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Novel Pyridine and Chromene Hybrids via Multicomponent Reactions of Cyanoacetohydrazide: Synthesis, Mechanistic Insights, and Spectral Characterization

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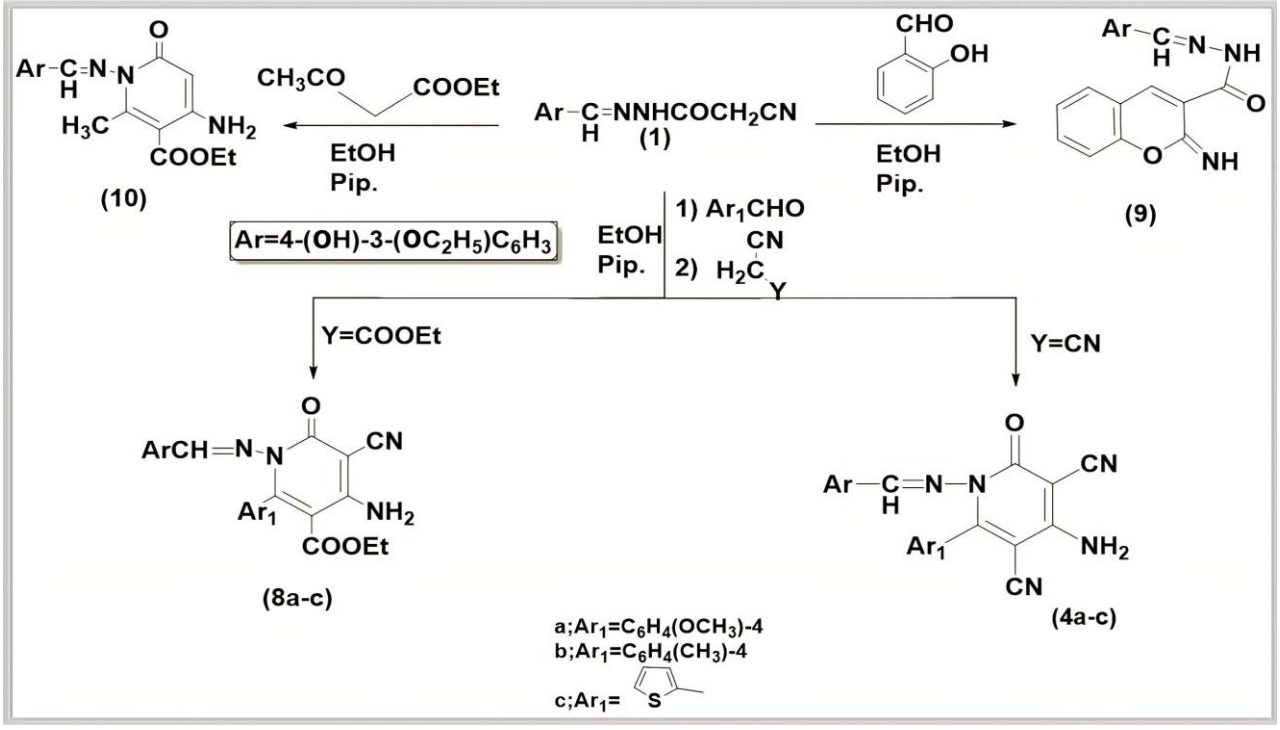
ABSTRACT

Cyanoacetohydrazide, a versatile building block containing both nucleophilic and electrophilic sites, was exploited to develop new pyridine and chromene derivatives bearing a 4-hydroxy-3-ethoxyphenyl moiety. A series of nitrogen- and oxygen-based heterocycles was generated through multicomponent synthetic approaches using diverse aromatic aldehydes, malononitrile, ethyl cyanoacetate, and salicylaldehyde. Proposed reaction mechanisms involved sequential steps, including Knoevenagel condensation, Michael addition, and intramolecular cyclization. Structural identities of the obtained. IR and NMR spectroscopy, together with elemental analysis, supported the proposed chemical structures of the compounds, all of which verified the expected functional groups and ring frameworks. The incorporation of ethylvanillin as a primary aldehyde source enhanced the pharmacophoric potential of the final molecules. The developed procedures furnished regioselective products in excellent yields under mild conditions. Overall, the findings highlight the applicability of cyanoacetohydrazide in constructing complex heterocyclic frameworks, offering promising scaffolds for future studies in medicinal chemistry, drug design, and functional materials. These findings offer a strong basis for additional biological analysis of the produced substances.

Graphical abstract



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1. Introduction

Cyanoacetohydrazide [1] is a highly versatile precursor in heterocyclic synthesis due to its bifunctional structure, which includes two centers, which are electrophilic, located at the carbon atoms of the carbonyl and cyano groups, and two nucleophilic sites positioned at the methylene (-CH_2-), and NH moieties [2]. This dual reactivity enables the formation of a broad range of heterocyclic systems in moderate environments. Pyridine (C_5H_5N) is a basic six-membered heterocyclic aromatic compound structurally related to benzene, where one CH group is replaced by a nitrogen atom. Like benzene, it contains a fully delocalized π-electron system of six electrons, which confers aromatic stability and planarity to the molecule. The conjugation of these electrons over the ring satisfies Hückel's rule, making pyridine a prototypical example of aromatic heterocycles. The shared π-electron cloud and alternating double bonds contribute to its electronic properties and reactivity[3]. Also, Pyridine rings are commonly found in numerous naturally occurring compounds, including essential vitamins such as vitamin B_6 (pyridoxine) and niacin (vitamin B_3), as well as biologically important coenzymes like nicotinamide adenine dinucleotide (NAD). They are also present in alkaloids such as trigonelline, which occur in various plant sources [4]. The most important property of pyridine in medicinal chemistry is its ability to enhance the water solubility of drug molecules. This is primarily attributed to its weak basicity, which contributes to better pH stability and improved pharmacokinetic properties. Notably, more than 7,000 pharmaceutical compounds are known to incorporate pyridine as a central structural scaffold [5] Additionally, pyridine is among the most extensively utilized heterocyclic scaffolds and has been reported to display diverse biological activities [6–8] including antitubercular [9], anticancer [10], antiviral [11], antitubercular [12] and antimicrobial [13]. Several pharmaceutical agents incorporate a pyridine nucleus and have demonstrated antimalarial activity [14], antidiabetic [15], antioxidant [16], anti-inflammatory [17], and anti-amoebic activities [18]. Moreover, fusion of the pyridine ring with a benzene ring yields a quinoline nucleus, a key structural scaffold found in several broad-spectrum antibiotics. These antibiotics, such as moxifloxacin, nadifloxacin, levofloxacin, ozenoxacin, and nalidixic acid, are effective against both Gram-positive and Gram-negative bacteria. Their bactericidal activity is attributed to the inhibition of bacterial DNA replication and interference with RNA synthesis, which ultimately disrupts protein synthesis [19, 20] (Figure 1).

