INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Research Article

Molecular Docking Simulations Through Gold Software for Nortopsentin-1,3,4-Oxadiazole Analogues

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ARTICLE INFO

Published: 30 June 2025
Keywords:
Nortopsentin marine alkaloids, 1,3,4-oxadiazoles, gold software, Molecular docking studies.
DOI:
10.5281/zenodo.15775575

ABSTRACT

A new series of ten Nortopsentin-1,3,4-Oxadiazole analogues were designed, synthesized and in-silico screened for their molecular docking studies through GOLD software. The docking studies clearly presented the binding modes of the indole compounds in the active site of the colchicine binding site of the tubulin receptor. Among all selected compounds the 8a has higher binding affinity, before and after docking pose software.

INTRODUCTION

Nortopsentins A–C and its analogue D, which has a 2,4-bis (3'-indolyl) imidazole skeleton, shown antifungal activity against Candida albicans, antibacterial activity against Bacillus subtillis, and invitro cytotoxicity against P338 cells (IC_{50},4.5 - 20.7 µM). In addition, it was discovered that N-methyl derivatives of nortopsentins significantly increased P338 activity in comparison to the parent drugs' activity (IC_{50}, 0.8 - 2.1 µM) [1-3]. The various analogues of Nortopsentin marine alkaloids, in which imidazole moiety was replaced by furan-isoxazole [4], thiazole [5], pyrrole [6], thiophene [7], triazinones [8], pyrazole [9], and pyridine [10] were already reported by the researchers across the world and these analogues were showed potent inhibitory activity against tumor cell lines (GI_{50} < 0.01 to 89.4 µM). In continuation of the research work, our colleagues synthesized Nortopsentin-1,3,4-Oxadiazole analogues and evaluated for their anticancer activities against MCF-7, MDA-MB-231, A549, and HeLa cell lines by using MTT reduction assay. Now, our group extended this research work towards molecular docking simulations of

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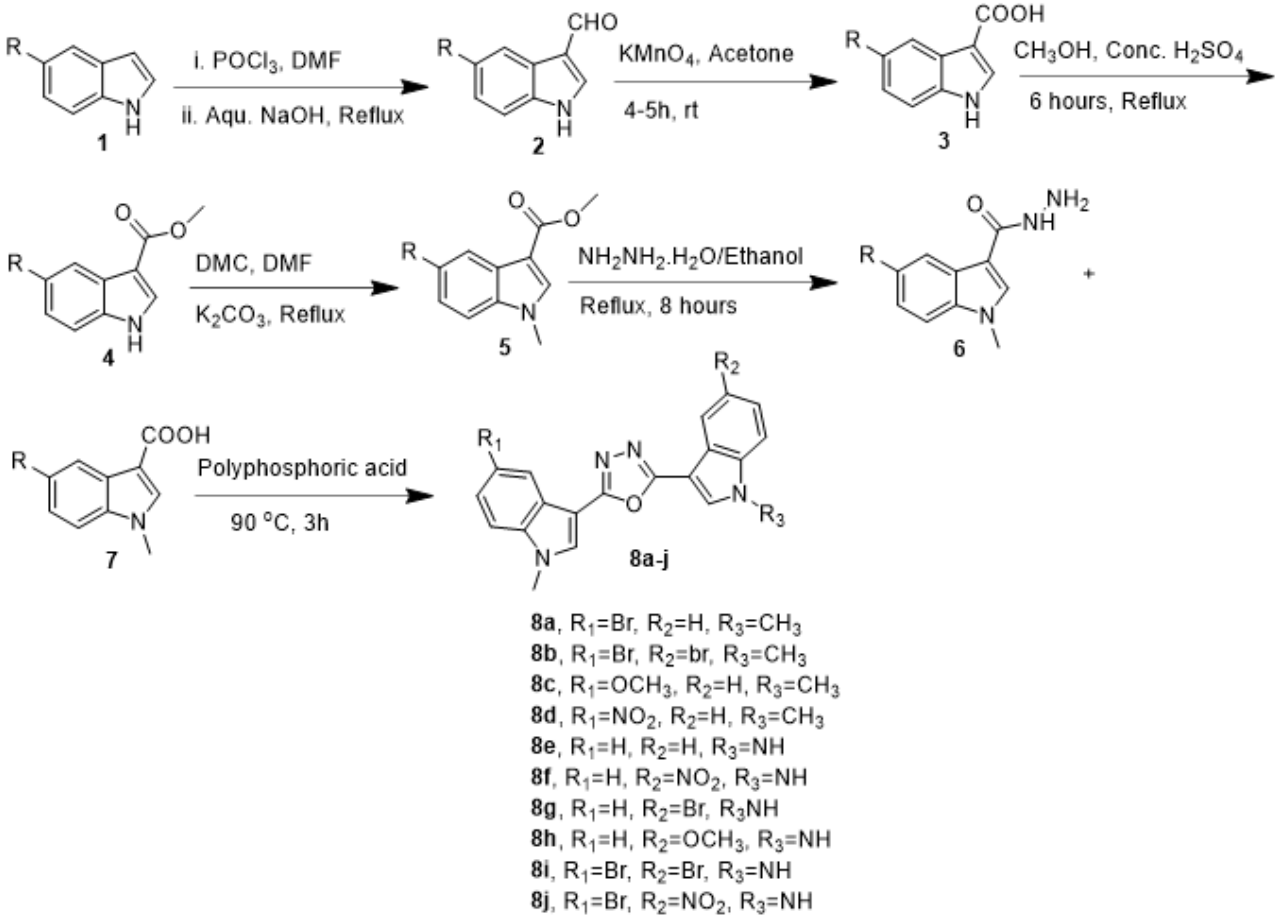
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

