substitution. These designed molecules were docked into the AHL binding site of LuxR receptor. The results of this preliminary inhibitory screening suggested that the designed inhibitors possessing a bicyclic hetero cyclic ring system

Design of Ahl analogues:

In the present investigation the design of AHL analogues was carried out by structural comparison of previously reported LuxR inhibitors. Acyl homoserine lactone was taken as prototype for the design of AHL analogues as Quorum sensing (LuxR) inhibitors.

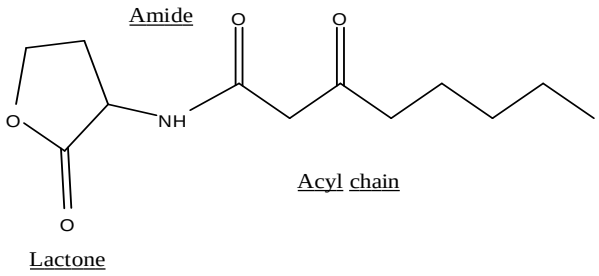
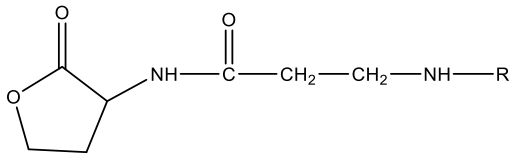


Fig1.1: General structure of AHL

Table 1 Structure of Designed AHL analogues



Entry	Ligand	R
1	4A	Amide
2	4B	2-Pyridyl
3	4C	2-Pyrimidyl
4	4D	2-thienyl
5	4E	2-napthyl
6	4F	2-hydroxyphenyl
7	4G	1,3,4 triazol-2-yl
8	4H	N-(2-oxotetrahydrofuran-3-yl)-3-(quinazolin-2-ylamino) propanamide
9	4I	N-(2-oxotetrahydrofuran-3-yl)-3-(quinolin-7-ylamino) propanamide
10	4J	3-methyl butanoic acid
11	4K	4-Methyl Pentanoic acid

Molecular property calculations:

The 2D structures of the designed AHL analogues were drawn by using Chemdraw software. The structures were saved in .cdx format and mol format for further conversion. The molecular properties such as molecular weight, rotatable bonds, LogP, topological surface area (TPSA), hydrogen bonds donors (HBD) and hydrogen bond acceptors (HBA) of the selected inhibitors were calculated by using MOLINSPIRATION tool[28]. The 2D structures of selected inhibitors in mol2 format were submitted to MOLINSPIRATION. The calculated molecular properties of newly designed AHL analogues are given in the table 1.1 The 2D structures were converted into 3D structures by using PRODRG server[29] employing energy minimization. The generated and energy minimized 3D structures were downloaded as PDB coordinates with polar hydrogens. These PDB structures were used in the molecular docking studies.