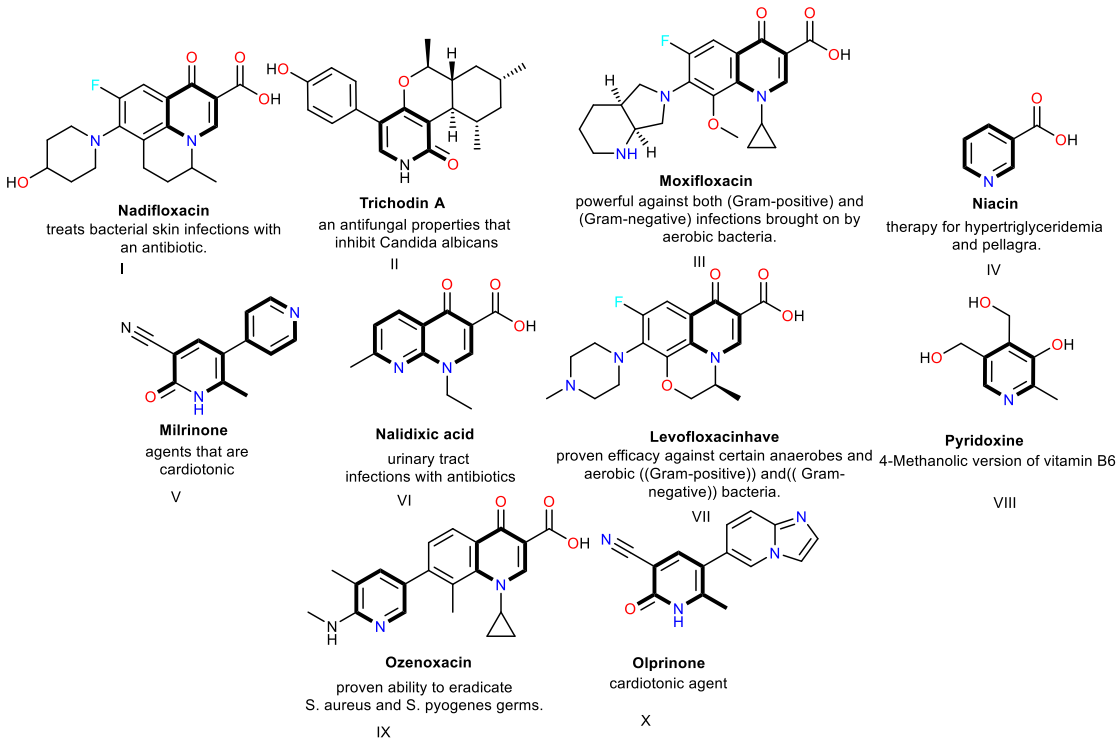


Figure 1. Selected examples of pharmacologically active compounds featuring pyridine or pyridinone cores

Building upon prior studies and continuous efforts in the design and synthesis of biologically active heterocyclic compounds [21–25]. Nitrogen-containing heterocycles have demonstrated significant biological potential [26–28] and play a crucial role in modern drug discovery and development [29]. Among them, the six-membered ring pyridine nucleus is particularly prominent and occurs naturally in many bioactive molecules, including alkaloids (e.g., nicotine), vitamins (e.g., niacin and pyridoxine), and coenzymes [30]. While pyridine itself is commonly used in organic laboratories as a solvent, Applications for its derivatives can be found in a variety of industries, including functional nanomaterials, organometallic ligands, and asymmetric catalysis [31, 32] In medicinal chemistry, pyridine based scaffolds are among the most widely used frameworks due

to their (i) unique heteroaromatic nature, (ii) synthetic versatility, (ii) strong impact on pharmacological profiles, and (iv) frequent incorporation as pharmacophores in drug candidates [33] . These structural attributes have supported the development of a variety of broad-spectrum medicines [34] and agrochemical products [35, 36]. Furthermore, the introduction of functional groups, including sulfamide, hydrazide, amino, hydroxy, and methoxy, has been demonstrated to enhance pyridine's biological action, containing substances [37]. Consequently, pyridine scaffolds remain highly valued among nitrogen-based heterocycles for their diverse biological, medicinal, chemical, physical, and optical properties. Chromene-derived heterocyclic systems represent a notable category of oxygen-containing molecules, attracting significant interest owing to their structural versatility and broad spectrum of biological and pharmacological activities [38]. These fused benzopyran systems occur frequently in a variety of natural goods. And synthetic drugs, displaying activities such as anti-inflammatory [39], antimicrobial [40], anticancer, antioxidant, and antidiabetic effects [41]. From the previous literature survey, the authors were interested in synthesizing new pyridone and chromene derivatives having a 4-hydroxy-3-ethoxy-phenyl scaffold *via* multicomponent reactions using cyanoacetohydrazide as a key precursor for improving antimicrobial activity.

2. Materials and methods

A computerized device was employed to determine the degrees of melting, which were recorded without correction. The infrared spectra (KBr) were measured using a Shimadzu 440 spectrophotometer. NMR spectra of ^{1}H and ^{13}C were obtained at 500 MHz and 126 MHz, respectively. TMS is employed as a reference for internal use. On silica gel 60F254 plates, TLC was utilized to monitor the reaction's progress under UV light.

2.1. Synthesis of 3-ethoxy-4-hydroxybenzylidene 2-cyano-N'-acetohydrazide (1)

Acetic acid was added in little drops as a catalyst to a solution that contained cyanoacetohydrazide (0.01 mol) and ethylvanillin (0.01 mol) in absolute EtOH (20 mL). After allowing the mixture to reflux for three hours, it was permitted to cool to room temperature. To obtain compound (1) with great purity and good yield, Filtration, drying, and recrystallization of the precipitated material from ethanol were performed.

