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Synthesis and Evaluation of Anti-Proliferative Potential of 2-((2-chloroquinolin-3-yl) methylene)-3,4-dihydronaphthalen-1(2*H*)-ones in Breast Cancer

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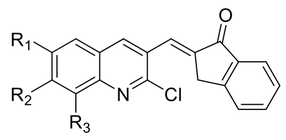
INTRODUCTION & AIM

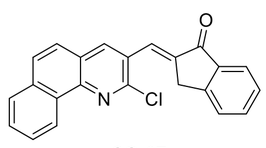
Microtubules of the mitotic spindle are critical for cell division and represent established targets for anticancer agents such as paclitaxel and vinblastine. However, resistance to these drugs poses a major clinical challenge, necessitating the discovery of novel tubulin-targeting compounds. In this study, a series of chloroquinoline derivatives was synthesized, characterized, and evaluated for antiproliferative activity against breast cancer cell lines MCF-7 and MDA-MB-231. The aim was to identify potent tubulin inhibitors by targeting the colchicine binding site, supported by molecular docking and dynamics simulations using the tubulin crystal structure (PDB ID: 1SA0), to guide future anticancer drug development.

METHOD

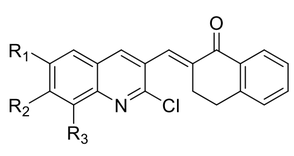
The proposed ligands (CQ-01 to CQ-18) were tested against MCF-7 and MDAMB-231 cancer cell lines using MTT Assays, and Dose-Response curves were analyzes using Graphpad Prism-10 Software. Docking studies with b-tubulin (PDB: 1SA0) were performed using AutoDockGPU after structural minimization via Avogadro. Molecular dynamics simulations were executed with GROMACS, and results were analyzed using PyMOL and LigPlot software.



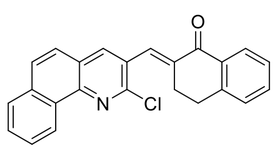
CQ-01 - CQ-06 , CQ-08



CQ-07



CQ-09 - CQ-15 , CQ-17



CQ-16

Table 1: Substitutions at R_1 and R_2 sites of the ligands.

Ligand	R_1	R_2	R_3
CQ-01 / CQ-09	H	H	H
CQ-02 / CQ-10	CH_3	H	H
CQ-03 / CQ-11	CH_3	CH_3	H
CQ-04 / CQ-12	CH_3O	H	H
CQ-05 / CQ-13	H	CH_3O	H
CQ-06 / CQ-15	H	Cl	H
CQ-14	H	H	CH_3O
CQ-08 / CQ-17	Br	H	H

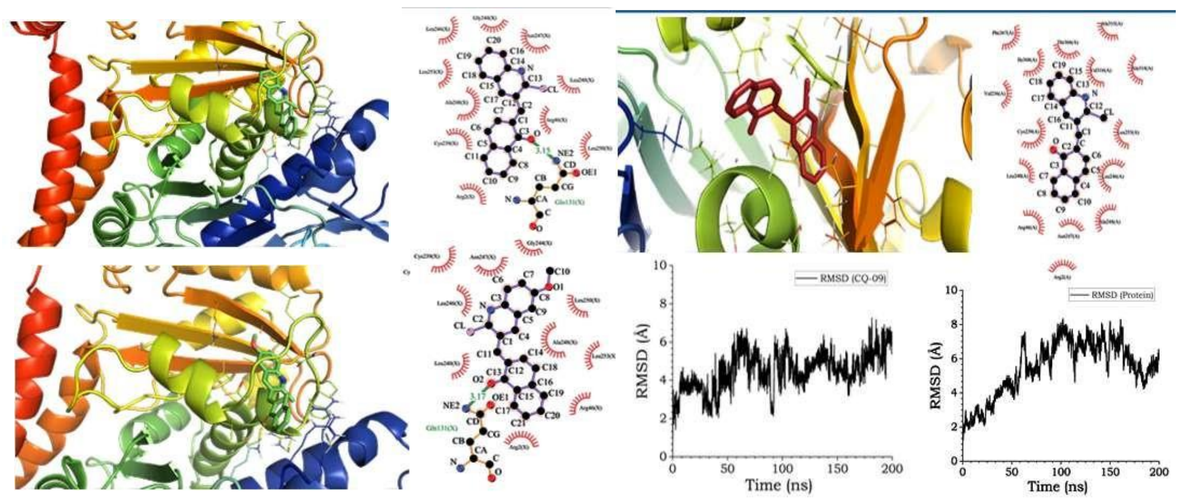
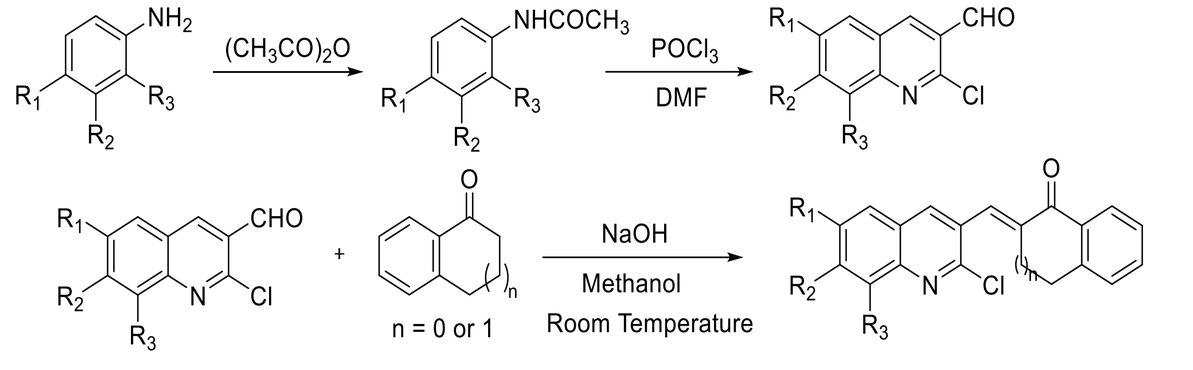


