

In-Silico Studies on Selected Active Constituents of *Corbichonia decumbens* Against Allergic Bronchopulmonary Aspergillosis

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Research Article

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***In- Silico* Studies on Selected Active Constituents of *Corbichonia decumbens* Against Allergic Bronchopulmonary Aspergillosis**

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ABSTRACT

Herbs have been employed in the treatment of various diseases and other medicinal purposes for a long time and they've been the zest of our life. *Corbichonia decumbens* an erect, short-lived succulent herb is found to possess zenith medicinal properties. At a first, the *in-silico* activity of the plant has been determined to carry out a modification in the Surfactant Protein-D (SP-D) which plays a pivotal role in defense against the Allergic Bronchopulmonary Aspergillosis (ABPA). The SP-D protein has been modified using *in-silico* tools thus making it more robust in containing ABPA. The protein SP-D when combined with the plant compound 1-methyl-3,5-dinitro-1,2,4-triazole had binding energy of -6.98 and interactions with active site residue ASN-236, LYS-246, GLU-232, PHE-234 and, GLN-236. Being one of the first *in-silico* works carried out in this plant species it aims to provide a substantial base for future works and unwrap the potential of this herb in all aspects of medicinal plant science.

KEYWORDS: *In-silico*, Herb Medicine, Herb-drug interaction, Docking Approach, ABPA

Introduction

The use of plants in the preparation of medicine and ethnobotanical studies is being practiced since time immemorial. The term medicinal plants have been in force since ancient times and these medicinal plants are used in the preparation of traditional medicines. In India, the use of herbs is mentioned in Vedic scriptures. In India, it is believed that the taxonomical rank of classification & naming of plants in the Sanskrit language is much older than that of Latin and Greek languages and the study dates back to the Vedic period from 2500 BC to 600 BC (Balkrishna, Mishra and Srivastava, 2019). Parts of plants such as fruits, flowers, seed, stem, bark, leaf, stigma, or a root can be classified as herbs nowadays. At first, the 'herb' referred to non-woody plants, as well as those that came from trees and shrubs. The medicinal plants find a varied application in the manufacture of food, flavonoids, medicine, perfumes and also utilized for sacred activities (NHP, 2016). *Corbichonia decumbens* belonging to the family of Lophiocarpaceae is an erect, prostrate-ascending annual or short-lived perennial succulent herb up to 50cm. in height, sometimes with woody rootstock found in the pavements in and around the Annur region of Coimbatore. This potential herb can be well utilized as an effective source of the drug for various diseases as they have an intrinsic capacity to synthesize aromatic substances such as phenols, and their derivatives (Geissman, 1963). These secondary metabolites tend to exhibit their therapeutic tendencies. These idiosyncratic attributes of plants are the main reason for the researchers to employ them in the drug preparation to reduce the dependency on inorganic compounds. The ethanolic leaf extract of *Corbichonia decumbens* displayed a good activity in the antimicrobial assay. The ethanolic leaf extract exhibited a much appreciable zone of inhibition against *Aspergillus fumigatus* with Ciprofloxacin as standard (DHA & Arunprasath, 2020). The Gas Chromatography-Mass Spectrometry (GCMS) for *C. decumbens* ethanolic extract revealed the major 30 compounds which had the bio-potential for becoming an effective drug (Saranya & Arunprasath, 2019), this preliminary analysis paved the way for the *in-silico* works that were carried out in this plant. The disease Allergic Bronchopulmonary Aspergillosis (ABPA) results from IgE-induced pulmonary response to aspergillus species (Kanu & Patel, 2008). ABPA can be classified as a severe condition in children, adolescents, and adults with cystic fibrosis (CF) (M. B. De Almeida *et al.*, 2006). The Surfactant Protein D (SP-D) a lung surfactant protein also called *collectins* are known to interact with carbohydrate structures on the surfaces of a wide range of pathogens, such as viruses, bacteria, and fungi via their carbohydrate recognition domains (CRDs) and enhance phagocytosis and killing by neutrophils and macrophages (Wright, 2005). SP-D is believed to play a vital role in innate immunity in the lungs by binding through its multiple C- type lectin domains to carbohydrate structures present on a range of viruses, bacteria, yeasts, and fungi (Reid, 1998). Bio-informatics tools helped in the successful visualization of the target-compound interactions, as drug discovery programs primarily start with the identifications of suitable drug targets, which are biomolecules such as proteins, enzymes,

and ion-channels (Terstappen & Reggiani, 2001). The initial steps of drug validation can be obtained through *in-silico* and animal models, but the outcome can only be obtained through human clinical trials. The study aims to bring out the efficient use of SP-D with the plant compound of *C. decumbens* against ABPA disease and to emphasize the significance of *C. decumbens* as a potential herb as it is one of the first *in-silico* works in this plant to date.

