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Sustainable access to novel pyridone scaffolds: Efficient one-pot, three-component synthesis in PEG-400

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ABSTRACT

This study presents a straightforward and efficient method for synthesizing a novel series of 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one derivatives through a one-pot, three-component reaction. The process employs 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one, diverse aromatic aldehydes, and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one in polyethylene glycol (PEG-400) as an environmentally benign solvent. The methodology prioritizes efficiency, scalability, and reduced environmental impact, offering a practical route to functionalized pyridinones.

We report a catalyst-free protocol for the efficient synthesis of biologically relevant heterocycles, notably functionalized pyridinones. This method features high atom economy, broad functional group tolerance, and minimal purification steps, embodying the sustainable chemistry principles. All products were characterized by multi-spectroscopic analyses ($^{1}H/^{13}C$ NMR, IR, MS) and elemental analysis. Furthermore, single-crystal X-ray diffraction provided unambiguous structural confirmation for a representative derivative.

1. Introduction

Heterocycles are essential scaffolds in pharmaceutical science, forming bioactive molecules, natural products, and biomolecules [1,2]. Nitrogen-containing fused heterocycles are particularly significant, comprising ~60 % of FDA-approved drugs and enabling applications in both therapeutics and materials [3]. Among these, the 2-pyridone motifa six-membered ring with a nitrogen adjacent to a carbonylis a privileged pharmacophore [4,5]. Its dual hydrogen-bonding capacity and favorable physicochemical properties (e.g., metabolic stability, balanced lipophilicity) underpin diverse bioactivities, including anti-inflammatory, antiproliferative, antiviral, and antidiabetic effects [6,7]. Clinically relevant derivatives include anticancer (Compound A [5]), Alzheimer's (Compound B [8]), and antifungal (Compound C [9]) agents (Fig. 1).

Notably, bis-pyridones hybrid architectures integrating two 2-pyridone cores are emerging as potent drug candidates, leveraging synergistic interactions to address complex disease pathways [10,11]. This structural class highlights the untapped potential of multi-heterocyclic systems in developing next-generation therapeutics.

Recent reports detail methods for synthesizing pyridone-core compounds. However, current approaches suffer from limitations such as by-product formation, low yields, complex pathways, narrow functional group tolerance, the use of toxic reagents, and metal catalyst requirements [12–16]. Therefore, developing simple and efficient routes to novel heterocycles remains crucial in organic synthesis. Multicomponent reactions (MCRs) offer efficient routes to diverse fused-ring heterocycles, particularly valuable in drug discovery [17,18].

Polyethylene glycol (PEG) is an established, sustainable reaction medium and phase transfer catalyst for diverse organic transformations. Its hydrophilic polyether structure facilitates hydrogen bonding via ether oxygen atoms, promoting bond cleavage/formation and enhancing reactivity [19,20]. PEG is further valued for its safety, eco-friendly profile (non-toxic, biodegradable, recyclable, low-cost), thermal stability, non-volatility, high flash point, and non-corrosive nature, enhancing its utility in green chemistry [21]. These attributes collectively position PEG as a practical and environmentally responsible choice for modern synthetic methodologies.

Significant efforts have focused on expanding pyridone-containing heterocycles due to their medicinal relevance and low toxicity. Building on our prior work in heterocyclic synthesis [22,23], we present an efficient strategy to access novel 1-benzyl-3-((1-benzyl-4-benzylamino-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)

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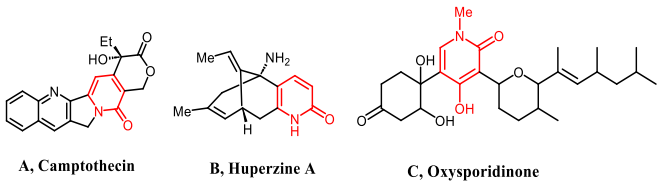


Fig. 1. Some biologically active pyridone-based compounds.

(methyl)-4-hydroxy-6-methylpyridin-2-one. This approach involves a one-pot reaction of 1-benzyl-4-hydroxy-6-methylpyridin-2-one, aromatic aldehydes and 1-benzyl-4-benzylamino-6-methylpyridin-2-one under catalyst-free conditions in PEG-400, which appeared to play a dual role of solvent and catalyst (Scheme 1).

2. Results and discussion

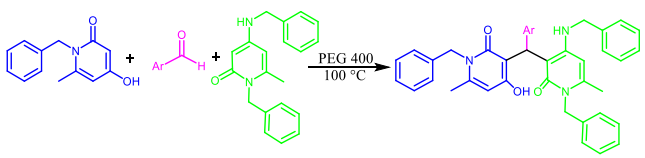
The one-pot reaction of 1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (**1**), 4-methylbenzaldehyde (**2a**), and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1H)-one **(3)** was selected as a model system to systematically optimize reaction conditions. Initial screening under catalyst-free conditions in ethanol (reflux) achieved a moderate yield of the target product 50 % (Table 1, entry 1), serving as a baseline for further refinement. A systematic solvent screening was conducted to optimize the model reaction. Initial evaluation of protic solvents, including water, and aprotic polar solvents (DMF, DMSO) or low-polarity options (acetonitrile, toluene, CH_3Cl) revealed no significant yield improvement (Table 1, Entries 2–6). These results underscored the need for alternative solvent systems. Guided by green chemistry principles, polyethylene glycols (PEG-400, PEG-2000, PEG-4000) were investigated due to their broad solubility and eco-friendly profile. Remarkably, PEG-400 substantially enhanced reaction efficiency and reduced reaction time (Table 1, Entry 7), attributed to its ability to interact with liberated water during the Knoevenagel condensation, shifting the equilibrium toward product formation [24].

