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FULL PAPER

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Microwave-assisted *N*-alkylation of amines with alcohols catalyzed by $MnCl_2$: Anticancer, docking, and DFT studies

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Abstract

A new protocol for the *N*-alkylation of amines with alcohols for the synthesis of tertiary amines in the presence of $MnCl_2$ as a catalyst, under microwave conditions, is described. The advantages of this protocol include stable reaction profiles, a wide substrate variety, excellent yields, low cost, high yields, and easy workup conditions. The anticancer efficacy of all the synthesized compounds was tested in vitro against various cancer cell lines, such as MCF-7, MDA-MB-231 (human breast), HT-29, HCT 116 (colon cancer), A549 (human lung carcinoma), and Vero cells. Among the screened compounds, **3e**, **3h**, and **3i** demonstrated potent anticancer activity, with compound **3h** surpassing the reference drug cisplatin against A549, MCF7, MDA-MB-231, and HCT116 cancer cells. The introduction of an electron-withdrawing group on the phenyl ring resulted in increased anticancer activity. The most potent compounds, **3e**, **3h**, and **3i**, were tested against VEGFR-2, HER2, and EGFR in multikinase inhibition assays, with compounds **3h** and **3i** showing improved potency against the HER2 kinase. The compounds formed two H-bonds with amino acids, indicating that they had a high affinity for the target HER2 kinase (PDB ID: 3RCD), according to the docking analysis. The absorption, distribution, metabolism, excretion, and toxicity properties of the optimized analogs were also assessed in vitro, enabling the discovery of promising anticancer agents. Finally, the B3LYP level was used to measure density functional theory geometry optimization and the related quantum parameters for the active compounds.

KEYWORDS
amines, anticancer, DFT, microwave, molecular docking, *N*-alkylation

1 | INTRODUCTION

Millions of people around the world are affected by cancer, a global health problem.[1] Cancer deaths are more frequent than cardiovascular disease deaths in many countries, according to the current perception and population-based Prospective Urban Rural Epidemiology research.[2] Cancer is the leading cause of death, according to the World Health Organization and the number of cancer cases will rise to 22 million by 2030.[3] The dramatic rise in the number of cancer cases around the world means that new drugs and prevention approaches are required. The quest for novel anticancer scaffolds, with the aim of finding novel antitumor agents with high efficacy and low toxicity, has an increasing interest in medicinal chemistry. Piperazines and pyrimidines are fortunate scaffolds that have gained a