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Synthesis and anticancer evaluation of 3-substituted quinolin-4-ones and 2,3-dihydroquinolin-4-ones

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ABSTRACT

A series of 3-aryl-5,7-dimethoxyquinolin-4-ones **8** and 3-aryl-5,7-dimethoxy-2,3-dihydroquinolin-4-ones **13** were synthesized in good yields. Demethylation under a range of conditions afforded the corresponding 5-hydroxy and 5,7-dihydroxy derivatives. Biological evaluation against a range of cancer cells lines showed that the quinolin-4-one scaffold was more cytotoxic than the reduced 2,3-dihydroquinolin-4-one scaffold. The most active monohydroxy compound **15f** demonstrated 85.9–99% reduction in cell viability against the cell lines tested.

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1. Introduction

Isoflavones are a group of naturally occurring phytochemicals that are found predominantly in legume plants (*Leguminosae*). They have been reported to exhibit a variety of biological properties including *anti*-inflammatory, neuroprotective function, *anti*-osteoporotic, antiplatelet, antibacterial and antitumor activities.[1–7] Isoflavones also play a role in the prevention of cancers, coronary heart diseases, menopausal symptoms and osteoporosis.[8–13]

Replacement of the pyran oxygen with a nitrogen atom in the isoflavone nucleus gives rise to the corresponding 3-phenyl quinolone scaffold. Due to their structural similarity, 3-phenyl quinolones might be anticipated to possess similar biological properties to isoflavones. For example, isobavachalcone **1** and the quinolone analogues of isoflavones **2** have been found to exhibit strong inhibitory effects on platelet aggregation (Fig. 1).[14,15] Furthermore, when compared with the corresponding isoflavones, the 3-aryl-1*H*-quinolin-4-one analogues showed greater *anti*-proliferative activity and a more specific mechanism of action.[15]

It has been well established that the presence and position of hydroxyl and methoxy substituents plays an important role in determining the biological activity of isoflavanones.[16–18] Generally, analogues with substituents at positions 5 and 7 are the most active.

As part of an ongoing research project into the development of isoflavones with potent anticancer activity, it was of interest to examine the synthesis and biological activity of 3-aryl-quinolin-4-ones and 3-aryl-2,3-dihydroquinolin-4-ones bearing a similar oxygenation pattern to the most active isoflavones.

2. Results and discussion

2.1. Synthesis of 3-aryl-quinolin-4-ones

The synthesis of the target compounds was accomplished through slight modification of previously reported methods (Scheme 1).[19] Treating of ethyl arylacetates **3** with ethyl formate **4** in the presence of sodium hydride yielded α-aryl-β-ketoesters **5**. Subsequent reaction with 3,5-dimethoxyaniline **6** at reflux in toluene afforded enamines **7** as the *Z* isomer only. Alternatively, a mixture of both *Z* and *E* isomers was produced when the reaction was performed in ethanol at room temperature. The two isomers were not separated as it was found that both isomers could successfully undergo cyclisation. Initial attempts to cyclise enamines **7** at 250 °C in Dowtherm for 1.5 h[19] resulted in poor yields of the target 3-aryl-quinolin-4-ones **8**. Higher yields were obtained by heating enamines **7** at 250 °C for 15–20 min in diphenyl ether/biphenyl (4:1). The products could be obtained in high purity by trituration with light petroleum and filtration of the residue (Table 1).

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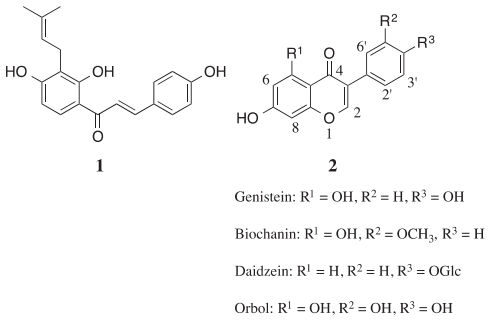
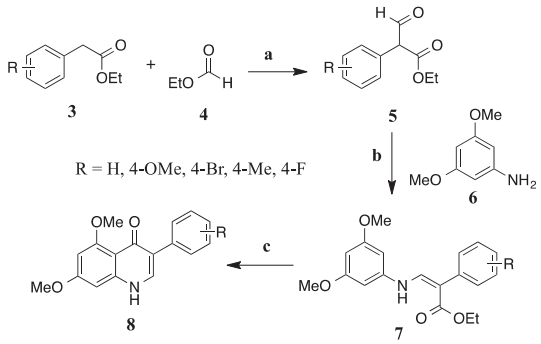


Figure 1. Isobavachalcone **1** and isoflavone derivatives **2**.



Scheme 1. Reagents and conditions: (a) NaH, anhydrous Et_2O, 40 °C, 4 h; (b) toluene, reflux, 20 h; (c) diphenyl ether/biphenyl (4:1), 250 °C, 20 min.

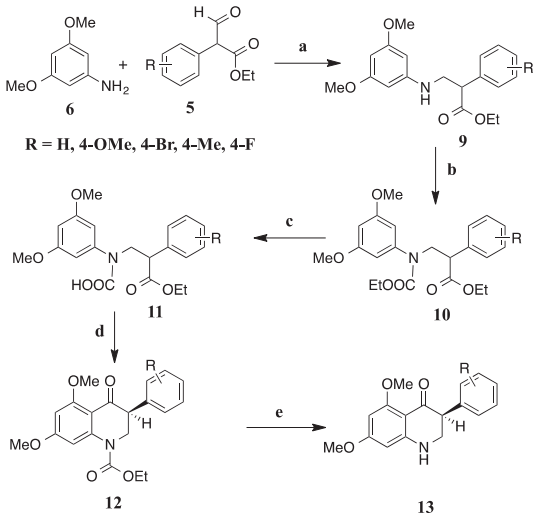
2.2. Synthesis of 3-aryl-2,3-dihydroquinolin-8-ones

Direct reduction of 3-aryl-quinolin-4-ones **8** was examined as the most efficient manner of preparing the corresponding dihydroquinolone derivatives. However, treatment of 3-aryl-quinolin-4-ones **8** with reducing agents such as $NaBH_4$, $LiAlH_4$, or hydrogenation in the presence of Pd/C in EtOH led only to recovery of the starting materials. Probable reason for the inertness of the compound **8** towards reduction is its insolubility.

