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Research Article

Molecular Biology for Better Medical Science

Lantadenes Targeting NF-KB in Cancer: Molecular Docking and ADMET Predictions

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Abstract: Natural products and their scaffolds encompasses an array of molecular entities as starting points for drug designing and discovery. In the past two decades, phytochemically driven Lantadenes and their modified analogues have attracted lots of attention due to their tumor necrosis factor-α induced nuclear factor-kappa B inhibition and consequently their promising anticancer potential. Earlier reports described the synthesis of esters at C-3 and C-22 of pentacyclic triterpenoid Lantadene, and their evaluation to inhibit tumor necrosis factor-α induced nuclear factor-kappa B along with cytotoxicity against A549 lung cancer cells. In the modern drug discovery process, molecular docking have become an integral part of drug design. Combination of computational platforms and experimental strategies have allowed many successful stories in the discovery of new structure-based or mechanism drugs. Thus as a continuation of our research concerning Lantadenes and their significance, present study has been undertaken to predict binding mode, pharmacokinetic and drug likeness using Vlife MDS Biopredicta and ADMETlab tools. *In silico* inspired grip docking approach was utilized to estimate binding interactions of all the optimized Lantadenes and their modified ester against nuclear factor-kappa B receptor (PDB ID: 1LE9). In addition, all the compounds were screened for pharmacokinetic profile and drug likeness as an important consideration for the selection of compounds with desirable prosperities using ADMETlab tools. Ligand-receptor analysis revealed Lantadene parent nuclei and their modified analogues as potent inhibitors of nuclear factor-kappa B receptor based on binding energy (-21.16 to -42.56 kcal/mol), number of interactions and bond length. Furthermore, most of the analogues were found to have good ADMET profiles. Cumulative computational analyses provided the lead Lantadene analogue 10 and can be considered as a potential candidate for detailed mechanistic studies against lung cancer.

Keywords: Natural products, Lantadenes, NF-κB inhibitors, lung cancer, *In silico* studies

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1. INTRODUCTION

In 2018, the World Health Organization (WHO) reported around 18.1 million cases, 9.6 million deaths from cancer disease along with prediction of this number to get double in size by 2040. Lung cancer is the most commonly diagnosed (11.6% of all cases) and leading cause of death among all the cancers with approximately 18.4% of all deaths.[1] Cancer management is generally more complex than that of other diseases treatment and involve different approaches like surgery, systemic therapy, radiotherapy as well as combination therapies.[2-3] At the molecular level, it has been established that nuclear factor-kappa B (NF-κB) is an important transcription factor linked with onset & progression of inflammation and pathophysiology of cancer, consequently over expressed in a variety of solid tumors, including lung cancer.[4-5] Natural products and their unique structures provide a rich source of inspiration for drug development. As far as plants are concerned, weeds are relatively high in bioactive secondary compounds and hold promising roles in drug discovery. One such weed *Lantana camara* has attracted a lot of attention as a vital source of bioactive metabolites and it can be used as an important source for new pharmaceuticals for the treatment of human ailments.[6-7] Published reports with extensive study and research findings on *Lantana camara* indicated the role of its different extracts and active secondary metabolites in rheumatism, ulcers, skin itches, leprosy, scabies, toothache, stomachache, tumors, anemia, malaria, nematicidal, bactericidal, wound healing, antihyperglycemic, antihypertensive, anticancer *etc.*[8-9] Some of the metabolites like Lantadene A and B (pentacyclic triterpenoids) from the weed *Lantana camara* have been known to possess anti-antitumor potential by inhibiting cell division.[10-13] *In vivo* anticancer studies has showed delayed and reduced papillomas formation, slight increase in the average body weight and increased survival rate of mice treated with Lantadene and its congeners, in comparison to the diseased group in 2 stage carcinoma model using 7,12 dimethylbenz[a] anthracene (DMBA), and 12-O-tetradecanoylphorbol-13-acetate (TPA) as cancer inducer and promoter.[14] Further, number of existing reports on Lantadenes and their derivatives with modifications at ring A and D showed marked anti-tumor and anti-inflammation potential via down-regulation of NF-κB, c-Jun, Bcl-2,and inhibiting Akt protein and NF-κB activation.[15-20] Recent work on Lantadene scaffold described the synthesis of various Lantadene modified analogues figure1 and their evaluation as antitumor potential & inhibition of tumor necrosis factor-alpha-induced (TNF-α induced) NF-κB activation using lung adenocarcinoma A549 cell line. These analogues displayed significant anti-proliferative activity and provided us with 10 and 12 as promising candidates against lung cancer.[21] *In silico* based virtual screening have become an integral part of academic and industrial research. One of the technique like molecular docking has been extensively used in last two decades for macromolecular targets identifications, prediction of binding affinity and activity of the molecules.[22] Further, high-throughput screening have significantly increased the success rate of drug with the advances in ADME prediction tools where molecules can be exclusively accessed for their molecular structure determination, and proliferating drug likeness rapidly.[23-24] Drug discovery and development through such search engines not only increases the reproducibility of experiments, but reduces the amount of consumables needed, and minimizes the risk of drug withdrawal from clinical trials.[25] Thus, as a continuation of our on-going research on Lantadene derivatives and their significant anticancer potential, in the present study, efforts have been made to get the molecular insights of drug receptor interaction *i,e* molecular docking, drug likeness and their ADMET predictions to optimize the pharmacophore for NF-κB inhibition.

