

Synthetic Approaches and Anticancer Activities of 3-Cyano-2-Pyridone Derivatives

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Abstract: 3-Cyano-2-substituted pyridines, particularly 3-cyano-2-pyridone derivatives, represent an important class of nitrogen-containing heterocyclic compounds with broad pharmacological potential. This mini-review aims to highlight some of the synthetic approaches for preparing these derivatives and shed light on their diverse biological activities, with particular emphasis on their anticancer properties. Recent studies have demonstrated that these compounds exhibit promising anticancer activity through modulation of multiple molecular targets, including PIM-1 kinase, BIRC5, tubulin, EGFR, VEGFR-2, and BRAF. Several reported derivatives showed potent inhibitory activity, underscoring the significance of structural optimization in improving their biological efficacy. Overall, 3-cyano-2-substituted pyridines represent valuable scaffolds for the development of novel multitarget anticancer agents and continue to attract considerable interest in medicinal chemistry research.

Keywords: 3-cyano-2-pyridone; anticancer; BIRC5; BRAF; cyanopyridine; EGFR; PIM-1; synthesis; tubulin; VEGFR-2.

I. INTRODUCTION

Nitrogen-containing heterocyclic compounds constitute a highly significant class of organic compounds and serve as key structural motifs in a wide variety of natural products and synthetic pharmaceuticals. Owing to their structural diversity and the presence of versatile functional groups, these compounds have attracted considerable attention in drug discovery and in the design of advanced functional materials [1-3]. The remarkable biological and pharmacological potential of nitrogen-containing heterocycles has consequently stimulated extensive research into the development of novel biologically active heterocyclic scaffolds, particularly pyridine derivatives [4-6].

Pyridine derivatives represent one of the most important classes of nitrogen-containing heterocyclic compounds, owing to their broad range of pharmacological properties and significant synthetic utility. The pyridine ring is frequently incorporated into the structures of pharmaceutical agents and serves as a valuable building block in organic and medicinal chemistry [7, 8]. In addition, the pyridine nucleus constitutes an important structural component of several biologically active compounds, particularly anti-inflammatory and anticancer agents [9-11]. Several substituted pyridine derivatives, including streptonigrone, streptonigrin, and lavendamycin, have been reported to exhibit significant anticancer activity, whereas cerivastatin has been identified as an inhibitor of the HMG-CoA reductase enzyme [12]. Furthermore, certain substituted pyridine derivatives have demonstrated antagonistic activity toward leukotriene B₄ receptors, highlighting the broad therapeutic potential of this heterocyclic scaffold [13, 14].

Among the various pyridine-based heterocyclic systems, cyanopyridine derivatives have received considerable attention because of their remarkable structural diversity and broad spectrum of biological activities. Numerous cyanopyridine derivatives have been reported to exhibit promising antimicrobial [15-17], antioxidant [18-20], antibiotic [21-23], anti-

inflammatory [24, 25], analgesic [26], anticonvulsant [27], and anticancer [28-30] properties. In particular, 3-cyano-2-pyridone derivatives have emerged as valuable pharmacologically active scaffolds owing to their diverse biological activities, including antimicrobial [16, 31-33], antidepressant [34], and anticancer effects [30, 32, 35].

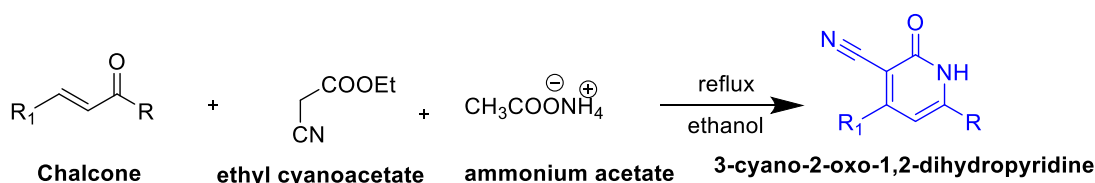
The promising anticancer potential of these compounds has attracted particular interest, as their biological activity may involve interaction with several molecular targets associated with cancer development and progression. Reported targets include PIM1 kinase [35-39], tubulin [40], phosphodiesterase 3 (PDE3) [7, 35, 41-43], and survivin protein [30, 35, 44-46]. The ability of cyanopyridine and 3-cyano-2-pyridone derivatives to interact with multiple biological targets further highlights their potential as valuable scaffolds for the design and development of novel anticancer agents. Therefore, in this context, The various reported pharmacological activities and general methods for the synthesis of 3-cyano-2-pyridone derivatives will be the particular focus of this review.