bis(indolyl)-1,3,4-oxadiazole derivatives through gold software.

RESULTS AND DISCUSSION:

The Vilsmeir - Haack reaction transformed indoles 1 into indole-3-carboxaldehydes 2. Corresponding carboxylic acid 3 compounds were produced by oxidizing aldehyde 2 derivatives with potassium permanganate and acetone. Simple esterification was performed on the derivatives using concentrated H_2SO_4 as a dehydrator and gave ester compound 4. Additionally, dimethyl carbonate and K_2CO_3 were used to methylate the ring nitrogen, which was then refluxed in DMF for four hours and afford N-methyl ester compound 5. Ultimately, the carbohydrazide derivatives 6 were produced by refluxing the N-protected ester with ethanolic hydrazine hydrate. Bis(indolyl)oxadiazole 8 compounds were produced by further reacting these carbohydrazide derivatives **6** with various indole-3-carboxylic acids **7** at 90 °C for three to four hours while a solid phase catalyst, polyphosphoric acid, was present.



Scheme 1: Synthesis of Nortopsentin-1,3,4-Oxadiazole analogues 8a-j

Result and discussion: Molecular docking studies

The total 10 designed and sketched this ligands (**8a-j**) was taken further to prepared the ligand in DSv2.5. The total 68 conformation been generated and average conformations per ligand is 6.80 (Figure 1A and 1B). The min, max, and average pair-wise RMSDs are: 0, 2.04, and 0.51 Å respectively. The molecular docking studies of

indole agents against tubulin receptor have been reported several times. The current docking studies clearly presented the binding modes of the indole compounds in the active site of the colchicine binding site of the tubulin receptor. Among all selected compounds the 8a has higher binding affinity, before and after docking pose has been shown in Figure 1C and 1D. The higher ligDock score (133.316) and GOLD fitness score (52.17) of compound 8a and involve in interacting amino acids are Gln247, Ala354, Cys241, Thr240, Thr239, Gly237, Val238, Val318, Thr376, Ile378, Ala317, Ala316, Thr353, Leu248 and Lys352 . The best strucure of 8a has shown in Figure 2A and eye catching the interacting aminoacids has shown in Figure 2B from Ligplus program [11]. The present compounds consist of the both indole and oxadiazole rings; it was observed that the binding mode of the ligands in the active site bind with mostly Thr353 and Ala354 amino acids to oxygen and nitrogen atoms of oxadiazole rings. The –NH atom of indazole ring was responsible for the Thr353 (8a, 8b, 8c, 8d, 8e, 8g and 8h) and with Lys352 when it is bounded (8i) and Ala317 with 8j (Figure 3 and Table 1). The compound 8i has also exhibited higher binding (GOLD score 50.12) and involved in direct interacting amino acids are Lys 352, Ala354, Cys241, Thr376 residues whereas binding pocket amino acids are Thr376, Thr239, Phe377, Ile378, Gly237, Ala316, Ala317, Lys352, Thr353, Leu248, Gly247, Ala354, Cys241, Val318, Thr240 and Val238 shown in Table 1.