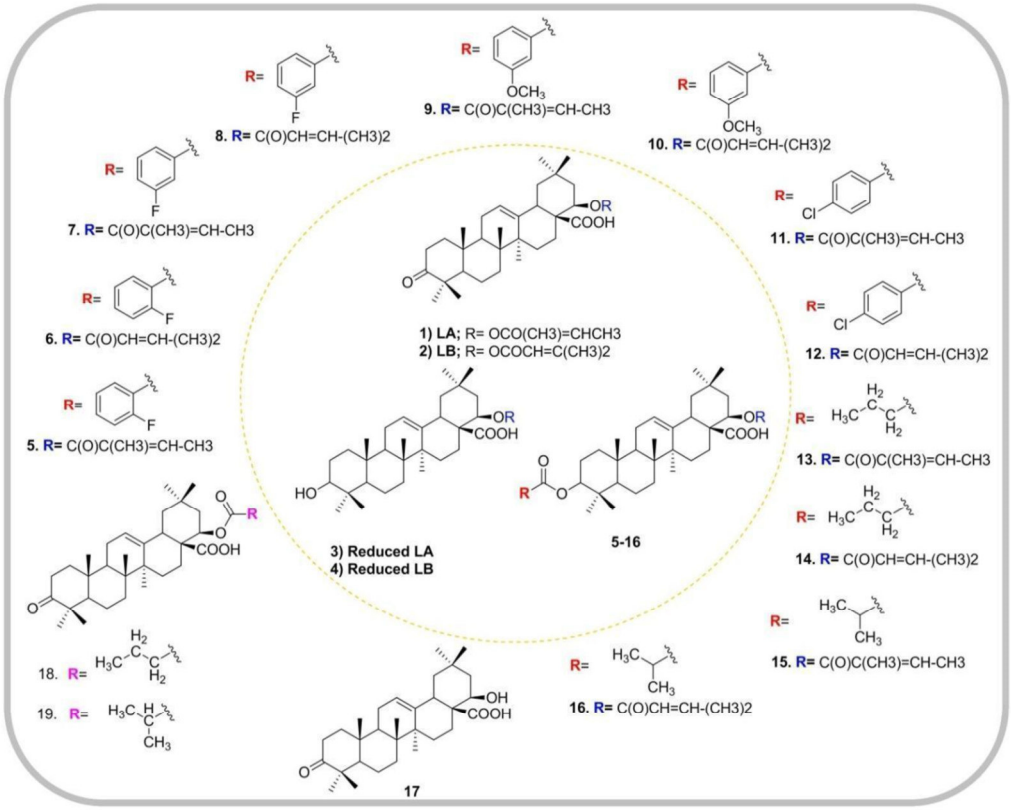

Fig 1. *Lantadenes (1-4) and their modified analogues (5-19) from published report.*[21]

