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RESEARCH ARTICLE

p-TSA Catalyzed One-Pot Synthesis of Novel Chromen and Benzo[h]quinoline-Based Trisubstituted Methanes

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ABSTRACT

A straightforward one-pot synthesis of novel trisubstituted methanes (TRSMs) has been attained through a three-component reaction involving 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one, 4-amino-2*H*-chromen-2-one, and various aldehyde derivatives, using *p*-TSA. *p*-Toluene sulfonic acid (*p*-TSA), a non-toxic, cost-effective, easily accessible, and environmentally friendly organic acid catalyst, was investigated for its ability to mediate this reaction. The salient features of this protocol are: good to excellent yields of products (84%–92%), short reaction times, excellent compatibility with various functional groups, and a cost-effective catalyst that eliminates the need for column chromatography. Furthermore, these TRSMs are expected to make significant contributions as highly valuable compounds in drug design and the development of novel therapies, owing to their broad and diverse biologically active moieties. The structures of these newly synthesized TRSMs were determined using IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis.

1 | Introduction

Tri-substituted methanes (TRSMs) [1, 2] exhibit fascinating chemical properties due to their unique structure, where a central sp^3 hybridized carbon atom is linked to three other moieties. This class of compounds stands out for its distinctive arrangement, highlighting the significance of the central carbon atom and its chemical reactivity in organic chemistry [3–5]. Furthermore, they can also serve as molecular chemosensors [6], be utilized in dendrimer synthesis [7], and function as organic photoconductors [8].

TRSMs linked to chromen-2-one (coumarin) are highly valued for their diverse pharmacological applications [9–17]. They have also been studied as acetylcholinesterase inhibitors to reduce the progression of Alzheimer's disease [18, 19]. The electron-rich structure of 4-amino-2*H*-chromen-2-one is a key element in coumarin derivatives, enabling the synthesis of various heterocyclic compounds [20, 21]. They have an amino group and a carbon enamine that are highly reactive to electrophiles [22–24]. Compounds **A** and **B** display anticancer and antioxidant activity, respectively. Compound **C** was evaluated for antitumor activity [25, 26] (Figure 1A–C).

Similarly, the polynuclear azaheterocycle benzo[*h*]quinoline moiety with extended π–π conjugation is a crucial scaffold in organic chemistry, optoelectronics, and agriculture [27–31]. Incorporating the benzo[*h*]quinoline structure into the design of specific compounds can create new derivatives with biological activity. For example, compound (**D**) is effective for DNA-intercalating antitumor agents [32] (Figure 1D). In addition to the extensive therapeutic benefits, benzo[*h*]quinoline is also used as a coupling component for the preparation of some new azo disperse dyes [33] (Figure 1E).

Therefore, the design of a novel heterocyclic scaffold of trisubstituted methanes (TRSMs) incorporating both chromene and benzo[*h*]quinoline pharmacophores could serve as a valuable framework for medicinal chemistry studies and future drug discovery. Although synthetic protocols for TRSMs have been previously reported with different bioactive molecules [34–36], there remains a significant demand for more efficient and straightforward methodologies that allow the incorporation of diverse and novel pharmacophoric units. A literature review shows that most approaches rely on similar starting materials with minimal innovation. Current methods often suffer from low yields, by-product formation, limited functional group compatibility, and the use of toxic or metal-based catalysts [37–42].

In continuation of our ongoing studies on the synthesis of new heterocyclic compounds with potential biological activities [43, 44], we have, for the first time, established new products from the TRSMs family using multicomponent reactions (MCRs) that are compatible with green chemistry. MCRs, as powerful synthetic tools, offer an efficient, sustainable approach to synthesizing complex molecules by forming multiple bonds in a single step, reducing waste and cost [45–47]. Notably, organocatalysts such as *p*-TSA have gained significant attention for their low toxicity, metal-free nature, and forming C–C and C–heteroatom bonds in organic synthesis [48–50]. To this end, we present the first synthesis of novel Chromen and Benzo [*h*] quinoline-based TRSMs. This was achieved via a one-pot, three-component reaction catalyzed by *p*-TSA in ethanol (Scheme 1).

2 | Results and Discussion

To explore the feasibility and screening conditions, a three-component reaction of 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (**1**, 1 mmol), 4-amino-2*H*-chromen-2-one (**2**, 1 mmol), and 4-chlorobenzaldehyde (**3a**, 1 mmol) was selected as a model reaction. The model reaction was performed in various solvents like H_2O, EtOH, H_2O/EtOH (1:1), MeOH, acetic acid, CH_3CN, DMF, PEG 400, DCM, and solvent-free (Table 1, entries 1–10). The experimental findings demonstrated that ethanol acts as an optimal and essential solvent for this reaction (Table 1, entry 2). Furthermore, the model reaction was scrutinized using various catalysts, including DABCO, L-proline, K_2CO_3, *p*-TSA, and acetic acid in ethanol at reflux (Table 1, entries 11–15). Notably, *p*-toluenesulfonic acid exhibited exceptional performance in terms of both reaction yield and temporal efficiency (Table 1, entry 14).

However, given the environmentally favorable characteristics of *p*-toluenesulfonic acid (*p*-TSA) [48], including its water solubility, compatibility with polar organic solvents, non-toxic nature, ease of handling, cost efficiency, and straightforward work-up procedures, its selection was made for investigating the reaction scope in ethanol under reflux conditions. Following the determination of optimal catalyst and solvent conditions, the influence of catalyst concentration variations on the model reaction was examined (Table 2, entries 1–4). Superior reaction outcomes were observed at reduced catalyst loadings, with optimal performance being achieved at 10 mol% catalyst concentration (Table 2, entry 2).