Materials and methods

The plant compounds which were already obtained from GC-MS analysis (Saranya & Arunprasath, 2019) were retrieved from online databases such as;

PDB, PubChem & Pass Online

The 3D protein structure for the Surfactant Protein- D (SP-D) is recovered from the Protein Data Bank database (PDB ID: 4M18). Dynamic web page region was anticipated utilizing LigSite online apparatus. The PASS ONLINE predicts 4130 types of biological activities, for which the difference between probabilities will be active (Pa) and probabilities will be inactive (Pi) was calculated. The Pa-Pi values for activities randomly selected from the total list of predicted biological activities will be used as independent regression variables are perused.

Lipinski rule of 5 helps in distinguishing between drug-like and non-drug-like molecules (Yongqiang Zhang *et al.*, 2020). It predicts a high probability of success or failure due to drug-likeness for molecules complying with 2 or more of the following rules.

- Molecular mass less than 500 Dalton
- High lipophilicity (expressed as LogP less than 5)
- Less than 5 hydrogen bond donors
- Less than 10 hydrogen bond acceptors
- Molar refractivity must between 40-130

Molecular Docking Study

MGL tools with AutoGrid4 and AutoDock4 will be used to set up and to perform blind docking calculations between the Ligands and Protein. A crystallized 3-dimensional structure was obtained from the Protein Data Bank (PDB). Receptor (protein) and ligand (complex) files were prepared using Auto Dock Tools. The protein was enclosed in a box with grid points in x, y, and z directions and a grid spacing of 0.375 Å (Holt *et al.*, 2008). The center of the grid is set to -6.516, 30.278, and -1.951 Å. Lamarckian genetic algorithms, as implemented in Auto Dock, were employed to perform docking calculations. All other guidelines are default settings. For every individual docking case, the lowest energy docked confirmation, according to the Auto Dock scoring function and several hydrogen bonds was selected as the binding mode. The output from Auto Dock was rendered with PyMol.

Pymol

PyMOL is one of a few open-source visualization tools which are used in structural biology. A part of the software's name refers to the fact that it extends, and is extensible by the Python programming language. All the bindings are visualized by using the Structure Visualizing tool pymol viewer, the interaction between the chemical compounds and target protein (DeLano, 2002).

Results

The retrieved compounds were analyzed for PASS prediction (Table 1) from which the activity of compounds was confirmed. Further, the compounds were subjected to Absorption, Distribution, Metabolism, and Excretion properties, and the results were tabulated (Table 2). The compounds weren't found to violate Lipinski's rule of five. First-hand knowledge of this information is much necessary before drug discovery as it has a great impact on the cost, labor, and time duration. Lipinski's rule of five is also called Pfizer's rule of five or the rule of thumb to evaluate drug-likeness to indicate the following properties like molecular weight, octanol/water partition coefficient, hydrogen bond donor, and acceptor. The results of docking studies were recorded in (Table 3) and it revealed the compound 1-methyl-3, 5-dinitro-1, 2,4-triazole from *Corbichonia decumbens* with SP-D shows binding energy of -6.98 (Fig 1). The interactions were observed using Pymol.