2. MATERIALS AND METHODS

2.1 Dataset

We have chosen the dataset of recently synthesised and evaluated Lantadenes (1-4) and their modified analogues (5-19) from the published report as indicated in Figure 1.[21]

2.2 Molecular Docking

2.2.1 Target Identification and Protein Preparation

X-ray crystal structure of NF-κB (PDB ID: 1LE9) was downloaded from a protein data bank (http://www.rcsb.org) complexed with co-factors. Protein structure was analyzed, reprocessed, and refined using the protein preparation protocol. Water molecules were removed from the protein structure and their valency was maintained by addition of hydrogen molecules. Further, protein structure integrity was assessed, checked, followed by the insertion of incomplete or missing residues and removal of co-factors via Loop Builder tool. The optimized receptor protein was then saved in .mol 2 format and utilized for the further studies.

2.2.2 Ligand Standardization

Two-dimensional (2D) structures of all the test compounds *i,e* Lantadene analogues (1-19) and Bortezomib were sketched using Chem-Draw Ultra 8.0 and converted into their corresponding three-dimensional (3D) structures with the help of VLife converter module. All the molecules were energetically, geometrically minimized and optimized with default settings up to the rms gradient of 0.01 using Merck Molecular Force Field (MMFF). The conformer generated with least energy was subjected for further studies.

2.2.3 Ligand Docking

"BioPredicta module", a comprehensive and integrated graphical user interface program of the VLife MDS 4.6, *i.e*., was used to prepare, run, and analyze the docking simulations on the HP Pentium IV 2.80 GHz Processor/ Microsoft Win XP Home Edition system.[26] It is an advanced and swift tool, equipped with grip docking feature have been used to identify the critical binding mode of all of the optimized molecules against NF-κB receptor. In drug receptor interaction studies, an optimal binding and subsequently affinity prediction with respect to ligand pose always remains an important criteria.[27-28] Docking results being generated with different conformations and orientation are referred as ligand pose. Best pose identified with the least energy in terms of D score is taken forward for the subsequent analysis and identification of putative binding interactions associated with active amino acid residues of the binding domain.

2.3 ADMET Predictions

Early predictions of physicochemical properties like absorption, distribution, metabolism , excretion and toxicity (ADMET) have become a prime/ fundamental consideration to reduce the chances of drug failure at the clinical level.[29] Taking into consideration, a preliminary predictive *in silico* pharmacokinetic studies including absorption (Papp Caco-2 permeability; human intestinal absorption), distribution [plasma protein binding (PPB); blood brain barrier (BBB)], metabolism (P450 CYP3A4 inhibitor; P450 CYP3A4 substrate; P450 CYP2C9 inhibitor) elimination [half life time (T ½); clearance rate (CL)], and toxicity [hERG (hERG blockers); human hepatotoxicity (H-HT); LD50 of acute toxicity (LD50); ames mutagenicity (AMES)][30] are being studied for all the Lantadene analogues using ADMETlab (http://admet.scbdd.com/) online server.

2.4 Drug Likeness: Rule of Five

Drug discovery and development strongly rely upon optimizing ligand affinity for a specific receptor, enhancing functional potency and selectivity, and improving drug like properties for optimal pharmacokinetics and oral bioavailability.[31] Lipinski's "rule of five" provides an adequate set of guidelines to select the orally bioavailble drug like molecules based on their molecular weight <500 Da, number of hydrogen-bond donors <5, number of hydrogen-bond acceptors <10, and calculated octanol- water partition coefficient 1-5 and low polar surface area (tPSA< 140 Å).[32] The descriptor calculations of the compounds were determined using the Vlife MDS tool.