Further optimization explored catalytic systems in PEG-400. However, DABCO and PTSA prompted byproduct formation, diminishing yields (Table 1, entries 10–11). Catalyst-free conditions in PEG-400 proved optimal, achieving superior efficiency. Comparatively, neat conditions at 100 °C yielded only 60 % product (Table 1, entry 12), reinforcing PEG-400's dual role as solvent and equilibrium modulator. This methodology aligns with sustainable synthesis goals, offering a scalable, catalyst-free approach with minimal environmental impact.

Eventually, different temperatures were screened (Table 1, entries 13–15), and the best results (95 %) were obtained at 100 °C (Table 1, entry 7). It is important to mention that the solvent and temperature undeniably affect the synthesis of the 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one derivatives.

Finally, a catalyst-free reaction in PEG at 100 °C was chosen as the optimal condition for the respective model reaction (Table 1, entry 7).

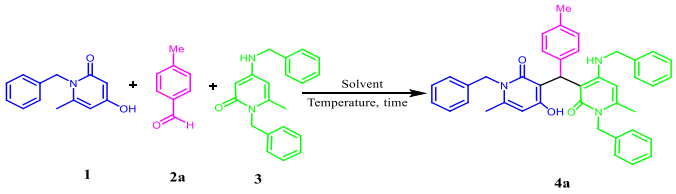
A diverse library of target compounds **4a-m** was synthesized via systematic exploration of aromatic and heteroaromatic aldehydes, demonstrating robust compatibility with both electron-withdrawing and



Ar: 4-Me-C_6H_4, 4-Br-C_6H_4, C_6H_5, 4-CN-C_6H_4, 4-NO_2-C_6H_4, 4-F_3C-C_6H_4, 4-MeO-C_6H_4, 4-Cl-C_6H_4, 3-Cl-C_6H_4, 3-NO_2-C_6H_4, 3-Br-C_6H_4, Furan-2-yl, Tiophen-2-yl

Scheme 1. Synthesis of new 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one derivatives.

Table 1
Optimization of reaction in various solvents, catalysts, and temperatures of **4a**[a].



Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Yield (%)[b]
1	EtOH	–	Reflux	4	50
2	H_2O		Reflux	12	50
3	DMF		110	12	50
5	DMSO		110	12	60
4	CH_3CN	–	reflux	3	40
5	Toluene	-	reflux	3	80
6	CH_3Cl	–	Reflux	4	40
7	**PEG 400**	**-**	**100**	**1.5**	**95**[c]
8	PEG 2000	–	100	3	85
9	PEG 4000	–	100	3	70
10	PEG 400	DABCO	100	4	50
11	PEG 400	PTSA	100	4	30
12	–	–	100	3	60
13	PEG 400	–	110	1.5	95
14	PEG 400		70	4	50
15	PEG 400	–	rt	12	20

[a] Reaction conditions: 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (1.0 mmol), 4-methylbenzaldehyde (1.1 mmol), and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one (1.0 mmol) in solvent.
[b] Isolated yield.
[c] Bold values indicate better results than other conditions.

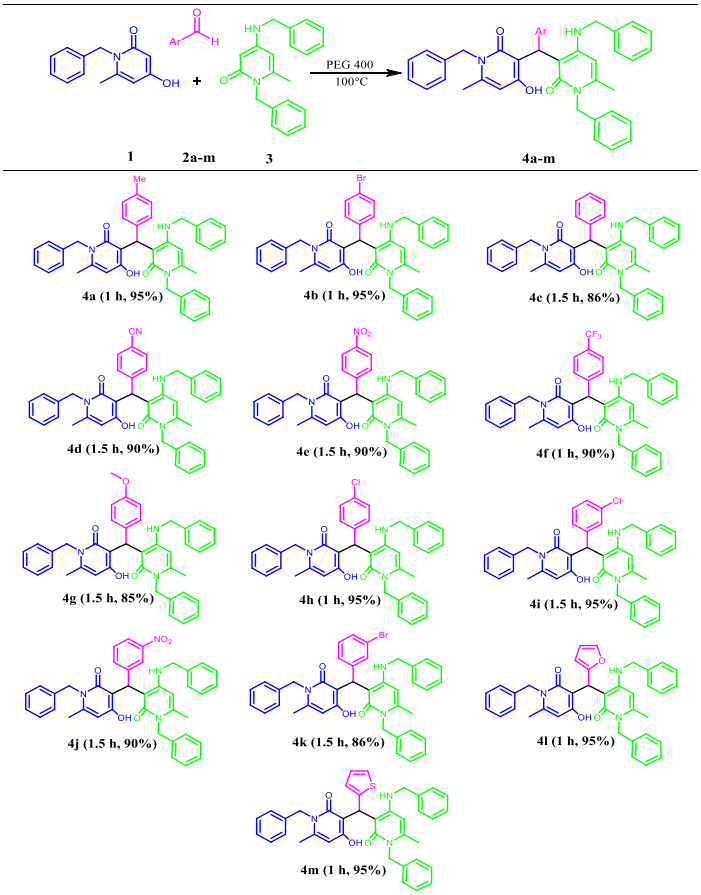
electron-donating substituents (Table 2). Notably, these substituents significantly enhanced reaction efficiency, achieving high yields of desired products. In contrast, aliphatic aldehydes (e.g., butyraldehyde, acetaldehyde, cinnamaldehyde) failed to generate products, highlighting the reaction's selectivity for aromatic systems.