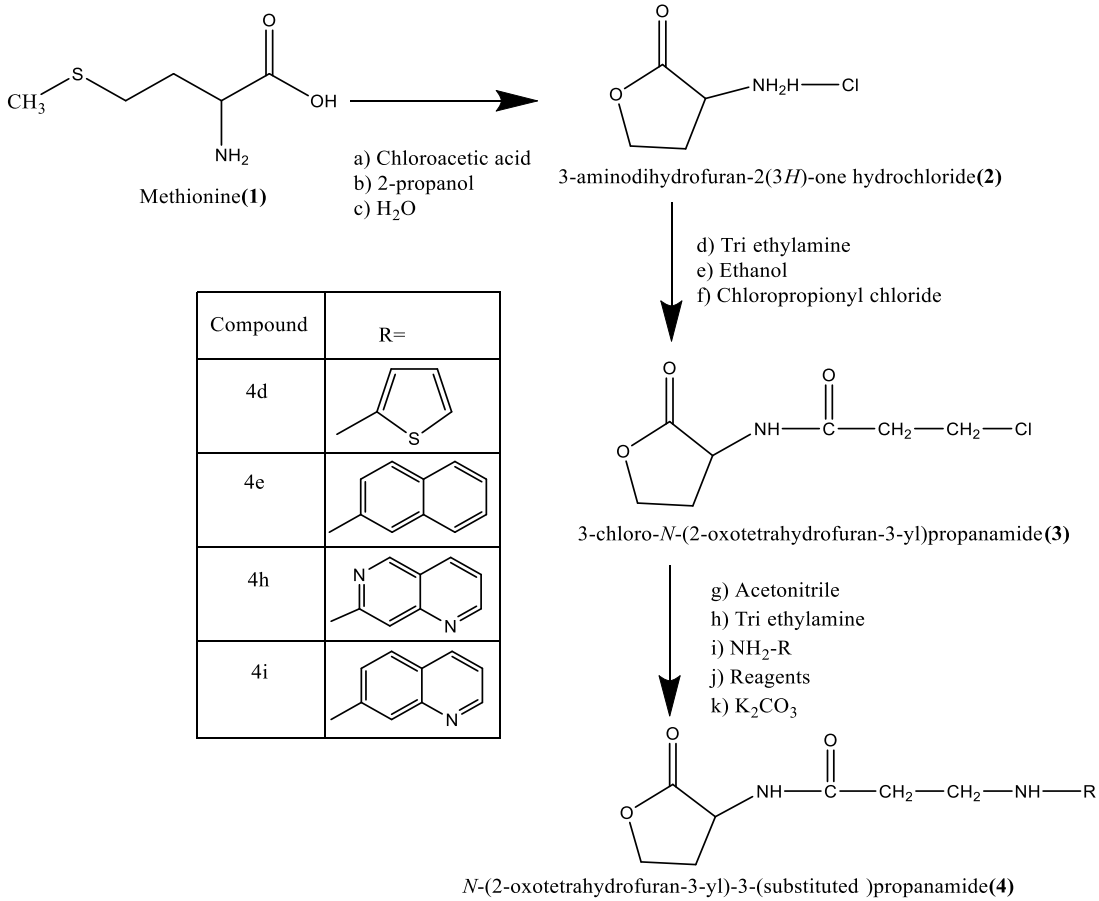
Molecular Docking studies:

Molecular docking studies were carried out with AUTODOCK 4.2.6[32] software for the target protein, the 3D structure of LuxR-type transcription factor CviR from *Chromobacterium violaceum* complex with selective inhibitor Chlorolactone (PDB ID 3QP5)[31] downloaded from protein data bank. The docking of designed ligands into the active site of *3QP5 (*X=15.83, Y=16.347, Z=26.775 with grid dimensions*)* was performed according to the standard procedure. The docking score in terms of binding energy and binding interactions of docked molecules were considered to analyze and identify potential molecules. Prior to the docking of test compounds, the docking method was validated with existing inhibitor molecule within the protein.

Synthetic Methodology:

The proposed molecules were synthesized following appropriate steps outlined in the scheme-I.

Synthesis of N-(2-oxotetrahydrofuran-3-yl) propanamides (4D, 4E, 4H and 4I)



Compound	R=
4d	
4e	
4h	
4i	

SCHEME-I

Materials and Methods

All the required chemicals were purchased from Sd. fine chemicals Ltd, E. Mark, NR chemicals Ltd and Aldrich chemicals. All the solvents used were of analytical grade. Each reaction step was monitored by TLC and the purity of the compounds was checked by TLC (silica gel 60 F254 0.25 mm precoated aluminium plates) using appropriate solvent systems which were selected by trial-and-error method. Visualization and identification of the spots on TLC plates was performed in UV chamber.