3. RESULTS AND DISCUSSION

3.1 Molecular docking

Down-regulation of NF-κB by Lantadenes represents a promising therapeutic approach towards the lung adenocarcinoma. Using molecular docking a core technology, authors have made efforts to understand ligand-receptor interactions, and to identify possible binding modes of all the Lantadene analogues and their corresponding interactions with NF-κB receptor using Bortezomib as reference drug. Number of published reports indicated the role of Bortezomib in inhibition of NF-κB activation,[33] but present study is an effort to report its potential binding interactions with NF-κB (PDB ID: 1LE9) for the first time. Table 1 is reflecting the hydrogen, hydrophobic, van der Waals forces and charge interactions involved with active amino acid residues of the receptor by the data set of Lantadenes (1-4), its modified analogues (5-19) and Bortezomib (reference drug).

Table 1. ***Detailed docking parameters including D score, ligand pose and forces involved in interaction with active amino acid residues of 1LE9***

Ligands	Ligand pose	D score	Forces involved in interaction with active amino acid residues		
			Hydrogen bond	Hydrophobic interaction	Vander wall forces
1	6	-36.30	LEU193A 3.28Å	GLY44A 3.28Å, MET32A 3.20 Å	ARG30A 2.98 Å, GLY31 A 2.41 Å
2	2	-42.56	-	GLY31A 2.94 Å, ARG33A 2.43 Å, ARG35A 2.18 Å	ARG35A 2.53 Å LYS28A 2.54 Å
3	24	-37.03	GLU193A 2.45 Å	ARG35A 3.52 Å MET35A 3.35 Å GLY44A 3.51 Å	LYS28A 2.60 Å ARG35 2.53 Å
4	11	-40.57	GLN29A 2.48 Å ARG30A 2.07 Å GLY31A 2.37 Å	GLU49A 2.82 Å LYS28A 2.73 Å GLY31A 3.52 Å	LYS28A 2.42 Å ARG33A 2.80 Å
5	30	-31.30	-	LYS28A 2.166 Å GLY31A 3.88 Å ARG33A 3.93 Å	GLN26A 2.84 Å LYS28A 2.40 Å GLU49A 3.74 Å
6	15	-30.94	GLN29A 1.94 Å	LYS28A 2.71 Å, AGR33A 4.1 Å	LYS28A 2.48 Å GLY31A 2.61 Å ARG33A 2.46 Å
7	27	-27.39	-	GLY31a 2.94 Å ARG33a 3.23 Å LYS195A 3.38 Å	LYS28A 2.99 Å GLN29A 2.56 Å AGR33A 3.31 Å-
8	24	-26.38	-	LYS28A 2.57 Å AGR33A 3.29 Å SER51A 3.74 Å	LYS28A 2.92 Å GLY31A 2.74 Å
9	4	-37.77	ARG33A 3.523Å ARG35A 1.70 Å	GLY31A 3.52 Å ARG35A 1.06 Å GLU193A 3.71 Å	ARG33A 2.43 Å LYS195A 2.51 Å
10	6	-40.14	ARG33A 2.36 Å ARG35 A 1.73 Å	GLY31A 3.65 Å ARG35A 2.83 Å LYS195A 3.68 Å MET 32A 3.89 Å	ARG30A 2.92 Å ARG35A 2.43 Å ALA43A 2.42 Å
11	28	-21.16	GLN29A 2.31 Å	LYS28A 1.79 Å GLY31A 3.72 Å ARG33A 3.86 Å	GLN26A 3.01 Å LYS195A 2.62 Å GLU49A 2.75 Å
12	26	-39.32	GLN29A 1.94 Å	LYS28A 2.71 Å ARG33A 3.93 Å GLUA 4.66 Å	LYS28A 2.46 Å ARG33A 2.50 Å GLU193 Å 2.43 Å
13	19	-31.95	-	LYS28A 3.41 Å GLY31A 3.28 Å ARG33A 4.22 Å	LYS28A 2.42 Å GLY31A 2.56 Å LYS195 2.40 Å
14	17	-27.62	GLN29A 2.44 Å	ARG50A 2.38 Å LYS28A 3.42 Å GLY31A 4.08 Å	LYS28A 2.62 Å ARG33 2.69 Å LYS195 2.69 Å
15	19	-38.54	-	LYS28A 2.977 Å GLY31A 3.01 Å ARG33A 3.55 Å	LYS28 A 2.44 Å GLU49 Å 3.11 Å ARG30 2.92 Å
16	20	-33.00	-	LYS28A 4.20 Å GLY31A 3.57 Å ARG30A 4.99 Å	LYS28A 2.47 Å ARG30 2.72 Å GLY31A 2.95 Å
17	14	-27.51	-	LYS28A 3.04 Å ARG33A 4.08 Å GLY31A 3.67 Å	LYS28A 2.76 Å ARG33A 2.89 Å GLY31A 2.75 Å
18	1	-36.84	-	LYS28A 2.84 Å ARG33A 3.71 Å GLY31A 3.35 Å	LYS28A 2.69 Å ARG33A 2.44 Å GLY31A 2.60 Å
19	29	-35.05	-	LYS28A 3.54 Å GLY31A 3.85 Å LYS195A 4.24 Å	LYS28A 2.88 Å ARG33 3.01 Å GLY31A 3.09 Å
Bortezomib	16	-57.97	-	LYS28A 4.08Å, LYS28A 3.48Å, GLY31A 3.51Å	LYS28A 2.60Å GLY31A 2.51Å GLU193A 2.87Å