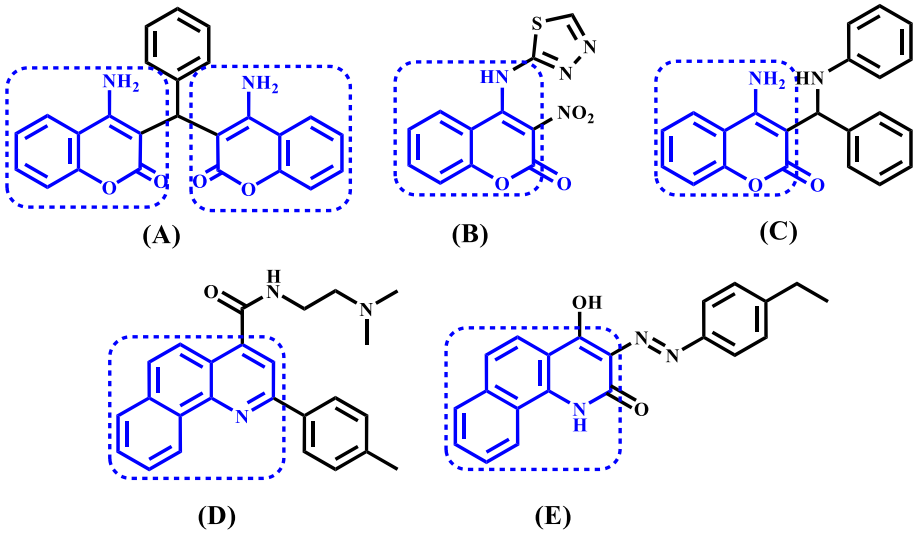
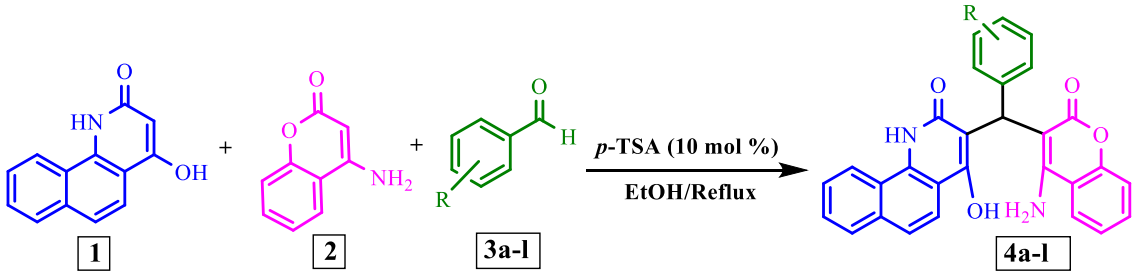
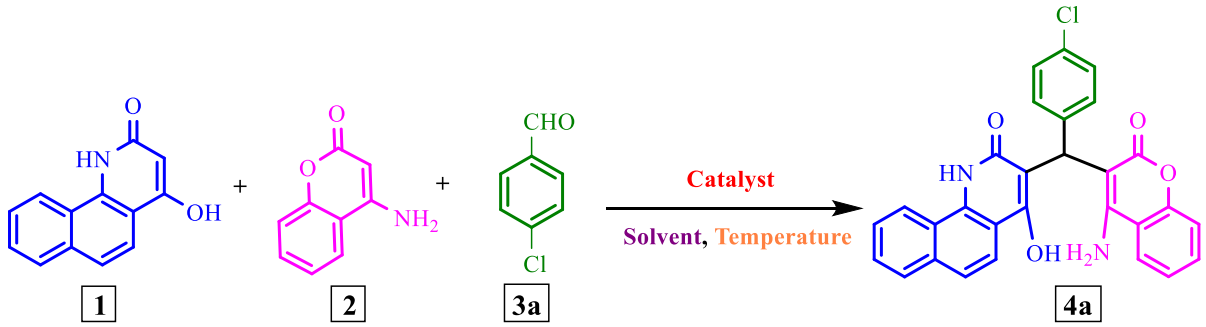


FIGURE 1 | Some biologically active 4-amino-2*H*-chromen-2-one and benzo[*h*]quinoline moieties containing compounds.



SCHEME 1 | *p*-TSA-catalyzed synthesis of trisubstituted methanes.

TABLE 1 | Optimization of reaction conditions of **4a**[a].



Entry	Catalysts (10 mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	—	H_2O	Reflux	6	20
2	—	EtOH	Reflux	6	63
3	—	EtOH/H_2O (1:1)	Reflux	6	26
4	—	MeOH	Reflux	6	35
5	—	Acetic acid	Reflux	5	48
6	—	CH_3CN	Reflux	8	39
7	—	DMF	110	8	42
8	—	PEG 400	110	8	29
9	—	CH_2Cl_2	r.t	5	25
10		Solvent-free	110	3	32
11	DABCO	EtOH	Reflux	6	37
12	L-proline	EtOH	Reflux	6	34
13	K_2CO_3	EtOH	Reflux	6	68
14	***P*-TSA**	**EtOH**	**Reflux**	**3**	**91**
15	AcOH	EtOH	Reflux	6	72

[a]Reaction conditions: 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1.0 mmol), 4-amino-2*H*-chromen-2-one (1.0 mmol), and 4-chlorobenzaldehyde (1.0 mmol), 10 mol% catalysts in solvent (5 mL).
[b]Isolated yield.

