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Better Docking Efficacy of Methylsulfonylbenzene Based Beta-lapachone Analogs over Other Functional Groups with NQO1 Protein and Their Therapeutic Implications in Breast Cancer

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ABSTRACT: Beta-lapachone (β -lap) has potent antitumour efficacy which reduce solid cancers that over-expressed NAD(P)H:quinone oxidoreductase-1 (NQO1). To investigate β -lap's efficacy MCF-7 and MDA-MB-231 breast cancer cell lines were used in many reports indicating over-expression of NQO1. The results infer that β -lap significantly inhibited NQO1 protein expression. Crystallographic structure of holo-human NQO1 belong to space group P2₁ and diffract to 2.0 Å resolution. The asymmetric unit contains two homodimers. Compared to diverse paraquinone, generation of new therapeutic orthoquinone is necessary to control the invasion and metastasis of breast cancer. Based on beta-lapachone as scaffold and by taking different functional groups into consideration a combinatorial library was created. Consequently Methylsulfonylbenzene functional group contained analogs scored better comparison to others with Vina. Accordingly beta-2119 (name given according to SMIlib) was deemed as the best analog. Different category of NQO1 prepared and docked with newly generated analogs, design and tabulation form after giving total scoring and positional values.

KEYWORDS: Beta-lapachone, NQO1, Linkers and functional groups, SMIlib, MGL tools, Vina, Pymol

I. INTRODUCTION

Recently, the advent of targeted therapy required to explore novel therapeutic ligand for controlling the invasion and metastasis of breast cancer. β -lap an orthoquinone is associated with the cytoplasmic flavoenzyme NQO1 (NAD(P)H:quinone oxidoreductase-1). NQO1 is found in solid tumor showing over-expression up to 5- to 200-fold but less in normal tissues. Incidentally the tumor value and resistance decay are based on the presence highly toxic compounds like β -lap and allied, Generating Combinatorial Library with SMIlib based on β -lap as scaffolds gives approx 60 molecules in this experiment, which extended the scope of finding better affinity of ligand-receptor complexes along with a comparison of different anti tumor drug's affinities. Docking using vina gives the different best binding modes of ligand-receptor complexes where minimal value of scoring as shown in log tables indicating significant affinity of that molecule. Five different categories of NQO1 has been prepared in silico for analysing and comparing the docking results of the selected molecules. Own colour based methods has been adopted for better evaluation. The experimented best scoring values (as per SMIlib) of beta-2149, beta-2119 (among all molecules) evidence that these molecules are having better affinity with the holo or apo form of NQO1 and generates the best binding modes and stability, comparison to others of the repositories such as E6a in 5EAL.pdb and other anticancer drugs being in use. Number and distances of generated hydrogen bond with protein amino acids, FAD by ligand had been analysed in terms of Pymol. Structural and biophysical analyses had shown that NQO1 must contain bound FAD in order to bind with ligand high affinity.

II. OVERVIEW OF NQO1, SCAFFOLD, LINKERS AND FUNCTIONAL GROUPS

1. NQO1 as Cytoplasmic flavoenzyme : NQO1 is a cytoplasmic flavoenzyme also known as quinone reductase¹, menadione reductase or DT-diaphorase is encoded by a gene located on chromosome 16q22. NQO1 reduced by NADH or NADPH and directly reduce quinones to hydroquinones [Zhu et al.,2013;Ross et al.,2000]. Superoxide scavenging, xenobiotic detoxification and the maintenance of endogenous antioxidant vitamins are the major functions of NQO1 [Siegel et al.,2004]. NQO1 protect the normal cells against oxidative damages and carcinogenesis. It is believed that antioxidant role of NQO1 indirectly responsible for the disruption of the NQO1 gene or genetic polymorphism which enhanced the chances of chemical-induced toxicity and cancers [Su XL et al.,2012;Radjendirane et al.,1998]. NQO1 over-expressed in many human tumors, including breast cancer, lung cancer, cholangiocarcinoma, melanoma, and pancreatic cancer [Garate et al.,2010;Awadallah et al.,2008;Siegel et al.,20012;Bey et al.,2013].

