

# Computational approach in searching for dual action multitarget inhibitors for osteosarcoma

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ORIGINAL ARTICLE

# Computational approach in searching for dual action multitarget inhibitors for osteosarcoma

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## ABSTRACT

Osteosarcoma is a common primary malignant bone tumor that typically manifests in the second decade of life. This study aimed to identify osteogenic compounds that potentially serve as multitarget inhibitors for osteosarcoma. The study was a molecular docking study of nine Food and Drug Administration-approved compounds with osteogenic properties to the key membrane proteins of osteosarcoma. The ligands used were raloxifene, simvastatin, dexamethasone, risedronate, ibandronate, zoledronic acid, ascorbic acid, alendronate, and  $\beta$ -glycerophosphate, whereas the target proteins used were RET, fibroblast growth factor receptor 1, KIT, PDGFRA, VEGFR1, and VEGFR2. Chem3D version 15.0.0.106 was used for ligand preparation, and AutoDockTools version 1.5.6 was used for protein preparation, whereas molecular docking was conducted using AutoDock Vina. Raloxifene, simvastatin, and dexamethasone had the lowest binding activity to the target proteins. The binding affinity of raloxifene was from  $-8.4$  to  $-10.0$  kcal mol<sup>-1</sup>, that of simvastatin was  $-8.3$  to  $-9.2$  kcal mol<sup>-1</sup>, whereas dexamethasone ranged from  $-6.9$  to  $-9.1$  kcal mol<sup>-1</sup>. Most types of interactions were hydrophobically followed by hydrogen bonding. The current study suggests that raloxifene, simvastatin, and dexamethasone have the potential to act as multitarget inhibitors for osteosarcoma with the ability to induce bone remodeling.

**Key words:** Bone cancer, cancer, large bone defect, molecular docking, raloxifene, simvastatin

## INTRODUCTION

Osteosarcoma is a type of primary malignant bone tumor that commonly affects children and adolescents. The average prevalence rate of osteosarcoma in males is 4.3 per million and 3.4 per million in females.<sup>[1,2]</sup> Osteosarcoma is difficult to diagnose because the clinical signs are not always

obvious. This includes the absence of spontaneous fractures or severe pain events at the early stages. In addition, with rapid tumor growth, the tumor will have a huge potential to metastasize to other organs.<sup>[1,3]</sup> Radiotherapy is ineffective against osteosarcoma, whereas surgical resection may result in postoperative recurrence and metastasis. Osteosarcoma also causes large bone defects prone to self-healing, resulting in movement restrictions and negatively impacting the patient's quality of life.<sup>[1,2,4-6]</sup>

Membrane proteins are important targets in disease progression and their treatment.<sup>[7,8]</sup> Several protein tyrosine kinases have been linked to the progression of osteosarcoma.<sup>[9]</sup> For example, a proto-oncogene protein

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called RET. Mutations in the RET gene have become the second-most frequently mutated cancer-predisposing gene in osteosarcoma patients.<sup>[10-12]</sup> Besides RET, another protein associated with osteosarcoma progression is the fibroblast growth factor receptor 1 (FGFR1). FGFR1 stimulated osteosarcoma growth<sup>[13]</sup> and was linked to poor response to therapy.<sup>[9]</sup> In addition to RET and FGFR1, a protein called KIT (c-kit) was associated with osteosarcoma. KIT-positive tumors exhibited lower necrosis postchemotherapy and worse response to chemotherapy. Moreover, platelet-derived growth factor receptors (PDGFR) also play functional roles in tumorigenesis.<sup>[14]</sup> In relation to tumor angiogenesis, vascular endothelial growth factor (VEGF) expression is linked to an increased risk of lung metastasis and poor prognosis for tumor-free survival.<sup>[15]</sup>

Tian *et al.* revealed that targeting a single membrane protein may not be effective in osteosarcoma.<sup>[9]</sup> Due to this, we aimed to identify multitarget compounds for osteosarcoma. In this study, nine Food and Drug Administration (FDA)-approved small compounds with osteogenic properties were docked to six key osteosarcoma proteins. The use of osteogenic compounds is intended to have two effects: to inhibit tumor growth through interaction with key proteins and to induce bone growth when there is a complication with a large-sized bone defect. Moreover, the use of FDA-approved drugs is to ensure the safety of candidate osteosarcoma inhibitors. This study will contribute to finding the dual action of multitarget small compounds that potentially inhibit osteosarcoma and simultaneously induce bone remodeling.

