

Caulerpenyne Compounds from Macroalgae *Caulerpa sertularioides* against MDM2-p53 Protein as an Anticancer Target

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Abstract

Cancer remains a major global health burden, and limitations of current anticancer therapies highlight the need for safer and more effective alternatives. The mousedouble minute 2 (MDM2) and tumor protein p53 interaction plays a crucial role in tumor progression by negatively regulating p53 tumor suppressor activity, making it an attractive molecular target for anticancer drug development. Marine macroalgae are recognized as promising sources of bioactive secondary metabolites with potential anticancer properties. This study aimed to investigate the potential of caulerpenyne, a sesquiterpenoid compound derived from the macroalgae *Caulerpa sertularioides*, as an inhibitor of the MDM2-p53 protein complex using an in silico molecular docking approach. Molecular docking was performed using AutoDock Vina, with validation conducted through redocking of the native ligand, yielding an RMSD (Root Mean Square Deviation) value of 0.69 Å, indicating a reliable docking protocol. Drug-likeness and pharmacokinetic properties were evaluated using SwissADME, showing that caulerpenyne fulfills Lipinski's rule of five with favorable ADME (absorption, distribution, metabolism, and excretion) characteristics. Docking results demonstrated that caulerpenyne binds to the MDM2-p53 receptor with a binding free energy of -6.2 kcal/mol and an inhibition constant of 28.5 μ M. Interaction analysis revealed hydrogen bonding, hydrophobic, and π -interactions with key amino acid residues involved in p53 binding, including histidine 75 (HIS75) and tyrosine 79 (TYR79). Although its binding affinity is lower than that of established synthetic inhibitors, caulerpenyne exhibits a comparable interaction pattern with critical residues of the MDM2 binding pocket. These findings suggest that caulerpenyne has potential as a natural lead compound targeting the MDM2-p53 pathway. Further experimental validation through in vitro and in vivo studies is required to confirm its biological efficacy and therapeutic potential.

Keywords: Caulerpenyne; *Caulerpa sertularioides*; MDM2-p53; molecular docking; anticancer

Introduction

Cancer is a leading cause of death worldwide (WHO, 2025), in Indonesia, cancer is the third leading, with more than 408.661 new cases and nearly 242.099 deaths in 2022, with the highest number of deaths due to breast, cervical, lung, and colorectal cancer (Kemenkes, 2024). Treating cancer has been a highly complex process. Conventional treatment approaches, such as surgery, chemotherapy, targeted therapy and radiotherapy, have been used (Debela et al., 2021; Zafar et al., 2025). However, these generate considerable side effects that decrease the patient's quality of life, and despite improvements in diagnosis and treatments in recent years (Agena et al., 2023).

P53, known as the genome's guardian and a tumor suppressor protein (TP53), act as

transcription factor for various cellular proteins such as MDM2 (mousedouble minute 2 protein), p21, Fas, Bax, p48, PTEN, B99, PAI that related to apoptosis, cell-cycle arrest, senescence, glycoysis, TCA cycle, differentiation, cell fate, and suppression of cancer cells progression. Recently, role of MDM2-p53 in cellular immunity have been reported. It is evident that a highly activated from of the p53 protein leads to suppression of inflammation. MDM2-p53 is able to affect processes such as DNA synthesis and repair by interaction with DNA polymerase, DHFR ((dihydrofolate reductase), centrosome amplification, and the MRN DNA complex containing Mre11, Rad50 and Nbs1 (Brummer & Zeiser, 2024; Jahoor Alam, 2021; Shoaib et al., 2023a; Subhasree et al., 2013).

Marine organisms, mainly macroalgae, are sources of natural compounds with multiple

biological activities, which can decrease the risk of many diseases (Agena et al., 2023; Effendi et al., 2024). The macroalgae *Caulerpa sertularioides* produce a variety of secondary metabolites such as caulerpenyne. Caulerpenyne is a sesquiterpenoid-structured secondary metabolite which has some bioactivities such as antiproliferative, apoptotic activities, inhibitors of lipoxygenase, and 5-lipoxygenase, etc. Secondary metabolites of this are responsible for complex modulation network induced in AMPK (adenosine 5'-monophosphate-activated protein kinase), ER (endoplasmic reticulum) stress, mitochondrial stress, PTP1B (Protein tyrosine phosphatase 1B) inhibition and cell cycle stop pathways, metabolic reprogramming in cancer cells, apoptosis and cell cycle arrest in cancer metabolism (Agena et al., 2023; Mert-Ozupek et al., 2022). Studies on caulerpenyne are still limited to general anticancer activity, and the specific mechanism against p53 hasn't been widely explored. Therefore molecular studies are needed to predict the interaction to elucidate the potential caulerpenyne from *C. sertularioides* as an anticancer candidate by targeting the p53 protein. Furthermore, this also provides a scientific basis for the development of natural-based therapies from tropical macroalgae.

