A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2026**, (2) 202612580

Synthesis and isomerization of novel hydroxypyridinone–cinnamoyl hybrid compounds

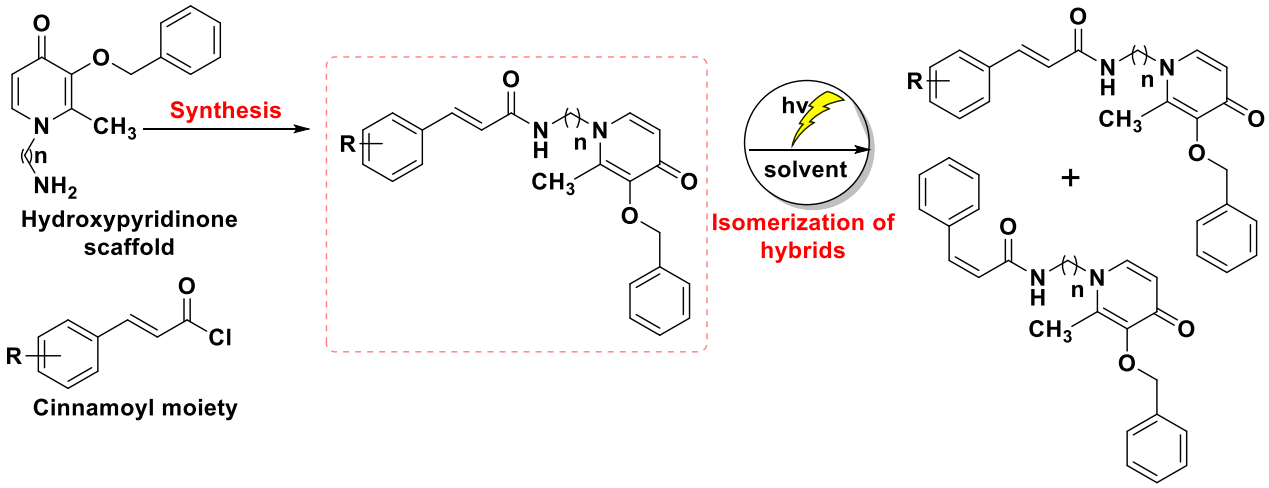
Thisundiwi Malusela[a], Ampfarisaho L. Netsianda[a], Simon S. Mnyakeni-Moleele[a], Eric Morifi,[b] and Mpelegeng V. Bvumbi[a*]

*[*a] Department of Chemistry, University of Venda, Thohoyandou, Private Bag X5050, 0950.*
[b]School of Chemistry, University of the Witwatersrand, Private Bag X 3, Wits, 2050.
Email: Mpelegeng.Bvumbi@univen.ac.za

Received 03-11-2026 **Accepted** 05-25-2026 **Published on line** 06-04-2026

Abstract

Hydroxypyridinones are privileged scaffolds with metal-chelating and pharmaceutical properties, while cinnamoyl derivatives are recognized for their broad bioactivities. In this work, the design and synthesis of these compounds were achieved through a molecular hybridization strategy, which combines the pharmacophoric moieties of bioactive substances to produce a new hybrid compound with enhanced affinity and efficacy. The conjugated hybrids were synthesized in low to moderate yields. The investigation of the *E*/*Z* isomerization mixture highlights interactions affecting double-bond geometry.



Keywords: Hydroxypyridinone, cinnamic acid, hybrids, synthesis, isomerization

Cite as *Arkivoc* **2026**, (2) 202612580
DOI: https://doi.org/10.24820/ark.5550190.p012.580

Introduction

Conjugation in organic chemistry is crucial in drug design, as it covalently attaches functional units, such as pharmacophores or scaffolds, to enhance molecular characteristics and therapeutic efficacy.[1] Combining multiple scaffolds into one novel compound, covalently linked with synergistic properties, will result in a higher potency than the sum of its individual parts. Covalently linked compounds also increase the bioavailability of each compound at the same target, improve pharmacokinetic properties, and solubility.[2]

There is one promising approach in drug discovery that has been reported to enhance the activity of synthesized organic compounds, namely, molecular hybridization (MH). MH is a strategy that combines the pharmacophoric moieties of bioactive substances to produce a new hybrid compound with enhanced biological activity.[3] Two bioactive moieties can be linked in different types to a single hybrid compound with multi-target functionalities. A fused hybrid occurs when two moieties fuse without a linker; each molecule contributes a functional group to form the connection between them. A merged hybrid is formed when two biologically active pharmacophores are combined into a single molecule, with some structural parts of each pharmacophore overlapping. Linked hybrids involve connecting two pharmacophores via a chemical linker, such as an alkyl chain, amide, or ester, as illustrated in Figure 1.

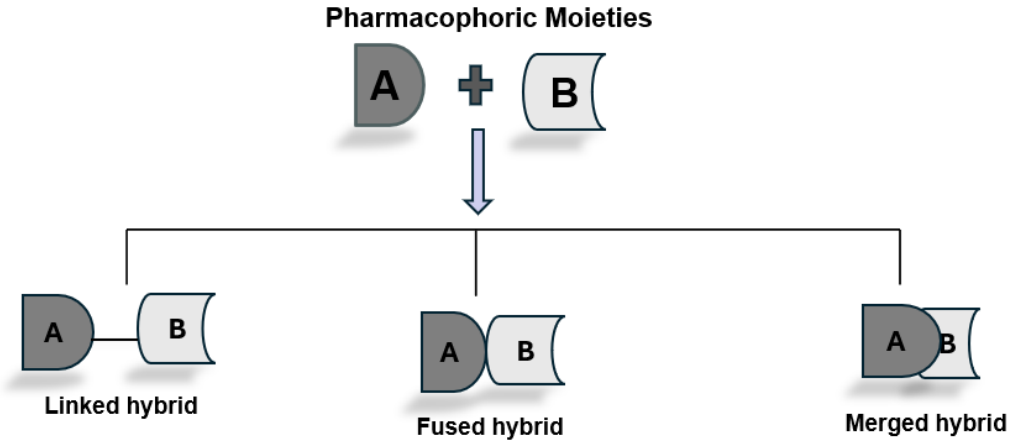


Figure 1. Illustration of different types of hybrids.[4]

In this study, the linked hybrids of hydroxypyridinone and cinnamic acid are reported. Cinnamic acid is an aromatic fatty acid that is naturally found in plants, composed of a phenyl ring with an acrylic acid group. Its derivatives include ferulic acid, caffeic acid, sinapic acid, and p-coumaric acid (Figure 2).[5] The presence of an alkenic group substituted on the phenyl ring gives cinnamic acid either a *cis* or a *trans* isomer.[6] Cinnamoyl derivatives are reported and recognized for a broad spectrum of biological activities, including antimalarial, anticancer, anti-HIV, and anti-tubercular properties, among others.[7] Hydroxypyridinones, on the other hand, are metal chelates with a six-membered ring skeleton. They have been considered 'privileged structures' for drug design, owing to their importance as a nitrogen-containing heterocyclic nucleus, and have attracted increasing attention in medicinal chemistry and drug discovery over the past decade.[8]