The proposed mechanism for the formation of 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one is based on the literature survey [25,26]. In the proposed mechanism, PEG activates the aromatic aldehyde **2**; this is followed by the Knoevenagel condensation between **2** and 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one (**1**) to yield the intermediate (**I**). The third molecule (1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one) then adds to the olefinic carbon in (**I**), by a Michael addition to generate intermediate **(II)**. Finally, target compound **4** is produced through[1,3]H transfer (Scheme 2).

3. Conclusion

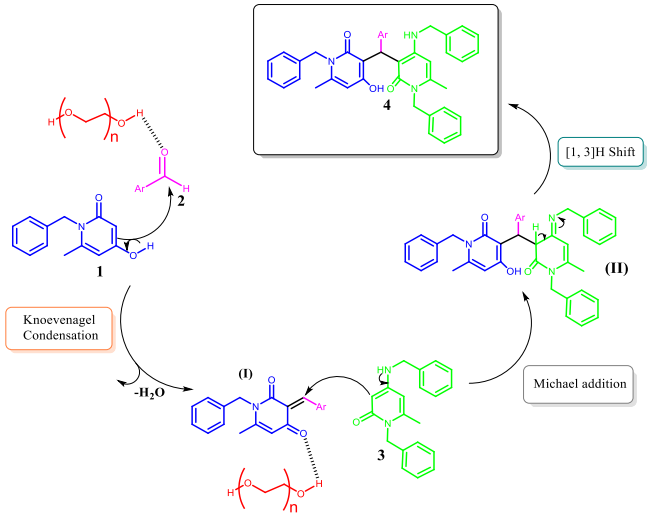
In summary, we report a green, efficient, and scalable one-pot three-component synthesis of novel 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1*H*)-one derivatives from 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one, diverse aromatic aldehydes, and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one in the eco-friendly medium PEG-400. This method demonstrates excellent atom economy, broad substrate compatibility, minimal byproduct formation, and straightforward purification. The structural diversity of the synthesized derivatives positions them as promising candidates for biological evaluation, with potential applications in medicinal chemistry and drug discovery. This work aligns with sustainable chemistry goals, offering a practical platform for accessing functionalized heterocycles under mild, catalyst-free conditions.

Table 2
Synthesis of products[a].



[a]Reaction conditions: 1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (1.0 mmol), various aromatic aldehydes (1.1 mmol), and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1H)-one (1.0 mmol) in PEG-400 (0.5 ml) at 100 °C.

[a] Reaction conditions: 1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one (1.0 mmol), various aromatic aldehydes (1.1 mmol), and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1H)-one (1.0 mmol) in PEG-400 (0.5 ml) at 100 °C.



Scheme 2. The plausible mechanism for the synthesis of **4**.

4. Experimental

4.1. General

All chemicals and solvents used in this project were obtained from Merck. Melting point measurement of all compounds reported in this project was done using an Electrothermal 9100 device. The samples were placed in the form of KBr tablets to record infrared spectra (FT-IR) in a Thermo-Nicolet AVATAR 370 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were prepared at frequencies of 300.13 and 75.47 MHz, respectively, in DMSO-d_6 and $CDCl_3$ by Bruker AVANCE DRX-300. The mass spectrum was recorded by a Varian Mat CH-7 instrument at 70 eV. Elemental analysis of the compounds was conducted using a Thermo Finnigan Flash EA microanalyzer. X-ray crystal structure data were collected using a Bruker D8 VENTURE PHOTON 100 CMOS diffractometer with graphite monochromated Cu Kα radiation at a temperature of 296(2) K. The reported 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one were prepared according to literature procedures, respectively [27,28].

Structural elucidation of **4a-m** was confirmed through multi-spectroscopic analysis (^{1}H/^{13}C NMR, IR, mass spectrometry) and elemental data (Supplemental Information). For example, **4a** exhibited distinct IR absorptions at 3263 cm^{-1} (N–H stretch), 1643 cm^{-1}, and