In drug-receptor interactions, binding energy is indicated in terms of negative D score that reflects their binding affinity, compactness and spontaneous encroachment of the ligand towards its active site. Reference drug Bortezomib is found to interact with NF-κB (PDB ID: 1LE9) receptors and afforded a D score -57.97. Table 1 indicates the moderate to comparable binding affinity of Lantadenes, and their modified analogues towards the 1LE9 with D score ranging from -21.16 to -42.56 kcal/mol. Moderate to good affinity has been observed for the compounds 9-10, 12, 15, 18 as indicated in table 1, in comparison to parent Lantadenes (1-4) with -36.30 to 42.56 Kcal/mol, except for 5-8, 11, 13-14, 16-17 and 19 with weak affinity. The cumulative *in vitro* cytotoxicity, TNF-α induced NF-κB activation inhibitory activities and *in silico* studies rendered us with potential molecule 10. Its high negative D score, thus high affinity towards protein 1LE9:-40.14 kcal/mol is in agreement with *in vitro* studies. High affinity of this molecule can be considered on account of the significant and strong interactions including hydrogen (ARG33A 2.36 Å, ARG35 A 1.73 Å), hydrophobic (GLY31A 3.65 Å, ARG35A 2.83 Å, LYS195A 3.68 Å, MET32A 3.89 Å) and van der Waals forces (ARG30A 2.92 Å, ARG35A 2.43 Å, ALA43A 2.42 Å) in closer proximity. Further, this high activity and more negative D Score is governed on account of involvement and interaction of 3β-isobutyryloxy side chain at the C-22 of Lantadene analogue 10 with ARG33A, LYS195A and ALA43A with bond distance of 2.36 Å, 2.83 Å and 2.42Å through hydrogen bond, hydrophobic and van der Waals interaction. Importance of the C-22 ester side chain is further indicated and reflected by the decreased activity of the compound 17. Without C-22 ester side chain there is absence of hydrogen bond interactions and presence of hydrophobic interaction at comparatively longer bond distance. Present observations are found to be in agreement with previous report,[21] and suggested that the C-22 electrophilic α,β-unsaturated ester side chain seems to play a critical role in binding with active amino acid residues of the receptor corresponding to the biological activity. Consistent with our binding hypothesis, the reference drug Bortezomib was found to be engaged with different amino acid residues through hydrophobic interaction (LYS28A 4.08Å, LYS28A 3.48Å, GLY31A 3.51Å) and van der Waals forces (LYS28A 2.60Å, ASP217A 4.73 Å) affording the molecule to interact with least energy -57.97 kcal/mol. The docked complex and three-dimensional (3D) representations of the lead analogue 10 and reference drug Bortezomib are shown in Figure 2a and 2b respectively.