TABLE 2 | Optimization of the catalyst concentration of **4a**[a].

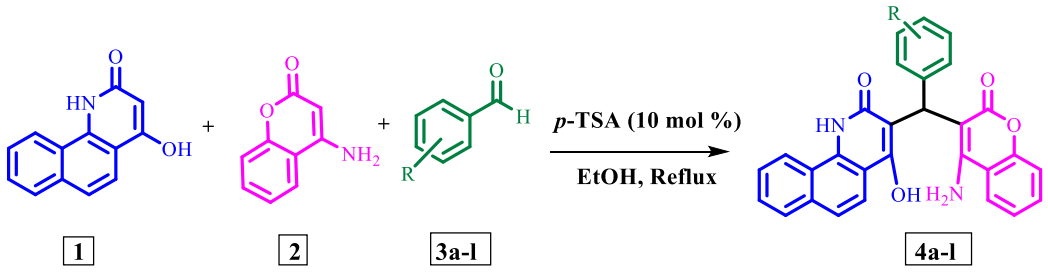
Entry	*p*-TSA (mol%)	Solvent	Time (h)	Yield (%)[b]
1	5	EtOH	5	70
2	**10**	**EtOH**	**3**	**91**
3	15	EtOH	3	80
4	20	EtOH	3	74

Note: The importance of key parameters is highlighted bold: *p*-toluenesulfonic acid is noted for its exceptional performance.
[a]Reaction conditions: 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1.0 mmol), 4-amino-2*H*-chromen-2-one (1.0 mmol), and 4-chlorobenzaldehyde (1.0 mmol), mol% *p*-TSA in solvent (5 mL).
[b]Isolated yield.

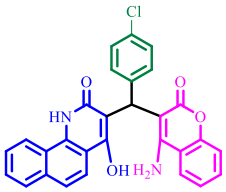
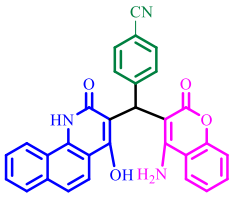
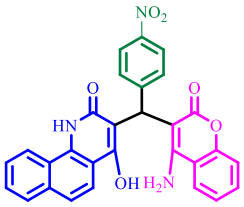
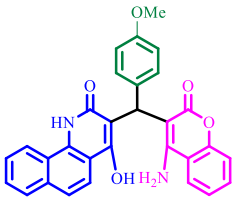
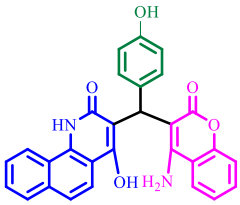
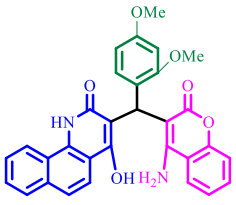
Following optimization of reaction conditions, the generality of the methodology was systematically evaluated using a series of aromatic aldehydes bearing both electron-withdrawing (including 4-NO_2, 4-CN, 4-Cl, 4-CF_3, 2-Cl, and 3-Br) and electron-donating (comprising 4-OMe, 2,4-OMe, and 4-OH) substituents (Table 3). As evidenced by the results, all substrates were efficiently converted to their corresponding products within short reaction times, affording good to excellent yields (Table 3, compounds **4a–l**). To further expand the scope of the reaction, thiophene-2-carbaldehyde (as a heterocyclic aldehyde) reacted efficiently to produce the desired product in an excellent yield of 91% (Table 3, **4k**). Finally, propionaldehyde, acetaldehyde, capraldehyde (Hexanal), and butyraldehyde (as aliphatic aldehydes) were examined, and trace amounts of products were obtained in the optimized reaction conditions. The chemical structure of all products **4a–l** was deduced from FT-IR, ^{1}H-NMR,^{13}C-NMR, Mass, and CHN analysis (Supporting Information S1).

For example, the IR spectrum of compound **4a** confirms its successful synthesis, showing characteristic bands at 3473 (OH stretching), 3403, and 3333 (NH_2 stretching), 3137 (NH stretching), and 1634 and 1592 cm^{-1} (C=O stretching). The ^{1}HNMR spectrum of **4a** exhibited three singlet signals at

TABLE 3 | Substrate scope of optimized reaction for the synthesis of novel trisubstituted methanes[a].

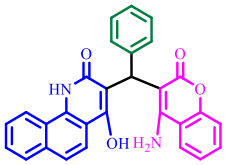
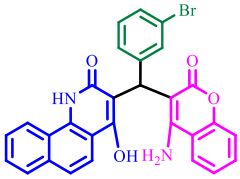
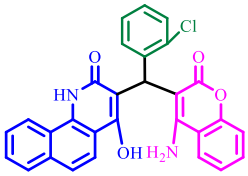
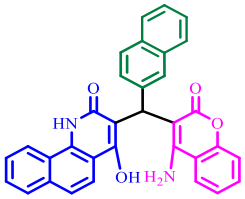
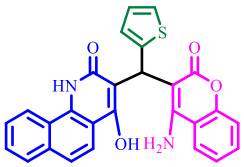
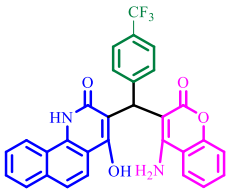


