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DESIGN, SYNTHESIS AND MOLECULAR DOCKING STUDIES OF NOVEL BIS-L-PROLINE INTERCALATORS AS POSSIBLE ANTICANCER AGENTS

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Abstract:

In the present study, L-proline derivatives and linker chains are designed, synthesized and were characterized using spectral analysis. In the present study, 14 L-proline derivatives were synthesised among which five derivatives were consisting of symmetrical linker chains and nine derivatives are of asymmetrical linker chains. The synthesised compounds are then interacted through H-bond interactions with Topoisomerase-I (Human DNA) enzyme active sites. The docking analysis of L-proline derivative reveals that, among 14 compounds synthesised, compound IVL_6 and $IIIL_4$ were found to be more potent towards Topoisomerase-I enzyme with London dG scoring values of -12.8472 and -11.5501 respectively. All the synthesized compounds were then characterized using spectral analysis. Hence the present study forms the basis for the synthesis and characterization of L-proline derivatives as possible bis-intercalators to potentially act as anticancer agents.

Key words: *Topoisomerase I enzyme, L-proline derivatives, docking analysis, H-bond interactions and anticancer agents.*

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INTRODUCTION:

As per the reports received from WHO (World health Organization), cancer is the second deadliest disease responsible for global cause of deaths. The rate of incidence of lung cancer among all the cancer types is of high priority followed by breast cancer in females and then to colorectal cancer [1]. Hence keeping in view the mortality rate due to cancer, it is mandatory to develop new anticancer agents. In the present study, an attempt is made to develop novel L-proline derivatives as possible anticancer agents.

Docking Studies:

Selection of PDB Structure

PDB (Protein Data Bank) is a collection of structures in crystal form for protein molecules having ligands bounded including co-activators. The X-ray crystal arrangement of human DNA topoisomerase in association with camptothecin and covalent complexation with the A22 base pair DNA duplex has been acquired from PDB based on the Ramachandran's plot analysis and with excellent resolution. [2, 3]. The structure is chosen as a result of its high resolution 3.0 when compared to alternative possibilities. According to the Ramachandran's plot study, human DNA topoisomerase (1T8I) possesses 87.3% of its residues in the quadrangle's most beneficial zone, and there isn't a single residue in the quadrangle's least advantageous area [4, 5].

Ligand Generation and Optimization

The structures of the synthesised L-proline derivatives were drawn utilising ACD/ChemSketch (12.0) software and then saved in to mol file format [6, 7]. The stored ligand compounds were subsequently uploaded into Molecular Operating Environment (MOE) and strengthened using a systematic conformer searching, geometrical optimise, and minimization of energy of the least energy structures using the MMFF94 (Merck Molecular Force Field) [8, 9]. The various compounds were then stored in mol file format for further binding investigations.

Structure based pharmacophore generation

A pharmacophore technique based on structure was used to identify the key component of the active site that can influence the binding of the ligand. The interaction generating approach evaluates the active sites for acceptors, hydrophobes, and donors using an input receptor and a predetermined active site [10-12]. An interaction map is the calculation's output. The density of the vectors in the hydrogen bond interaction site is specified by the density of polar site parameter. The density of points in the interaction site for lipophilic atoms is specified by the density of lipophilic atoms parameter [13, 14].

ADMET

MOE offers techniques for evaluating an organism's ligand's disposition and potential toxicity. The Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) protocols offer published models that you can use to compute and analyse ADMET parameters [15]. In addition, you can use particular rules based on the presence or absence and frequency of particular chemical groups to eliminate ligands that are not likely drug-like, unsuitable leads, etc. [16].