A yellow solid was obtained from ethanol with 64% yield; m.p.= 220–22 ° C. IR (v/cm^{-1}, KBr): characteristic bands at 1698 (C=O), 2276 (C≡N), 2973 (aliphatic C–H), 3071 (aromatic C–H) and 3208 (NH), ^{1}H NMR (DMSO-d_6, 500 MHz, δ ppm): two singlets at 11.58 and 9.40 ppm that represent the protons NH and OH (D_2O interchangeable); a singlet at 7.84 ppm (methine-H); aromatic resonances at 7.24 (s, 1H), 7.03 (d, J = 10 Hz, 1H), and 6.78 (d, J = 5 Hz, 1H); a quartet at 4.02 ppm (2H, –OCH_2), a singlet at 3.91 ppm (2H, CH_2), and a triplet at 1.30 ppm (3H, CH_3). ^{13}C NMR (126 MHz, δ ppm, DMSO-d_6):164.93 (C=O), 159.00, 148.91 (C–OH), 145.34 (C=N), 140.51, 125.77, 122.13, 116.70 (C≡N), 111.41, 64.45 (–OCH_2), 25.30, 15.20 (–CH_3). Elemental analysis: $C_{12}H_{13}N_3O_3$ (247.25) computed: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.58; H, 5.14; N, 17.25.

2.2. Typical synthetic route for compounds (4a–c)

Synthesis of 4-amino-6-aryl-1-((3-ethoxy-4-hydroxybenzylidene)amino)pyridine-3,5-dicar bonitrile 2-oxo-1,2-dihydro (4a-c)

Cyanoacetohydrazide derivative (1) (0.01 mol) was dissolved in 20 ml of pure EtOH, and three drops of piperidine were introduced as a catalyst. To this solution, an equimolar quantity (0.01 mol) of either 4-methoxybenzaldehyde, 4-methylbenzaldehyde, or 2-thiophenecarboxaldehyde was added while stirring constantly. The mixture of reactions underwent three hours of reflux. Following that, 0.01 mol of malononitrile was incorporated. And the reflux was maintained for six more hours. After filtering out the precipitated products, cold ethanol was used to clean them, and then ethanol was used to further purify them.

2.2.1. Synthesis of 4-amino-1-((3-ethoxy-4-hydroxybenzylidene)amino)-6-(4-methoxyphenyl)- 3-dicarbonitrile-2-oxo-1,2-dihydropyridine (4a)

Orange crystalline solid (EtOH); m.p. = 165–67 °C; yield: 82%. IR (KBr, ν cm^{-1}): 3367, 3152 (–NH_2), aliphatic C–H (2918), aromatic C–H (3074), 2225, 2207 (C≡N), and 1693 (C=O, respectively). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.28 (s, 1H, OH, D_2O-exchangeable), 8.07 (s, 1H, CH–methine), 7.91 (s, 1H, Ar–H), 7.39 (d, J = 10 Hz, 1H, Ar–H), 7.13 (d, J = 5 Hz, 1H, Ar–H), 6.87 (d, J = 10 Hz, 2H, Ar–H), 6.80 (d, J = 10 Hz, 2H, Ar–H), 5.20 (s, 2H, NH_2, D_2O-exchangeable), 4.01 (q, J = 10 Hz, 2H, –OCH_2), 3.76 (s, 3H, –OCH_3), and 1.30 (t, J = 5 Hz, 3H, –CH_3)..^{13}C NMR (126 MHz, DMSO-d_6, δ ppm): 165.02, 161.58 (C=O), 161.41, 159.13 (C=N), 149.81 (C–OH), 147.64, 144.82, 134.05, 130.73, 126.92, 125.76, 122.15, 116.62 (C≡N), 115.51, 111.47, 102.23, 99.59, 64.46 (–OCH_2), 55.87 (–OCH_3), 14.38 (CH_3). Elemental analysis: $C_{23}H_{19}N_5O_4$ (429.44). Calcd: C, 64.33; H, 4.46; N, 16.31. Found: C, 64.13; H, 4.00; N, 16.44.

2.2.2. Synthesis of 4-amino-1-((3-ethoxy-4-hydroxybenzylidene)amino)-2-oxo-6-(p-tolyl) -3,5-dicarbonitrile-1,2-dihydropyridine (4b)

Yellow solid crystal (EtOH); yield: 73%; m.p. = 260-62 °C. IR (KBr, ν cm^{-1}): 3454, 3399 (–NH_2), 3070 (aromatic C–H), 2970 (aliphatic C–H), 2220 (C≡N), 1642 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 8.52 (s, 1H, OH, D_2O-exchangeable), 7.40 (s, 1H, methine-H), 7.36 (s, 1H, Ar–H), 7.34 (d, J = 5 Hz, 1H, Ar–H), 7.22 (d, J = 5 Hz, 1H, Ar–H), 7.20 (d, J = 5 Hz, 2H, Ar–H), 6.84 (d, J = 5 Hz, 2H, Ar–H), 5.61 (s, 2H, –NH_2, D_2O exchangeable), 4.02 (q, J = 5 Hz, 2H, –OCH_2), 2.36 (s, 3H, –CH_3), 1.33 (t, J = 10 Hz, 3H, –CH_3). ^{13}C NMR (126 MHz, DMSO-d_6, δ ppm): 161.10 (C=O), 159.82, 157.93 (C=N), 157.19 (C–OH), 150.62 (C=C–Ar), 147.64, 140.58, 132.21, 128.51, 126.05, 123.84, 116.98, 116.11 (2×C≡N), 111.90, 107.05, 99.76, 94.32, 86.89, 64.38 (–OCH_2), 21.49 (–CH_3), 15.25 (–CH_3). Elemental analysis: $C_{23}H_{19}N_5O_3$ (413.44).

Calculated: C, 66.82; H ,4.63; N, 16.94. Found: C, 66.15; H, 4.57; N, 16.67.

2.2.3. Synthesis 4-amino-1-((3-ethoxy-4-hydroxybenzylidene)amino)-2-oxo-6-(thiophen-2-yl)- 3,5-dicarbonitrile (1,2-dihydropyridine) (4c)

Brown crystalline solid (EtOH); Yield: 88%; m.p. = 180-82 °C. IR (KBr, ν cm^{-1}): 3298, 3180 (–NH_2), 3090 (aromatic C–H), 2977 (aliphatic C–H), 2202 (C≡N), 1628 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, δ ppm): 8.83 (s, 1H, OH, exchangeable by D_2O), 8.51 (s, 1H, methine-H), 7.84 (d, 1H, Ar–H), 7.73 (t, 1H, Ar–H), 7.58 (d, J = 15 Hz, 1H, Ar–H), 7.38 (d, J = 5 Hz, 1H, Ar–H), 7.31 (s, 1H, Ar–H), 6.95 (d, J = 5 Hz, 1H, Ar–H), 5.82 (s, 2H, –NH_2, exchangeable with D_2O), 3.94 (q, J = 5 Hz, 2H, –OCH_2), 1.33 (t, J = 10 Hz, 3H, –CH_3). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, δ ppm): 184.81, 179.32 (2×C–S), 161.15 (C=O), 156.33 (C=N), 153.01 (C–OH), 147.86 (C=C–Ar), 138.48, 136.63, 134.30, 129.15, 126.40, 116.06 (C≡N), 112.51, 106.81, 104.34, 99.98, 64.42 (–OCH_2), 14.35 (–CH_3). Elemental analysis: $C_{20}H_{15}N_5O_3S$ (405.43). Calculated: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.18; H, 3.66; N, 17.19.

