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Designed Tripeptides as Potent NPM1 Oligomerization Inhibitors: A Molecular Docking and Dynamics Study Toward New Anticancer Drug Candidates

Safia Lounici[1,2*], Djamila Kherbouche[3], Iméne Lafri[4], Noureddine Missoum[5], Amina Ghomri[3], Lynda Boutekrabt[6]

[1] Laboratory of Biological and Agronomic Sciences, University Amar Telidji of Laghouat. 03000 Laghouat. Algeria s.lounici@lagh-univ.dz
[2] Department of Agricultural Sciences, Faculty of Sciences, University Amar Telidji of Laghouat, 03000 Laghouat. Algeria
[3]Ecole Supérieure en Sciences Appliquées de Tlemcen ESSA TlemcenB. P.165 belhorizon 13000 Tlemcen. Algeria. ghomrighomri1@gmail.com
[4]Agropastoralisme Research Center, 17000 Djelfa. Algeria imene.lafri@crapast.dz
[5] Faculty of Technology, Hassiba Benbouali University of Chlef, Algeria. n.missoum@univ-chlef.dz
[6]Algerian School of Higher Business ESAA, El Mohammadia, 16000 Algiers. Algeria. l.boutekrabt@mesrs.dz

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ABSTRACT

Inhibition of nucleophosmin enzyme is nowadays considered as a key in many type cancer treatments .Actually researchers investigate (developed) a significant number of synthetics inhibitors of nucleophosmin enzyme. NPM1 is over-expressed in a number of solid tumours from different histological origin, this makes it a high targeted protein. However, an efficient inhibitor still a scientific issue. putative small molecular inhibitor SMI (NSC348884) synthetic inhibitors and tripeptides were identified as the most efficient ones. Currently, molecular modeling presents a powerful procedure to rationalize experimental observations and to design new drugs with desirable activities. In this work, on the basis of the reported NSC348884, and tripeptides, we designed another nine compounds consisting of donor or acceptor moieties and the cyclic conjugation. We studied their interactions with NPM1 and their affinities to binding with the active site using molecular docking. Simulation and modification of theoretical affinities were done using Molecular Operating Environment software (MOE). Obtained results showed numbers of key residues and specific interactions at the binding site of nucleophosmin enzyme; we noted also particularly implication of the Tyrosine 29 amino acid and the presence of the aromatics interactions. As main observation we conclude that Tryptophan-*argenine*-Tryptophan *tripeptide is the most important inhibitor candidate of nucleophosmin enzym among designed molecules.*

KEYWORDS: *Molecular modeling; Molecular dynamics; Cancer; NPM1; oligomerisation properties , aromatic residues, active site MOE(Molecular Operating Environment).*

1. INTRODUCTION

Nucleophosmin1 (NPM1) is one of the vital proteins of the nucleolus, and it has been considered as one of the most abundant proteins in the granular region of the nucleoli throws it contribution in preserving nucleolar structure [1, 2]. Recently, it has been shown that NPM1 is implicated in many cellular functions [3-5]. Indeed, NPM1 plays an important role in the DNA replication, recombination, transcription, and repair[4,6-8], ribosome assembly and export [9-10]. The NPM1 functions is occurred by the interaction with different proteins, one of these interactions is that NPM1 contribute to the p14 alternate reading frame tumor suppressor- oncogene product-P53 p14ARF-HDM2-p53 signalling axis in deferent cellular facts [11–13]. However, NPM1 is highly unstable and shows low anti-proliferative activity in interaction with mutant p14ARF [14]. On the other hand, the NPM1 over-expression leads to its interaction with myelocytomatosis (c-MYC) and induce hyper-proliferation and transformation activities [15].