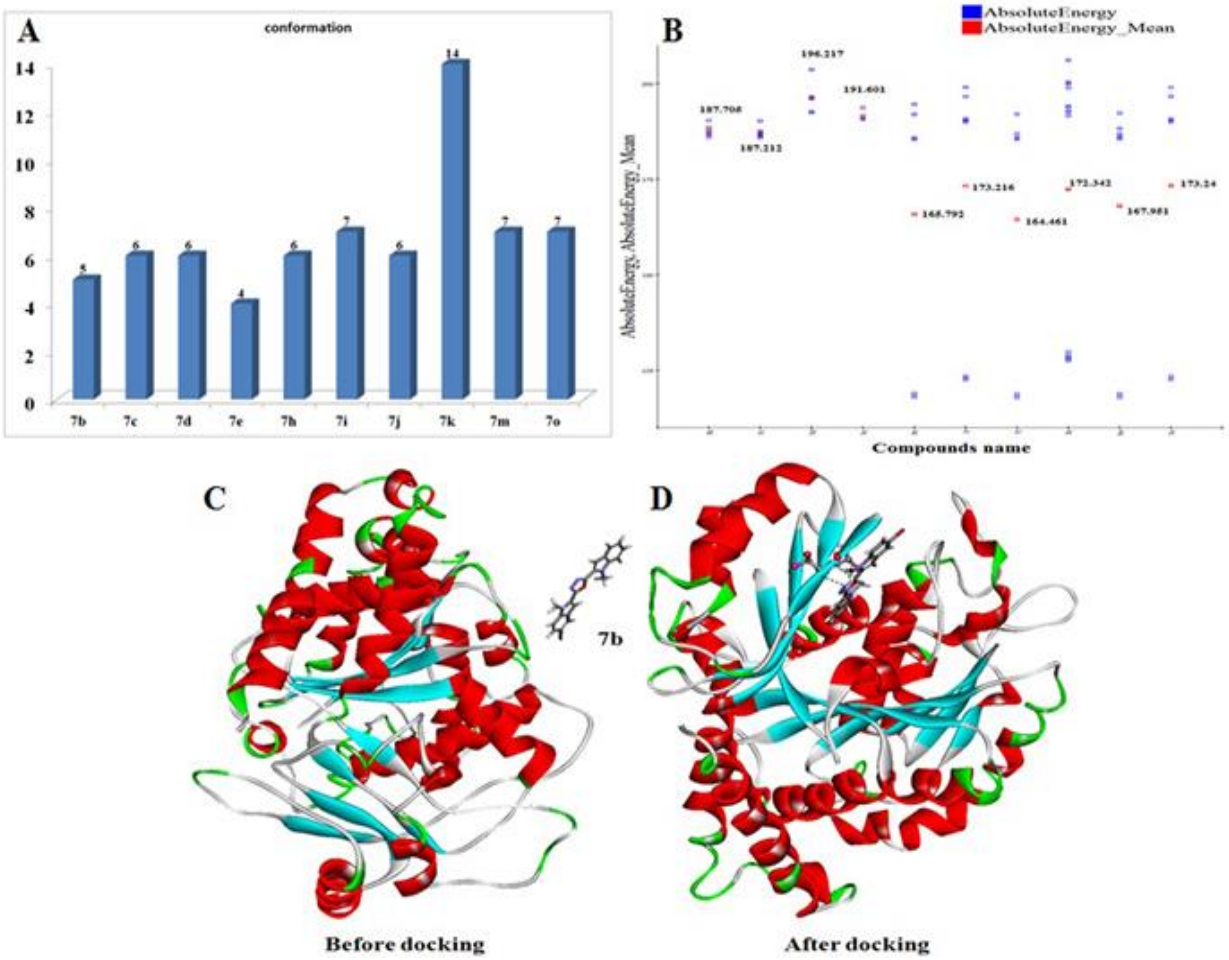


Figure 1: The designed ligands (8a-j) have been prepared in DSv2.5 and interaction with higher binding affinities in DSv2.5 and GOLD program. A: represents the number of conformer generated by each ligand. B: the mean absolute energy of each ligand with different absolute energy of each ligand. C: it is being before interaction pose with ligand (8a). D: It is pose of ligand after docked with binding pocket and it interact with amino acids the interaction studies of higher binding affinity of ligand (8j) with known binding sites of Thr353 and Ala354 residues of PDB ID 1SA0 of chain A.

