Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-025-03237-5

ORIGINAL PAPER

Diversity-oriented synthesis of novel benzo[*h*]quinoline and pyrimidine-tethered tri-substituted methane using L-proline as an effective bio-organo-catalyst

Sajedeh Alizadeh[1] · **Abbas Ali Esmaeili**[1]

Received: 17 January 2025 / Accepted: 15 May 2025

Abstract

We present the synthesis of a novel series of tri-substituted methane (TRSM) derivatives via an efficient one-pot, three-component reaction. This reaction combines 4-hydroxybenzo[h]quinolin-2(1*H*)-one, aromatic aldehydes, and 1,3-dimethyl-6-aminouracil, catalyzed by L-proline in ethanol. Our primary aim is to create a new TRSM scaffold by incorporating diverse pharmacophore moieties into a unified structure, providing a foundation for future drug discovery and medicinal chemistry studies. Key advantages of this approach include the use of an organocatalyst, a streamlined experimental process, and the absence of toxic byproducts. Notably, the methodology eliminates the need for time-consuming column chromatography, offering a cleaner, more efficient synthesis. The chemical structures of the products were confirmed through IR, NMR, mass spectrometry, and elemental analysis, validating the successful formation of the desired derivatives.

Keywords Tri-substituted methane · L-proline · 4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one · Aminouracile

Introduction

Tri-substituted methanes (TRSMs) are compounds with a central sp3-hybridized carbon bonded to three substituent groups, classified as symmetrical or unsymmetrical based on the substitution pattern [1]. These compounds, including triarylmethanes (TRAMs), are crucial building blocks in many approved medications. Chemists continuously design new TRSM derivatives to enhance drug-target interactions by exploring novel chemical spaces around the TRSM core [2]. Beyond their pharmaceutical applications, TRAMs are also valuable in material science, serving as metal ion sensors, fluorescent probes, and organic dyes [3–5]. Furthermore, they are utilized in dendrimer synthesis [6]. TRSMs have gained significant attention for their broad biological activities, including inhibition of protein tyrosine phosphatase 1B [7], and as antimalarial, antiviral, and anti-HCV agents [8, 9]. Additionally, they demonstrate anticancer properties and the ability to block potassium channels, further highlighting their therapeutic potential [10, 11].

Benzoquinoline, an azaheterocyclic compound with extended π–π conjugation, holds significant promise due to its diverse applications, including potential anticancer, antioxidant, and antidiabetic activities [12–17]. The quinolone ring system, a cornerstone structure in first-line antibiotics, is renowned for its extensive bioactivities, such as antiviral and antiparasitic effects [18–23], and has recently gained attention as an emerging class of biomarkers in cancer therapy [24–26].

Pyrimidine stands out as a distinctive and highly versatile pharmacophore, playing a crucial role in the design and development of a wide array of clinically approved drugs, such as sulfadiazine and sulfamerazine [27–30]. The incorporation of amino uracil moieties [31], alongside structural motifs like benzoquinoline, quinolone, and pyrimidine, highlights their exceptional therapeutic potential and broad applicability in medicinal chemistry. These structural frameworks continue to inspire innovative drug discovery and underscore their significance in advancing modern pharmacotherapy. Representative examples of bioactive molecules incorporating these pharmacophores are illustrated in (Fig. 1A, B), showcasing their chemical diversity and pharmacological significance. Additionally, bioactive compounds with a

---

✉ Abbas Ali Esmaeili
abesmaeili@um.ac.ir

[1] Department of Chemistry, Faculty of Science, Ferdowsi University of Mashhad, P.O.Box 9177948974, Mashhad, Iran

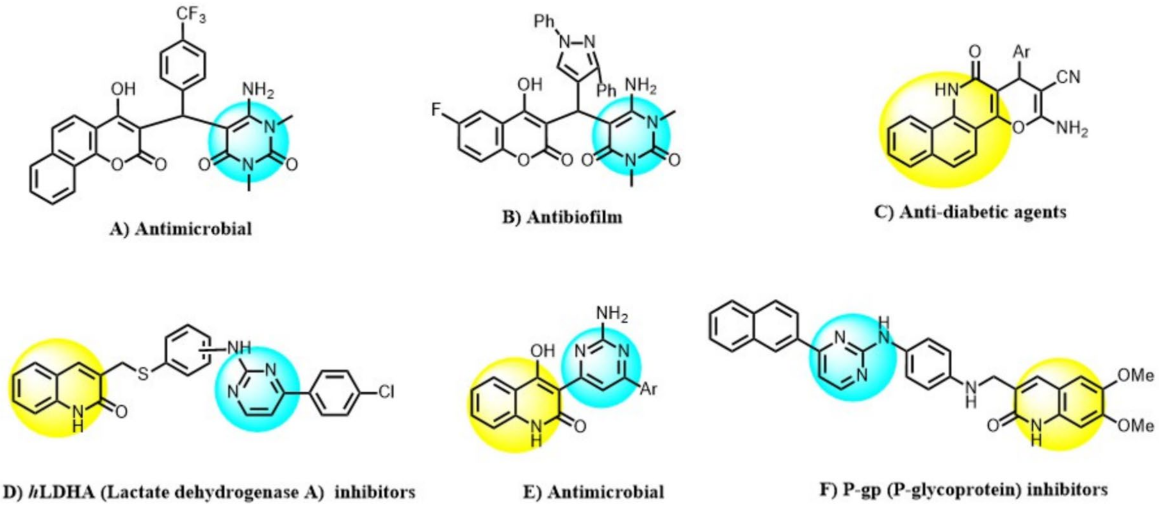


Fig. 1 Some biologically active compounds including pyrimidine, benzoquinoline, and quinolone moieties

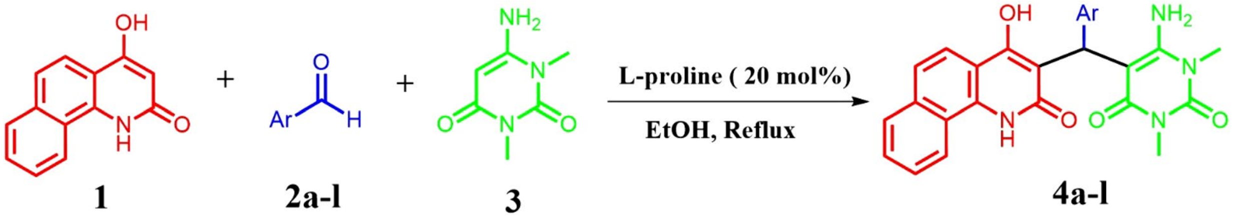
range of active pharmacophores, including benzoquinoline, quinolone, and pyrimidine moieties, are presented in Fig. 1C–F, emphasizing their versatility and broad-spectrum therapeutic applications [15, 32–34]. These findings highlight the integral role of these pharmacophores in advancing drug discovery and development.