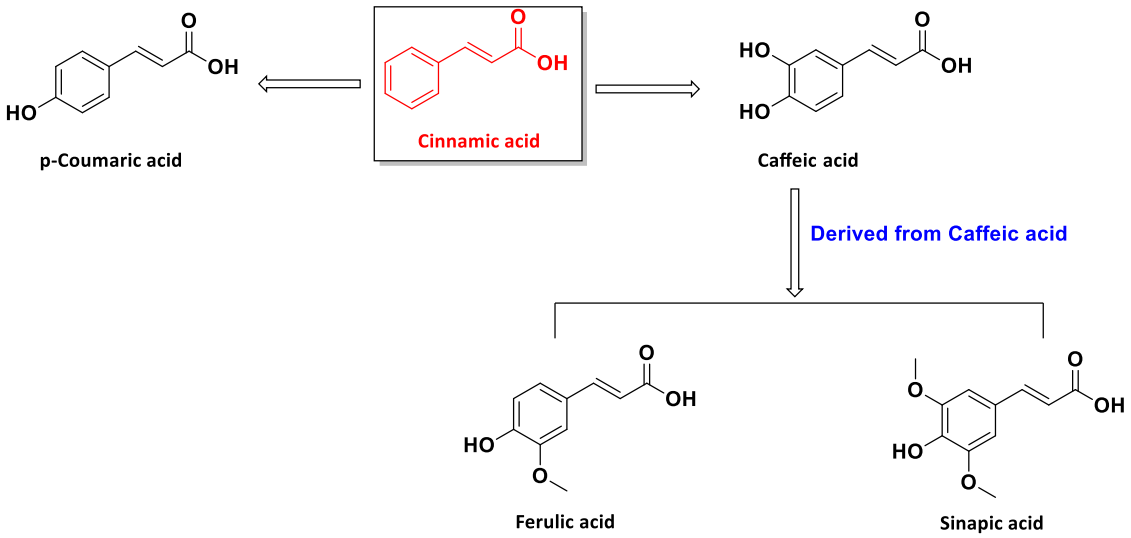


Figure 2. Cinnamic acid derivatives.

Beyond the parent scaffolds, numerous studies have reported structurally diverse, conjugated derivatives of cinnamoyl systems, including hybrids incorporating heterocycles, aminoquinolines, chalcones, and other pharmacophores, to enhance biological activity and modulate physicochemical properties.[9] Similarly, hydroxypyridinone derivatives have been extensively functionalized through conjugation with aromatic systems, peptides, and drug-like fragments to improve metal-binding selectivity and pharmacokinetic properties.[10] The successful application of conjugation strategies to both cinnamoyl and hydroxypyridinone frameworks highlights their versatility as building blocks in hybrid drug design. Therefore, the development of hydroxypyridinone–cinnamoyl conjugates represents a rational approach aimed at combining the pharmacological advantages of both scaffolds within a single molecular framework.[11]

Given the conjugated double-bond system these hybrids exhibit, we decided to investigate their isomerization behavior. Photochemical isomerization is a light-induced process that enables the interconversion of geometric isomers by exciting π-electrons in unsaturated systems.[12] In cinnamoyl derivatives, the presence of an α,β-unsaturated double bond allows the existence of distinct *E* and *Z* isomers, which can display different physicochemical and biological properties.[13] In this study, the photoisomerization behavior of hydroxypyridinone–cinnamoyl hybrids was investigated to understand their conformational stability and response to UV irradiation. This evaluation provides insight into their structural behavior under light exposure and the potential influence of geometric isomerism on their biological activity.

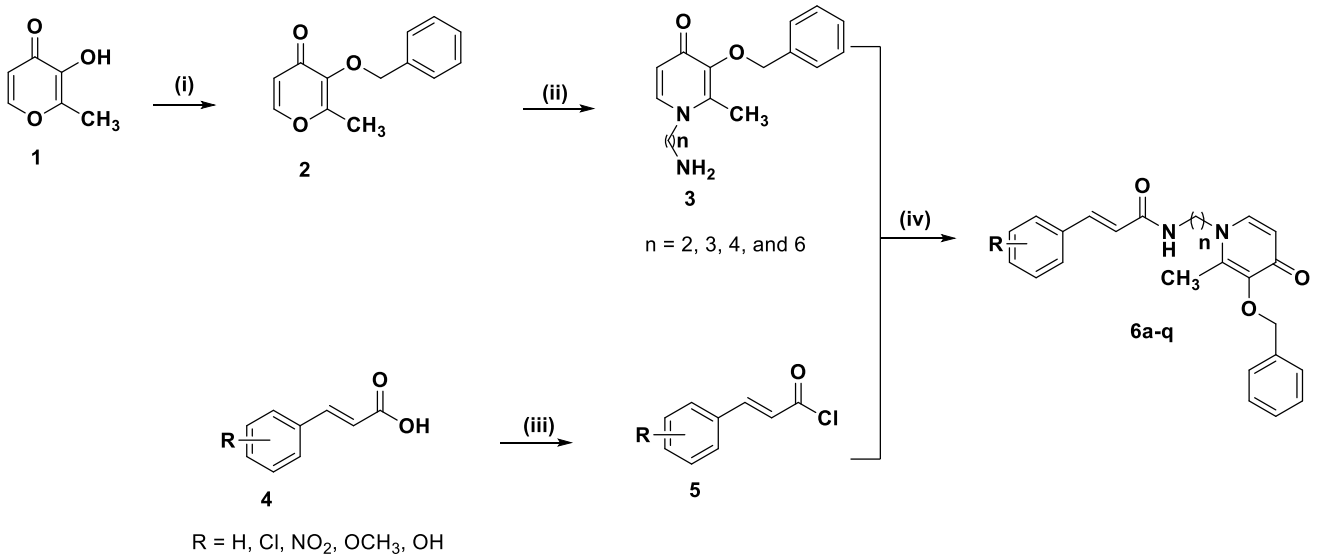
Results and Discussion

Chemistry (Synthesis)

The synthesis of hydroxypyridinone–cinnamoyl hybrid compounds is outlined in Scheme 1. Protection of 3-hydroxy-2-methyl-4-pyrone with benzyl chloride (BnCl) in methanol at 95–100 °C afforded compound **2**. Alkylation of **2** with a series of aliphatic diamines where n = 2, 3, 4, and 6 in an ethanol/water mixture gave the key intermediates **3**.[14]

In parallel, substituted cinnamic acids at the para position **4**, where R = H, OCH_3, NO_2, Cl, and OH, were converted to the corresponding cinnamoyl chlorides **5** using thionyl chloride ($SOCl_2$) in dry toluene.[15,16] Finally,

coupling of intermediates **3** and **5** was achieved via nucleophilic acyl substitution in dry dichloromethane, using triethylamine as a base at room temperature for 24 h, to afford the target hybrids **6a–q** in yields of 8–42% (Table 1). The structures of all synthesized compounds were confirmed by ^{1}H and ^{13}C NMR, IR, and Mass spectroscopy.



Scheme 1. Reagents and conditions: (i) BnCl, MeOH, 2M NaOH, 95-100 °C, 24 h; (ii) Diamines, NaOH, EtOH/H_2O, 75 °C, 6 h; (iii) $SOCl_2$, Dry toluene, DMF, rt, 12 h; (iv) Et_3N, Dry DCM, rt, 24 h.

The isolated yields of compounds **6a–6q** were strongly influenced by both the electronic nature of the aromatic substituent and linker length. Nitro-substituted derivatives consistently afforded the lowest yields, likely due to reduced intermediate stability and increased susceptibility to competing side reactions during coupling and purification. Methoxy-substituted derivatives generally gave improved yields, which may be attributed to electronic stabilization of the conjugated cinnamoyl framework and cleaner acylation profiles, while chloro-substituted analogs exhibited intermediate behavior. The hydroxyl-substituted derivative (**6m**) showed reduced yield, likely due to competing interactions associated with the free phenolic group. Linker length also affected reaction efficiency, with three- and four-carbon spacers providing optimal yields, suggesting a favorable balance between conformational flexibility and steric accessibility for amide bond formation.

The successful formation of the hydroxypyridinone–cinnamoyl hybrid framework was confirmed by detailed NMR spectroscopy, with compound **6h** serving as a representative example (Figure 3). In the ^{1}H NMR spectrum, the formation of the amide linkage is evidenced by the appearance of an NH proton, originating from the alkylated 3-hydroxy-2-methyl-4-pyrone intermediate. While the corresponding amine NH_2 signal in the precursor was expected in the 2.0–1.5 ppm region, acylation resulted in a pronounced downfield shift, giving rise to a broad singlet at δ 8.30 ppm, consistent with an amide NH proton.