Experiment shows that NPM1 is over-expressed in a number of solid tumours from different histological origin considering prostate [16], liver [17], thyroid [18], colon [19], gastric [20], pancreas [21], gloma, glioblastoma [22,23] and astrocytoma [24]. As a result the NPM1 has been proposed as an prognostic marker of many maLigandnancies [24,25]. Actually, the specific contribution of NPM1 over-expression in

cancer development is not totally understood but it may be malty-factorial. Nevertheless, It has been shown that, NPM1 participate in many cell proliferation mechanisms throw it three distinct structural domains, the C-terminal nucleic acid binding domain, the histone binding middle domain and the N-terminal oLigandomerization domain [26].

Very recently, scientists managed to invent new molecules to treat haematological maLigandnancies solid tumours where NPM1 gene is mutated and also where the gene is over-expressed [3–6,27,28]. Indeed, a number of molecules targeting NPM1 protein are developed by strategies.

The most known molecules targeting NPM1 throw the oLigandomerization properties by destroying its 3d structure and loss its functions are putative small molecular inhibitor SMI (NSC348884) which was first developed to block the oLigandomerisation[29], also the 5-((N-benzyl-1H-indol-3-yl)methylene)pyrimidine-2,4,6 (1H,3H,5H) trione (YTR107) [30–32] and REV37-47 that follows another strategy by targeting the HIV-1 virus interaction site in the same domain to prevent the use of HIV-1 for the NPM1 as a key of transcription mechanism [33], and will prevent most of the NPM1 anti-apoptotic activities [39]. Some other molecules targets the C-terminus domain, like as avrainvilamide [34–36], TmPyP4 [37], ATRA/ATO [38] and other no selective systems that attack several activities, such as interfering with NPM1 post-translational modifications, like as CK2- mediated phosphorylation concerning the role of the phosphorylation on the activity of NPM1 [39].

We note that in particular the NSC348884 effective activity has been proved on several tumours [29].

Molecular docking becomes imperative tool in drug discovery due to the development of informatics devices. The pertinent basic theories, with sample algorithms and scoring functions, and the performance of available docking software are largely employing in drug design[40-42].

In the present study we interactions of a series of molecules (NSC348884 (Ligand 1) the synthetic molecules Gnemonol B , t-diptoindonesin b (Lig 3,4) molecules and the designed tripeptides (Ligand 9-12) an number of designed other structural molecules (Ligands 2,5-8)) with the oligomerization domain of NPM1 by molecular modelling tools in a large spectrum in order to highlight factors encouraging interactions between the NPM1 phosphoprotein and chosen molecules interacting while destruction the dimer formation and up regulation of p53 and inducing apoptosis .

2. MATERIALS AND METHODS:

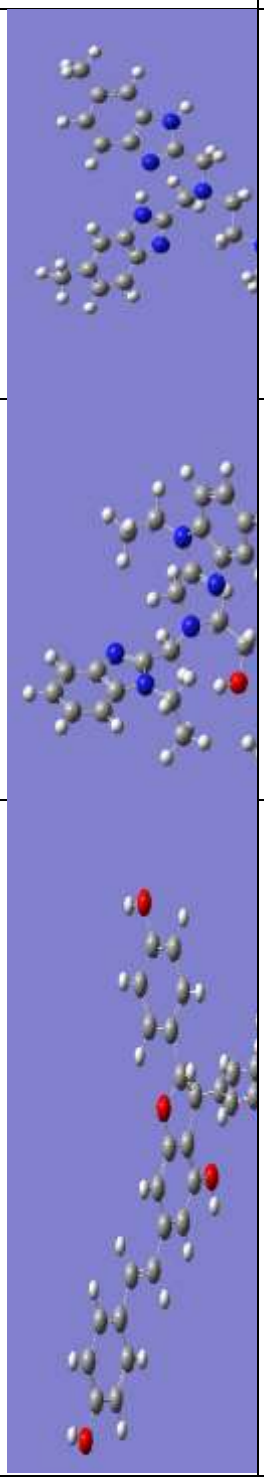
2.1. Preparation of enzyme and inhibitors:

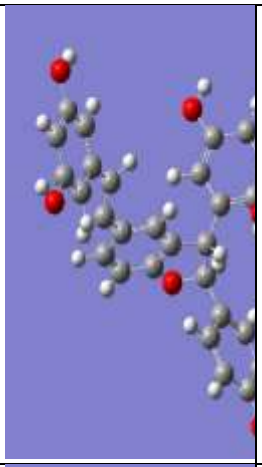
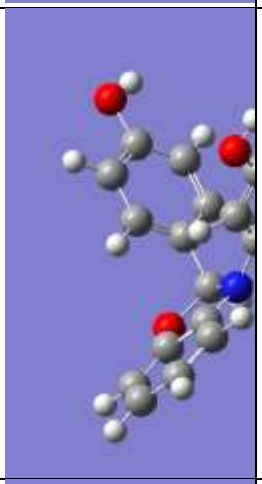
Download of the Homo sapiens NPM1 structure was done from PROTEIN DATA BANK (code2P1B) with three dimensional structure obtained by X-ray diffraction (resolution 2.75 Å) (Figure 1). We Note that the NPM1 crystallizes as a decamere (Figure 1) with 2950 residues a mass of 108,18 KD. The downloaded structure was simplified to a pentamere of 1475 residues to proceed easily to identification of oLigandomerisation sites.

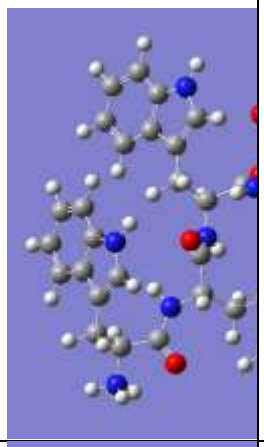
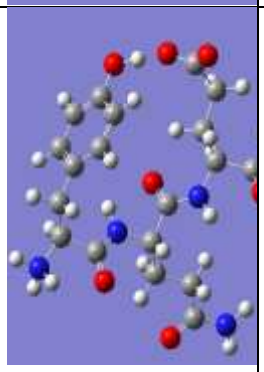
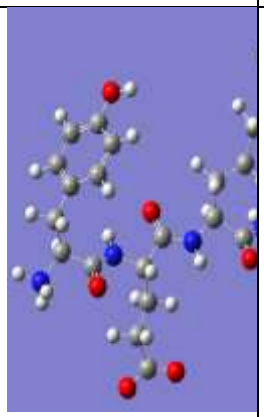
The oLigandomerisation function is assured on the hydrophobic interface between monomers in the pentameric ring and was targeted according to the identification of the amino acids referred to Qi, W. et al. [29], and the structure was analysed to identify the amino acids that construct the oLigandomerisation sites. The chosen sites showed an homological position according to the protein structure (figure1).

The reference Ligand was chosen according to Qi, W. et al. [29] that demonstrated a remarkable synergic effect of NSC348884 with doxorubicin. The Ligands (probable inhibitors) were chosen according to theirs aromatic residues comparing with the volume of the oLigandomerisation identified cavities. Probable inhibitors, (Ligand 1,3 and 4) were downloaded from Pub Chem data base the designed inhibitors (Ligand 2, 5-8) were designed chemical coumpound and (ligand 9-12) represent designed polypeptids, minimized energies of Ligands and their optimised geometries (table1) are obtained using MOE software [43].