Table 1 Activity of Compounds

Compound Name	PubChem ID	Compound Activity (Pass Online)																																							
Quinoline	7047	<table border="1"> <tr><td>0.358</td><td>0.151</td><td>Leukopenia</td></tr> <tr><td>0.251</td><td>0.046</td><td>Carcinogenic, group 3</td></tr> <tr><td>0.344</td><td>0.139</td><td>Respiratory failure</td></tr> <tr><td>0.266</td><td>0.065</td><td>Carcinogenic, mouse</td></tr> <tr><td>0.283</td><td>0.082</td><td>Mydriatic</td></tr> <tr><td>0.231</td><td>0.032</td><td>Carcinogenic, group 2B</td></tr> <tr><td>0.261</td><td>0.062</td><td>Carcinogenic, rat, male</td></tr> <tr><td>0.257</td><td>0.069</td><td>Irritation</td></tr> <tr><td>0.341</td><td>0.154</td><td>Anorexiant</td></tr> <tr><td>0.212</td><td>0.026</td><td>Mutagenic, Salmonella</td></tr> <tr><td>0.214</td><td>0.028</td><td>Mutagenic</td></tr> <tr><td>0.350</td><td>0.164</td><td>Bronchoconstrictor</td></tr> </table>	0.358	0.151	Leukopenia	0.251	0.046	Carcinogenic, group 3	0.344	0.139	Respiratory failure	0.266	0.065	Carcinogenic, mouse	0.283	0.082	Mydriatic	0.231	0.032	Carcinogenic, group 2B	0.261	0.062	Carcinogenic, rat, male	0.257	0.069	Irritation	0.341	0.154	Anorexiant	0.212	0.026	Mutagenic, Salmonella	0.214	0.028	Mutagenic	0.350	0.164	Bronchoconstrictor			
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1,1-Diethoxy-2-methylpropane	519415	<table border="1"> <tr><td>0.664</td><td>0.005</td><td>Eye irritation, weak</td></tr> <tr><td>0.685</td><td>0.028</td><td>Hypercholesterolemic</td></tr> <tr><td>0.722</td><td>0.069</td><td>Shivering</td></tr> <tr><td>0.681</td><td>0.031</td><td>Respiratory failure</td></tr> <tr><td>0.656</td><td>0.012</td><td>Adrenal cortex hypoplasia</td></tr> <tr><td>0.672</td><td>0.032</td><td>Gastrointestinal hemorrhage</td></tr> <tr><td>0.679</td><td>0.044</td><td>Nausea</td></tr> <tr><td>0.673</td><td>0.047</td><td>Pure red cell aplasia</td></tr> <tr><td>0.641</td><td>0.024</td><td>Hyperuricemia</td></tr> <tr><td>0.622</td><td>0.005</td><td>Skin irritation, moderate</td></tr> <tr><td>0.639</td><td>0.025</td><td>Hypomagnesemia</td></tr> <tr><td>0.622</td><td>0.008</td><td>Skin irritative effect</td></tr> <tr><td>0.669</td><td>0.043</td><td>Photosensitizer</td></tr> </table>	0.664	0.005	Eye irritation, weak	0.685	0.028	Hypercholesterolemic	0.722	0.069	Shivering	0.681	0.031	Respiratory failure	0.656	0.012	Adrenal cortex hypoplasia	0.672	0.032	Gastrointestinal hemorrhage	0.679	0.044	Nausea	0.673	0.047	Pure red cell aplasia	0.641	0.024	Hyperuricemia	0.622	0.005	Skin irritation, moderate	0.639	0.025	Hypomagnesemia	0.622	0.008	Skin irritative effect	0.669	0.043	Photosensitizer
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Table 2 ADME Property of plant compound

Molecule	mol_MW (Molecular weight)	acptHB (Acceptor - Hydrogen Bonds)	donorH B (Donor - Hydrogen Bonds)	BBB permeant	GI Absorption	Rule of Five (Lipinski's rule)
Quinoline	146.23	2	0	Yes	High	0
Gentisyl alcohol	173.09	6	0	No	High	0
1,1-Diethoxy-2-methylpropane	129.16	1	0	Yes	High	0
1-methyl-3,5-dinitro-1,2,4-triazole	140.14	3	3	No	High	0
2,4-Dichloropyrrolo[3,2-d]pyrimidine	188.01	2	1	Yes	High	0

Table 3 Interactions of plant compounds with SP-D

Name of ligand	Binding energy	Residues Interacted	Bond length (Å)	No. of bonds formed
Quinoline	-5.25	GLY-237(C-O)	3.5	1
Gentisyl alcohol	-5.06	LEU-233(O-H)	2.3	7