In an alternate strategy, the targeted 2,3-dihydroquinolin-4-(1*H*)-ones were prepared in five steps from 3,5-dimethoxyaniline **6** and α-aryl-β-ketoesters **5** (Scheme 2). Condensation of 3,5-dimethoxyaniline **6** and α-aryl-β-ketoesters **5** was attempted with various reducing agents, yielding mixed results. Reduction with $NaBH(OAc)_3$ afforded ethyl 3-(3,5-dimethoxyphenylamino)-2-arylacrylate **7** instead of the desired ethyl 3-(3,5-dimethoxyphenylamino)-2-arylpropanoate **9**. On the other hand, the use of $NaBH_4$ generated products **7** and **9** in 20% and 50% yield, respectively. The reaction was finally optimized through use of $NaBH_3CN$, which gave the desired 3-(3,5-dimethoxyphenylamino)-2-arylpropanoates **9** in 65–70% yield. The –NH group was protected using ethyl chloroformate in the presence of pyridine, and the resulting esters **10** were subjected to base hydrolysis to afford the corresponding acids **11**.

Table 1
Yields of 3-aryl-quinolin-4-ones

Compound	R	Yield (%)
8a	4-Br	59
8b	4-F	59
8c	4-Me	51
8d	4-OMe	58
8e	H	70
8f	3-Br	55
8g	2,5-OMe	48



Scheme 2. Reagents and conditions: (a) $NaBH_3CN$, MeOH, reflux, 8 h; (b) ethyl chloroformate, pyridine, CH_2Cl_2, rt, 5 h; (c) 1 N NaOH, MeOH, rt, overnight; (d) PPA, 70 °C, 30 min; (e) 5% NaOH, MeOH, rt, 3 h.

Initial attempts to cyclise acids **11** with H_2SO_4 or trifluoroacetic anhydride (TFAA) were unsuccessful, leading only to the recovery of the starting material along with baseline impurities. Encouragingly, cyclisation with polyphosphoric acid (PPA) at 70 °C for 30 min under N_2 successfully gave the desired 3-aryl-2,3-dihydroquinolin-8-one esters **12** in 75–85% yield.[20] Higher temperatures or prolonged heating lowered reaction yields and increased the formation of baseline impurities. The protecting group was cleaved using 5% NaOH in methanol to generate the corresponding 5,7-dimethoxy-2,3-dihydroquinolin-4-(1*H*)-ones **13** in good yield (Table 2). The ^1H NMR spectrum of 5,7-dimethoxy-3-aryl-2,3-dihydroquinolin-4-(1*H*)-one **13b** showed two methoxy resonances at δ 3.78 and 3.82, doublets at δ 5.81 and 5.71 (J = 3 Hz) corresponding to H6 and H8, respectively, and the NH proton resonance at δ 4.68. Further structural confirmation of analogue **13** was obtained by X-ray crystallography (Fig. 2).

3. Demethylation of 3-aryl-quinolin-4-ones and 3-aryl-2,3-dihydroquinolin-4-ones

Hydroxy substituted flavones are typically more potent than their methoxy counterparts.[16–18] Demethylation of the synthesized 5,7-dimethoxyquinolin-4-ones **8** and 5,7-dimethoxy-2,3-dihydroquinolin-4-ones **13** was therefore investigated.

Heating 5,7-dimethoxyquinolin-4-ones **8** with HBr in AcOH for 3 days or refluxing with $AlCl_3$ in chlorobenzene, afforded a complex mixture of inseparable products. On the other hand, demethylation of 5,7-dimethoxy-2,3-dihydroquinolin-4-ones **13** with $AlCl_3$ in chlorobenzene at reflux produced the corresponding dihydroxy analogues **14** in yields of 15%. The reaction yields were increased to 45–50% when conducted using 5 equiv of BBr_3 in dichloromethane (Scheme 3, Table 3).

Table 2
Yields of 3-aryl-2,3-dihydroquinolin-4-ones

Compound	R	Yield (%)
13a	4-Br	59
13b	4-F	59
13c	4-Me	51
13d	4-OMe	58
13e	H	70

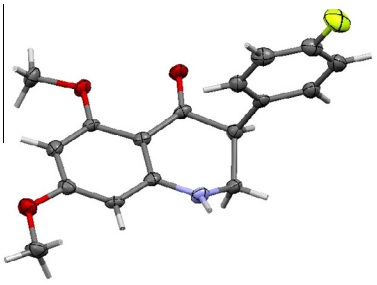
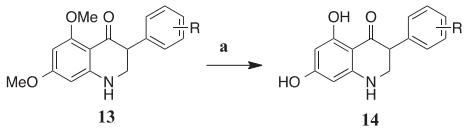


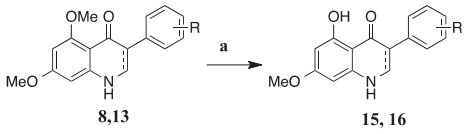
Figure 2. ORTEP diagram of quinolin-4-one **13b**.[21]



Scheme 3. Reagents and conditions: (a) BBr_3, CH_2Cl_2, rt, overnight.

Table 3
Yields of targeted 3-aryl-5,7-dihydroxy-2,3-dihydroquinolin-4-ones

Compound	R	Yield (%)
14a	4-Br	48
14d	4-OMe	45
14e	H	44



Scheme 4. Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$-NaI, CH_3CN, 100 °C, 8 h.

Table 4
Yields of 3-aryl-5-hydroxy-7-methoxyquinolin-4-ones **15** and 2,3-dihydroquinolin-4-ones **16**

Compound	R	Yield (%)
15a	4-Br	89
15b	4-F	86
15c	4-Me	86
15d	4-OMe	81
15e	H	84
15f	3-Br	79
16a	4-Br	89
16c	4-Me	86
16d	4-OMe	81
16e	H	84

Due to the difficulties associated with the demethylation of 5,7-dimethoxyquinolin-4-ones **8** under harsh conditions, attention turned to selective demethylation of C5 using milder conditions. Chemoselective cleavage of the C5-methoxy group was achieved by treating quinolin-4-ones **8** with cerium(III) chloride-NaI at 100 °C in acetonitrile[22] to give monohydroxy compounds **15** in 79–89% (Scheme 4, Table 4). Mechanistically, the reaction proceeds via chelation of the C4-carbonyl and C5-methoxy groups to cerium, which facilitates the selective demethylation of C5. Similar reaction of 2,3-dihydroquinolin-4-ones **13** afforded the corresponding monohydroxy analogues 16 in high yields.