All the synthesized compounds were purified by recrystallization using appropriate solvents which were selected by trialand error method. IR spectra (KBr discs cm^{-1}) of the purified compounds were recorded on FTIR spectrophotometer (SHIMADZU 8400 series) and thermo Nicholet nexus 60. Mass spectra of the compounds were recorded on Agilent 1100 series. Melting points were determined using open capillary tubes on ANALAB melting point apparatus. ^{1}HNMR spectra were recorded on BRUKER 400 MHz spectrometer using $CDCl_3$ as solvent and tetra methyl silane as an internal standard.

Preparation of 3-aminodihydrofuran-2(3H)-1dihydrochloride (2)

L-Methionine(6gr) was added to chloroacetic acid and 2-propanol at 0 °C in a portion-wise manner. The resulting mixture was stirred overnight at ambient temperature and then poured into ice-cold water with vigorous stirring. After stirring for 1 h, the white solid precipitate was collected by filtration. The filter cake was washed with ice-cold water before being dried under vacuum and recrystallized from ethanol.

Preparation of 3-chloro-N-(2-oxotetrahydrofuran-3-yl)propanamide(2)

Four equivalents of chloropropionyl chloride were added drop wise over one hour to the amine in ethanol (**2**) solution. Then the solution was left to stir overnight. The desired product was isolated as precipitate after pouring reaction mixture to an ice-cold water. Precipitate was filtered, washed with cold water and dried. Recrystallized using 95% ethanol.

Preparation of N-(2-oxotetrahydrofuran-3-yl)-3-(thiophen-2-ylamino) propenamide

(3) were dissolved in 20 ml of acetonitrile, 0.02 mol of triethylamine was added dropwise to this solution with stirring. The reaction mixture was refluxed for 24 h, evaporated in rotary evaporator, cooled, and poured into crushed ice and then basified with solid potassium carbonate. The resulting precipitate was filtered, washed with water (3 times 100 ml). The solid residue obtained was recrystallized from methanol to yield the desired compounds.

3-chloro-N-(2-oxotetrahydrofuran-3-yl)

propanamide (0.01 mol) and corresponding heteroaromatic primary amine(R-NH_2) 0.02 mol were dissolved in 20 ml of acetonitrile, 0.02 mol of triethylamine was added dropwise to this solution with stirring. The reaction mixture was refluxed for 24 h, evaporated in rotary evaporator, cooled and poured into crushed ice and then basified with solid potassium carbonate. The resulting precipitate was filtered, washed with water (3 times 100 ml). The solid residue obtained was recrystallized from methanol to yield the desired compounds.

Results and discussion

Molecular properties calculation

The idea behind the calculation and consideration of molecular properties in this study is, firstly to examine or to identify the relationship between the molecular properties of selected inhibitor molecule and second is to assess any possible relationship between the molecular properties of designed quorum sensing inhibitors. These findings could be helpful in the further designing of novel agents in this study. The molecular weight is restricted to below 300 in the designed analogues.

Table 2 Molecular property of the AHL analogues

Entry	Ligand	MOL.WT	No.RotBond	LogP	TPSA	HBD	HBA
1	4A	215.21	4	-2.42	110.52	7	4
2	4B	249.27	5	-0.89	80.32	6	2
3	4C	250.26	5	-1.4	93.21	7	2
4	4D	254.31	5	-0.21	67.43	5	2
5	4E	298.34	5	1.19	67.43	5	2
6	4F	264.34	5	-0.47	87.66	6	3
7	4G	239.24	5	-2.22	109	8	3
8	4H	300.00	5	0.35	93.21	7	2
9	4I	299.33	5	-0.01	80.32	6	2
10	4J	272.3	7	-2.79	104.73	7	3
11	4K	286.33	8	-2.26	104.73	**7**	3
12	CL	297.74	6	1.15	64.64	5	1

Molecular Docking studies

Molecular docking was employed to study the binding patterns of the selected inhibitors with the appropriate target proteins (autoinducers). In order to validate the docking methodology used in the docking studies, the co-crystallized inhibitor (Ligand code- HLC) bound to the target protein(3QP5) was removed. Further the inhibitor was re-docked into

the respective binding site of the protein. The docked (low energy) and co-crystallized conformations were further superimposed to check their conformational relevance. The current docking procedure followed in the present study, re-produced the conformation almost equal to the co-crystallized conformation of the inhibitors used CL in the active site of CViR protein (PDB ID 3QP5).