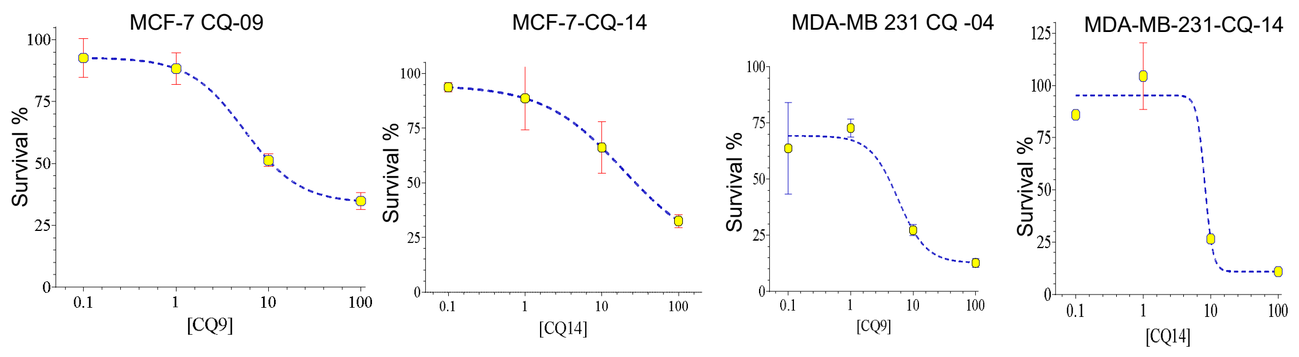
Fig. 1. Docking representation of CQ-09 and CQ-14 with the β-chain of tubulin. (A) CQ-09 in the tubulin binding cavity. (B) Active site residues showing one H-bond between NE2 of Gln131 and the O atom of CQ-09. (C) Binding pose of CQ-14 in the β-chain. Docking was performed using AutoDockGPU with 1000 GA runs.

Ligand	Binding Energy (kcal/mol)	Ligand	Binding Energy (kcal/mol)	Ligand	Binding Energy (kcal/mol)
CQ-01	-8.76	CQ-07	-9.69	CQ-13	-9.68
CQ-02	-8.75	CQ-08	-9.02	CQ-14	-9.62
CQ-03	-9.11	CQ-09	-9.11	CQ-15	-9.53
CQ-04	-9.04	CQ-10	-9.34	CQ-16	-9.78
CQ-05	-9.02	CQ-11	-9.67	CQ-17	-9.49
CQ-06	-9.15	CQ-12	-9.50		

RESULTS & DISCUSSION



Scheme 1: A general representation of the synthetic scheme of 2-((2-hloroquinolin-3-yl)Methylene)-3,4-dihydronaphthalen-1(2*H*)-one derivatives.



A graphical representation of the Dose-Response Curve of CQ-09 and CQ-14 with MCF-7 and MDAMB-231 cancer cell lines. MTT assay performed at four concentrations (0.1, 1, 10, and 100 mM) for the screening of molecules The absorbance was taken using Cytation-7 instrument and the curve analysis was done with Graph Pad Prism-10 software.

Compound Code	IC_{50} (µM)	Compound Code	IC_{50} (µM)	Compound Code	IC_{50} (µM)
CQ-01	> 100	CQ-07	> 100	CQ-13	78.64
CQ-02	> 100	CQ-08	> 100	CQ-14	19.04
CQ-03	> 100	CQ-09	13.05	CQ-15	39.91
CQ-04	> 100	CQ-10	> 100	CQ-16	84.97
CQ-05	> 100	CQ-11	> 100	CQ-17	13.75
CQ-06	98.19	CQ-12	96.65		

The IC_{50} values of ligands CQ-01 to CQ-17 were determined from cell survival percentage versus the logarithm of ligand concentration using the MTT assay. As shown in Table 3 and Table 4, CQ-09 and CQ-14 exhibited the lowest IC_{50} values against MCF-7 and MDA-MB-231 cell lines, respectively, indicating higher cytotoxic potency.

CONCLUSION

The synthesized chloroquinoline derivatives exhibited significant antiproliferative activity against breast cancer cells, with CQ-9 and CQ-14 showing the most potent effects. Molecular docking and dynamics studies confirmed strong interactions with the colchicine binding site of tubulin, supporting their mechanism as microtubule inhibitors. These findings highlight the potential of chloroquinoline derivatives as promising anticancer agents targeting tubulin.

FUTURE WORK / REFERENCES

Structural modifications guided by computational modeling may yield next-generation tubulin inhibitors capable of overcoming drug resistance in cancer therapy.