Given the pharmaceutical significance of tri-substituted methane derivatives, several methods have been developed for their synthesis. However, these approaches often suffer from low yields, limited functional group compatibility, and reliance on metal catalysts [35–37]. Consequently, there is a pressing need for greener, more efficient synthetic strategies that facilitate the assembly of small molecules into complex structures.

In this context, we design and synthesize novel compounds incorporating benzo[h]quinoline and aminouracil moieties at the C-5 position of the TRSM system, maximizing structural diversity with minimal synthetic steps. Multicomponent reactions (MCRs) offer an efficient, eco-friendly route to a wide range of biological probes, intermediates, and drugs [38, 39]. Notably, organocatalysts such as L-proline have gained significant attention for their low toxicity, environmental safety, and metal-free nature in organic synthesis [40, 41]. To the best of our knowledge, no previous reports describe a molecular scaffold combining hydroxybenzo[h]quinolin-2(1H)-one and aminouracil fragments linked by a benzyl group. Building on our prior work [42, 43], we present the first synthesis of novel 6-amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(aryl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione derivatives. This was achieved via a one-pot, three-component reaction catalyzed by L-proline in ethanol (Scheme 1).

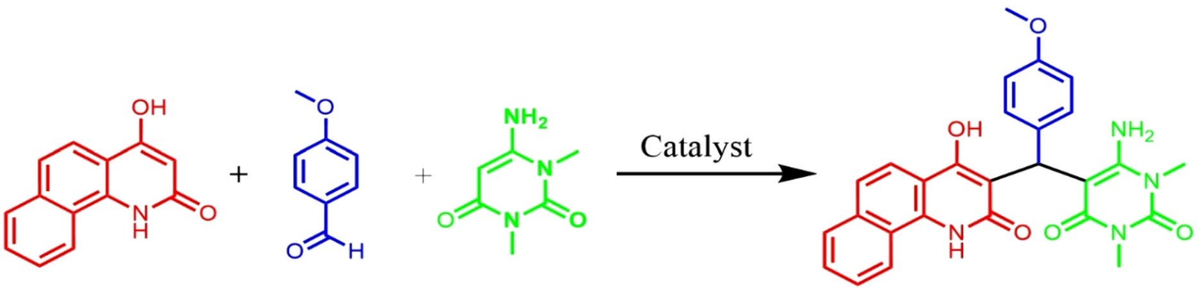
Results and discussion

To optimize reaction conditions, a three-component reaction involving 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (**1**), 4-methoxybenzaldehyde (**2a**), and 1,3-dimethyl-6-aminouracil (**3**) was chosen as a model. Initially, the reaction was carried out without a catalyst in ethanol under reflux conditions for 6 h, yielding only a trace amount of the desired product 4a (Table 1, entry 1). Subsequently, various catalysts, including p-Toluenesulfonic acid (PTSA), 1,4-diazabicyclo[2.2.2]octane (DABCO), and L-proline, were tested to improve efficiency and reduce reaction time



Scheme 1 Synthesis of new 6-amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(aryl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione derivatives

Table 1 Optimization of the reaction conditions of **4a**[a]



Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (min)	Yield (%)[b]
1	EtOH	–	Reflux	360	Trace
2	EtOH	PTSA (20)	Reflux	120	30
3	EtOH	DABCO (20)	Reflux	120	89
4	**EtOH**	**L-proline (20)**	**Reflux**	**90**	**95**[c]
5	EtOH	L-proline (10)	Reflux	90	90
6	EtOH	L-proline (30)	Reflux	120	95
7	CH_3CN	L-proline (20)	Reflux	120	80
8	CH_2Cl_2	L-proline (20)	Reflux	120	30
9	H_2O	L-proline (20)	Reflux	120	40
10	EtOH/Water (1:1)	L-proline (20)	90	120	45
11	–	L-proline (20)	110	120	50
12	EtOH	L-proline (20)	rt	120	Trace
13	EtOH	L-proline (20)	60	120	25
14	EtOH	L-proline (20)	90	90	95

[a] Reaction conditions: 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1.0 mmol), 4-methoxybenzaldehyde (1.0 mmol), and 1,3-dimethyl-6-aminouracil (1.0 mmol) in EtOH (3 mL) at reflux conditions, by using 20 mol% L-proline

[b] Isolated yield

[c] Bold values indicate better results than other conditions

(Table 1, entries 2–4). The best yield was achieved with L-proline as an organocatalyst under reflux in ethanol (Table 1, entry 4).

