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Molecular Docking Studies of Bis (Indolyl) Oxadiazole Derivatives

M. Subba Rao*[1], Y. Pavani[1], Ch. Chandrasekhar[2] and K. Gopinath[1]

1. Department of Chemistry, Acharya Nagarjuna University, Nagarjuna Nagar – 522 510, Andhra Pradesh, **INDIA**
2. Department of Chemistry, University College of Engineering (Autonomous), Jawaharlal Nehru Technological University, Kakinada – 533 003, Andhra Pradesh, **INDIA**

Email: mannamsrao@gmail.com

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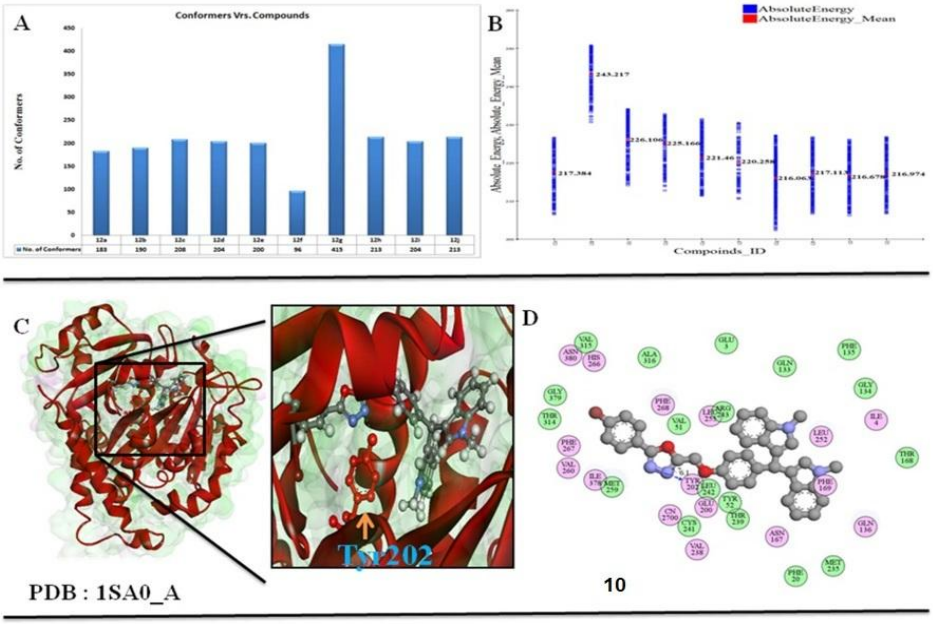
ABSTRACT

*The molecular docking studies of ten bis(indolyl) oxadiazoles **1-10** with tubilin receptor as putative target were studied. In these docking studies, We explained the the binding modes of the indole compounds in the active site of the colchicine binding site of the tubulin receptor using the Discovery Studio (DSv2.5) and GOLD installed in Window7.*

GRAPHICAL ABSTRACT



Keywords: Bis(indolyl) oxadiazoles, Tubilin receptor, Discovery Studio (DSv2.5), GOLD installed Window7.

INTRODUCTION

Cancer is the second leading cause of mortality in developed countries. The international research agency on cancer research projects declared that the fatality rates due to cancer are higher in less developed countries and an estimated 14 million people developed cancer in 2012 with nearly 8 % increased deaths. These cancer cases may enhance globally up to 19.3 million by 2025 [1]. Currently, chemotherapy is the most important treatment for cancer and the ultimate goal is to destroy the cancer cells without any harmful effect on the normal cells and has achieved significant success through the discovery of various new drugs. Despite of this progress, the discovery of most potent anticancer agents is a challenging issue in cancer chemotherapy for the future generations.

Many heterocyclic fused systems exhibit potent antitumor activities against a panel of various human tumor cancer cell lines [2-9]. M.J. Ahsan et.al., designed and synthesized a series of new bis (indolyl) oxadiazole derivatives and screened their anticancer activities against MCF-7 (breast), KB (oral), Colo-205 (Colo) and A-549 (lung) cancer cell lines [4] and showed significant anticancer activities compared to Etoposide. Here the compounds exhibited cytotoxicity with GI_{50} values ranges from <0.1 to 3.9 µM, while the positive control etoposide showed cytotoxicity with GI_{50} in the range of 0.13 – 3.08 µM respectively.