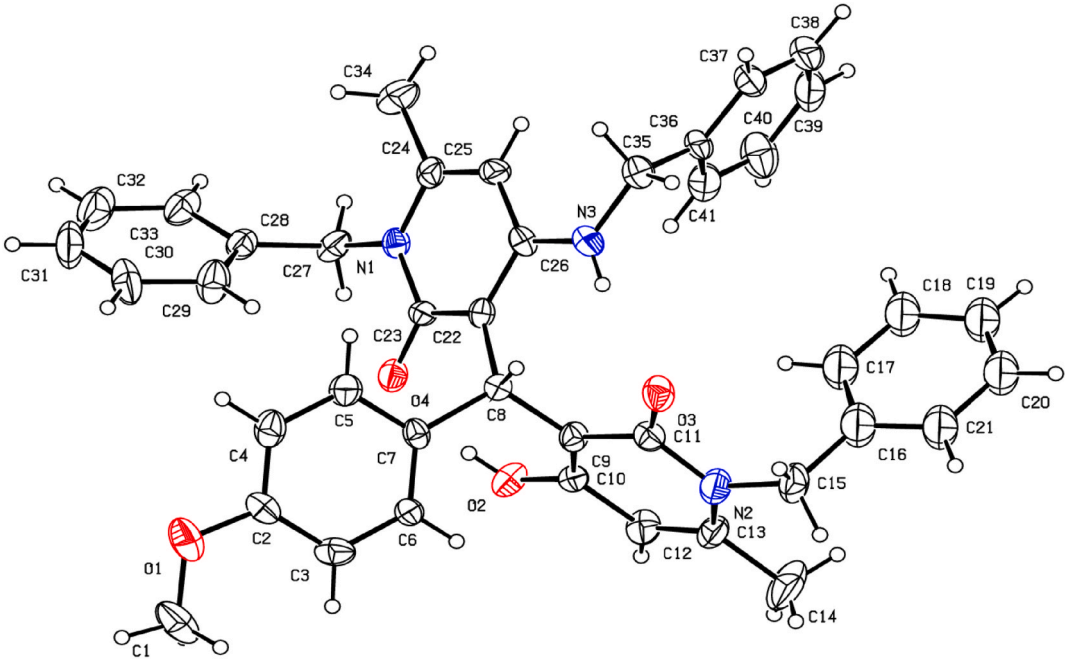


Fig. 2. X-ray crystal structure of product **4g**.

1556 cm^{-1} (C═O vibrations). Its ^{1}H NMR spectrum displayed three methyl singlets (δ = 2.19–2.26 ppm), a methine resonance at δ = 6.00 ppm, and NH/OH singlets at δ = 8.20 and 13.33 ppm, respectively. The ^{13}C NMR spectrum confirmed the structure of **4a**, while mass spectrometry revealed a molecular ion peak at *m/z* 622 (M+), consistent with the proposed framework.

Additionally, the structure of a representative compound was examined using single-crystal X-ray diffraction analysis (Fig. 2). The chemical structure and the stereochemistry of product **4g** were clearly and successfully confirmed (CCDC 2390728): $C_{41}H_{39}N_3O_4$: MW = 637.75. For more information, see the supporting file for the X-ray crystallographic data of compound **4g**. Crystal structure analysis on colorless needle-shape single-crystal of compound **4g** shows that this compound is crystallized in triclinic crystal system and $P\,\bar{1}$ space group. In the crystal structure of compound **4g**, there are two N–H···O and O–H···O intramolecular hydrogen bonds in each molecule of compound **4g** which is shown in Supporting information Fig S53. Crystal packing of the compound **4g** which show the relation between molecules in crystal structure is shown in Fig. S54. X-ray crystal structure and refinement data are shown in Table S1. Also, selected bond length, angles and hydrogen bonds are summarized in Tables S4–S6 respectively.

4.1.1. Typical procedure for the synthesis of 1-benzyl-4-hydroxy-6-methylpyridin-2(1H)-one 1

A mixture of 4-hydroxy-6-methyl-2H-pyran-2-one (4 mmol) and benzylamine (5 mmol) in water (16 mL) was stirred under reflux for 12 h. At the end of the reaction, the mixture was allowed to cool to room temperature; the crude product was filtered and washed with diethyl ether. The desired product was obtained in yields ranging from 85 % to 92 %. The melting point was determined to be 227 °C, and the mass spectrometry exhibited a molecular ion peak at m/z 215 (M+).

4.1.2. Typical procedure for the synthesis of 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1H)-one 3

In a 50-mL reaction vial, 4-hydroxy-6-methyl-2H-pyran-2-one (10 mmol), benzylamine (22 mmol), and 15 mL of acetic acid (HOAc) were combined. The vial was then capped and heated at 100 °C for 4 h. After the reaction was complete, as confirmed by TLC (using a 6:4 hexane/ethyl acetate solvent system), the mixture was diluted with 10 mL of water. The resulting precipitate was filtered and washed with diethyl ether. The desired product was obtained in yields of between 87 and 96 %. Mp 190 °C, MS: m/z 304 (M^+).

4.1.3. General procedure for the synthesis of 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(aryl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one derivatives 4

A mixture of 1-benzyl-4-hydroxy-6-methylpyridin-2(1*H*)-one **1** (1.0 mmol), aromatic aldehyde **2** (1.1 mmol), and 1-benzyl-4-(benzylamino)-6-methylpyridin-2(1*H*)-one **3** (1.0 mmol), in PEG-400 (0.5 mL) was stirred at 100 °C for the specified duration (as indicated in Table 2). Then, a mixture of methanol and water (1:2 ratio, 3 mL) was added to the reaction mixture. The solid residue was collected by filtration, washed with MeOH: H_2O (3*3 mL), and then dried to yield the pure products, labeled as **4a–3m**.