The para-substituted aromatic rings in the synthesized compounds correspond to AA'BB' spin systems. While compound **6h** displayed clearly resolved second-order splitting characteristics with δ 7.60 – 7.45 ppm region (m, 4H) consistent with the expected second-order splitting pattern, other derivatives exhibited less pronounced second-order effects due to signal overlap and differences in Δν/J values, leading to experimentally observed apparent doublets rather than fully resolved multiplet patterns.

Table 1. Percentage yields of compounds **6a-q**

Compound	n	R	Yield (%)
6a		H	32
6b	2	OCH_3	18
6c		NO_2	13
6d		Cl	13
6e		H	22
6f	3	OCH_3	37
6g		NO_2	8
6h		Cl	37
6i		H	39
6j	4	OCH_3	42
6k		NO_2	8
6l		Cl	36
6m		OH	12
6n		H	18
6o	6	OCH_3	15
6p		NO_2	10
6q		Cl	25

The ^{1}H NMR spectrum displayed a characteristic olefinic proton resonance at δ 6.62 ppm (for **6h**) as a doublet (*J* = 15.8 Hz, 1H), consistent with a *E* α,β-unsaturated system. The corresponding second olefinic proton was not observed as a separately resolved signal because it resonates within the aromatic region (δ 7.40 – 7.32 ppm), where significant overlap with aryl proton resonances occurs. Such overlap is influenced by the electronic effects of the phenyl ring. Nevertheless, the large vicinal coupling constant (*J* = 15.8 Hz) strongly supports coupling between two *E*-olefinic protons and confirms the assigned *E*-configuration of the conjugated alkene moiety in compound **6h**.

The aromatic protons of the 3-benzyl-2-methyl-4-pyridinone core are observed as two doublets at δ 7.64 and 6.18 ppm, each integrating for one proton. The benzyl substituent is clearly identified by a multiplet at δ 7.35 ppm corresponding to five aromatic protons, together with a singlet at δ 5.01 ppm integrating for two benzylic methylene protons. The methyl group attached to the pyridinone ring appears as a singlet at δ 2.15 ppm, integrating for three protons.

The alkyl linker connecting the hydroxypyridinone and cinnamoyl fragments is evident from three methylene signals, each integrating for two protons, observed at δ 3.91, 3.19, and 1.79 ppm, confirming successful alkylation and chain integrity.

The ^{13}C NMR spectrum of compound **6h** displays 21 distinct carbon resonances, comprising seven quaternary carbons, nine methine carbons, four methylene carbons, and one methyl carbon, in agreement with the proposed structure. Notably, the appearance of the amide carbonyl carbon at δ 165.53 ppm (C7) provides clear evidence of successful coupling between intermediates **3** and **5**. In addition, the methylene carbon adjacent to the amide nitrogen appears at δ 39.5 ppm (C8), further supporting formation of the target hybrid compound.

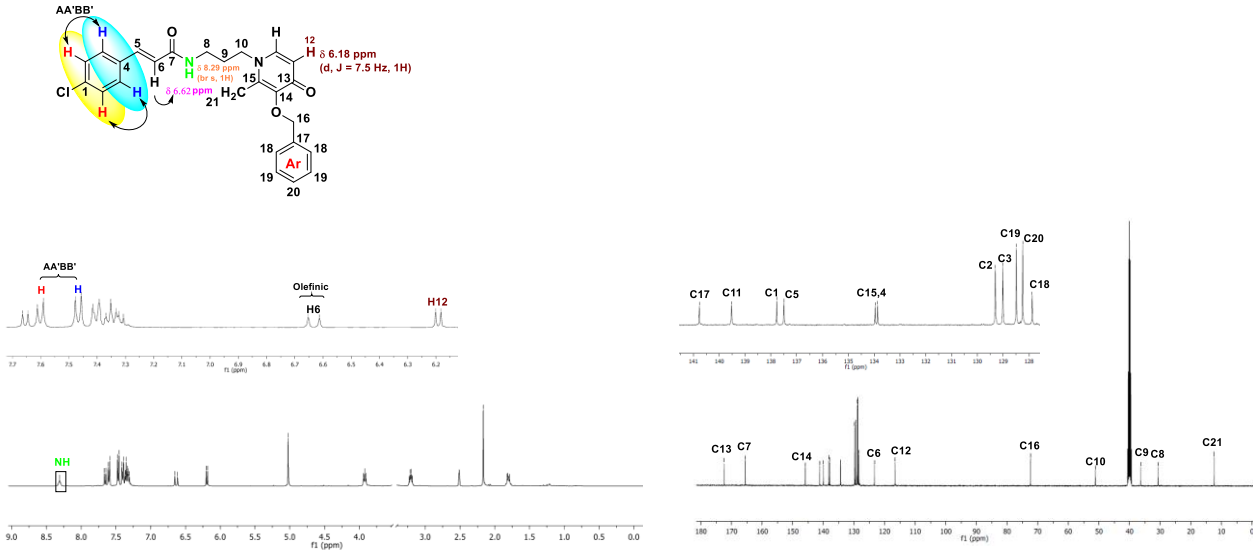


Figure 3. ^{1}H and ^{13}C NMR spectra of compound **6h.**

The IR spectrum of compound **6h** also confirmed the structure, showing a broad absorption band at 3257 cm^{-1}, corresponding to the N-H stretch. The absorptions around 3022 cm^{-1} for the aromatic C-H stretch, another aliphatic C-H stretch at absorption band 2931 cm^{-1}, carbonyl group C=O at 1659 cm^{-1}, aromatic C=C stretch at 1545 cm^{-1}, C-N at 1292 cm^{-1}, and C-O vibration at 1159 cm^{-1} confirmed the structure.

Finally, the HRMS mass-to-charge ratio (*m/z*) of compound **6h**, with molecular formula $C_{25}H_{25}ClN_2O_3$, was calculated to be 437.1554, and the m/z ratio was 437.1627 (M+H).

Photochemical isomerization of hydroxypyridinone–cinnamoyl hybrids

Photochemical isomerization of the synthesized hydroxypyridinone–cinnamoyl hybrid compounds was investigated to evaluate their *E/Z* geometric interconversion. This is a process in which absorption of light energy induces a change in molecular geometry without altering the molecular formula. In cinnamoyl systems, this process typically occurs across the carbon–carbon double bond of the α, β-unsaturated side chain.

For the isomerization study, the final compounds were dissolved in methanol and irradiated with UV light at 254nm for up to 6 h. Reaction progress was monitored by collecting aliquots at defined time intervals (1, 3, and 6 h). Each aliquot was transferred into a 50 mL round-bottom flask, and the solvent was removed under reduced pressure using a rotary evaporator. The resulting residue was dissolved in DMSO-d_6, followed by acquisition of the corresponding ^{1}H NMR spectrum.

Isomerization was evaluated by monitoring changes in the alkenic proton signals of the cinnamoyl moiety. Figure 4 shows the ^{1}H NMR spectrum of compound 6h prior to post-irradiation (t = 0 to t = 6). Photoirradiation of the conjugated alkene system resulted in partial E→Z isomerization, as evidenced by changes in the olefinic proton resonances in the ^{1}H NMR spectra. Quantitative analysis of the integrated diagnostic olefinic signals revealed an *E: Z* ratio of 74:26 at the photostationary state. These results indicate that the *E*-isomer remains the predominant species under the employed irradiation conditions, while a significant proportion of the *Z*-isomer is formed upon photo-induced isomerization.

The olefinic proton doublet at δ 6.62 ppm with a coupling constant (*J*) of 15.8 Hz was assigned as the initial alkene based on the coupling constant between the olefinic protons of the (*E)* configuration. Upon UV irradiation, new alkenic proton doublets appeared at δ 6.69 ppm (*J* 12.8 Hz) and δ 6.04 ppm (*J* 12.7 Hz), corresponding to the formation of the (*Z)*-isomer. The lower coupling constants observed for the (*Z)*-isomer relative to the (*E)*-isomer are consistent with the reduced dihedral angle between the vinylic protons in the *Z* configuration.