Survey of literature reveals that, the biological activities of compounds explained by using molecular docking studies with particular proteins [10-13]. Now, we explained the molecular docking studies of ten bis(indolyl) oxadiazoles **1-10** with tubulin receptor as putative target which are not reported on these molecules to the best of my knowledge.

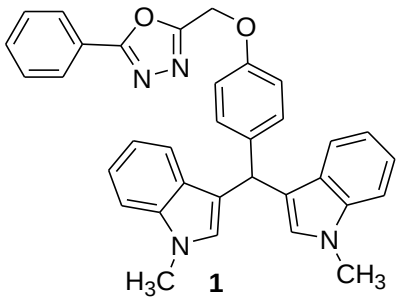
MATERIALS AND METHODS

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) [14]. The protein was prepared by protein preparation (DSv2.5) wizard and the protocol followed in HGPRT inhibitors design and validation [15,16]. 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 [17, 18] 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.

RESULTS AND DISCUSSION

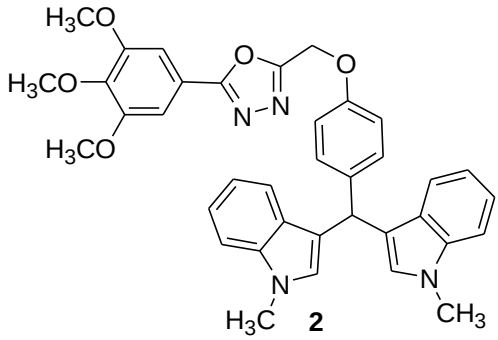
The following ten 1,3,4- oxadiazole linked bisindole (**1-10**) derivatives were taken for docking studies. They were-

1. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-phenyl-1,3,4-oxadiazole (1, $C_{34}H_{28}N_4O_2$):**



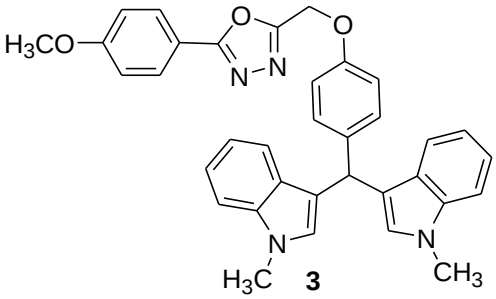
1

2. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (2, $C_{37}H_{34}N_4O_5$):**



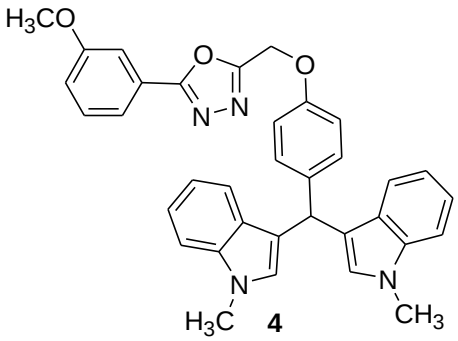
2

3. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(4-methoxyphenyl)-1,3,4-oxadiazole (3, $C_{35}H_{30}N_4O_3$):**



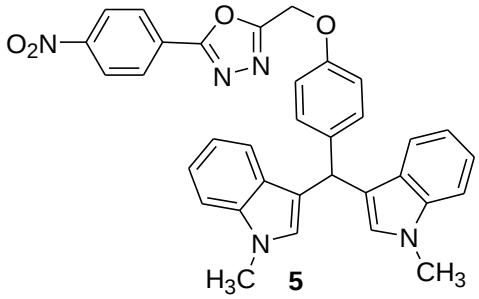
3

4. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(3-methoxyphenyl)-1,3,4-oxadiazole (4, $C_{35}H_{30}N_4O_3$):**