1 2 3a-l 4a-l

Entry	Product	Time (h)	Yield (%)[b]	mp (°C)	^{1}HNMR (δ, ppm) H (C_{SP}^3)	^{1}CNMR (δ, ppm) C_{SP}^3	^{1}CNMR (δ, ppm) C=O
4a		3	91	244–246	6.21	35.5	166.0, 162.1
4b		2.5	89	254–256	6.30	36.4	166.1, 165.9
4c		3	85	277–280	6.34	36.5	166.1, 165.9
4d		3.5	90	276–277	6.20	35.1	166.1, 165.9
4e		3	87	270–272	6.14	35.1	165.9, 166.1
4f		4	86	255–256	6.16	32.1	165.7, 162.1

(Continues)

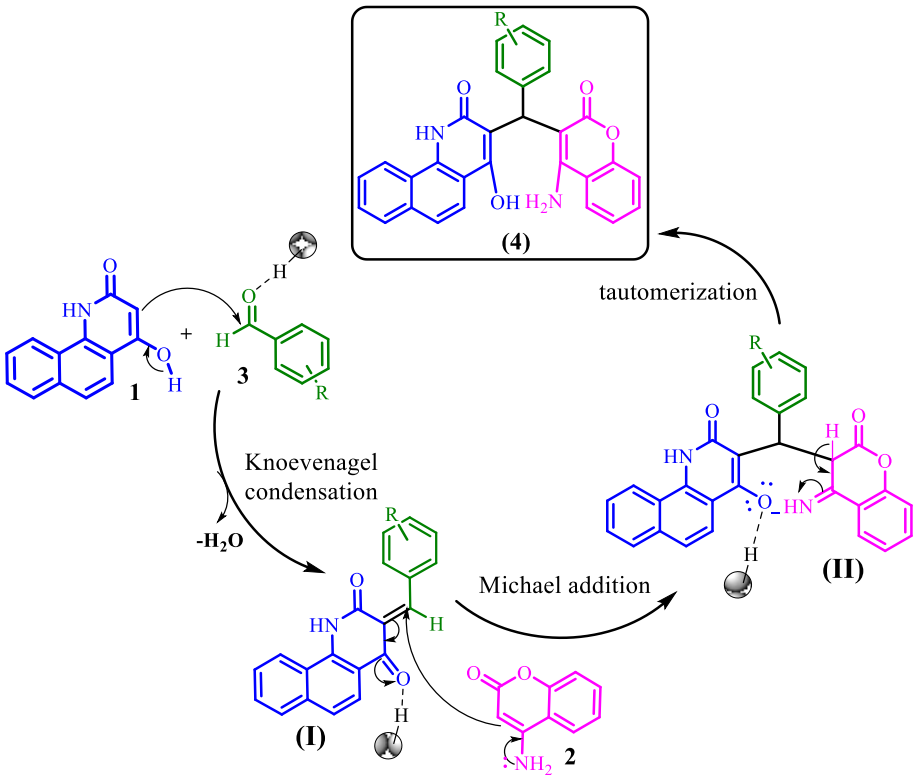
TABLE 3 | (Continued)

Entry	Product	Time (h)	Yield (%)[b]	mp (°C)	^{1}HNMR (δ, ppm)	^{1}CNMR (δ, ppm)	
					H (C_{SP}^3)	C_{SP}^3	C=O
4g		3	90	285–286	6.24	35.9	166.1, 166
4h		3.5	91	285–286	6.27	34.9	166.0, 165.9
4i		4	84	255–256	6.31	35.5	165.3, 165.4
4j		3	87	266–267	6.44	36.2	166.1, 162.3
4k		3	91	266–267	6.08	35.0	164.1, 165.7
4l		2	92	210–212	6.31	36.1	166.1, 166.0

[a]Reaction with 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1.0 mmol), 4-amino-2*H*-chromen-2-one (1.0 mmol), aldehydes (1 mmol), with 10 mol% of *p*-TSA in 5 mL EtOH at reflux.
[b]Isolated yield.

$\delta = 12.33$, 11.87, and 8.45 ppm, corresponding to OH, NH, and NH_2 groups. Fourteen characteristic protons on the aromatic rings appeared as four doublet signals at $\delta = 8.96$ ($J = 6.9$ Hz), 8.22 ($J = 9.5$ Hz), 7.34 ($J = 8.6$ Hz), 7.19 ($J = 8.7$ Hz) ppm, a doublet of doublet signal at $\delta = 7.99$ ($J = 15.4$, 9.3 Hz) ppm, and two multiple signals at $\delta = 7.70$–7.47 ppm. Finally, the methine group proton appeared as a singlet signal at $\delta = 6.21$ ppm. Moreover, the ^{13}CNMR spectrum of **4a** confirmed 27 distinct resonances, consistent with the suggested structure. The peaks at $\delta = 166$ and $\delta = 162.1$ ppm indicated the presence of two carbonyl groups in the proposed structure. According to the mass spectra of **4a**, molecular ion peaks appeared with the appropriate m/z values.

The conceptual mechanism for synthesizing heteroaryl-trisubstituted methanes is presented in Scheme 2. Based on the reported literature [48], we presumed that *p*-TSA plays an imperative role in this protocol. It may increase the electrophilic character of the carbonyl carbon of aldehydes (**3**) and facilitate the nucleophilic attack of the carbanion of 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (**1**) to form the α,β-unsaturated intermediate (**I**) via the Knoevenagel condensation reaction with the loss of water. 4-amino-2*H*-chromen-2-one (**2**) may then undergo nucleophilic attack on the intermediate (**I**) to form intermediate (**II**) via a Michael addition, and *p*-TSA may increase the electrophilicity of the intermediate (**I**). Next, tautomerization of (**II**) gave the desired TRSM (**4**).