These results suggested that the current docking methodology is valid, and it could be used for the docking of designed molecules on the target protein. Hence this validated docking procedure was used to carry out the molecular docking studies of selected inhibitors with their appropriate targets. After completion of the docking, the docking results were extracted from the appropriate .dlg file.

Binding interactions of HLC with CviR protein:

When we re-docked the co-crystallized inhibitors with appropriate proteins the obtained docking energy of the best conformation was -8.73 kcal/mol for HLC(LuxR). The main residues involved in the active site of CViR, chlorolactone (LuxR) are TRP 84, TYR 88, SER155, ASP97, and PHE126. Later, all the designed molecules(4A-4K) were docked with the target protein following the above-mentioned valid procedure. The binding affinity and interaction of the each of the inhibitor was studied considering the least energy conformation of the inhibitor. The binding energies of all the docked ligands (top ten conformations) are presented in table3.

Further, the best docking poses of all the docked ligands were superimposed to identify common binding patterns if any. This could be helpful in the selection of potent ligands. The docking analysis revealed that among the designed analogues ligands 4D, 4E, 4H and 4I were found to have best binding affinities and favorable interactions with the target active site. However, all the molecules have good binding capabilities and hence it is worthwhile to synthesize such analogs for further studies.

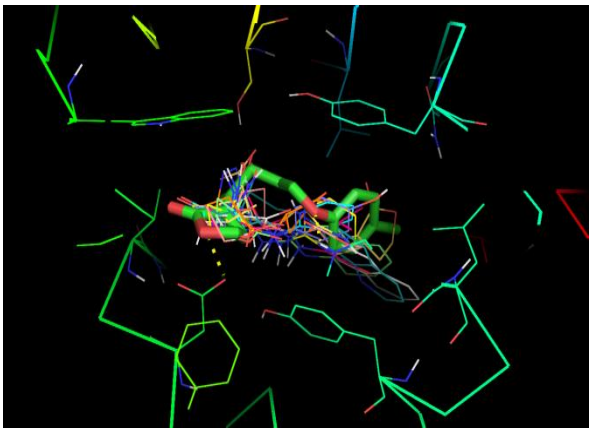


Fig 1 Superimposition of all the designed AHL analogues (4A-4K) and CL(Highlighted) in the active site of the protein PDB ID 3PQ5.

Table 3 Binding energies of top ten conformations of AHL analogues (4A-4K).

AHL ANALO-GUES	Binding Energies(kcal/mole)	Binding Interactions	No of H bonds
4A	-6.61	ASP97, SER155, ILE99, LEU57, TRP84 and TYR80	2
4B	-7.80	ASP97, SER155 and TYR80	3
4C	-7.38	ASP97, SER155, TRP84 and LEU100	3
4D	**-8.34**	**TRP84, ASP97, SER155, TRP80 and TYR88**	**4**
4E	**-8.73**	**ASP97, TRP84 and TRP84**	**2**
4F	-7.76	ASP97, SER155 and PHE126	3
4G	-7.02	ASP97, TRP80, LEU100 and ILE99	4
4H	**-8.65**	**ASP97, TRP84, TYR88 and LEU100**	**4**
4I	**-8.75**	**ASP97, TRP84, TYR88 and PHE126**	**4**
4J	-6.79	ASP97, TRP84 and PHE126	3
4K	**-8.22**	**ASP97, TRP84, LEU155 and SER155**	**4**

Analysis of binding interactions of AHL analogues

The docking analysis of 4A in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-6.61 kcal/mol). The AHL analogue 4A forms an *H* bond with ASP 97, O forms

H bond with SER 155. These interactions are essential for the inhibition. The other interacting amino acid residues are ILE 99, LEU 57, TRP 84 and TYR 80.