Ernster and Navazio first identified NQO1 in the late 1950s Ernster et al.,[1958]. Many reports stated that NQO1 expression in most human tissue types indicating the function as a antioxidant and can protect against natural and exogenous quinones. Recently it has been observed that NQO1 expression is higher in pancreatic adenocarcinomas compared to non-tumor tissues [Lyn-cook et al., 2006]. Strong IHC staining of NQO1 found in intrahepatic cholangiocarcinoma comparison to weakly stained of non-tumor bile ducts and liver parenchyma. Primary melanomas shown NQO1 over expression compared with dysplastic nevi and this is mostly found in the initiation stage of melanoma development [Cheng et al.,2010]. Among 176 patients, 61.9 % showed strongly positive rate of NQO1 protein in breast cancer, and was significantly higher than in DCIS (ductal carcinoma in situ) 31.1%, hyperplasia tissues (13.6%) and adjacent non-tumor tissues (13.5%). Late clinical stage, Her2 expression, lymph node metastasis, and DFS and 10-year overall survival rates in breast cancer is directly related with high-level expression of NQO1 protein [Yang et al.,2014].

2.Beta Lapachone as Scaffold :[Yang yang et al.,2017] hypothesized expression levels of EMT markers with western blot in NQO1-positive MCF-7 and MDA-MB-231 breast cancer cells following β -lap treatment reduced cell migration and invasion by suppressing EMT progression in vitro, which is critical clinical events related to cancers. Experimented results indicating β -lap reduced cell migration and invasion by using wound healing, migration and transwell assays. β -lap showed significantly increased epithelial markers E-cadherin expression and decreased the mesenchymal markers expressions of Vimentin and MMP-9 in the MCF-7 and MDA-MB-231 breast cancer cell lines after IF analysis along with decreased transcription factors Snail and Twist. [Yang yang et al., 2017]. Xenograft model established into a nude mice by the subcutaneous dorsal implantation of MDA- MB-231 cells. Experiment confirmed after 4 weeks of treatment with β -lap that β -lap reduced tumour growth compared with the control. Moreover H&E and immuno-histochemical (IHC) staining were performed on tumours from 3 mice in each group. H&E staining results showed in the low-dose β -lap treated tumour group necrosis increased compared with the control group and high level of necrosis among the high-dose β -lap-treated tumour group. The IHC results showed in the high-dose β -lap-treated tumour group the increased expression of E-cadherin and decreased expression of Ki-67, Vimentin, snail, phosphorylation of Akt, S6, and 4EBP1 compared with the other groups. Chorioallantoic membrane (CAM) invasion assay using hematoxylin and eosin (H&E) staining confirmed the effect of β -lap on MCF-7 and MDA-MB-231 breast cancer cell invasion on cells. The invasion was markedly reduced by β -lap treatment, which indicating that β -lap inhibited the invasion of breast cancer cells in vivo [Yang yang et al.,2017].

3.Design of Small sized Libraries by Combinatorial Assembly: The “Scaffold-Linker-Functional Group” (SLF) approach define the way of arranging three building blocks a scaffold, a variable linker, and a variable functional group to get maximize diversity while reducing the size of a scaffold-based library. Combinatorial chemistry as a tool, to designing a library in infinite variations on a core template are theoretically possible [Alper et al.,1994]. In drug discovery process, it is expectable to get the maximum of information [Bradley et al.,2003] out of a minimum of experiments. To date, a lot of combinatorial structure rather large virtual libraries generation tools have been developed [Beavers et al.,2002]. Hit rate dont directly proportioned with the possible number of compounds but sometime generated molecules are not synthetically easily available. Indeed, to stay in the order of magnitude of a thousand compounds [Nilakantan et al.,2003] virtual combinatorial libraries are assessed by different techniques such as genetic algorithms [Wright et al.,2003], Monte Carlo calculations [Langer et al.,2004], artificial neural network,or simply statistical sampling with user-defined property ranges [Weaver et al.,2004]. Recently SMILIB[Schuller et al.,2003]

and COREGEN [Aronov et al.,2004] also based on homology and molecular diversity concepts, combining with a limited number of functional groups (cations, anions, hydrogen bond acceptor-donor systems, aromatics/lipophilics).

III. MATERIALS AND METHODS

Materials :Open Babel for conversion of formats needed by different softwares[O'Boyle et al.,2011], Betalaphone as scaffold with different linkers and Functional groups, available towards anti cancer drugs(for comparison), SMIlib for combinatorial library development, VMD for extractions of ligands, Autodock vina for molecular docking [O. Trott et al.,2011],Auto dock tool within MGL tool for pdbqt formation,VMD for extraction and visualization of protein[<https://www.ks.uiuc.edu/Research/vmd/vmd-1.3/ug/node4.html>], Pymol bonding analysis.