II. GENERAL METHODS FOR SYNTHESIS OF 3-CYANO-2-OXA-PYRIDINES

The synthesis of 3-cyano-2-pyridone analog has been documented using multiple reported methods; herein we have stated the general methods for their synthesis.

A. From chalcones (α,β -unsaturated ketones)

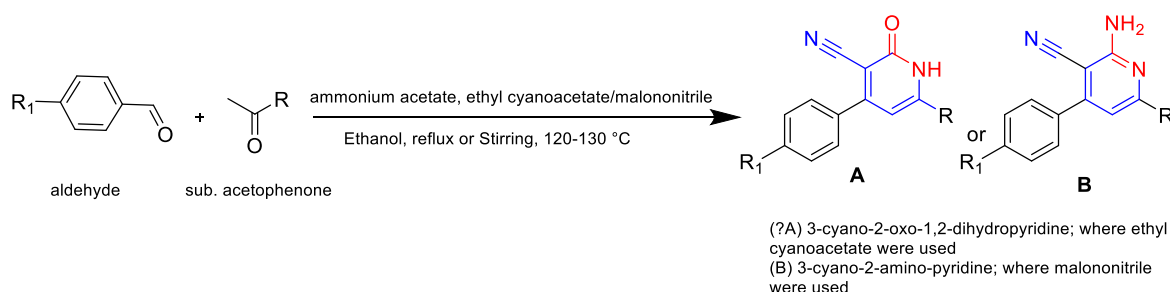
The 3-cyano-2-oxo-1,2-dihydropyridines were formed when chalcone reacted with ethyl cyanoacetate in an ethanol solution containing an excess of ammonium acetate under reflux conditions; however, the reaction afforded low yields (approximately 60–70%) and was time-consuming, requiring more than 24 hours over two steps (**Scheme 1**) [47-49].



Scheme 1: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from chalcones.

B. One-pot multi-component reaction

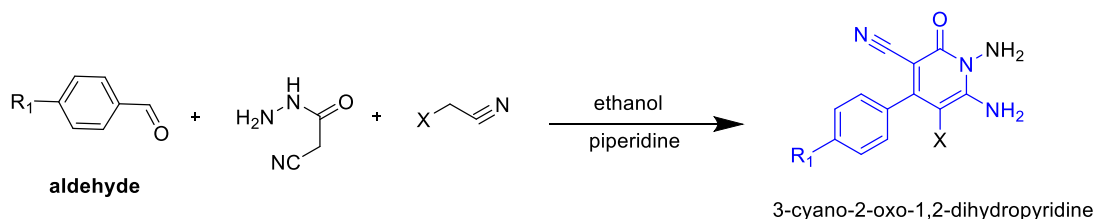
A suitable aldehyde, an excess of ammonium acetate in a solvent such as ethanol, butanol, or toluene, and a substituted acetophenone, ethyl cyanoacetate, or malononitrile are required for this method. On the other hand, this approach takes over 12 hours and but also has poor yields (around 60%) [50, 51]. The synthesis can also be performed in a one-pot without the use of solvents by combining an appropriate aldehyde, ammonium acetate, and ethyl cyanoacetate or malononitrile in equimolar proportions. Stir the mixture constantly at 120–130°C for 10–15 minutes to ensure a smooth reaction. This method is quick and effective, producing high yields (up to 90%) in a short amount of time (**Scheme 2**) [47, 52].



Scheme 2: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines via one pot reaction with/ without solvent from substituted ketone and aldehyde.

C. One-pot multi-component reaction via piperidine as a base

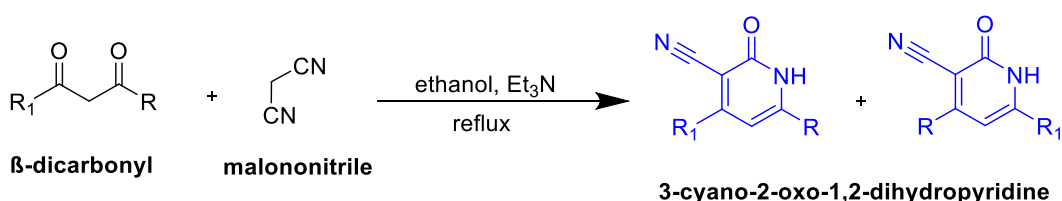
A one-pot reaction involving 2-cyanoacetohydrazide, an activated nitrile, and a suitable aldehyde in ethanol is used in this synthesis technique. The product is 3-cyano-2-oxo-1,2-dihydropyridine, which is achieved by a catalytic quantity of piperidine (**Scheme 3**) [47, 53]



Scheme 3: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines via on-pot reaction using piperidine as catalyst.