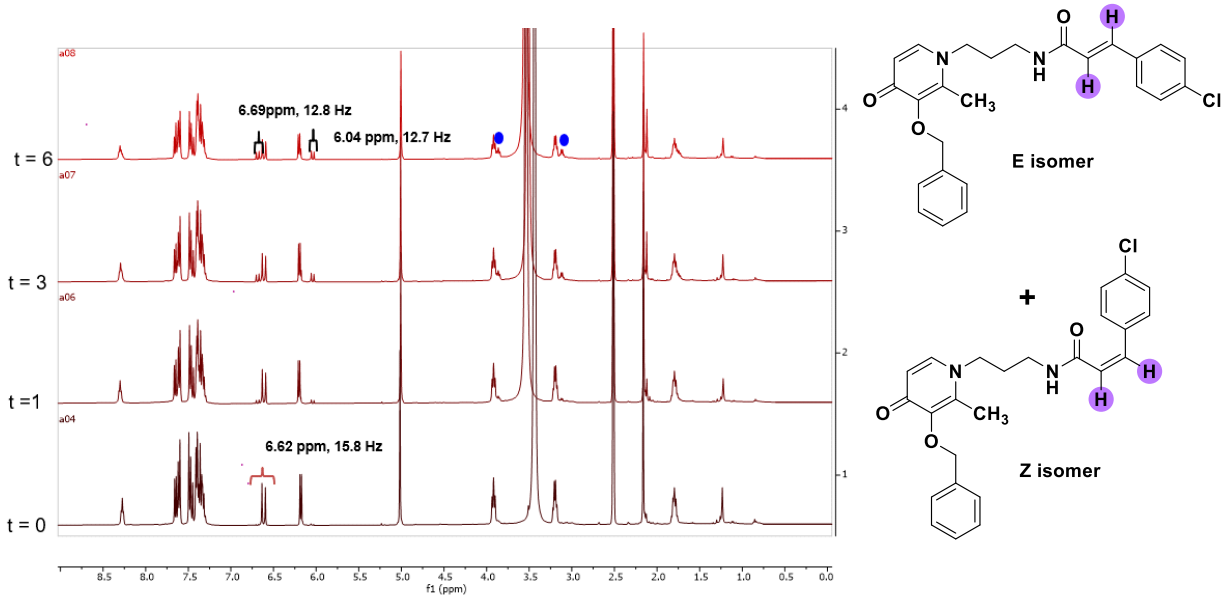


Figure 4. Isomerization ^{1}H NMR spectra of compound **6h.**

The observed chemical shifts and coupling constants are consistent with literature reports for cinnamoyl *E/Z* isomers, confirming the successful photochemical isomerization of the hydroxypyridinone–cinnamoyl hybrid scaffold.[17]

Notably, the isomerization did not proceed to completion, as both (*E)*- and (*Z)*-isomers coexisted even after prolonged irradiation. This observation is consistent with the establishment of a photo-stationary equilibrium, in which continuous UV exposure promotes both forward (*E* → *Z*) and reverse (*Z* → *E*) isomerization processes until a steady-state ratio is reached. The persistence of the (*E*)-isomer may be attributed to its greater thermodynamic stability relative to the (*Z)*-isomer and/or to the absorption characteristics of the (*Z)*-isomer, which may facilitate back-isomerization under the same irradiation conditions.[18]

While the present study did not include a systematic comparative kinetic analysis across all linker lengths, linker length may influence the isomerization behavior. This might happen by modulating molecular

flexibility and conformational accessibility around the cinnamoyl chromophore. Longer linkers may permit greater conformational freedom, facilitating geometric rearrangement during photoisomerization, whereas shorter linkers may impose conformational constraints.[19]

Although this effect is mechanistically plausible, a systematic comparative investigation across the full series would be required to establish definitive structure–isomerization relationships.

Conclusions

The synthesis and analysis of novel hydroxypyridinone-cinnamoyl hybrids were conducted using established synthetic methods with modified conditions. All of the hybrid compounds were obtained in low-to-moderate yields. Hydroxypyridinone-cinnamoyl hybrids were responsive to isomerization and have UV-absorbing characteristics brought by olefinic protons in the cinnamic acid moiety. When the hydroxypyridinone-cinnamoyl hybrids absorbed light at a desired wavelength, the structures formed a mixture of *E*/*Z* isomers. Although the preliminary results of the compounds showed no antitubercular activity against *M. tuberculosis* H37RvMA at the tested concentrations, the work establishes a useful synthetic platform. It expands the chemical space of hydroxypyridinone-based hybrids, which may be valuable for future investigations against other biological targets.

Experimental Section

General. All reagents and starting materials used in this project were purchased from Merck and were of synthesis-grade quality. The chemicals were used directly without further purification. Toluene and dichloromethane (DCM) were freshly distilled and stored over 4Å molecular sieves. Thin-layer chromatography (TLC) was used to monitor all reactions, and analyses were conducted on Macherey-Nagel ALUGRAM Sil G/UV254 plates pre-coated with 0.25 mm silica gel 60 Å. The spots were visualized by exposing the plates to ultraviolet light at 254 nm. Solvent was removed from the reactions under reduced pressure using a rotary evaporator. All synthesized compounds were purified using combiflash chromatography and glass column chromatography. Proton nuclear magnetic resonance (^{1}H NMR; 400 MHz) and carbon nuclear magnetic resonance (^{13}C NMR; 101 MHz) spectra were recorded in dimethyl sulfoxide (DMSO-d_6) on a Bruker spectrometer. Chemical shifts were reported in a δ scale in parts per million (ppm). Coupling constants (*J* values) are expressed in Hertz (Hz). The following NMR abbreviations were used: *s* (singlet), *d* (doublet), *dd* (doublet of doublets), *t* (triplet), *q* (quartet), *p* (quintet), *m* (multiplet), and *br* (broad signal). A Bruker Optics 7.0 Alpha Fourier-transformed Infrared (FTIR) spectrophotometer was used to analyze the functional groups and chemical structures of the materials. The absorptions were reported using the wavenumber scale in the 500-4000 cm^{-1} range. UV irradiation of the synthesized hybrid compounds was performed in centrifuge tubes containing methanol. The solution of hydroxypyridinone-cinnamoyl hybrids was placed in a Spectroline UV lamp operating at 254 nm with an intensity of 390 μW/cm^2. UV irradiation was conducted for 6 hours, and aliquots were taken at 1-, 3-, and 6-hour time intervals.

General procedure for the conjugation of 1-(2-aminoethyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one and 4-substituted cinnamoyl chloride (6a-q). A mixture of diamines-3-benzyl-2-methylhydroxypyridinones (1.0 equiv.), trimethylamine (Et_3N) (1.2 equiv.) in dry dichloromethane (DCM) (30 mL) was stirred at room temperature for 30 minutes. The 4-substituted cinnamoyl chloride (1.2 equiv.) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours, protected from light.

The progress of the reaction was monitored by thin-layer chromatography (TLC). After completion, the solvent was evaporated from the mixture under reduced pressure using a rotavapor. The residue was dissolved in an ethyl acetate/5% NaOH mixture (1:1). The reaction was worked up by liquid-liquid extraction with 5% NaOH, and the organic layer was washed with water. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the excess solvent was removed under reduced pressure. The products were then purified by column chromatography and Combi Flash chromatography using a mixture of ethyl acetate/ methanol.