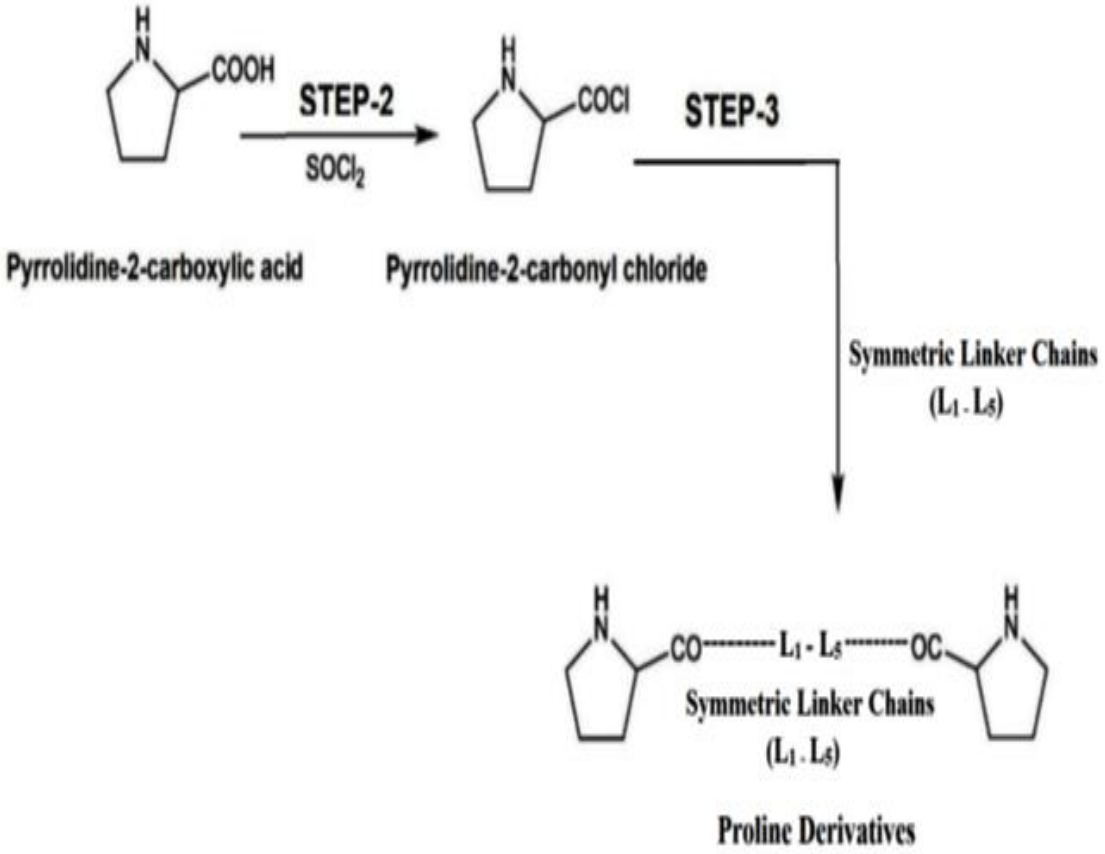
ADMET - Human Intestinal Absorption

After oral delivery, this model forecasts human intestinal absorption (HIA). In contrast to blood-brain penetration, intestinal absorption is measured as a percentage of the substance ingested rather than as a ratio of concentrations. A substance is considered well-absorbed if at least 90% of it enters a person's bloodstream [17].

The ellipses outline areas where it is anticipated to find well absorbed compounds: The 95% ellipse is predicted to contain 95% of well absorbed compounds, and the 99% ellipse should contain 99% of well absorbed compounds. Keep in mind that the location of any given component does not always indicate how well, moderately, or poorly it will be absorbed. However, absorption typically decreases rather quickly outside the 95% ellipse [18].

MATERIALS AND METHODS:

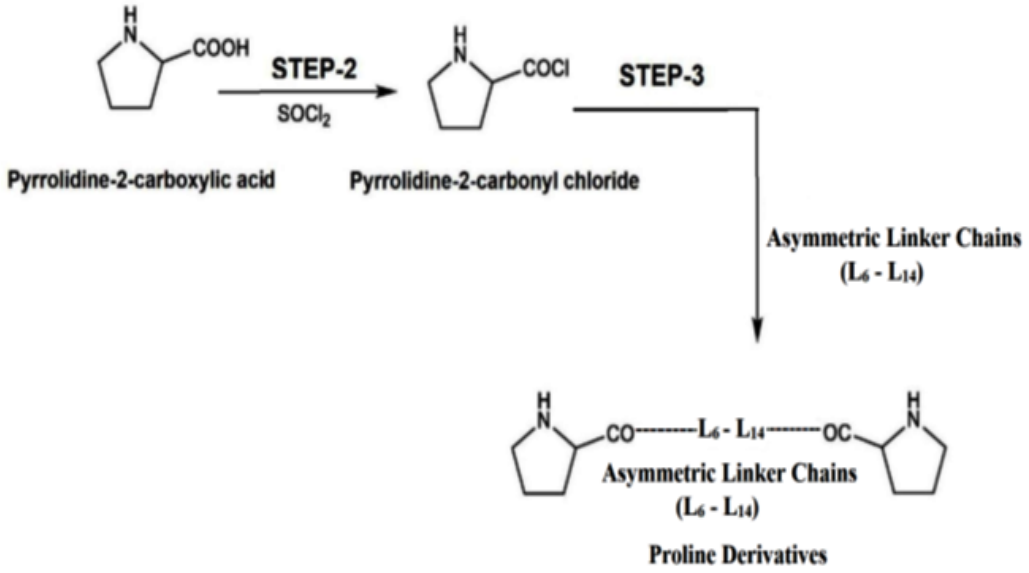
Scheme-I
Synthesis of L-Proline Derivatives with Symmetric Linker Chains