Methods :Download the 5EAI.pdb,5EA2.pdb from protein category under the site "www.ncbi.nlm.nih.gov" [43], which is a holo human NQO1 bounded with E6a and without E6a(5EA2). Along with this beta lapachone (26420993 39093585631. sdf) had been downloaded from pubchem.The bounded ligand as E6a was extracted from 5EAI through VMD software which is anticancer drug. After extracting the E6a through VMD, the modified protein treated here as 3rd category pdb which is equivalent to original holo 5EA2(4th category here) in repository. Similarly after extracting FAD and E6a from 5EAI and only FAD from 5EA2 the 2nd and 5th category were developed. Below mentioned are the different linkers and Functional group taken into account in this experiment.

linkers-

[A][R1] , [A]S(=O)(N[R1])=O , [A]C(N[R1])=O , [A]C(O[R1])=O , [A]O[R1] , [A]C[R1]

Functional Groups

[A]C , C(C[A])(C)(C)C , [A]CCOC , C1(=CC=C(C=C1)C[A])OC , N1(CC[A])CCCCC1 , C(=O)([O])C[A]

[A]C1=CC=CC=C1 , C(C(F)(F)F)[A] , C1=CC(=CC=C1S(=O)(=O)C)[A] , N1(C(CSC1C)=O)C[A]

After this with the help of SMIlib tool, 60 new analogs had been generated based on betalaphone as scaffold. Now these analogs with other anticancer drugs (Mytomyacin C, Camptothecin, Doxorubicin, Paclitaxel, DNQ, Tectoquinone) were docked by Vina in the 1st space of the 1st category NQO1 protein (where the docking made for ligand- centre of the 1st space- (center_x=- 50,center_y=20,center_z=-40) and size had choosen as size_x =22,size_y =24,size_z =26 , Spacing=1.00) of 5EAI for just evaluating highest negative score of docked molecules. After docking score values were analysed. Now 10 betalaphone's analogs taking into consideration with mentioned anti-cancer drugs for rest 4 category's docking. Below shown the table giving details of spaces of 4 categories where total newly selected 18 molecules including anti-cancer drugs were docked. To show the configuration file format here beta 2119 named molecule was taken as classical example.

2nd,3rd,4th,5th Categories of NQO1 protein Docking with beta-smi-exam2.1.1.9.pdb :