4.1.4. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(p-tolyl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one (4a)

White solid; (0.59 g, 95 %) mp: 220–222 °C; IR (KBr) (υ_{max}/cm^{-1}): 3263 (NH), 3141, 3030, 1643, 1556 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.19 (3H, s, CH_3), 2.24 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.27–4.68 (2H, m, CH_2), 5.01, 5.21 (2H, AB-quartet, $^{2}J_{HH}$ = 15 Hz, CH_2), 5.34, 5.43 (2H, AB-quartet, $^{2}J_{HH}$ = 15 Hz, CH_2), 6.00 (1H, s, CH), 6.03 (1H, s, ArH), 6.16(1H, s, ArH), 6.96 (2H, d, $^{3}J_{HH}$ = 7.9 Hz, ArH), 7.02–7.16 (6H, m, ArH), 7.28 (11H, ddt, $^{3}J_{HH}$ = 13.2, 9.0, 5.4 Hz, ArH), 8.20 (1H, s, NH), 13.33 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 21, 36.4, 46.3, 46.6, 47.3, 98.1, 103.6, 105.3, 108, 126.5, 126.6, 126.7, 126.9, 127.4, 127.5, 128.9, 129.1, 129.1, 134.3, 137.6, 137.8, 138, 139.3, 145.8, 146.1, 156, 163.2, 166, 166.3; MS: (m/z, %): 622 (M^+,72), 535 (53), 314 (73), 301 (82), 226 (46), 148 (59), 91 (100), 57 (64). Anal. Calcd for $C_{41}H_{39}N_3O_3$ (621.78): C, 79. 20; H, 6.32; N, 6.76 %. Found: C, 79. 11; H, 6.13; N, 6.57 %.

4.1.5. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-bromophenyl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one (4b)

White solid; (0.65 g, 95 %) mp: 222–224 °C; IR (KBr) (υ_{max}/cm^{-1}): 3261 (NH), 3137, 3029, 1642, 1552 (C═O); ^{1}H NMR (300.13 MHz,

DMSO-d_6): δ (ppm) 2.20 (3H, s, CH_3), 2.24 (3H, s, CH_3), 4.30–4.64 (2H, m, CH_2), 5.05, 5.20 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 5.31, 5.43 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 6.01 (2H, s, CH & ArH), 6.19 (1H, s, ArH), 7.04 (4H, dd, $^3J_{HH} = 14.3$, 7.8 Hz, ArH), 7.12 (2H, d, $^3J_{HH} = 7.3$ Hz ArH), 7.28 (11H, dt, $^3J_{HH} = 18.5$, 7.5 Hz, ArH), 7.43 (2H, d, $^3J_{HH} = 8.2$ Hz, ArH), 8.16 (1H, s, NH), 13.26 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 36.5, 46.3, 46.7, 47.3, 98.2, 103.6, 104.8, 107.5, 118.7, 126.6, 126.6, 126.9, 127.4, 127.5, 127.6, 128.9, 129.1, 129.2, 134, 137.7, 137.9, 139.2, 140.3, 146.2, 146.4, 156, 163.1, 166, 166.1; MS: (*m/z*, %): 686 (M^+,68), 597 (45), 471 (40), 378 (71), 300 (89), 196 (61), 90 (100). Anal. Calcd for $C_{40}H_{36}BrN_3O_3$ (686.65): C, 69.97; H, 5.28; N, 6.12 %. Found: C, 69.94; H,5.22; N, 6.11 %.

4.1.6. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(phenyl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one (4c)

White solid; (0.52 g, 86 %) mp: 219–221 °C; IR (KBr) (υ_{max}/cm^{-1}): 3264 (NH), 3084, 3056, 1643, 1576 (C═O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.19 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.42–4.60 (2H, m, CH_2), 4.96, 5.29 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.49, 5.54 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.84 (1H, s, CH), 6.05 (1H, s, ArH), 6.35 (1H, s, ArH), 7.17 (5H, dd, $^3J_{HH} = 12.5$, 7.3 Hz, ArH), 7.28–7.36 (15H, m, ArH), 8.47 (1H, s, NH) 13.44 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.4, 20.8, 37, 46.8, 47, 47.7, 98.1, 104.4, 106.3, 108.5, 125.4, 126.3, 126.5, 126.8, 127, 127.2, 127.2, 127.9, 128.6, 128.7, 128.8, 137.1, 137.2, 138.9, 140.3, 144.4, 145, 156.1, 159.9, 163.5, 166.4, 166.6; MS: (*m/z*, %): 608 (M^+, 15), 520 (100), 426 (10), 300 (18), 90 (99). Anal. Calcd for $C_{40}H_{37}N_3O_3$ (607.75): C, 79.05; H, 6.14; N, 6.91 %. Found: C, 79.00; H, 6.12; N, 6.87 %.

4.1.7. 4-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(1-benzyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl) benzonitrile (4d)

White solid; (0.59 g, 93 %) mp: 230–232 °C; IR (KBr) (υ_{max}/cm^{-1}): 3268 (NH), 3133,3060, 2228 (CN), 1639, 1550 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.21 (3H, s, CH_3), 2.25 (3H, s, CH_3), 4.36–4.63 (2H, m, CH_2), 5.06, 5.21 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 5.30, 5.42 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 6.03 (1H, s, CH), 6.10 (1H, s, ArH), 6.21 (1H, s, ArH),7.03–7.09 (2H, m, ArH), 7.10–7.16 (2H, m, ArH), 7.26 (9H, td, $^3J_{HH} = 6.4$, 3.9 Hz, ArH), 7.34 (4H, dd, $^3J_{HH} = 8.4$, 6.6 Hz, ArH), 7.73 (2H, d, $^3J_{HH} = 8.4$ Hz, ArH), 8.16 (1H, s, NH), 13.19 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 37.3, 46.4, 46.9, 47.4, 98.3, 103.6, 107.1, 108.4, 119.7, 126.6, 126.6, 127.4, 127.4, 127.5, 127.6, 127.7, 129, 129.1, 132.3, 137.4, 137.6, 137.8, 139.1, 146.5, 146.7, 146.9, 147.3, 156, 163.1, 165.7, 166; MS: (*m/z*, %): 632 (M^+,12), 544 (32), 324 (77), 300 (83), 196 (18), 90 (100), 65 (70). Anal. Calcd for $C_{41}H_{36}N_4O_3$ (632.76): C, 77.83; H, 5.73; N, 8.85 %. Found: C, 77.80; H, 5.72; N, 8.85 %.