SYMMETRIC LINKER CHAINS (L_1 to L_5)

L_1	=	Urea
L_2	=	Ethylenediamine
L_3	=	Malonamide
L_4	=	*N*-(Aminoacetyl) glycinamide
L_5	=	*N, N*-Bis-(2-aminoacetyl) ethylene diamine

Scheme-II
Synthesis of L-proline derivatives with asymmetric linker chains



ASYMMETRIC LINKER CHAINS (L_6 to L_{14})

L_6	=	Glycinamide
L_7	=	2-(N-Ureido)acetamide
L_8	=	*N*$_1$-(2-Acetamido)glycinamide
L_9	=	*N*$_1$-(2-Aminoethyl)glycinamide
L_{10}	=	Malamide
L_{11}	=	*N*$_1$ *N'*-Bis(2-aminoethyl)malamide
L_{12}	=	4-Aminobenzamide
L_{13}	=	4-Amino-N-(2-aminoethyl)benzamide
L_{14}	=	4-Amino-N-(2-acetamido)benzamide

Spectral analysis:

Spectral data of *N*, *N*'-(1-oxoethane-1,2diyl)dipyrrolidine-carboxamide (IVL_6)

IR (KBr, cm^{-1}): 3418.0 (N-H Pyrrolidine), 3180.0 (CONH 2^0 amide), 2924.0 (C-H pyrrolidine), 1767 (C=O amide keto).

^{1}H NMR Spectrum (DMSO, δppm): δ=2.0 (m, 1H, 2^0 amide), 2.80 (2H, -CH_2, pyrrolidine), 1.96 (2H, -CH_2, pyrrolidine), 1.64 (2H, -CH_2, Pyrrolidine), δ=3.69 (t, 1H, CH, pyrrolidine), 8.03 (t, 1H, -NH, 2^0 amide), 10.0 (s, 1H, -NH, imide), 4.09 (s, 2H, CH_2).

Mass Spectrum (ESI, Positive) of the compound recorded its molecular ion, [M^+] at m/z 268 equal to its mass (Mol. Wt).

Spectral data of *N*, *N*'-[iminobis (2-oxoethane-2, 1-diyl)]dipyrrolidine-2-carboxamide (IIIL_4)

IR (KBr, cm^{-1}): 3461.0 (N-H Pyrrolidine), 3081.0 (CONH 2^0 amide), 2920.0 (C-H pyrrolidine), 1719 (C=O amide keto).

^{1}H NMR Spectrum (DMSO, δppm): δ=2.0 (m, 1H, 2^0 amide), 2.80 (2H, -CH_2, pyrrolidine), 1.96 (2H, -CH_2, pyrrolidine), 1.64 (2H, -CH_2, pyrrolidine), δ=3.69 (t, 1H, CH, pyrrolidine), 8.03 (t, 1H, -NH, 2^0 amide), 10.0 (s, 1H, -NH, imide), 4.09 (s, 2H, CH_2).

Mass Spectrum (ESI, Positive) of the compound has recorded its molecular ion: [M^+] at m/z 325 equal to its mass (Mol. Wt).

