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Docking studies for the Development of Potent Quorum Based Anti-Virulence Therapeutics for the infections caused by *Pseudomonas aeruginosa*

Mumba Patrick[1], Rajesh Kumar[1], Gurvinder Singh[1], Charanjit Kaur[2], Pardeep Kumar Sharma[1]*

[1]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara, Punjab, India-144411

[2]Khalsa College of Pharmacy, Amritsar, Punjab, India-143001

ABSTRACT:

For a long time, bacteria were considered as self-directed unicellular organisms which shows the collective behaviour but up to lesser extent. However, we currently value that bacterial cells are actually communicative among themselves. This communication or coordination between bacterial population via signal molecules known as autoinducers or pheromones that diffuse in and out of bacterial cells. As the bacterial population increases the concentration of these signal molecules increases and the expressions of virulence factors are activated by this quorum sensing process. In *Pseudomonas aeruginosa*, quorum sensing controls many of these expressions of virulence factors. This study focused on the inhibition of these target proteins, so that a new series of molecules which can be used in the development of potent Quorum based anti-virulence therapeutics for targeting infections caused by *Pseudomonas aeruginosa*.

Keywords: Unicellular, autoinducers, pheromones, virulence factors, signal molecules, quorum sensing, *Pseudomonas aeruginosa*.

INTRODUCTION

In the majority detecting pathways in microbes are made out of a few principle parts, including microorganism's populaces, flag atoms, protein activators and target qualities. The capacity of majority detecting is required for some microbes like *Pseudomonas aeruginosa* cause illness and infection.[1] Majority detecting framework is a case of multicellular conduct in the unicellular universe of microorganisms, autoinducer is accepted that the adjust of concoction

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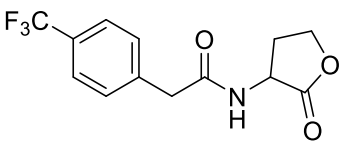
messages amongst life forms and cells is a one of a kind-properties in eukaryotic cells. Once the grouping of particles outside the microscopic organisms surpasses the edge, the flagging pathways are actuated and the microorganism reaction the messages by adjusting the quality expression and tweaking physiological procedures in an aggregate mode.[2] The populace thickness subordinate in the microscopic organism's co-ordinate quality expression is finished by the Quorum detecting mechanism. Quorum detecting directly the bacterial procedures as well as it incorporates beneficial interaction, harmfulness, bioluminescence, anti-toxin creation and biofilm formation.[3, 4]

Quorum sensing (QS) is a bacterial cell to cell correspondence arrangement that incorporates the age, disclosure, and response to extracellular hailing particles called autoinducers (AIs).[5, 6] AIs total in nature as the bacterial masses thickness additions, and organisms screen this information to follow changes in their cell numbers and all things considered alter quality articulation.[7, 8] QS controls characteristics that prompt activities that are productive when performed by get-togethers of minuscule life forms acting in synchrony. Structures constrained by QS join bioluminescence, sporulation, ability, hostile to contamination age, biofilm game plan, and danger figure release.[9-12]

Signal molecules involved in Quorum sensing

Blackwell and co-workers have done a comparison analysis of synthetic quorum sensors modulators on *Pseudomonas aeruginosa,* the beta-keto amides structure natural, non-natural and mimics were docked and these following compounds were found to be more potent.[13] The most potent compounds as per experimental results from the varying group of compounds a shown in Table 1.