***N*-(2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) ethyl)cinnamamide (6a).** A mixture of 1-(2-aminoethyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.87 g, 3.36 mmol), triethylamine (Et_3N) (0.57 mL, 4.04 mmol) in dry dichloromethane (DCM) (30 mL) was stirred at room temperature for 30 minutes. Cinnamoyl chloride (0.67 g, 4.04 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a cream-white solid (0.35g, 32 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (br t, *J* 5.8 Hz, 1H), 7.56 (app d, *J* 6.8 Hz, 2H), 7.52 (d, *J* 7.5 Hz, 1H), 7.46-7.38 (m, 3H), 7.36-3.28 (m, 5H, aromatic, olefinic), 6.59 (d, *J* 15.8 Hz, 1H, olefinic), 6.14 (d, *J* 7.5 Hz, 1H aromatic), 4.99 (s, 2H), 3.99 (t, *J* 6.2 Hz, 2H), 3.45-340 (m, 2H), 2.21 (s, 3H)**.** ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.8, 166.02, 145.8, 141.2, 140.1, 139.7, 138.3, 135.2, 129.4, 128.8, 128.7, 128.2, 128.1, 127.9, 121.6, 116.5, 72.3, 52.1,39.3, 12.4. IR (cm^{-1})**:** 3280 (N-H stretch), 2930 (C-H stretch), 1659 (C=O), 1576 (C=C), 1284 (C-N), 1164 (C-O). HRMS (ESI+): *m/z* $[M+H]^+$ Calculated for $C_{24}H_{24}N_2O_3$: 389. 1787; found: 389.1860.

***(E)-N*-(2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) ethyl)-3-(4-methoxyphenyl)acrylamide (6b).** A mixture of 1-(2-aminoethyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.80 g, 3.10 mmol), triethylamine (Et_3N) (0.52 mL, 3.72 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-methoxy cinnamoyl chloride (0.73 g, 3.72 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a cream-white solid (0.25 g, 18 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (br t, *J* 5.7 Hz, 1H), 7.52-7.50 (m, 3H), 7.43-7.26 (m, 6H, aromatic, olefinic), 6.96 (d, *J* 8.4 Hz, 2H), 6.44 (d, *J* 15.7 Hz, 1H, olefinic), 6.15 (d, *J* 7.5 Hz, 1H, aromatic), 4.99 (s, 2H), 3.98 (t, *J* 6.0 Hz, 2H), 3.78 (s, 3H), 3.41 (bs, 2H (overlapping with moisture peak from the DMSO-d_6 solvent), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 166.4, 160.9, 145.9, 141.4, 140.2, 139.5, 138.3, 129.8, 128.9, 128.7, 128.3, 127.8, 119.4, 116.5, 114.9, 72.4, 56.6, 55.8, 52.3, 12.5.

IR (cm^{-1}): 3207 (N-H stretch), 2934 (C-H stretch), 1658 (C=O), 1580 (C=C), 1284 (C-N), 1163 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{25}H_{26}N_2O_4$: 419.1893; found: 419.1961.

***(E)-N*-(2-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1*(4H)*-yl) ethyl-3-(4-nitrophenyl)acrylamide (6c).** A mixture of 1-(2-aminoethyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.87 mmol), triethylamine (Et_3N) (065 mL, 4.64 mmol) in dry dichloromethane (DCM) (30 mL) was stirred at room temperature for 30 minutes. The 4-nitro cinnamoyl chloride (0.65g, 4.64 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.14 g, 13 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, *J* 5.6 Hz, 1H), 8.24 (d, *J* 8.6 Hz, 2H, aromatic), 7.83 (d, *J* 8.7 Hz, 2H, aromatic), 7.55 (add d, *J* 6.9 Hz, 2H), 7.44 – 7.28 (m, 6H, aromatic, olefinic), 6.83 (d, *J* 15.9 Hz, 1H, olefinic), 6.15 (d, *J* 7.5 Hz, 1H, aromatic), 4.98 (s, 2H), 4.01 (t, *J* 6.0 Hz, 2H), 3.44 (br s, 2H (overlapping with moisture peak from the DMSO-d_6 solvent), 2.21 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 165.5, 148.1, 145.9, 141.9, 140.2, 138.9, 138.3, 137.4, 129.6, 129.2, 128.9, 128.7, 126.4, 124.6, 116.5, 72.4, 52.2, 37.5, 12.5. IR (cm^{-1}): 3246 (N-H stretch), 2924 (C-H stretch), 1660 (C=O), 1543 (C=C), 1285 (C-N), 1157 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{24}H_{23}N_3O_5$:434.1638; found:434.1713.

***(E)-N*-(2-(3-(benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) ethyl)-3-(4-chlorophenyl)acrylamide (6d).**

A mixture of 1-(2-aminoethyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.80 g, 3.09 mmol), triethylamine (Et_3N) (065 mL, 3.72mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-chloro cinnamoyl chloride (0.52 g, 3.72 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a yellow solid (0.17 g, 13%,). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (br t, *J* 5.5 Hz, 1H), 7.59 (d, *J* 8.2 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.38 – 7.32 (m, 6H, aromatic, olefinic), 6.60 (d, *J* 15.8 Hz, 1H, olefinic), 6.15 (d, *J* 7.4 Hz, 1H), 4.98 (s, 2H), 3.99 (t, *J* 6.0 Hz, 2H), 3.32 (dd, *J* 13.7, 7.6 Hz, 2H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.5, 165.9, 145.9,141.4, 140.2, 138.5,138.3 134.6, 134.2, 129.9, 129.5, 128.9, 128.8, 128.3, 122.8, 116.6, 72.4, 52.2,38.9, 12.5. IR (cm^{-1}): 3276 (N-H stretch), 2924 (C-H stretch), 1650 (C=O), 1592 (C=C), 1246 (C-N), 1156 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{24}H_{23}ClN_2O_3$:423.1397; found: 423.1471.

***N*-(3-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) propyl)cinnamamide (6e).** A mixture of 1-(3-aminopropyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.67 mmol), triethylamine (Et_3N) (0.062 mL, 4.41 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The cinnamoyl chloride (0.73 g, 4.41 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown paste (0.32g, 22 %). ^{1}H NMR (400 MHz, DMSO) δ 8.45 (br t, *J* 5.3 Hz, 1H), 7.67 (d, *J* 7.5 Hz, 1H), 7.56 (app d, *J* 7.1 Hz, 2H), 7.38-7.30 (m, 8H, aromatic, olefinic), 6.66 (d, *J* 15.8 Hz, 1H, olefinic), 6.18 (d, *J* 7.5 Hz, 1H), 5.01 (s, 2H), 3.92 (t, *J* 7.3 Hz, 2H), 3.19 (t,7.4 Hz,2H), 2.15 (s, 3H), 1.80 (q, *J* 7.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 172.0, 165.3, 145.4, 140.9, 139.6, 138.8, 137.8, 134.9, 129.5, 129.0, 128.5, 128.3, 127.9, 127.6, 122.2, 116.1, 71.9, 50.8, 35.8, 30.2, 11.9. IR (cm^{-1}): 3262 (N-H stretch), 2952 (C-H stretch), 1657 (C=O), 1549 (C=C), 1247 (C-N), 1157 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{25}H_{26}N_2O_3$: 403.1943; found: 403.2015.

***(E)*-*N*-(3-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1*(4H)*-yl) propyl)-3-(4-methoxyphenyl)acrylamide (6f).** A mixture of 1-(3-aminopropyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.50 g, 1.83 mmol), triethylamine (Et_3N) (031 mL, 2.20 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-methoxy cinnamoyl chloride (0.40 g, 2.20 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a yellow solid (0.38 g, 37 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (br t, *J* 5.3 Hz, 1H), 7.66 (d, *J* 7.5 Hz, 1H), 7.51 (d, *J* 8.6 Hz, 2H), 7.40 – 7.35 (m, 6H, aromatic, olefinic), 6.96 (app d, *J* 8.6 Hz, 2H), 6.49 (d, *J* 15.8 Hz, 1H, olefinic), 6.16 (d, *J* 7.5 Hz, 1H), 5.01 (s, 2H), 3.91 (t, *J* 7.3 Hz, 2H), 3.78 (s, 3H), 3.18 (dd, *J* 12.2, 6.2 Hz, 2H), 2.15 (s, 3H,), 1.86 – 1.69 (t, *J* 7.4 Hz, 2H,). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 165.9, 160.8, 145.9, 141.1, 139.9, 138.9,138.3, 129.6, 128.7, 128.3, 127.9, 120.1, 116.5, 114.9, 72.3, 55.7, 51.1, 36.2, 30.7, 12.3**.** IR (cm^{-1}): 3262 (N-H stretch), 2933 (C-H stretch), 1621 (C=O), 1545 (C=C), 1288 (C-N), 1171 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{26}H_{28}N_2O_4$:434.2049; found: 434.1713.