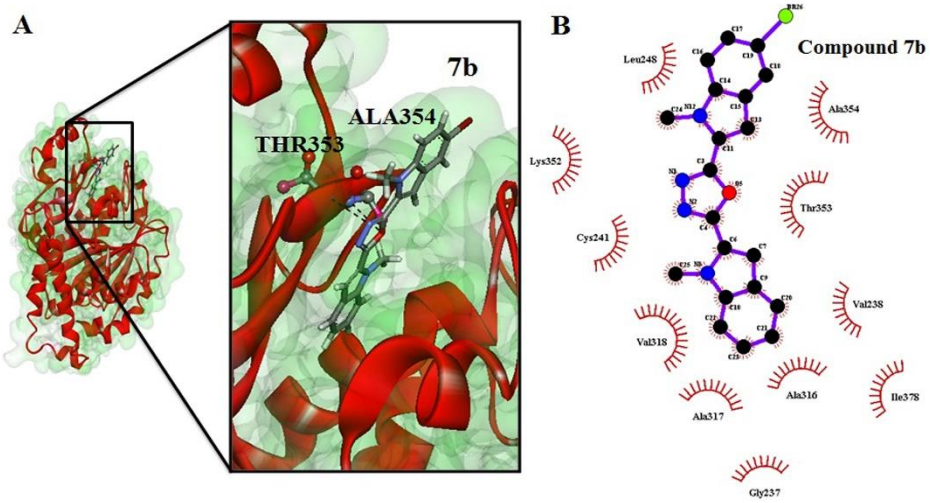
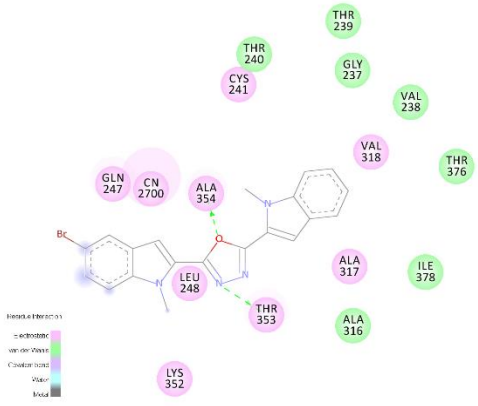
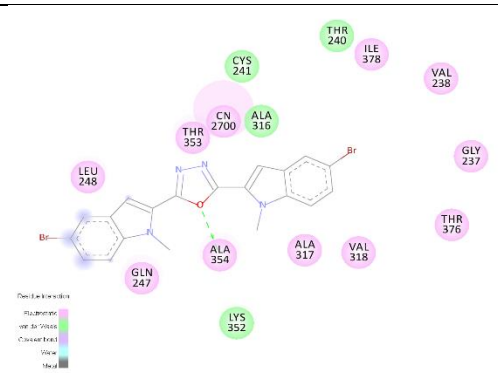
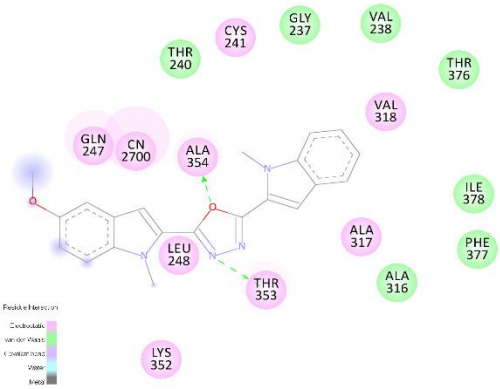
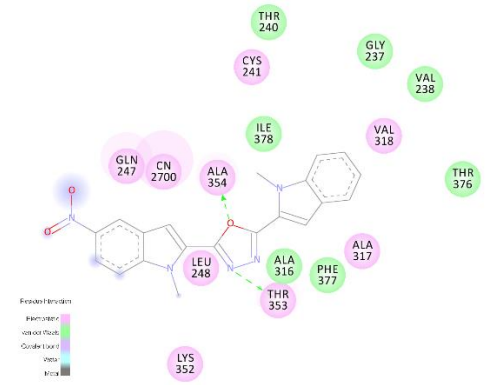