## MATERIALS AND METHODS

### Ligand and protein preparation

These compounds used as ligands were raloxifene, simvastatin, dexamethasone, risedronate, ibandronate, zoledronic acid, ascorbic acid, alendronate, and  $\beta$ -glycerophosphate. The chemical structures of all ligands were obtained from PubChem. The ligand structure was prepared based on Gani *et al.*<sup>[16]</sup> In brief, structures were designed in ChemDraw 15.0.0.106 and optimized in Chem3D 15.0.0.106.

Furthermore, six docking target structures were downloaded from the Protein Data Bank. These proteins are RET (PDB ID: 6NEC), FGFR1 (PDB ID: 4V05), KIT (PDB ID: 4U0I), PDGFRA (PDB ID: 6JOL), VEGFR1 (PDB ID: 3HNG), and VEGFR2 (PDB ID: 3VHE). Proteins were created in PDBQT format using AutoDockTools version 1.5.6, which modified water molecules and solvent residues, added Kollman charges, and repaired missing atoms. Protein validation was carried out by calculating the protein's root mean square deviation (RMSD) with its co-crystalline ligand using PyMOL software version 2.3.4 (Schrödinger LLC). RMSD value of fewer than three angstroms is considered good docking replication.<sup>[17-19]</sup>

### Molecular docking

All procedures, including molecular docking, were performed using an Intel® Celeron® 2955U at 1.40 GHz processor, 2.00 GB of RAM 64-bit operating system. The technique of docking used in this study was the targeted docking method.<sup>[16,17]</sup> Grid box size and centers used for each protein are listed in Table 1. The protein binding pocket used in the present study was also validated with DoGSiteScorer. Finally, Discovery Studio Visualizer was used to visualize the molecular interactions.

## RESULTS

*In silico* molecular docking study of small compounds was carried out in searching multitarget small compounds for bone cancer treatment. Nine small compounds used were molecules that have been used to increase bone growth, treat osteoporosis, or are known to have osteogenic activity. The protein targets used were RET, FGFR1, KIT, PDGFRA, VEGFR1, and VEGFR2. These proteins have been used as target proteins for osteosarcoma treatment.

The binding pockets used for each protein are present in Figure 1. This binding pocket was also where the co-crystalline ligands bound with each protein. RMSD value of co-crystalline ligands with the protein were  $2.800 \pm 0.008$ ,  $1.575 \pm 0.161$ ,  $1.171 \pm 0.010$ ,  $0.871 \pm 0.001$ ,  $0.610 \pm 0.030$ , and  $0.504 \pm 0.010$  for RET, FGFR1, KIT, PDGFRA, VEGFR1, and VEGFR2, respectively. The binding affinity between ligands and protein is present in Table 2. Raloxifene, simvastatin, and dexamethasone had the lowest binding activity among all ligands. The binding affinity of raloxifene was from  $-8.4$  to  $-10.0$  kcal mol<sup>-1</sup>, simvastatin was from  $-8.3$  to  $-9.2$  kcal mol<sup>-1</sup>, whereas dexamethasone ranged from  $-6.9$  to  $-9.1$  kcal mol<sup>-1</sup>. The molecular interaction between raloxifene, simvastatin, and dexamethasone with the target proteins is present in Figure 2, whereas their respective interaction type is in Table 3. Most interaction types that were present were hydrophobically followed by hydrogen bonds.