2.3. Representative synthetic method for compounds (8a–c)

Synthesis of 5-cyano-1-((3-ethoxy-4-hydroxybenzylidene)amino)- 6- oxo-1,6-dihydropyridine -3-carboxylate ethyl 4-amino-2-aryl (8a-c)

A stirred solution of cyanoacetohydrazide derivative 1 (0.01 mol) in pure ethanol (20 mL) was supplemented with 3 drops of piperidine, a catalytic amount. The mixture underwent refluxing for three hours after an equimolar quantity (0.01 mol) of either 4-methylbenzaldehyde, 4-thiophenecarboxaldehyde, or 4-methoxybenzaldehyde was added to this solution. Following the addition of ethyl cyanoacetate (0.01 mol), the heating procedure was continued for an additional six hours under reflux. After cooling, filtering, cleaning with cold ethanol, and recrystallizing from ethanol, the precipitated material was refined to yield the necessary components.

2.3.1. Synthesis of 4-amino ethyl -5-cyano 2-(4-methoxyphenyl)-1-((3-ethoxy-4-hydroxybenzylidene)amino) 3-carboxylate-6-oxo-1,6-dihydropyridine (8a)

Orange crystalline solid (EtOH); Yield: 70%; m.p. = 170–72 °C. IR (KBr, ν cm^{-1}): 3308, 3200 (–NH_2), 2975 (aliphatic C–H), 2208 (C≡N), 1716 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, δ ppm): 9.44 (s, 1H, OH, D_2O-exchangeable), 8.51 (s, 1H, methine-H), 8.15 (d, J = 5 Hz, 1H, Ar–H), 8.06 (d, J = 5 Hz, 1H, Ar–H), 7.65 (s, 1H, Ar–H), 7.46 (d, J = 5 Hz, 2H, Ar–H), 7.05 (d, J = 5 Hz, 2H, Ar–H), 5.60 (s, 2H, –NH_2, D_2O-exchangeable), 4.23 (q, J = 5 Hz, 2H, –OCH_2), 3.99 (q, J = 5 Hz, 2H, –OCH_2), 3.74 (s, 3H, –OCH_3), 1.32 (t, J = 5 Hz, 3H, –CH_3), 1.25 (t, J = 10 Hz, 3H, –CH_3). Elemental analysis: $C_{25}H_{24}N_4O_6$ (476.49). Calculated: C, 63.02; H, 5.08; N, 11.76. Found: C, 63.10; H, 5.00; N, 11.65.

2.3.2. Synthesis of ethyl 4-amino 5-cyano -1-(amino(3-ethoxy-4-hydroxybenzylidene)) -6-oxo-2-(p-tolyl) One,6-dihydropyridine -3-carboxylate (8b)

Orange crystalline solid (EtOH); Yield: 66%; m.p. = 192–94 °C. IR (KBr, ν cm^{-1}): 3297, 3200 (–NH_2), 2974 (aliphatic C–H), 2208 (C≡N), 1716 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, δ ppm): 9.43 (s, 1H, OH, D_2O-exchangeable), 8.03 (s, 1H, methine-H), 7.66 (s, 1H, Ar–H), 7.48 (d, J = 5 Hz, 1H, Ar–H), 7.28 (d, J = 10 Hz, 1H, Ar–H), 6.91 (d, J = 5 Hz, 2H, Ar–H), 6.70 (d, J = 5 Hz, 2H, Ar–H), 5.26 (s, 2H, NH_2, D_2O-exchangeable), 4.25 (q, J = 10 Hz, 2H, –OCH_2), 4.00 (q, J = 5 Hz, 2H, –OCH_2), 2.23 (s, 3H, –CH_3), 1.33 (t, J = 5 Hz, 3H, –CH_3), 1.26 (t, J = 5 Hz, 3H, –CH_3). ^{13}C NMR (126 MHz, DMSO-*d*$_6$, δ ppm): 164.72, 162.18 (2C=O), 154.54 (C=N), 148.64, 148.52 (C–OH), 147.84 (C=C–Ar), 147.72, 131.52, 129.62, 128.36, 120.48, 116.17 (CN), 114.57, 114.36, 112.54, 101.73, 100.00, 92.57, 64.41, 63.36 (2 -OCH_2), 22.90 (CH_3), 21.18, 15.25 (2 -CH_3). Elemental analysis: $C_{25}H_{24}N_4O_5$ (460.49). Calculated: C, 65.21; H, 5.25; N, 12.17. Found: C, 65.15; H, 5.20; N, 12.10.

2.3.3. Synthesis of ethyl 4-amino-5-cyano-1-((3-ethoxy-4-hydroxybenzylidene)amino)-6-oxo-2-(th- iophen-2-yl)-1,6-dihydropyridine-3-carboxylate (8c)

Brown crystalline solid (EtOH); Yield: 84%; m.p. = 240–42 °C.IR (KBr, ν cm^{-1}): 3203, 3100 (–NH_2), 2978 (aliphatic C–H), 2208 (C≡N), 1692 (C=O). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, δ ppm): 9.67 (s, 1H, OH, D_2O-exchangeable), 8.59 (s, 1H, methine-H), 8.19 (d, J = 5 Hz, 1H, Ar–H), 8.00 (d, 1H, Ar–H), 7.67 (t, J = 15 Hz, 1H, Ar–H), 6.97 (d, 1H, Ar–H), 6.80 (s, 1H, Ar–H), 6.67 (d, 1H, Ar–H), 5.72 (s, 2H, –NH_2, D_2O-exchangeable), 4.45 (q, J = 10 Hz, 2H, –OCH_2), 4.29 (q, J = 5 Hz, 2H, –OCH_2), 1.34 (t, J = 5 Hz, 3H, –CH_3), 1.28 (t, J = 5 Hz, 3H, –CH_3). Elemental analysis: $C_{22}H_{20}N_4O_5S$ (452.49). Calculated: C, 58.40; H, 4.46; N, 12.38. Found: C, 58.35; H, 4.25; N, 12.40

2.4. Synthesis of 4-hydroxybenzylidene N'-(3-ethoxy)-2-imino-2H-chromene-3-carbohydrazide (9)

A cyanoacetohydrazide derivative (1) and salicylaldehyde (0.01 mol) were dissolved in 20 milliliters of alcohol with a couple of piperidine drops. The mixture of reactions was refluxed for three hours before cooling. It was purified by recrystallization from ethanol after the precipitated solid was removed by filtering.