Table 5
Average cell viability of the treated cell lines (concentration of 25 μM)

Entry	H460[a]	DU145[b]	A-431[c]	HT-29[d]	MCF7[e]
8a	33.5 ± 0.4	74.8 ± 2.3	69.1 ± 0.4	26.2 ± 1.0	35.3 ± 2.0
8b	86 ± 1.1	88.7 ± 4.5	103.1 ± 1.3	113.6 ± 4.2	
8c	53.8 ± 0.8	76.6 ± 3.1	89.9 ± 0.0	101.7 ± 1.9	
8f	43.9 ± 0.8	71.8 ± 5.1	66.5 ± 2.3	37.8 ± 0.8	
13d	94.3 ± 4.2	91.1 ± 0.9	89.6 ± 1.8	105.7 ± 1.0	85.1 ± 4.8
13e	87.6 ± 2.7	95.4 ± 1.0	98.3 ± 4.1	98.8 ± 1.6	83.6 ± 5.7
14e	74.5 ± 2.0	83.1 ± 1.4	98.5 ± 0.8	98.5 ± 0.8	121.3 ± 3.1
15a	65.5 ± 3.4	73.5 ± 1.0	104.1 ± 3.0	29.2 ± 1.7	52.6 ± 0.5
15b	38.9 ± 2.7	43.4 ± 1.7	71.4 ± 5.6	31.2 ± 0.5	
15c	50.7 ± 1.1	85.1 ± 1.2	76.5 ± 1.4	29.6 ± 1.4	
15f	2.0 ± 0.3	10.0 ± 1.0	1.0 ± 1.5	14.1 ± 0.3	
16d	94.1 ± 2.2	105.7 ± 1.7	107.7 ± 3.1	97.3 ± 0.9	85.7 ± 2.8
16e	78.0 ± 1.6	81.6 ± 2.5	90.8 ± 1.9	90.8 ± 1.9	83.2 ± 3.5

Cell viability is a measure of the% of metabolically active cells. A value of 0% is indicative of total cell growth inhibition.
[a] Lung carcinoma
[b] Prostate carcinoma
[c] Skin (epidermoid) carcinoma
[d] Colon adenocarcinoma
[e] Breast adenocarcinoma

4. Biological activity

Selected quinolin-4-ones and 2,3-dihydroquinolin-4-ones were screened for anticancer activity (Table 5). In vitro growth inhibition assays were performed at a fixed concentration of 25 μM in a range of cancer cell lines, including H460 lung carcinoma, DU145 prostate carcinoma, A-431 skin (epidermoid) carcinoma, HT-29 colon adenocarcinoma and MCF7 breast adenocarcinoma.

Among the tested compounds, quinolin-4-ones **15** showed moderate activity against HT-29 colon adenocarcinoma cell lines and quinolin-4-one **8a** against H460 lung carcinoma, HT-29 colon adenocarcinoma and MCF7 breast adenocarcinoma. In general, the monohydroxy analogues **15** demonstrated superior activity to their dimethoxy counterparts **8**, as anticipated. An exception to this rule was compound **8a**, which exhibited 33.5%, 69.1% and 35.3% greater cell growth inhibition in H460 lung carcinoma, A-431 skin carcinoma and MCF7 breast adenocarcinoma cell lines, respectively, when compared to its monohydroxy derivative **15a**. Dimethoxyquinoline **8c** was also 8.5% more potent than its monohydroxy analogue **15c** in the DU145 prostate carcinoma cell line.

Compound **15f** showed the greatest reduction (85.9–99.0%) in cell viability across the cell lines tested. This could potentially be attributed to the change from a *para* to a *meta* substitution pattern in ring B, potentially leading to more favourable steric interactions at the active sites. By comparison, the corresponding *para* derivative **15a** showed much weaker activity against the same cell lines.

A dose–response study was subsequently performed for compound **15f** against the selected cell lines in order to better understand its level of activity. Compound **15f** was the most active against the HT-29 colon adenocarcinoma and A-431 skin carcinoma cell lines, with IC_{50} values of 3.6 ± 0.2 and 5.5 ± 0.6 μM, respectively. The compound exhibited similar activity against H460 lung carcinoma (IC_{50} = 9.2 ± 0.8 μM) and DU145 prostate carcinoma (IC_{50} = 9.5 ± 2.7 μM) cell lines, but was least effective in the MCF7 breast adenocarcinoma cell line, with an IC_{50} value of 21.9 ± 1.9 μM. Furthermore, quinolone **15f** was found to have an IC_{50} value of 6.7 ± 1.2 μM against MRC-5 normal human lung fibroblasts, demonstrating a significant difference ($p < 0.05$) compared to the HT-29 colon adenocarcinoma cell line. This difference suggests potential for the development of such compounds as possible therapeutics for colon adenocarcinomas.

In contrast to the quinolin-4-ones, the tested 2,3-dihydroquinolin-4-ones **13**, **14** and **16** did not show any significant anticancer

activity. Furthermore, no consistent trend was observed between the biological activity and the number of hydroxyl substituents on the compounds. The activity of the 3-phenyl analogues against H460 lung carcinoma cells increased in the order **13e** < **16e** < **14e** as the degree of demethylation increased. On the other hand, the monohydroxy derivative **16e** was the most active analogue against DU145, A-431 and HT-29 cell lines while the dihydroxy compound **14e** was the most active against the MCF7 breast adenocarcinoma cell line. Additionally, the dimethoxy 3-(4-methoxyphenyl) analogue **13d** was more active against DU145 and A-431 cell lines while the corresponding monohydroxy compound **16d** was more active against the HT-29 cell line. However, the two compounds displayed similar activity in the H460 and MCF7 cell lines.

5. Conclusion

A series of 3-aryl-5,7-dimethoxyquinolin-4-ones **8** and 3-aryl-5,7-dimethoxy-2,3-dihydroquinolin-4-ones **13** were synthesized in good yields. Chemoselective cleavage of the C5-methoxy group using cerium(III) chloride and sodium iodide in acetonitrile successfully afforded the corresponding monohydroxy derivatives **15** and **16** in high yields. The dihydroxy derivatives 3-aryl-5,7-dihydroxy-2,3-dihydroquinolin-4-ones **14** were obtained by demethylation with BBr_3 in dichloromethane.

Anticancer screening of selected compounds showed that the quinolin-4-one scaffold was more active than the reduced 2,3-dihydroquinolin-4-one scaffold. The monohydroxy compound **15** were generally more potent than their dimethoxy counterparts **13** in the tested cell lines. Overall, the most active analogue was compound **15f**, which demonstrated 85.9–99.0% reduction in cell viability across all the cell lines tested.