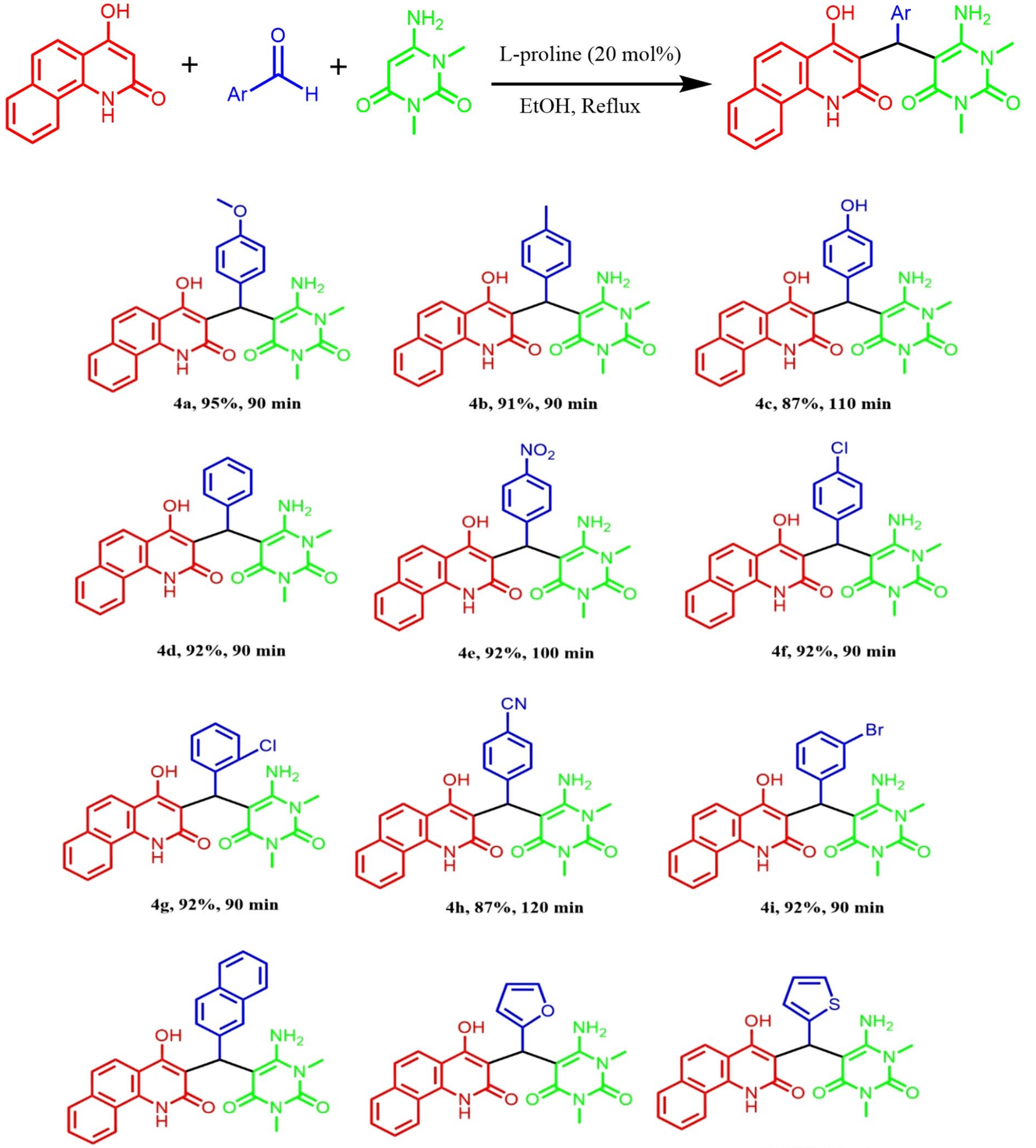
To optimize catalyst loading, we tested 10 mol%, 20 mol%, and 30 mol% of L-proline in the model reaction (Table 1, entries 4–6). The optimal yield of 95% was achieved with 20 mol% of the catalyst, with higher catalyst concentrations showing no improvement (Table 1, entry 4, entry 6).

We then examined various solvents, including EtOH, CH_3CN, CH_2Cl_2, H_2O, and EtOH/H_2O (1:1), using 20 mol% L-proline (Table 1, entries 7–10). Ethanol provided the best combination of reaction time and yield (Table 1, entry 4). Temperature optimization revealed that reflux conditions gave the highest yield (95%) (Table 1, entry 4), with elevated temperatures offering no further benefit (Table 1, entry 14), while lowering the temperature reduced the yield (Table 1, entries 12 and 13). The optimal, metal-free, and environmentally friendly conditions for this reaction were 20 mol% L-proline in ethanol under reflux (Table 1, entry 4).

After optimizing the reaction conditions, we explored the scope of the reaction for synthesizing various 3-benzyl-substituted pyrimidinobenzo[*h*]quinolines. The electronic effects of different aldehyde substituents were tested, including electron-withdrawing groups (4-CN, 4-NO_2, 4-Br, 3-Br, 4-Cl, 2-Cl) and electron-releasing groups (4-OH, 4-MeO, 4-Me). We also evaluated heterocyclic aldehydes. The results demonstrated the efficiency of the L-proline-catalyzed one-pot reaction, yielding the desired products in good to excellent yields (83–95%) as summarized in Table 2. However, no desired products were obtained when aliphatic aldehydes (butyraldehyde, acetaldehyde, cinnamaldehyde) were tested under the optimized conditions.

Further attempts to achieve cyclization using various dehydration agents [44], including P_2O_5, $POCl_3$, $SOCl_2$, and p-TSA in dry toluene under reflux conditions, were unsuccessful. This lack of cyclization may be attributed to the stability of compound **4**, which resists intramolecular annulation. Additionally, the conjugation of the carbonyl (amide) group with the enamine moiety in compound **3**

Table 2 Synthesis of novel 6-amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(aryl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione derivatives[a]