RESULTS

Docking Studies:

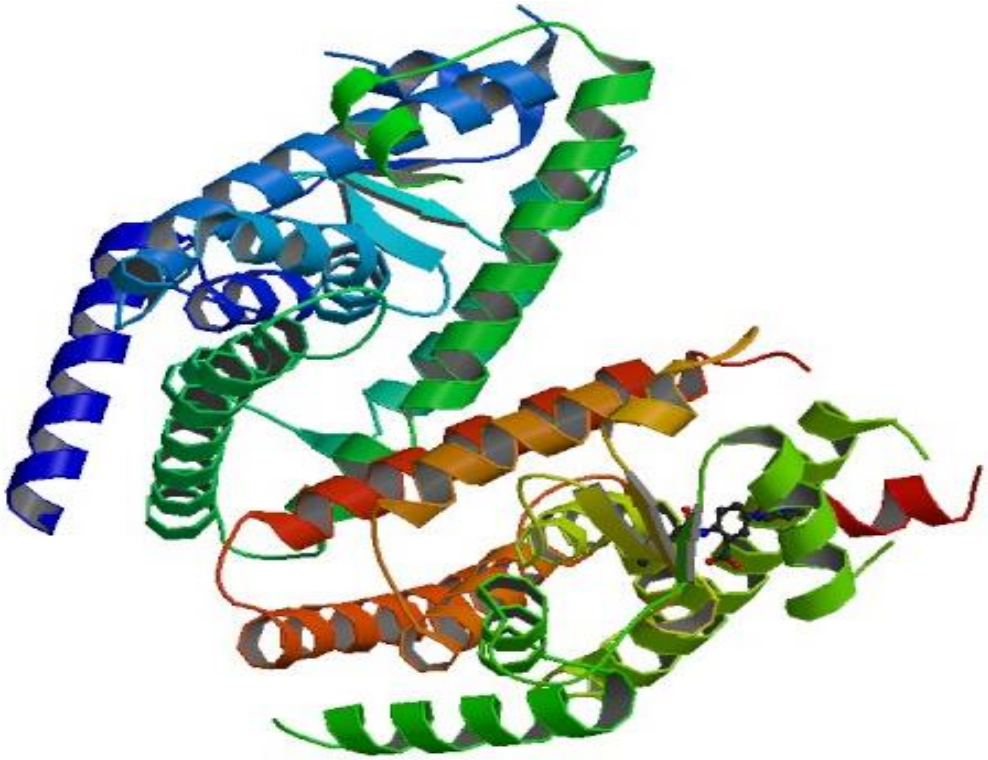


Figure 1. Crystal structure of the human DNA topoisomerase (PDB ID: 1T8I)

Table 1. Physical data of Scheme-I compounds

Compounds	Linker Chain	Molecular formula	Molecular weight	IUPAC name
$IIIL_1$	-NHCONH-	$C_{11}H_{18}N_4O_3$	254.23504	*N*-[(pyrrolidin-2-ylcarbonyl) carbamoyl] pyrrolidine-2-carboxamide
$IIIL_2$	$-NHCH_2CH_2NH-$	$C_{12}H_{22}N_4O_2$	254.37801	*N*, *N*'-ethane-1,2-diyldipyrrolidine-carboxamide
$IIIL_3$	$-NHCOCH_2CONH-$	$C_{13}H_{20}N_4O_4$	296.3255032	*N*, *N*'-bis (pyrrolidin-ylcarbonyl) propanediamide
$IIIL_4$	$-NHCH_2CONHCOCH_2NH-$	$C_{13}H_{20}N_4O_4$	296.33444	*N*, *N*'-[iminobis (2-oxoethane-2, 1-diyl)] dipyrrolidine-2-carboxamide
$IIIL_5$	$-NHCH_2CONHCH_2CH_2NHCOCH_2NH-$	$C_{16}H_{28}N_6O_4$	368.4311	N,N'-((ethane-1,2-diylbis(bis(2-oxoethane-2,1-diyl)) bis (pyrrolidine-2-carboxamide