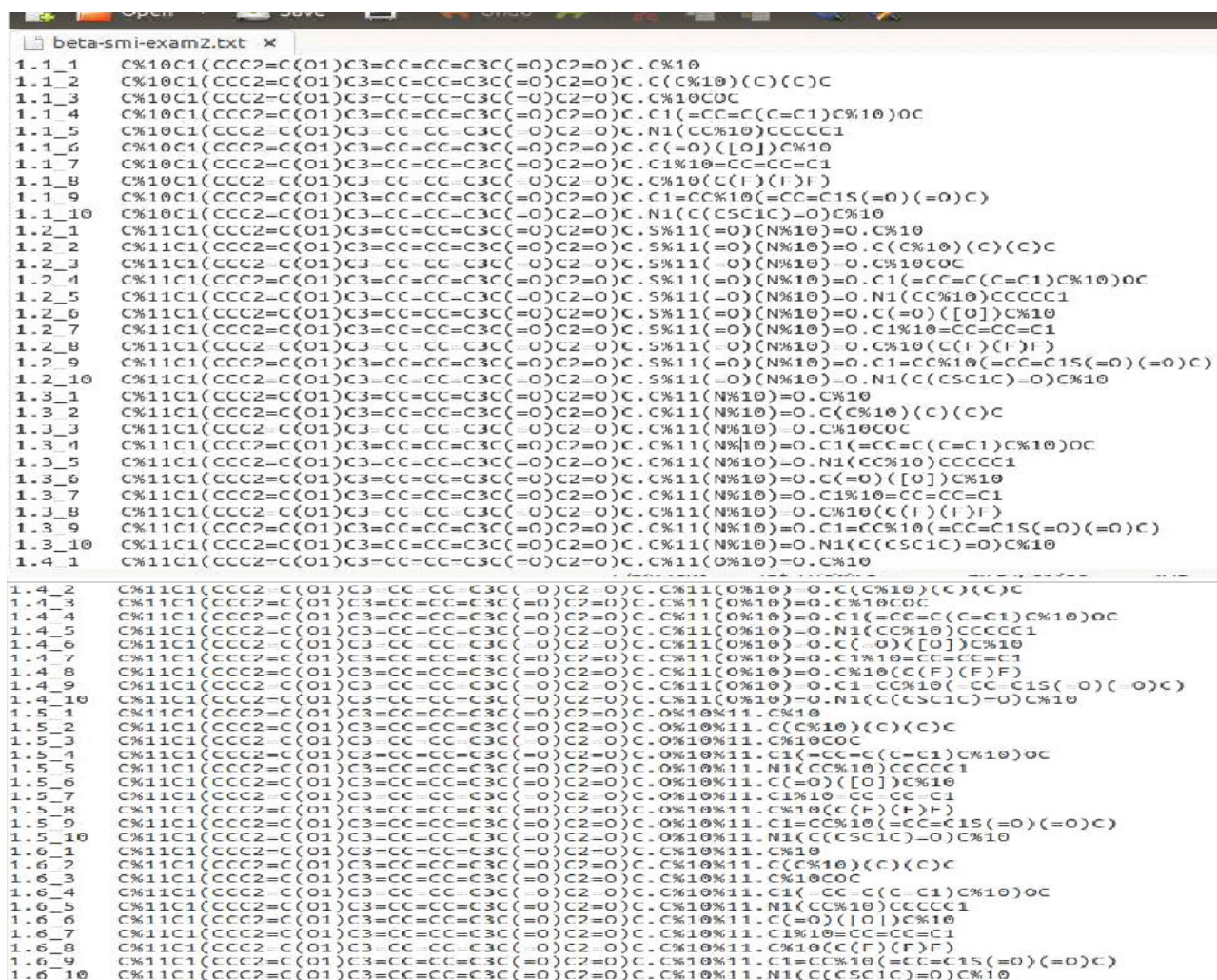
1stReceptor =	mmdb_5eaim.pdbqt	3 rd default mmdb_5EA2.pdbqt
Ligand =	beta_smi_exam2_1_1_9nm.pdbqt	5ea2-beta_smi_exam2_1_1_9.pdbqt
center_x =	-31	-10
center_y =	17	-6
center_z =	35	19
size_x =	30	30
size_y =	26	26
size_z =	28	28
2 nd -Receptor =	mmdb_5eaim.pdbqt	4 th -default mmdb_5EA2m.pdbqt
Ligand =	beta_smi_exam2_1_1_9nm.pdbqt	5ea2-beta_smi_exam2_1_1_9m.pdbqt
center_x =	-31	-10
center_y =	17	-6
center_z =	35	19
size_x =	30	30
size_y =	26	26
size_z =	28	28

Table :1

After 2nd space docking based on the scoring values only 4 analogs were selected and evaluated using Pymol by measuring hydrogen bond distance, numbers and surrounding 3A aminoacids presence of that analog.

IV. RESULTS AND DISCUSSION

Smiles formats were generated of 60 analogs of Beta-lapachone by after the enumeration protocol by proper arranging of linkers and functional groups shown in Table2. Eventually the numbers were written before the smile formats of every molecules indicate the number of scaffold, linker & Functional groups(FG). As 1.1_1 means only one scaffold (β -lap) combined with 1st linker & 1st FG of that category and created the molecule which are represented by the mentioned 1.1_1 numbered smile.