		SER-239(H-O)	2.9	
		(O-N)	2.8	
		GLN-238(H-N)	1.9	
		(O-O)	3.5	
		ALA-264(H-O)	2.2	
		GLY-237(O-N)	3.3	
1,1-Diethoxy-2-methylpropane	-3.45	LYS-246(O-N)	3.1	2
		(O-N)	2.7	
1-methyl-3,5-dinitro-1,2,4-triazole	-6.98	ASN-236(O-N)	3.2	7
		LYS-246(O-N)	2.8	
		GLU-232(O-O)	2.8	
		(N-O)	3.0	
		(O-O)	3.1	
		PHE-234(O-O)	2.9	
		GLN-236(O-N)	2.9	
2,4-Dichloropyrrolo[3,2-d]pyrimidine	-5.17	GLU-232(H-O)	2.1	1

PYMOL INTERACTIONS

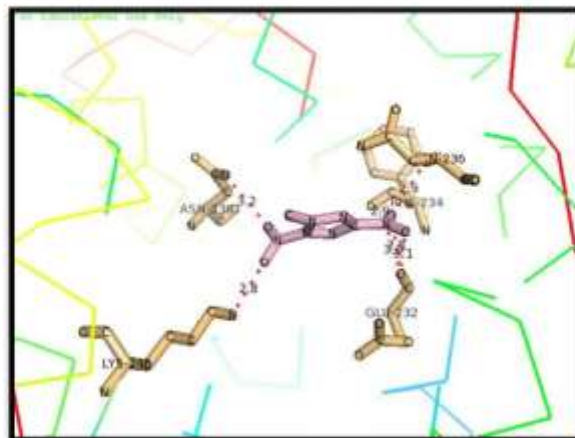


Fig 1 1-methyl-3, 5-dinitro-1, 2, 4-triazole Vs SP-D

This compound displayed excellent binding energy of -6.98.

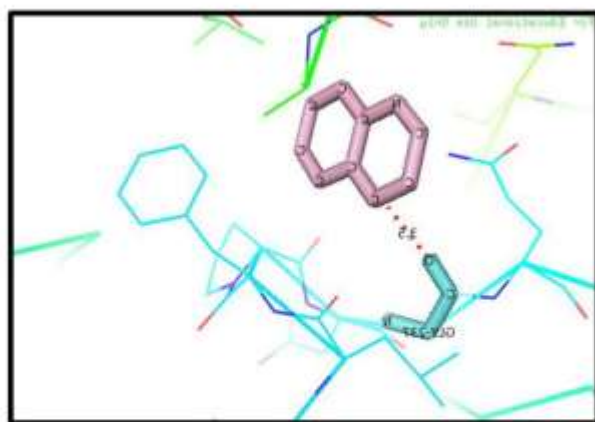


Fig 2 Quinoline Vs SP-D

Binding energy of this compound- 5.25



Fig 3 2,4-Dichloropyrrolo[3,2-d]pyrimidine Vs SP-D

Binding Energy of this compound- 5.17

Discussion

The disease Allergic Bronchopulmonary Aspergillosis (ABPA), caused by the fungi *Aspergillus fumigatus* is a hypersensitivity lung disease which is rarely found in 10% of persons having cystic fibrosis (Keown *et al.*, 2019). A positive response to this disease was created using the *in-silico* tools which succeeded in the successful docking analysis. The ABPA is more ubiquitous in patients who have been diagnosed of asthma (David *et al.*, 1999). The compounds displayed an acceptable binding energy with surfactant protein D, as these are lung surfactant related hydrophilic proteins that have been implicated in surfactant homeostasis and pulmonary innate immunity (U. Kishore *et al.*, 2002). It is believed that synthesis and secretion of this collectin increases with acute injury and epithelial activation (Dennis R. Voelker *et al.*, 2005). Binding of SP-D with this phyto-compounds will surely aid in the development of a more activated protein target which in-turn can produce striking result thereby providing an insight into the development and modification of a target in the fungal disease caused by *A. fumigatus*. The docking studies of 1-methyl-3, 5-dinitro-1, 2, 4-triazole with SP-D revealed 5 active sites, a similar result was also shown in the transport of GLUT-1 (Richard J. Naftalin *et al.*, 2006). As to get a conclusive result the same receptor was docked with five different ligands so as to bring out the variance. A similar work was carried to evaluate the ability of each docking protocol in order to identify the binding of the same receptor with two different ligands (Ricci and Netz *et al.*, 2009).