Table 2. Physical data of Scheme-II compounds

Compounds	Linker Chain	Molecular formula	Molecular weight	IUPAC name
IVL_6	-$NHCH_2CONH$-	$C_{12}H_{20}N_4O_3$	268.33504	*N*, *N*'-(1-oxoethane-1,2diyl) dipyrrolidine-carboxamide
IVL_7	-$NHCH_2CONHCH_2CONH$-	$C_{15}H_{27}N_5O_4$	325.4801	*N*-[2-oxo-2-({2-oxo-2-[(pyrrolidin-2-ylcarbonyl) amino] ethyl} amino) ethyl]pyrrolidine-2-carboxamide
IVL_8	-$NHCONHCH_2CONH$-	$C_{13}H_{21}N_5O_4$	311.3255032	*N*-({2-oxo-2-[(pyrrolidin-2-ylcarbonyl) amino] ethyl} carbamoyl) pyrrolidine-2-carboxamide
IVL_9	-$NHCH_2CONHC\ H_2CH_2NH$-	$C_{14}H_{25}N_5O_3$	311.33444	oxo[(pyrrolidin-2-ylcarbonyl) amino]ethyl}amino) ethyl] pyrrolidine-2- carboxamide
IVL_{10}	- $NHCO(CH_2)_2OHCONH$	$C_{16}H_{30}N_4O_3$	326.4311	2-hydroxy-N, N'-bis (pyrrolidin-2-ylcarbonyl) butanediamide
IVL_{11}	-$NH(CH_2)_2NHCOCHOHCH_2CONH(CH_2)_2NH$-	$C_{18}H_{32}N_4O_5$	412.58198	2-hydroxy-N^1, N^4-bis(2-(pyrrolidine-2-carboxamido) ethyl) succinamide
IVL_{12}	-$NHArCONH$-	$C_{17}H_{22}N_4O_3$	330.3554	*N*-({4-[(pyrrolidin-2-ylcarbonyl) amino] phenyl} carbonyl) pyrrolidine-2-carboxamide
IVL_{13}	-$NHArCONH(CH_2)_2NH$	$C_{19}H_{27}N_5O_3$	373.40046	N-(2-(4-(pyrrolidine-2-carboxamido) benzamide) ethyl) pyrrolidine-2-carboxamide
IVL_{14}	-$NHArCONHCH_2CONH$-	$C_{19}H_{25}N_4O_4$	387.458632	N-(4-((2-oxo-2-(pyrrolidine-2-carboxamido) ethyl) carbamoyl) phenyl) pyrrolidine-2-carboxamide

Activity Tables

Table 3. Summary of docking studies of Scheme-I compounds ($IIIL_1$ to $IIIL_5$)

Name	Electrostatic energy	Van der waals energy	Lib Dock score	Interacting amino acids	Interacting atoms	H-bond distance
$IIIL_1$	4.411	4.306	-8.9475	LEU98 LYS106 LEU204, Leu204, Tyr156 Glu155.Ala103, Ala145	B11:H24 - A: LEU98:O: B11:H25- A: LEU204:HD11 B9:H29 - A: LYS106:HZ2	1.458000
$IIIL_2$	10.39	4.471	-8.1289	LYS231, ALA238, ASP234, LYS248, LEU349	B12:H24 - A: LEU98:O: B12:H26 - A: LEU204:HD12 B12:H28 - A: LYS108:HZ3	1.634000
$IIIL_3$	4.419	3.376	-7.6394	LEU98 LYS105 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A1:H25 - A: LEU98:O: A1:H25 - A: LEU98:C: A1:H31 - A: LYS105:CD A1:H31 - A: LYS105:HD1 A1:H31 - A: LYS105:HD3	1.428000
$IIIL_4$	11.81	3.427	-11.5501	LEU98 LYS105 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A2:H25 - A: LEU98:O: A2:H25 - A: LEU98:C: A2:H31 - A: LYS105:CD A2:H31 - A: LYS105:HD2 A2:H31 - A: LYS105:HD3	1.736000
$IIIL_5$	4.377	4.324	-10.9808	LEU98 LYS105 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A3:H25 - A: LEU98:O A3:H25 - A: LEU98:C: A3:H31 - A: LYS105:CD: A3:H31 - A: LYS105:HD1 A3:H31 - A:	1.351000

Table 4. Summary of docking studies of Scheme-II compounds ($IIIL_6$ to $IIIL_{14}$)

Name	Electrostatic energy	Van der waals energy	Lib Dock score	Interacting amino acids	Interacting atoms	H-bond distance
IVL_6	4.319	4.367	-12.8472	LEU98 LYS105 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A2:H25 - A: LEU98:O: A2:H25 - A: LEU98:C: A2:H31 - A: LYS105:CD A2:H31 - A: LYS105:HD1 A2:H31 - A: LYS105:HD3	1.725000
IVL_7	11.81	3.437	-10.8318	LEU98 LYS104 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A3:H25 - A: LEU83:O: A3:H25 - A: LEU84:C A3:H31 - A: LYS104:CD A3:H31 - A: LYS104:HD2 A3:H32 - A: LYS105:HD1	1.536000