6. Experimental section

6.1. Materials and methods

Melting points (uncorrected) were measured using a Mel-Temp melting point apparatus. Microanalyses were performed by the Microanalysis Unit of the University of Otago, New Zealand. Infrared spectra were recorded as Nujol mulls on a Perkin-Elmer 298 or a Perkin-Elmer 580B spectrometer. Ultraviolet-visible spectra were recorded in methanol (unless otherwise stated) on a Hitachi UV-3200 spectrometer. ^1H and ^{13}C NMR spectra were obtained in the designated solvents on a Bruker AC300F (300 MHz) spectrometer. ^1H NMR data were recorded as follow: chemical shift measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling constant (J) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), quintet (quin) and multiplet (m). ^{13}C NMR chemical shifts are reported in ppm downfield from TMS and identifiable carbons are given. The EI and ES mass spectra were recorded on an AEI MS 12 mass spectrometer at 70 eV ionizing potential and 8000 V accelerating voltage with an ion source temperature of 210 °C. Kieselgel 60H (Merck, Art 7736) was employed for flash chromatography and thin layer chromatography (t.l.c.) was performed on DC Aluminium Foil Kieselgel F_{254} (Merck, Art 5554). Solvents and reagents were purified by literature methods. Petroleum ether refers to the hydrocarbon fraction of boiling range 60–80 °C. compounds were detected by short and long ultraviolet light and with iodine vapor.

6.2. General procedure for the preparation of quinolin-4-ones

6.2.1. Ethyl 2-formyl-2-aryl acetate (5a–g)

To a suspension of sodium hydride (49.4 mmol, 60% dispersion in oil) in anhydrous diethyl ether (150 mL) under a nitrogen atmosphere was added ethyl formate **4** (61.65 mmol) dropwise, followed by the addition of ethyl 2-arylacetate **3** (41.1 mmol) at room temperature. The reaction mixture was stirred at 40 °C for 4 h, quenched with water (100 mL), and the ethereal layer was separated. The aqueous layer was washed with ether (100 mL), acidified with 10% HCl (8 mL), and extracted with ethyl acetate (3 × 150 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give ethyl 2-formyl-2-aryl acetate **5** as colourless oil. The compound was used in subsequent reactions without further purification.

6.2.2. *(Z)*-Ethyl 2-aryl-3-((3,5-dimethoxyphenyl)amino)acrylate (7a–g)

A mixture of 3,5-dimethoxyaniline **6** (36.9 mmol) and ethyl 2-formyl-2-aryl acetate **5** (36.9 mmol) in toluene (100 mL) was heated at reflux for 20 h. On cooling, the reaction mixture was diluted with toluene (50 mL) and washed with water (100 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified using column chromatography (2% ethyl acetate in *n*-hexane) to give the title compound **7** as a white solid.

6.2.3. *(Z)*-3-Aryl-5,7-dimethoxyquinolin-4(1*H*)-one (8a–g)

(Z)-Ethyl-3-((3,5-dimethoxyphenyl)amino)-2-aryl acrylate **7** (4.9 mmol) was added in portions to a mixture of biphenyl and diphenyl ether (1:4) and the resulting solution was heated at 250 °C for 20 min. On cooling, the title compound **8** precipitated out of the reaction mixture. The product was collected by filtration and then washed with *n*-hexane as a pale yellow solid.

6.2.4. Ethyl 3-((3,5-dimethoxyphenyl)amino)-2-aryl propanoate (9a–e)

To a solution of 3,5-dimethoxyaniline **6** (36.9 mmol) and ethyl 2-formyl-2-aryl acetate **5** (36.9 mmol) in methanol (100 mL) was added sodium cyanoborohydride (73.8 mmol). After the bubbling subsided, the mixture was heated to reflux for 8 h and the reaction was monitored using TLC. After completion, the methanol was concentrated under reduced pressure and the resulting oil was taken up in ethyl acetate and washed with water (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a yellow oil. The crude oil was purified using column chromatography (2% ethyl acetate in *n*-hexane) to yield the title compound **9** as a yellow oil.

6.2.5. Ethyl 3-((3,5-dimethoxyphenyl)(ethoxycarbonyl)amino)-2-aryl propanoate (10a–e)

Ethyl chloroformate (38.6 mmol) was added dropwise to a mixture of ethyl 3-((3,5-dimethoxyphenyl)amino)-2-aryl propanoate **9** (25.7 mmol) and pyridine (51.5 mmol) in dichloromethane (100 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 5 h and then poured into a mixture of dichloromethane and water (100 mL, 1:1). The dichloromethane layer was separated and washed successively with 10% HCl (100 mL), sat. $NaHCO_3$ (100 mL) and saturated aqueous sodium chloride (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give **11** as yellow oil, which was used in the subsequent step without further purification.

6.2.6. Ethyl 3-((3,5-dimethoxyphenyl)(ethoxycarbonyl)amino)-2-aryl propanoic acid (11a–e)

Ethyl 3-((3,5-dimethoxyphenyl)(ethoxycarbonyl)amino)-2-aryl propanoate **10** (20.8 mmol) in aqueous sodium hydroxide (1 N) and methanol (1:1, 100 mL) was stirred at room temperature overnight. The reaction mixture was concentrated to about half the volume under reduced pressure, diluted with water and extracted with ethyl acetate (100 mL). The aqueous layer was acidified with 10% HCl to pH 2 and extracted with ethyl acetate (3 × 100 mL).

These organic extracts were combined, washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the title compound **11** as a yellow oil.

6.2.7. Ethyl 5,7-dimethoxy-3-aryl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (12a–e)

A mixture of ethyl 3-((3,5-dimethoxyphenyl)(ethoxycarbonyl)amino)-2-aryl propanoic acid **11** (4.4 mmol) and polyphosphoric acid (4.4 mmol) was heated at 70 °C for 30 min under a nitrogen atmosphere. The resulting mixture was cooled to 0 °C, and was taken up in a mixture of dichloromethane–water (1:1, 100 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The combined organic extracts were washed with saturated sodium bicarbonate (2 × 150 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to give a crude oil which was purified by column chromatography (15% ethyl acetate in *n*-hexane) to give the title compound **12** as a white solid.

6.2.8. 5,7-Dimethoxy-3-aryl-2,3-dihydroquinolin-4(1*H*)-one (13a–e)

To a solution of ethyl 5,7-dimethoxy-3-aryl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate **12** (2.7 mmol) in MeOH (10 mL) was added NaOH pellets (13.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for about 1 h and the reaction progress was monitored by TLC. After completion, the solvent was evaporated under reduced pressure and the resulting solid was taken up in ethyl acetate (100 mL). The solution was washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude solid was purified by column chromatography (25% ethyl acetate in *n*-hexane) and recrystallized from MeOH to give compound **13** as white crystals.

6.2.9. 5,7-Dihydroxy-3-aryl-2,3-dihydroquinolin-4(1*H*)-one (14a, e, d)

To a solution of 5,7-dimethoxy-3-aryl-2,3-dihydroquinolin-4(1*H*)-one **13** (0.8 mmol) in dichloromethane (10 mL) was added boron tribromide (4.1 mmol) at 0 °C. The reaction was stirred at room temperature overnight. The resulting mixture was diluted in dichloromethane (50 mL), washed with sat. $NaHCO_3$ (50 mL), water (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified using column chromatography (12% ethyl acetate in *n*-hexane) to give the title compound **14** as a yellow solid.