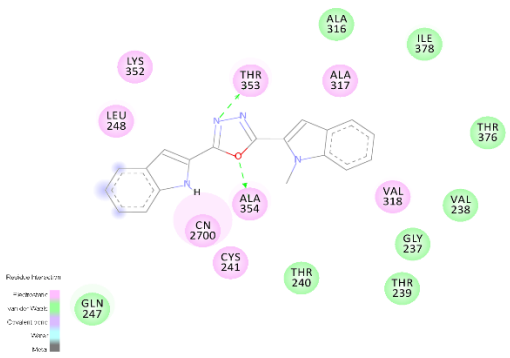
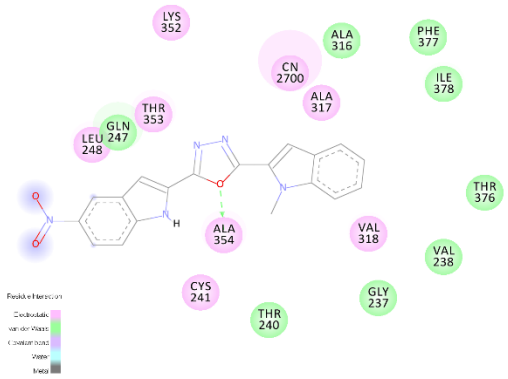
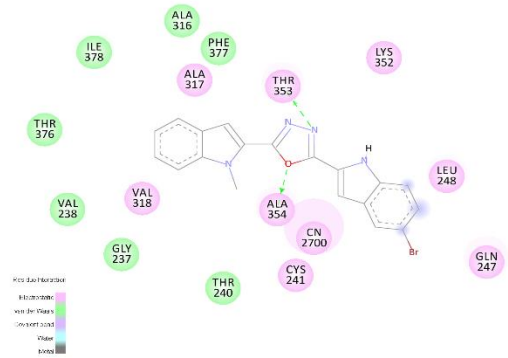
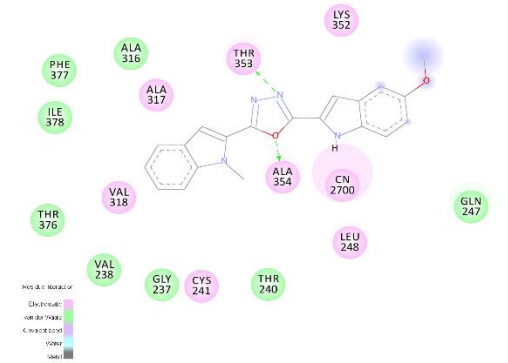
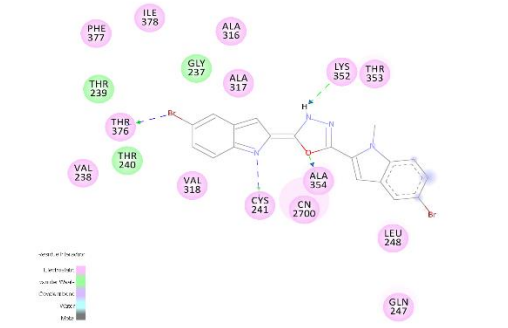