IVL_8	4.329	3.268	-10.7508	LEU98 LYS108LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A4:H25 - A: LEU98:O: A4:H25 - A: LEU97:C A4:H32 - A: LYS108:CD A4:H32 - A: LYS104:HD2 A4:H32 - A: LYS108:HD3	1.614000
IVL_9	4.429	4.702	-9.1867	LEU98 LYS108LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A5:H27 - A: LEU97:O A5:H28 - A: LEU96:C A5:H32 - A: LYS108:CD: A5:H32 - A: LYS104:HD3 A5:H32 - A: LYS104:HD3	1.584000
IVL_{10}	11.83	3.472	-8.5462	LEU99 LYS104 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A2:H24 - A: LEU99:O A2:H26 - A: LEU99:C A3:H32 - A: LYS104:CD: A3:H32 - A: LYS106:HD3 A3:H32 - A: LYS104:HD3	1.637000
IVL_{11}	4.339	4.483	-9.0780	LEU98 LYS105LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A4:H24 - A: LEU98:O: A4:H28 - A: LEU98:C: A4:H33 - A: LYS105:CD A6:H32 - A: LYS108:HD3 A6:H32 - A: LYS108:HD3	1.356000
IVL_{12}	3.429	4.463	-8.9076	LEU97 LYS104LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A6:H25 - A: LEU98:O: A6:H24 - A: LEU97:C A7:H31 - A: LYS104:CD: A7:H32 - A: LYS104:HD2 A7:H32 - A: LYS108:HD3	1.642000
IVL_{13}	10.78	3.402	-10.0633	LEU98 LYS105 LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A2:H28 - A: LEU98:O: A2:H28 - A: LEU97:C A2:H31 - A: LYS105:CD A3:H33 - A: LYS108:HD2 A3:H33 - A: LYS104:HD3	1.736000
IVL_{14}	3.483	3.2070	-9.6120	LEU98 LYS104LEU207, Leu204, Tyr156 Glu155.Ala103, Ala145	A2:H24 - A: LEU83:O: A2:H25 - A: LEU85:C A2:H33 - A: LYS104:CD A2:H33 - A: LYS108:HD2 A2:H33 - A: LYS108:HD3	1.532000

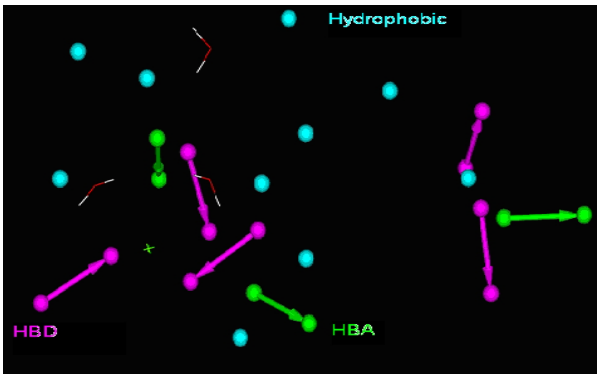


Figure 2. Centre point of cluster feature compound IVL_6 with

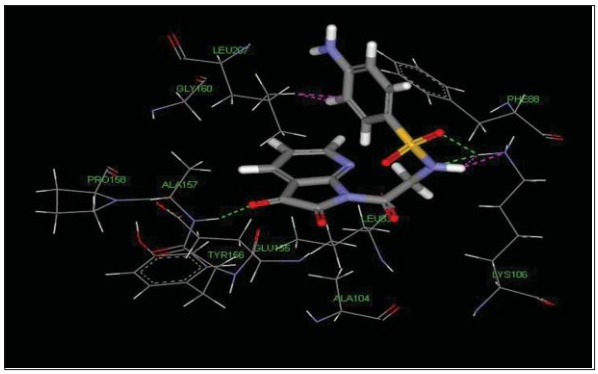


Figure 3. Hydrogen bond interactions of Human DNA Topoisomerase-I enzyme

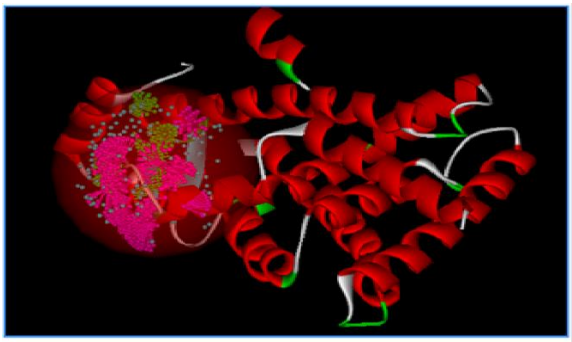


Figure 4. Cluster Feature of Interaction Generation Green), H- Bond Donor (Pink),

