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Molecular docking studies of new thiazolidin-4-one derivatives as combretastatin A4 analogues

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ABSTRACT

In the present study, a series of thiazolidin-4-one derivatives were designed as analogues of combretastatin A4 (CA4); a known anti-tubulin agent. The molecular structures incorporate either a 3,4,5-trisubstituted phenyl ring or a 3-alkoxy-4-methoxyphenyl ring, with the two aromatic systems connected *via* an amide linkage and a thiazolidin-4-one scaffold. Structural variation was introduced through different substituents (R groups) on the 4-methoxyphenyl ring. All compounds, along with CA4 as the reference molecule, were subjected to molecular docking studies targeting the tubulin β-2B chain (Protein Data Bank code: 8QEA). The docking results revealed that the newly synthesized molecules exhibit binding affinities and inhibition constant (K_i) values comparable to those of CA4. These findings suggest that the designed thiazolidin-4-one derivatives warrant further experimental investigation for their potential as anti-tubulin (i.e., anti-cancer) agents.

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1. Introduction

Chemotherapeutic agents remain among the most effective strategies for cancer treatment. Several anti-cancer compounds exert their effects through distinct mechanisms, including interaction with structural proteins such as tubulin; a key component in the mitotic process. Tubulin polymerizes to form microtubules, which are essential for cell division[1,2]. Accordingly, the inhibition of tubulin polymerization by specific molecules can induce apoptosis and arrest the cell cycle

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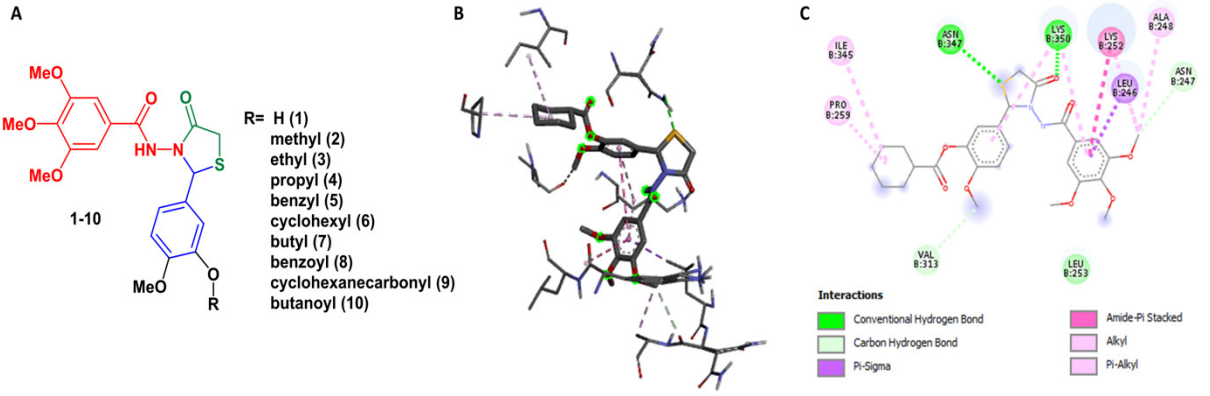

Figure 1. *(A): General structure of the designed compounds 1–10. (B): The best pose of compound 9 at the combretastatin A4 binding site, in 3D. (C): The best pose of compound 9 at the combretastatin A4 binding site, in 2D.*

at the G2/M phase, thereby suppressing cancer cell proliferation[3,4].

Taxol and Vinca alkaloids are well-known inhibitors of tubulin polymerization; however, their clinical utility is limited by adverse effects and the emergence of drug resistance[5]. Combretastatin A4 (CA4), a natural compound, is recognized as a potent tubulin inhibitor. Its structure comprises a 3,4,5-trimethoxyphenyl ring and a 3-hydroxy-4-methoxyphenyl ring connected *via* a cis-configured double bond (C=C), which facilitates an interaction with the β-tubulin subunit at the colchicine-binding site, thereby inhibiting tubulin polymerization[6]. This mechanism not only disrupts microtubule formation, but also selectively inhibits angiogenesis by obstructing tumor-associated blood supply.

Moreover, CA4 and its analogues exhibit promising activity against multidrug-resistant cancer phenotypes. Nonetheless, the compound's therapeutic potential is hindered by the isomerization of its active *cis*-isomer to the biologically inactive *trans*-isomer[7]. Consequently, there is growing interest in the development of structurally related molecules that retain the pharmacophoric features of CA4 while offering enhanced stability, potency, and selectivity.

Molecular docking is a widely employed computational technique for evaluating the interaction of designed compounds with biological targets. In the present study, we report a series of 1,3-thiazolidin-4-one derivatives as structural analogues of CA4, and investigate their binding interactions with the CA4 site on the tubulin β-2B chain using molecular docking simulations.

2. Methodology

The three-dimensional structure of the tubulin β-2B chain (PDB code: 8QEA) was retrieved from the Protein Data Bank in PDB format. Ligands, water molecules, and chains A and C were removed by using the BIOVIA Discovery Studio Visualizer. Polar hydrogen atoms and Kollman charges were added by using AutoDock Tools. Docking parameters were set as follows: exhaustiveness: 50; grid box center coordinates (x, y, z): 11.39, -16.58, and 17.42; grid box dimensions (x, y, z): 16.22, 18.72, and 18.18, respectively.