Table1: The potent compounds from Blackwell series

S. No	***N*-acylated l-homoserine lactone (AHL) signal**	**2UV0 binding affinity**
1		-9.16

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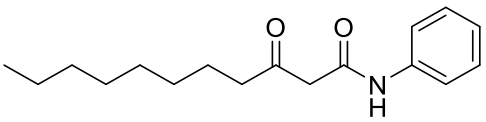
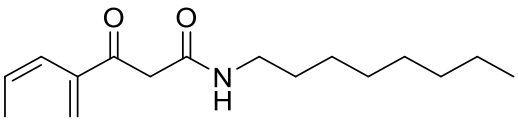
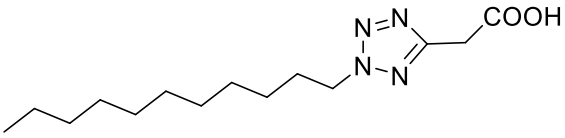
2		-9.75
3		-9.07
4		-9.21

Types of Quorum sensing systems

Quorum sensing in Gram-negative bacteria:

Majority detecting complex has been recognized in more than 25 gram-negative microbes' species over the previous decades; and among these species' majority detecting framework in *Vibrio fischeri*, *Pseudomonas aeruginosa* and *Agrobacterium tumefaciens* are more considered. Discoveries demonstrate that an extensive variety of real procedures, for example, antibiotics biosynthesis, bioluminescence, swimming, swarming, twitching, the development and conjugation, spread of biofilm, virulence markers creation, sporulation, and so on in these bacterial species are directed by majority detecting, the most studies on majority detecting are performed on bioluminescence property in *Vibrio fischeri*.[2, 3]

Quorum sensing in Gram-positive bacteria

Gram-positive microorganisms utilize peptides, called auto-initiating peptides (AIPs), as tagging particles. Once transported to the cell, auto-initiating peptides are handled and discharged. When population density increases, then the extracellular AIP concentration is found to be high and it links to a related layer bound two-segmented receptor called histidine kinase. Generally, restricting enacts the receptor's kinase action, it passes the phosphate after auto phosphorylation to a related cytoplasmic reaction controller. This phosphorylated cytoplasmic reaction controller actuates analysis of the QS region qualities. The gram-positive microorganism's QS, AIPs are transported to the cell cytoplasm where they communicate with

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translation elements to balance the elucidation component's action and thus, balance quality expression changes.[14]

Cases of correspondence in gram-positive microscopic organisms are comE/comD framework in *Streptococcus pneumonia*, the TraR/TraI destructiveness framework in phytopathogen *Agrobacterium tumefaciens* and cross breed delivery person framework in *Vibrio harveyi* and control of Ti plasmid transport in *Agrobacterium tumefaciens*. [15]

Quorum sensing in *Pseudomonas aeruginosa*

The majority detecting arrangement of *P. aeruginosa* made out of two sets of qualities as principle constitutive qualities. One set comprises of LasI and LasR qualities, R protein and encoding C12-HSL auto-inducer synthase, individually. Alternative combination called Rhl is synthesised out of encoding synthase, RhlI and RhlR qualities, and R protein, separately. The synthesis of QS framework produces C4-HSL autoinducer, delivers a little measure of *N*-hexanoyl-L-homoserine-lactone (HHL).[16] There is likewise an administrative quality named QScR (Quorum Sensing Control Receptor) in this framework that creates an administrative protein works as an inhibitor of protein LasR. Elements of the qualities of QS framework in *P. aeruginosa*are between related and don't work autonomously, as it were, one might say that the outflow of Rhl qualities is under control through R protein of LasR gene under Las.[17]

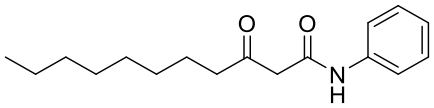

Fig1: 3-oxo-*N*-phenylundecanamide

Autoinducers

Autoinducers are little diffusible flagging atoms which are created by microbes in the majority detecting framework. These autoinducers (AI) are isolated into two classifications, autoinducers sort 1 or AI-1, which are species-particular and utilized for intraspecies correspondence. Autoinducers sort 2 or AI-2 are not particular and go about as a global dialect. Autoinducers sort 2 don't connect for interspecies correspondence, additionally empower the

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microscopic organisms to convey microorganisms, for example, parasites and protozoa to arrange their own particular conduct in a populace of microorganisms.[18]

MATERIALS AND METHODS

For the processing of antagonism of 2uv0 and 3ix3 receptors, Protein Data Bank (PDB), Autodock Vina 4.5 software along with MGL tools version 1.5.6, and ChemDraw professional 17.1 software was used. Further their binding affinities and analysis of interaction between protein and ligands were interpreted.