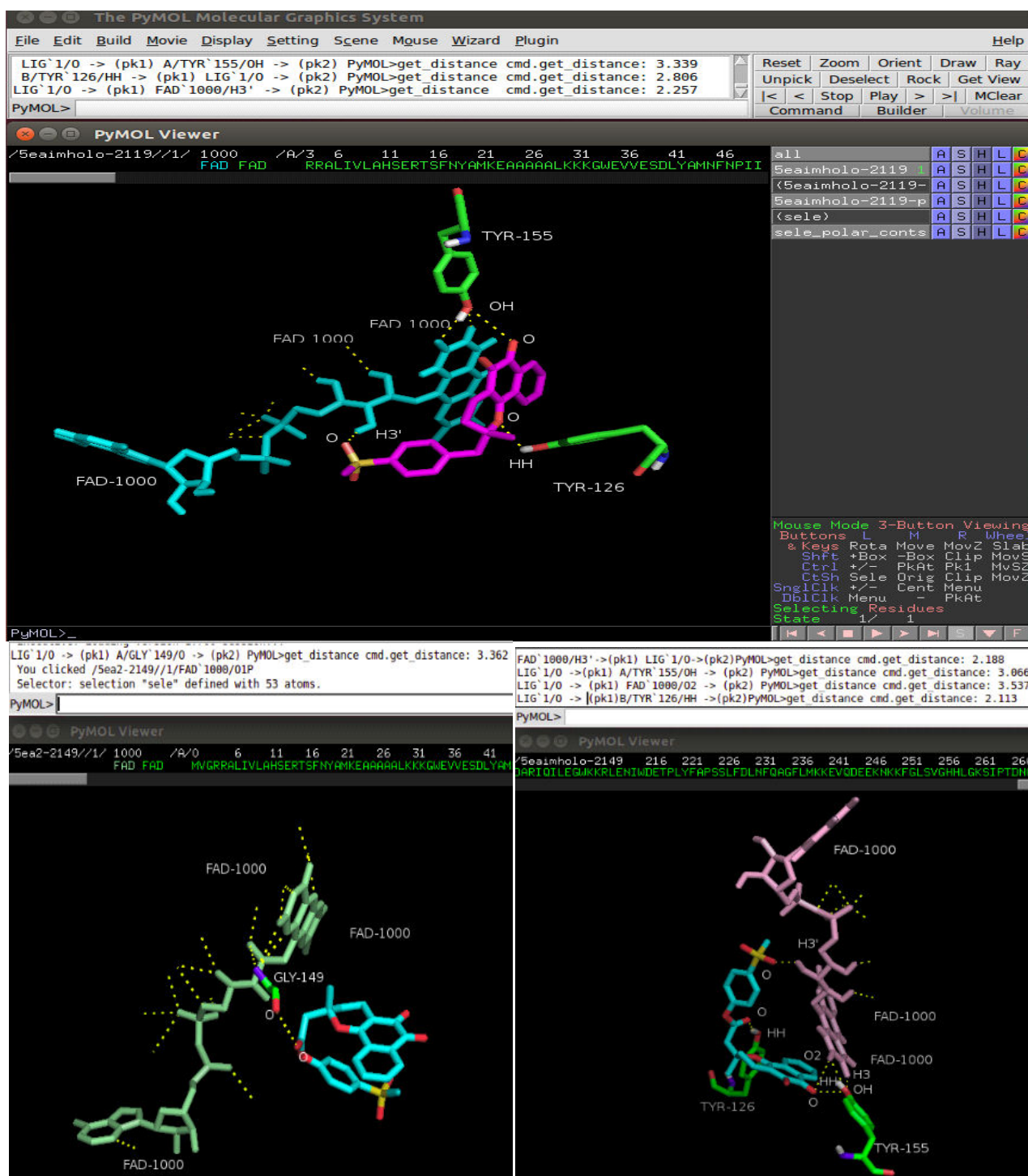
Category	SMILES String
1.1_1	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10</chem>
1.1_2	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C(C%10)(C)(C)C</chem>
1.1_3	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10COC</chem>
1.1_4	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C1(=CC=C(C=C1)C%10)OC</chem>
1.1_5	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.N1(C%10)CCCCC1</chem>
1.1_6	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C(=O)([O])C%10</chem>
1.1_7	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C1%10=CC=CC=C1</chem>
1.1_8	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10(C(F)(F)F)</chem>
1.1_9	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.1_10	<chem>C%10C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.N1(C(C5C1C)-O)C%10</chem>
1.2_1	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C%10</chem>
1.2_2	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C(C%10)(C)(C)C</chem>
1.2_3	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C%10COC</chem>
1.2_4	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C1(=CC=C(C=C1)C%10)OC</chem>
1.2_5	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.N1(C%10)CCCCC1</chem>
1.2_6	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C(=O)([O])C%10</chem>
1.2_7	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C1%10=CC=CC=C1</chem>
1.2_8	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C%10(C(F)(F)F)</chem>
1.2_9	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.2_10	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.S%11(=O)(N%10)=O.N1(C(C5C1C)-O)C%10</chem>
1.3_1	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C%10</chem>
1.3_2	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C(C%10)(C)(C)C</chem>
1.3_3	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C%10COC</chem>
1.3_4	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C1(=CC=C(C=C1)C%10)OC</chem>
1.3_5	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.N1(C%10)CCCCC1</chem>
1.3_6	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C(=O)([O])C%10</chem>
1.3_7	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C1%10=CC=CC=C1</chem>
1.3_8	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C%10(C(F)(F)F)</chem>
1.3_9	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.3_10	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(N%10)=O.N1(C(C5C1C)-O)C%10</chem>
1.4_1	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C%10</chem>
1.4_2	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C(C%10)(C)(C)C</chem>
1.4_3	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C%10COC</chem>
1.4_4	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C1(=CC=C(C=C1)C%10)OC</chem>
1.4_5	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.N1(C%10)CCCCC1</chem>
1.4_6	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C(=O)([O])C%10</chem>
1.4_7	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C1%10=CC=CC=C1</chem>
1.4_8	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C%10(C(F)(F)F)</chem>
1.4_9	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.4_10	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%11(O%10)=O.N1(C(C5C1C)-O)C%10</chem>
1.5_1	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C%10</chem>
1.5_2	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C(C%10)(C)(C)C</chem>
1.5_3	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C%10COC</chem>
1.5_4	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C1(=CC=C(C=C1)C%10)OC</chem>
1.5_5	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.N1(C%10)CCCCC1</chem>
1.5_6	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C(=O)([O])C%10</chem>
1.5_7	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C1%10=CC=CC=C1</chem>
1.5_8	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C%10(C(F)(F)F)</chem>
1.5_9	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.5_10	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.O%10%11.N1(C(C5C1C)-O)C%10</chem>
1.6_1	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C%10</chem>
1.6_2	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C(C%10)(C)(C)C</chem>
1.6_3	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C%10COC</chem>
1.6_4	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C1(=CC=C(C=C1)C%10)OC</chem>
1.6_5	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.N1(C%10)CCCCC1</chem>
1.6_6	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C(=O)([O])C%10</chem>
1.6_7	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C1%10=CC=CC=C1</chem>
1.6_8	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C%10(C(F)(F)F)</chem>
1.6_9	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.C1=CC%10(=CC=C1S(=O)(=O)C)</chem>
1.6_10	<chem>C%11C1(CCC2=C(O1)C3=CC=CC=C3C(=O)C2=O)C.C%10%11.N1(C(C5C1C)-O)C%10</chem>

