

Novel Nabumetone-Chalcone-Based Pyridine Hybrids: Synthesis, Characterization, and Cytotoxic Activity against the A549 Lung Cancer Cell Line and Normal Human Dermal Fibroblasts (HDFn).

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Abstract:

Background: Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality, necessitating the continuous discovery of targeted therapies.

Aim of the Study: This study aimed to synthesize and characterize six novel nabumetone-derived heterocyclic compounds (4-9) by integrating chalcone derivatives with pyridine-derived scaffolds and evaluate their cytotoxic activity.

Materials and Methods: The structures of these compounds were validated by Infrared Spectroscopy, Proton Nuclear Magnetic Resonance (¹H-NMR), and Carbon Nuclear Magnetic Resonance (¹³C-NMR) Spectroscopy. All substances were evaluated for their capacity to inhibit cancer cells via the MTT assay in the A549 lung cancer cell line and normal human dermal fibroblasts (HDFn). We established the IC₅₀ values for all drugs using a 48-hour incubation period.

Results: The para-pyridone compound (6) had the highest cytotoxicity against cancer cells (31.82 µg/mL), whereas the meta-pyridine compound (8) also showed significant cytotoxicity (38.09 µg/mL). Compound (6) exhibited biological activity that surpassed that of the reference medication, Erlotinib, a contemporary chemotherapeutic agent (34.10 µg/mL). Furthermore, both compounds (6) and (8) had considerable Selectivity Indices (SI: 4.92 and 3.90, respectively).

Discussion: Our research demonstrates that both the fundamental architecture of each chemical and the locations of its functional groups are crucial in influencing its biological activity.



Conclusion: These findings suggest that both substituted pyridone cores and substituted 2-aminopyridine cores may serve as promising scaffolds for further optimization and biological evaluation.

Keywords: Nabumetone, Chalcone derivatives, 2-Pyridone-3-carbonitrile derivatives, 2-Amino-3-cyanopyridine derivatives, A549 cells, MTT assay.

1. Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). The disease is highly heterogeneous, characterized by late-stage diagnosis, high metastatic potential, and diverse symptoms depending on the anatomical origin in the bronchial tree (2). Non-small cell lung cancer (NSCLC) is the most common category of lung cancer. It mainly includes adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Among these, adenocarcinoma is the most frequent histological subtype, and the A549 cell line is widely used as an in vitro model of human lung adenocarcinoma (3). Molecular targeted therapy has emerged as an effective alternative with a more tolerable toxicity profile, overcoming the limitations of traditional chemotherapy, which attacks both healthy and proliferating cells indiscriminately (4). Monoclonal antibodies and small-molecule inhibitors are the main therapeutic modalities of this therapeutic approach (5). The FDA has so far approved a few small-molecule protein kinase inhibitors that selectively inhibit cellular signaling pathways, thereby stopping tumor progression (6,7). Receptor tyrosine kinases (RTKs) are important regulators of normal cellular processes, such as growth and metabolism; however, their deregulation through gain-of-function mutations or genomic amplification has been strongly associated with the development of several human cancers (8,9). A well-known member of this family is the epidermal growth factor receptor (EGFR), a transmembrane tyrosine kinase. Overexpression and mutations in EGFR have

been directly linked to initiation and progression of several malignancies, including lung cancer (10–12). Despite their clinical activity, acquired resistance limits the long-term efficacy of first-generation EGFR inhibitors (e.g., erlotinib). The secondary mutation EGFR T790M is an important resistance mechanism, as it increases the affinity for ATP and thus decreases the inhibitory efficacy of reversible ATP-competitive inhibitors (13). These limitations indicate a necessity to investigate a chemically diverse set of scaffolds with varying structural features for the discovery of new molecular interactions and improvement of anticancer efficacy. Therefore, the development and biological evaluation of novel heterocyclic hybrids represent a rational strategy for the discovery of new lead compounds for the treatment of NSCLC. Nabumetone is a non-narcotic methyl ketone containing a naphthalene core and a very valuable pharmacological profile (14). Nabumetone was selected as the parent scaffold based on both biological and synthetic considerations. Later studies showed that nabumetone inhibits tumor growth in preclinical studies. Nabumetone has been reported to suppress intestinal tumorigenesis in a dose-dependent manner, with downregulation of Bcl-2 and induction of apoptosis (15). More recently, nabumetone-derived heterocyclic compounds have shown antiproliferative activity against different cancer cell lines, including A549 lung cancer cells, encouraging further exploration of this scaffold in the design of anticancer drugs (16–19). Nabumetone contains an enolizable methyl ketone functionality; the



methyl ketone group enables Claisen–Schmidt condensation with substituted pyridine aldehydes, facilitating the construction of the chalcone intermediates used in the present study. This property distinguishes nabumetone from other NSAIDs, such as naproxen and diclofenac, which are carboxylic acid derivatives and do not have the same methyl ketone functionality. Also, the chalcones (1,3-diphenyl-2-propene-1-one) are flexible and highly reactive pharmacophores (20). They are usually synthesized via the conventional Claisen-Schmidt condensation, and their alpha, beta-unsaturated carbonyl groups enable the synthesis of a variety of heterocyclic derivatives through ring-closure reactions (21,22). Nitrogen heterocycles, especially pyridine and its isomeric derivative, pyridone, are very important in medicinal chemistry (23–25). Because of their distinctive heteroaromatic structural characteristics and their capacity for extensive functionalization and participation in significant chemical reactions, they are superb pharmacophores for the design of broad-spectrum therapeutic agents (26–28). This rationale leads to the hybridization of these active structural motifs and the linkage of a naphthalene moiety to a pyridine/pyridone scaffold via a chalcone intermediate, providing structurally diverse compounds for further evaluation as potential anticancer agents. So, the aim of this study was to synthesize and characterize a series of novel nabumetone-derived pyridine/pyridone hybrids and to evaluate their cytotoxic activity against A549 lung cancer cells and their selectivity toward normal human dermal fibroblasts (HDFn), using erlotinib as a reference drug. The study also aimed to investigate the influence of scaffold type and substituent position on the observed biological activity.

2. Materials and Methods

The experimental work was conducted at different research facilities.

Melting-point determination and the FT-IR analysis of the synthesized compounds were performed at the College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

The ^1H NMR and ^{13}C NMR analyses were carried out at the University of Tehran, Tehran, Iran.