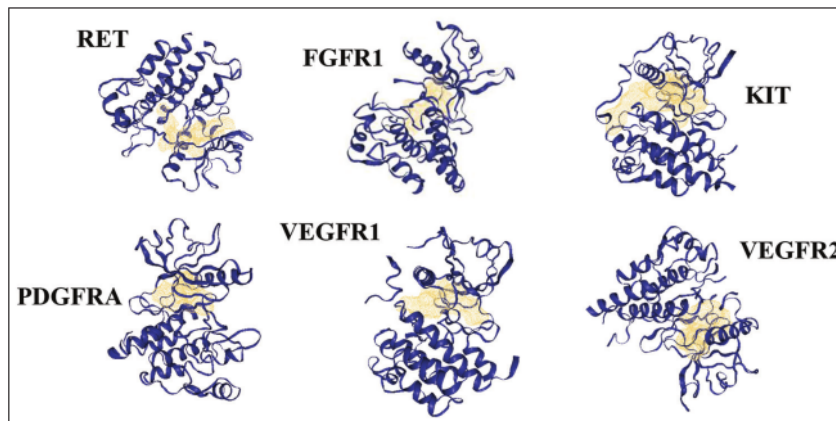
## DISCUSSION

Our present study showed that three FDA-approved drugs potentially serve as multitarget inhibitors for osteosarcoma. They are raloxifene, simvastatin, and

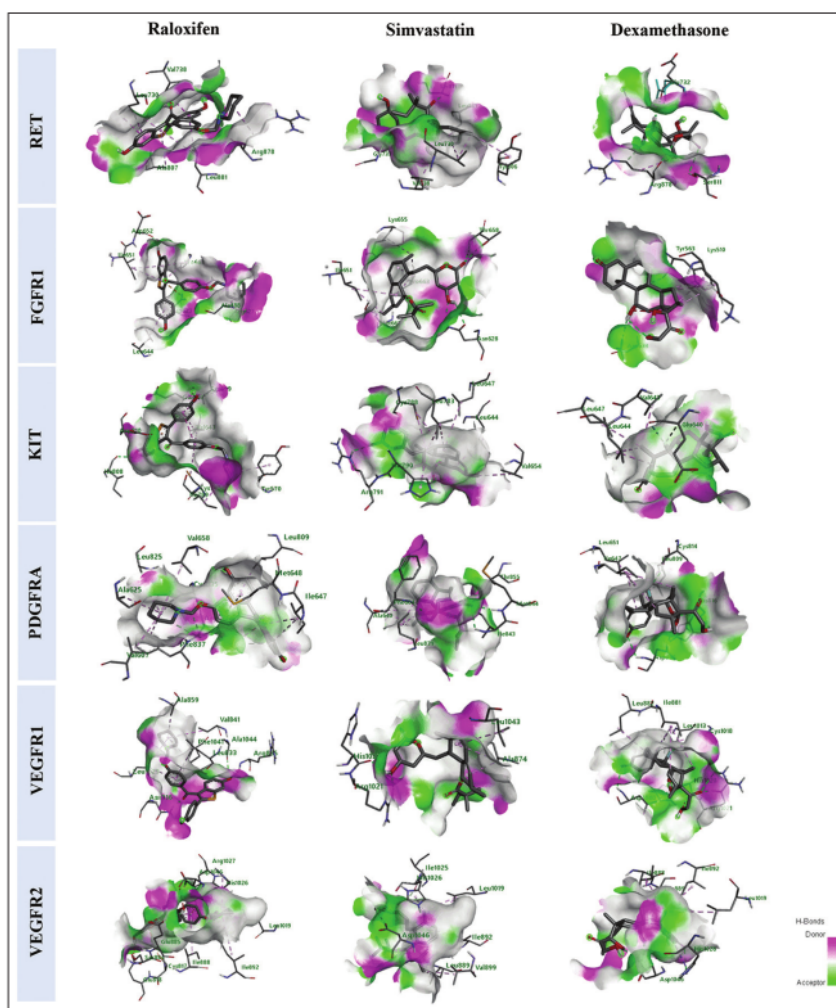
**Table 1: Grid box size and centers used**