Retrieval of protein structures

Two protein structures (PDB ID: 2UV0 and 3IX3)[19, 20] were retrieved from protein data bank and used molecular docking using Autodock Vina 4.5 software. Protein structure 2UV0 comprises of chain E, F, G, and H in which total residues in single chain were observed as 175 respectively. However, protein structure 3IX3 embrace total 2 chains i.e. A, B, in which total number residues in single chain were recorded as 173 respectively.

Retrieval of ligand structures

Thirty-two molecules were chosen on the basis of literature and mentioned in table 2. There are some thiazoles derivatives which are reported in this category.[21] But, we are not including them for this study.Their structures were drawn by using ChemDraw professional 17.1 software were MM2 optimized and then converted to .mol2 format in Chem3d software. Further, selected molecules were docked against both proteins receptors.

Table 2. Selected compounds for the study along with their Smiles notation

S. No.	Compounds	Smiles notation
1.	3-oxo-*N*-phenyldodecanamide[22]	CCCCCCCCCC(CC(NC1=CC=CC=C1)=O)=O
2.	*N*-cyclopentyl-3-oxododecanamide	CCCCCCCCCC(CC(NC1CCCC1)=O)=O

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3.	*N*-(3,4-dimethylphenyl)-3-oxododecanamide[23]	CCCCCCCCCC(CC(NC1=CC(C)=C(C)C=C1)=O)=O
4.	*N*-(2,2-diphenylethyl)-3-oxodecanamide	CCCCCCCC(CC(NCC(C1=CC=CC=C1)C2=CC=CC=C2)=O)=O
5.	*N*-(4-fluorophenyl)-3-oxododecanamide[16]	CCCCCCCCCC(CC(NC1=CC=C(F)C=C1)=O)=O
6.	*N*-(2-fluorophenyl)-3-oxododecanamide	CCCCCCCCCC(CC(NC1=CC=CC=C1F)=O)=O
7.	*N*-(3,5-difluorophenyl)-3-oxododecanamide	CCCCCCCCCC(CC(NC1=CC(F)=CC(F)=C1)=O)=O
8.	*N*-(2,6-difluorophenyl)-3-oxododecanamide	CCCCCCCCCC(CC(NC1=C(F)C=CC=C1F)=O)=O
9.	*N*-(furan-2-yl)-3-oxododecanamide	CCCCCCCCCC(CC(NC1=CC=CO1)=O)=O
10.	1-((3-(4-chlorophenyl)-1-methyl-*1H*-pyrazol-5-yl)amino) undecane-2,4-dione	CN1C(NCC(CC(CCCCCCC)=O)=O)=CC(C2=CC=C(Cl)C=C2)=N1
11.	1-((2-(cyclohex-1-en-1-yl)ethyl)amino) undecane-2,4-dione	CCCCCCCC(CC(CNCCC1=CCCCC1)=O)=O
12.	1-((2-(cyclohex-1-en-1-yl)ethyl)amino) undecane-2,4-dione	CCCCCCCCCC(CC(NC1=CC([N+]([O-])=O)=CC=C1)=O)=O
13.	*N*-(4-methoxyphenyl)-3-oxododecanamide	CCCCCCCCCC(CC(NC1=CC=C(OC)C=C1)=O)=O