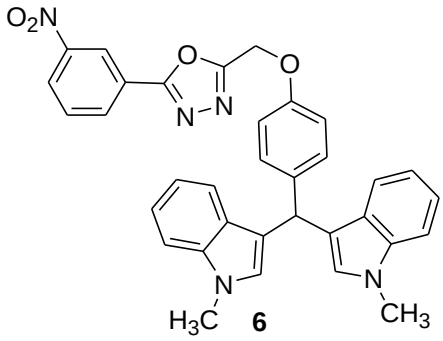
4

5. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(4-nitrophenyl)-1,3,4-oxadiazole (5, $C_{34}H_{27}N_5O_4$):**



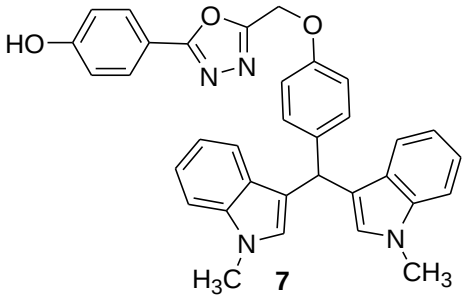
5

6. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(3-nitrophenyl)-1,3,4-oxadiazole (6, $C_{34}H_{27}N_5O_4$):**



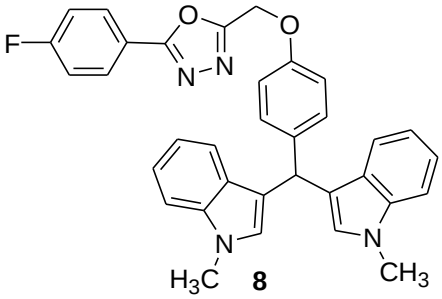
6

7. **4-[5-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-1,3,4-oxadiazol-2-yl]phenol (7, $C_{34}H_{28}N_4O_3$):**



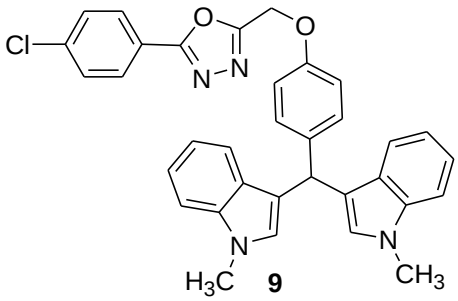
7

8. **2-(4-[Di(1-methyl-1*H*-3-indolyl)methyl]phenoxymethyl)-5-(4-fluorophenyl)-1,3,4-oxadiazole (8, $C_{34}H_{27}FN_4O_2$):**



8

9. **[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]methyl4-[di(1-methyl-1*H*-3-indolyl) methyl]phenyl ether (9, $C_{34}H_{27}ClN_4O_2$):**



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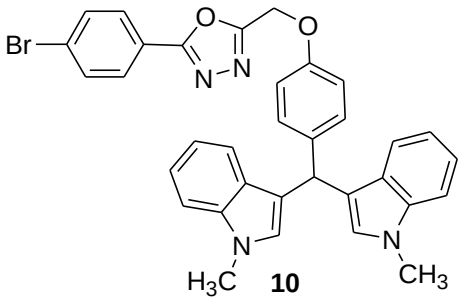
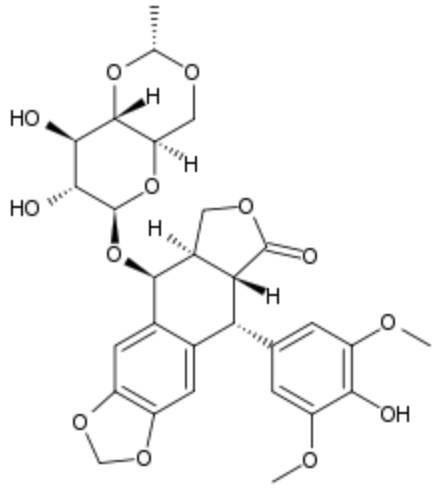
10. **[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]methyl4-[di(1-methyl-1*H*-3-indolyl)methyl]phenyl ether (10, $C_{34}H_{27}BrN_4O_2$)**