The cytotoxicity evaluation using the MTT assay was conducted at the Iraqi Center for Cancer and Medical Genetics Research, Mustansiriyah University, Baghdad, Iraq.

2.1. Chemicals and Instrumentation

All reagents and solvents were of analytical quality and used as supplied without further purification. Nabumetone, malononitrile, ethyl cyanoacetate, and several pyridine carbaldehydes (2-, 3-, and 4-carbaldehydes) were acquired from Sigma-Aldrich (Germany), Fluka (Germany), and Hyperchem (China). The melting points were measured using a Stuart electric melting point device (England) in open capillary tubes and were uncorrected. Infrared (FT-IR) spectra were obtained using a Bruker spectrometer (Germany) using KBr pellets. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained using a Bruker spectrometer (Germany) in DMSO-d_6 as the solvent, with tetramethylsilane (TMS) used as the internal standard. Chemical shifts (δ) are expressed in parts per million (ppm).

2.2. General Synthesis Procedures

2.2.1. General Procedure for the Synthesis of Chalcone Derivatives (1-3)

An aqueous solution of sodium hydroxide (NaOH) (0.08 g, 2 mmol) was first dissolved in a mixed solvent of 100% methanol and deionized water (5:2.5 mL), yielding a 1% solution. In a separate beaker, (0.456 g, 2 mmol) of nabumetone was dissolved in a



mixed solvent of diethyl ether and absolute methanol (5:10 mL). Subsequently, pyridinyl derivatives (Pyridine-2-carbaldehyde, Pyridine-3-carbaldehyde, pyridine-4-carbaldehyde) (214 mg, 2 mmol) were added and mixed until completely dissolved, and then the sodium hydroxide solution was gradually added while stirring at room temperature for 24 hours. The precipitate was filtered, rinsed with cold water and diethyl ether, and recrystallized from methanol to afford pure compounds (1-3) (29,30).

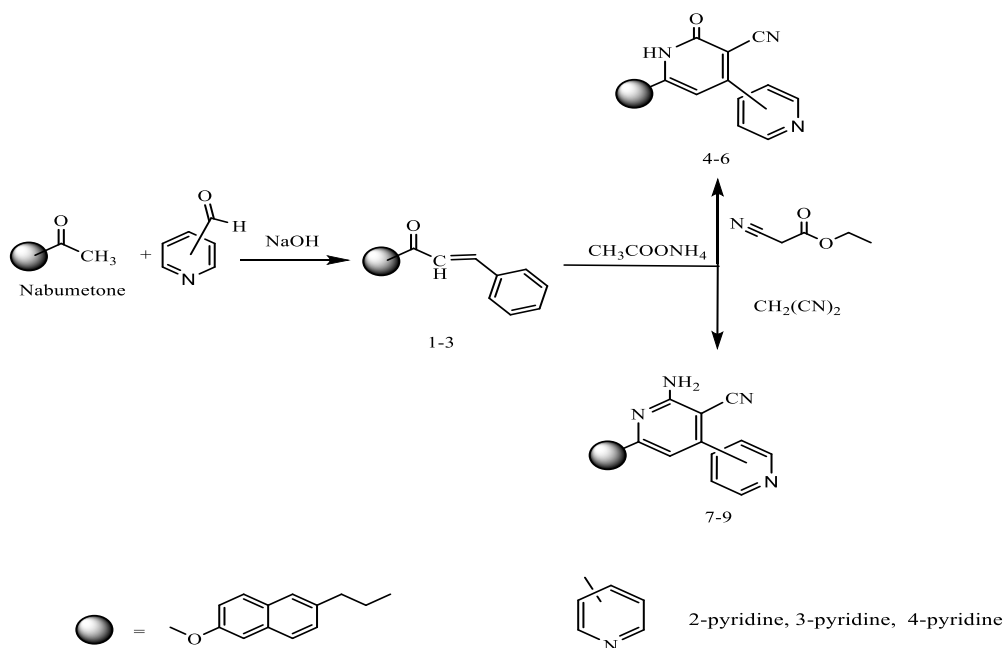
2.2.2. General Procedure for the Synthesis of Pyridone Derivatives (4-6)

Dissolve chalcone derivatives (1-3) (331.4 mg, 1 mmol) with ethyl cyanoacetate (113 mg, 1 mmol) and ammonium acetate (0.616 g, 8

mmol) in 12 mL of 100% ethanol, then reflux in an oil bath at 80°C for 3-6 hours. A precipitate was produced, filtered while the mixture was still hot, and then washed with cold water and acetone to give the final compounds (4-6) (31,32).

2.2.3. General Procedure for the Synthesis of 2-Aminopyridine Derivatives (7-9)

Chalcone derivatives (1-3) (331.4 mg, 1 mmol) were mixed with malononitrile (0.528 g, 8 mmol) and ammonium acetate (0.616 g, 8 mmol) in 12 mL of absolute ethanol, then refluxed in an oil bath at 80°C for 3- 5 hours. A precipitate was formed, filtered while the mixture was heated, then transferred to cooled water, and finally washed with acetone to obtain the final compounds (7-9) (33,34).



Scheme (1): Synthesis of Pyridone Derivatives (4-6) and 2-Aminopyridine Derivatives (7-9) from chalcone derivatives (1-3).

2.3. Characterization Data of the Synthesized Compounds

5-(6-methoxynaphthalen-2-yl)-1-(pyridin-2-yl) pent-1-en-3-one (1):

Light brown powder, m.p. 125–127 °C, FT-IR (cm^{-1}): 3053 (Ar-CH stretching), 2931, 2839 (Aliphatic CH stretching), 1654 ($\text{C}=\text{O}$ stretching), 1631 ($\text{C}=\text{C}$ stretching, α , β -unsaturated), 1604 ($\text{C}=\text{N}$ stretching, pyridine), 1504 ($\text{C}=\text{C}$ stretching, aromatic), 1265, 1029 ($\text{C}-\text{O}-\text{CH}_3$ stretching). ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ : 2.90–2.93 (t, 2H, CH_2 β to $\text{C}=\text{O}$), 3.01–3.03 (t, 2H, CH_2 α to $\text{C}=\text{O}$), 3.81 (s, 3H, OCH_3), 7.01–7.03 (d, 1H, Ar- H), 7.17 (s, 1H, Ar-H), 7.28–7.29 (d, 1H, Ar-H), 7.40–7.42 (m, 2H, Pyridine-H), 7.46 (d, 1H, Pyridine-H), 7.61 (s, 1H, Ar-H), 7.67 (d, 1H, vinylic-H α to $\text{C}=\text{O}$), 7.70 (d, 1H, vinylic-H β to $\text{C}=\text{O}$), 7.73–7.77 (m, 2H, Ar-H), 8.51–8.52 (d, 1H, Pyridine-H). ^{13}C NMR (300 MHz, $\text{DMSO}-d_6$) δ : 32.37, 44.56, 55.59 (OCH_3), 106.18, 119.15, 124.23, 124.43, 125.73, 127.55, 127.75, 129.03, 129.39, 131.08, 131.69, 134.53, 136.71, 138.79, 150.23, 151.36, 157.39 ($\text{C}-\text{OCH}_3$), 199.09 ($\text{C}=\text{O}$).