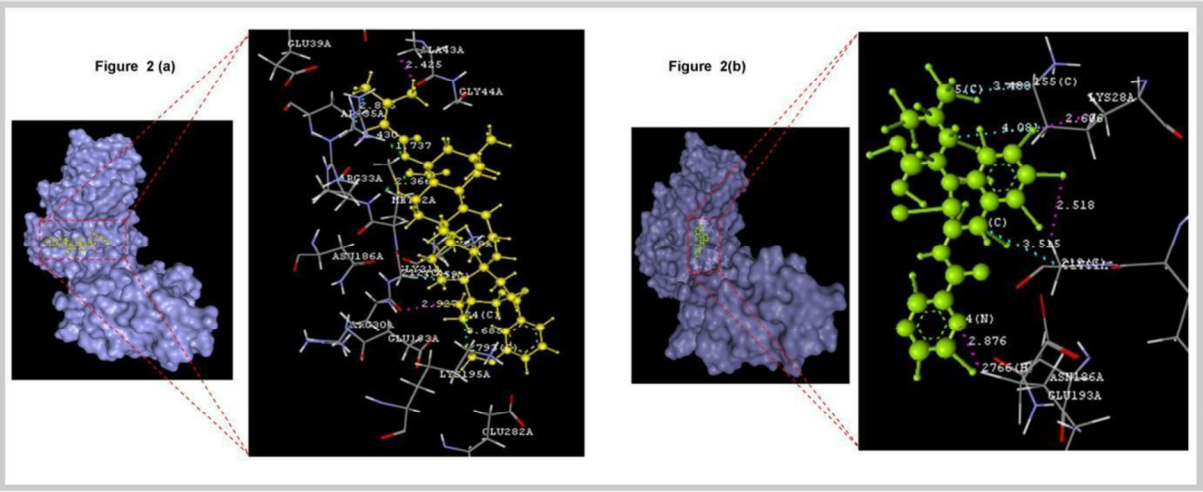

Fig 2. ***Three-dimensional (3D) representations of molecular interactions of lead analogue 10 (2a) and Bortezomib reference drug (2b) with amino acid residues of 1LE9***

3.2 ADMET Predictions

Early stage resolution of pharmacokinetic and toxicity properties of drug candidates remains a key step for drug development. With this aim all the Lantadene analogues have been assessed for their pharmacokinetic (ADME) parameters and drug toxicity predictions using ADMET lab web interface as shown in table 2.