10

11. **Etoposide:**



Etoposide

Molecular docking studies: The total 11 designs (including Etoposide) and sketch the ligands (**1-10**) was taken further to prepared the ligand in DSv2.5 including Etoposide as taken positive control. The total 2126 conformation been generated and average conformations per ligand is 193.27 (**Figure 1A and B**). The min, max, and average pair-wise RMSDs are: 0, 5.61, and 0.15 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. The docking scores of the Bis(indolyl) oxadiazole ligands were shown in **table 1**. The reference ligand colchicine was exhibited the interactions, but the complete

ligand was surrounded by the hydrophobic active site residues include Val238, Al354, Val318, Lys352, Ala317, Ala316, Cys241, Leu255, Ala250, Leu252, Leu242 and Val51. 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 were sometimes opposite. The –NH atom of indole ring was responsible for the Tyr202 (**5**, **7** and **10**) and with Ala317 when it is bounded (**3**) opposite to previous one. In case of compound **10**, the presence of the bromophenyl on the oxadiazole ring exhibited higher binding score, LigDock (89.5998) and GOLD score (69.95) with interacting amino acids are Asn380, Val315,His266, Ala316, Glu3, Phe268, Val51, Leu255, Arg243, Gln133, Phe135, Gly134, Leu252, Ile4, Thr168, Phe169, Gln136, Met235, Phe20, Asn167, Thr239, Tyr52, Leu242, Glu200, Tyr202, Val238, Cys241, Met259, Ile378, Val260, Rhe267, Thr314 and Gly379 (**Figure 1C and D**) and **Table 2**. The Pi sigma interaction takes place between benzene ring and Leu248 of compound **1**. The Pi-pi interaction takes place between oxadiazole and Phe244 of compound **4**. The other interactions also take place between nitrogen atoms of oxadiazole ring and Arg320 amino acid of protein whereas oxygen atom compound **4** interacts with Cys356. The 2D interaction and interacting amino acids of all compounds were shown in table 2.