CONCLUSION

The chemical compound 1-methyl-3,5-dinitro-1,2,4-triazole had a much significant binding energy of -6.98 and interactions with active site residue ASN-236, LYS-246, GLU-232, PHE-234 and, GLN-236. A wide variety of compounds were selected for this study but after the scrutinizing only handful of standard compounds were considered. The above plant compounds could be explored more for ABPA & the identification of an efficient and potential drug molecule by enhancing the activity of SP-D protein and thus making it a super protein by combining this compound.

AUTHOR CONTRIBUTIONS

Arunprasath- Conceptualization, supervision and review. Sreeram- Methodology, data extraction, writing-original draft preparation. Revathi- Data Analysis

FUNDING

No funds, grants, or other support was received.

DECLARATIONS

Conflict of Interest

There are no conflict of interest in this study to declare.

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Figures

PYMOL INTERACTIONS

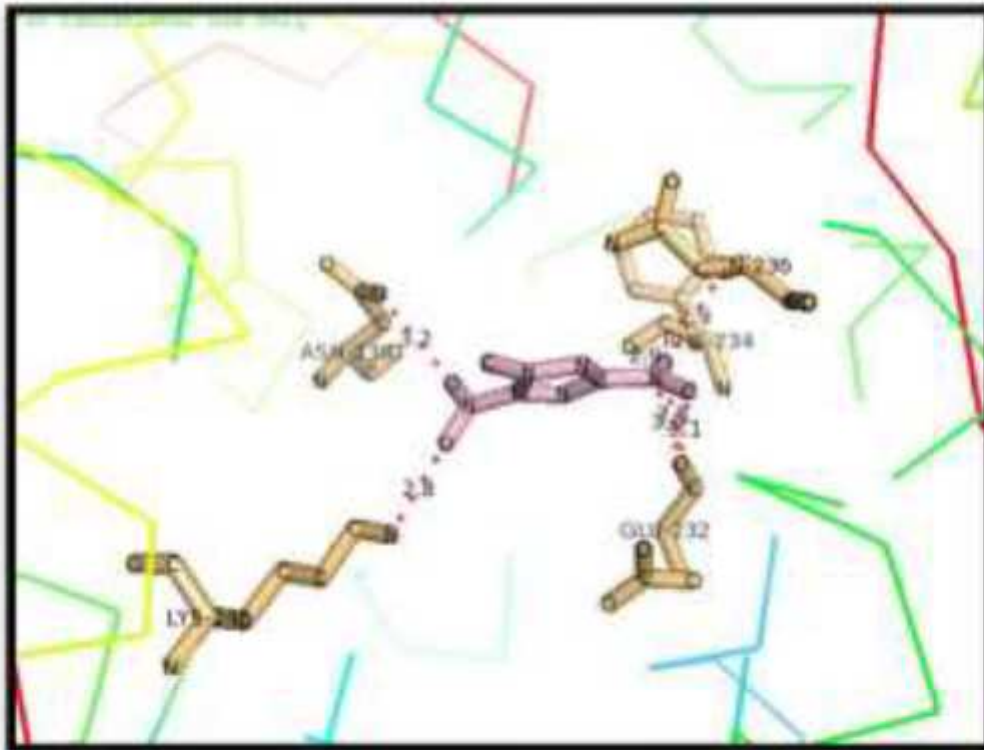


Fig 1 1-methyl-3, 5-dinitro-1, 2, 4-triazole Vs SP-D

This compound displayed excellent binding energy of -6.98.