Materials and Methods

Hardware and software. This research was conducted using a computer with windows 11 64-bit specifications, an Intel® Core™ i5-1334U (1.30 GHz), 16 GB of RAM, and a 128 MB Intel(R) UHD Graphics. These software used was AutoDock Vina (<https://vina.scripps.edu>), Biovia Discovery Studio (<https://discover.3ds.com>), PyRx (<https://pyrx.sourceforge.io>), and Notepad++ (<https://notepad-plus-plus.org>).

Ligan preparation. The secondary metabolites selected from the literature, the ligand used are caulerpenyne (Mert-Ozupek et al., 2022). All ligan analyzed with Lipinski by assessing the chemical properties of ligands such as H donor, H acceptor, and log P. The 3D structures of ligands were obtained by downloading Structure Data File (SDF) from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>).

Protein preparation. The protein used in the molecular modeling studies selected from literature (Kurmi et al., 2025; Shoaib et al., 2023) and were retrieved from RCSB PDB (Research Collaboratory for Structural Bioinformatics Protein Data Bank) (<https://www.rcsb.org/>). The crystal structure of receptors against MDM2-p53 (PDBID: 5ZXF; resolution: 1.25 Å). The crystal structures were rebuilt and both water and small molecules were removed. To perform energy minimization and geometry optimization, polar hydrogen were added, and non-polar hydrogens were merged into the molecules by using AutoDock Tools-1.5.7. before the docking studies, Kollman charges were added, and the related receptors were saved in the PDBQT format.

In silico analysis of pharmacokinetic ADME and drug-likeness. The drug-likeness of the compounds was calculated using SwissADME (<https://swissadme.ch>). The molecular structure of compounds were converted into SMILES format.

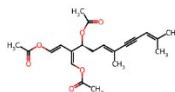
Molecular docking studies. To examine the selected ligands on related receptors, molecular docking experiments were carried out with AutoDock Vina. After the minimization process, the grid box resolution was set at 8.584, -19.462, and -5.682 along the x, y, and z points, respectively. The grid dimensions were adjusted to 40×40×40 for molecular studies.

Results and Discussion

Drug-likeness analysis and ADME properties

The analysis results are shown in Table 1. All test compounds met the criteria of Lipinski's rule, namely, Log P should be less than five, polar surface area, the number of hydrogen bond donors should be less than five, hydrogen acceptors should be less than ten and the molecular weight should be less than 500 with no more than one violation. The property refers to the similarity of compound to the properties of an oral drug (Bang et al., 2025). Thus, properties such as adsorption, distribution, and permeability of all test compound are similar to those of an oral drug.

Table 1. Pharmacokinetic properties of compounds caulerpenyne

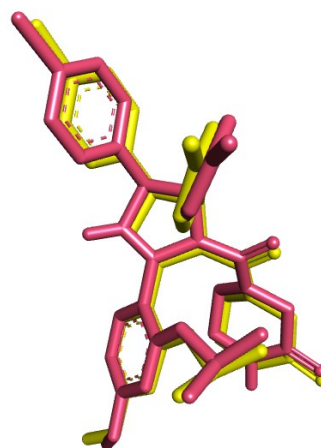
Compound	Molecular weight (g/mol)	Number heavy atoms	Number aromatic heavy atoms	Number rotatable bonds	Number of H-bond acceptor	Number of H-bonds donors	Molar refractivity	TPSA (Å)	Log P _{o/w}	Lipinski/violation
	374.43	27	0	10	6	0	103.18	78.90	3.83	Yes/0

Validation and molecular docking

The validation process is carried out by redocking the native ligands against the target protein, the MDM2-p53. The method is considered valid if RMSD value from the re-docking results is $< 2 \text{ \AA}$ (BenchChem, 2025). The RMSD value obtained from the re-docking was $0.69 \text{ \AA}$. This indicates that the molecular docking method is valid. Regarding the conformation, the structure result from the re-docking of the native ligand can be seen in Figure 1.

The docking process for the ligand molecular test was carried out following validated parameters from re-docking of native ligands. To obtain the best ligand, the screening results obtained from the molecular docking, as described further, were continued by assessing the binding free energy of each ligand. A test ligand with a lower binding free energy than native ligand indicates a higher affinity for the receptor compared to the native ligand (Alibay et al., 2022). Furthermore, analysis was also performed by observing the

molecular interactions between the test ligand and amino acid residues on the receptor. The results of the molecular docking is shown in Table 2.