Table 1: Molecular structures of the 12 used inhibitors

Ligand	Molecular structure	IUPAC name	PubChem CID	Other name	Chemical formula
Ligand 1		N1,N1,N2,N2-tetrakis((6-methyl-1H-benzo[d]imidazol-2-yl)methyl)ethane-1,2-diamine	335974	NSC348884	C38H40N10
Ligand 2		1,3-bis(bis((1-ethyl-1H-benzo[d]imidazol-2-yl)methyl)amino) propan-2-ol			C43H50N10O
Ligand 3		5-[(2S,3S)-4-hydroxy-6-[(2S,3S)-4-hydroxy-6-[(2S,3S)-4-hydroxy-2-(4-hydroxyphenyl)-6-[(*E*)-2-(4-hydroxyphenyl)ethenyl]-2,3-dihydro-1-benzofuran-3-yl]-2-(4-hydroxyphenyl)-2,3-dihydro-1-benzofuran-3-yl]-2-(4-hydroxyphenyl)-2,3-dihydro-1-benzofuran-3-yl]benzene-1,3-diol	16148652	Gnemonol B	C56H42O12

Ligand 4		5-((E)-2-((2S,2'S,3S,3'S)-3'-(3,5-dihydroxyphenyl)-6'-hydroxy-2,2'-bis(4-hydroxyphenyl)-2,2',3,3'-tetrahydro-[3,4'-bibenzofuran]-5-yl)vinyl)benzene-1,3-diol	643710	t-diptoindonesin b	C42H32O9
Ligand 5		5-((2S,2'R)-6'-hydroxy-2,2'-bis(4-hydroxyphenyl)-2H-[3,4'-bibenzo[d]oxazol]-3'(2'H)-yl)benzene-1,3-diol			C32H24N2O7
Ligand 6		bis(2-(bis((1H-imidazol-2-yl)methyl)amino)ethyl)glycine			C22H31N11O2
Ligand 7		(2-(bis((5-methyl-1H-imidazol-2-yl)methyl)amino)ethyl)(2-(((4-methyl-1H-imidazol-2-yl)methyl)((5-methyl-1H-imidazol-2-yl)methyl)amino)ethyl)carbamic acid			C25H37N11O2

Ligand 8		N1-(2-(bis((4-methyl-1H-imidazol-2-yl)methyl)amino)ethyl)-N2,N2-bis((4-methyl-1H-imidazol-2-yl)methyl)ethane-1,2-diamine			C24H37N11
Ligand 9		((S)-2-ammonio-3-(1H-indol-3-yl)propanoyl)-L-tryptophyl-L-tryptophyl-L-tryptophanate		(4trp)	C44H42N8O5
Ligand 10		(S)-4-((S)-5-amino-2-((S)-2-ammonio-3-(4-hydroxyphenyl)propanamido)-5-oxopentanamido)-5-(((S)-1-carboxylato-2-(1H-indol-3-yl)ethyl)amino)-5-oxopentanoate		tyr-gln-glu-trp	C30H35N6O9
Ligand 11		(S)-5-(((S)-5-((amino(iminio)methyl)amino)-1-(((S)-1-carboxylato-2-(1H-indol-3-yl)ethyl)amino)-1-oxopentan-2-yl)amino)-4-((S)-2-ammonio-3-(4-hydroxyphenyl)propanamido)-5-oxopentanoate		tyr-glu-arg-trp	C31H40N8O8

Ligand 12		((S)-5-((amino(iminio)methyl)amino)-2-((S)-2-ammonio-3-(1H-indol-3-yl)propanamido)pentanoyl)-L-tryptophanate		trp-arg-trp	C28H35N8O4

2.2. Computational Details

The enzyme and Ligands structures were minimised. Energy minimizing was done under following conditions: Temperature = 300 °K, pH = 7, geometries minimisation was performed using molecular mechanics method with the MMFF94x force field implanted in MOE software [43]and the AM1Hamiltonian. Docking was performed using the MOE [43].

3. RESULTS AND DISCUSSION

3.1 Molecular Docking

The obtained results by molecular docking are given in table 2.