Table :2 Selected 10 analogs with best negative scores were docked with above mentioned 2nd, 3rd, 4th and 5th category of NQO1 prepared and extracted by VMD. The table given below depict the scoring values after docking and each molecule's category wise scores had been added in "Total value" column and was given as position value at the column. The Position value is determined by the adding of positional value of a molecule of a particular category.

Table : 3

Name of Ligand	1 st Category	2 nd	3 rd	4 th	5 th	Total Value	Positioned Value
Mytomycin C	-5.9	-8.4	-7.6	-6.2	-7.3	-35.4	
Beta-Lapachone	-6.4	-8.4	-9.1	-6.8	-7.7	-38.4	
Campothecin	-7.4	-9.8	-9.2	-7.9	-8.5	-42.8	8
Doxorubicin	-6.5	-9.1	-8.5	-7	-8.6	-39.7	
Paclitaxin	-5.8	-9	-7.9	-7	-7	-36.7	
DNQ	-6.6	-9.1	-8.8	-6.9	-7.9	-39.3	
Tectoquinone	-6.5	-8.4	-8.7	-6.7	-7.8	-38.1	
E6A	-6.9	-10	-9.2	-7.8	-8.3	-42.2	4
Beta-2149	-7.2	-11.2	-10.1	-7	-9.7	-45.2	23
Beta-2129	-7.4	-10.7	-9.9	-8	-9.2	-45.2	20
Beta-2167	-7.4	-10.5	-10.1	-8	-8.8	-44.8	18
Beta-2169	-7.8	-10.6	-10.1	-8	-9.1	-45.6	23
Beta-2157	-7.3	-10.2	-10	-8	-8.6	-44.1	14
Beta-2139	-7.5	-10.3	-10.2	-7.9	-9.2	-45.1	18
Beta-2137	-7.3	-10.4	-10.2	-7.5	-8.5	-43.9	13
Beta-2119	-7.5	-10.6	-10.6	-7.8	-9.2	-45.7	23
Beta-2138	-6.8	-9.4	-9.6	-7.3	-8	-41.1	1
Beta-2118	-6.9	-9.4	-9.1	-7.4	-7.6	-40.4	