The docking analysis of 4B in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-7.80 kcal/mol). The AHL analogue **4B** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond with SER 155, these interactions are essential for binding. Another H bond formed between -NH of the pyridine with TYR 80 amino acid residue is important for inhibition.

The docking analysis of 4C in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-7.38kcal/mol). The AHL analogue **4C** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond with SER 155 and other O bond with TRP 84, these interactions are essential for binding. Another H bond formed between -NH of the pyrimidine with LEU 100 amino acid residue is important for inhibition.

The docking analysis of 4D in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-8.34 kcal/mol) The AHL analogue **4D** –NH attached to lactone ring forms an *H* bond with TRP 84 and ASP 97, however, O of lactone ring forms H bond with SER155, and other O bond with TRP 80, these interactions are essential for binding. Another H bond formed between -NH of the thiophene with TYR 88 amino acid residue is important for inhibition.

The docking analysis of 4E in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-8.73 kcal/mol). The AHL analogue **4E** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond with TRP 84, these interactions are essential for binding. Another O bond attached to lactone ring with TRP 84 amino acid residue is important for inhibition.

The docking analysis of 4F the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-7.76 kcal/mol). The AHL analogue **4F** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond with SER 155, these interactions are essential for binding. Another H bond formed between -NH of the phenol with PHE 126 amino acid residue is important for inhibition.

The docking analysis of 4G in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-7.02 kcal/mol). The AHL analogue **4G** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond bond with TRP 80, these interactions are essential for binding. Another H bond formed between -NH of the triazole with LEU100 and with ILE99 amino acid residue is important for inhibition.

The docking analysis of 4H in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-8.65 kcal/mol). The AHL analogue **4H** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond bond with TRP 84, these interactions are essential for binding. Another H bond formed between -NH of the quinazoline with TYR 88 and with LEU 100 amino acid residue is important for inhibition.

The docking analysis of 4I in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-8.75 kcal/mol). The AHL analogue **4I** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond bond with TRP 84, these interactions are essential for binding. Another H bond formed between -NH of the quinoline with TYR 88 and with PHE 126 amino acid residue is important for inhibition.

The docking analysis of 4J in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-6.79 kcal/mol). The AHL analogue **4J** –NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond bond with TRP84, these interactions are essential for binding. Another H bond formed between -NH of the valine with PHE 126 amino acid residue is important for inhibition.

The docking analysis of 4K in the active site of CviR revealed that, it has good binding affinity within the active site. The binding energy of the top conformation was (-8.22 kcal/mol). The AHL analogue **4k**-NH attached to lactone ring forms an *H* bond with ASP 97, however, O of lactone ring forms H bond with TRP 84, these interactions are essential for binding. Another H bond formed between -NH of the LEU with SER 155 amino acid residue is important for inhibition.