6.2.10. 5-Hydroxy-7-methoxy-3-aryl-quinolin-4(1*H*)-one (15a–f)

A suspension of 5,7-dimethoxy-3-aryl-quinolin-4(*1H*)-one **8** (0.65 mmol), $CeCl_3.7H_2O$ (1 mmol) and NaI (1 mmol) in acetonitrile (5 mL) was heated at reflux overnight. The brown suspension was cooled to room temperature, and concentrated under reduced pressure. The solid residue was then taken up in ethyl acetate, and washed with aqueous $Na_2S_2O_3$ (1 M, 10 mL) and brine (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the target compound **15** as a yellowish solid.

6.2.11. 5-Hydroxy-7-methoxy-3-aryl-2,3-dihydroquinolin-4(1*H*)-one (16a, c, d, e)

A suspension of 5,7-dimethoxy-3-aryl-2,3-dihydroquinolin-4(1*H*)-one **13** (1 mmol), $CeCl_3.7H_2O$ (1.5 mmol) and NaI (1.5 mmol) in acetonitrile (50 mL) was refluxed overnight. The brown suspension was cooled to room temperature, and concentrated under reduced pressure. The solid residue was then taken up in ethyl acetate (100 mL), washed with aqueous $Na_2S_2O_3$ (1 M, 50 mL), brine solution (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified using column chromatography (8% ethyl acetate in *n*-hexane) to give the title compound **16** as a yellow solid.

6.3. Experimental procedure for biological screening

6.3.1. Cell culture

All cell lines were cultured at 37 °C, under 5% CO_2 in a humidified atmosphere and were maintained in Dulbecco's modified Eagle's medium (Gibco, Invitrogen) supplemented with 10% foetal bovine serum.

6.3.2. In vitro growth inhibition assays

In vitro growth inhibition assays were performed in triplicate using the Alamar Blue assay. Briefly, cells in logarithmic phase growth were seeded onto 96 well plates at an optimal fixed density using a Multidrop 384 (Thermo Scientific) and allowed to adhere. After 24 h incubation test compounds and vehicle only controls were added to duplicate wells using a Hamilton Nimbus robotic platform. After 72 h drug exposure, metabolic activity was detected by addition of Alamar blue reagent and determined by measurement of fluorescence intensity (excitation 555 nm, emission 585 nm) using a SpectraMax M5 (Molecular Devices) plate reader. Percentage cell viability was determined at a fixed drug concentration of 25 μM. A value of 0% is indicative of total cell growth inhibition.

6.4. Experimental data

6.4.1. (*Z*)-Ethyl 2-(4-bromophenyl)-3-((3,5-dimethoxyphenyl) amino)acrylate (7a)

White solid (9.45 g, 63%). Mp 142–144 °C; UV (MeOH): λ_{max} 210 (ε 86178 $cm^{-1}\,M^{-1}$), 330 (79512) nm; IR (KBr): ν_{max} 3297, 2969, 2843, 1664, 1588, 1455, 1371 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H, $\underline{CH_3}CH_2$), 3.70 (s, 6H, OMe), 4.18 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 6.08 (s, 3H, ArH), 7.13 (d, J = 8.7 Hz, 2H, ArH2′, ArH6′), 7.25 (d, J = 12.4 Hz, 1H, =CH), 7.37 (d, J = 8.7 Hz, 2H, ArH3′, ArH5′), 10.24 (d, J = 12.4 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.8 (Me), 55.8 (2 × OMe), 60.5 (OCH_2), 94.8 (ArC2, ArC6), 95.3 (ArC4), 102.4 (=CCOO), 120.4 (ArC4′), 131.4 (ArC3′, ArC5′), 131.5 (ArC2′, ArC6′), 137.2 (ArC1′), 143.9 (=CH), 144.9 (ArC1), 162.3 (ArC3, ArC5), 169.3 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{21}BrNO_4$ $(M+H)^+$ 406.0654. Found 406.0644; Anal. Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.25; H, 5.04; N, 3.56.

6.4.2. (*Z*)-Ethyl 3-((3,5-dimethoxyphenyl)amino)-2-(4-fluorophenyl)acrylate (7b)

White solid (10.6 g, 61%). M.p. 106-108 °C; UV (MeOH): λ_{max} 210 (ε 145517 $cm^{-1}\,M^{-1}$), 247 (80689), 333 (188276) nm; IR (KBr): ν_{max} 3283, 3067, 2999, 2974, 2940, 2898, 2840, 1672, 1589, 1206, 1156, 1072, 782, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H, $\underline{CH_3}CH_2$), 3.70 (s, 6H, OMe), 4.17 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 6.07 (m, 3H, ArH), 6.94 (m, 2H, ArH3′, ArH5′), 7.21 (m, 2H, ArH2′, ArH6′), 7.24 (d, J = 12.8 Hz, 1H, =CH), 10.20 (d, J = 12.8 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.8 (Me), 55.8 (2 × OMe), 60.5 (OCH_2), 94.7 (ArC2, ArC6), 95.1 (ArC4), 102.5 (=CCOO), 115.1 (ArC3′), 115.3 (ArC5′), 131.5 (ArC2′, ArC6′), 131.6 (ArC1′), 142.8 (=CH), 143.8 (ArC1), 162.3 (ArC3, ArC5), 163.5 (ArC4′) 169.6 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{21}FNO_4$ $(M + H)^+$ 346.1455. Found 346.1444; Anal. Calcd for $C_{19}H_{20}FNO_4$: C, 66.08; H, 5.84; N, 4.06. Found: C, 66.09; H, 5.91; N, 4.15.

6.4.3. (*Z*)-Ethyl 3-((3,5-dimethoxyphenyl)amino)-2-(*p*-tolyl) acrylate (7c)

White solid (10 g, 60%). Mp 126–128 °C; UV (MeOH): λ_{max} 209 (ε 100775 $cm^{-1}\,M^{-1}$), 334 (78294) nm; IR (KBr): ν_{max} 3296, 3085,

3021, 2991, 2968, 2940, 1664, 1648, 1477, 1295, 1198, 1154, 1055, 780, 708, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.2 Hz, 3H, $\underline{CH_3}CH_2$), 2.28 (s, 3H, MeAr′), 3.69 (s, 6H, OMe), 4.17 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 6.08 (m, 3H, ArH), 7.07 (d, J = 7.9 Hz, 2H, ArH3′, ArH5′), 7.15 (d, J = 8.3 Hz, 2H, ArH2′, ArH6′), 7.26 (d, J = 12.8 Hz, 1H, =CH), 10.19 (d, J = 12.4 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.8 (Me), 21.5 (MeAr′), 55.3 (OMe), 55.8 (OMe), 60.4 (OCH_2), 94.5 (ArC2, ArC6), 95.1 (ArC4), 102.4 (=CCOO), 129.5 (ArC1′), 129.6 (ArC5′), 129.9 (ArC3′), 135.3 (ArC2′, ArC6′), 136.2 (ArC4′), 143.6 (=CH), 145.0 (ArC1), 162.2 (ArC3, ArC5), 169.8 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{24}NO_3$ $(M+H)^+$ 342.1756. Found 342.1750; Anal. Calcd for $C_{20}H_{23}NO_3$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.28; H, 6.93; N, 4.19.