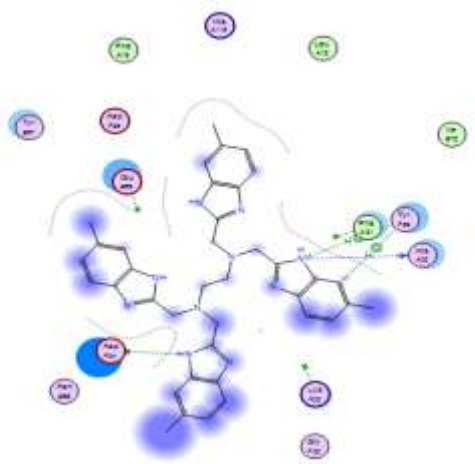
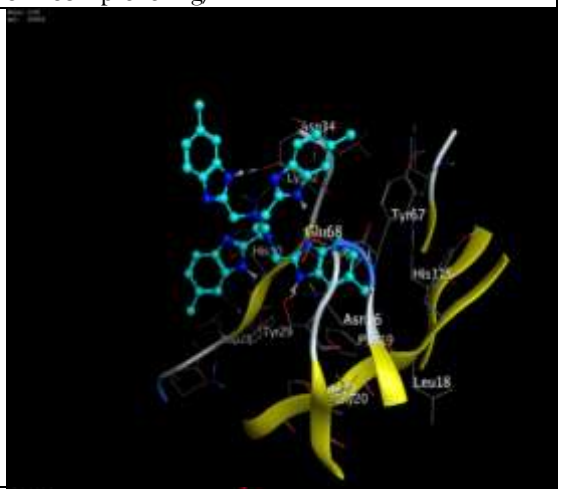
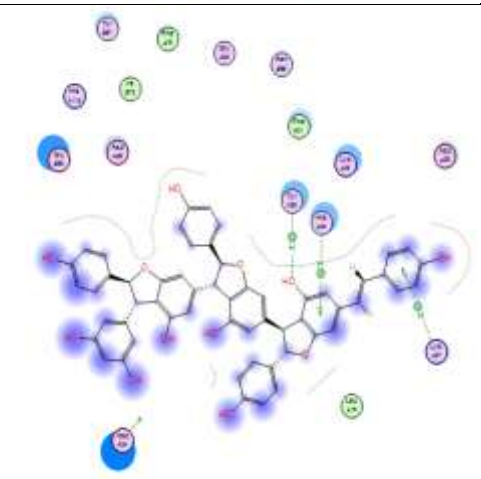
Table 2: Energy Balance of the 12 complexes (Kcal / mol).

Ligand	Score 1	Rmsd-refine	E-conf	E-Place	E-Score1	E-refine	Score 2
Ligand 1 (ref)	-6.9885	2.8911	55.4753	-79.0213	-9.4204	-23.322361	-6.98859692
Ligand 2	-6.5878	7.4494	103.1078	-58.8359	-8.0890	-13.9857	-6.5878
Ligand 3	-7.4499	2.1452	100.9941	-123.0248	-13.5863	-29.2534	-7.4499
Ligand 4	-7.2988	4.1308	63.1034	-88.7368	-11.9870	-26.4208	-7.2988
Ligand 5	-4.7391	5.0882	70.7201	-66.5502	-9.9914	-15.0789	-4.7391
Ligand 6	-6.4633	3.7428	48.2137	-79.3703	-9.5806	-22.2226	-6.4633
Ligand 7	-6.8483	2.1034	59.1823	-115.1698	-9.7835	-20.2245	-6.8483
Ligand 8	-6.2761	2.5059	30.0943	-80.1896	-10.1385	-20.5610	-6.2761
Ligand 9	-7.1809	1.8781	-14.3976	-36.3976	-10.7701	-18.6687	7.1809
Ligand 10	-7.2479	3.8560	-174.4928	-74.1110	-12.6827	-27.0987	-7.2479
Ligand 11	-7.1349	2.7174	-383.9608	-65.6051	-12.5306	-27.3671	-7.1349
Ligand 12	-7.1729	1.8362	-291.8596	-96.1032	-12.8858	-29.6456	-7.1729