SCHEME 2 | Proposed reaction mechanism for the synthesis of novel heteroaryl-trisubstituted methane derivatives

3 | Conclusion

This study presents a novel multicomponent synthetic strategy for preparing bioactive heteroaryl-substituted methane derivatives using *p*-TSA as an eco-friendly and biodegradable catalyst. This approach offers several advantages, including broad functional group tolerance, mild reaction conditions, and high product yields, all achieved without the need for chromatographic purification. The presence of —NH_2, —OH, CO, and free groups in these products can be used as coordination ligands in metal complexation studies as well as in heterocycle chemistry for further functionalization. It is anticipated that the synthetic accessibility of these novel TRSM derivatives will facilitate a comprehensive investigation of their pharmacological properties and therapeutic potential.

4 | Experimental

4.1 | General

All solvents and reagents were obtained from Merck (Germany) and Sigma-Aldrich (Buchs, Switzerland) and employed as received without additional purification. Melting points were determined in open capillaries using an Electrothermal 9100 melting point apparatus. FT-IR spectra were recorded on a Nicolet Avatar 370 instrument using KBr pellets. Proton and carbon-13 NMR spectra were acquired on a Bruker Avance DRX-300 spectrometer operating at 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C, with DMSO-d_6 as the solvent; chemical shifts are reported in parts per million (ppm). Mass spectrometry was performed on a Varian Mat CH-7 spectrometer at an ionization energy of 70 eV. Elemental compositions (C, H, N) were determined using a Thermo Finnegan Flash EA analyzer.

4.2 | General Procedure for the Synthesis of 4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one 1

A mixture of 1-naphthylamine (10 mmol) and diethyl malonate (5 mmol) was heated with polyphosphoric acid (five to six times by weight of 1-naphthylamine) at 150°C for 6 h. Afterward, the mixture was allowed to cool, and the flask containing the solidified gum was filled with water. The procedure was followed by standing in the refrigerator for 24 h. After this period, the resulting precipitated solid was filtered out, washed extensively with water, and then allowed to dry in the air. The crude product was dissolved in a 0.1 M sodium hydroxide solution (10 mL), and any undissolved material was removed by filtration. The resulting filtrate was then neutralized using a 10% v/v hydrochloric acid solution, forming a precipitate. This residue was subsequently recrystallized from dimethylformamide (DMF) to give 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one **1** [33].

4.3 | General Procedure for the Synthesis of Compounds 4a–l

A mixture of 4-hydroxybenzo[*h*]quinolin-2(1*H*)-one (1 mmol), 4-amino-2*H*-chromen-2-one (1 mmol), and an aromatic aldehyde (1 mmol) was dissolved in ethanol (5 mL) in a 25 mL round-bottom flask. To this solution, *p*-toluenesulfonic acid

(*p*-TSA, 10 mol%) was added as a catalyst. The reaction mixture was refluxed under stirring for 4 h, and the progress was monitored by thin-layer chromatography (TLC) using a hexane–ethyl acetate (4:6) system as the eluent. Upon completion, the mixture was allowed to cool to room temperature. The resulting precipitate was filtered using a Büchner funnel, washed thoroughly with ethanol, and dried. The crude product was further purified by recrystallization from an ethanol/DMF mixture, affording the desired compounds in good to excellent yields (84%–92%).

4.4 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-Chlorophenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4a)

White powder; (0.45 g, 91%) mp: 244°C–246°C. IR (KBr) (υ_{max}/cm^{-1}): 3473 (OH), 3403, 3333 (NH_2), 3137 (NH), 3068, 1634 (C═O), 1592 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.33 (1H, s, OH), 11.87 (1H, s, NH), 8.96 (1H, d, ^3J = 6.9 Hz, ArH), 8.45 (2H, s, NH_2), 8.22 (1H, d, ^3J = 9.5 Hz, ArH), 7.99 (2H, dd, ^3J = 15.4, 9.3 Hz, ArH), 7.70 (4H, m, ArH), 7.47 (2H, m, ArH), 7.34 (2H, d, ^3J = 8.6 Hz, ArH), 7.19 (2H, d, ^3J = 8.7 Hz, ArH), 6.21 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166, 162.1, 156.4, 152.3, 138, 135.1, 134.5, 133.1, 130.8, 128.9, 128.8, 128.6, 127.1, 124.9, 123.9, 123, 122.8, 121.9, 120.5, 117.6, 115, 112.1, 109.6, 96.8, 35.5; MS (m/z, %): 495 (M^+, 10), 494 (25), 334 (52), 160 (100), 132 (82). Anal. Calcd for $C_{29}H_{19}ClN_2O_4$: C, 70.38; H, 3.87; N, 5.66%. Found: C, 70.23; H, 3.71; N, 5.57%.