5-(6-methoxynaphthalen-2-yl)-1-(pyridin-3-yl) pent-1-en-3-one (2):

Beige powder, m.p. 128–130 °C, FT-IR (cm^{-1}): 3053 (Ar-CH stretching), 2934, 2843 (Aliphatic CH stretching), 1653 ($\text{C}=\text{O}$ stretching), 1630 ($\text{C}=\text{C}$ stretching, α , β -unsaturated), 1603 ($\text{C}=\text{N}$ stretching, pyridine), 1504 ($\text{C}=\text{C}$ stretching, aromatic), 1265, 1229 ($\text{C}-\text{O}-\text{CH}_3$ stretching). ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 3.00–3.04 (t, 2H, CH_2 β to $\text{C}=\text{O}$), 3.11–3.15 (t, 2H, CH_2 α to $\text{C}=\text{O}$), 3.85 (s, 3H, OCH_3), 6.95–6.98 (d, 1H, vinylic-H α to $\text{C}=\text{O}$), 7.09–7.13 (d, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.40–7.42 (d, 1H, Ar-H), 7.48–7.51 (t, 1H, Pyridine-H), 7.66 (s, 1H, Ar-H), 7.68–7.70 (d, 1H, vinylic-H β to $\text{C}=\text{O}$), 7.73–7.78 (m, 2H, Ar-H), 7.99–8.06 (d, 1H, Pyridine-H), 8.53–8.55 (d, 1H, Pyridine-H), 8.86 (s, 1H, Pyridine-

H). ^{13}C -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 34.48, 42.80, 55.63 (OCH_3), 106.33, 119.09, 124.09, 126.75, 127.30, 128.01, 128.97, 129.32, 129.68, 132.51, 133.43, 135.68, 136.12, 142.80, 148.64, 151.56, 157.44 ($\text{C}-\text{OCH}_3$), 200.01 ($\text{C}=\text{O}$).

5-(6-methoxynaphthalen-2-yl)-1-(pyridin-4-yl) pent-1-en-3-one (3):

Off-white powder, m.p. 132–134 °C, FT-IR (cm^{-1}): 3051 (Ar-CH stretching), 2932, 2839 (Aliphatic CH stretching), 1653 ($\text{C}=\text{O}$ stretching), 1632 ($\text{C}=\text{C}$ stretching, α , β -unsaturated), 1605 ($\text{C}=\text{N}$ stretching), 1500 ($\text{C}=\text{C}$ stretching, aromatic), 1265, 1229 ($\text{C}-\text{O}-\text{CH}_3$ stretching). ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 2.86–2.92 (t, 2H, CH_2 β to $\text{C}=\text{O}$), 3.06–3.12 (t, 2H, CH_2 α to $\text{C}=\text{O}$), 3.86 (s, 3H, OCH_3), 7.12–7.15 (d, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.32–7.35 (d, 2H, Ar-H and vinylic-H α to $\text{C}=\text{O}$), 7.47 (s, 1H, Ar-H), 7.55–7.56 (d, 2H, Ar-H ortho to β vinylic carbon), 7.58 (d, 1H, vinylic-H α to $\text{C}=\text{O}$), 7.75–7.80 (m, 2H, Ar-H), 8.72–8.76 (d, 2H, Ar-H meta to β vinylic carbon). ^{13}C -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 36.05, 42.50, 55.60 (OCH_3), 106.22, 119.04, 123.99, 126.73, 127.32, 128.05, 128.96, 129.33, 133.39, 133.98, 142.56, 146.68, 150.63, 157.37 ($\text{C}-\text{OCH}_3$), 199.29 ($\text{C}=\text{O}$).

6'-(2-(6-methoxynaphthalen-2-yl) ethyl)-2'-oxo-1',2'-dihydro-[2,4'-bipyridine]-3'-carbonitrile (4) :

Red powder, Yield: 74%, m.p. 261–263 °C, FT-IR (KBr, cm^{-1}): 3415 (NH stretching, amide), 3042 (Ar-CH stretching), 2935, 2837 (Aliphatic CH stretching), 2216 ($\text{C}\equiv\text{N}$ stretching), 1674 ($\text{C}=\text{O}$ stretching), 1598 ($\text{C}=\text{N}$ stretching, pyridine), 1552 ($\text{C}=\text{C}$ stretching, aromatic), 1265, 1028 ($\text{C}-\text{O}-\text{CH}_3$ stretching). ^1H -NMR (300 MHz, $\text{DMSO}-d_6$) δ : 2.94–2.99 (t, 2H, CH_2 β to pyridone ring), 3.07–3.12 (t, 2H, CH_2 α to pyridone ring), 3.87 (s, 3H, OCH_3), 6.40 (s, 1H, Pyridone-H), 7.13–7.16



(d, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.30–7.32 (d, 1H, Ar-H), 7.35–7.37 (t, 1H, Pyridine-H), 7.40–7.43 (t, 1H, Pyridine-H), 7.51–7.53 (d, 1H, Pyridine-H), 7.65 (s, 1H, Ar-H), 7.74–7.78 (m, 2H, Ar-H), 8.74–8.76 (d, 1H, Pyridine-H), 12.89 (s, 1H, NH). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 36.01, 37.07, 55.61 (OCH₃), 103.01, 106.30, 115.69 (CN), 116.34, 119.07, 120.01, 123.94, 126.72, 127.30, 128.02, 128.98, 129.30, 133.41, 133.96, 136.47, 149.07, 154.01, 156.01, 157.40 (C-OCH₃), 161.47 (C=O), 170.02.