S: the final score; is the score of the last step, rmsd_refine: the mean square deviation between the laying before refinement and after refinement pose, E_conf: energy conformer, E_place: score of the placement phase, E_scor1: score the first step of notation, E_refine: score refinement step and number of conformations generated by ligand E_scor2: score the first step notation, number of poses: Number of conformations

Table 2 shows that all Ligands interact with the enzyme by presenting negative scores better than reference Ligand. Ligand 5 presents the highest score value (-4.7391 Kcal/mol) and it is than considered as the last reactive one, looking on complementarity with the active site. It turned out from the obtained results that, the Ligands affinities and complementarities with the active site are classified as follow:
Ligand3 (-7,4499 Kcal/mol) > Ligand12 (-7.3416Kcal/mol) > Ligand4 (-7,2988 Kcal/mol) > Ligand10 (-7.2479Kcal/mol) > Ligand9 (-7.1809Kcal/mol) > Ligand11 (-7.1349Kcal/mol) > Ligand1(ref) (-6.9885Kcal/mol) > Ligand7 (-6.8483Kcal/mol) > Ligand2 (-6.5878 Kcal/mol) > Ligand6 (-6.4633Kcal/mol) > Ligand8 (-6.2761Kcal/mol) > Ligand5 (-4.7391Kcal/mol).
Our results show that, Ligand 3 and Ligand 4 (Pub Chem downloaded) and the designed Ligands(9-12), formed more stable complexes comparing with the reference Ligand, on the other hand the designed Ligand 12 present best affinity via the enzymatic active site, which leads to the conclusion that it can constitute a good candidate for a new NPM1 inhibitor. Although compounds L3 and L12 have strong binding affinities with NPM1 protein in the docking simulation.
In order to optimize factors influencing complex stabilities and the complementarity of combination between our considered Ligands and the active site we discussed in table 3 and 4 the 2D and 3D interaction diagrams and bond distances between Ligands which gave best docking score and amino acids of protein active site.

Table 3: Diagrams of interactions 2D and 3D (enzyme-ligands)

