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# Insights into the structural/conformational requirements of cytotoxic oxadiazoles as potential chemotherapeutic target binding agents

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ABSTRACT

A few novel previously synthesized 2,5-disubstituted 1,3,4-oxadiazoles with cytotoxic activity (**1**–**17**) were subjected to combined docking/quantum mechanical studies against chemotherapeutic targets. Selected macromolecular targets were those that were previously known to be inhibited by 1,3,4-oxadiazoles. Within this work, favorable binding modes/affinities of the oxadiazoles toward validated cancer targets were elucidated. Some oxadiazole structures exhibited $\Delta G_b$s comparable to or stronger than crystallographic ligands that were previously demonstrated to inhibit such targets. On the basis of obtained results, a general structure activity/binding relationship (SAR/SBR) was developed and a few 2,5-disubstituted 1,3,4-oxadiazole structures were proposed and virtually validated as potential cytotoxic candidates. To get more insight into structure binding relationship of candidate molecules within best correlated targets, docked conformation of the best *in silico in vitro* correlated oxadiazole structure was analyzed in terms of intermolecular binding energy components by functional B3LYP in association with split valence basis set using polarization functions (Def2-SVP). We believe that such modeling studies may be complementary to our previous results on the synthesis and cytotoxicity assessment of novel 1,3,4-oxadiazole derivatives through extending the scope of privileged structures toward designing new potential anti-tumor compounds.



## 1. Introduction

Compounds possessing diverse heterocyclic nucleuses have obtained special significance in drug discovery and design. Among such privileged scaffolds, five-membered 1,3,4-oxadiazole ring has attracted considerable concern in medicinal chemistry due to the broad range of pharmaceutical and biological activities, such as anticancer [1], antifungal [2], antibacterial [3], antiviral [4], analgesic [5], anti-inflammatory [6], antihypertensive [7], anti-convulsant [8] and anti-diabetic [9] effects. Moreover, various synthetic approaches toward 1,3,4-oxadiazoles have facilitated the investigation of their chemical and biological properties.

A number of 2,5-disubstituted 1,3,4-oxadiazole structures have been reported to exhibit cytotoxic activity through the inhibition of different growth factors, enzymes and kinases including telomerase, histone deacetylase (HDAC), methionine aminopeptidase (MetAP), thymidylate synthase (TS), glycogen synthase kinase-3 (GSK), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and focal adhesion kinase (FAK) [10].

Among mentioned targets, the major mechanism responsible for anticancer potency of 1,3,4-oxadiazole derivatives relates to the inhibition of telomerase enzyme. In a few separated studies, different 1,3,4-oxadiazole derivatives were synthesized and screened for their telomerase inhibitory activity against MCF-7 and other cancer cell lines. The major assessed compounds were 1,4-benzodioxane, 2-chloro pyridine, acyl hydrazone and quinoline containing 1,3,4-oxadiazole derivatives [11–14].

Structure activity relationship (SAR) studies of two different series of synthetic 1,3,4-oxadiazoles revealed that for HDAC inhibition three pharmacophoric requirements are zinc binding group, linker and surface recognition cap group [15]. HDAC inhibitors can suppress the phosphorylation of human telomerase reverse transcriptase (hTRT) by protein kinase B (PKB/Akt) through regulation of telomerase activity [16]. This can represent an innovative strategy to design compounds which co-targets (PKB-Akt) and

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telomerase.

Study of 1,4-benzodioxane containing 1,3,4-oxadiazoles revealed their potentiality for inhibition of telomerase, GSK-3 beta and MetAP pathway [17,18]. Likewise, benztriazol and phenylethanone containing derivatives demonstrated potential FAK inhibitory activity [19,20]. In another study, the inhibitory activity against TS varied with the substituents on different positions of benzene ring joined to 1,3,4-oxadiazole and increased with the incorporation of electron withdrawing groups into the phenyl ring [21].

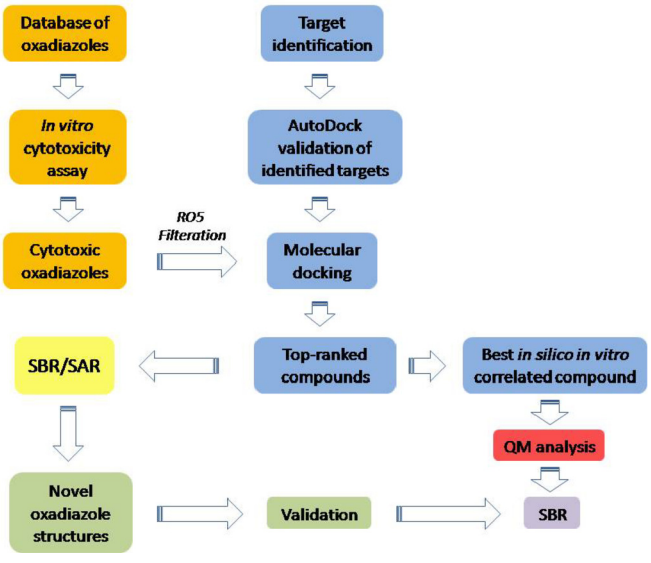
It seems that pyrrole triazine analogs of 1,3,4-oxadiazole are potential VEGF-2 inhibitors [22,23]. A series of 2,4-bis diphenylamine oxadiazole derivatives have been reported with promising EGFR tyrosine kinase inhibitory activity [24]. Moreover; it was known that inhibition of EGFR signaling not only had an antiproliferative and therapeutic effects but also increased sensitivity to cytotoxic therapies.