4.1.8. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-nitrophenyl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4e)

White solid; (0.59 g, 90 %) mp: 228–230 °C; IR (KBr) (υ_{max}/cm^{-1}): 3260 (NH), 3129, 3072, 1639, 1556 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.24 (3H, s, CH_3), 2.28 (3H, s, CH_3), 4.41–4.51 (2H, m, CH_2), 5.09, 5.22 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.30, 5.43 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 6.05 (1H, s, CH), 6.13 (1H, s, ArH), 6.24 (1H, s, ArH), 7.07 (2H, d, $^3J_{HH} = 7.6$ Hz, ArH), 7.12–7.16 (2H, m, ArH), 7.26–7.37 (13H, m, ArH), 8.11–8.18 (3H, m, ArH & NH), 13.13 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 37.3, 46.4, 46.8, 47.4, 98.4, 103.6, 107.2, 123.6, 126.6, 127.4, 127.5, 127.6, 127.8, 128, 128.9, 129.1, 129.2, 129.2, 137.4, 137.6, 137.8, 139, 145.9, 146.5, 146.7, 149.7, 155.9, 163.2, 166.6, 166; MS: (*m/z*, %): 652 (M^+,2), 649 (10), 562 (30), 433 (10), 344 (25), 327 (33), 300 (90), 285 (34), 211 (38), 196 (50), 90 (100), 65 (78). Anal. Calcd for $C_{40}H_{36}N_4O_5$ (652.12): C, 73.60; H, 5.56; N, 8.58 %. Found: C, 73.58; H,5.52; N, 8.57 %.

4.1.9. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-(trifluoromethyl)phenyl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one (4f)

White solid; (0.61 g, 90 %) mp: 200–202 °C; IR (KBr) (υ_{max}/cm^{-1}): 3264 (NH), 3129, 3028, 1639, 1557 (C═O), 1495 (C–F); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.21 (3H, s, CH_3), 2.30 (3H, s, CH_3), 4.39–4.61 (2H, m, CH_2), 4.98, 5.27 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.46, 5.52 (2H, AB-quartet, $^2J_{HH} = 6$ Hz, CH_2), 5.85 (1H, s, CH), 6.04 (1H, s, ArH), 6.31 (1H, s, ArH), 7.15 (4H, dd, $^3J_{HH} = 15.5$, 7.2 Hz, ArH), 7.27–7.41 (13H, m, ArH), 7.54 (2H, d, $^3J_{HH} = 8.1$ Hz, ArH), 8.42 (1H, s, NH) 13.31 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.41, 20.85, 37.10, 46.97, 47.09, 47.77, 98.19, 104.42, 105.56, 108.01, 124.63 (q, $^1J_{CF} = 271.6$ Hz, CF_3), 124.90 (q, $^3J_{CF} = 3.4$ Hz, CH-C-CF_3), 126.22, 126.48, 126.67, 126.79, 127.13, 127.24, 127.38, 127.51(q, $^2J_{CF} = 31.6$ Hz, C-CF_3), 128.68, 128.74, 128.83, 136.83, 137.05, 138.56, 144.80, 144.91, 145.34, 156.14, 163.41, 166.39, 166.51; MS: (*m/z*, %): 676 (M^+, 54), 675 (90), 586 (9), 301 (89), 213 (90), 198 (20), 108 (85), 90 (100). Anal. Calcd for $C_{41}H_{36}F_3N_3O_3$ (675.75): C, 72.78; H, 5.37; N, 6.22 %. Found: C, 72.73; H,5.34; N, 6.20 %.

4.1.10. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-methoxyphenyl)methyl)-4-hydroxy-6-methylpyridin-2(1H)-one (4g)

White solid; (0.54 g, 85 %) mp: 193–195 °C; IR (KBr) (υ_{max}/cm^{-1}): 3267 (NH), 3141, 3029, 1642, 1556 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.21 (3H, s, CH_3), 2.24 (3H, s, CH_3), 3.72 (3H, s, CH_3), 4.33–4.64 (2H, m, CH_2), 5.03, 5.22 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.34, 5.43 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 5.99 (1H, s, CH), 6.02 (1H, s, ArH), 6.17 (1H, s, ArH), 6.82 (2H, d, $^3J_{HH} = 8.6$ Hz, ArH), 6.98 (2H, d, $^3J_{HH} = 8.3$, ArH), 7.11 (4H, dd, $^3J_{HH} = 13.0$,7.5, ArH), 7.21–7.41 (11H, m, ArH), 8.18 (1H, s, NH), 13.34 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 36, 46.3, 46.6, 47.3, 55.4, 98.1, 103.6, 105.4, 108.2, 113.7, 126.6, 126.7, 127.4, 127.4, 127.5, 128.9, 129.1, 129.1, 132.4, 135.8, 138, 139.3, 145.8, 146.1, 154.4, 155.9, 157.4163.2, 166, 166.24, 166.24; MS: (*m/z*, %): 637 (M^+,15), 549 (5), 329 (25), 300 (49), 90 (75), 43 (100). Anal. Calcd for $C_{41}H_{39}N_3O_4$ (637.75): C, 77.21; H, 6.16; N, 6.59 %. Found: C, 77.18; H, 6.13; N, 6.11 %.