	2D complexe Lig/NPM1	3D complexe Lig/NPM1
Lig 1		
Lig 3		

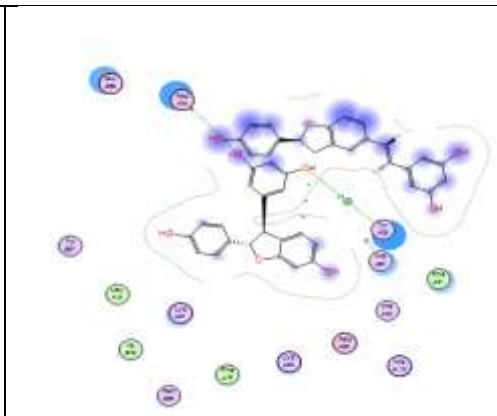
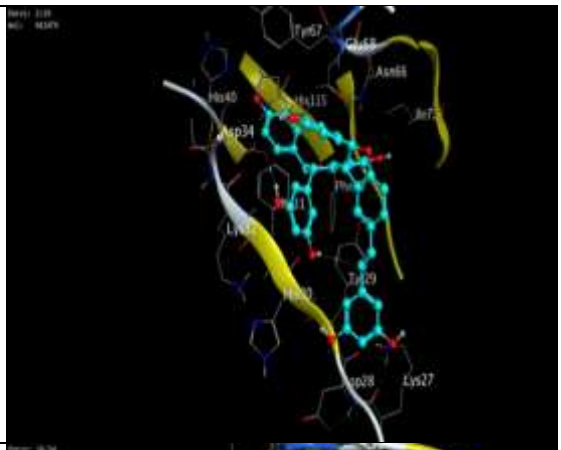
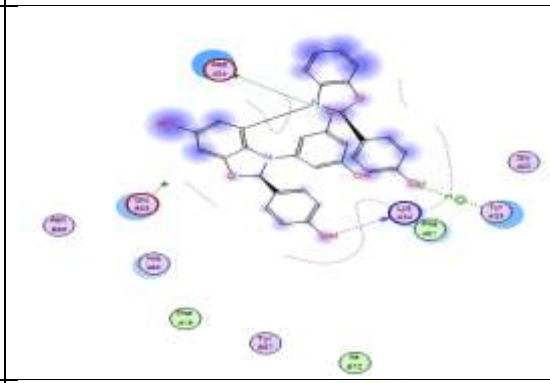
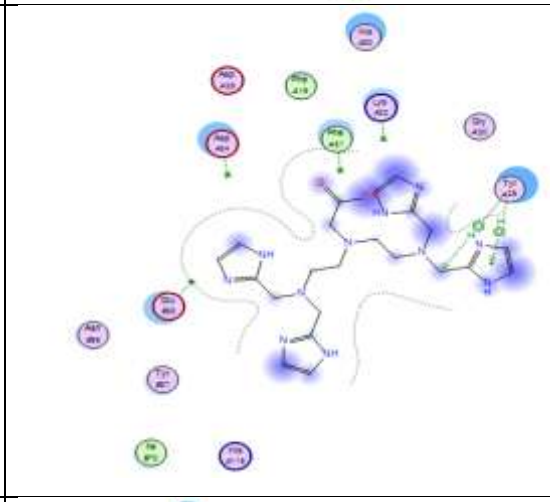
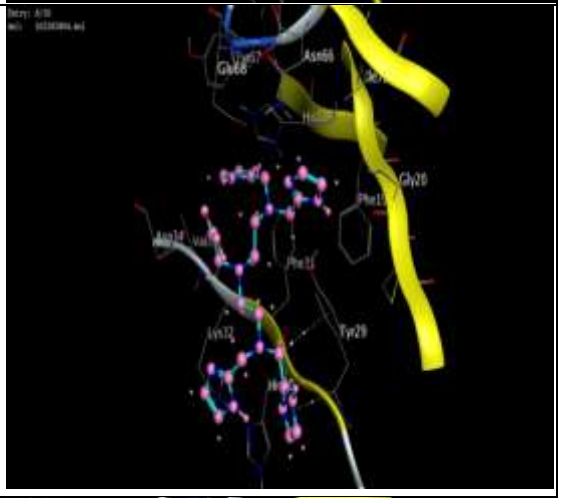
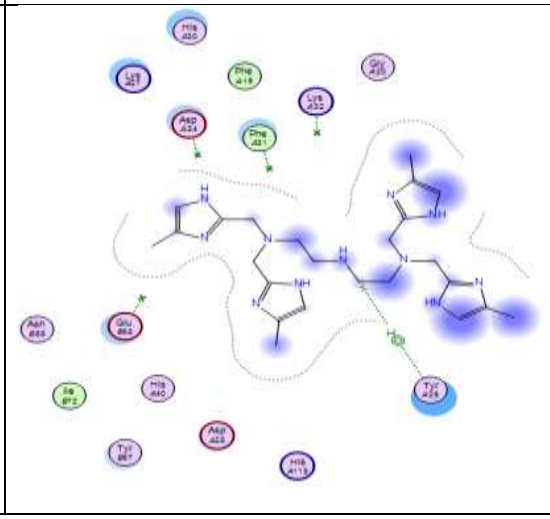
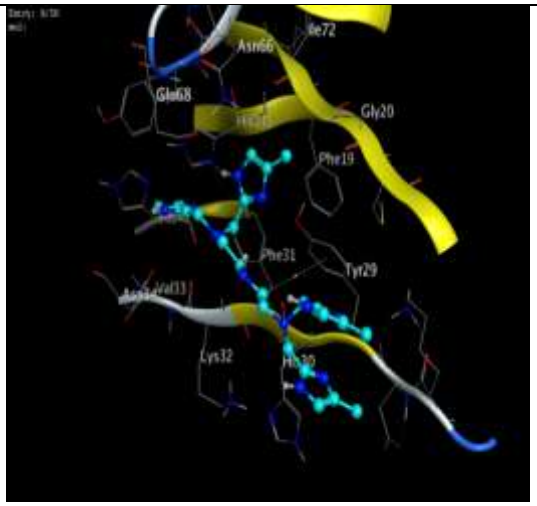
Lig 4		
Lig 5		
Lig 6		
Lig8		