D. From β -dicarbonyl compounds

The chosen β -dicarbonyl molecule is refluxed in ethanol with equimolar amounts of malononitrile and triethylamine, while being stirred continuously for 15 minutes (**Scheme 4**) [47, 54, 55].



Scheme 4: Synthesis of 3-cyano-2-oxo-1,2-dihydropyridines from β -dicarbonyl compound

III. BIOLOGICAL ACTIVITY OF 3-CYANO-2-SUBSTITUTED PYRIDINE

The pyridine nucleus is a well-established scaffold in medicinal chemistry due to its broad range of biological activities [56, 57]. Numerous substituted cyanopyridine derivatives have demonstrated significant pharmacological effects, including antihypertensive, antipyretic, anti-inflammatory, analgesic, cardiotonic, antimicrobial, and anticancer activities [58, 59] (**Fig. 1**). In addition, several clinically relevant compounds containing the pyridine ring, such as streptonigrin, streptonigrone, and lavendamycin, have attracted considerable attention for their promising anticancer properties. Furthermore, a number of pyridine-based derivatives have been investigated as topoisomerase inhibitors and have shown potent cytotoxic effects against various human cancer cell lines, highlighting their potential as valuable candidates for anticancer drug development [59].

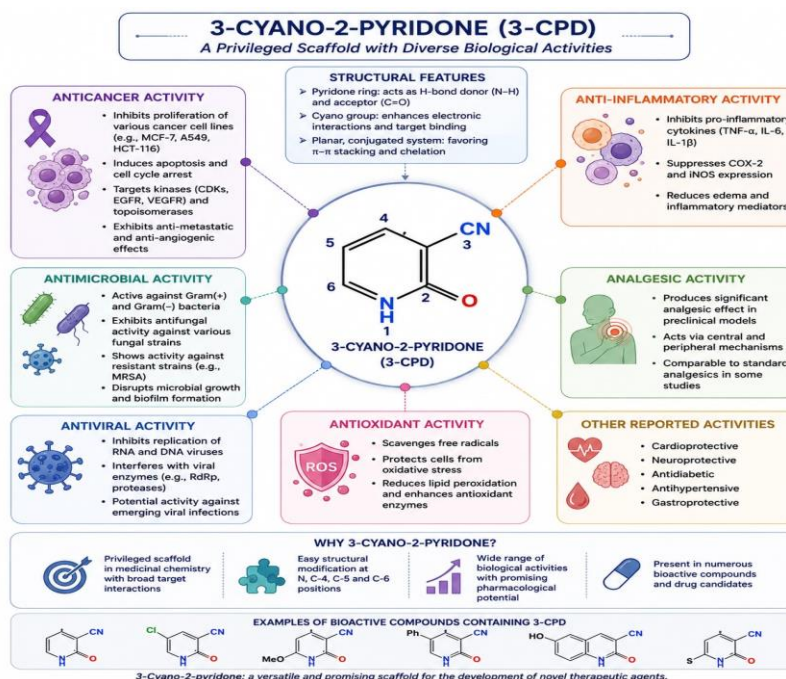


Fig. 1: Different biological activities of 3-cyano-2-pyridone ring

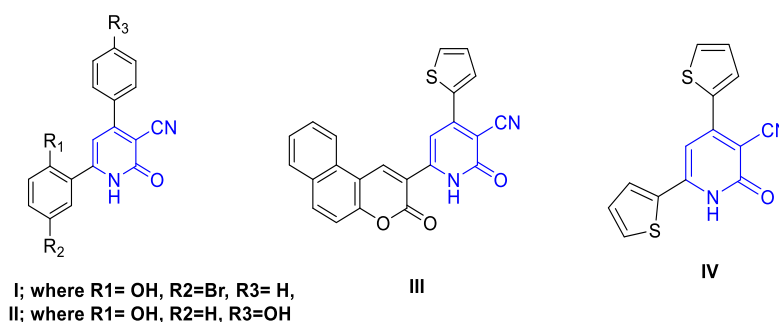
A. 3-Cyano-2-oxa-pyridines with anticancer activity

Several 3-cyano-2-oxopyridine analog have demonstrated promising and potent anticancer activity [30, 32] in comparison to several different cell lines [59, 60]. These compounds have garnered considerable attention due to their anticancer prospective, as they are capable of acting on multiple biological targets through diverse modes of action [47].

a. 3-Cyano-2-substituted pyridine as PIM-1 kinase inhibitor

A number of kinase families govern translation and transcription in cells. One such family, PIM kinases, so called because of the "proviral integration site in Moloney murine leukemia virus," is essential for many cellular functions and signal transduction pathways. Many biological cascades, including those involved in cell survival, differentiation, and proliferation, rely on these ubiquitously expressed kinases [61]. Cancer cells went into cell death and arrest when it was inhibited [62].