4.5 | 4-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-Hydroxy-2-Oxo-1,2-Dihydrobenzo[*h*]quinolin-3-yl)methyl)benzonitrile (4b)

White powder; (0.43 g, 89%) mp: 254°C–256°C. IR (KBr) (υ_{max}/cm^{-1}): 3464 (OH), 3399, 3379 (NH_2), 3164 (NH), 3068, 2234 (CN), 1639 (C═O), 1613 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.34 (1H, s, OH), 11.83 (1H, s, NH), 8.96 (1H, d, ^3J = 9.8 Hz, ArH), 8.47 (2H, s, NH_2), 8.22 (1H, d, ^3J = 9.6 Hz, ArH), 7.99 (2H, dd, ^3J = 12.3, 9.2 Hz, ArH), 7.77 (1H, s, ArH), 7.74 (2H, s, ArH), 7.72–7.66 (3H, m, ArH), 7.47 (2H, t, ^3J = 8.6 Hz, ArH), 7.40 (2H, d, J = 8.4 Hz, ArH), 6.30 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 165.9, 162.2, 156.5, 152.4, 145.4, 135.2, 134.6, 133.2, 132.6, 128.9, 128.6, 128.1, 127.1, 124.9, 123.9, 123.1, 122.9, 122, 120.5, 119.5, 117.6, 115, 112, 109.3, 109.1, 96.3, 36.4; MS (m/z, %): 485 (M^+, 11), 325 (12), 275 (90), 160 (92), 102 (20). Anal. Calcd for $C_{30}H_{19}N_3O_4$: C, 74.22; H, 3.94; N, 8.66%. Found: C, 73.46; H, 3.71; N, 7.89%.

4.6 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-Nitrophenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4c)

White powder; (0.43 g, 85%) mp: 277°C–280°C. IR (KBr) (υ_{max}/cm^{-1}): 3425 (OH), 3374, 3333 (NH_2), 3138 (NH), 3068, 1687 (C═O), 1639 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.36 (1H, s, OH), 11.84 (1H, s, NH), 8.96 (1H, d, ^3J = 9.6 Hz, ArH), 8.50 (2H, s, NH_2), 8.23 (1H, d, ^3J = 8.1 Hz, ArH), 8.14 (2H, d, ^3J = 8.9 Hz, ArH), 7.98 (2H, t, ^3J = 9.0 Hz, ArH), 7.69 (4H, t, ^3J = 9.2 Hz, ArH), 7.48 (4H, t, ^3J = 8.5 Hz, ArH), 6.34 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 165.9, 162.2, 156.5, 152.4, 147.7, 146.2, 135.3, 134.6, 133.2, 128.9, 128.7, 128.3, 127.1, 124.9, 124, 123.9, 123.1, 122.9, 122, 120.5, 117.6, 115, 112.1, 109.4, 96.3, 36.5; MS (m/z, %): 505 (M^+, 5), 345 (70), 295 (85), 210 (92), 160 (95). Anal. Calcd for $C_{29}H_{19}N_3O_6$: C, 68.91; H, 3.79; N, 8.31%. Found: C, 68.49; H, 3.41; N, 7.92%.

4.7 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-Methoxyphenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4d)

White powder; (0.44 g, 90%) mp: 276°C–277°C. IR (KBr) (υ_{max}/cm^{-1}): 3482 (OH), 3374, 3325 (NH_2), 3139 (NH), 3051, 1646 (C═O), 1612 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.28 (1H, s, OH), 11.90 (1H, s, NH), 8.96 (1H, d, ^3J = 9.8 Hz, ArH), 8.42 (2H, s, NH_2), 8.21 (1H, d, ^3J = 8.2 Hz, ArH), 7.97 (2H, d, ^3J = 9.0 Hz, ArH), 7.68 (4H, t, ^3J = 7.0 Hz, ArH), 7.52–7.39 (2H, m, ArH), 7.07 (2H, d, ^3J = 8.8 Hz, ArH), 6.85 (2H, d, ^3J = 8.8 Hz, ArH), 6.20 (1H, s, CH), 3.73 (3H, s, CH_3); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 165.9, 162, 157.8, 156.2, 152.3, 135, 134.5, 132.9, 130.4, 128.9, 128.5, 127.8, 127, 124.8, 123.9, 123, 122.8, 122, 120.5, 117.5, 115, 114.1, 112.1, 110.1, 97.4, 55.4, 35.1; MS (m/z, %): 491 (M^+, 10), 330 (80), 280 (40), 209 (95), 160 (95), 132 (98). Anal. Calcd for $C_{30}H_{22}N_2O_5$: C, 73.46; H, 4.52; N, 5.71%. Found: C, 73.22; H, 3.98; N, 5.36%.

4.8 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-Hydroxyphenyl)methyl)-4-Hydroxybenzo[h]quinolin-2(1*H*)-one (4e)

White powder; (0.42 g, 87%) mp: 270°C–272°C. IR (KBr) (υ_{max}/cm^{-1}): 3644 (OH), 3372, 3355 (NH_2), 3147 (NH), 3060, 1633 (C═O), 1612 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.24 (1H, s, OH), 11.87 (1H, s, NH), 9.20 (1H, s, OH) 8.95 (1H, d, ^3J = 8.9 Hz, ArH), 8.37 (2H, s, NH_2), 8.20 (1H, d, ^3J = 8.0 Hz, ArH), 7.99 (2H, dd, ^3J = 17.2, 8.3 Hz, ArH), 7.75–7.66 (4H, m, ArH), 7.47 (2H, t, ^3J = 9.2 Hz, ArH), 6.95 (2H, d, ^3J = 8.4 Hz, ArH), 6.69 (2H, d, ^3J = 8.6 Hz, ArH), 6.14 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 165.9, 162, 146.1, 155.8, 152.3, 134.9, 134.5, 133, 129, 128.6, 127.7, 127.1, 124.8, 123.8, 123, 122.8, 121.9, 120.5, 117.5, 115.6, 115, 112.1, 110.2, 97.6, 35.1; MS (m/z, %): 315 (M^+, 161) (5), 260 (62), 209 (65), 161 (60), 132 (32). Anal. Calcd for $C_{29}H_{20}N_2O_5$: C, 73.10; H, 4.23; N, 5.88%. Found: C, 73.08; H, 4.23; N, 5.87%.