Table 4: Results Bonds between atoms of compounds and residues of active site

	Atom of compound	Involved Receptor atoms	Involved Receptor residues	Type of Interaction bond	Distance (Å)	Energies (kcal/mol)
L1	N4	O	HIS 30	H-donor	2.99 3.16	-1.02
	N5	OD2	ASP 34 TYR	H-donor	4.45	-6.04
	N5	6-ring	29 TYR 29	H-Pi	4.12	-0.7
	C30	6-ring	PHE357	H-Pi		-0.6
L3	O6	6-ring	TYR 29	H-Pi	3.51	-0.8
	6-ring	CA	LYS 27	Pi-H	4.15	-0.9
	6-ring	CB	HIS 30	Pi-H	4.30	-0.6
L4	O 4	OD2	ASP 34	H-donor	3.02	-1.6
	O 5	6-ring	TYR 29	H-Pi	4.53	-0.8
L5	O 5	OD2	ASP 34	H-donor	2.89	-0.9
	O 6	O	LYS 32	H-donor	3.07	-1.4
	O 7	6-ring	TYR 29	H-Pi	3.66	-1.50
L6	C	6-ring	TYR 29	H-Pi	3.92	-0.7
	5-ring	CA	TYR 29	Pi-H	4.19	-0.6
L8	C12	6-ring	TYR29	H-Pi	4.58	-0.6
L12	N 1	OD1	ASP 34	H-donor	2.72	-12.7
	N 27	CA	PHE 31	H-accptor	3.37	-0.7
	O 50	CA	PHE 31	H-accptor	2.88	-13.7
	O 50	N	LYS 32	H-accptor	2.97	-3.3
	O 75	NZ	LYS 32	H-accptor	2.88	-13.7
	N 1	OD1	ASP 34	Ionic	7.72	-6.6
	O 75	NZ	LYS 32	Ionic	2.88	-5.3
	6-ring	N	HIS 30	Pi-H	4.45	-0.7

Obtained results show that:
The Tyrosine (TYR) 29 amino acid of the active site present a key and it is implicated in all complex studies, in addition, the aromatics interactions are governing and exist and this give us a conclusion that for designing better inhibitors of NPM1 we have to focalize on the aromatics rings. However, one comparing between the molecular structures of the Ligand with the best score Ligand 3 and the Ligand with the highest score so the least active Ligand 5, we perceive that Ligand 3 molecular structure is characterized with an important conjugaton, compared with Ligand 5, so one can conclude that the conjugation property is an important factor one designing new NPM1 inhibitors.

CONCLUSION

In the present paper, we examined theoretically probable inhibition of NPM1 enzyme by chosen Ligand by using molecular modeling. Obtained results showed that our designed Ligand 12 ((S)-5-((amino(iminio)methyl)amino)-2-((S)-2-ammonio-3-(1H-indol-3-yl)propanamido)pentanoyl)-L-tryptophanate) presents a more improved affinity with NPM1 enzyme. Results encourages us to support Ligand 12 as hypothetical and reliable candidates for prostate cancer treatment during the first stage and even breast cancer containing aromatic rings with conjugated structures. These interactions between NPM1 and those inhibitors are undergoing through different kinds of interactions x-ring, Pi-H, H-donnor and H-acceptors. Our results show also that in our designed series of ligands 9-11 are also good probable inhibitors of NPM1, so in the designed series the tripeptides present the best probable inhibitors and can be considered as a principal structure for developing a new drugs fating against cancer pathologies. Those predicted structures are not toxic and can be easily synthesized.

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