6'-(2-(6-methoxynaphthalen-2-yl) ethyl)-2'-oxo-1',2'-dihydro-[3,4'-bipyridine]-3-carbonitrile (5):

Brown powder, Yield: 80%, m.p. 264–265 °C, FT-IR (KBr, cm⁻¹): 3234 (NH stretching, amide), 3015 (Ar-CH stretching), 2909, 2843 (Aliphatic CH stretching), 2216 (C≡N stretching), 1651 (C=O stretching), 1609 (C=N stretching, pyridine), 1572, 1533 (C=C stretching, aromatic), 1223 (C-N stretching, pyridone), 1263, 1026 (C-O-CH₃ stretching). ¹H-NMR (300 MHz, DMSO-d₆) δ: 2.95–2.99 (t, 2H, CH₂ β to pyridone ring), 3.07–3.13 (t, 2H, CH₂ α to pyridone ring), 3.86 (s, 3H, OCH₃), 6.46 (s, 1H, Pyridone-H), 7.12–7.16 (d, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.35–7.37 (d, 1H, Ar-H), 7.40–7.43 (t, 1H, Pyridine-H), 7.55 (s, 1H, Ar-H), 7.66 (d, 1H, Pyridine-H), 7.74–7.78 (m, 2H, Ar-H), 7.98–8.00 (d, 1H, Pyridine-H), 8.75 (s, 1H, Pyridine-H), 12.83 (s, 1H, NH). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 36.09, 37.11, 55.60 (OCH₃), 103.29, 106.30, 115.79 (CN), 118.63, 119.05, 123.79, 126.69, 127.31, 128.01, 129.00, 129.32, 131.01, 133.41, 135.99, 137.71, 149.84, 154.97, 157.39 (C-OCH₃), 160.05, 165.01 (C=O).

6-(2-(6-methoxynaphthalen-2-yl) ethyl)-2-oxo-1,2-dihydro-[4,4'-bipyridine]-3-carbonitrile (6) :

Yellow powder; Yield: 86%, m.p. 270–272 °C, FT-IR (KBr, cm⁻¹): 3412 (NH stretching,

amide), 3042 (Ar-CH stretching), 2941, 2837 (Aliphatic CH stretching), 2216 (C≡N stretching), 1676 (C=O stretching), 1599 (C=N stretching, pyridine), 1555 (C=C stretching, aromatic), 1225 (C-N stretching, pyridone), 1265, 1030 (C-O-CH₃ stretching). ¹H-NMR (300 MHz, DMSO-d₆) δ: 2.93–2.99 (t, 2H, CH₂ β to pyridone ring), 3.07–3.13 (t, 2H, CH₂ α to pyridone ring), 3.86 (s, 3H, OCH₃), 6.46 (s, 1H, Pyridone-H), 7.12–7.16 (d, 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.37–7.38 (d, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 7.55–7.59 (m, 2H, Pyridine-H), 7.74–7.78 (m, 2H, Ar-H), 8.72–8.75 (m, 2H, Pyridine-H), 12.43 (s, 1H, NH). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 34.49, 35.15, 55.63 (OCH₃), 102.99, 106.33, 116.35 (CN), 119.09, 121.01, 122.72, 126.77, 127.30, 127.99, 128.97, 129.32, 133.44, 134.97, 143.32, 150.64, 156.09, 157.45 (C-OCH₃), 160.02, 165.01 (C=O).

2'-amino-6'-(2-(6-methoxynaphthalen-2-yl) ethyl) [2,4'-bipyridine]-3'-carbonitrile (7) :

Reddish-brown powder, Yield: 75%, m.p. 212–214 °C, FT-IR (KBr, cm⁻¹): 3464, 3412 (NH₂ stretching), 3235 (Overtone of NH₂ bending), 3053 (Ar-CH stretching), 2943, 2845 (Aliphatic CH stretching), 2208 (C≡N stretching), 1637 (NH₂ bending), 1614 (C=N stretching, pyridine), 1584 (C=C stretching, aromatic), 1258, 1024 (C-O-CH₃ stretching). ¹H-NMR (300 MHz, DMSO-d₆) δ: 3.08–3.10 (t, 2H, CH₂ β to pyridine ring), 3.49–3.51 (t, 2H, CH₂ α to pyridine ring), 3.86 (s, 3H, OCH₃), 6.67 (s, 2H, NH₂), 7.12–7.15 (d, 1H, Ar-H), 7.25 (s, 1H, Ar-H), 7.32–7.34 (m, 2H, Ar-H & Pyridine-H), 7.38–7.40 (t, 1H, Pyridine-H), 7.49 (s, 1H, Ar-H), 7.73–7.78 (m, 2H, Ar-H), 7.92–7.95 (t, 1H, Pyridine-H), 7.98 (s, 1H, Pyridinyl-H), 8.72–8.74 (d, 1H, Pyridine-H). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 36.09, 37.11, 55.60 (OCH₃), 93.29, 96.82, 106.30, 115.79 (CN), 118.63, 119.05, 123.79, 126.69, 127.31, 128.01, 129.00, 129.32,



133.41, 135.99, 137.71, 149.84, 154.15, 154.97, 157.39 (C-OCH₃), 161.01, 165.02.

2-'amino-6'-(2-(6-methoxynaphthalen-2-yl)ethyl)-[3,4'-bipyridine]-3'-carbonitrile (8) :

Mustard yellow powder, Yield: 83%, m.p. 216–218 °C, FT-IR (KBr, cm⁻¹): 3472, 3404 (NH₂ stretching), 3233 (Overtone of NH₂ bending), 3115 (Ar-CH stretching), 2930 (Aliphatic CH stretching), 2216 (C≡N stretching), 1632 (NH₂ bending), 1612 (C=N stretching, pyridine), 1578 (C=C stretching, aromatic), 1261, 1028 (C-O-CH₃ stretching). ¹H-NMR (300 MHz, DMSO- d₆) δ: 3.08–3.10 (t, 2H, CH₂ β to pyridine ring), 3.49–3.51 (t, 2H, CH₂ α to pyridine ring), 3.87 (s, 3H, OCH₃), 6.81 (s, 2H, NH₂), 7.12–7.15 (d, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.37–7.39 (d, 1H, Ar-H), 7.52 (s, 2H, Ar-H & Pyridine-H), 7.63–7.65 (t, 1H, Pyridine-H), 7.73–7.78 (m, 2H, Ar-H), 8.49–8.51 (d, 1H, Pyridine-H), 8.68–8.70 (d, 1H, Pyridine-H), 9.29 (s, 1H, Pyridine-H). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 36.01, 37.07, 55.61 (OCH₃), 93.57, 96.48, 106.30, 115.69 (CN), 119.07, 123.94, 126.72, 127.30, 128.02, 128.98, 129.30, 133.41, 133.96, 135.93, 136.47, 146.66, 149.07, 152.28, 157.40 (C-OCH₃), 161.01, 163.57.