6.4.4. (*Z*)-Ethyl 3-((3,5-dimethoxyphenyl)amino)-2-(4-methoxyphenyl) acrylate[19] (7d)

White solid (11.2 g, 63.5%). M.p. 94-96 °C, lit.[19] 93–94 °C (EtOH); ^1H NMR (300 MHz, $CDCl_3$): δ 1.21 (t, J = 7.1 Hz, 3H, $\underline{CH_3}$-CH_2), 3.69 (s, 6H, OMe), 3.74 (s, 3H, OMe), 4.17 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 6.04-6.07 (m, 3H, ArH), 6.81 (d, J = 8.4 Hz, 2H, ArH2′ & ArH6′), 7.17–7.25 (m, 3H, ArH3′, ArH5′, =CH), 10.16 (d, J = 12.4 Hz, 1H, NH).

6.4.5. (*Z*)-Ethyl 3-((3,5-dimethoxyphenyl)amino)-2-phenylacrylate[19] (7e)

White solid (12.2 g, 60%). Mp 72–74 °C, lit.[19] 75–76 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J = 6.9 Hz, 3H, $\underline{CH_3}CH_2$), 3.80 (s, 6H, OMe), 4.30 (q, J = 6.9 Hz, 2H, $\underline{CH_2}CH_3$), 6.17 (d, J = 2.1 Hz, 2H, ArH), 6.20 (d, J = 2.1 Hz, 2H, ArH), 7.27–7.37 (m, 5H, Ph), 7.41 (d, J = 11.7 Hz, 1H, =CH), 10.35 (d, J = 12.6 Hz, 1H, NH).

6.4.6. (*Z*)-Ethyl 2-(3-bromophenyl)-3-((3,5-dimethoxyphenyl) amino)acrylate (7f)

White solid (9.2 g, 61.5%). Mp 84–86 °C; UV (MeOH): λ_{max} 210 (ε 223837 cm^{-1} M^{-1}), 244 (75581), 333 (204069) nm; IR (KBr): ν_{max} 3384, 3062, 2984, 2936, 2898, 2837, 1655, 1607, 1251, 1194, 1065, 1024, 796, 718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.22 (t, J = 7.1 Hz, 3H, $\underline{CH_3}CH_2$), 3.70 (s, 6H, OMe), 4.18 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 6.08 (m, 3H, ArH), 7.12 (d, J = 7.5 Hz, 1H, ArH6′), 7.18 (m, 1H, ArH5′), 7.28 (m, 1H, ArH4′), 7.26 (d, J = 12.8 Hz, 1H, =CH), 7.41 (t, J = 1.5 Hz, 1H, Ar′H2), 10.25 (d, J = 12.5 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.7 (Me), 55.8 (2 × OMe), 60.5 (OCH_2), 94.9 (ArC2, ArC6), 95.4 (ArC4), 102.2 (=CCOO), 122.3 (ArC3′), 128.5 (ArC6′), 129.4 (ArC2′), 129.8 (ArC5′), 132.7 (ArC4′), 140.4 (ArC1′), 142.6 (=CH), 144.2 (ArC1), 162.3 (ArC3, ArC5), 169.2 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{21}BrNO_4$ $(M+H)^+$ 406.0654. Found 406.0644; Anal. Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.96; N, 3.45. Found: C, 56.25; H, 5.08; N, 3.54.

6.4.7. (*Z*)-Ethyl 2-(2,5-dimethoxyphenyl)-3-((3,5-dimethoxyphenyl) amino)acrylate (7g)

White solid (7.1 g, 46.5%). Mp 114–116 °C; UV (MeOH): λ_{max} 209 (ε 52907 cm^{-1} M^{-1}), 322 (33333) nm; IR (KBr): ν_{max} 3315, 2981, 2937, 2837, 1693, 1589, 1494, 1154, 1036, 772, 734, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H, $\underline{CH_3}$-CH_2), 3.67 (s, 6H, MeO), 4.13 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 5.97–6.05 (m, 3H, ArH), 6.70–6.88 (m, 3H, ArH2′, ArH4′, ArH6′), 7.21 (d, J = 12.8 Hz, 1H, =CH), 10.09 (d, J = 12.4 Hz, 1H, NH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.6 (Me), 55.6 (2 × OMe), 55.7 (2 × OMe), 59.94 (OCH_2), 94.6 (2 × ArC), 99.2 (ArC), 111.5 (=CCOO), 112.3 (ArC6′), 113.1 (ArC3′), 114.1 (ArC4′), 117.8 (ArC1′), 142.6 (=CH), 143.1 (ArC), 151.7 (ArC3′), 152.3 (ArC5′), 161.8 (ArC3, ArC5), 169.5 (C=O); HRMS (ESI) m/z Calcd for $C_{21}H_{26}NO_6$ $(M+H)^+$ 388.1760. Found 388.1750.

6.4.8. 3-(4-Bromophenyl)-5,7-dimethoxyquinolin-4(1*H*)-one (8a)

Pale yellow solid (1 g, 59%). Mp 312–314 °C; UV (1% CF_3COOH/MeOH): λ_{max} 208 (ε 48052 cm^{-1} M^{-1}), 263 (128961), 303 (10389) nm; IR (KBr): ν_{max} 3263, 3076, 2931, 1627, 1604, 1523, 1466, 720, 692 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.79 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.32 (d, J = 2.1 Hz, 1H, ArH6), 6.51 (d, J = 2.4 Hz, 1H, ArH8), 7.52 (d, J = 8.4 Hz, 2H, ArH2′, ArH6′), 7.60 (d, J = 8.4 Hz, 2H, ArH3′, ArH5′), 7.88 (s, 1H, H2), 11.58 (br s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.7 (OMe), 56.0 (OMe), 91.6 (ArC6), 95.0 (ArC8), 111.8 (ArC), 119.4 (ArC3), 120.5 (ArC4′), 130.8 (ArC2′, ArC6′), 130.9 (ArC3′, ArC5′), 136.1 (ArC2), 136.3 (Ar′C1), 143.9 (ArC), 161.8 (ArC5), 162.3 (ArC7), 173.9 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{15}BrNO_3$ $(M+H)^+$ 360.0235. Found 360.0229.

