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Synthesis, biological evaluation and molecular docking studies of new pyrimidine derivatives as potent dual EGFR/HDAC inhibitors

G. Sivaiah [a], M.S. Raghu [b], S.B. Benaka Prasad [a,*], A.M. Anusuya [c], K. Yogesh Kumar [a], Fahd Alharethy [d], M.K. Prashanth [e,*], Byong-Hun Jeon [f,*]

[a] Department of Chemistry, Faculty of Engineering and Technology, Jain University, Ramanagara, 562 112, India
[b] Department of Chemistry, New Horizon College of Engineering, Bengaluru, 560 103, India
[c] Department of chemistry, Sapthagiri College of Engineering, Bengaluru, 560 057, India
[d] Department of Chemistry, College of Science, King Saud University, Riyadh, 11451, Saudi Arabia
[e] Department of Chemistry, B N M Institute of Technology, Bengaluru, 560 070, India
[f] Department of Earth Resources and Environmental Engineering, Hanyang University, 222, Wangsimni-ro, Seongdong-gu, Seoul, 04763, Republic of Korea

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ABSTRACT

Pyrimidine scaffolds are an exceptional kind of heterocyclic ring that may be used to create and develop novel anticancer drugs. As a result, the current work described the design and synthesis of novel pyrimidine derivatives (5a-j) as potent dual inhibitors of epidermal growth factor receptor (EGFR) and integrating histone deacetylase (HDAC). Using elemental analysis and spectroscopic techniques, the structure of the newly synthesized compounds was elucidated. All the compounds were tested *in vitro* against MCF-7, HepG2 and A549 cell lines for their antiproliferative properties. Compared to the reference medication erlotinib, compounds 5 h and 5i demonstrated remarkably improved effectiveness against MCF-7, HepG2 and A549 cell lines and better safety towards normal WI-38 cells. The EGFR and HDAC inhibitory effects of compounds 5a, 5c, 5 g, 5 h, and 5i were assessed. With IC_{50} values of 8.43 and 6.91 nM, respectively, the compounds 5 h and 5i demonstrated considerable inhibition against EGFR L858R/T790M mutant kinase. Compound 5i had a strong inhibitory effect compared to reference drug Vorinostat (SAHA) against the investigated isoenzymes of HDAC1, HDAC2, HDAC4, and HDAC6 with an IC_{50} values of 22.73, 20.08, 3100, and 3.71 nM, respectively. Additionally, docking studies were performed to determine the binding mode of potent compounds 5 h and 5i, towards the potential target EGFR, HDAC1 and HDAC6 proteins. Furthermore, all of these results suggested that the target compounds 5 h and 5i might be seen as viable lead candidates for the dual inhibition of both EGFR and HDAC enzymes, which would enable the identification of novel anticancer agents.

1. Introduction

Cancer is a serious health issue in both developed and developing nations. It is characterized by the unchecked and aggressive growth of aberrant cells. Cancer is the second most leading disease-causing death worldwide, behind cardiovascular disorders [1]. Tumours have a very complicated aetiology and exhibit resistance to treatment as well as recurrence. Numerous therapeutic targets have been found as a result of the extensive molecular study on tumours [2]. As a result, the majority of currently approved medications that were created using the single-target, single-drug approach are less successful in treating complex, multigenic, and mixed cancers. Their lack of selectivity, systemic toxicity, drug resistance, and dose-related adverse effects might all be contributing factors [3]. Notably, multi-target medications have the potential to overcome the issues of cancer resistance and recurrence by concurrently targeting biological molecules and different signal pathways implicated in the growth of tumours. These medications can provide additive or even synergistic antitumor effects [4]. In order to address the global health problem, it is thus imperative that new, powerful multi-target anticancer medicines be developed and introduced. This presents a significant challenge and area of considerable interest for the medicinal chemistry community [5,6]. These agents should also have fewer side effects and a more desired safety profile.

In reality, the most desirable targets for cancer treatment are HDACs

* Corresponding author.
E-mail addresses: sb.benakaprasad@jainuniversity.ac.in (S.B.B. Prasad), prashanthmk87@gmail.com (M.K. Prashanth), bhjeon@hanyang.ac.kr (B.-H. Jeon).

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