2-amino-6-(2-(6-methoxynaphthalen-2-yl)ethyl)-[4,4'-bipyridine]-3-carbonitrile (9) :

Greenish-yellow powder, Yield: 87%, m.p. 220–222 °C, FT-IR (KBr, cm⁻¹): 3474, 3379 (NH₂ stretching), 3227 (Overtone of NH₂ bending), 3055 (Ar-CH stretching), 2932 (Aliphatic CH stretching), 2214 (C≡N stretching), 1655 (NH₂ bending), 1603 (C=N stretching, pyridine), 1572 (C=C stretching, aromatic), 1263, 1028 (C-O-CH₃ stretching). ¹H-NMR (300 MHz, DMSO- d₆) δ: 3.07–3.09 (t, 2H, CH₂ β to pyridine ring), 3.49–3.51 (t, 2H, CH₂ α to pyridine ring), 3.87 (s, 3H, OCH₃), 6.83 (s, 2H, NH₂), 7.13–7.16 (d, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.36–7.39 (d, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.63 (s, 1H,

Pyridine-H), 7.73–7.78 (m, 2H, Ar-H), 8.00–8.02 (d, 2H, Pyridine-H), 8.68–8.70 (d, 2H, Pyridine-H). ¹³C-NMR (75 MHz, DMSO-d₆) δ: 36.03, 37.11, 55.60 (OCH₃), 92.94, 96.87, 106.18, 115.63 (CN), 118.62, 123.50, 126.75, 127.34, 128.04, 128.95, 129.34, 133.40, 135.90, 145.50, 150.40, 152.48, 157.38 (C-OCH₃), 161.12, 163.50.

2.4 .Biological Evaluation

2.4.1 .Cell Culture

A549 (human lung adenocarcinoma) and HdFn (human dermal fibroblasts) cell lines were cultured in RPMI 1640 medium containing 15% FBS, 100 IU/ml Penicillin, 100 µg/ml Streptomycin, and 1% Sodium Bicarbonate. Cell lines were maintained in a humidified incubator (37 °C, 5% CO₂). Subsequently, the cell lines were harvested with Trypsin/EDTA (1% Trypsin/1% EDTA) and counted with a hemocytometer for use in assays (35).

2.4.2 .In Vitro Cytotoxicity (MTT Assay)

The reference drugs and synthesized compounds were evaluated by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay (Intron Biotech, Korea) . A549 and HDFn cells were separately seeded into 96-well culture plates at a volume of 200 µL of complete culture medium per well and incubated for 24 h at 37 °C to allow adequate cell attachment. After an incubation period, the culture medium was completely decanted from each well, and fresh medium containing two-fold serial dilutions of each of the assessed experimental drug candidate concentrations (12.5, 25, 50, 100, 200, and 400 µg/mL) was added to each well for an additional 48 hr incubation period. All treatments and controls were performed in triplicate. Afterward, cell viability was evaluated using the MTT assay. Cells were treated with 10 µL of MTT solution and incubated for 4 hr at 37 °C in 5% CO₂ .The



supernatant was discarded, and the formed formazan crystals were dissolved by adding 100 μ L of dimethyl sulfoxide (DMSO) to each well, followed by a 5 min incubation to ensure complete dissolution (36). The Half-Maximal Inhibitory Concentration (IC₅₀), defined as the concentration that reduces cell viability by 50%, was calculated by nonlinear regression analysis of the dose-response curves (37). IC₅₀ values were calculated by nonlinear regression analysis of the concentration-response curves using GraphPad Prism software. The selectivity index (SI) was calculated as the ratio of the IC₅₀ value in normal HDFn cells to that in A549 cancer cells.

3 .Results

3.1 .Synthesis analysis

3.1.1. Proposed Reaction Mechanisms

The formation of these rings follows a Michael addition-cyclization sequence. Ammonium acetate plays a dual role, acting as a basic catalyst to generate the carbanion and as a source of nitrogen for the ring closure.

3.1.2. Mechanism of synthesis of Chalone derivatives (1-3)

The mechanism for synthesizing base-catalyzed chalone derivatives is shown in Scheme 2. The aldol condensation process transpires between Nabumetone and various

aldehyde derivatives, namely pyridine-2-carbaldehyde, pyridine-3-carbaldehyde, and pyridine-4-carbaldehyde, including the following steps (38).

- **Step 1: Formation of the enolate ion**

The initial step is an acid-base reaction. Hydroxide acts as a base, removing an acidic α -hydrogen to produce a reactive enolate.

- **Step 2: Nucleophilic addition (alkoxide formation)**

In a nucleophilic addition process, the carbonyl carbon of pyridylaldehyde is attacked by the nucleophilic enolate, forming an intermediate alkoxide.