***(E)*-*N*-(3-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(**4H)-**yl) propyl)-3-(4-nitrophenyl)acrylamide (6g).** A mixture of 1-(3-aminopropyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.90 g, 3.30 mmol), triethylamine (Et_3N) (0.55 mL, 3.97 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-nitro cinnamoyl chloride (0.84 g, 3.97 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.19 g, 8 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (br t, *J* 5.4 Hz, 1H), 8.25 (d, *J* 8.3 Hz, 1H), 7.83 (app d, *J* 8.7 Hz, 2H), 7.66 (d, *J* 7.5 Hz, 1H), 7.38-7.33 (m, 6H, aromatic, olefinic), 6.83 (d, *J* 15.8 Hz, 1H, olefinic), 6.16 (d, *J* 7.5 Hz, 1H,), 5.01 (s, 2H), 3.93 (t, *J* 7.3 Hz, 2H), 3.20 (t, *J* 7.4, 2H), 2.16 (s, 3H), 1.62 – 1.57 (m, 2H).^{13}C NMR (101 MHz, DMSO) δ 172.4, 169.6, 164.9, 164.8, 147.9, 145.9, 142.0, 139.9, 138.3, 129.1, 128.7, 128.3, 127.1, 126.9, 124.6, 116.5, 72.3, 51.1, 37.2, 36.4, 12.3. IR (cm-1): 3259(N-H stretch), 2928 (C-H stretch), 1661 (C=O), 1594 (C=C), 1248 (C-N), 1108 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{25}H_{25}N_3O_5$:448.1794; found:448.1866.

***(E)-N*-(3-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) propyl)-3-(4-chlorophenyl)acrylamide (6h).** A mixture of 1-(3-aminopropyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.67 mmol), triethylamine (Et_3N) (0.062 mL, 4.41 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-chloro cinnamoyl chloride (0.87 g, 4.41 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a light brown solid (0.60g, 37 %). ^{1}H NMR (400 MHz, DMSO) δ 8.29 (broad s, 1H), 7.64 (d, *J* 7.5 Hz, 1H), 7.60 – 7.45 (m, AA'BB', 4H), 7.40 – 7.32 (m, 6H, aromatic, olefinic), 6.62 (d, *J* 15.8 Hz, 1H, olefinic), 6.18 (d, *J* 7.5 Hz, 1H), 5.01 (s, 1H), 3.91 (t, *J* 7.3 Hz, 2H), 3.19 (dd, *J* 12.3, 6.3 Hz, 2H), 2.15 (s, 3H, CH_3), 1.79 (t, *J* 7.4, 2H). ^{13}C NMR (101 MHz, DMSO) δ 171.9, 165.1, 145.4, 140.8, 139.5, 137.8, 137.5, 133.9, 129.3, 129.0, 128.5, 128.3, 127.9, 122.9, 116.1, 71.9, 50.7, 35.9, 30.2, 11.9. IR (cm^{-1}): 3257 (N-H stretch), 2931 (C-H stretch), 1659 (C=O), 1545 (C=C), 1292 (C-N), 1159 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{25}H_{25}ClN_2O_3$: 437.1554; found: 437.1627.

***N*-(4-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) butyl)cinnamamide (6i).** A mixture of 1-(4-aminobutyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.50 mmol), triethylamine (Et_3N) (0.60 mL, 4.20 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The unsubstituted cinnamoyl chloride (0.70 g, 4.20 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a yellow solid (0.57 g, 39 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (br t, *J* 5.2 Hz, 1H), 7.55 (d, *J* 7.5 Hz, 1H), 7.42 (app d, *J* 7.1 Hz, 2H), 7.37 – 7.32 (m, 9H, aromatic, olefinic), 6.64 (d, *J* 15.8 Hz, 1H, olefinic), 6.16 (d, *J* 7.4 Hz, 1H), 5.01 (s, 2H), 3.88 (t, *J* 7.2 Hz, 2H), 3.19 (dd, *J* 12.2, 6.2 Hz, 2H), 2.14 (s, 3H), 1.58 (dd, *J* 14.1, 7.2 Hz, 2H), 1.50 – 1.37 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 165.5, 145.8, 141.3, 140.0, 139.1, 138.2, 135.5, 129.9, 129.5, 129.0, 128.7, 128.4, 128.0, 122.8, 116.5, 72.3, 52.9, 38.7, 28.2, 26.5, 12.4. IR (cm^{-1}): 3247 (N-H stretch), 2916 (C-H stretch), 1658 (C=O), 1546 (C=C), 1218 (C-N), 1189 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{26}H_{28}N_2O_3$:417.2100; found:417.2170.

***(E)-N*-(4-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(4*H*)-yl) butyl)-3-(4-methoxyphenyl)acrylamide (6j)**. A mixture of 1-(4-aminobutyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.50 g, 1.75 mmol), triethylamine (Et_3N) (0.30 mL, 3.50 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-methoxy cinnamoyl chloride (0.42 g, 3.97 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a yellow solid (0.23 g, 42 %) ^{1}H NMR (400 MHz, DMSO) δ 8.14 (br t, *J* 5.4 Hz, 1H), 7.50 (d, *J* 7.5 Hz, 1H), 7.50 (app d, *J* 8.6 Hz, 2H), 7.37 – 7.29 (m, 6H, aromatic, olefinic), 6.96 (app d, *J* 8.5 Hz, 2H), 6.48 (d, *J* 15.7 Hz, 1H, olefinic), 6.16 (d, *J* 7.4 Hz, 1H), 5.00 (s, 2H), 3.88 (t, *J* 7.2 Hz, 2H), 3.77 (s, 3H), 3.17 (d, *J* 6.0 Hz, 2H), 2.14 (s, 3H), 1.69 – 1.47 (m, 2H), 1.50 – 1.35 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 172.4, 165.9, 160.8, 145.8, 141.4, 140.1, 138.9,138.2, 129.7,129.1 128.8, 128.4, 128.0, 120.3, 116.5, 114.9, 72.3, 55.8, 53.0, 38.6, 28.2, 26.6, 12.4. IR (cm^{-1}): 3279 (N-H stretch), 2933 (C-H stretch), 1654 (C=O), 1545 (C=C), 1287 (C-N), 1172 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{27}H_{30}N_2O_4$:447.2206; found:447.2280.

***(E)-N*-(4-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) butyl)-3-(4-nitrophenyl)acrylamide (6k).** A mixture of 1-(4-aminobutyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.50 g, 1.75 mmol), triethylamine (Et_3N) (0.30 mL, 3.50 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-nitro cinnamoyl chloride (0.44 g, 3.97 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a light-brown solid (0.28 g, 8 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (br t, *J* 5.4 Hz, 1H), 8.25 (d, *J* 8.3 Hz, 2H), 7.83 (d, *J* 8.5 Hz, 1H), 7.52 (app d, *J* 7.5 Hz, 2H), 7.52 (d, *J* 15.8 Hz, 1H, olefinic), 7.37 – 7.32 (m, 5H, aromatic), 6.82 (d, *J* 15.9 Hz, 1H, olefinic), 6.15 (d, *J* 7.5 Hz, 1H), 5.01 (s, 2H), 3.89 (t, *J* 7.2 Hz, 2H), 3.20 (d, *J* 6.1 Hz, 2H), 2.15 (s, 3H), 1.60 (t, *J* 7.4 Hz, 2H), 1.43 (t, *J* 7.0 Hz, 2H).**^{13}C** NMR (101 MHz, DMSO-d_6) δ 172.3, 164.8, 147.9, 145.8, 142,5, 142.1, 141.1, 139.9, 138.2, 136.7, 129.9, 128.9, 128.7, 128.3, 124.6, 124.2,116.5, 72.2), 52.9, 38.7, 28.1, 26.4, 12.4. IR (cm^{-1}): 3278 (N-H stretch), 2930 (C-H

stretch), 1660 (C=O), 1594 (C=C), 1284 (C-N), 1192.39 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{26}H_{27}N_3O_5$: 462.1951; found: 462.2029.