4.9 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(2,4-Dimethoxyphenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4f)

White powder; (0.45 g, 86%) mp: 255°C–256°C. IR (KBr) (υ_{max}/cm^{-1}): 3415 (OH), 3363, 3211 (NH_2), 3137 (NH), 3043, 1629 (C═O), 1614 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.23 (1H, s, OH), 11.68 (1H, s, NH), 8.94 (1H, d, ^3J = 8.7 Hz, ArH), 8.16 (1H, d, ^3J = 8.2 Hz, ArH), 8.00 (4H, d, ^3J = 9.7 Hz, NH_2, ArH), 7.73–7.61 (4H, m, ArH), 7.44 (2H, d, ^3J = 8.7 Hz, ArH),

7.07(1H, d, ^3J = 8.5 Hz, ArH), 6.57–6.44 (2H, m, ArH), 6.16 (1H, s, CH), 3.75 (3H, s, CH_3), 3.55 (3H, s, CH_3); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 165.7, 162.1, 159.5, 158.7, 154.2, 152.1, 134.8, 134.4, 132.5, 128.9, 128.5, 127, 124.6, 123.7, 123, 122.7, 121.9, 120.5, 119.4, 117.4, 115.1, 112, 110.2, 104.5, 99.3, 98.6, 56.1, 55.5, 32.1; MS (m/z, %): 521 (M^+, 10), 358 (7), 310 (75), 274 (100), 209 (50), 160 (92), 132 (87). Anal. Calcd for $C_{31}H_{24}N_2O_6$: C, 71.53; H, 4.65; N, 5.38%. Found: C, 70.72; H, 4.18; N, 5.06%.

4.10 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(Phenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4g)

White powder; (0.41 g, 90%) mp: 285°C–286°C. IR (KBr) (υ_{max}/cm^{-1}): 3463 (OH), 3329 (NH_2), 3138 (NH), 3051, 1647 (C═O), 1613 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.30 (1H, s, OH), 11.88 (1H, s, NH), 8.96 (1H, d, ^3J = 9.8 Hz, ArH), 8.42 (2H, s, NH_2), 8.22 (1H, d, ^3J = 8.2 Hz, ArH), 8.03 (1H, d, ^3J = 8.0 Hz, ArH), 7.97 (1H, t, ^3J = 8.9 Hz, ArH), 7.76–7.67 (4H, m, ArH), 7.49 (2H, d, ^3J = 7.2 Hz, ArH), 7.29 (2H, d, ^3J = 7.6 Hz, ArH), 7.24–7.16 (3H, m, ArH) 6.24 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 166, 162.1, 156.3, 152.3, 138.8, 135.1, 134.5, 133.1, 129, 128.8, 128.6, 127.1, 126.8, 126.2, 124.9, 123.9, 123, 122.8, 122, 120.5, 117.6, 115, 112.1, 109.8, 97.2, 35.9; MS (m/z, %): 460 (M^+, 48), 296 (100), 245 (20), 210 (18), 160 (35). Anal. Calcd for $C_{29}H_{20}N_2O_4$: C, 75.64; H, 4.38; N, 6.08%. Found: C, 75.19; H, 3.98; N, 5.63%.

4.11 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(3-Bromophenyl)methyl)-4-Hydroxybenzo[h]quinolin-2(1*H*)-one (4h)

White powder; (0.49 g, 91%) mp: 285°C–286°C. IR (KBr) (υ_{max}/cm^{-1}): 3458 (OH), 3342 (NH_2), 3148 (NH), 3072, 1638 (C═O), 1614 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.33 (1H, s, OH), 11.87 (1H, s, NH), 8.96 (1H, d, ^3J = 9.8 Hz, ArH), 8.46 (2H, s, NH_2), 8.21 (1H, d, ^3J = 8.2 Hz, ArH), 7.97 (2H, d, ^3J = 8.8 Hz, ArH), 7.73–7.64 (4H, m, ArH), 7.51–7.37 (3H, m, ArH), 7.34–7.17 (3H, m, ArH), 6.27 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166, 165.9, 162.1, 156.4, 152.3, 142, 135.2, 134.5, 133.1, 130.9, 129.5, 129.2, 128.9, 128.6, 127.1, 126.1, 124.9, 123.9, 123.1, 122.9, 122.2, 122, 120.5, 117.6, 115, 112, 109.4, 96.56, 34.9; MS (m/z, %): 539 (M^+, 5), 380 (75), 324 (90), 295 (72), 209 (28), 160 (98). Anal. Calcd for $C_{29}H_{19}BrN_2O_4$: C, 64.58; H, 3.55; N, 5.19%. Found: C, 64.08; H, 3.43; N, 4.92%.