4.1.11. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(4-chlorophenyl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4h)

White solid; (0.61 g, 95 %) mp: 208–210 °C; IR (KBr) (υ_{max}/cm^{-1}): 3262 (NH), 3137, 3029, 1644, 1556 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.21 (3H, s, CH_3), 2.24 (3H, s, CH_3), 4.33–4.63 (2H, m, CH_2), 5.05, 5.20 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.31, 5.42 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 6.01 (1H, s, CH), 6.03 (1H, s, ArH), 6.19 (1H, s, ArH), 7.02–7.10 (4H, m, ArH), 7.10–7.15 (2H, m, ArH), 7.26 (9H, ddt, $^3J_{HH} = 7.6$, 5.1, 2.2 Hz, ArH), 7.30–7.39 (4H, m, ArH), 8.16 (1H, s, NH), 13.26 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 36.4, 46.4, 46.7, 47.3, 98.2, 103.6, 104.5, 107.6, 126.6, 126.6, 127.4, 127.5, 127.5, 128.2, 128.5, 128.9, 129.1, 129.1, 129.1, 137.7, 137.9, 139.2, 139.9, 146.2, 146.4, 155.8, 156.1, 163.2, 163.2, 166; MS: (*m/z*, %): 642 (M^+,30), 554 (90), 333 (90), 301 (94), 90 (100), 57 (48). Anal. Calcd for $C_{40}H_{36}ClN_3O_5$ (642. 20): C, 74.81; H, 5.65; N, 6.54 %. Found: C, 74.80; H, 5.52; N, 6.52 %.

4.1.12. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(3-chlorophenyl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4i)

White solid; (0.61 g, 95 %) mp: 220–222 °C; IR (KBr) (υ_{max}/cm^{-1}): 3268 (NH), 3129, 3027, 1644, 1558 (C═O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.19 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.37–4.59 (2H, m, CH_2), 4.81, 5.21 (2H, AB-quartet, $^2J_{HH} = 15$ Hz, CH_2), 5.52, 5.68 (2H, AB-quartet, $^2J_{HH} = 18$ Hz, CH_2), 5.83 (1H, s, CH), 6.03 (1H, s, ArH), 6.27 (1H, s, ArH), 7.17 (11H, q, $^3J_{HH} = 9.0$ Hz, ArH), 7.29–7.41 (8H, m, ArH),

8. 40 (1H, s, NH), 13.35 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.4, 20.8, 36.8, 46.8, 47, 47.7, 98.1, 104.4, 105.6, 107.9, 124.7, 125.6, 126.2, 126.5, 126.6, 126.8, 127.1, 127.2, 127.3, 128.7, 128.8, 128.9, 129.2, 134, 136.8, 137.1, 138.6, 142.8, 144.6, 145.3, 156.1, 163.4, 166.4, 166.5; MS: (*m/z*, %): 642 (M^+, 35), 640 (73), 552 (1), 424 (3), 333 (85), 300 (100), 243 (28), 90 (95). Anal. Calcd for $C_{40}H_{36}ClN_3O_3$ (642.120): C, 74.81; H, 5.65; N, 6.54 %. Found: C, 74.59; H, 5.61; N, 6.50 %.

4.1.13. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(3-nitrophenyl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4j)

Yellow solid; (0.59 g, 90 %) mp: 212–214 °C; IR (KBr) (υ_{max}/cm^{-1}): 3255 (NH), 3125, 3088, 1642, 1556 (C═O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.21 (3H, s, CH_3), 2.30 (3H, s, CH_3), 4.42–4.57 (2H, m, CH_2), 4.80, 5.20 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 5.53, 5.66 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 5.89 (1H, s, CH), 6.03 (1H, s, ArH), 6.31 (1H, s, ArH), 7.09 (2H, d, $^3J_{HH}$ = 7.6 Hz, ArH), 7.14–7.21 (2H, m, ArH), 7.26–7.34 (10H, m, ArH), 7.44 (2H, t, $^3J_{HH}$ = 7.9 Hz, ArH), 7.60 (1H, d, $^3J_{HH}$ = 7.8, ArH), 8.05 (1H, dd, $^3J_{HH}$ = 8.1, 2.3 Hz, ArH), 8.17 (1H, s, ArH), 8.41 (1H, s, NH) 13.23 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.4, 20.8, 36.9, 47, 47.1, 47.8, 98.4, 104.4, 104.9, 107.7, 120.7, 122, 126.2, 126.3, 126.5, 126.9, 127.2, 127.2, 127.4, 128.7, 128.8, 128.9, 132.8, 136.5, 137, 138.3, 143, 145, 145.7, 148.5, 156.3, 163.3, 166.3, 166.4; MS: (*m/z*, %): 653 (M^+,35), 563 (75), 437 (20), 388 (15), 343 (60), 300 (95), 256 (28), 148 (37), 90 (85). Anal. Calcd for $C_{40}H_{36}N_4O_5$ (652.75): C, 73.60; H, 5.56; N, 8.58 %. Found: C, 73.57; H,5.52; N, 8.55 %.