4a, 95%, 90 min

4b, 91%, 90 min

4c, 87%, 110 min

4d, 92%, 90 min

4e, 92%, 100 min

4f, 92%, 90 min

4g, 92%, 90 min

4h, 87%, 120 min

4i, 92%, 90 min

4j, 87%, 110 min

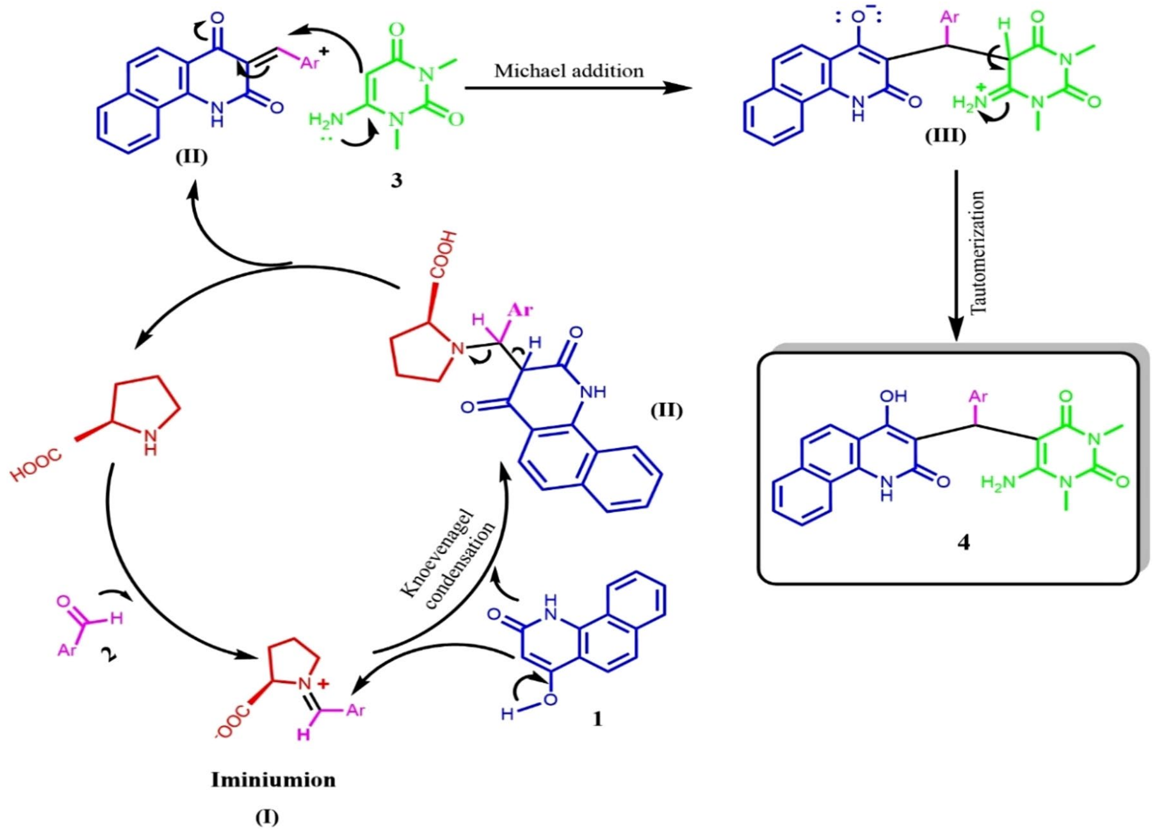
4k, 83%, 60min

4l, 84%, 60 min

[a] Reaction conditions: 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1.0 mmol), various aromatic aldehydes (1.0 mmol) and 1,3-dimethyl-6-aminouracil (1.0 mmol) in EtOH (3 ml) at Reflux conditions, by using 20 mol% L-proline

likely reduces the nucleophilicity of the amine group, hindering the cyclization process.

The chemical structures of all products **(4a–l)** were entirely elucidated by IR, ^{1}HNMR, ^{13}CNMR, mass spectroscopic data, and element analysis (supplemental data). For instance, compound **4a** showed characteristic IR stretching frequencies at 3387 cm^{-1} (corresponding to the hydroxyl group), 3137 cm^{-1} (NH), and 1697, 1667, and 1622 cm^{-1} (consistent with carbonyl groups). In the ^{1}H NMR spectrum of **4a**, the three methyl groups in the compound demonstrate signals at $\delta = 3.18$, $\delta = 3.41$ ppm, and $\delta = 3.72$ ppm, respectively. The signal at $\delta = 5.88$ corresponded to the



Scheme 2 The plausible mechanism for the synthesis of product

CH-Ar methine group. Additionally, two doublets appeared at δ = 6.81 ppm ($^3J = 8.8$ Hz) and δ = 7.07 ppm ($^3J = 8.6$ Hz), representing the aromatic ring's protons. Finally, three singlet signals were observed at δ = 7.83, 12.20, and 12.97 ppm, associated with NH_2, NH, and OH groups, respectively. The ^{13}C NMR spectrum of **4a** confirmed twenty-five separate peaks, in agreement with the proposed structure. According to the mass spectra of **4a**, the molecular ion peak appeared at m/z 485 (M^+).

The proposed mechanism for the formation of product **4**, based on previously reported literature [45], is outlined in Scheme 2. The reaction begins with the formation of an iminium ion intermediate (**I**) from the aromatic aldehyde (**2**) and L-proline. This intermediate undergoes Knoevenagel condensation with 4-hydroxybenzo[*h*]quinoline-2(1*H*)-one (**1**), forming intermediate (**II**). Subsequently, Knoevenagel adduct (**II**) reacts with 1,3-dimethyl-6-aminouracil (**3**) via a Michael addition, generating intermediate (**III**). Finally, tautomerization of (**III**) yields the desired TRSM (**4**).

The reaction was carried out in two stages to confirm the proposed pathway. In the first stage, the aromatic aldehyde (**2**) was treated with 4-hydroxybenzo[h]quinolin-2(1H)-one **(1)** in ethanol in the presence of L-proline as a catalytic system. Notably, the Knoevenagel adduct **(II)**, generated in situ, exhibited high reactivity and promptly reacted with a second equivalent of **1** via a bis-condensation pathway. This rapid sequential transformation led to the exclusive formation of 3,3'-((4-methoxyphenyl)methylene)bis(4-hydroxybenzo[h]quinolin-2(1H)-one), which was isolated. As a result, the intermediate product (**II**) could not be isolated under the reaction conditions. Interestingly, when the reaction was conducted as a one-pot three-component process, 1,3-dimethyl-6-aminouracil (**3**), as a better Michael donor, rapidly underwent Michael addition with the Knoevenagel adduct (**II**), selectively yielding the desired product (**4**). These findings provide strong experimental support for the proposed reaction mechanism.

Conclusion

We have developed an efficient strategy for the straightforward synthesis of a novel series of 3-benzyl-substituted pyrimidino benzo[h]quinolines (**4a–l**) via a one-pot, three-component reaction using L-proline as an effective bio-organo-catalyst. This approach offers several advantages, including mild reaction conditions, rapid synthesis, and good to excellent yields. The method provides a reliable means to construct complex heterocyclic structures and offers valuable insights for developing new therapeutic agents. We anticipate that the accessibility of these new TRSMs will encourage further exploration of their potential biological activity.

Experimental

General information

The solvents and chemicals were purchased from Merck and Sigma-Aldrich companies. The Electrothermal 9100 apparatus was used to melt points in the open capillary tube. FT-IR spectroscopy characterized the products using KBr disks on a Nicolet Avatar 370 FT-IR Thermal instrument. C and H spectra were verified using a Bruker DRX-300 Avance spectrometer at 75 and 300 MHZ. The mass spectra were recorded using a Varian Mat CH-7 at ev. Thermo Finnegan Flash EA was used to perform elemental analysis for C, H, and N. 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one was made following the same procedure as before [46].

General procedure for the synthesis of 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1)

A mixture of 1-naphthyl amine (1.0 equiv), diethyl malonate (1.0 equiv), and PPA (3.0 equiv) was heated at 170 °C for 1h. The temperature was then gradually increased to 200 °C and maintained for an additional 2 h. Afterward, the mixture was cooled to room temperature. A saturated solution of NaOH was added, and the mixture was left overnight. The precipitate formed was filtered by suction and then acidified with concentrated HCl to a pH of 3. The resulting precipitate was filtered, washed with water, and dried at ambient temperature, yielding the target compound with a 63% yield.