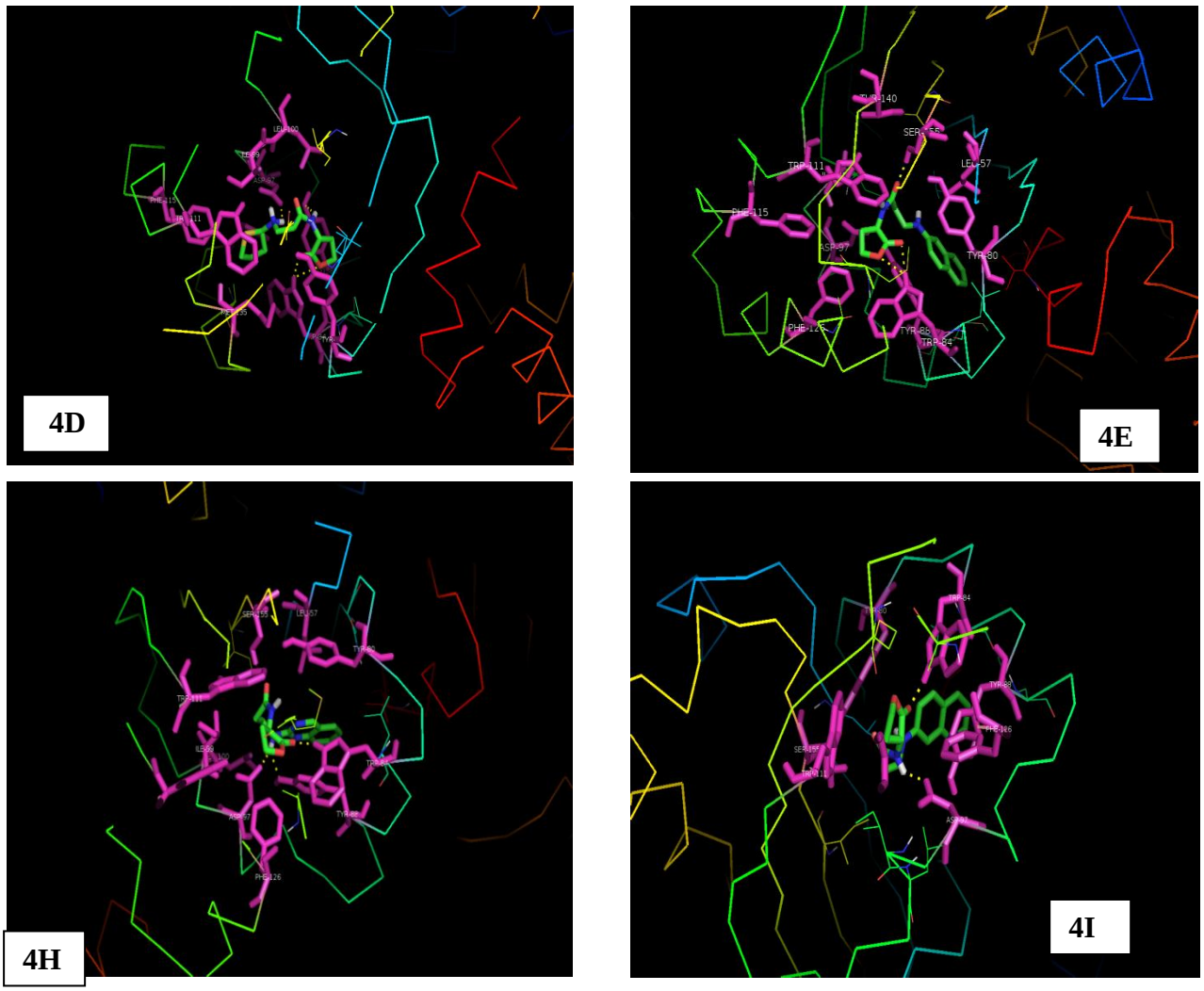


Fig: 2a, 2b, 2c and 2d Interactions of 4D, 4E, 4H and 4I with active site of CviR (PDB ID 3QP5) Synthesis

Table 4: Physical data of synthesized compounds

S.NO	COMP	MOL. FORMULA	MOL.WT	M.P(^{0}C)	%YIELD
1	2	$C_4H_8ClNO_2$	137.56	127	89
2	3	$C_7H_{10}ClNO_3$	191.61	190	75
3	4d	$C_{11}H_{14}N_2O_3S$	254.31	280	78
4	4e	$C_{17}H_{18}N_2O_3$	298.34	240	77
5	4h	$C_{15}H_{16}N_4O_3$	300.31	230	74
6	4i	$C_{16}H_{17}N_3O_3$	299.13	418	75

The proposed AHL analogues were synthesized by employing Scheme-I. The starting material 3-aminodihydrofuran-2(3H)-1 hydrochloride (2) was prepared by

stirring the solutuions of chloroacetic acid and 2-propanol in littile amount of water with L-methionine at ambient temperature overnight. The purity of the comound was confirmd by a single spot in TLC , Melting Point and the structure was confirmed by FTIR, C=O stretch of lactone peak at 1074 cm^{-1}. The IR spectrum showed absorption peaks at 3320 cm^{-1} and 2920 cm^{-1} due to N-H and C-H stretch. All the synthesized compounds were obtained in good yield.