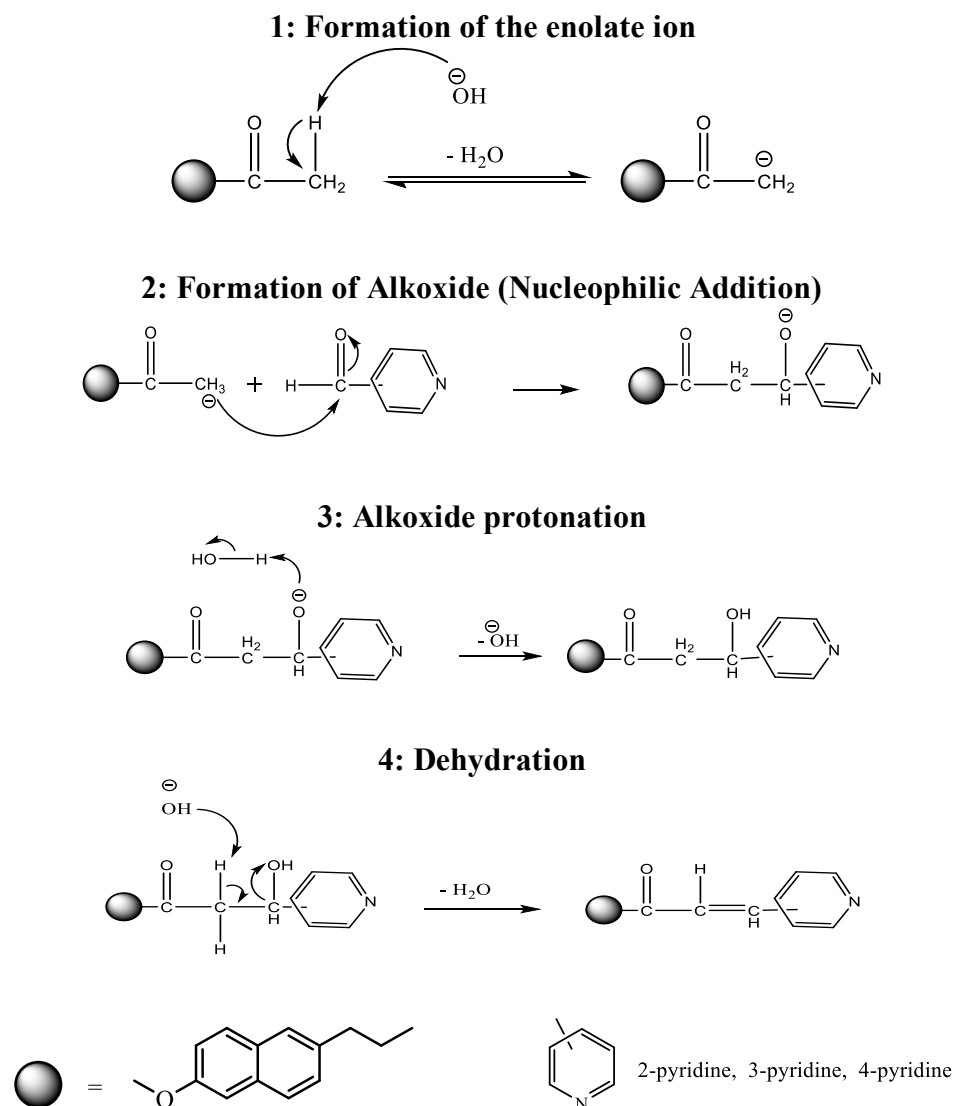
- **Step 3: Alkoxide protonation**

The alkoxide deprotonates a water molecule, yielding a hydroxide ion and a β -hydroxyketone, the aldol product.

- **Step 4: Dehydration**

The hydroxide functions as a base, removing the acidic β -hydrogen to form the reactive enolate. The enolate's negative charge is used to generate a carbon-carbon double bond (C=C) and to displace a leaving group, regenerating the hydroxide and forming the final product, the conjugated ketone.



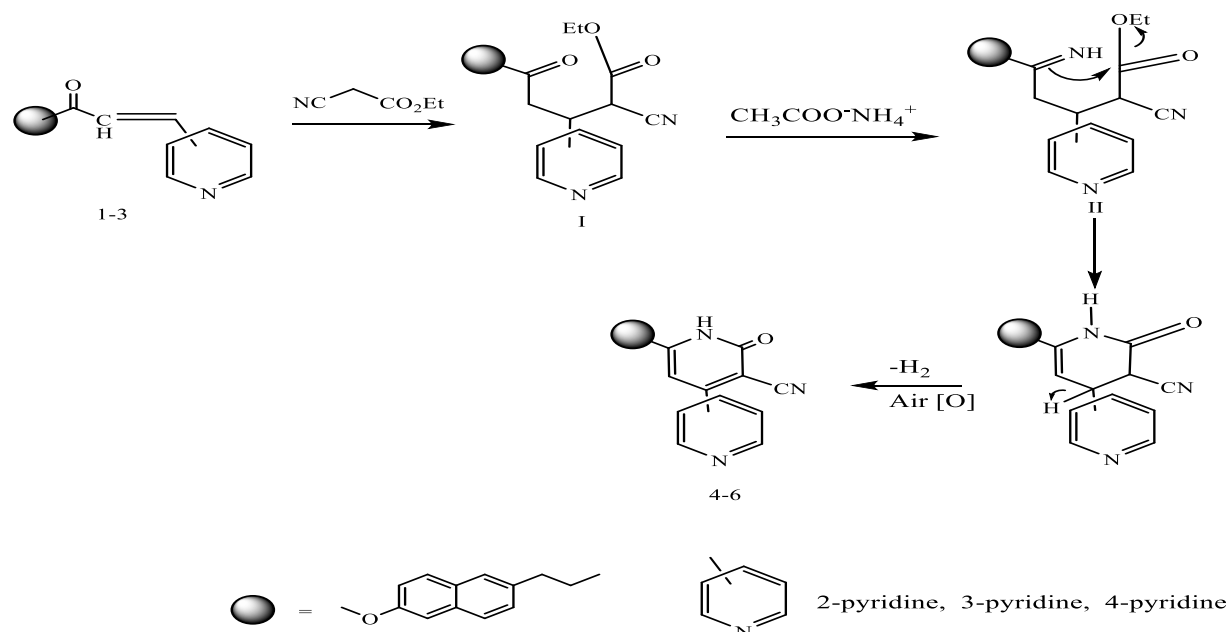


Scheme (2): Mechanism of chalcone preparation.

3.1.3. Mechanism of synthesis of 2-pyridone-3-carbonitrile derivatives (4-6):

As shown in Scheme 3, this mechanism involves the cyclo-condensation of chalcones (1-3) with ethyl cyanoacetate and ammonium acetate. The initial step involves the formation of an open-chain Michael adduct (I) via the

reaction of ethyl cyanoacetate with chalcone derivatives (1-3). This is followed by a reaction with ammonium acetate, yielding an imine intermediate (II). The final products (4-6) are subsequently obtained via cyclization, isomerization, and aromatization (39).