Orange crystalline solid; yield 77%; m.p.=240–42 °C. IR (KBr, ν, cm^{-1}): 3048 (NH), 2933 (CH-aliph.), 1685 (C=O, amide). ^{1}H NMR (500 MHz, DMSO-*d*$_6$, δ ppm): 8.73 (s, 1H, OH, exchangeable with D_2O), 8.24 (s, 1H, methine-H), 7.73 (s, 1H, NH, exchangeable by D_2O), 7.67 (s, 1H, NH, exchangeable by D_2O), 7.52–6.76 (m, 7H, Ar–H), 6.72 (s, 1H, pyran-H), 3.97 (q, J = 5 Hz, 2H, –OCH_2), 1.27 (t, J = 5 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d$_6$, δ ppm): 163.35, 159.19 (2C=O), 153.91 (C–OH), 152.39 (C=N), 147.59, 147.27 (C=C–Ar), 136.65, 134.22, 130.62, 124.50, 120.13, 119.90, 118.72, 117.18, 116.27, 114.97, 112.80, 94.72, 64.52 (–

OCH_2), 15.19 ($-CH_3$). Elemental analysis $C_{19}H_{17}N_3O_4$ (351.36): Computed: C, 64.95; H, 4.88; N, 11.96. Found: C, 64.54; H, 4.78; N, 11.35.

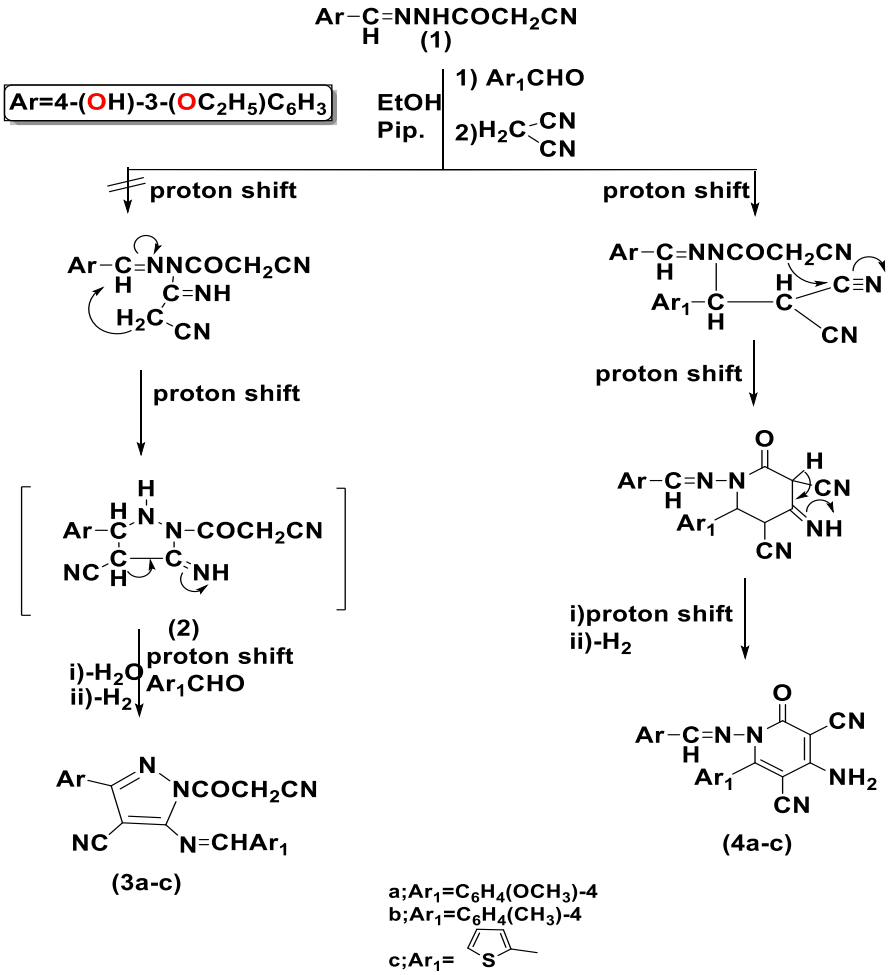
2.5. Synthesis of 4-amino ethyl (amino)-2-methyl-1-((3-ethoxy-4-hydroxybenzylidene) 1-,6-dihydropyridine-6-oxo 3-carboxylate (10)

A small amount of piperidine is used as a catalyst. A combination of cyanoacetohydrazide derivative (1) (0.01 mol) and ethyl acetoacetate (0.01 mol) was dissolved in 20 milliliters of absolute ethanol. After six hours of reflux heating, the reaction mixture was allowed to reach room temperature. Filtration was used to recover the precipitated solid, which was then cleaned with cold ethanol and refined by recrystallization from ethanol.

Yellow crystalline solid (EtOH); Yield: 69%; M.p.= 208–10 °C. IR (KBr, ν/cm^{-1}): 3300, 3188 (NH_2), 2971 (aliphatic C–H), 1686 (C=O). ^{1}H NMR (500 MHz, DMSO-d_6, δ ppm): 9.44 (s, 1H, OH, D_2O exchangeable), 8.53 (s, 1H, methine-H), 7.40 (s, 1H, Ar-H), 7.23 (d, J = 10 Hz, 1H, Ar-H), 6.87 (d, J = 10 Hz, 1H, Ar-H), 6.64 (s, 1H, pyridine-H), 5.58 (s, 2H, NH_2, D_2O exchangeable), 4.07 (q, J = 5 Hz, 2H, $-OCH_2$), 3.94 (q, J = 5 Hz, 2H, $-OCH_2$), 2.88 (s, 3H, CH_3), 1.36 (t, J = 5 Hz, 3H, CH_3), 1.30 (t, J = 15 Hz, 3H, CH_3). ^{13}C NMR (126 MHz, DMSO-d_6, δ ppm): 164.71, 161.11 (2C=O), 157.84, 154.12 (C=N), 150.78, 147.67 (C–OH), 144.66 (C=C-Ar), 130.43, 125.97, 123.86, 117.93, 112.05, 99.91, 64.40, 61.20 (2 -OCH_2), 22.63 (CH_3), 19.07, 15.20 (2 -CH_3). Analysis of the elements ($C_{18}H_{21}N_3O_5$, 359.38): Calculated: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.13; H, 5.70; N, 11.54.