***(E)-N*-(4-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) butyl)-3-(4-chlorophenyl)acrylamide (6l).** A mixture of 1-(4-aminobutyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (0.50 g, 1.75 mmol), triethylamine (Et_3N) (0.30 mL, 3.50 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-chloro cinnamoyl chloride (0.42 g, 3.97 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a light-brown solid (0.15 g, 36 %). δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (br t, *J* 5.5 Hz, 1H), 7.61 – 7.57 (m, 4H), 7.47 -7.45 (m, 3H), 7.42 – 7.28 (m, 5H), 6.64 (d, *J* 15.7 Hz, 1H), 6.15 (d, *J* 7.4 Hz, 1H), 5.01 (s, 2H), 3.88 (t, *J* 7.2 Hz, 1H), 3.18 (d, *J* 5.9 Hz, 2H), 2.14 (s, 3H), 1.61 – 1.55 (m, 2H), 1.44 – 1.40 (m, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 165.3, 145.8, 141.2, 139.97, 138.23, 137.67, 134.41, 134.31, 130.62, 129.7, 128.9, 128.7, 123.6, 116.5, 72.3, 52.9, 38.6, 28.1, 26.5, 12.4. IR (cm^{-1}): 3287 (N-H stretch), 2927 (C-H stretch), 1655 (C=O), 1543 (C=C), 1292 (C-N), 1159 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{26}H_{27}ClN_2O_3$: 451.1710; found: 451.1784.

***(E)-N*-(4-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) butyl)-3-(4-hydroxyphenyl)acrylamide (6m).** A mixture of 1-(4-aminobutyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.50 mmol), triethylamine (Et_3N) (0.78 mL, 4.20 mmol) in dry dichloromethane (DCM) (30 mL) was stirred at room temperature for 30 minutes. The 4-hydroxy cinnamoyl chloride (1.00 g, 4.20 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a yellow solid (0.5 g, 12 %,).^{1}H NMR (400 MHz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO) δ 8.03 (br t, *J* 5.5 Hz, 1H), 7.73 (d, J 8.2 Hz, 1H), 7.38 – 7.30 (m, 10H, aromatic, olefinic), 6.78 (d, *J* 8.4 Hz, 1H), 6.40 (d, *J* 15.7 Hz, 1H, olefinic), 5.02 (s, 2H), 3.87 (d, *J* 7.1 Hz, 2H), 3.14 (d, *J* 5.4 Hz, 3H), 3.05 – 2.94 (m, 2H), 2.51 (d, *J* 11.6 Hz, 2H), 1.45 (d, *J* 15.5 Hz, 2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 172.6, 169.5, 165.8, 161.5, 159.3, 141.2, 140.4, 139.0, 138.2, 129.7, 129.0, 128.7, 127.3, 126.4, 119.3, 116.3, 72.3, 53.1, 48.6, 31.7, 27.6, 12.1. IR (cm^{-1}): 3259 (N-H stretch), 2918 (C-H stretch), 1650 (C=O), 1583 (C=C), 1277 (C-N), 1168 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{26}H_{28}N_2O_4$: 433.2049; found: 433.2118.

***N*-(6-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) hexyl)cinnamamide (6n).** A mixture of 1-(6-aminohexyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.18 mmol), triethylamine (Et_3N) (0.54 mL, 3.82 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The cinnamoyl chloride (0.75 g, 3.82 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.26 g, 18 %).^{1}H NMR (400 MHz, DMSO) δ 8.14 (br t, *J* 5.4 Hz, 1H), 7.54 (d, *J* 7.5 Hz, 1H), 7.41 (app d, *J* 7.1 Hz, 2H), 7.42 – 7.32 (m, 9H, aromatic, olefinic), 6.61 (d, *J* 15.8 Hz, 1H, olefinic), 6.15 (d, *J* 7.5 Hz, 1H), 5.01 (s, 2H), 3.84 (t, *J* 7.3 Hz, 2H), 3.15 (dd, *J* 12.6, 6.5 Hz, 2H), 2.13 (s, 3H), 1.56 (dd, *J* 14.2, 7.2 Hz, 2H), 1.42 (dd, *J* 13.9, 6.8 Hz, 2H,), 1.29 – 1.21 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.9, 164.9, 145.3, 140.9, 139.6, 138.6, 137.8, 135.0, 129.5, 129.0, 128.6, 128.3, 127.9, 127.6, 122.4, 116.0, 71.8, 52.8, 38.7, 30.1, 29.0, 26.0, 25.5, 11.9. IR (cm^{-1}): 3260 (N-H stretch), 2928 (C-H stretch), 1658 (C=O), 1549 (C=C), 1282 (C-N), 1179 (C-O). HRMS(ESI+): *m/z* $[M+H]^+$ Calculated for $C_{28}H_{32}N_2O_3$: 445.2413; found: 445.2488.

***(E)-N*-(6-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) hexyl)-3-(4-methoxyphenyl)acrylamide (6o).** A mixture of 1-(6-aminohexyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.18 mmol), triethylamine (Et_3N) (0.54 mL, 3.82 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-methoxy cinnamoyl chloride (0.75 g, 3.82 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.22 g, 15 %).**^{1}H NMR** (400 MHz, DMSO) δ ^{1}H NMR (400 MHz, DMSO) δ 8.09 (br t, *J* 5.5 Hz, 1H), 7.62 (d, *J* 7.5 Hz, 1H), 7.49 (app d, *J* 8.6 Hz, 2H), 7.36 – 7.31 (m, 6H, aromatic, olefinic), 6.94 (app d, J 8.6 Hz, 2H), 6.46 (d, *J* 15.7 Hz, 1H, olefinic), 6.22 (d, *J* 7.4 Hz, 1H), 5.00 (s, 2H), 3.85 (t, *J* 7.3 Hz, 2H), 3.75 (s, 3H), 3.16 – 3.07 (m, 2H), 2.12 (s, 3H), 1.58 –

1.48 (m, 2H), 1.41 (t, *J* 10.3 Hz, 2H), 1.25 – 1.21 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 172.0, 165.7, 160.5, 145.3, 141.7, 139.9, 138.6, 137.7, 129.4, 128.9, 128.5, 128.2, 127.7, 119.9, 116.0, 114.6, 72.2, 55.5, 53.2, 38.9, 30.2, 29.2, 26.2, 25.6, 12.2. IR (cm^{-1}): 3266 (N-H stretch), 2930 (C-H stretch), 1657 (C=O), 1552 (C=C), 1286 (C-N), 1168 (C-O). HRMS(ESI+): *m/z* [M+H]$^+$ Calculated for $C_{29}H_{34}N_2O_4$: 475.2519; found: 475.2592.