In continuation to our interest in structure based design of small molecule heterocyclic structures as potential bioactive compounds, a series of novel cytotoxic1-(5-aryl-1,3,4-oxadiazol-2-yl)-1-(1H-pyrrol-2-yl) methanamines [25] were subjected to combined molecular docking/quantum mechanical (QM) simulations in order to estimate their binding mode/affinity toward several validated chemotherapeutic targets. For more clarification, general procedure of the work is represented schematically (Scheme 1).

## 2. Materials and methods

### 2.1. Ligand data set

A series of cytotoxic 1,3,4-oxadizole derivatives (Table 1) were subjected to *in silico* studies [25]. Candidate molecules were checked in terms of Lipinski's rule of five (RO5) [26] and it was revealed that for almost all of the compounds, no deviation from the expected criteria occurred except for compounds **16** and **17** which exhibited a little deviation just in one of their parameters (ClogP 5.24 & 5.51, respectively). Accordingly, the whole candidate ligands could be classified as drug-like structures [26] (Fig. 1).




**Scheme 1.** Schematic flowchart of *in silico* analysis of 1,3,4-oxadiazole derivatives within chemotherapeutic targets.

### 2.2. Target data set

All radiographic 3D *holo* structures of selected targets (BCL-2, PBD ID: **4AQ3** [27]; EGF, PDB ID: **3W33** [28]; Enoyl-acp Reductase, PDB ID: **1QSG** [29]; FAK, PDB ID: **4KAO** [30]; GSK-3 beta, PDB ID: **1Q41** [31]; HDAC, PDB ID: **5IX0** [32]; MetAP, PDB ID: **1YW7** [33]; telomerase, PDB ID: **5CQG** [34]; TS, PDB ID: **4E5O** [35] and VEGF, PDB ID: **3VO3** [36]) were retrieved from the Brookhaven protein data bank (http://www.rcsb.org/) with resolutions in the range of 1.52–2.40 Å. Macromolecular structures were subjected to optimization step in order to minimize the crystallographic induced bond clashes using steepest descent method. All the pre-processing steps were done by Auto-Dock Tools 1.5.4 (ADT) [37] according to the previous reports [38]. The biological importance of the selected targets with regard to cancer therapy is summarized through separate paragraphs.

#### 2.2.1. Bcl-2

The Bcl-2 family proteins are essential regulators of apoptosis which dictate cellular survival or death decisions by regulating the integrity of the mitochondrial outer membrane (MOM) [39], and include three subgroups of proteins that either promote cell survival (e.g., Bcl-2 and Bcl-$x_L$), initiate cell killing (e.g., Bcl-2-interacting mediator of cell death (Bim), p53 upregulated mediator of apoptosis (Puma) or Bcl-2-interacting domain (Bid) or activate the effector pathways of apoptosis (Bax, Bak) [40]. As a result, Bcl-2 is an anti-apoptotic protein possessing an important role in various types of cancers like breast which is encoded by the Bcl-2 gene [41].

#### 2.2.2. Epidermal growth factor

Epidermal growth factor (EGF) plays a considerable role in tumor development and progression, including cell proliferation, regulation of apoptotic cell death, angiogenesis and metastatic spread by binding to its receptor, EGFR [42]. Due to the overexpression of EGFR in various types of epithelial cancers, like pancreatic, colorectal, breast, and lung cancer, it has been thought that EGFR is an appropriate target for cancer therapy [43].

#### 2.2.3. Enoyl-acyl carrier protein reductase

Human fatty acid synthase (FAS) is a large, multi-domain protein that synthesizes long chain fatty acids. Human enoyl-acyl carrier protein-reductase (hENR) is one of the FAS catalytic domains, also is the last enzyme in the fatty acid elongation cycle which reduces the substrate enoyl-thioester to an acyl moiety [44]. Because fatty acids are primarily provided by diet, FAS is normally expressed at low levels. However, high levels of FAS expression have been found in many human cancers including breast, prostate, colon, ovary and lung [45].

#### 2.2.4. Focal adhesion kinase

Focal adhesion kinase (FAK) is a cytoplasmic non-receptor tyrosine kinase that is expressed ubiquitously and specifically localized in focal adhesions [46]. Integrin-mediated FAK activation pathway is proven to be involved in survival mechanisms and plays a critical role in the adhesion, invasion, and metastasis of tumor cells [47]. High expressions of FAK have been observed in both endometrial hyperplasia and carcinoma, implying that FAK may play an important role in epithelial-mesenchymal transition (EMT) and migration during endometrial carcinogenesis [48].

#### 2.2.5. Glycogen synthase kinase 3 beta

Glycogen synthase kinase-3 (GSK-3) is a moon-lighting kinase which phosphorylates multiple proteins on serine and threonine residues [49]. The GSK-3 gene family consists of two highly