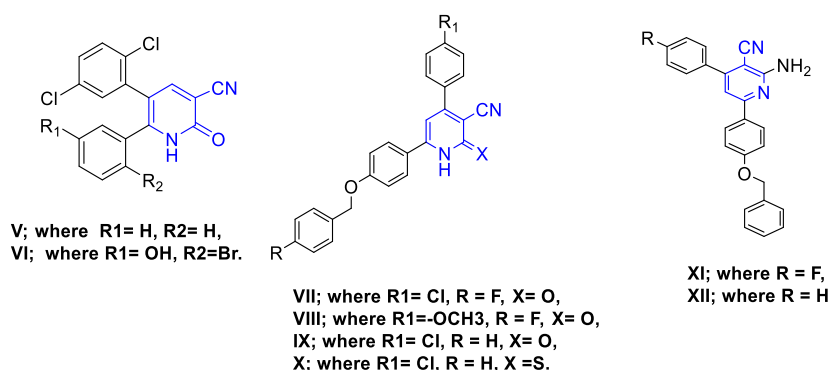
PIM-1 kinase a proto-oncogene that encodes a serine/ threonine kinase has been found to be over revealed in a various cancer cell lines [63]. Cheney et al. reported a novel cyanopyridine analogues that showed strong inhibitory action against PIM-1 kinase [64]. Compound I emerged as the strongest inhibitor, with an IC_{50} of 50 nM. Several recent studies have documented various cyanopyridine analog as effective PIM-1 kinase inhibitors, encompassing compound II (IC_{50} = 0.84 μ M), compound III (IC_{50} = 0.43 μ M), and compound IV (IC_{50} = 0.99 μ M), utilizing the 4,6-diaryl-3-cyano-2-substituted pyridine scaffold as a structural framework for these inhibitors [30, 50, 65, 66].



b. 3-Cyano-2-substituted pyridine as BIRC5 inhibitor

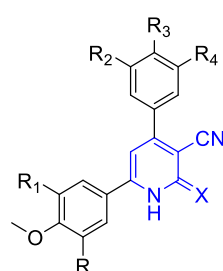
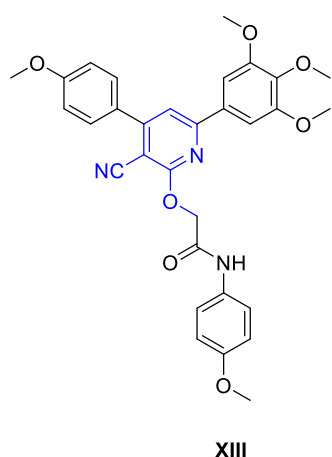
BIRC5, the smallest member of the inhibitor of apoptosis protein (IAP) family, is encoded by the BIRC5 gene in humans. It has recently arisen as a promising drug target because of its dual function in cancer, contributing both to advancement of the cell cycle and suppression of apoptosis [67]. BIRC5 is markedly displayed in the majority of human tumors and in fetal tissues, yet it is markedly absent in the majority of terminally differentiated adult tissues. The level of BIRC5 in tumor cells is frequently linked with unfavorable prognosis and declined patient survival. This specific display profile makes BIRC5 an ideal target for cancer therapy [63].

Indeed, several molecular strategies aimed at inhibiting BIRC5 display and/or function are emerging as prospective therapeutic strategies in cancer treatment [67]. One such class includes 3-cyano-2-substituted pyridine analog with increased lipophilicity. Compounds V–XII demonstrated anticancer activity through suppression of the BIRC5 protein. An increase in lipophilicity was observed as a result of an improved binding affinity to BIRC5 caused by the addition of a halogen atom to the pyridone scaffold at the para position [30, 45, 48].