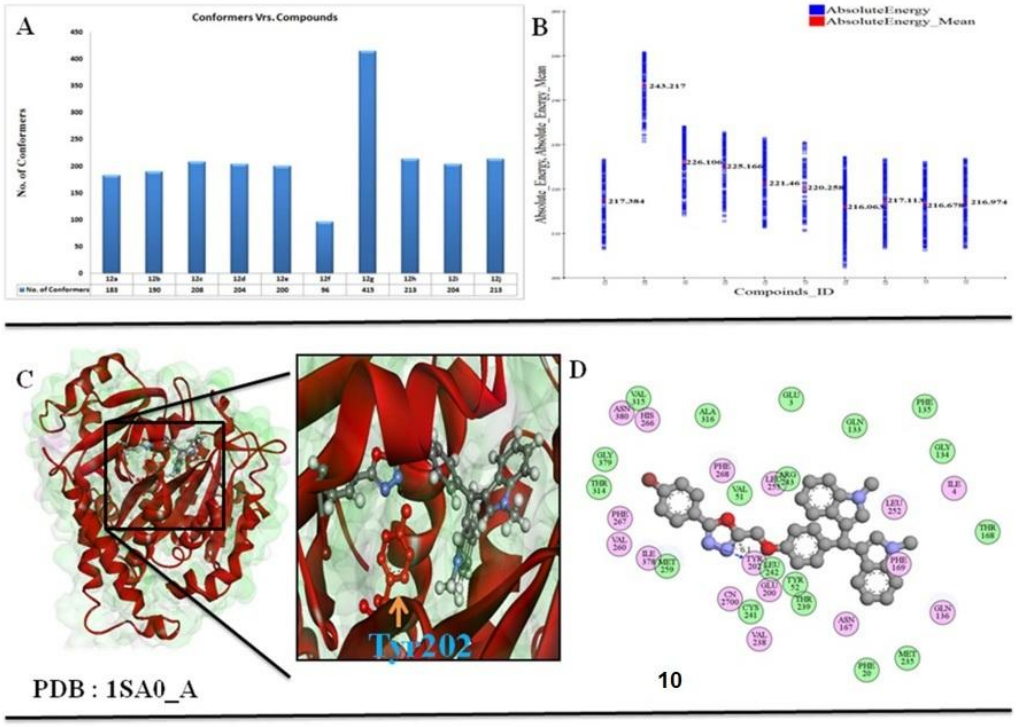


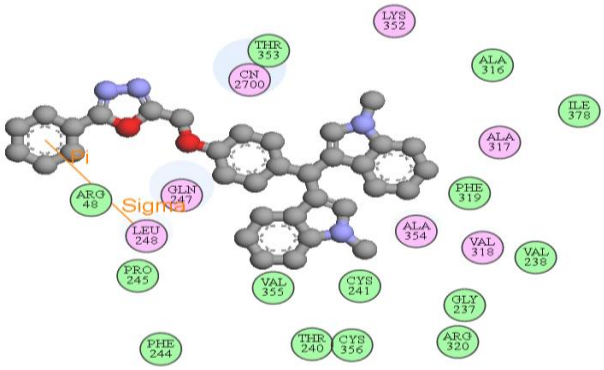
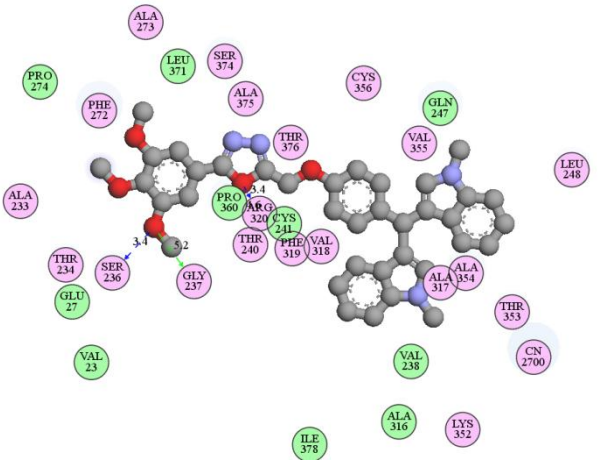
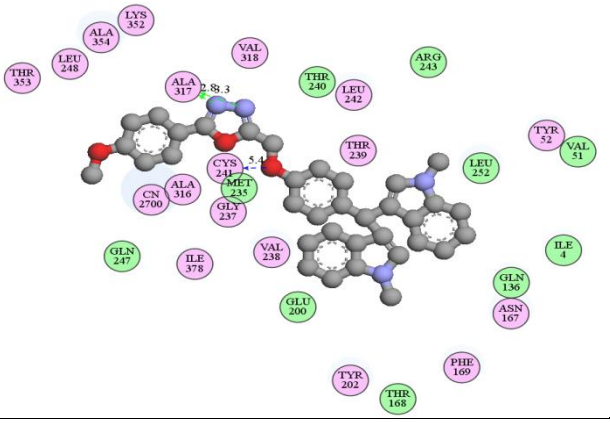
Figure 1: The designed ligands (1-10) have been prepared in DSv2.5 and interaction with higher binding affinities with respect with reference drug molecules (etoposide). A: represents the number of conformer generated by each ligand. B: the mean absolute energy of each ligands with different absolute energy of each ligand. C: the interaction studies of higher binding affinity of ligand (10) with known binding sites of PDB ID 1SA0 of chain A. D: The 2D structure of binding site of 10 of amino acids involved in interaction (Tyr202).