**Figure 1.** Visualization of the validation results of the molecular docking method; re-docking of the native ligand MDM2 (note: yellow is the initial native ligand, pink is the re docked native ligand)**Table 2.** Molecular docking results of secondary metabolites of the *C. Sertulariodes* to the MDM2-p53 receptor

Ligand	Bond free energy (kcal/mol)	Inhibition constant (μM)	Number of amino acid residues
Caulerpenyne	-6.2	28.5	8

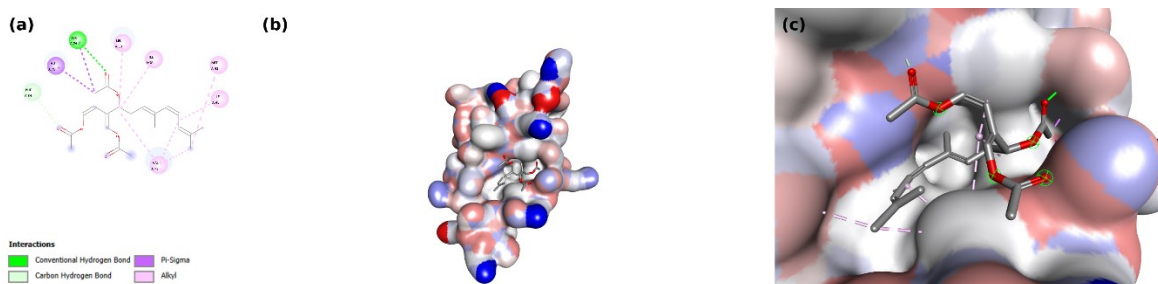
**Figure 2.** Molecular interactions between caulerpenyne and the MDM2 receptor in 2D (a) and 3D (b,c). (Note: green for hydrogen bonds, pale green for van der Waals bonds, and pink for alkyl bonds)

Table 2 shows that caulerpenyne has a binding energy of -6.2 kcal/mol against the MDM2-p53 receptor with inhibition constant of $28.5 \mu\text{M}$. This value indicates a fairly stable and spontaneous interaction, although its

affinity is still lower than synthetic inhibitors such as nutlin-3 which are reported to have stronger binding energies and inhibition constants in the nanomolar range (Azme et al., 2025; Koo et al., 2022; Yang et al., 2024).

Nevertheless, these results remain relevant because they indicate the initial potential of secondary metabolites from *C. sertularioides* disruptors of the MDM2-p53 interaction (Shoaib et al., 2023).

Interaction visualization shows that caulerpenyne bind to eight amino acid residues in the MDM2 binding pocket (Figure 2). Conventional hydrogen bonds with TYR A:79, pi-sigma interactions with HIS A:75, and hydrophobic bonds with residues LEU A:33, ILE A:78, VAL A:72 ILE A:40, and MET A:41, indicate that caulerprnyne is capable of forming a fairly extensive interaction network. In addition, carbon-carbon hydrogen bonds with PHE A:34 strengthen the stability of the complex. This interaction pattern is in line with previous reports that emphasize the importance of a combination of hydrogen and hydrophobic bonds in maintaining the stability of the MDM2-ligan complex (Azme et al., 2025; Yang et al., 2024).

Compared with previous studies, synthetic inhibitors such as nutlin-3 and idasanutlin were found to interact with key MDM2 residues, including HIS A:75 and TYR A:79, which are also found in caulerpenyne interactions. This suggests that, despite caulerpenyne's lower affinity, it still targets critical residues involved in p53 binding. Thus, caulerpenyne can be viewed as a natural molecule that partially mimics the binding mechanism of synthetic inhibitors, although structural optimization is still required to improve its affinity and specificity (Azme et al., 2025; Oraibi et al., 2025; Shoaib et al., 2023).

Overall, these results confirm that caulerpenyne has potential as a natural candidate molecule in the development of p53 pathway-based reactivation therapies. These findings are consistent with the research trend exploring marine metabolites as a source of bioactive compounds with anticancer activity (Liu et al., 2025; Wen et al., 2025). However, further validation through *in vitro* and *in vivo* assays is needed to confirm the biological activity, toxicity, and bioavailability of caulerpenyne before it can be considered as a clinical candidate (Khan et al., 2020; Tsukamoto, 2025).

Conclusions

This study demonstrates that caulerpenyne, a secondary metabolite derived from the marine macroalgae *C. sertularioides*, exhibits promising interactions with the MDM2-p53 protein complex based on validated *in silico* molecular docking analysis. Caulerpenyne fulfilled Lipinski's rule of five and showed favorable ADME properties, indicating its potential as an orally active compound. Molecular docking results revealed a stable and spontaneous interaction with the MDM2 binding pocket, involving key amino acid residues critical for p53 regulation, such as HIS75 and TYR79, through hydrogen bonding and hydrophobic interactions. Although its binding affinity is lower than that of established synthetic inhibitors, the interaction pattern suggests that caulerpenyne can partially mimic the binding mechanism of known MDM2 inhibitors. Therefore, caulerpenyne represents a promising natural lead compound for targeting the MDM2-p53 pathway in anticancer therapy, warranting further investigation through *in vitro* and *in vivo* studies to confirm its biological activity, safety, and therapeutic potential.

Conflict of Interest

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.

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Ethical approval

None.

Author contribution

BAS designed the concept, performed the research, analyzed the data, and checked the final manuscript.

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