3. Results and Discussion

The methods used for synthesis and mechanistic pathways for the preparation of the target pyridine and chromene derivatives, using cyanoacetohydrazide derivative (1) as starting material, are illustrated in Schemes (1–3). Ethylvanillin, which contains a reactive aldehyde functional group, participates readily with active methylenes and yielded pyridine and chromene derivatives; schemes (1-3). Compound (1) was synthesized *via* condensation of ethylvanillin with cyanoacetohydrazide in ethanol under reflux, with Acetic acid added in a few drops as a catalyst. The compound's infrared spectrum (1) revealed distinctive bands of absorption at 1698 cm^{-1} (amidic carbonyl), 2276 cm^{-1} (cyano), and 3208 cm^{-1} (imino), confirming the presence of the respective functional groups; scheme (1).



Scheme 1. Synthesis of 3,5-dicyano-pyridine-2-one derivatives (4a-c)

The spectrum of ^{1}H NMR of compound (1) recorded in DMSO-d_6 showed a quartet at δ 4.02 ppm and a triplet at δ 1.30 ppm, which correspond to the protons (-OCH_2) and (-CH_3), respectively. Two aromatic proton signals were visible as doublets at δ 7.03 and δ 6.79 ppm, with coupling constants of 10 and 5 Hz. A singlet

at δ 7.24 ppm was identified as the ethylvanillin unit's aromatic proton. Broad, exchangeable singlets observed at δ 9.40 and 11.58 ppm were due to (OH) and amine (NH) protons. Additionally, a methine proton appeared at δ 7.84 ppm, while a methylene (CH_2) signal was observed at δ 3.91 ppm. Moreover, Compound (1)'s ^{13}C NMR spectra showed distinctive features at δ 116.70, 64.45, and 15.20 ppm, which were assigned to the cyano (CN), methylene (-OCH_2), and methyl (-CH_3) carbons, respectively. Additional significant resonances appeared at δ 148.91, 159.00, and 164.93 ppm, corresponding to carbons bonded to nitrogen (C=N), phenolic hydroxyl (C–OH), and carbonyl groups, respectively. An additional resonance at δ 25.30 ppm was assigned to the methylene (CH_2) carbon. This research focuses on the preparation of pyridine derivatives *via* a multicomponent reaction approach. In this strategy, cyanoacetohydrazide derivative (1) was reacted with malononitrile and some aromatic aldehydes, including *p*-tolualdehyde, *p*-methoxy benzaldehyde, and thiophen carboxaldehyde under reflux in an ethanol containing piperidine in a catalytic quantity. The analytical and spectroscopic data afforded derivatives of 3,5-dicyanopyridine-2-one (4a-c) instead of pyrazole-4-carbonitrile derivatives (3a-c); Scheme (1).

The mechanism of pyridone formation initiates with the NH group used as nucleophilie attack on the β-carbon of α-cyano-cinnamonitrile and forms an adduct; Then the carbanion of (CH_2) attacks the cyano group and cyclizes to form 2-pyridone (4a-c); Scheme (1).

The spectral and analytical data obtained were fully consistent with the proposed molecular structures of the synthesized compound (4a–c). Characteristic absorption peaks in the IR spectra were observed, representing the functional groups C=O, -NH_2, and -CN, appearing at their expected frequencies. Signals from the -OCH_2 and -CH_3 protons were identified as a quartet at δ 4.01 ppm and a triplet at δ 1.30 ppm in the ^1H NMR spectra (DMSO-d_6) of compound (4a). Two aromatic protons resonated as doublets at δ 6.80 and 7.41 ppm, both having a coupling constant of J = 10 Hz. In addition, a separate singlet showed up at δ 7.91 ppm, equal to the ethylvanillin part's residual aromatic proton. An extensive interchangeable resonance at δ 5.20 ppm corresponded to the –NH_2 of the pyridin-2-one ring. The ethylvanillin unit's hydroxyl proton was seen as a downfield singlet at δ 8.28 ppm. Moreover, the methoxy (–OCH_3) group revealed a singlet at δ 3.76 ppm. For substance (4a), the observed ^{13}C NMR spectra displayed peaks at δ 116.62, 64.46, 55.87, and 14.38 ppm, which were attributed to the cyano (–CN), methylene (–OCH_2), (–OCH_3), and methyl (–CH_3) carbons, respectively. Additional downfield resonances were observed at δ 159.13, 161.41, 161.58, and 165.02 ppm, corresponding to carbons bonded to nitrogen (C=N), the amino group (C–NH_2), phenolic hydroxyl (C–OH), and the carbonyl group (C=O). For the pyridin-2-one derivative (4b), the ^1H (DMSO-d_6) NMR spectrum showed a distinct resonance at δ 2.36 ppm, assignable to a –CH_3 group. In the NMR spectra of ^{13}C, signals were detected at δ 15.25 and δ 21.49 ppm, corresponding to methyl carbons. Notable downfield signal appeared at δ161.10 ppm, which was assigned to the carbon (C=O) group, Scheme 1