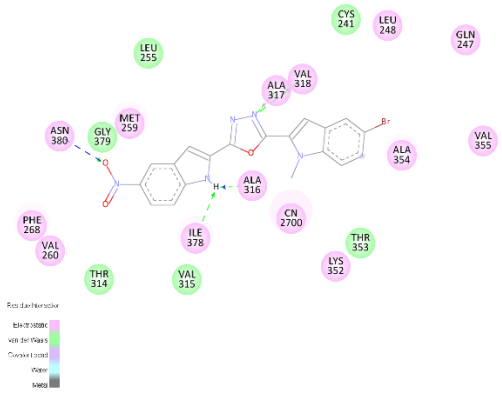
Figure 2: A. The compound (**8a**) has higher score and interacting amino acids are Thr353 and Ala354 residues. B Ligplus result of **8a** compound with interacting amino acids.

Table 1: The compounds (7 series) docked with protein and pose 2D interaction.

S. No.	Code No.	Lig Dock score	GOLD	Best pose interaction	Interacting amino acids
1.	**8a**	133.316	52.17		Gln247, Ala354, Cys241, Thr240, Thr239, Gly237, Val238, Val318, Thr376, Ile378, Ala317, Ala316, Thr353, Leu248, Lys352
2.	**8b**	124.126	49.50		Leu248, Thr353, Ala316, Cys241, Thr240, Ile378, Val238, Gly237, Thr376, Val318, Ala317, Lys352, Ala354, Gln247

					
3.	**8c**	Not dock	50.95		Gln247, Ala354, Thr240, Cys241, Gly237, Val238, Val318, Thr376, Ile378, Phe377, Ala316, Ala317, Thr353, Leu248, Lys352
4.	**8d**	122.467	51.32		Gln247, Ala354, Ile378, Cys241, Thr240, Gly237, Val238, Val318, Thr376, Ala317, Phe377, Ala316, Thr353, Leu248, Lys352
5.	**8e**	Not dock	50.07		Leu248, Lys352, Thr353, Ala317, Ala316, Ile378, Thr376, Val238, Val318, Gly237, Thr239, Thr240, Cys241, Ala354, Gln247

6.	**8f**	112.421	49.01		Leu248, Gln247, Thr353, Lys352, Ala317, Ala316, Phe377, Ile378, Thr376, Val238, Val318, Gly237, Thr240, Ala354, Cys241
7.	**8g**	120.363	50.23		Ile378, Ala316, Phe377, Ala317, Thr353, Lys352, Leu248, Gln247, Cys241, Ala354, Thr240, Val318, Gly237, Val238, Thr376
8.	**8h**	116.165	49.76		Ile378, Phe377, Ala316, Ala317, Thr353, Lys352, Gln247, Leu248, Ala354, Thr240, Cys241, Gly237, Val238, Val318, Thr376
9.	**8i**	Not Dock	50.12		Thr376, Thr239, Phe377, Ile378, Gly237, Ala316, Ala317, Lys352, Thr353, Leu248, Gly247, Ala354, Cys241, Val318, Thr240, Val238

10.	**8j**	107.671	48.61		Asn380, Gly379, Met259, Leu255, Ala317, Val318, Cys241, Leu248, Gln247, Val355, Ala354, Thr353, Lys352, Ala316, Ile378, Val315, Thr314, Val260, Phe268

Material And Methods: Molecular Docking Studies

The molecular docking studies were performed using the Discovery Studio (DSv2.5) and GOLD installed in Window7. The X ray crystallographic structure of tubulin with colchicines as reference ligand (PDB: 1SA0) at resolution 3.58 Å with r value 0.233 (obs.) was downloaded from the protein data bank (PDB) [12]. The protein was prepared by protein preparation (DSv2.5) wizard and the protocol followed in HGPRT inhibitors design and validation [13, 14]. The protein consists of the heterodimeric and homodimeric chains and among them, the chain B with colchicine was employed in the current docking studies. The chain B consists of two different ligands, first one is colchicine and next one is guanosine-5'-diphosphate (GDP) along with metal (Mg+) binding site. However, the binding site selection using define site was generated around the colchicine binding site. All the ligands (7 series) were sketched in chemdraw, saved in .mol files, imported in maestro panel and prepared by prepared ligand module in DSv2.5. The high throughput screening with Dock ligands (libDock) module in DSv2.5 and GOLD program were employed for current docking studies. All docking results (LibDock and GOLD fitness score) were analyzed and figures generated in DSv2.5.

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HOW TO CITE: Eeduri Ramya Devi, Gaadupudi Purna Chandra Rao*, Molecular Docking Simulations Through Gold Software for Nortopsentin-1,3,4-Oxadiazole Analogues, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 6, 5953-5960. https://doi.org/10.5281/zenodo.15775575