After arranging the docking scores in Table 3, it was then quite easy to evaluate the selected ligands for further process. Starting from the table first, it was observed that in case of Mytomycin C as per docking with 5 different categories it was evident that no position comparison was significant to others within that category. Hence, the Total Value was found to be -35.4 and it was the lowest including the positioned value amount to 0. In case of campothecin who scored -7.4 with 4th position within 1st category and 6th position with 4th category. Consequently It's Total Value was -42.8 and Positioned Value 8. Similarly for β -lap, Doxorubicin, Paclitaxin, DNQ, Tectoquinone and E6A Total Values were found to be -38.4, -39.7, -36.7, -39.3, -38.1, -42.2 respectively. Accordingly it may be inferred that of all 8 important molecules (wellknown Anti-Cancer drugs), it was observed that only Campothecin and E6A (in comparison with others), scored better in Total Value and Positioned Value. Therefore inferentially the scoring values of B-lap analogs particularly the 2149 molecule (just mentioning the number instead of full name) obtained 1st position with 2nd category having a Total Value of -45.2 and Positioned value of 23. While in other case of 2169 which it positioned 1st with 1st category and had Total Value of -45.6 and position Value of 23. Similarly the remaining case of 2119 which scored 1st with 3rd category revealed a Total Value of -45.7 and Positioned Value of 23. Among 10 selected β -lap analogs, only the above 3 molecule's disclosed a total value of >45 and Positioned Value of >=22. But interestingly all 3 molecules got 1st position individually with different category, especially 2119 and 2169, which scored -10.6 with 1st position in 3rd category and -11.2 with 1st position in 1st category. During narrowing the series of molecules it was found that Beta-smi-exam2139 though scored -45.1 in Total Value but Position Value was 18 and had not scored highest negative value with any category except 2nd and 3rd position with 3rd and 1st category respectively. So it was less prioritized and not kept it for further process. In the same way the Beta-smi-exam2167 scored the Total Value was -44.8 and Position Value was 18. Besides it had not scored highest negative with any category except 3rd position with 3rd category. So it was less prioritized and not kept it for further process. Similarly In case of Beta-smi-exam2137 the Total Value was -43.9 and Position Value was 13 and without highest negative score to any category except 2nd position with 3rd category and hence it was as less prioritized and was not kept for further process. Furthermore holo NQO1 was prioritized as the presence of FAD help to strenghten the binding affinity of the complex and as per pymol the position of particular analog with interacted amino acid were evident. The number of bonds and its distances offer the clear pictures on the affinity of the complexes evaluated in light of Pymol.