Density Functional Theory (DFT) calculations were performed by using the ORCA 5.0.3 software package[8]. Ligands were fully optimized by using the BP86 functional in conjunction with the def2-TZVP basis set for all atoms, and the auxiliary basis set of Weigend (def2/J)[9,10].

3. Results and Discussion

A series of thiazolidin-4-one derivatives were de-

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signed as structural mimics of CA4. Each molecule features either a 3,4,5-trimethoxyphenyl or a 3-alkoxy-4-methoxyphenyl ring, connected *via* an amide group and a 1,3-thiazolidin-4-one scaffold.

Molecular docking simulations were conducted for ligands 1–10 against the CA4 (*cis*) binding site of the tubulin β-2B chain (PDB code: 8QEA). The calculated binding affinities (in kcal/mol) for the ligands 1–10 were -7.3, -7.2, -7.2, -7.3, -7.6, -7.7, -7.1, -7.9, -8.2, and -7.6, respectively. For CA4, the binding affinity was -7.4 kcal/mol. These results indicate that all designed compounds exhibit favourable binding interactions comparable to CA4.

Ligand 9 demonstrated the most favourable binding pose, with a binding affinity of -8.2 kcal/mol (Figure 1). Its interaction with the target protein (8QEA) involved two hydrogen bonds: ASN_{374} with the sulfur atom (2.69 Å) and LYS_{350} with the oxygen atom (2.49 Å). Additionally, two carbon–hydrogen interactions were observed: ASN_{274} with the methoxy group's carbon atom (3.77 Å) and VAL_{313} with another methoxy carbon (3.55 Å).

The inhibition constant (K_i) values were calculated using the equation $K_i=exp(\Delta G/RT)$, yielding the following results (in μM) for ligands 1–10: 4.457, 5.276, 5.276, 4.457, 2.686, 2.269, 6.247, 1.619, 0.976, and 2.686, respectively. Ligand 9 exhibited the lowest K_i value, thereby indicating the highest predicted efficacy.

4. Conclusion

A series of 1,3-thiazolidin-4-one derivatives were developed as structural analogues of CA4 and were evaluated through molecular docking against the CA4 (*cis*) binding site of the tubulin β-2B chain (PDB code: 8QEA). All compounds demonstrated favourable binding affinities and inhibition constants, with ligand 9 (featuring a cyclohexanecarbonyl substituent) exhibiting the most potent interaction profile. These findings support the potential of these compounds for further experimental validation as anti-cancer agents.

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Conflicts of interest

None exist.

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References

1. Anand U., Dey A., Chandel A.K.S., Sanyal R., Mishra A., Pandey D.K., *et al.* Cancer chemotherapy and beyond: current status, drug candidates, associated risks and progress in targeted therapeutics. *Genes Dis.* 10(4), 1367–1401, 2022. DOI: 10.1016/j.gendis.2022.02.007
2. Khwaja S., Kumar K., Das R., Negi A.S. Microtubule associated proteins as targets for anticancer drug development. *Bioorg. Chem.* 116, 105320, 2021. DOI: 10.1016/j.bioorg.2021.105320
3. Naumova N., Šachl R. Regulation of cell death by mitochondrial transport systems of calcium and Bcl-2 proteins. *Membranes (Basel)* 10(10), 299, 2020. DOI: 10.3390/membranes10100299
4. Thomas E., Gopalakrishnan V., Hegde M., Kumar S., Karki S.S., Raghavan S.C., *et al.* A novel resveratrol based tubulin inhibitor induces mitotic arrest and activates apoptosis in cancer cells. *Sci. Rep.* 6, 34653, 2016. DOI: 10.1038/srep34653
5. Gaspari R., Prota A.E., Bargsten K., Cavalli A., Steinmetz M.O. Structural basis of *cis*- and *trans*-combretastatin binding to tubulin. *Chem* 2(1), 102–113, 2017. DOI: 10.1016/j.chempr.2016.12.005

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6. Singh S.B. Discovery, synthesis, activities, structure-activity relationships, and clinical development of combretastatins and analogs as anticancer drugs. A comprehensive review. *Nat. Prod. Rep.* 41(2), 298–322, 2024. DOI: 10.1039/d3np00053b
7. Abdul Hussein S.A., Razzak Mahmood A.A., Tahtamouni L.H., Balakit A.A., Yaseen Y.S., Al-Hasani R.A. New combretastatin analogs as anticancer agents: design, synthesis, microtubules polymerization inhibition, and molecular docking studies. *Chem. Biodivers.* 20(4), e202201206, 2023. DOI: 10.1002/cbdv.202201206
8. Neese F. Software update: the ORCA program system – version 5.0. *WIREs Comput. Mol. Sci.* 12(5), e1606, 2022. DOI: 10.1002/wcms.1606
9. Becke A.D. A new mixing of Hartree–Fock and local density-functional theories. *J. Chem. Phys.* 98(2), 1372–1377, 1993. DOI: 10.1063/1.464304
10. Weigend F., Ahlrichs R. Balanced basis sets of split valence, triple zeta valence and quadruple zeta valence quality for H to Rn: design and assessment of accuracy. *Phys. Chem. Chem. Phys.* 7(18), 3297–3305, 2005. DOI: 10.1039/b508541a

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