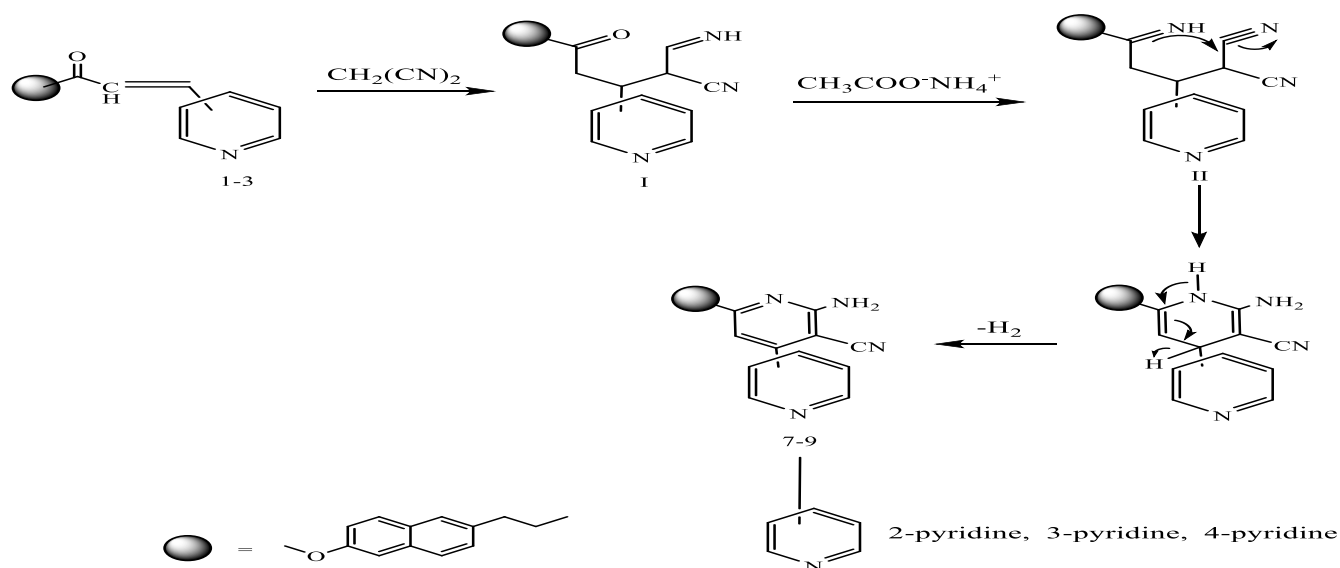


Scheme (3): Mechanism for the synthesis of the 3-cyano 2-pyridone series from chalcone derivatives.

3.1.4. Mechanism of synthesis of 2-aminopyridine-3-carbonitrile derivatives (7-9):

The mechanism of the synthesis is illustrated in Scheme 4, which comprises the following reaction: chalcone derivatives (1-3) react with malononitrile and ammonium acetate.

Initially, a compound (I) is generated via a Michael addition reaction between malononitrile and chalcone derivatives (1-3). This is followed by a reaction with ammonium acetate to form an imine intermediate (II), which is then cyclized to yield the final products (7-9) (40).



Scheme (4): Mechanism for the synthesis of the 2-amino-3-cyanopyridine derivatives from chalcone derivatives.

3.2. Spectroscopic Characterization and Structural Transformation

The chemical structures of the newly synthesized hybrid (1-3) were confirmed by comparative spectroscopic analysis using FT-IR, ^1H -NMR, and ^{13}C -NMR. In the FT-IR, the characteristic strong absorption band of the Nabumetone carbonyl group at 1705.07 cm^{-1} was completely absent in all synthesized chalcone derivatives. The successful formation of chalcone derivatives was identified by the emergence of a new carbonyl ($\text{C}=\text{O}$) stretching band in the region at $(1653.00\text{--}1654.92)\text{ cm}^{-1}$, and the appearance of a new $\text{C}=\text{C}$ unsaturated stretching band at $(1629.85\text{--}1631.78)\text{ cm}^{-1}$.

The ^1H -NMR results indicate the disappearance of the singlet CH_3 protons of nabumetone at (2.11) ppm and the appearance of a doublet peak for the CH_2 proton of α -vinyl protons at (3.01-3.15) ppm and for the CH_2 proton of β -vinyl protons at (2.86-3.04) ppm, as well as the appearance of a multiplet peak for CH protons at (7.40-7.42).

The ^{13}C -NMR results have revealed peaks at (199.09-200.01) ppm, which represent the $\text{C}=\text{O}$, (42.50-44.56) ppm for the α -vinyl carbon, and (32.37-36.05) ppm for the β -vinyl carbon, and the disappearance of the CH_3 peak at (30.24) of nabumetone in all synthesized chalcone derivatives.

In the case of the pyridone derivatives (4-6), the presence of a lactam was confirmed by a new $\text{C}=\text{O}$ band in the infrared spectrum at $1651.07\text{--}1676.14\text{ cm}^{-1}$, along with a sharp $\text{C}\equiv\text{N}$ band at 2216.21 cm^{-1} . Additionally, the ^1H -NMR of these compounds showed a diagnostic pyridone NH singlet between 12.43 and 12.89 ppm and a characteristic C5-H singlet from the pyridone ring between 6.40 and 6.46 ppm. Similarly, the ^{13}C -NMR spectra of these compounds showed the appearance of a new lactam $\text{C}=\text{O}$ peak at $160.02\text{--}161.47\text{ ppm}$ and a nitrile carbon at $115.69\text{--}116.35\text{ ppm}$, confirming the pyridone architecture. In contrast, the 2-aminonicotinonitrile series (7-

9) was found to contain a primary amine (NH_2). FT-IR spectra of this substance showed two distinct bands corresponding to the asymmetric and symmetric stretching of the NH_2 group, ranging from 3464.15 to 3473.80 cm^{-1} .

In the ^1H -NMR, there was a broad exchangeable singlet representing two protons within the chemical shift range of 6.67- 6.83 ppm. The construction of the pyridine backbone in this series of compounds was further verified by the presence of a C5-H proton with a chemical shift of 7.52-7.98 ppm and by the carbon that correlates with the nitrogen (C2-NH_2), which showed a ^{13}C NMR chemical shift of 161.01-161.12 ppm. Each of these conversion steps indicated that the original structure of Nabumetone was still entirely intact because the methoxy (OCH_3) singlet chemical shift remained at 3.86- 3.87 ppm with a corresponding carbon shift of 55.60- 55.63 ppm, as well as the triplet-triplet pattern created by the ethylene bridge in the aliphatic region.