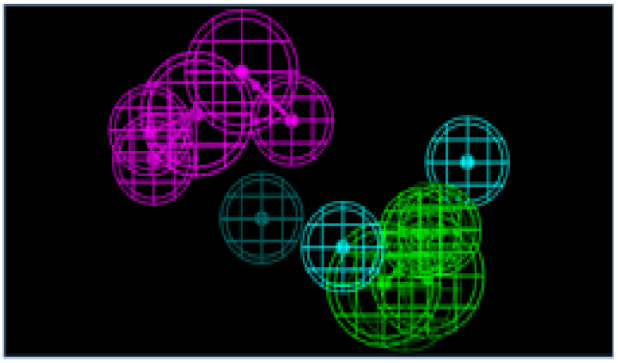


Figure 5. Pharmacophore Features H-Bond Acceptor Blue (Hydrophobic)

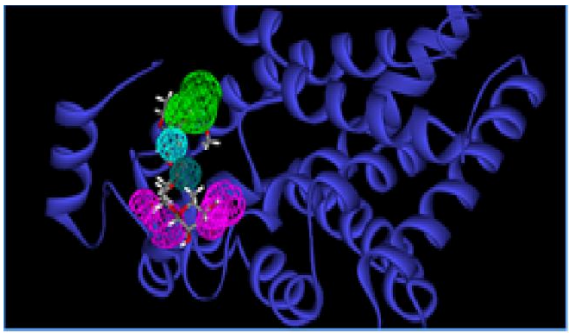


Figure 6. Visualization of IVL_6 Molecule with Pharmacophore Features and Receptor Molecule is Shows in Solid ribbon model

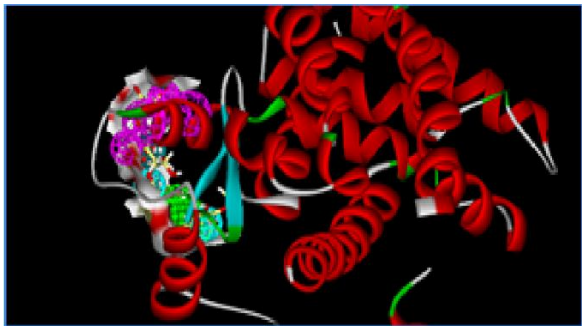


Figure 7. Visualization of $IIIL_4$ Molecule with features and receptor Molecule Shows in Solid Ribbon Mode is

