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Discovery of thieno[3,2-c]pyran-based leads for liver, lung and glioma cancer: synthesis, docking-guided optimization and apoptotic profiling

Abhishek Jauhari,[a] Pooja,[b] Lakshay Taneja,[c] Ajay Kumar Yadav,[c] Ismail Althagafi,[d] Ramendra Pratap *[e] and Dharmendra Kumar Yadav *[f]

Thieno[3,2-c]pyran is a versatile heterocyclic framework recognised as a core scaffold in numerous synthetic anticancer agents and naturally occurring alkaloids exhibiting potent antitumor activity across various malignancies, including lung, liver, breast, and prostate cancers. In this study, we report the synthesis of a series of substituted thieno[3,2-c]pyran derivatives and their biological evaluation against human hepatocellular carcinoma (HepG2) and lung adenocarcinoma (A549) cell lines. The *in vitro* cytotoxicity assays revealed promising IC_{50} values: **5a** exhibited 13.65 ± 0.32 μM (HepG2) and 12.35 ± 0.30 μM (A549), while **5n** showed 13.26 ± 0.32 μM (HepG2) and 12.36 ± 0.30 μM (A549). Apoptosis-induction studies confirmed the anticancer potential of these compounds. However, compound **5e** works well against Glioma cancer with a promising IC_{50} value of 26 μM (LN229). We have also performed the testing of selected compounds against the non-cancerous cell line HEK293 under the same conditions and concentration, and no cytotoxicity. Among the synthesized compounds, **5a** and **5n** demonstrated significant binding affinities in molecular docking studies, with docking scores of −8.834 and −8.994 kcal mol^{-1} against liver cancer targets, and −7.925 and −7.871 kcal mol^{-1} against lung cancer targets, respectively. To further confirm the EGFR inhibition, selected compounds were tested agaist EGFR overexpressed glioma cell line, and good cytotoxicity confirms the proposed pathway. These findings suggest that compounds **5a**, **5e** and **5n** warrant further investigation as lead molecules for the development of targeted therapies for liver, glioma and lung cancers.

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1 Introduction

Cancer, characterized by the abnormal growth of cells in the body, is a major global health concern. According to the American Cancer Society (ACS), it is estimated that cancer causes approximately 1700 deaths daily, contributing to around 15% of all human deaths worldwide. Cancer cells often evade apoptosis, leading to unchecked growth and angiogenesis—hallmarks of all cancer types.[1–4] Apoptosis is essential for preventing cancer, and targeting this process is a highly effective cancer treatment strategy. Many anticancer drugs focus on various stages of the intrinsic and extrinsic apoptotic pathways.[5,6]

Lung cancer is one of the most prevalent cancers, with the highest rates of morbidity and mortality globally. Despite existing chemotherapeutic treatments, many are inadequate due to serious side effects and drug resistance.[7] Therefore, developing safe and effective new treatments for lung cancer is critical. According to global cancer statistics from 2018, lung cancer accounts for 11.6% of all diagnosed cancer cases and is the leading cause of cancer death, responsible for 18.4% of all cancer-related deaths. Lung cancer is primarily classified into two histological groups: Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC), with NSCLC accounting for approximately 85% of lung cancers. NSCLC is further divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

A significant challenge in treating NSCLC is that when one of the targeted pathways in signal transduction is blocked, others can serve as escape mechanisms for cancer cells.[8–11]

Thienopyran is a prominent heterocyclic structure that serves as the foundation for many pharmacologically significant compounds, particularly those with anticancer properties.[11] Fused pyran[12–19] derivatives have shown promising results in cancer treatment by targeting cellular pathways that inhibit cancer cell growth, induce apoptosis, and disrupt vital

[a]*Department of Neurological Surgery, University of Pittsburgh, 15213, USA*
[b]*Department of Chemistry, Sri Venkateshwara College, Delhi, 110021, India*
[c]*Dr B. R. Ambedkar Center for Biomedical Research, University of Delhi, North Campus, Delhi, 110007, India*
[d]*Department of Chemistry, Faculty of Science, Umm Al-Qura University, Makkah, 21955, Saudi Arabia*
[e]*Department of Chemistry, University of Delhi, North Campus, Delhi, 110007, India. E-mail: rpratap@chemistry.du.ac.in; ramendrapratap@gmail.com*
[f]*Department of Biologics, College of Pharmacy, Gachon University, Hambakmoeiro 191, Yeonsu-gu, Incheon 21924, Republic of Korea*

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