Table 2. Pharmacokinetic features (*In silico* ADMET) predictions

Ligands	Absorption		Distribution		Metabolism			Elimination		Toxicity		
	Papp (Caco-2 Permeability) cm/s	HIA (Human Intestinal Absorption)	PPB (Plasma Protein Binding) %	BBB (Blood Brain Barrier)	P450 CYP3A4 substrate	P450 CYP3A4 inhibitor	P450 CYP2C9 inhibitor	$T_{1/2}$ (Half Life Time) hr	CL (Clearance Rate) mL/min/kg	hERG (hERG Blockers)	H-HT (Human Hepato-toxicity)	AMES (Ames Muta-genicity)
1	-5.03	+	86.84	+	+	-	-	2.00	1.42	-	-	-
2	-5.02	+	86.93	-	+	-	-	1.88	1.39	-	-	-
3	-5.24	+	87.53	-	+	-	-	2.01	1.44	-	-	-
4	-5.25	+	87.46	-	+	-	-	1.89	1.42	-	-	-
5	-5.08	+	87.62	-	+	+	-	2.38	1.39	+	-	-
6	-5.07	+	86.59	-	+	+	-	2.34	1.39	+	-	-
7	-5.08	+	87.17	+	+	+	+	2.27	1.36	+	-	-
8	-5.08	+	86.63	-	+	+	-	2.17	1.36	+	-	-
9	-5.16	+	87.57	-	+	+	+	2.45	1.35	-	-	-
10	-5.17	+	87.38	-	+	+	-	2.35	1.35	-	-	-
11	-5.08	+	87.14	-	+	+	+	2.38	1.32	-	-	-
12	-5.09	+	86.47	-	+	+	-	2.32	1.31	+	-	-
13	-5.01	+	87.04	+	+	+	-	2.12	1.32	-	-	-
14	-5.01	+	87.09	+	+	-	-	2.06	1.32	-	-	-
15	-5.01	+	87.43	-	+	+	-	2.17	1.34	-	-	-
16	-5.01	+	87.30	-	+	-	-	2.11	1.33	-	-	-
17	-5.05	+	86.34	+	+	-	-	1.95	1.38	-	-	-
18	-5.05	+	86.69	+	+	-	-	1.88	1.44	-	-	-
19	-5.04	+	84.97	+	+	-	-	1.96	1.46	-	-	-

Papp Caco-2Permeability (Optimal: higher than -5.15 Log unit or -4.70 or -4.80); HIA (>30%:HIA is +ve; < 30%: HIA is -ve) +ve: greater affinity, –ve values: low affinity, PPB (90% Significant with drugs that are highly protein-bound and have a low therapeutic index); BBB (BB ratio >=0.1: BBB+; BB ratio <0.1: BBB-); T 1/2 (> 8 h: high; 3 h <CI< 8 h: moderate; < 3 h:low); CL(> 15 mL/min/kg: high; 5 mL/min/kg <CI< 15 mL/min/kg: moderate; < 5 mL/min/kg: low). –ve values mean low affinity while +ve values indicate greater affinity.

Caco-2 permeability represents an important parameter to determine the oral absorption and permeability in early phases of drug design with optimal value higher than -5.15 cm/s.[34] All the modified Lantadene analogues (5-19) showed the permeability values in range from -5.01 to -5.25 cm/s and the lead analogue showed comparable permeability with its highest value -5.17 cm/s. In addition, all the compounds qualified HIA% with value ≥30% a key parameter for oral bioavailability absorption related to the permeation of compounds through biological membrane under the influence of physicochemical characteristics.[35] PPB of drugs is a well-recognised phenomenon and plays a critical role in the dynamics of chemical inside the body.[36] Predicted information indicated the binding potential of all the Lantadene analogues in range of 84.97 % to 87.62% in comparison to reference value 90%, including the lead analogue 10 with comparable PPB. Another parameter BBB, as the name indicate facilitate the selective transport of drug molecule between the blood and the parenchyma.[37] The predicted observations indicated Lantadene (2) and their modified analogues (3-6, 8-12, 15-16) cannot cross the BBB which will add to their safety profiles. As well as, the fate of administered drugs is mainly influenced by their metabolism, that involves enzymatic modification or degradation of the drug molecules corresponding to their therapeutic response.[38] Table 2, is indicating the possible metabolism of the parent compounds (1-4) and their analogues with P450 CYP3A4 substrate, P450 CYP3A4 inhibitor and P450 CYP2C9 inhibitor. Positive and negative symbols against each compound reflects its metabolism by respective enzymes. All the compounds (1-19) showed low predicted $T_{1/2}$ ranging from 1.88 to 2.45 hr (>8h: high; 3h<Cl< 8h: moderate; <3h: low) and clearance rate 1.31 to 1.46 mL/min/kg w.r.t the standard values of high >15 mL/min/kg, moderate 5mL/min/kg<Cl< 15mL/min/kg, and low <5 mL/min/kg: low half time periods.[30, 39] Drug induced toxicity is a major cause for drug withdrawal from the market and remain a key concern for the development of novel molecules.[40] All the compounds (1-19) indicted negative test for H-HT and AMES test. Except for compounds 5-8 and 12 all the analogues showed non-toxicity towards hERG. Cumulative observations also indicated lead analogue 10 as a safe or non toxic molecule.