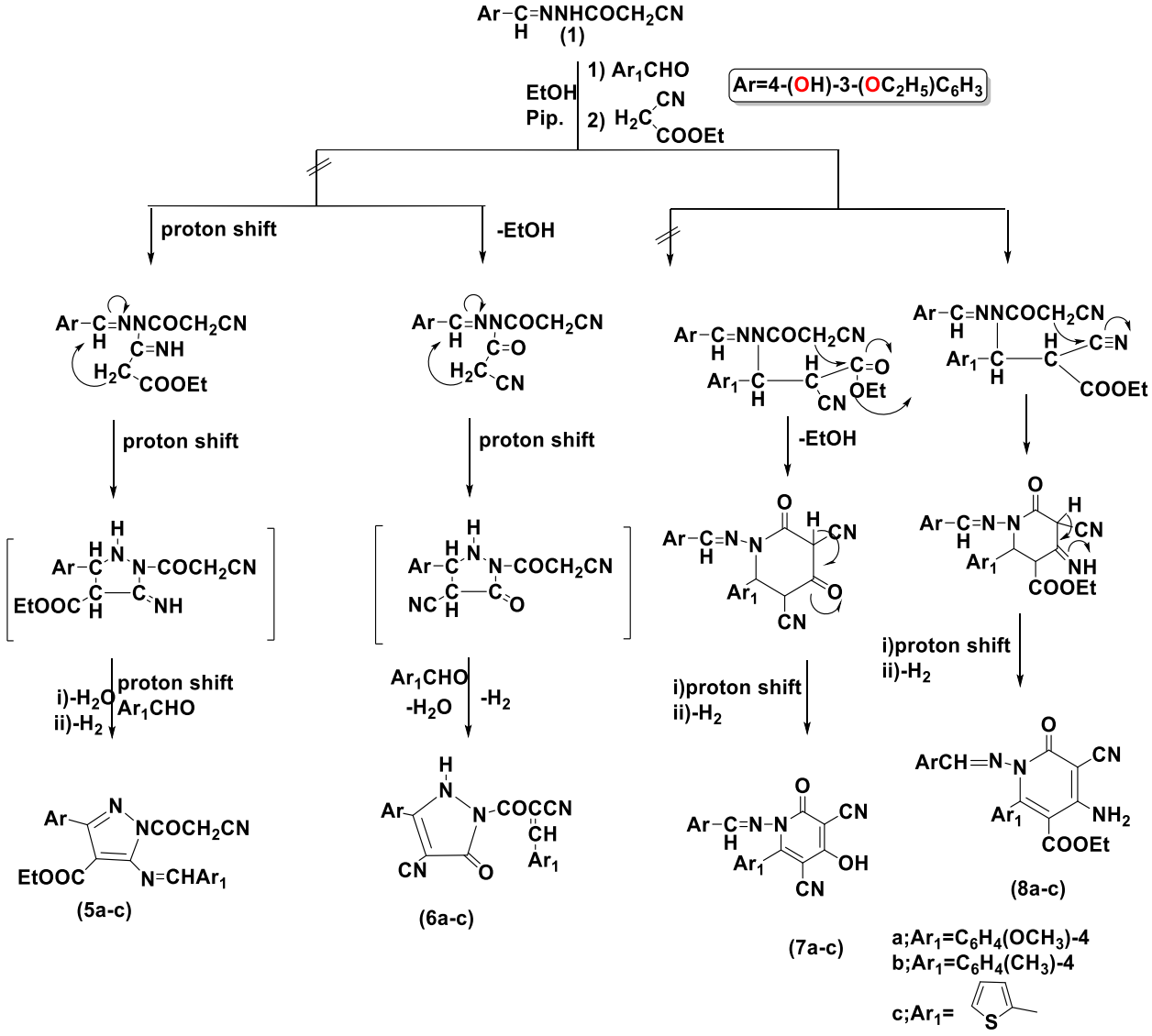
The pyridine-2-one series (8a–c) was obtained by treating cyanoacetohydrazide derivative (1) with different aromatic aldehydes, including p-methoxybenzaldehyde, p-tolualdehyde, and thiophen carboxaldehyde, in ethanol with a trace amount of piperidine as a catalyst. Subsequent addition of ethyl cyanoacetate led directly to the desired products in good yields, rather than isolating intermediates (5, 6, or 7a–c). Structural assignments were supported by elemental and spectral analyses, and a plausible mechanism for the generation of 2-oxo-pyridine derivatives (8a–c) is outlined in Scheme 2, The mechanism of pyridone formation initiates with NH group used as nucleophilie attack β-carbon of α ethoxy carbonyl cyano cinnamonitrile and form adduct; Then carbanion of (CH_2) attack cyano group and cyclize to form 2-pyridone (8a-c); Scheme (2).

Combining elemental analysis and spectroscopic methods allowed for the confirmation of the structures of the pyridine-2-one derivatives (8a–c). Absorption peaks were visible in compound (8a)'s infrared spectra at 3308, 3201, 2208, and 1716 cm^{-1}, which were ascribed to the functionalities of amino, cyano, and carbonyl. The ^1H NMR spectra (DMSO-d_6) showed quartet signals at δ 4.19 and 3.95 ppm together with triplets at δ 1.32 and 1.25 ppm, which were attributed to methylene and methyl protons of two ethoxy substituents. A singlet resonance at δ 3.74 ppm was consistent with a methoxy group. For compound (8c), the proposed structure was corroborated by both analytical and spectral evidence. Its IR spectra revealed bands at 2208 and 1692 cm^{-1} that corresponded to cyano (–C≡N) and carbonyl functionalities, as well as distinctive peaks at 3330 and 3203 cm^{-1} caused by the amino group. The compound's ^1H NMR spectra (8c) in DMSO-d_6 displayed two distinct quartets at δ 4.25 and 4.43 ppm together with triplets at δ 1.26 and 1.31 ppm, which are characteristic of the methylene and methyl protons of two ethyl substituents. The aromatic region (δ 6.62–8.19 ppm) showed multiple resonances integrating for six protons. A sharp singlet at δ 9.67 ppm was consistent with a hydroxyl group, whereas the amino protons (–NH_2) were responsible for another singlet at δ 5.72 ppm. Furthermore, the ascribed structure was validated by the appearance of a downfield singlet for the methine proton (=CH) at δ 8.59 ppm; Scheme 2

When cyanoacetohydrazide derivative (1) reacted with salicylaldehyde under reflux in ethanol with piperidine as a base catalyst, the reaction afforded compound (9), identified as a 2-iminochromene. The identity of this product was verified through elemental composition, together with spectral evidence. The mechanistic equations of 2-pyridone and chromene derivatives formation (9,10) are illustrated in Scheme 3.