6.4.9. 3-(4-Fluorophenyl)-5,7-dimethoxyquinolin-4(1*H*)-one (8b)

Pale yellow solid (1 g, 59%). Mp 262–264 °C; UV (1% CF_3COOH/MeOH): λ_{max} 203 (ε 36034 cm^{-1} M^{-1}), 237 (52586), 266 (60344), 316 (23017) nm; IR (KBr): ν_{max} 3072, 2939, 1624, 1560, 1255, 1199, 1162, 1109, 1073, 777, 719, 708 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.77 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.31 (d, J = 2.1 Hz, 1H, ArH6), 6.50 (d, J = 2.4 Hz, 1H, ArH8), 7.16 (m, 2H, ArH3′, ArH5′), 7.63 (m, 2H, ArH2′, ArH6′), 7.84 (s, 1H, H2), 11.53 (br s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.8 (OMe), 56.1 (OMe), 91.8 (ArC6), 95.0 (ArC8), 111.6 (ArC), 114.6 (ArC3′), 114.9 (ArC5′), 121.0 (ArC3), 130.8 (ArC2′), 130.9 (ArC6′), 136.1 (ArC2, ArC1′), 144.0 (ArC), 161.9 (ArC5, ArC1′), 162.8 (ArC7), 174.3 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{15}FNO_3$ $(M+H)^+$ 300.1036. Found 300.1027.

6.4.10. 5,7-Dimethoxy-3-(*p*-tolyl)quinolin-4(1*H*)-one (8c)

Pale yellow solid (0.9 g, 51.5%). Mp 282–284 °C; UV (1% CF_3COOH/MeOH): λ_{max} 207 (ε 149789 cm^{-1} M^{-1}), 261 (192405) nm; IR (KBr): ν_{max} 3264, 3076, 2932, 2858, 1627, 1604, 1521, 1225, 1209, 1156, 1117, 700, 671 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, MeAr′), 3.77 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.30 (d, J = 2.4 Hz, 1H, ArH6), 6.50 (d, J = 2.4 Hz, 1H, ArH8), 7.14 (d, J = 8.1 Hz, 2H, ArH3′, ArH5′), 7.48 (d, J = 8.1 Hz, 2H, ArH2′, ArH6′), 7.77 (s, 1H, H2), 11.46 (br s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 21.2 (MeAr′), 56.7 (OMe), 57.7 (OMe), 92.8 (ArC6), 99.6 (ArC8), 113.6 (ArC), 117.5 (ArC3′, ArC5′), 119.0 (ArC3), 129.4 (ArC2′), 129.7 (ArC6′), 129.9 (ArC1′), 130.4 (ArC2), 138.2 (ArC4′), 144.1 (ArC), 165.0 (ArC5), 166.7 (ArC7), 173.2 (C=O); HRMS (ESI) m/z Calcd for $C_{18}H_{18}NO_3$ $(M + H)^+$ 296.1286. Found 296.1275.

6.4.11. 5,7-Dimethoxy-3-(4-methoxyphenyl)quinolin-4(1*H*)-one[19] (8d)

Pale yellow solid (1 g, 58%). Mp 264–266 °C, lit.[19] 262-263 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 3.87 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.40 (d, J = 3.0 Hz, 1H, ArH6), 6.60 (d, J = 3.0 Hz, 1H, ArH8), 7.01 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.63 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 7.84 (d, J = 3.0 Hz, 1H, H2), 11.55 (br s, 1H, NH).

6.4.12. 5,7-Dimethoxy-3-phenylquinolin-4(1*H*)-one[19] (8e)

Pale yellow solid (1.2 g, 70.5%). Mp 176–178 °C, lit.[19] 179–180 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 3.81 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.44 (d, J = 2.0 Hz, 1H, ArH6), 6.57 (d, J = 2.0 Hz, 1H, ArH8), 7.26–7.36 (m, 3H, ArH′), 7.62 (m, 2H, ArH′), 7.99 (s, 1H, H2).

6.4.13. 3-(3-Bromophenyl)-5,7-dimethoxyquinolin-4(1*H*)-one (8f)

Pale yellow solid (0.95 g, 55%). Mp 268–270 °C; UV (1% CF_3-$COOH$/MeOH): λ_{max} 211 (ε 114049 cm^{-1} M^{-1}), 262 (252479), 317

(20247) nm; IR (KBr): ν_{max} 3075, 2931, 2837, 1629, 1591, 1560, 1222, 1199, 1158, 1110, 781, 723, 707, 687 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.36 (d, J = 1.5 Hz, 1H, ArH6), 6.54 (d, J = 1.5 Hz, 1H, ArH8), 7.32 (t, J = 7.9 Hz, 1H, ArH6′), 7.44 (d, J = 7.9 Hz, 1H, ArH5′), 7.61 (d, J = 7.5 Hz, 1H, ArH4′), 7.92 (s, 2H, ArH2′, =CH), 11.62 (br s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.8 (OMe), 56.1 (OMe), 91.8 (ArC6), 95.2 (ArC8), 111.8 (ArC), 120.2 (ArC3), 121.4 (ArC3′), 127.6 (ArC6′), 129.2 (ArC2′, ArC5′), 130.2 (ArC4′),131.5 (ArC1′), 139.4 (ArC2), 144.0 (ArC), 161.9 (ArC5), 162.4 (ArC7), 173.8 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{15}BrNO_3$ $(M+H)^+$ 360.0235. Found 360.0227.

6.4.14. 3-(2,5-Dimethoxyphenyl)-5,7-dimethoxyquinolin-4(1*H*)-one (8g)

Pale yellow solid (0.85 g, 47.7%). Mp 230–232 °C; UV (1% CF_3COOH/MeOH): λ_{max} 206 (ε 146733 cm^{-1} M^{-1}), 255 (254773), 300 (28140) nm; IR (KBr): ν_{max} 3081, 2935, 2831, 1626, 1557, 1219, 1108, 1068, 722, 678 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.62 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.31 (d, J = 2.2 Hz, 1H, ArH6), 6.49 (d, J = 2.2 Hz, 1H, ArH8), 6.80 (m, 2H, ArH2′, ArH4′), 6.92 (m, 1H, ArH6′), 7.60 (s, 1H, H2), 11.40 (br s, 1H, NH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.7 (OMe), 55.8 (OMe), 56.1 (OMe), 56.4 (OMe), 91.7 (ArC6), 94.8 (ArC8), 111.5 (ArC6′), 112.6 (ArC), 112.9 (ArC4′), 118.3 (ArC3′), 119.7 (ArC3), 126.9 (ArC1′), 137.0 (ArC2), 151.8 (ArC2′), 153.1 (ArC5′, ArC),161.7 (ArC5), 162.2 (ArC7), 173.7 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{20}NO_5$ $(M+H)^+$ 342.1341. Found 342.1330.