3.3 Drug Likeness: Rule of Five

Rule of 5 has been widely adopted and the first step filter useful in defining druggability. Molecular weight remains an important criteria and an obvious choice for absorption and permeation time as a function of drug weight. Molecular weight of all the Lantadene analogues were found in the range of 540.78 to 693.36 Da except for the molecules 18-19 (472.70 less than 500 Da) which is further in agreement with the statement that the natural driven molecules and their semi synthetic derivatives generally remained an exceptional cases among the approved drugs due to their more complex ring system. For oral drugs, log P value between 1-5 is often considered the optimal value to achieve a balance between permeability and first-pass clearance. Almost all the Lantadenes (1-19) found to deviate from the optimal range and their high logP value (log P 6.20 to 10.24) indicated the possible need of optimization of hydrophilicity profile before their preclinical or clinical evaluation. Polar surface area, a descriptor that signifies total polar surface area (tPSA) and correlates with molecular passive transport through the membrane and therefore allows the prediction of transport properties of drugs. All the molecules fall in the optimal range 77.76 to 99.13 $Å^2$ in comparison to the critical value that should be <140 $Å^2$. According to the Lipinski rule of five, compounds with <5 hydrogen-bond donors and <10 hydrogen-bonds acceptors are generally considered with good absorption or permeation characteristics. Present findings indicated that all the molecules (1-19) fulfilled these criteria as indicated in table 3.

Table 3. ***Lipinski's rule of five: drug likeness of the compounds***

Compound	Molecular weight eright	Log P	Hydrogen bond acceptor	Hydrogen bond donor	Total polar surface area
1	552.79	7.93	4	1	80.67
2	552.79	7.93	4	1	80.67
3	554.81	7.72	4	2	83.83
4	554.81	7.72	4	2	83.83
5	676.91	9.72	5	1	89.90
6	676.91	9.72	5	1	89.90
7	676.91	9.72	5	1	89.90
8	676.91	9.72	5	1	89.90
9	688.94	9.59	6	1	99.13
10	688.94	9.59	6	1	99.13
11	693.36	10.24	5	1	89.90
12	693.36	10.24	5	1	89.90
13	624.90	9.07	5	1	89.90
14	624.90	9.07	5	1	89.90
15	624.90	8.92	5	1	89.90
16	624.90	8.92	5	1	89.90
17	472.70	6.20	3	3	77.76
18	540.78	7.76	4	1	80.67
19	540.78	7.62	4	1	80.67

4. CONCLUSION

Continuing our research interests in Lantadenes and their analogues as anticancer agents, present study was an effort to get the molecular insights into ligand receptor interactions, *in silico* based pharmacokinetics and descriptors calculations. The predictive studies indicated the broader scope of Lantadenes as anticancer agents and offered compound **10** as an attractive starting point for its further evaluation and detailed mechanistic studies.

5. FUNDING ACKNOWLEDGEMENT

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6. AUTHORS CONTRIBUTION STATEMENT

Ms. Monika, carried out the research study, analysed & evaluated the results and drafted the manuscript. Dr. Manu Sharma has reviewed and corrected the manuscript. Current research work is an extension of the earlier published work where Monika, Ankesh Sharma and Vaibhav Aggarwal synthesized these molecules during their post graduation studies (M. Pharmacy) and Dr Manu Sharma supervised the research work. (Corresponding author) Dr. Neelima Dhingra is Ph.D. mentor of first author (Ms Monika) and present work is part of Monika PhD research outcomes. Dr Neelima has conceptualized, designed the study and guided at all stages. All the work and revision has been carried out in her supervision.

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8. CONFLICT OF INTEREST

Conflict of interest declared none.

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