3-Chloro-N-(2-oxotetrahydrofuran-3-yl)

propanamide (3) was synthesized by condensation of compound obtained in the previous step (2) with four equivalents of propionyl chloride added drop wise over 1hour to the aqueous amine solution. After over night stirring , the product was obtained by pouring the solution in Ice cold water and

recrystallized by using ethanol. The IR spectrum of compound (3) showed an absorption peak at 3277 cm^{-1} and 1688 cm^{-1} due to N-H stretch and C=O stretch and also 1273 cm^{-1} (C-N stretch).

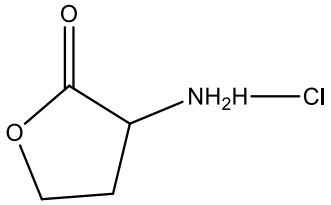
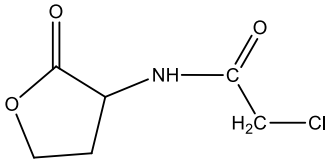
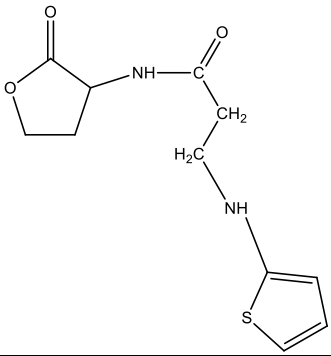
The compound 4d was synthesizd by condensation of compound(3) with appropriate heteroaromatic primary amine(2-amino lactone) in triethylamine and basified with potassium carbonate. The structure was confirmed by FTIR, mass, and ^{1}H NMR spectral data. The IR spectum of compound showed absorption peak at 2939cm^{-1} due to C-H stretch and absorption peak at 3200cm^{-1} due to N-H stretch and 1716 cm^{-1}due to c=o stretch confirms the formation of 4D compound.

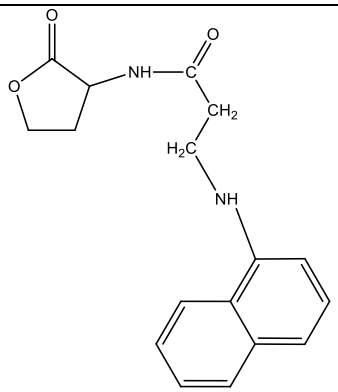
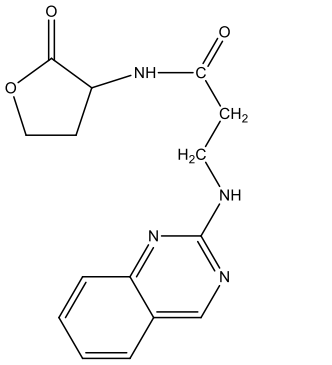
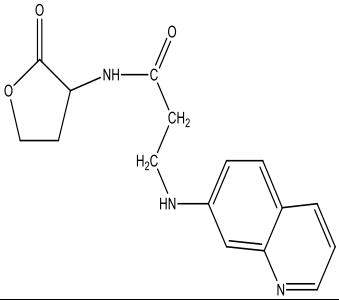
Another IR spectum of compound showed absorption peak at 3226cm^{-1} due to N-H stretch and absorption peak at 3054cm^{-1} due to C-H stretch and 1720 cm^{-1}due to c=o stretch confirms the formation of 4E compound.Compounds 4E, 4H and 4I were synthesized and characterized by employing the above mentioned procedures.