4.1.14. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(3-bromophenyl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4k)

White solid; (0.59 g, 86 %) mp: 200–202 °C; IR (KBr) (υ_{max}/cm^{-1}): 3265 (NH), 3133, 3063, 1649, 1557 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.21 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.35–4.60 (2H, m, CH_2), 4.95, 5.18 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 5.44, 5.49 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 6.03 (1H, s, CH), 6.08 (1H, s, ArH), 6.19 (1H, s, ArH), 7.07–7.14 (4H, m, ArH), 7.21–7.31 (10H, m, ArH), 7.32–7.39 (5H, m, ArH), 8.17 (1H, s, NH), 13.25 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.1, 20.4, 36.7, 46.4, 46.7, 47.3, 98.3, 103.6, 107.4, 109.1, 122.1, 125.6, 126.6, 126.6, 127.4, 127.5, 127.6, 128.5, 128.9, 129.1, 129.2, 129.3, 130.5, 137.4, 137.7, 137.9, 139.2, 143.8146.3, 146.5, 156.1, 163.1, 165.6, 166; MS: (*m/z*, %): 687 (M^+,50), 599 (50), 472 (50), 379 (70), 349 (35), 300 (99), 289 (59), 197 (59), 104 (55), 91 (100), 65 (68), 42 (53). Anal. Calcd for $C_{40}H_{36}BrN_3O_3$ (686.65): C, 69.97; H, 5.28; N, 6.12 %. Found: C, 69.89; H, 5.22; N, 6.11 %.

4.1.15. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(furan-2-yl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4l)

White solid; (0.57 g, 95 %) mp: 240–242 °C; IR (KBr) (υ_{max}/cm^{-1}): 3249 (NH), 3137, 3029, 1648, 1558 (C═O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.16 (3H, s, CH_3), 2.26 (3H, s, CH_3), 4.40–4.57 (2H, m, CH_2), 5.04, 5.19 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 5.52, 5.47 (2H, AB-quartet, $^2J_{HH}$ = 15 Hz, CH_2), 5.79 (1H, s, CH), 6.02 (1H, s, ArH), 6.11–6.23 (2H, m, ArH), 6.32–6.40 (1H, m, ArH), 7.16 (4H, d, $^3J_{HH}$ = 7.1 Hz, ArH), 7.29 (11H, d, $^3J_{HH}$ = 5.6 Hz, ArH), 7.36 (1H, s, ArH), 8.27 (1H, s, NH), 13.40 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.4, 20.8, 33, 46.8, 47, 47.7, 97.9, 104.4, 105.5, 107.5, 110.4, 126.3, 126.6, 126.8, 127, 127.2, 128.6, 128.7, 128.8, 129.2, 137, 137.1, 138.7, 140.4, 144.6, 145.1, 153.9, 155.1, 163.6, 166.1, 166.4, 168.9; MS: (*m/z*, %): 598 (M^+, 64), 572 (2), 510 (51), 380 (5), 301 (100), 290 (75), 213 (58), 197 (35), 90 (80). Anal. Calcd for $C_{38}H_{35}N_3O_4$ (597.71): C, 76.36; H, 5.90; N, 7.03 %. Found: C, 76.32; H,5.88; N, 7.01 %.

4.1.16. 1-benzyl-3-((1-benzyl-4-(benzylamino)-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(thiophen-2-yl)methyl)-4-hydroxy-6-methylpyridin-2 (1H)-one (4 m)

White solid; (0.58 g, 95 %) mp: 220–222 °C; IR (KBr) (υ_{max}/cm^{-1}): 3240 (NH), 3113, 3026, 1647, 1557 (C═O); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm) 2.16 (3H, s, CH_3), 2.27 (3H, s, CH_3), 4.30–4.68 (2H, m, CH_2), 4.98, 5.28 (2H, AB-quartet, $^2J_{HH}$ = 18 Hz, CH_2), 5.46, 5.60 (2H, AB-quartet, $^2J_{HH}$ = 18 Hz, CH_2), 5.81 (1H, s, CH), 6.03 (1H, s, ArH), 6.46 (1H, s, ArH), 6.84 (1H, d, $^3J_{HH}$ = 3.5 Hz ArH), 6.93 (1H, t, $^3J_{HH}$ = 4.4 Hz, ArH), 7.18 (5H, d, $^3J_{HH}$ = 7.5 Hz, ArH), 7.29 (11H, d, $^3J_{HH}$ = 20.8 Hz, ArH), 8.46 (1H, s, NH), 13.66 (1H, s, OH); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.4, 20.8, 34.3, 46.8, 47, 47.7, 98, 104.5, 106.1, 109.3, 122.9, 123.6, 126.3, 126.6, 126.8, 127.1, 127.2, 128.6, 128.7, 128.8, 137, 137.2, 138.7, 144.7, 145.4, 146.1, 155.3, 163.5, 166.2, 166.4, 176.7; MS: (*m/z*, %): 614 (M^+, 9), 525 (1), 397 (5), 300 (95), 286 (51), 278 (78), 218 (78), 161 (77), 110 (54), 90 (100), 44 (58). Anal. Calcd for $C_{38}H_{35}N_3O_3S$ (613.78): C, 74.36; H, 5.75; N, 6.85 %. Found: C, 74.32; H,5.71; N, 6.84 %.

CRediT authorship contribution statement

Sajedeh Alizadeh: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Abbas Ali Esmaeili:** Writing – review & editing, Supervision, Investigation, Formal analysis, Conceptualization. **Mohammad Javad Sharifnia:** Writing – original draft, Methodology, Investigation. **Behrouz Notash:** Formal analysis, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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Data availability

Data will be made available on request.

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