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Synthesis, Biological Evaluation, and Molecular Docking of Novel Pyrazole-Nitrone Derivatives as EGFR-targeted Anticancer Agents

Mousa NAJ[1ID], Salman HH[1ID], Alsaad HN[1ID]

[1]*Department of Pharmaceutical Chemistry, College of Pharmacy, University of Basrah, Iraq*

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Abstract
Objective: This study aimed to design, synthesise, and characterise some novel pyrazole-nitrone derivatives and evaluate their potential as anticancer agents targeting EGFR-expressing lung cancer cells. Biological evaluation included cytotoxicity assessment against A549 (lung cancer) and HdFn (normal fibroblast) cell lines, alongside in-silico docking and ADME profiling to predict drug-likeness and pharmacokinetic behaviour. We hypothesised that the presence of electron-donating groups (EDGs) at the para position of the aryl ring would enhance the cytotoxicity and selectivity of the nitrone derivatives by improving their interaction with EGFR and reducing off-target toxicity.
Methods: The synthesis started with the Vilsmeier-Haack reaction to prepare 4-formyl-3-(3-nitrophenyl)-1-phenyl-1H-pyrazole. N-substituted phenylhydroxylamines were obtained by reducing nitrobenzene derp tolylivatives, followed by condensation with the aldehyde to afford nitrones. The synthesised compounds were evaluated for anticancer activity against A549 lung cancer cells and HdFn normal dermal fibroblast cells using the MTT assay. Additionally, molecular docking studies were performed to investigate interactions with the EGFR tyrosine kinase.
Results: The IC_{50} values indicated that compound 7a exhibited the most potent activity, with an IC_{50} of 85.62 µg/mL against A549 cells and a high selectivity index (SI) of 5.5. Pre-ADME in silico analyses showed favourable oral bioavailability and no predicted CNS side effects for all tested compounds.
Conclusion: Spectroscopic data from FT-IR, ^{1}H-NMR, and ^{13}C-NMR confirmed successful target compound syntheses. Biological evaluation revealed that compound 7a demonstrated promising anticancer activity with a favourable selectivity index (SI = 5.5) toward cancer cells over normal cells, indicating its potential as a promising EGFR-targeted therapeutic agent.

Keywords: Nitrone compounds, Pyrazole, A549 cell, Docking study, *pre*-ADME study

Plain English Summary

These compounds were designed in the lab and carefully analysed to confirm their structure using different techniques. Tested the effects of these compounds on human lung cancer cells (A549) and compared them to their effects on normal cells. One of the compounds, designated as 7a, exhibited potent anticancer activity and demonstrated a particular affinity for targeting cancer cells without harming healthy ones. In addition, computer simulations (called molecular docking) showed that these compounds could effectively bind to a key protein (EGFR) involved in cancer growth. The study also utilised specialised tools to predict how the compounds behave within the body, including their absorption rates, safety profiles, and potential for side effects. Overall, this research highlights compound 7a as a promising starting point for developing new cancer treatments with fewer side effects.

Correspondence:
Mousa, Noor AA
Department of Pharmaceutical Chemistry,
College of Pharmacy,
University of Basrah,
Iraq
pgs.nooralhuda.jaleel@uobasra.edu.iq