General procedure for the synthesis of 4

4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one **1** (1mmol), aromatic aldehyde **2** (1 mmol), and 1,3-dimethyl-6-aminouracil **3** (1 mmol) and L-proline (0.05 g, 20 mol%) were taken in EtOH (3.0 mL) in a round-bottom flask and refluxed for the time indicated in Table 2. After completion of the reaction as indicated by TLC, the solid precipitate was filtered off and washed with methanol (3 mL) and water (3 mL), respectively; Finally, dried to afford the pure product **4a–l**.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(4-methoxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4a)

Cream solid; (0.46 g, 95%) mp: 301–302 °C; IR (KBr) (υ_{max}/cm^{-1}): 3387, 3137, 3056, 2949, 1697, 1667, 1622 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.41 (3H, s, CH$_3$), 3.72 (3H, s, CH$_3$), 5.88 (1H, s, CH), 6.81 (2H, d, $^{3}J_{HH}=8.8$ Hz, ArH), 7.07 (2H, d, $^{3}J_{HH}=8.6$ Hz, ArH), 7.68 (3H, d, $^{3}J_{HH}=9.4$ Hz, ArH), 7.83 (2H, s, NH$_2$), 7.97 (2H, t, $^{3}J_{HH}=10.9$ Hz, ArH), 8.96 (1H, d, $^{3}J_{HH}=5.3$ Hz, ArH), 12.20 (1H, s, NH), 12.97 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.5, 30.8, 34.7, 55.4, 88.3, 111.1, 112.5, 113.9, 120.6, 122, 122.6, 123, 127, 127.8, 128.4, 128.9, 131.2, 134.4, 134.8, 150.7, 155.9, 157.6, 162, 164.2, 166.4; MS: (m/z, %): 485 (M^{+}, 5), 325 (100), 310 (38), 295 (65), 268 (42), 209 (33), 154 (95), 81 (48). Anal. Calcd for $C_{27}H_{24}N_4O_5$ (485): C, 66.93; H, 4.99; N, 11.56%. Found: C, 66.90; H, 4.98; N, 11.56%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(p-tolyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4b)

White solid; (0.42 g, 91%) mp: 310–312 °C; IR (KBr) (υ_{max}/cm^{-1}): 3361, 3137, 3043, 2945, 29.12, 1701, 1671, 1621 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 2.27 (3H, s, CH$_3$), 3.18 (3H, s, CH$_3$), 3.41 (3H, s, CH$_3$), 5.90 (1H, s, CH), 7.05 (4H, s, ArH), 7.68 (3H, t, $^{3}J_{HH}=7.6$ Hz, ArH), 7.81 (2H, s, NH$_2$), 7.97 (2H, dd, $^{3}J_{HH}=13.9$, 9.0 Hz, ArH), 8.96 (1H, s, ArH), 12.18 (1H, s, NH), 12.88 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 21, 28.5, 30.8, 35.1, 88.2, 110.9, 112.5, 120.6, 122, 122.6, 123, 126.7, 127, 128.3, 128.9, 129.1, 134.4, 134.7, 134.8, 136.4, 150.7, 156, 162, 164.6, 166.4; MS: (m/z, %): 468(M^{+},10), 312 (18), 309 (98), 295 (100), 280 (38), 253 (83), 209 (43), 154 (88), 115(85). Anal. Calcd for $C_{27}H_{24}N_4O_4$ (468.51): C, 69.22; H, 5.16; N, 11.96%. Found: C, 66.20; H, 4.98; N, 11.96%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(4-hydroxyphenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4c)

White solid; (0.41 g, 87%) mp: 265–267 °C; IR (KBr) (υ_{max}/cm^{-1}): 3566, 3382,3157, 3060, 2953, 1689, 1666, 1622 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.41 (3H, s, CH$_3$), 5.85 (1H, s, CH), 6.67 (2H, d, $^{3}J_{HH}=8.7$ Hz, ArH), 6.96 (2H, d, $^{3}J_{HH}=8.6$ Hz, ArH), 7.67 (3H, t, $^{3}J_{HH}=7.5$ Hz, ArH), 7.80 (2H, s, NH$_2$), 7.97 (2H, t, $^{3}J_{HH}=10.4$ Hz, ArH), 8.94 (1H, d, $^{3}J_{HH}=9.7$ Hz, ArH), 9.14 (1H, s, OH), 12.11 (1H, s, NH), 12.97 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.5, 30.8, 34.7, 88.4, 111.2, 112.5, 115.4, 120.7, 122, 122.6, 123, 127, 127.7, 128.3, 128.9, 129.4, 134.4, 134.7, 150.7, 155.6, 155.9, 162; MS: (m/z, %): 315 [M-154]$^{+}$ (24), 294 (32), 254 (48), 209 (45), 154 (98), 113 (35), 81 (97). Anal. Calcd for $C_{26}H_{22}N_4O_5$ (470.49): C, 66.38; H, 4.71; N, 11.91%. Found: C, 66.30; H, 4.71; N, 11.98%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(phenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4d)

White solid; (0.42 g, 92%) mp: 304–306 °C; IR (KBr) (υ_{max}/cm^{-1}): 3472, 3325, 3133, 2949, 1698, 1663, 1625 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.19 (3H, s, CH$_3$), 3.42 (3H, s, CH$_3$), 5.95 (1H, s, CH), 7.21 (5H, dd, $^{3}J_{HH}$ = 18.8, 7.6 Hz, ArH), 7.67 (3H, t, $^{3}J_{HH}$ = 7.6 Hz, ArH), 7.84 (2H, s, NH$_2$), 7.97 (2H, t, $^{3}J_{HH}$ = 7.2 Hz, ArH), 8.97 (1H, d, $^{3}J_{HH}$ = 5.3 Hz, ArH), 12.22 (1H, s, NH), 12.98 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 35.5, 88.1, 110.8, 112.5, 120.6, 122, 122.6, 123, 125.9, 126.8, 127, 128.4, 128.5, 128.9, 134.4, 134.8, 139.6, 150.8, 156.1, 162, 164.3, 166.4; MS: (m/z, %): 454 (M^{+}, 20), 295 (100), 241 (95), 210 (44), 154 (80), 82 (68). Anal. Calcd for $C_{26}H_{22}N_4O_4$ (454.49): C, 68.71; H, 4.88; N, 12.33%. Found: C, 68.68; H, 4.88; N, 12.32%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(4-nitrophenyl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4e)

Cream solid; (0.46 g, 92%) mp: 308–309 °C; IR (KBr) (υ_{max}/cm^{-1}): 3479, 3127, 3076, 2994, 1698, 1671, 1622 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.42 (3H, s, CH$_3$), 6.02 (1H, s, CH), 7.47 (2H, d, $^{3}J_{HH}$ = 8.8 Hz, ArH), 7.63–7.47 (3H, m, ArH), 7.92 (2H, s, NH$_2$), 7.99 (2H, dd, $^{3}J_{HH}$ = 9.9, 4.6 Hz, ArH), 8.12 (2H, d, $^{3}J_{HH}$ = 8.9 Hz, ArH), 8.97 (1H, d, $^{3}J_{HH}$ = 5.2 Hz, ArH), 12.29 (1H, s, NH), 12.92 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 36.1, 87.5, 110.2, 112.4, 120.6, 122, 122.8, 123, 123.7, 127.1, 128.3, 128.5, 128.9, 134.5, 135, 146, 148.5, 150.7, 156.1, 162.1, 164.4, 166.1; MS: (m/z, %): 499(M^{+},23), 341 (95), 294 (32), 154 (100), 81 (39). Anal. Calcd for $C_{26}H_{21}N_5O_6$ (499.48): C, 62.52; H, 4.24; N, 14.02%. Found: C, 62.32; H, 4.24; N, 14.08%.