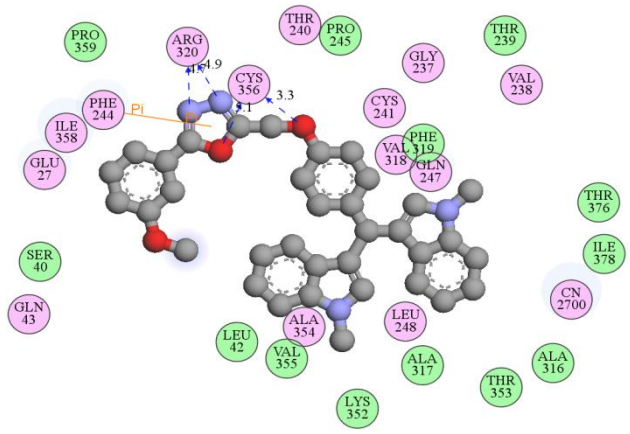
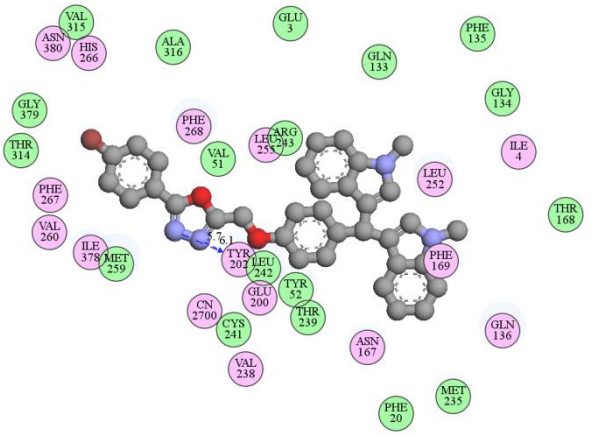
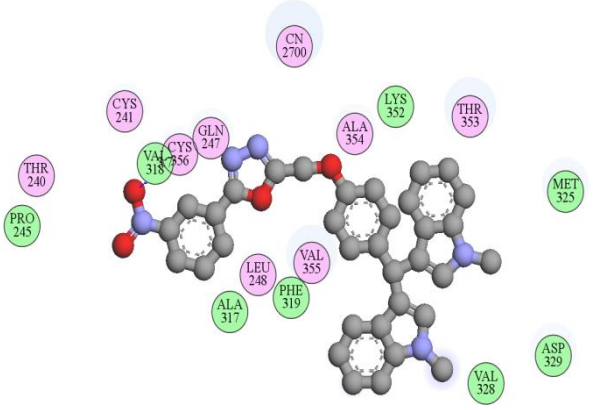
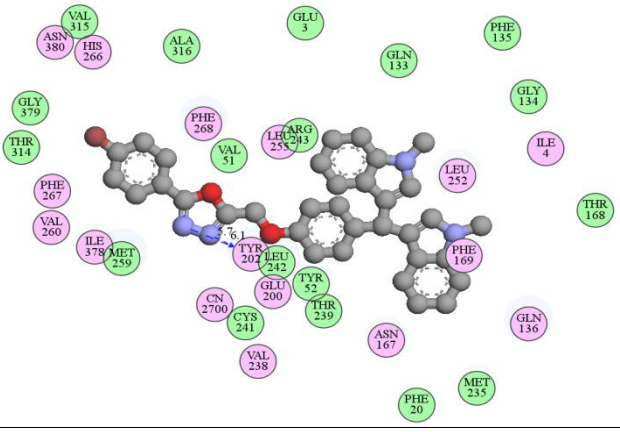
Table 1: The compounds (1-10) having invitro reports with docking score (LigDock and GOLD)