4.12 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(2-Chlorophenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4i)

White powder; (0.42 g, 84%) mp: 255°C–256°C. IR (KBr) (υ_{max}/cm^{-1}): 3603 (OH), 3390, 3358 (NH_2), 3160 (NH), 3061, 1679 (C═O), 1630 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.33 (1H, s, OH), 11.60 (1H, s, NH), 8.94 (1H, s, ArH), 8.22–7.95 (5H, m, ArH, NH_2), 7.77, 7.61 (4H, m, ArH), 7.50–7.36 (4H, m, ArH), 7.36–7.21 (2H, m, ArH), 6.31 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 165.4, 165.3, 162.4, 155.1, 152.3, 137.4, 135.1, 134.5, 133, 132.9, 130.4, 129.6, 128.9, 128.6, 128.5, 127.4, 127.1, 124.8, 123.8, 123, 122.9, 121.9, 120.4, 117.5, 114.9, 111.8, 109.4, 97, 35.5; MS (m/z, %): 494 (M^+, 6), 295 (70), 278 (25), 160 (35), 132 (22). Anal. Calcd for $C_{29}H_{19}ClN_2O_4$: C, 70.38; H, 3.87; N, 5.66%. Found: C, 70.34; H, 3.88; N, 5.66%.

4.13 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(Naphthalen-2-yl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4j)

White powder; (0.44 g, 87%) mp: 266°C–267°C. IR (KBr) (υ_{max}/cm^{-1}): 3470 (OH), 3333 (NH_2), 3179 (NH), 3056, 1647 (C═O), 1613 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.37 (1H, s, OH), 11.88 (1H, s, NH), 9.05–8.95 (1H, m, ArH), 8.47 (2H, s, NH_2), 8.26 (1H, d, ^3J = 8.1 Hz, ArH), 8.01 (2H, d, ^3J = 8.9 Hz, ArH), 7.88–7.73 (4H, m, ArH), 7.69 (4H, d, ^3J = 13 Hz, ArH), 7.44 (5H, ddd, ^3J = 21.2, 16, 9.2 Hz, ArH), 6.44 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 162.3, 156.4, 152.4, 136.7, 135.2, 134.5, 133.6, 133.1, 132, 128.9, 128.6, 128.3, 128.1, 127.7, 127.1, 126.4, 126, 125.8, 124.9, 124.6, 123.9, 123.1, 122.8, 122, 120.6, 117.6, 115.1, 112.2, 109.9, 97.2, 36.2; MS (m/z, %): 511 (M^+, 10), 348 (92), 294 (98), 209 (90), 160 (92). Anal. Calcd for $C_{33}H_{22}N_2O_4$: C, 77.63; H, 4.34; N, 5.49%. Found: C, 77.41; H, 4.30; N, 5.31%.

4.14 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(Thiophen-2-yl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4k)

White powder; (0.45 g, 91%) mp: 266°C–267°C. IR (KBr) (υ_{max}/cm^{-1}): 3650 (OH), 3456, 3346 (NH_2), 3138 (NH), 3068, 1643 (C═O), 1613 (C═O); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 8.12 (2H, d, ^3J = 8.1 Hz, ArH), 7.98 (4H, s, OH, NH_2), 7.75–7.64 (3H, m, ArH), 7.52–7.32 (6H, m, ArH), 6.90 (1H, dd, ^3J = 5.3, 3.5 Hz, ArH), 6.72 (1H, d, ^3J = 3.5 Hz, ArH), 6.08 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 165.7, 164.1, 155.5, 154.3, 152.5, 152.3, 144.2, 143.9, 134.8, 134.3, 133.3, 133, 128.6, 126.8, 124.5, 124.4, 124.3, 123.8, 123.4, 117.3, 114.9, 110.1, 95.5, 35; MS (m/z, %): 467 (M^+, 10), 413 (52), 302 (98), 250 (51), 209 (43), 160 (43). Anal. Calcd for $C_{27}H_{18}N_2O_4S$: C, 69.52; H, 3.89; N, 6.01%. Found: C, 69.50; H, 3.85; N, 6.00%.

4.15 | 3-((4-Amino-2-Oxo-2*H*-Chromen-3-yl)(4-(Trifluoromethyl)phenyl)methyl)-4-Hydroxybenzo[*h*]quinolin-2(1*H*)-one (4l)

White powder; (0.46 g, 92%) mp: 210°C–212°C. IR (KBr) (υ_{max}/cm^{-1}): 3477 (OH), 3432, 3387 (NH_2), 3141 (NH), 3068, 1633 (C═O), 1613 (C═O), 1119 (C-F); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 12.33 (1H, s, OH), 11.85 (1H, s, NH), 8.99–8.93 (1H, m, ArH), 8.47 (2H, s, NH_2), 8.22 (1H, d, ^3J = 8 Hz, ArH), 8.04–7.95 (2H, m, ArH), 7.74–7.63 (6H, m, ArH), 7.49 (2H, dd, ^3J = 8.1, 3.0 Hz, ArH), 7.41 (2H, d, ^3J = 8.1 Hz, ArH), 6.31 (1H, s, CH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm) 166.1, 166, 162.2, 156.5, 152.4, 144.2, 135.2, 134.5, 133.1, 128.9, 128.6, 127.7, 127.8 (q, $^2J_{CF}$ = 31.6 Hz, C-CF_3), 127.1, 125.6 (q, $^3J_{CF}$ = 3.7 Hz, CH-C-CF_3), 124.8, 124.9 (q, $^1J_{CF}$ = 271.6 Hz, CF_3) 123.9, 123, 122.8, 122, 120.6, 117.6, 115, 112.2, 109.4, 96.6, 36.1; MS (m/z, %): 527 (M^+, 56), 363 (74), 310 (100), 282 (77), 233 (63), 159 (76).

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Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** Supporting Information.