c. 3-Cyano-2-substituted pyridine as tubulin polymerization inhibitor

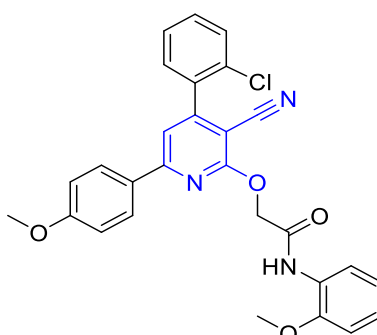
Tubulin, a critical target in cancer therapy, has emerged as a major focus in the development of antineoplastic drugs in recent years. Tubulin inhibitors bind to tubulin, disrupting its stability and interfering with its essential cellular functions, thereby efficiently eliminating tumor cells and producing therapeutic outcomes. Relative to traditional cytotoxic agents, tubulin inhibitors have demonstrated superior efficacy in cancer chemotherapy. These inhibitors primarily target four binding sites, all of which are located on the β -tubulin subunit [68]. Some 3-cyano-2-substituted pyridine analog have exhibited strong cytotoxic effects, surpassing that of combretastatin A4 (CA-4), as shown by compounds XIII-XVI that inhibits tubulin polymerization at quantities below micromolar [69]. The chemicals' anticancer effect is directly related to their ability to suppress β -tubulin polymerization [47].



XIV; where X = O, R = H, R₁=H, R₂=-OCH₃, R₃=-OCH₃, R₄=-OCH₃,
XV; where X = O, R =-OCH₃, R₁=-OCH₃, R₂=-OCH₃, R₃= OH, R₄= H,
XVI; where X = S, R=-OCH₃, R₁=-OCH₃, R₂=-OCH₃, R₃= OH, R₄= H.

d. 3-Cyano-2-substituted pyridine as EGFR inhibitors

The EGFR is a member of the ERBB family of tyrosine TK receptors. The EGFR signaling cascade has a central function in regulating cell proliferation, differentiation, division, survival, and the progression of cancer [70]. EGFR inhibitors block autophosphorylation either by targeting the extracellular growth factor-binding domain (monoclonal antibodies) or the intracellular ATP-binding site (small-molecule TKIs, also known as “nibs”) [71]. E. M. Lotfy [72] synthesized a series of 2-pyridone derivatives and evaluated their inhibitory activity against the EGFR tyrosine kinase enzyme. Among the synthesized compounds, compound XVII exhibited the highest inhibitory potency, with an (IC₅₀ value of 0.03 ± 0.06 μ M), surpassing the reference drug Erlotinib (IC₅₀ = 0.14 ± 0.05 μ M). These findings suggest that compound XVII possesses a strong affinity for the EGFR active site and may serve as a promising lead compound for the development of novel EGFR tyrosine kinase inhibitors.

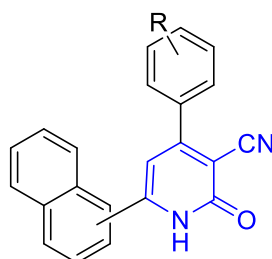


XVII

e. 3-Cyano-2-substituted pyridine as VEGFR-2 kinase inhibitors

VEGFR-2, a TK receptor, is often over displayed in a wide range of cancers. It has a pivotal role in tumor angiogenesis which is mainly regulated by vascular endothelial growth factor (VEGF), that binds to vascular endothelial growth factor receptors (VEGFRs) located on the cell surface, promoting blood vessel formation, tumor growth, and metastasis [73-75].

Therefore, targeting the VEGF/VEGFR pathway with therapeutic agents is an effective strategy for cancer treatment, as it inhibits angiogenesis and prevents the spread of metastatic tumors [75, 76]. An example of this approach, A. Abdelhaleem et.al, [77] reported a series of 4-aryl-3-cyano-6-(2-naphthyl)pyridine-2-ones compounds and evaluated their inhibitory activity against VEGFR-2 compared to Delphinidin as a reference drug. Among these compounds, The unsubstituted phenyl derivative **XVIII** exhibited good inhibitory activity against VEGFR-2, with an IC_{50} value of 0.69 nM. Compounds **XIX** and **XXI** demonstrated improved activity, showing IC_{50} values of 0.44 and 0.55 nM, respectively. Among all the synthesized derivatives, compound **XX** bearing a 4-chlorophenyl substituent, showed the highest inhibitory potency, with an IC_{50} of 0.23 nM, representing approximately a threefold increase in activity compared with the parent compound.