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14.	*N*-benzyl-3-oxodecanamide	CCCCCCCC(CC(NCC1=CC=CC=C1)=O)=O
15.	ethyl(3-oxodecanoyl) glycinate	CCOC(CNC(CC(CCCCCCC)=O)=O)=O
16.	ethyl(3-oxododecanoyl) alaninate	CCOC(C(C)NC(CC(CCCCCCCCC)=O)=O)=O
17.	ethyl(2-(3-nitrophenyl) acetyl)glycinate	CCOC(CNC(CC1=CC=CC([N+]([O-])=O)=C1)=O)=O
18.	ethyl(2-(4-bromophenyl) acetyl)glycinate	BrC1=CC=C(CC(NCC(OCC)=O)=O)C=C1
19.	*N*-phenylnonanamide	CCCCCCCCC(NC1=CC=CC=C1)=O
20.	ethyl(3-(3-iodophenyl) propanoyl) glycinate	IC1=CC=CC(CCC(NCC(OCC)=O)=O)=C1
21.	ethyl(2-phenylacetyl) glycinate	CCOC(CNC(CC1=CC=CC=C1)=O)=O
22.	ethyl(3-(4-methoxyphenyl) propanoyl)glycinate	COC1=CC=C(CCC(NCC(OCC)=O)=O)C=C1
23.	ethyl(3-(4-chlorophenyl) propanoyl)glycinate	O=C(NCC(OCC)=O)CCC1=CC=C(Cl)C=C1
24.	2-(4-bromophenyl)-*N*-cyclopentylacetamide	BrC1=CC=C(CC(NC2CCCC2)=O)C=C1
25.	*N*-cyclopentyl-2-(3-nitrophenyl)acetamide	O=C(NC1CCCC1)CC2=CC([N+]([O-])=O)=CC=C2
26.	*N*-cyclopentyl-4-(*1H*-indol-3-yl)butanamide	O=C(NC1CCCC1)CCCC2=CNC3=C2C=CC=C3

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27.	*N*-cyclopentyl-2-(4-methoxyphenyl)acetamide	O=C(NC1CCCC1)CC2=CC=C(OC)C=C2
28.	*N*-cyclopentyl-2-phenylacetamide	O=C(NC1CCCC1)CC2=CC=CC=C2
29.	2-([1,1'-biphenyl]-4-yl)-*N*-cyclopentylacetamide	O=C(NC1CCCC1)CC2=CC=C(C=C2)C3=CC=CC=C3
30.	*N*-methyl-2-(4-((trifluoromethyl) thio)phenyl) acetamide	CNC(CC1=CC=C(SC(F)(F)F)C=C1)=O
31.	2-(3-nitrophenyl)-*N*-phenylacetamide	O=C(NC1=CC=CC=C1)CC2=CC([N+]([O-])=O)=CC=C2
32.	2-(4-bromophenyl)-*N*-phenylacetamide	O=C(NC1=CC=CC=C1)CC2=CC=C(Br)C=C2

Preparation of receptor proteins

The both proteins 2N27 and 3J5R were prepared using Autodock Vina 4.5 software. Before initiating the process of protein preparation, all heteroatoms and co-factors were observed and removed from protein crystal structures even water molecules were also not present in both the crystal structures. The protein preparation includes repairing missing atoms, adding polar hydrogen's to atoms, no bond order with renumbering, addition of Kollaman charges.

Ligand preparation

All the ligands were prepared for molecular docking using Autodock Vina 4.5 software. The retrieved ligand structures were converted to PDBQT format in Autodock. Preparation of these ligands includes addition of polar hydrogen's, Kollaman charges, choosing torsion and detection of root.

Molecular docking

Autodock, molecular docking was done as described by Forli et al., 2006 [24] and also by Trott et al,, 2010 [25] which involve preparation of ligands and receptor's coordination files in

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PDBQT format, generation of grid box and configuration files. Each ligand was subjected to both the receptors as single docking run. Furthermore, interactions among ligands and both proteins were observed and compared with each other.

Results and discussion

Interpretation of calculated binding affinities

Out of all compounds, compound 29 was found to have high binding affinity with respect to other selected molecules. Compound 31, 26, 32, 25, 7, 20, 22, 23 showed binding affinity value -5.9, -5.7, -5.5, -5.3, -5.2, -5.2, -5.2 and -5.2 at 2UV0 and Compound 29, 31, 26, 32, 4, 7, 27, 12, shows -11.7, -10.5, -10.2, -10, -10, -9.6, -9.5 and -9.5 at 3IX3 respectively. All binding affinity values were represented in table 3.