Figure 1

Please view the figure caption in the figure

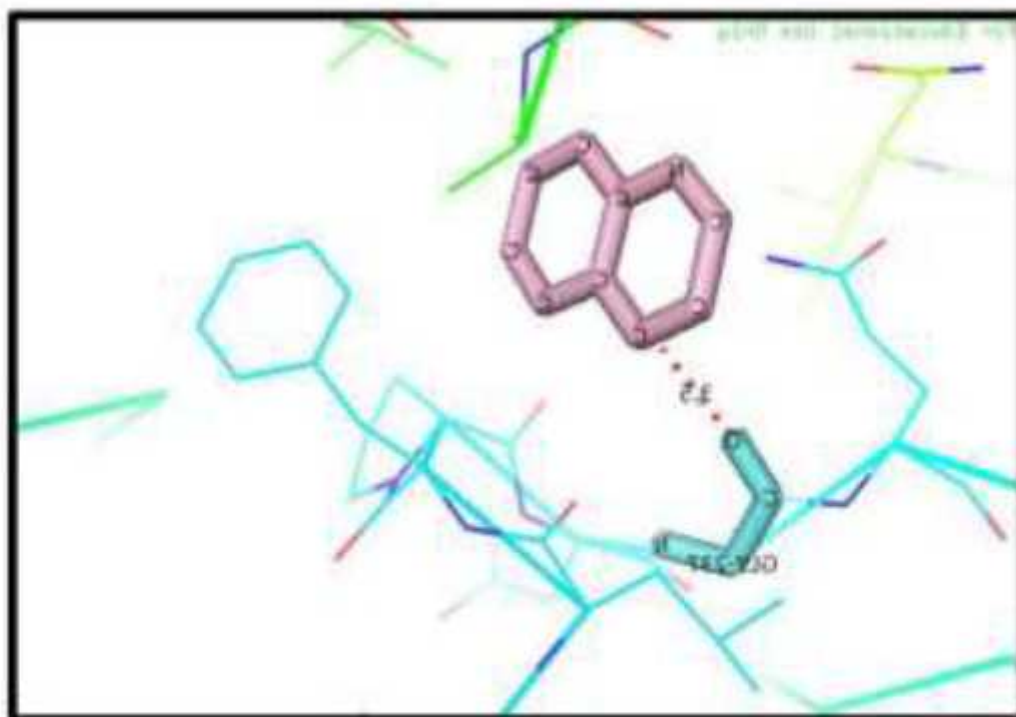


Fig 2 Quinoline Vs SP-D

Binding energy of this compound- 5.25

Figure 2

Please view the figure caption in the figure

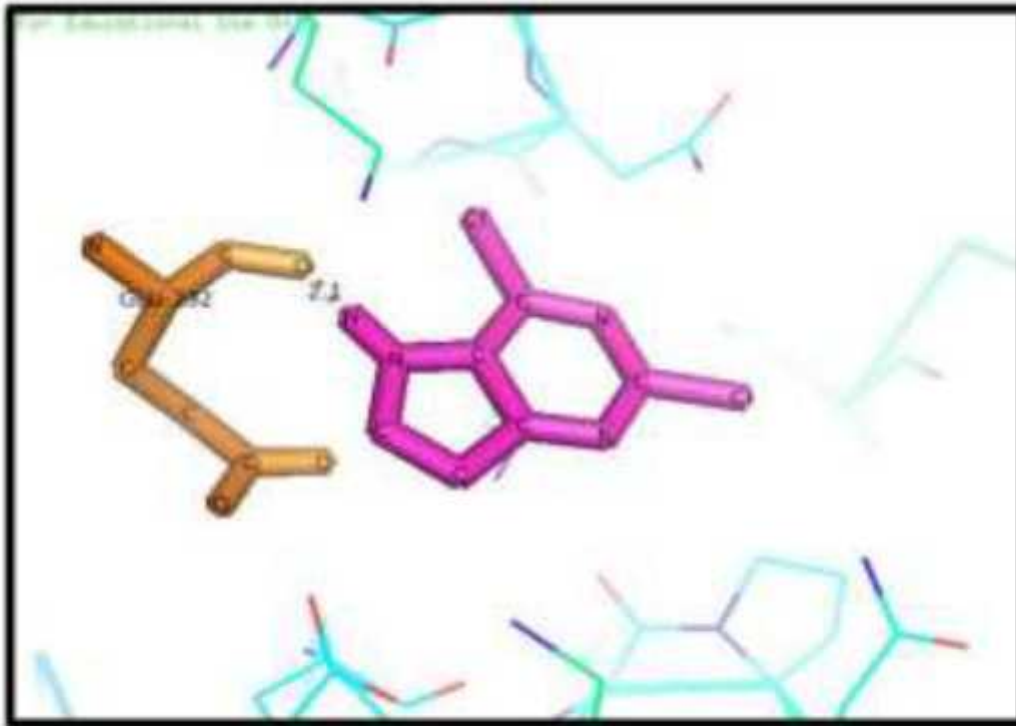


Fig 3 2,4-Dichloropyrrolo[3,2-d]pyrimidine Vs SP-D

Binding Energy of this compound- 5.17

Figure 3

Please view the figure caption in the figure