Protein	Size of grid box (Å)	Centers points (x, y, z)
RET	40×40×40	6.373, 3.561, -4.802
FGFR1	41×40×40	85.867, 0.933, 10.281
KIT	42×40×40	35.511, 10.553, 46.488
PDGFRA	43×40×40	-38.413, 157.049, 0.794
VEGFR1	44×40×40	3.911, 17.995, 32.857
VEGFR2	45×40×40	-24.303, -0.681, -8.955

FGFR1: Fibroblast growth factor receptor 1



**Figure 1:** Cartoon representation of target proteins with their binding sites from DoGSiteScorer



**Figure 2:** Interaction of raloxifene, simvastatin, and dexamethasone with target proteins



**Table 2: Binding affinity (kcal mol<sup>-1</sup>) of osteogenic compounds with the target proteins**

Ligand	Receptor					
	RET	FGFR1	KIT	PDGFRA	VEGFR1	VEGFR2
Raloxifene	-10.0	-7.9	-9.4	-8.4	-9.3	-9.0
Simvastatin	-9.2	-7.8	-8.3	-7.2	-9.1	-8.3
Dexamethasone	-6.9	-7.2	-8.0	-8.3	-9.1	-8.4
Risedronate	-6.6	-5.8	-5.9	-5.5	-6.0	-6.3
Ibandronate	-6.1	-6.0	-5.5	-4.9	-5.9	-5.8
Zoledronic acid	-5.6	-5.2	-5.4	-4.8	-5.7	-5.8
Ascorbic acid	-5.3	-5.4	-5.0	-5.6	-5.3	-5.4
Alendronate	-5.1	-4.6	-4.8	-4.3	-5.0	-5.5
B-glycerophosphate	-4.4	-4.5	-4.3	-4.7	-4.9	-4.7

FGFR1: Fibroblast growth factor receptor 1

**Table 3: Interaction types between raloxifene, simvastatin, and dexamethasone with the amino acids at the binding site of target proteins**

Receptor	Ligand	Interaction Type				
		Hydrogen	Electrostatic	Hydrophobic	Halogen	Unfavorable
RET	Raloxifene	-	-	LEU730, VAL738, ALA807, ARG878, LEU881	-	-
	Simvastatin	GLY733, SER811	-	LEU730, VAL738, TYR806, LEU881	-	-
	Dexamethasone	GLU732, SER811, ARG878	-	ARG878	-	-
FGFR1	Raloxifene	ASP652	ASP623	ALA488, ARG627, LEU644, ILE651, PRO663	-	-
	Simvastatin	ASN628, THR658	-	ILE651, LYS655, PRO663, MET667	-	-
	Dexamethasone	ASP634	-	LYS510, TYR563	TYR563	-
KIT	Raloxifene	GLU640, SER639, ILE808	ASP810	TYR570, SER639, VAL643, CYS788, ILE789	-	-
	Simvastatin	ARG791	-	LEU644, LEU647, VAL654, LEU783, CYS788, HIS790	-	-
	Dexamethasone	GLU640	-	VAL643, LEU644, LEU647	-	-
PDGFRA	Raloxifene	ASP837	ASP838	VAL607, ALA625, ILE647, MET648, VAL658, LEU809, LEU825, CYS835, PHE837	-	-
	Simvastatin	PHE604, ILE843, MET844, THR855	-	ALA640, LEU839	-	-
	Dexamethasone	CYS814, HIS816, ASP836	-	ILE647, LEU651, LEU809	-	-
VEGFR1	Raloxifene	ARG835, ASN916, ALA1044	-	LEU833, VAL841, ALA859, LEU1029, PHE1041	-	-
	Simvastatin	HIS1020, ARG1021	-	ALA874, LEU1043	-	-
	Dexamethasone	CYS1018, HIS1020, ARG1021, ASP1040	-	ILE881, LEU882, LEU1013, CYS1018	-	HIS1020
VEGFR2	Raloxifene	GLU818, GLU885	CYS817, GLU885, ARG1027, ASP1046	ILE888, ILE892, LEU1019, HIS1026	-	SER884, ASP1046
	Simvastatin	ILE1026, ASP1046	-	LEU889, ILE892, VAL899, LEU1019, HIS1026	-	-
	Dexamethasone	HIS1026, ASP1046	-	ILE888, LEU889, ILE892, LEU1019, HIS1026	-	-