The ^{1}HNMR of compound (4d) showed a singlet at δ8.25 correspond to NH proton of amide another singlet was observed atδ 6.2 correspond to NH at secondary amine. A multiple between δ6.8-7.2 correspond to Aromatic carbons. Another multiple was observed at 4.25 correspond to two CH_2 protons and one proton of lactone ring a multiplet at δ3.75 observed. This corresponds to CH_2 of lactone. 2.6 doublet and δ 2.48 doublets corresponds to 2-CH_2 group at side chain. Mass spectrum of 4d shows molecular peak at 255(m+1).

The ^{1}HNMR of compound (4e) showed a singlet at δ9.75 correspond to NH proton of amide another singlet was observed atδ6.25 correspond to NH and secondary amine. A multiplet between δ7.5-7.8 corresponds to Aromatic carbons. Another triplet was observed at 4.25 correspond to 2 CH_2 protons and one CH proton of lactone ring a multiplet at δ3.75 observed. this corresponds to CH_2 of lactone. 2.56 doublet and δ2.48 doublet corresponds to 2-CH_2 group side chain. Mass spectrum 4E shows peak at 299.

Table 5 Spectral data of synthesized compounds.

S.NO	Compound	Structure	IR (KBr Disc) cm^{-1}	^{1}H NMR spectra (400MHz, $CDCl_3$)	Mass spectra (m/z) value
1	2		1074.01(C-O-C)	----	-----
2	3		1085.01(C-O-C)	-----	----
3	4d		3,300(-NH) 1645(C=O)	δ 8.25 (s, 1H, NH), 6.2 (s, 1H, NH), 6.8-7.2 (m,3H, CH, thiophene), 3.75 (m, 1H,CH), 4.25 (t, 2H,CH_2).2.56 (d, 2H,CH_2), 2.48(d,2H,CH_2).	255(M+1)

4	4e		3226 (NH) 1645(C=O)	δ 9.75 (s, 1H,NH), 6.25 (s, 1H, NH), 7.5-7.8m,3H,CH), 3.75 (m, 1H,CH), 4.25 (t, 2H,CH_2).2.56 (d, 2H,CH_2), 2.48(d,2H,CH_2).	299(m+)
5	4h		-----	δ 8.32 (s, 1H,NH), 7.33(t, 1H, NH), 7.58-8.16(m,4H,CH) 9.43(s, 1H,CH), 2.41(t,2H,CH_2),3.45(s,2H,CH_2), 4.40(m,1H,CH).	301(M+1)
6	4i		------	δ8.32(s,1H,NH), 5.82 (s, 1H, NH), 7.33-8.71(m,5H,CH) 8.74(t,1H,CH), 2.41(t,2H,CH_2), 3.45(s,2H,CH_2).	299

CONCLUSION

In the present investigation quorum sensing signal mechanism in pathogenic bacteria was taken as target to design new molecules that would effectively target drug resistant bacteria. In view of this, design of novel AHL analogues for the inhibition of quorum sensing signals in the pathogenic bacteria was proposed and new molecules were designed based on the existing inhibitor Chlorolactone (HLC) which is co-crystallized with the quorum sensing protein CviR. The designed analogues were docked into the crystal structure of cviR protein using AUTODOCK. The docking results revealed that ligands 4D, 4E, 4H and 4I showed good binding affinity and favorable binding interaction within the active site of CviR. The synthesis of selected ligands was carried out. The synthesized compounds were characterized by physical and spectral data. These studies suggested the antipathogenic ability of the Synthesized Acyl Homo serine lactones analogues. Furthermore, the designed and synthesized structure could be useful as lead molecule for the development new class of antibacterial agents. Further, extensive experiments on pathogenic bacteria would give the insights into the pathogenic activity of the synthesized compounds.

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