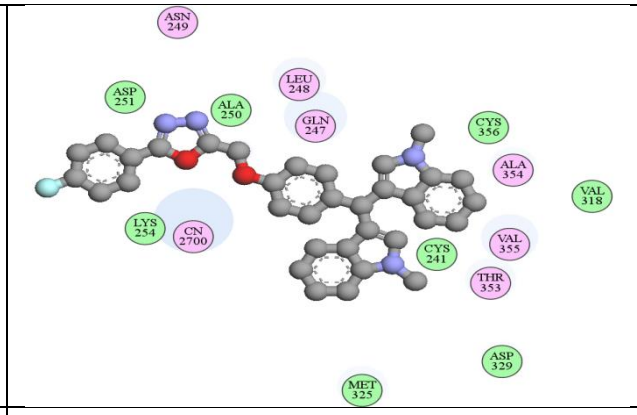
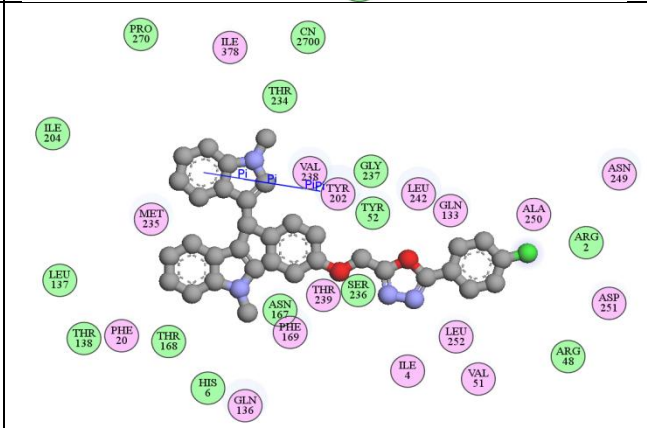
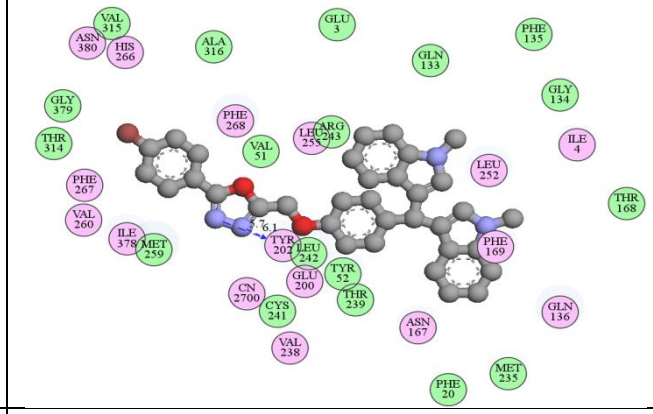
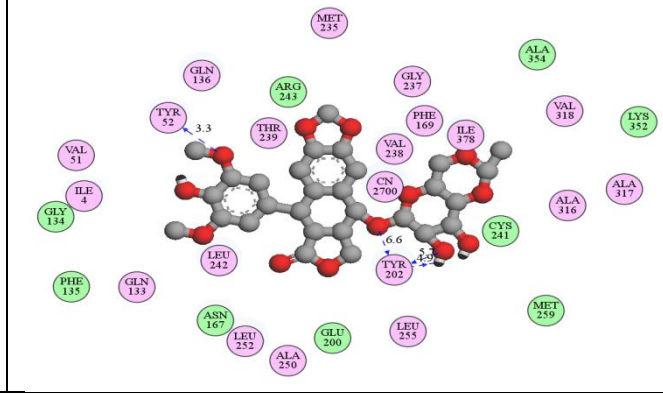
Compounds	Breast MCF-7	Oral KB	Colon Colo-205	Lung A-549	LigDock	GOLD score
1	1.9	2.7	3.8	0.1	127.681	57.05
2	<0.1	<0.1	1.3	<0.1	Not dock	63.41
3	0.12	-	0.13	<0.1	123.326	55.74
4	0.14	<0.1	<0.1	<0.1	126.055	50.77
5	-	3.9	2.9	2.1	112.477	47.41
6	4.5	2.3	-	-	Not dock	61.88

7	<0.1	0.11	-	<0.1	140.469	47.76
8	<0.1	0.18	0.15	<0.1	130.363	64.76
9	3.6	-	-	2.9	106.263	64.55
10	-	2.4	2.3	-	89.5998	69.95
Etoposide	2.11	0.31	0.13	3.08	Not dock	38.58

Table 2: The 2D interaction and interacting amino acids of all compounds (1-10)