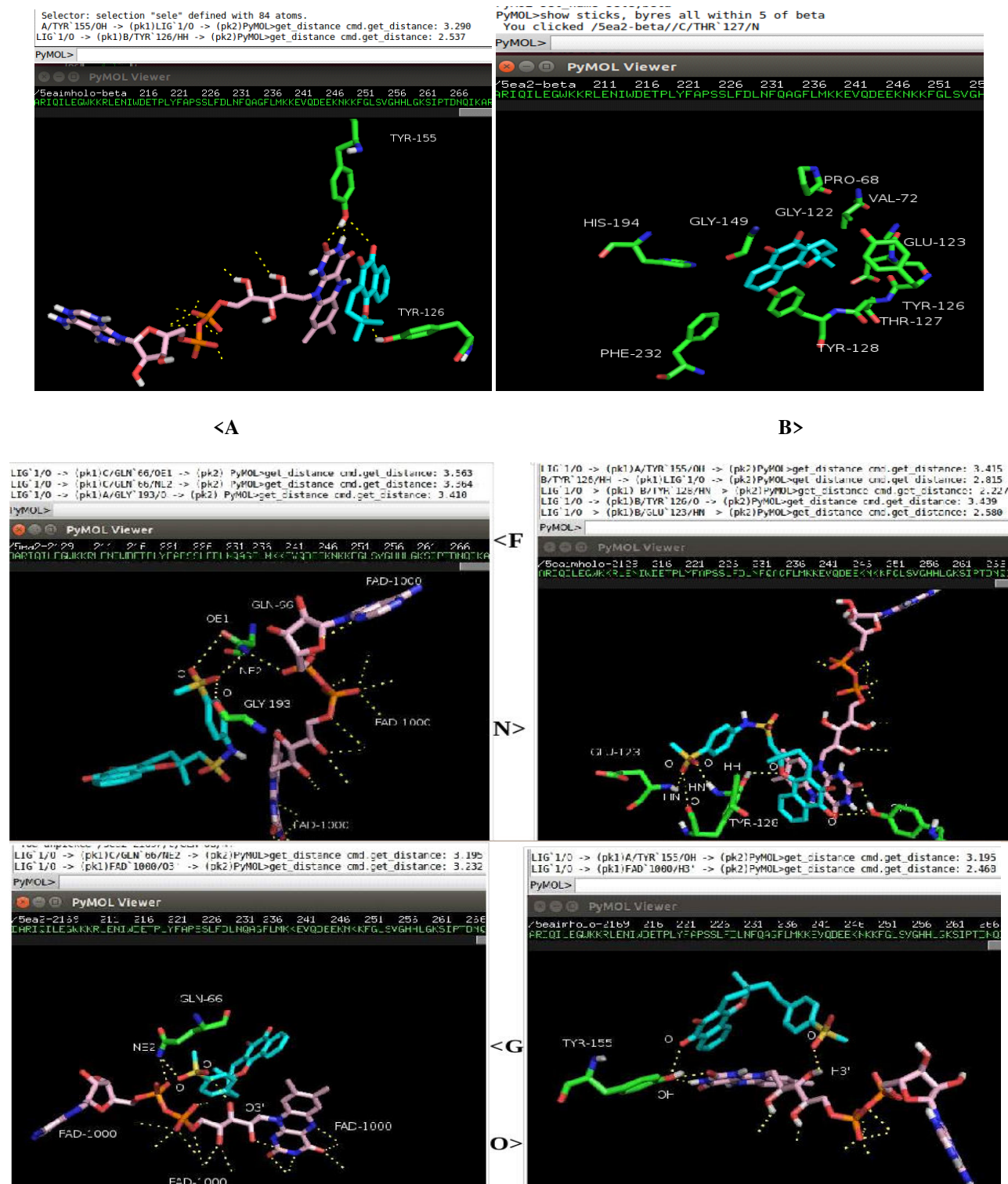


Figure 3 : A,B parts showing the interaction of Betalaphachone; F,N parts showing interaction of Beta-2129 and G,O parts showing beta-2169 where left side showing 4th and right side showing 3rd category protein docking.

V. CONCLUSION

According to proteomic dynamics of FAD its binding to NQO1 apo was known to cause significant overall changes in the protein structure and expression. The in-silico pursuit confirms that Methylsulfonylbenzene based analogs of betalapachone specially beta2119 scored highest with the holoNQO1 as illustrated in Figure 1 in comparison to Figure 3 (showing details of binding residues, bond distances and number of bonds for beta 2129, beta 2169 and a betalapachone). For each and every ligand the scoring values of vina were diverse as per the molecular structure of both the categories (3rd & 4th category) with similar type, but the 3rd category of proteins scored better than 4th. For instance in E6A, beta-2119, beta-2149 all the ligands when interacted with 3rd category scored a value of -9.2, -10.6, -10.1 respectively but when interacted with 4th category it scored -7.8, -7.8, -7 respectively. Most interestingly for these molecules and for other molecules the interacted residues with FADs were almost the same but only differences existed in the creation of bonds with corresponding differences in scoring values. GLY150 create a hydrogen bond mostly 2.08 Å distances which had not been generated in 4th category reactions. Similarly TYR155, PHE106, ASN18, THR147, GLN66 created the hydrogen bonds with the distances are 1.93 Å, 2.0 Å, 2.0 Å, 1.96 Å respectively. Moreover HIS11 created the salt bridge which was not found in 4th category. Thus **it was** experimentally proved that all Methylsulfonylbenzene based analogs of betalapachone specially beta2119, shown best affinities with holo human NQO1 found in breast tumour.

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