***(E)-N*-(6-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) hexyl)-3-(4-nitrophenyl)acrylamide (6p).** A mixture of 1-(6-aminohexyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.18 mmol), triethylamine (Et_3N) (0.54 mL, 3.82 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-nitro cinnamoyl chloride (0.67 g, 3.82 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.15 g, 10 %).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (broad s, 1H), 8.25 (d, *J* 8.5 Hz, 2H), 7.82 (app d, *J* 8.5 Hz, 2H), 7.65 – 7.48 (m, 3H, aromatic, olefinic),7.42-7.28 (m, 5H) 6.86, 6.86 (d, *J* 16.0 Hz, 1H olefinic), 6.14 (d, *J* 7.4 Hz, 1H), 5.01 (s, 2H), 3.84 (d, *J* 7.0 Hz, 2H), 3.17 (dd, *J* 12.2,6.2 Hz, 2H), 3.05 – 2.95 (m, 2H), 2.13 (s, 3H), 1.60 – 1.49 (m, 2H), 1.44 (dd, *J* 13.7, 6.9 Hz, 2H), 1.34 (d, *J* 7.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.3, 164.7, 145.7, 141.2, 139.9, 138.2, 136.6, 129.0, 128.7, 128.6,128.4, 128.3, 124.6, 116.5, 72.2, 53.2,39.2 30.5, 29.5, 26.5,25.88, 24.34, 23.1, 12.4. IR (cm^{-1}): 3270 (N-H stretch), 2932 (C-H stretch), 1621 (C=O), 1547 (C=C), 1247 (C-N), 1155 (C-O). HRMS(ESI+): *m/z* [M+H]$^+$ Calculated for $C_{28}H_{31}N_3O_5$:489.2264; found:489.3388.

***(E)-N*-(6-(3-(Benzyloxy)-2-methyl-4-oxopyridin-1(*4H*)-yl) hexyl)-3-(4-chlorophenyl)acrylamide (6q).** A mixture of 1-(6-aminohexyl)-3-(benzyloxy)-2-methylpyridin-4(1H)-one (1.00 g, 3.18 mmol), triethylamine (Et_3N) (0.54 mL, 3.82 mmol) in dry DCM (30 mL) was stirred at room temperature for 30 minutes. The 4-chloro cinnamoyl chloride (0.75 g, 3.82 mmol) in dry DCM (10 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 24 hours to afford a brown solid (0.38 g, 25 %). ^{1}H NMR (400 MHz, DMSO) δ 8.22 (br t, *J* 5.4 Hz, 1H), 7.64 – 7.53 (m, 3H), 7.46 – 7.40 (m, 2H), 7.40 – 7.25 (m, 6H, aromatic, olefinic), 6.65 (d, *J* 15.8 Hz, 1H, olefinic), 6.17 (d, *J* 7.5 Hz, 1H), 5.02 (s, 2H), 3.83 (t, *J* 7.3 Hz, 2H), 3.16 (dd, *J* 12.5, 6.2 Hz, 2H), 2.13 (s, 3H), 1.58 – 1.49 (m, 2H), 1.47 – 1.37 (m, 2H), 1.34 – 1.13 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.9, 164.8, 145.3, 140.8, 139.5, 137.7, 137.2, 133.9, 133.9, 129.2, 128.9, 128.6, 128.2, 127.9, 123.2, 116.0, 71.8, 52.8, 38.7, 30.0, 29.0, 26.1, 25.4, 11.9. IR (cm^{-1}): 3254 (N-H stretch), 2931 (C-H stretch), 1659 (C=O), 1550 (C=C), 1245 (C-N), 1178 (C-O). HRMS(ESI+): *m/z* [M+H]$^+$ Calculated for $C_{28}H_{31}ClN_2O_3$:479.2023; found: 479.2096.

Acknowledgements

This work was supported by funds provided by the National Research Foundation (Thuthuka Grant no: TTK220407250). We also thank the same NRF for the Ad Hoc scholarship offered to Ms. T. Malusela.

Supplementary Material

All ^{1}H and ^{13}C NMR, Mass, and IR spectra are available in the Supplementary Material file associated with this manuscript.

References

1. Gattu, R.; Ramesh, S.S.; Nadigar, S.; Ramesh, S. *Antibiotics* .**2023**, *12*, 532. https://doi.org/10.3390/antibiotics12030532

2. Müller-Schiffmann, A.; Sticht, H.; Korth, C. *BioDrugs.* **2012**, 26, 21-31. https://doi.org/10.2165/11597630-000000000-00000
3. Abu Almaaty, A.H.; Elgrahy, N.A.; Fayad, E.; Abu Ali, O.A.; Mahdy, A.R.; Barakat, L.A.; El Behery, M. Molecules, **2021**, 26, 4724. https://doi.org/10.3390/molecules26164724
4. Sanduja, M.; Gupta, J.; Virmani, T. *J. Appl. Pharm. Sci*. **2020**, *10*, 129-146. https://doi.org/10.7324/JAPS.2020.102019
5. Guo, L.; Wang, H.; Liu, F.; Duan, L.; Bao, L.; Wu, Z.; Ye, T.; Zhang, Y.; Wang, Y.; Cao, X.; Fang, W. *Pestic. Biochem. Physiol*. **2025**, *213*, 106539. https://doi.org/10.1016/j.pestbp.2025.106539
6. Ruwizhi, N.; Aderibigbe, B.A. *Int. J. Mol. Sci.* **2020**, *21*, 5712. https://doi.org/10.3390/ijms21165712
7. Feng, L.S.; Cheng, W.Q.; Su, H.Z.; Li, T.; Xiao, D.A.; Zhang, Z.L. *Arch. Pharm*. **2022**, 355, 2200052. https://doi.org/10.1002/ardp.202200052
8. He, M.; Fan, M.; Peng, Z.; Wang, G. *Eur. J. Med. Chem.* **2021**, 221, 113546. https://doi.org/10.1016/j.ejmech.2021.113546
9. Shalaby, M.A.; Rizk, S.A.; and Fahim, A.M. *Org. biomol. Chem*. **2023**, *21*(26), 5317-5346. https://doi.org/10.1039/D3OB00792H
10. Lin, S.; Liu, C.; Zhao, X.; Han, X.; Li, X.; Ye, Y; Li, Z. *Front. Chem*. **2022**, *10*, 869860. https://doi.org/10.3389/fchem.2022.869860
11. Porto, R.S.; and Porto, V.A. *Lett Drug Des. Discov.* **2024**, *21*, 2828.
12. Volarić, J.; Szymanski, W.; Simeth, N.A.; and Feringa, B.L. *Chem. Soc. Rev*. **2021**, *50*, 12377. https://doi.org/10.1039/D0CS00547A
13. Sumayya, P.C.; Jalala, V.K.; Ahammed, T.S.; Muraleedharan, K. *Comput. Biol. Chem*. **2022**, *101*, 107777. https://doi.org/10.1016/j.compbiolchem.2022.107777
14. Jin, B.; Zheng, R.; Peng, R.; Chu, S. *Molecules*. **2016**, *21*, 299. https://doi.org/10.3390/molecules21030299
15. Latli, B.; Hrapchak, M.; Savoie, J.; Zhang, Y.; Busacca, C.A; Senanayake, C.H. *J. Label Compd. Radiopharm*. **2017**, 60, 420. https://doi.org/10.1002/jlcr.3518
16. Pavić, K.; Perković, I.; Gilja, P.; Kozlina, F.; Ester, K.; Kralj, M.; Schols, D.; Hadjipavlou-Litina, D.; Pontiki, E.; Zorc, B. *Molecules*. **2016**, *21*, 1629. https://doi.org/10.3390/molecules21121629
17. Matsuhira, T.; Yamamoto, H.; Okamura, T.A.; Ueyama, N. *Org. Biomol. Chem.* **2008**, 6, 1926. https://doi.org/10.1039/B719960K
18. Rodríguez, R.B.; Iguchi, D.; Erra-Balsells, R.; Salum, M.L.; Froimowicz, P. *Polymers*. **2020**, *12*, 1527. https://doi.org/10.3390/polym12071527
19. Becker, M.R.; Morack, T.; Robertson, J.; Metternich, J.B.; Mück-Lichtenfeld, C.; Daniliuc, C.; Burley, G.A.; Gilmour, R. *Tetrahedron.* **2020**, *76*, 131198. https://doi.org/10.1016/j.tet.2020.131198