3.3. In Vitro Cytotoxicity

The anti-proliferative activities of the synthesized nabumetone-pyridine hybrids (4-9) were evaluated against the human lung adenocarcinoma (A549) cell line and the normal human dermal fibroblast (HDFn) cell line for 48 hours using the MTT assay. Table 1 summarizes the results, expressed as IC_{50} values and Selectivity Indices (SI). Figure 1 illustrates a graphical comparison of the cytotoxic activities. Among the synthesized compounds, compound (6) showed the lowest IC_{50} value against A549 cells at $31.82\text{ }\mu\text{g/mL}$, followed by compound (8) with an IC_{50} value of $38.09\text{ }\mu\text{g/mL}$. Compound (6) exhibited an IC_{50} value of $156.70\text{ }\mu\text{g/mL}$ against HDFn cells, corresponding to an SI value of 4.92, whereas compound (8) showed an IC_{50} value of $148.70\text{ }\mu\text{g/mL}$ against HDFn cells and an SI value of 3.90.



The reference drug erlotinib exhibited an IC_{50} value of 34.10 $\mu\text{g/mL}$ against A549 cells and 146.20 $\mu\text{g/mL}$ against HDFn cells, resulting in an SI value of 4.28.

Table (1): Cytotoxicity assay (IC_{50}) and selectivity index (SI) of the synthesized compounds and Erlotinib for 48 hr.

Compound	IC_{50} A549 $\mu\text{g/mL}$	IC_{50} HDFn $\mu\text{g/mL}$	Selectivity index (SI)
4	85.44	120.00	1.40
5	70.53	118.70	1.70
6	31.82	156.70	4.92
7	90.63	124.80	1.40
8	38.09	148.70	3.90
9	53.12	107.60	2.00
Erlotinib	34.10	146.20	4.28

$SI = IC_{50} (\text{HDFn}) / IC_{50} (\text{A549})$

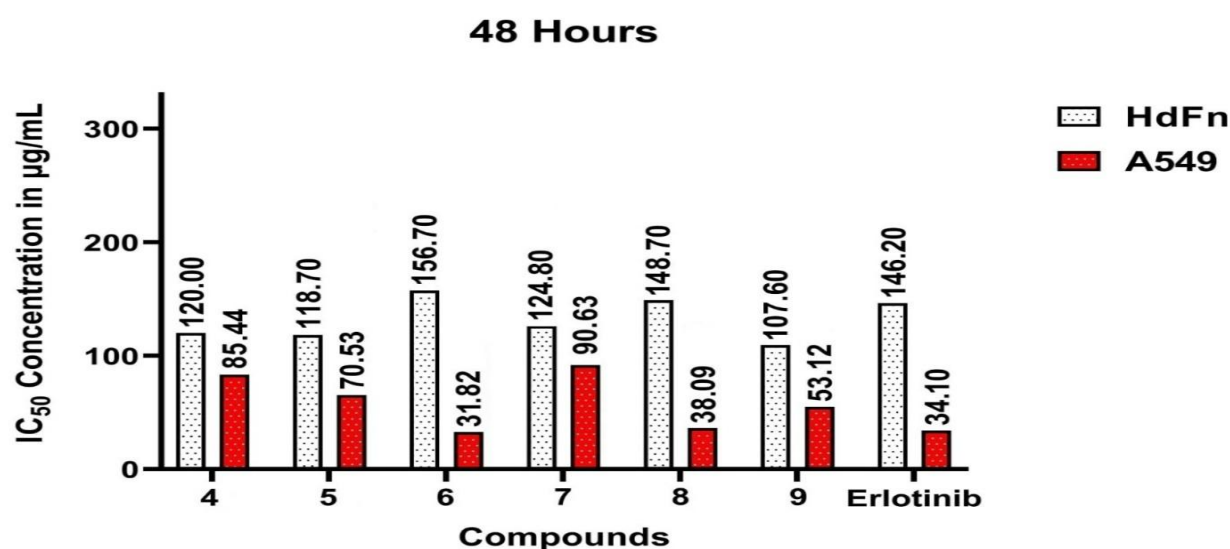


Figure 1: Comparison of IC_{50} values ($\mu\text{g/mL}$) of the synthesized compounds and erlotinib against A549 and HDFn cell lines for 48 hr.

4. Discussion

The spectroscopic findings supported the successful transformation of the nabumetone-derived chalcone intermediates into the corresponding pyridone and 2-amino-3-cyanopyridine derivatives. The shift of the carbonyl absorption from that of the parent nabumetone to the lower-frequency conjugated carbonyl region, together with the appearance of a C=C stretching band, supported formation of the chalcone intermediates. Subsequent appearance of characteristic lactam, nitrile, NH, and NH_2

signals in the FT-IR and NMR spectra provided further evidence for formation of the targeted heterocyclic systems. At the same time, retention of the methoxy and ethylene-linker signals indicated preservation of the nabumetone-derived naphthalene moiety throughout the synthetic transformations. The cytotoxicity results indicate that both scaffold type and substitution position influenced the biological activity of the synthesized compounds. Among the pyridone derivatives, compound (6) showed cytotoxic activity comparable to erlotinib against A549 cells,



with IC₅₀ values of 31.82 and 34.10 µg/mL, respectively. It also showed the highest selectivity index (SI = 4.92). Within the 2-amino-3-cyanopyridine series, compound (8) showed a good IC₅₀ value of 38.09 µg/mL and an SI value of 3.90.

Overall, the findings suggest that the para-substituted pyridone scaffold and the meta-substituted 2-amino-3-cyanopyridine scaffold provided the most favorable cytotoxicity and selectivity profiles among the tested compounds.

5. Conclusion

A series of novel nabumetone-derived pyridone and 2-amino-3-cyanopyridine compounds was successfully synthesized and structurally characterized using FT-IR, ¹H NMR, and ¹³C NMR spectroscopy. Among the tested compounds, the para-substituted pyridone derivative (6) exhibited the most favorable cytotoxicity and selectivity profile against A549 cells, while the meta-substituted 2-amino-3-cyanopyridine derivative (8) was the most active member of its series. The observed differences among the compounds indicate that both heterocyclic scaffold type and substitution position influence biological activity. These findings support further investigation of compounds (6) and (8) as potential lead structures for the development of anticancer agents.

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