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Original Research Article

Synthesis, Biological Activity, and Computational Examination of New 3-Cyano-2-oxa-pyridine Derivatives

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ABSTRACT

Numerous studies have been carried out into the chemistry of condensed heterocyclic compounds in terms of their medication discovery and various biological properties. Pyridines play an essential role in medicinal chemistry because they are widely available as natural compounds and have served as the foundation for several drugs on the market. In the current investigation, 3-cyano-2-oxa-pyridine derivatives 4a-e were synthesized by a one-pot multicomponent reaction, starting from substituted acetophenone, ethyl cyanoacetate, and aryl aldehydes in the presence of ammonium acetate. All the new products were subjected to proton nuclear magnetic resonance (^{1}H NMR), carbon nuclear magnetic resonance (^{13}C NMR), two-dimensional (2D)-NMR analysis using heteronuclear single quantum coherence spectroscopy (HSQC), and electron ionization (EI-MS). Additionally, an in vitro cytotoxicity test was performed on cervical carcinoma (HeLa) and cerebral glioblastoma multiforme (AMGM5) cells for every produced molecule. The results indicated that the tested compounds 4a, 4c, and 4e inhibited AMGM5 cells with average IC_{50} values of 656.4, 781.5, and 574.5 µM, respectively. Compounds 4a, 4b, and 4e, on the other hand, showed a cytotoxic action against the HeLa cell line, with average IC_{50} values of 558.5, 775.6, and 615.9 µM, respectively. The optimized geometry and reactivity descriptors were also analyzed, including the highest occupied molecular orbital (HOMO), least unoccupied molecular orbital (LUMO), energy band gap (ΔE), chemical potential (μ), electronegativity (χ), chemical hardness (η), chemical softness (S), and electrophilicity (ω). The experimental outcomes of the biological evaluation were consistent with the results of the investigation into their molecular modeling.

Keywords: Anticancer, Cyano-pyridines, Multicomponent reaction, DFT, Pharmacokinetics.

Introduction

Pyridine products have long been studied due to the abundance of pyridine in nature and its widespread use as the structural core of numerous medicinal pharmaceuticals.[1,2] These natural and manmade compounds have numerous uses in medication research and functional materials.[3,4] This has contributed to the creation of physiologically relevant heterocyclic compounds such as pyridine analogues.[5] Additionally, pyridine analogues are essential heterocyclic molecules with pharmacological and functional features that make them appealing as medicines and general synthetic building blocks.[6,7] The pyridine core is found in anti-inflammatory and anticancer drugs.[8] Anticancer medicines have been described as being comprised of pyridine derivatives, including different groups such as streptonigrone, streptonigrin, and lavendamycin, while cerivastatin has been reported as a hydroxymethylglutaryl-CoA reductase enzyme inhibitor.[9] Furthermore, substituted pyridines have been found to be leukotriene B-4 antagonists.[10] Cyanopyridine derivatives, on the other hand, have been demonstrated to have antibacterial,[11] antioxidant,[12] antibiotic,[13] anti-inflammatory,[14] analgesic,[15] anticonvulsant,[16] and anticancer[17] effects.

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3-Cyano-2-pyridones are analogous to the alkaloid ricinine, the first known alkaloid that contains a cyano group. The anticancer activity of 3-cyano-2-pyridone derivatives is exciting due to the numerous biological targets they may interact with, including phosphodiesterase 3 and the provirus integration site for the Moloney murine leukaemia virus-1 kinase and survival.[18,19] Encouraged by recent literature observations, some new pyridine derivatives were synthesized in this study, resulting in fascinating heterocyclic frameworks that are most beneficial for the construction of various chemical libraries of compounds with a variety of functional groups for examining unique biological agents. This study was aimed at synthesizing new 3-cyano-2-oxa-pyridine derivatives (4a-e) using substituted acetophenone, ethyl cyanoacetate, and aryl aldehydes in the presence of ammonium acetate. Moreover, they demonstrated anticancer efficacy against two cancer cell lines, namely cerebral glioblastoma multiforme and cervical carcinoma. The variations in biological activity induced by changes in the positions of substituted groups like H, Br, NH_2, and OCH_3 were explored as an outcome of this research. The synthesized compounds were subjected to theoretical calculations using the density-functional theory (DFT), an adverse medical device event (AMDE) assay, and by making comparisons with experimental data. These studies will provide insight into the molecular properties of novel pyridine derivatives.

Materials and Methods

Sources for cell lines and maintenance of cell cultures

Two cancer cell lines, namely cerebral glioblastoma multiforme (AMGM5) and cervical carcinoma (HeLa), were purchased from the IRAQ Biotechnology Cell Banking Centre in Basrah and grown in RPMI-1640 treated with 10% foetal bovine serum, 100 units/mL of the antibiotic penicillin, and 100 g/mL of minocycline. The cells were