FGFR1: Fibroblast growth factor receptor 1

dexamethasone. These compounds had the lowest binding affinity to the key proteins of osteosarcoma. Raloxifene is an approved nonsteroidal selective estrogen receptor modulator to treat postmenopausal osteoporosis.<sup>[20]</sup> In our present study, raloxifene showed

the lowest binding affinity to all osteosarcoma target proteins. Low binding affinity represents the stable interaction of a compound at the binding sites that may indicate inhibitory activity.<sup>[17]</sup> Previously, a study reported that raloxifene inhibited osteoclasts' activity

when cocultured with an osteosarcoma cell line.<sup>[21]</sup> However, there was no report regarding the anticancer activity of raloxifene to osteosarcoma. Due to this, further study is needed to prove the anticancer activity of raloxifene in bone cells or tissue.

Furthermore, our current study found that simvastatin is a compound that potentially serves as a multitarget inhibitor of osteosarcoma. Simvastatin is a fungal metabolite-derived lipophilic statin.<sup>[22]</sup> A previous study reported that simvastatin dose-dependently inhibited the growth of human osteosarcoma SaOS-2 and U2OS.<sup>[23,24]</sup> Simvastatin-induced cell apoptosis, increased Bax/Bcl-2 ratio, cleaved caspase-3, PARP protein, and altered cell cycle-regulating genes.<sup>[25]</sup> Other *in vitro* studies gave similar conclusions.<sup>[25]</sup> Moreover, *in vivo* study reported that simvastatin reduced tumor growth and bone metastasis in lung cancer through the Mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) signaling pathway.<sup>[24]</sup> This study provides additional information regarding the possibility of simvastatin as a multitarget inhibitor in osteosarcoma. However, further study is required to confirm our findings.

Another compound that potentially acts as a multitarget inhibitor of osteosarcoma is dexamethasone. Dexamethasone is a synthetic glucocorticoid with anti-inflammatory and immunosuppressant properties.<sup>[26,27]</sup> As one of the most widely used corticosteroids, dexamethasone has been used as adjuvant therapy for painful bone metastases.<sup>[28]</sup> In bone cancer, dexamethasone was previously reported to have a dose-dependent inhibitory activity indicated by interacting with glucocorticoid receptors.<sup>[28]</sup> Our study reveals stable interaction between dexamethasone and other membrane proteins. This suggests that dexamethasone might have multitarget inhibitory activity on osteosarcoma. However, further study is warranted to confirm our findings.

## CONCLUSION

*In silico* molecular docking study in searching multitarget inhibitors for osteosarcoma was conducted. From nine osteogenic compounds, raloxifene, simvastatin, and dexamethasone were three promising compounds as multitarget inhibitors for osteosarcoma based on their binding affinity and molecular interaction with the proteins targets. Raloxifene had binding affinities of -10.0, -7.9, -9.4, -8.4, -9.3, and -9.0 kcal mol<sup>-1</sup> to RET, FGFR1, KIT, PDGFRA, VEGFR1, and VEGFR2, respectively. Simvastatin had binding affinities of -9.2, -7.8, -8.3, -7.2, -9.1, and -8.3 kcal mol<sup>-1</sup>, respectively, to the same proteins. Moreover, dexamethasone had binding affinities of -6.9, -7.2, -8.0, -8.3, -9.1, and -8.4 kcal mol<sup>-1</sup> to the same proteins, respectively. Most interaction types that formed were hydrophobic and hydrogen bonds. Based on our study,

raloxifene, simvastatin, and dexamethasone potentially act as multitarget inhibitors for osteosarcoma.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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