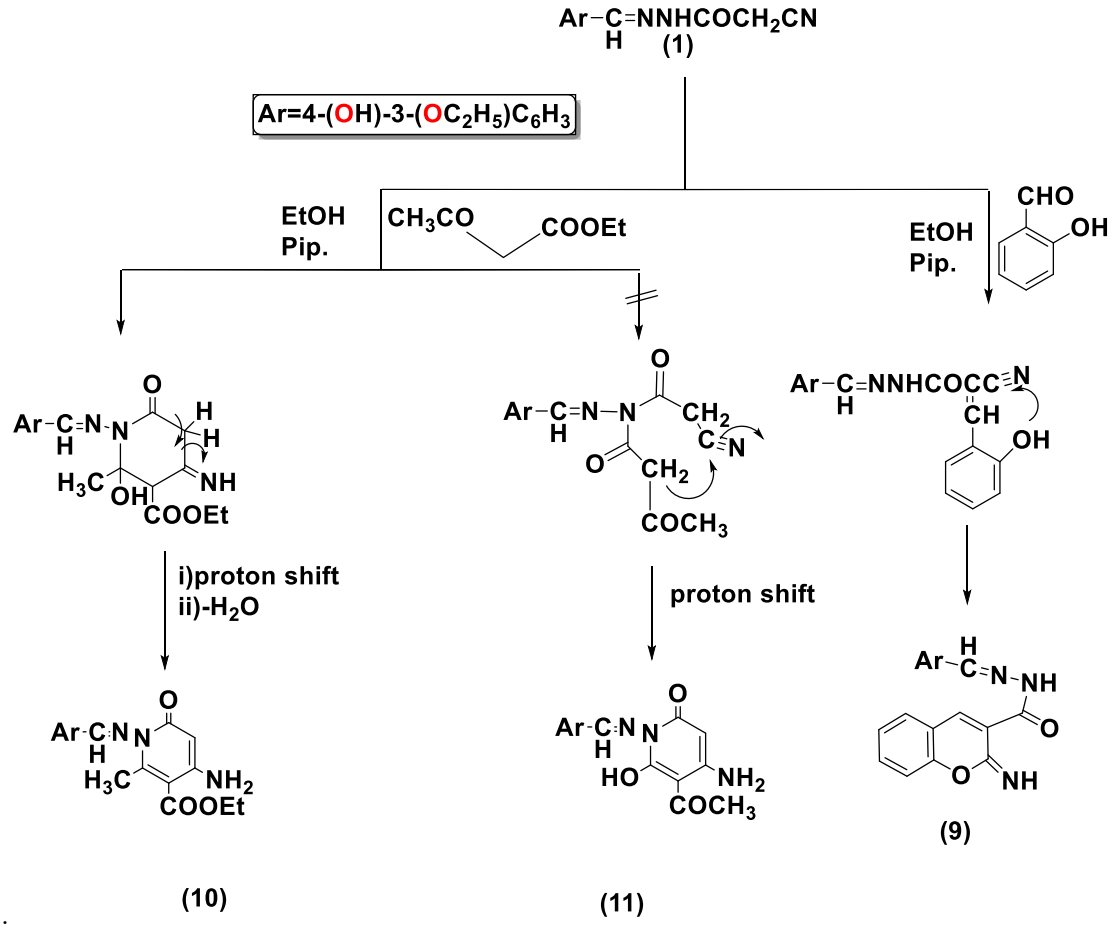
Compound (9) showed absorption bands in its infrared spectra at 3048 and 1685 cm^{-1}, attributable to the NH (imino) and C=O (carbonyl) functionalities. Notably, the lack of a C≡N stretching signal supported the complete conversion of the cyano functionality in the course of the reaction. Compound (9)'s ^1H NMR spectrum in DMSO-d_6 showed distinctive resonances: ethyl

group signals showed up as a triplet at δ 1.24 ppm and a quartet at δ 3.95 ppm. The chromene proton was indicated by a singlet at δ 6.72 ppm. In the aromatic area (δ 6.76–7.52 ppm), a multiplet representing seven protons was seen. A downfield singlet at δ 8.73 ppm was consistent with a phenolic OH proton, and two further signals at δ 7.67 and 7.73 ppm were attributed to NH groups. The NMR spectrum of (9) in ^{13}C further supported the proposed structure, showing signals at δ 163.35, 159.19, and 153.91 ppm, corresponding to the carbonyl carbon, phenolic carbon (C–OH), and imino carbon (C=NH), respectively. The ethyl group of the ethylvanillin fragment appeared at δ 64.52 ppm (OCH_2) and 15.19 ppm (CH_3), consistent with the expected substitution pattern, as illustrated in Scheme (3). Further research was done on the cyanoacetohydrazide derivative (1)'s chemical behavior toward active methylene reagents. Its reaction with ethyl acetoacetate in an equimolar ratio (1:1) resulted in the formation of a 2-oxo-pyridine derivative (10), as outlined in Scheme (3).



Scheme 2. Synthesis of 3-cyano-4-amino-pyridine-2-one derivatives (8a-c)

The combined spectroscopic results together with elemental composition analysis supported the proposed structure of the 2-oxo-pyridine derivative (10). The amino and carbonyl groups were identified by the IR spectrum's distinctive absorption bands, which were located at 3188 cm^{-1} and 1686 cm^{-1}, respectively. The methylene and methyl protons of two ethoxy substituents were represented by quartet and triplet signals at δ 4.07, 3.94 and δ 1.36, 1.30 ppm in the ^1H NMR spectra (DMSO-d_6). A methyl group connected to the pyridine ring was responsible for a singlet resonance at δ 2.88 ppm, and the hydroxyl group of the ethylvanillin moiety was responsible for another singlet at δ 9.44 ppm. The existence of the amino group was confirmed by a wide exchangeable singlet at δ 5.58 ppm. The NMR spectrum from ^{13}C further displayed resonances at δ 164.71, 161.11, and 154.12 ppm, characteristic of carbonyl and C–NH carbons. Additional signals at δ 64.40, 61.20, 19.07, and 15.20 ppm corresponded to two ethoxy groups, whereas δ 22.63 ppm was consistent with the methyl carbon. Collectively, these findings, along with the synthetic pathway illustrated in Scheme (3), provide strong evidence for the proposed structure.



Scheme 3. Synthesis of the new pyridine and chromene derivatives containing the ethylvanillin moiety (9), (10).

4. Conclusions

This work illustrates the successful design and preparation of a range of pyridine and chromene derivatives utilizing cyanoacetohydrazide as a highly adaptable synthetic precursor. Using multicomponent reaction strategies allowed the rapid and efficient assembly of multifunctional heterocyclic frameworks containing cyano, carbonyl, amino, and hydroxyl groups under mild conditions. Structural confirmation of all products was evidenced from IR, NMR spectra of ^{1}H and ^{13}C, and elemental analysis. Proposed mechanistic pathways for each transformation emphasized the bifunctional nature of cyanoacetohydrazide in directing regioselective cyclization. Incorporation of ethylvanillin as a core aromatic unit enhanced both molecular complexity and potential biological activity. Overall, the results highlight the value of this synthetic approach for constructing pharmacophore-rich heterocycles and expanding their applications in medicinal chemistry and functional materials. Future investigations will evaluate the synthesized compounds' antimicrobial, anticancer, and antioxidant potential.

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