6-Amino-5-((4-chlorophenyl)(4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4f)

Cream solid; (0.45 g, 92%) mp: 309–310 °C; IR (KBr) (υ_{max}/cm^{-1}): 3366, 3134, 3060, 2949, 1702, 1672, 1621 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.41 (3H, s, CH$_3$), 5.91 (1H, s, CH), 7.19 (2H, d, $^{3}J_{HH}$ = 8.3 Hz, ArH), 7.30 (2H, d, $^{3}J_{HH}$ = 8.3 Hz, ArH), 7.69 (3H, d, $^{3}J_{HH}$ = 9.4 Hz, ArH), 7.85 (2H, s, NH$_2$), 7.92–8.00 (2H, m, ArH), 8.94 (1H, s, ArH), 12.23 (1H, s, NH), 12.95 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 35.2, 87.9, 110.6, 112.5, 120.6, 122, 122.7, 123, 127, 128.3, 128.4, 128.8, 128.9, 130.5, 134.4, 134.9, 138.7, 150.7, 156.1, 162, 164.3, 166.2; MS: (m/z, %): 489 (M^{+}, 10), 328 (100), 294 (85), 272 (65), 209 (50), 153 (83), 81 (75). Anal. Calcd for $C_{26}H_{21}ClN_4O_4$ (489): C, 63.87; H, 4.33; N, 11.46%. Found: C, 62.32; H, 4.24; N, 11.38%.

6-Amino-5-((2-chlorophenyl)(4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4g)

White solid; (0.45 g, 92%) mp: 265–267 °C; IR (KBr) (υ_{max}/cm^{-1}): 3484, 3333, 3135, 3072, 1696, 1672, 1621 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.15 (3H, s, CH$_3$), 3.40 (3H, s, CH$_3$), 6.01 (1H, s, CH), 7.18–7.32 (2H, m, ArH), 7.41 (2H, dd, $^{3}J_{HH}$ = 16.2, 8.4 Hz, ArH), 7.59–7.77 (5H, m, ArH, NH$_2$), 8.01 (2H, d, $^{3}J_{HH}$ = 9.0 Hz, ArH), 8.93 (1H, d, $^{3}J_{HH}$ = 9.5 Hz, ArH), 12.24 (1H, s, NH), 12.86 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.5, 30.9, 34.8, 87.6, 110.1, 112.3, 120.6, 122, 122.8, 123, 127.1, 127.2, 128.2, 128.5, 129, 129.9, 130.5, 133, 134.5, 134.8, 137.7, 150.6, 155.4, 162.5, 164.1, 165.7; MS: (m/z, %): 489(M^{+}, 10), 451 (15), 296 (100), 271 (43), 211 (12), 154 (98), 81 (43), 35 (74). Anal. Calcd for $C_{26}H_{21}ClN_4O_4$ (488.93): C, 63.87; H, 4.33; N, 11.46%. Found: C, 63.37; H, 4.24; N, 11.28%.

4-((6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)(4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)methyl)benzonitrile (4h)

White solid; (0.41 g, 87%) mp: 272–274 °C; IR (KBr) (υ_{max}/cm^{-1}): 3472, 3399, 3137, 3059, 2953, 2226 (CN), 1699, 1624, 1505 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.17 (3H, s, CH$_3$), 3.39 (3H, s, CH$_3$), 5.98 (1H, s, CH), 7.40 (2H, d, $^{3}J_{HH}$ = 8.3 Hz, ArH), 7.71 (5H, t, $^{3}J_{HH}$ = 7.7 Hz, ArH), 7.87 (2H, s, NH$_2$), 7.92–8.01 (2H, m, ArH), 8.96 (1H, d, $^{3}J_{HH}$ = 6.7 Hz, ArH), 12.26 (1H, s, NH), 12.92 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 36, 87.5, 108.8, 110.2, 112.4, 119.6, 120.6, 122, 122.8, 123, 127, 128.1, 128.5, 128.9, 132.5, 134.5, 135, 146.2, 150.7, 156.1, 162.2, 164.1, 166.1; MS: (m/z, %): 479 (M^{+}, 5), 321 (66), 209 (5), 154 (100), 97 (16). Anal. Calcd for $C_{27}H_{21}N_5O_4$ (479.50): C, 67.63; H, 4.41; N, 14.61%. Found: C, 67.60; H, 4.41; N, 14.48%.

6-Amino-5-((3-bromophenyl)(4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4i)

White solid; (0.49 g, 92%) mp: 287–289 °C; IR (KBr) (υ_{max}/cm^{-1}): 3476, 3394, 3125, 3058, 2945, 1699, 1619, 1561 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.39 (3H, s, CH$_3$), 5.94 (1H, s, CH), 7.21 (2H, d, $^{3}J_{HH}$ = 6.9 Hz, ArH), 7.30–7.43 (2H, m, ArH), 7.68 (3H, t, $^{3}J_{HH}$ = 8.4 Hz, ArH), 7.84 (2H, s, NH$_2$), 7.98

(2H, t, $^3J_{HH} = 9.9$ Hz, ArH), 8.95 (1H, d, $^3J_{HH} = 6.4$ Hz, ArH), 12.24 (1H, s, NH), 12.97 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 35.4, 87.6, 110.3, 112.4, 120.6, 122, 122.1, 122.8, 123, 126.1, 127, 128.5, 128.9, 129.5, 130.6, 134.5, 134.9, 142.8, 150.7, 156.1, 162.1, 164.3, 166.1; MS: (m/z, %): 533 (M$^+$, 18), 476 (6), 457 (84), 376 (98), 317 (97), 294 (98), 208 (100), 167 (56), 153 (100), 81 (75). Anal. Calcd for $C_{26}H_{21}BrN_5O_4$ (533.38): C, 58.55; H, 3.97; N, 10.50%. Found: C, 58.55; H, 3.90; N, 10.42%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[*h*]quinolin-3-yl)(naphthalen-2-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4j)

