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Next-gen thiazole-sulphonamide hybrids as anti-lung cancer agents deciphered through *in vitro*, DFT, and docking synergy

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ABSTRACT

In continuation of our previous work, novel sulphonamide–thiazole hybrids were synthesized and evaluated for anticancer activity against NCI–H226 lung carcinoma cells, with WI-38 fibroblasts as a normal control. Among the tested compounds, fluoro-substituted compound 14 exhibited the highest potency (IC_{50} = 16.10 μg/mL) and selectivity (SI = 183.79), while halogen- and nitro-substituted analogs (4–6) showed moderate activity. Quantum mechanical studies using DFT (B3LYP/6-311G(d,p), SMD solvent) rationalized the observed SAR, highlighting the role of electronic and steric effects in modulating activity. Molecular docking revealed stronger binding of compound 14 to EGFR (−8.2 kcal/mol) than TP53 (−7.1 kcal/mol), suggesting EGFR as its primary target, with TP53 interactions supporting apoptotic signalling. ADMET predictions indicated favourable drug-likeness, low toxicity, and non-mutagenicity. Molecular dynamics simulations over 100 ns confirmed that compound 14 forms highly stable complexes with both EGFR and TP53, preserving secondary structures, and consistent hydrogen-bonding and hydrophobic interactions, with MM-GBSA free energies of ~ –75 kcal mol^{-1}. Free energy landscape and principal component analyses demonstrated conformational adaptability and long-term stability. Collectively, these results identify compound 14 as a potent, selective, and energetically favourable dual-target anticancer agent, providing a strong mechanistic foundation for further preclinical development.

1. Introduction

Cancer continues to be one of the most formidable global health challenges, ranking as the second leading cause of death after cardiovascular diseases. Alarmingly, more than 70 % of cancer-related fatalities are reported from developing and underdeveloped regions, where access to timely diagnosis and treatment remains limited [1]. The global incidence of cancer is on a steady rise, with mortality figures projected to reach approximately 12 million by 2030 [2]. Despite a deep understanding of the biochemical mechanisms underlying carcinogenesis, effective cancer treatment is still a major challenge [3]. Current treatment options, such as chemotherapy, radiotherapy, and targeted therapy, are often associated with limited efficacy, drug resistance, and adverse effects. Hence, designing and developing new drugs for cancer therapeutics continues to be a fascinating task for the people working in drug discovery [4,5]. Lung cancer is among the most common forms of malignant cancers and stands as the leading cause of cancer-related mortality worldwide [6]. Non-small cell lung cancer (NSCLC), being the most prevalent lung cancer, accounts for approximately 85 % of all cases worldwide [7]. Despite the significant advances in understanding of the disease and advanced treatment strategies, there is still a poor survival rate of lung cancer, raising a serious public concern. Therefore, it is increasingly important to find novel and effective therapeutic agents for the treatment of lung cancer [8,9].

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