XVIII; where R= H

XIX; where R= 4-NO₂

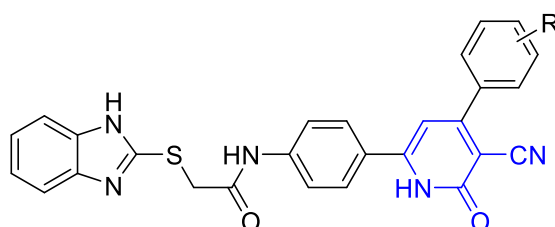
XX; where R= 4-Cl

XXI; where R= 3,4-di-OCH₃

f. 3-Cyano-2-substituted pyridine as BRAF inhibitors

BRAF is a serine/threonine kinase regulated by RAS that plays a key role in activating the MAPK signaling pathway. This pathway transmits extracellular signals to control essential cellular processes, including proliferation, differentiation, and survival [78]. Mutations in the BRAF gene, particularly the V600E mutation, lead to constitutive activation of this pathway, promoting uncontrolled cell growth and tumor progression. BRAF mutations are frequently detected in several cancers, including melanoma, colorectal, thyroid, and non-small cell lung cancers, making BRAF an important molecular target for anticancer therapy [79]. Although selective BRAF inhibitors have significantly improved clinical outcomes, the emergence of drug resistance has driven the development of new BRAF-targeted agents with enhanced efficacy and safety.

A study conducted by L. H. Al-Wahaib., et al [80] investigated 2-mercaptobenzimidazole/3-cyano-2-pyridone hybrids and found that compounds **XXII**, **XXIII**, **XXIV** exhibited moderate inhibition of BRAF^{V600E}, with IC_{50} values of 0.05, 0.22 and 0.78 μ M respectively, compared to vemurafenib, which had an IC_{50} value of 0.03 μ M. Compound **XXII** exhibited the highest inhibitory efficacy against BRAF^{V600E} (IC_{50} = 0.05 μ M) and was identified as an efficient inhibitor of cancer cell proliferation.

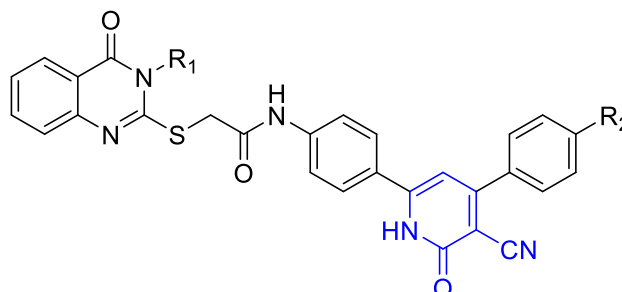


XXII; where R= 4-OCH₃

XXIII; where R= 3,4-di-OCH₃

XXIV; where R= N,N-dimethylamino

In a work by L. H. Al-Wahaibi., et al [81] a new group of quinazolin-4-one/3-cyano-2-pyridone hybrids was designed and tested for their activity against BRAF^{V600E}. The study showed that compounds XXV and XXVI had the most potent inhibitory activities against BRAF^{V600E}, with IC₅₀ values of 140 ± 10 nM and 190 ± 12 nM, respectively, being 2- and 3-fold less potent than Erlotinib which was chosen as the reference drug (60 ± 5 nM).



XXV; where R₁=Allyl, R₂= 4-OCH₃

XXVI; where R₁=Allyl, R₂= 4-Cl

IV. CONCLUSION

3-Cyano-2-pyridone derivatives represent a versatile nitrogen-containing heterocyclic platform with significant potential for medicinal-chemistry exploration. Their synthetic accessibility and the ability to diversify the 4- and 6-positions, the 2-oxo functionality, and appended pharmacophores have enabled the generation of compounds with activity against several cancer-relevant targets. The literature summarized in the supplied manuscript includes PIM-1 kinase, survivin/BIRC5, tubulin, EGFR, VEGFR-2, and BRAF V600E as prominent examples. The current evidence nevertheless supports a more cautious conclusion than the original manuscript. Reported potency values are assay-dependent, and direct comparison between different studies can be misleading. In addition, target inhibition, cellular antiproliferative activity, apoptosis, and molecular docking represent different evidentiary levels and should not be conflated. The available data suggest that structural changes around the 3-cyano-2-pyridone scaffold can strongly influence activity, but a generalizable SAR model remains incomplete. Future development should therefore prioritize systematic matched-series design, target-specific SAR, orthogonal biological validation, selectivity profiling, and characterization of ADME and safety-related properties. With these elements integrated into a coherent medicinal-chemistry strategy, the 3-cyano-2-pyridone scaffold could provide a useful starting point for the discovery and optimization of more selective anticancer leads.

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