Compounds	Complex structure of ligand with protein	Amino acids interaction
1		Thr353, Lys352, Ala316, Ala317, Ile378, Phe319, Ala354, Val318, Val238, Gly237, Arg320, Cys241, Cys356, Thr240, Val355, Phe244, Pro245, Gln247, Leu248, Arg48
2		Pro274, Phe272, Ala273, Leu371, Ser374, Ala375, Thr376, Cys356, Val355, Gln247, Leu248, Ala354, Ala317, Thr353, Val238, Val318, Phe319, Cys241, Arg320, Thr240, Pro360, Gly237, Ser236, Val23, Glu27, Thr234, Ala233
3		Thr353, Leu248, Ala354, Lys352, Ala317, Val318, Thr240, Leu242, Thr239, Arg243, Leu252, Tyr52, Val51, Ile4, Gln136, Asn167, Phe169, Thr168, Tyr202, Glu200, Val238, Ile378, Gly237, Met235, Cys241, Ala316, Gln247

4		Pro359, Arg320, Cys356, Thr240, Pro245, Cys241, Gly237, Val318, Phe319, Gln247, Thr239, Val238, Thr376, Ile378, Ala316, Thr353, Ala317, Leu248, lys352, Ala354, Val355, Leu42, Gln43, Se40, Gln27, Ile358, Phe244
5		Asn380, Val315, His266, Ala316, Phe268, Val51, Leu255, Arg243, Gln3, Gln133, Phe135, Gly134, Ile4, Leu252, Phe169, Gln136, Met235, Phe20, Asn167, Thr239, Tyr52, Gln200, Leu242, Tyr202, Val238, Cys241, Met259, Ile378, Val260, Phe267, Thr314, Gly379
6		Pro245, Thr240, Val318, Cys241, Cys356, Gln247, Ala254, Lys352, Thr353, Met325, Asp329, Val328, Val355, Phe319, Leu248, Ala317
7		Asn380, Val325, His266, Ala316, Phe268, Val51, Leu255, Arg243, Gln3, Gln133, Phe135, Gly134, Ile4, Leu252, Thr168, Phe169, Gln136, Met235, Phe20, Asn167, Thr239, Tyr52, Glu200, Leu242, Tyr202, Val238, Cys241, Met259, Ile378, Val260, Phe267, Thr314, Gly379

8		Asp251, Asn249, Ala250, Leu248, Gln247, Cyc356, Ala354, Val318, Val355, Thr353, Cys241, Asp329, Met325, Lys254
9		Pro270, Phe378, Thr234, Val238, Tyr202, Gly237, Tyr52, Leu242, Gln133, Ala250, Asn249, Arg2, Asp251, Arg48, Val51, Leu252, Ile4, Ser236, Thr239, Asn167, Phe169, Gln136, His6, Thr168, Phe20, Thr138, Leu137, Met235, Ile204
10		Asn380, Val315, His266, Ala316, Glu3, Phe268, Val51, Leu255, Arg243, Gln133, Phe135, Gly134, Leu252, Ile4, Thr168, Phe169, Gln136, Met235, Phe20, Asn167, Thr239, Tyr52, Leu242, Glu200, Tyr202, Val238, Cys241, Met259, Ile378, Val260, Rhe267, Thr314, Gly379
Etoposide		Tyr52, Gln136, Thr239, Arg243, Met235, Gly237, Val238, Phe169, Ile378, Al354, Val318, Lys352, Ala317, Ala316, Cys241, Met259, Tyr202, Leu255, Glu200, Ala250, Leu252, Asn167, Leu242, Gln133, Phe135, Gly134, Ile4, Val51

APPLICATIONS

The overall study of the ten bis(indolyl) oxadiazoles with tubilin receptor as putative target support the antitumor activity of these compounds against the four tumor cell lines.

CONCLUSIONS

The molecular docking studies of ten bis(indolyl) oxadiazoles **1-10** with tubilin receptor as putative target are reported and are performed using the Discovery Studio (DSv2.5) and GOLD installed in Window7.

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AUTHOR ADDRESS

1. **M. Subba Rao**
Department of Chemistry, Acharya Nagarjuna University,
Nagarjuna Nagar–522 510, Andhra Pradesh, India
Email: mannamsrao@gmail.com