

**Tropical Journal of Natural Product Research**Available online at <http://www.tjpnres.com>**Original Research Article****Synthesis, Biological Activity, and Computational Examination of New 3-Cyano-2-oxo-pyridine Derivatives**

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**ABSTRACT**

Pyridine衍生物已广泛应用于药物化学和天然产物研究。吡啶在医药化学中发挥着重要作用，因为它们是广泛可用的天然化合物，并且是许多药物的前体。在当前的研究中，3-氰基-2-酮-吡啶衍生物 $4a-e$ 通过一锅多组分反应从乙酸酐、乙酰氯、乙酰丙酸酯和丙烯酸酯在氨水存在下合成。所有新化合物都经过核磁共振光谱 ( $^1\text{H-NMR}$ )、碳核磁共振光谱 ( $^{13}\text{C-NMR}$ )、二维 NMR 分析 (HSQC) 和电子电离 (EI MS) 测定。此外，在 *vitro* 细胞毒性测试中进行了宫颈癌细胞系和人宫颈癌上皮细胞 (AMEM3) 的细胞毒性测试。结果表明，所合成的化合物 $4a$ ,  $4c$  和 $4e$ 抑制 AMEM3 细胞，平均 IC<sub>50</sub> 值为 696.4, 787.5 和 374.1  $\mu\text{M}$ ，分别。化合物 $4a$ ,  $4b$  和 $4c$ 在人宫颈癌细胞系中表现出细胞毒性作用，抑制 U251 细胞，平均 IC<sub>50</sub> 值为 238.0, 770.6 和 616.9  $\mu\text{M}$ ，分别。优化的几何形状和电荷密度分布也进行了分析，包括最高占据分子轨道 (HOMO)、能量禁带 (Eg)、电离电势 (IP)、电子亲和力 (EA)、电负性 (N)、电荷密度 (Q) 和超极化率 (μ)。这些参数的估算值与模型计算的结果是一致的。

**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.<sup>1-3</sup> These natural and synthetic compounds have numerous uses in medicine research and functional materials.<sup>4-6</sup> This has contributed to the creation of physiologically relevant heterocyclic compounds such as pyridine analogues.<sup>7</sup> Additionally, pyridine analogues are essential heterocyclic molecules with pharmacological and functional features that make them appealing as medicines and useful synthetic building blocks.<sup>8-10</sup> The pyridine core is found in anti-inflammatory and anticancer drugs.<sup>11</sup> Anticancer medicines have been described as being comprised of pyridine derivatives, including different groups such as streptophytin, streptonigrin, and laverdine, while cisplatin has been reported as a bidentate amminopolycatena-Pt(IV) complex.<sup>12</sup> Furthermore, substituted pyridine has been found to be leukotriene B<sub>4</sub> antagonist.<sup>13</sup> Cyano-pyridine derivatives, on the other hand, have been demonstrated to have antibacterial,<sup>14</sup> antidiabetic,<sup>15</sup> anti-inflammatory,<sup>16</sup> analgesic,<sup>17</sup> antioxidant,<sup>18</sup> and anticancer<sup>19</sup> effects.

3-Cyano-2-pyridones are analogous to the alkyl pyrimidines, the best-known alkaline that contains a cyano group. The biological activity of 3-cyano-2-pyridone derivatives is exciting due to the numerous biological targets they may interact with, including phosphodiesterase 3 and the primary integration site for the Moloney murine leukaemia virus 1 kinase and viral.<sup>20,21</sup> Encouraged by recent literature observations, some new cyano-pyridine derivatives were synthesized in this study, revealing an interesting heterocyclic compounds that are more beneficial for the continuation 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-pyridone derivatives ( $4a-e$ ) using substituted acetophenone, ethyl cyanoformate, and vinyl aldehydes in the presence of ammonia acetate. Moreover, they demonstrated antitumor activity against two cancer cell lines, namely cervical fibroblasts and midline and cervical carcinoma. The variations in biological activity induced by changes in the position of substituted groups like H, Br, NH<sub>2</sub>, and OCH<sub>3</sub> were explored as an outcome of this research. The synthesized compounds were subjected to theoretical calculations using the density-functional theory (DFT), an inverse medical device (AMEM3) assay, and making comparisons with experimental data. These studies will provide insight into the molecular properties of novel pyridine derivatives.

**Materials and Methods****Source for cell lines and maintenance of cell cultures**

Two cancer cell lines, namely cervical fibroblasts midline (AMEM3) and cervical carcinoma (313A), were purchased from the IRAQ Biotechnology Cell Banking Center in Basrah and grown in RPMI 1640 treated with 10% fetal bovine serum, 100  $\mu\text{g/ml}$  of the antibiotic penicillin, and 100  $\mu\text{g/ml}$  of minocycline. The cells were

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