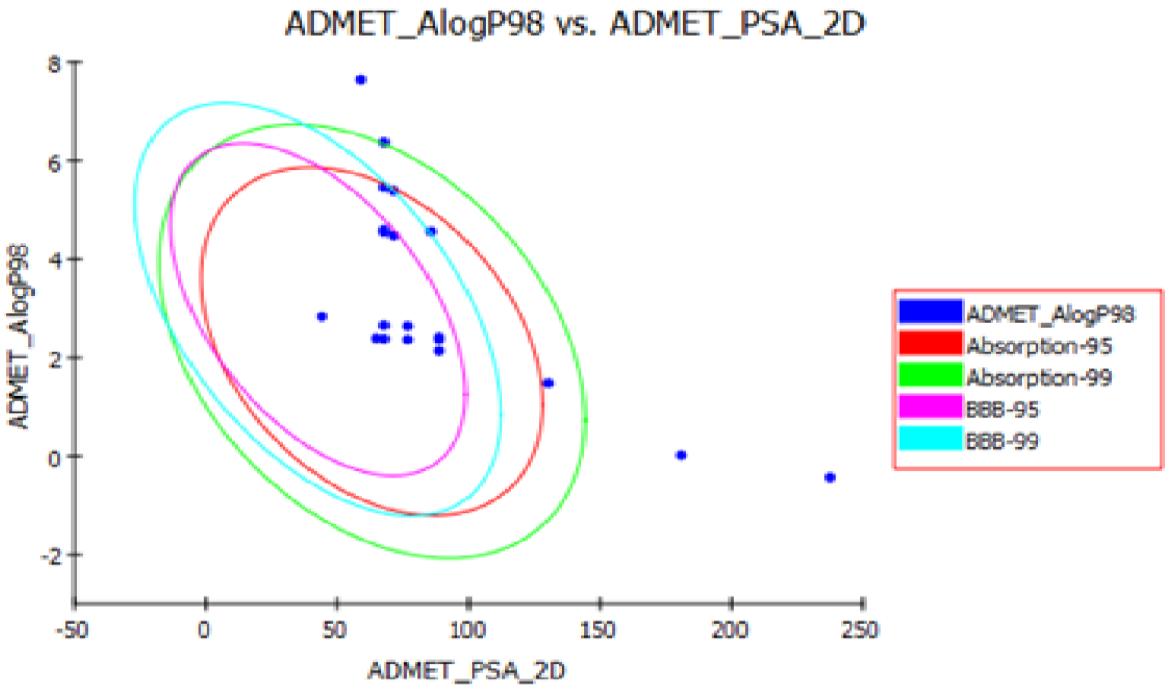


Figure 8. All ligand molecules are having good drug likeliness properties and all molecules with in the boundary limit

Table 5. Predicted fit values of compounds from the common feature-based hypothesis (Hypothesis-I)

Name	Fit value	PharmPrint
$IIIL_1$	4.023	'1111'
$IIIL_2$	4.023	'1111'
$IIIL_3$	3.365	'1111'
$IIIL_4$	4.563	'1111'
$IIIL_5$	3.837	'1111'
IVL_6	5.533	'1111'
IVL_7	3.539	'1111'
IVL_8	3.423	'1111'
IVL_9	1.473	'1111'
IVL_{10}	3.339	'1111'
IVL_{11}	3.353	'1111'
IVL_{12}	3.837	'1111'
IVL_{13}	2.467	'1111'
IVL_{14}	1.487	'1111'

Table 6. The predicted fit values of compounds from the structure-based pharmacophore model of human Topoisomerase-I

Name	Acceptor 13	Acceptor 9	Donor 28	Donor 49	Fit value	Hydrophobe 10	Hydrophobe 24	PharmPrint
$IIIL_1$	0	1	0	0	1.837	1	1	'011011'
$IIIL_2$	0	0	1	1	1.387	0	0	'101011'
$IIIL_3$	1	0	0	1	1.637	1	1	'101011'
$IIIL_4$	1	0	0	1	1.876	0	0	'011011'
$IIIL_5$	1	0	0	1	1.795	0	0	'011011'
IVL_6	1	1	1	1	1.938	1	1	'011011'
IVL_7	1	0	0	1	0.763	0	1	'011011'
IVL_8	1	0	0	1	0.837	1	0	'011110'
IVL_9	0	0	1	1	1.738	1	1	'001111'
IVL_{10}	1	1	1	1	1.837	1	1	'001111'
IVL_{11}	1	1	1	1	0.039	1	1	'011110'
IVL_{12}	1	1	1	1	1.837	1	1	'011110'
IVL_{13}	1	0	1	1	0.398	1	1	'001111'
IVL_{14}	1	1	1	1	1.837	1	1	'001100'

Table 7. Predicted ADMET properties of the compounds

Name	BBB	Absorption	Solubility	Hepatotoxicity	CYP2D6	PPB
$IIIL_1$	2	0	2	0	1	0
$IIIL_2$	2	1	1	0	1	0
$IIIL_3$	4	1	0	1	1	0
$IIIL_4$	4	1	0	0	1	2
$IIIL_5$	2	0	1	0	1	0
IVL_6	4	0	2	0	1	2
IVL_7	2	1	1	0	1	0
IVL_8	2	1	1	1	1	0
IVL_9	3	1	2	0	1	2
IVL_{10}	2	1	1	0	1	0
IVL_{11}	2	1	2	1	1	2
IVL_{12}	2	1	1	0	1	0
IVL_{13}	2	1	0	1	1	0
IVL_{14}	3	1	1	0	1	0

CONCLUSION:

Through docking investigations, the synthesised L-proline derivatives are tested in the present work for their anticancer potential against the targeted protein Topo isomerase-I. The docking results assessed the critical and particular interactions, which are important for characterising the affinity of these ligand molecules for the protein. Additionally, the results of the pharmacophore studies conducted identified the crucial chemical properties of the ligand and structural characteristics of the protein involved in the binding of the protein-ligand complex. Furthermore, these molecules have trustworthy ADMET characteristics. Together, the findings demonstrate that finding the most effective anticancer agents may be aided by the inhibitory activity of L-proline derivatives against Topo isomerase-I.

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