Table 3: Binding affinities of all selected compounds for both proteins (2UV0 and 3IX3)

S. No.	Compounds	Binding affinity (Estimated energy (Kcal/mol))		S. No.	Compounds	Binding affinity (Estimated energy (Kcal/mol))	
		2uv0	3ix3			2uv0	3ix3
1.	3-oxo-N-phenyldodecanamide	-4.6	-9	17.	ethyl(2-(3-nitrophenyl) acetyl)glycinate	-4.9	-8.4
2.	N-cyclopentyl-3-oxododecanamide	-4.4	-8.8	18.	ethyl(2-(4-bromophenyl) acetyl)glycinate	-4.5	-8
3.	N-(3,4-dimethylphenyl)-3-oxododecanamide	-4	-9.5	19.	N-phenylnonanamide	-4.5	-8.9
4.	N-(2,2-diphenylethyl)-3-oxodecanamide	-4.7	-10	20.	ethyl(3-(3-iodophenyl) propanoyl) glycinate	-5.2	-8.9
5.	N-(4-fluorophenyl)-3-oxododecanamide	-4.7	-9.3	21.	ethyl (2-phenylacetyl)glycinate	-4.5	-8.3
6.	N-(2-fluorophenyl)-3-oxododecanamide	-5.1	-9.2	22.	ethyl(3-(4-methoxyphenyl) propanoyl)glycinate	-5.2	-8.4
7.	N-(3,5-difluorophenyl)-3-oxododecanamide	-5.2	-9.6	23.	ethyl(3-(4-chlorophenyl) propanoyl)glycinate	-5.2	-8.4

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8.	N-(2,6-difluorophenyl)-3-oxododecanamide	-4.3	-9.4	24.	2-(4-bromophenyl)-N-cyclopentylacetamide	-5.2	-9.3
9.	N-(furan-2-yl)-3-oxododecanamide	-4.7	-8.5	25.	N-cyclopentyl-2-(3-nitrophenyl)acetamide	-5.3	-9.3
10.	1-((3-(4-chlorophenyl)-1-methyl-1H-pyrazol-5-yl)amino) undecane-2,4-dione	-4.2	-7.4	26.	N-cyclopentyl-4-(1H-indol-3-yl)butanamide	-5.7	-10.2
11.	1-((2-(cyclohex-1-en-1-yl)ethyl)amino) undecane-2,4-dione	-4.1	-9	27.	N-cyclopentyl-2-(4-methoxyphenyl) acetamide	-5.2	-9.5
12.	1-((2-(cyclohex-1-en-1-yl)ethyl)amino)undecane-2,4-dione	-4.3	-9.5	28.	N-cyclopentyl-2-phenylacetamide	-5	-9.2
13.	N-(4-methoxyphenyl)-3-oxododecanamide	-3.4	-8.1	29.	2-([1,1'-biphenyl]-4-yl)-N-cyclopentylacetamide	-5	-11.7
14.	N-benzyl-3-oxodecanamide	-5	-9	30.	N-methyl-2-(4-((trifluoromethyl) thio)phenyl)acetamide	-4.9	-8.3
15.	ethyl (3-oxodecanoyl) glycinate	-3.9	-7.9	31.	2-(3-nitrophenyl)-N-phenylacetamide	-5.9	-10.5
16.	ethyl(3-oxododecanoyl) alaninate	-3.9	-8.2	32.	2-(4-bromophenyl)-N-phenylacetamide	-5.5	-10

CONCLUSION

From the above study we can also conclude that among all the docked compounds in respect with both the receptors compound 29 with receptor 3ix3 showed to be more potent molecule which showed high binding affinity as well as inhibition properties, this molecule has opened up a novel to the discovery of more drugs which can be used in the development of potent Quorum based anti-virulence therapeutics for targeting infections caused by *Pseudomonas aeruginosa*.

CONFLICTS OF INTEREST

Declared none.

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