White solid; (0.44 g, 87%) mp: 284–286 °C; IR (KBr) (υ$_{max}$/cm^{-1}): 3358, 3141, 3047, 2994, 1702, 1667, 1620 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.18 (3H, s, CH$_3$), 3.44 (3H, s, CH$_3$), 6.12 (1H, s, CH), 7.41 (3H, t, $^3J_{HH} = 7.5$ Hz, ArH), 7.64–7.71 (4H, m, ArH), 7.73 (1H, s, ArH), 7.79 (2H, d, $^3J_{HH} = 8.8$ Hz, ArH), 7.85 (2H, s, NH$_2$), 8.00 (2H, d, $^3J_{HH} = 5.3$ Hz, ArH), 8.99 (1H, d, $^3J_{HH} = 9.6$ Hz, ArH), 12.28 (1H, s, NH), 12.97 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 19, 28.6, 30.9, 35.8, 56.5, 88.2, 110.8, 112.6, 120.8, 122.1, 122.7, 123, 124.6, 125.6, 126.2, 127, 127.6, 128.1, 128.4, 128.9, 132, 133.5, 134.5, 134.9, 137.4, 150.8, 156.1, 162.2, 164.4, 166.4; MS: (m/z, %): 505(M$^+$, 5), 344 (98), 288 (99), 209 (43), 154 (100), 97 (49), 81 (78). Anal. Calcd for $C_{30}H_{24}N_4O_4$ (504.55): C, 71.42; H, 4.79; N, 11.10%. Found: C, 70.35; H, 4.65; N, 11.11%.

6-Amino-5-(furan-2-yl(4-hydroxy-2-oxo-1,2-dihydro benzo[*h*]quinolin-3-yl)methyl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (4 k)

Cream solid; (0.37 g, 83%) mp: 236–238 °C; IR (KBr) (υ$_{max}$/cm^{-1}): 3464, 3386, 3140, 3047, 2998, 1696, 1619, 1559 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.20 (3H, s, CH$_3$), 3.39 (3H, s, CH$_3$), 5.84 (1H, s, CH), 6.05 (1H, s, ArH), 6.36 (1H, s, ArH), 7.50 (1H, s, ArH), 7.69 (3H, t, $^3J_{HH} = 9.0$ Hz, ArH), 7.81 (2H, s, NH$_2$), 7.97 (2H, d, $^3J_{HH} = 8.9$ Hz, ArH), 8.91 (1H, s, ArH), 12.19 (1H, s, NH), 12.98 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.5, 30.8, 31.6, 86.7, 106.4, 110.1, 110.7, 112.4, 120.6, 122, 122.7, 123, 127, 128.5, 128.9, 134.5, 134.8, 141.8, 150.6, 152.7, 155.2, 162.1, 164.3, 165.7; MS: (m/z, %): 444 (M$^+$, 5), 288 (8), 286 (82), 258 (22), 168 (25), 154 (70), 82 (65), 57 (53), 41 (45). Anal. Calcd for $C_{24}H_{20}N_4O_5$ (444.45): C, 64.86; H, 4.54; N, 12.61%. Found: C, 64.81; H, 4.52; N, 12.11%.

6-Amino-5-((4-hydroxy-2-oxo-1,2-dihydrobenzo[h]quinolin-3-yl)(thiophen-2-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (4l)

White solid; (0.39 g, 84%) mp: 270–272 °C; IR (KBr) (υ$_{max}$/cm^{-1}): 3464, 3390, 3138, 3067, 2945, 1698, 1619, 1559 (C=O); ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 3.20 (3H, s, CH$_3$), 3.41 (3H, s, CH$_3$), 6.06 (1H, s, CH), 6.71 (1H, s, ArH), 6.89 (1H, dd, $^3J_{HH} = 5.2$, 3.4 Hz, ArH), 7.29 (1H, d, $^3J_{HH} = 5.1$ Hz, ArH), 7.65–7.73 (3H, m, ArH), 7.87 (2H, s, NH$_2$), 7.95–8.03 (2H, m, ArH), 8.94 (1H, d, $^3J_{HH} = 6.9$ Hz, ArH), 12.20 (1H, s, NH), 13.24 (1H, s, OH); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 28.6, 30.9, 32.9, 88.5, 111.3, 112.5, 120.6, 122, 122.7, 123, 124.1, 124.4, 126.9, 127, 128.5, 128.9, 134.5, 134.9, 145.3, 150.6, 155.4, 162.2, 164.2, 165.8; MS: (m/z, %): 460 (M$^+$, 2), 305 (12), 301 (100), 274 (39), 245 (64), 154 (95), 81 (88), 57 (59). Anal. Calcd for $C_{24}H_{20}N_4O_4S$ (460.12): C, 62.60; H, 4.38; N, 12.17%. Found: C, 62.53; H, 4.32; N, 12.05%.

Supplementary information

The Supporting Information is available, and in it, ^{1}H and ^{13}C NMR, Mass, and FT-IR spectra are available.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13738-025-03237-5.

Acknowledgements The Ferdowsi University of Mashhad Research Department is acknowledged for financial support (Grant No. 3/61546).

Funding This research received no external funding.

Declarations

Conflict of interest The authors have no conflicts of interest to disclose.

References

1. M. Verma, A. Thakur, R. Sharma, R. Bharti, Curr. Org. Synth. **19**, 86–114 (2022)
2. D. Roy, R.P. Thakare, S. Chopra, G. Panda, Curr. Med. Chem. **30**, 974–998 (2023)
3. E.M. Nolan, S.J. Lippard, Chem. Rev. **108**, 3443–3480 (2008)
4. S. Mondal, A. Verma, S. Saha, Eur. J. Org. Chem. **2019**, 864–894 (2019)
5. D.F. Duxbury, Chem. Rev. **93**, 381–433 (1993)
6. L.A. Baker, L. Sun, R.M. Crooks, Bull. Korean Chem. Soc. **23**, 647–654 (2002)
7. B. Zhou, D.X. Liu, X.J. Yuan, J.Y. Li, Y.C. Xu, J. Li, Y. Li, J.M. Yue, Research **2018**, 1–9 (2018)
8. V. de Melo Mendes, A.G. Tempone, Acta Trop. **195**, 6–14 (2019)

9. A. Schafer, H. Cheng, R. Xiong, V. Soloveva, C. Retterer, F. Mo, S. Bavari, G. Thatcher, L. Rong, Antivir. Res. **157**, 47–56 (2018)
10. A. Kamal, Y.V. Srikanth, M.J. Ramaiah, M.N. Khan, M.K. Reddy, M. Ashraf, A. Lavanya, S.N. Pushpavalli, M. Pal-Bhadra, Bioorg. Med. Chem. Lett. **22**, 571–578 (2012)
11. H. Wulff, B.S. Zhorov, Chem. Rev. **108**, 1744–1773 (2008)
12. L. Oniciuc, D. Amăriucăi-Mantu, D. Diaconu, V. Mangalagiu, R. Danac, V. Antoci, I.I. Mangalagiu, Int. J. Mol. Sci. **24**, 8124–8138 (2023)
13. M. Asran, E.A. El-Helw, M.E. Azab, S.K. Ramadan, M.H. Helal, J. Iran. Chem. Soc. **20**, 3023–3032 (2023)
14. V. Antoci, L. Oniciuc, D. Amariucai-Mantu, C. Moldoveanu, V. Mangalagiu, A.M. Amarandei, C.N. Lungu, S. Dunca, I.I. Mangalagiu, G. Zbancioc, Pharmaceuticals **14**, 335–355 (2021)
15. H. Nikookar, M. Mohammadi-Khanaposhtani, S. Imanparast, M.A. Faramarzi, P.R. Ranjbar, M. Mahdavi, B. Larijani, Bioorg. chem. **77**, 280–286 (2018)
16. J.J. Chen, Y.H. Lin, S.H. Day, T.L. Hwang, I.S. Chen, Food Chem. **125**, 282–287 (2011)
17. X. Luo, L. Pedro, V. Milic, S. Mulhovo, A. Duarte, N. Duarte, M.J. Ferreira, Planta Med. **78**, 148–153 (2012)
18. H.L. Zhang, X.Q. Gan, Q.F. Fan, J.J. Yang, P. Zhang, H.B. Hu, Q.S. Song, Sci. Rep. **7**, 45805–45817 (2017)
19. Q. Lu, Z. Zhang, Y. Xu, Y. Chen, C. Li, J. Ethnopharmacol. **295**, 115388 (2022)
20. M. Karlgren, A. Vildhede, U. Norinder, J.R. Wisniewski, E. Kimoto, Y. Lai, U. Haglund, P. Artursson, J. Med. Chem. **55**, 4740–4763 (2012)
21. A. Ullah, N. Ullah, T. Nawaz, T. Aziz, Curr. Med. Chem. Anti-Cancer Agents **23**, 765–778 (2023)
22. L. Senerovic, D. Opsenica, I. Moric, I. Aleksic, M. Spasić, B. Vasiljevic, Adv. Microbiol. **14**, 37–69 (2020)
23. M. Saalim, J. Villegas-Moreno, B.R. Clark, Molecules **25**, 5689–5714 (2020)
24. E.J. Montagut, L. Vilaplana, M.T. Martin-Gomez, M.P. Marco, ACS Infect. Dis. **6**, 3237–3246 (2020)
25. A. Kania, W. Tejchman, A.M. Pawlak, K. Mokrzyński, B. Różanowski, B.M. Musielak, M. Greczek-Stachura, Molecules **27**, 1069–1085 (2022)
26. A.H. Abu Almaaty, N.A. Elgrahy, E. Fayad, O.A. Abu Ali, A.R. Mahdy, L.A. Barakat, M. El Behery, Molecules **26**, 4724–4738 (2021)
27. Y.F. Sui, D. Li, J. Wang, R.R. Bheemanaboina, M.F. Ansari, L.L. Gan, C.H. Zhou, Bioorg. Med. Chem. Lett. **30**, 126982–126990 (2020)
28. Y.F. Sui, M.F. Ansari, C.H. Zhou, Chem. Asian J. **16**, 1417–1429 (2021)
29. C.E. Mueller, D. Shi, M. Manning Jr., J.W. Daly, J. Med. Chem. **36**, 3341–3349 (1993)
30. D.R. Buckle, J.R. Arch, B.J. Connolly, A.E. Fenwick, K.A. Foster, K.J. Murray, S.A. Readshaw, M. Smallridge, D.G. Smith, J. Med. Chem. **37**, 476–485 (1994)
31. N.R. Emmadi, K. Atmakur, C. Bingi, N.R. Godumagadda, G.K. Chityal, J.B. Nanubolu, Bioorg. Med. Chem. Lett. **24**, 485–489 (2014)
32. I. Díaz, S. Salido, M. Nogueras, J. Cobo, Pharmaceuticals **15**, 792–821 (2022)
33. A. Krishna, V. Vijayakumar, S. Sarveswari, Chem. Select **5**, 7967–7972 (2020)
34. J. Laiolo, P.A. Lanza, O. Parravicini, C. Barbieri, D. Insuasty, J. Cobo, D.M. Vera, R.D. Enriz, M.C. Carpinella, Sci. Rep. **11**, 16856–16873 (2021)
35. P. Kumari, R. Bharti, T. Parvin, Mol. Divers. **23**, 205–213 (2019)
36. H.O. Foroughi, M. Kargar, Z. Erjaee, E. Zarenezhad, Monatsh. Chem. **151**, 1603–1608 (2020)
37. V.P. Jejurkar, C.K. Khatri, G.U. Chaturbhuj, S. Saha, Chem. Select **2**, 11693–11696 (2017)
38. T.E. Nielsen, S.L. Schreiber, Angew. Chem. Int. Ed. **47**, 48–56 (2008)
39. G. Graziano, A. Stefanachi, M. Contino, R. Prieto-Díaz, A. Ligresti, P. Kumar, A. Scilimati, E. Sotelo, F. Leonetti, Int. J. Mol. Sci. **24**, 6581–6608 (2023)
40. L. Albrecht, A. Albrecht, L. Dell'Amico, vol. 2, p. 768 (Wiley, 2022)
41. P. Sivaganesan, E. Chibisree, D. Bansal, J. Sarkar, S. Chaudhuri, New J. Chem. **47**, 20034–20040 (2024)
42. T. Tabibi, A.A. Esmaeili, Mol. Divers. **27**, 477–486 (2023)
43. M. Danehchin, A.A. Esmaeili, Res. Chem. Int. **12**, 1–18 (2021)
44. S. Ghaffari, A.A. Esmaeili, A. Khojastehnezhad, Org. Prep. Proced. Int. **53**, 537–545 (2021)
45. B.S. Vachan, M. Karuppasamy, P. Vinoth, S. Vivek Kumar, S. Perumal, V. Sridharan, J.C. Menéndez, Adv. Synth. Catal. **362**, 87–110 (2020)
46. B. Banerji, S.K. Killi, A. Katarkar, S. Chatterjee, Y. Tangella, C. Prodhan, K. Chaudhuri, Bioorg. Med. Chem. **2017**(25), 202–212 (2020)