6.4.15. Ethyl 2-(4-bromophenyl)-3-(3,5-dimethoxyphenylamino)propanoate (9a)

Yellow oil (10.6 g, 70%); UV (MeOH): λ_{max} 216 (ε 53906 cm^{-1} - M^{-1}); IR (KBr): ν_{max} 3404, 2917, 2848, 1724, 1592, 1515, 1485, 1459, 1409, 1370, 1193, 1172, 1070, 1010, 808, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.20 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.39 (dd, J = 6.0, 15.0 Hz, 1H, $\underline{CH}Ar'$), 3.74 (s, 6H, OMe), 3.88-3.95 (m, 2H, CH_2N), 4.14 (q, J = 6.0 Hz, 2H, $\underline{CH_2}CH_3$), 5.77 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 5.89 (t, J = 3.0 Hz, 1H, ArH4), 7.17 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 7.47 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.0 (Me), 46.5 (CHAr′), 50.1 (CH_2N), 55.1 (2 × OMe), 61.1 (OCH_2), 90.0 (ArC), 91.8 (2 × ArC), 121.6 (ArC4′), 129.7 (ArC2′, ArC6′), 131.9 (ArC3′, ArC5′), 135.7 (ArC1′), 148.9 (ArC), 161.7 (ArC3, ArC5), 172.3 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{23}BrNO_4$ $(M+H)^+$ 407.0810. Found 408.0800.

6.4.16. Ethyl 3-(3,5-dimethoxyphenylamino)-2-(4-fluorophenyl) propanoate (9b)

Yellow oil (12.6 g, 70%); UV (MeOH): λ_{max} 215 (ε 63043 cm^{-1} - M^{-1}); IR (KBr): ν_{max} 3406, 2936, 2841, 1724, 1594, 1508, 1460, 1202, 1058, 927, 808, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.32 (dd, J = 6.0, 12.0 Hz, 1H, $\underline{CH}Ar'$), 3.66 (s, 6H, OMe), 3.82–3.87 (m, 2H, CH_2N), 4.05 (q, J = 6.0 Hz, 2H, $\underline{CH_2}CH_3$), 5.70 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 5.82 (t, J = 3.0 Hz, 1H, ArH4), 6.93–6.99 (m, 2H, ArH3′, ArH5′), 7.17–7.21 (m, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.5 (Me), 47.2 (CHAr′), 50.4 (CH_2N), 55.6 (2 × OMe), 61.6 (OCH_2), 90.4 (ArC), 92.3 (2 × ArC), 116.1 (ArC3′), 116.3 (ArC5′), 130.0 (ArC2′), 130.1 (ArC6′), 133.0 (ArC1′), 149.5 (ArC), 162.1 (ArC3), 162.2 (ArC5), 164.3 (ArC4′), 173.1 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{23}FNO_4$ $(M+H)^+$ 348.1611. Found 348.1599.

6.4.17. Ethyl 3-(3,5-dimethoxyphenylamino)-2-*p*-tolylpropanoate (9c)

Yellow oil (13 g, 69.5%); UV (MeOH): λ_{max} 216 (ε 53906 cm^{-1} - M^{-1}); IR (KBr): ν_{max} 3361, 2824, 1714, 1597, 1514, 1452, 1418, 1369, 1337, 1193, 1062, 1018, 813, 782, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 2.26 (s, 3H, MeAr), 3.32 (dd, J = 6.0, 12.0 Hz, 1H, $\underline{CH}Ar'$), 3.65 (s, 6H, OMe), 3.79–3.89 (m, 2H, CH_2N), 4.08 (q, J = 6.0 Hz, 2H, $\underline{CH_2}CH_3$), 5.70 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 5.81 (t, J = 3.0 Hz, 1H, ArH4), 7.15–7.12 (m, 4H, ArH2′, ArH3′, ArH5′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.5 (Me), 21.5 (MeAr′), 47.2 (CHAr′), 50.8 (CH_2N), 55.6 (2 × OMe), 61.4 (OCH_2), 90.5 (ArC), 92.3 (2 × ArC), 128.3 (ArC3′, ArC5′), 130.0 (ArC2′, ArC6′), 134.2 (ArC1′), 137.8 (ArC4′), 149.8 (ArC), 162.2 (ArC3, ArC5), 173.4 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{26}NO_4$ $(M+H)^+$ 344.1862. Found 344.1847.

6.4.18. Ethyl 3-(3,5-dimethoxyphenylamino)-2-(4-methoxyphenyl)propanoate (9d)

Yellow oil (11.9 g, 67%); UV (MeOH): λ_{max} 201 (ε 84800 cm^{-1} M^{-1}), 217 (60800) nm; IR (KBr): ν_{max} 3405, 2935, 2838, 1723, 1595, 1510, 1247, 1202, 1173, 1058, 1030, 808, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.12 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.32 (dd, J = 6.0, 12.0 Hz, 1H, $\underline{CH}Ar'$), 3.67 (s, 6H, OMe), 3.73 (s, 3H, OMe), 3.78–3.84 (m, 2H, CH_2N), 4.06 (q, J = 6.0 Hz, 2H, $\underline{CH_2}CH_3$), 5.71 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 5.82 (t, J = 3.0 Hz, 1H, ArH4), 6.80 (d, J = 9.0 Hz, 2H,ArH2′, ArH6′), 7.14 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.5 (Me), 47.2 (CHAr′), 50.4 (CH_2N), 55.6 (2 × OMe), 55.7 (OMe), 61.4 (OCH_2), 90.5 (2 × ArC), 92.3 (ArC), 114.7 (ArC2′, ArC6′), 129.2 (ArC1′), 129.5 (ArC3′, ArC5′), 149.7 (ArC), 159.5 (ArC4′), 162.2 (ArC3, ArC5), 173.5 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{26}NO_5$ $(M+H)^+$ 360.1811. Found 360.1800.

6.4.19. Ethyl 3-(3,5-dimethoxyphenylamino)-2-phenylpropanoate (9e)

Yellow oil (11.2 g, 65%). UV (MeOH): λ_{max} 215 (ε 79487 cm^{-1} - M^{-1}); IR (KBr): ν_{max} 3406, 2936, 2840, 1723, 1594, 1454, 1202, 1172, 1057, 926, 808, 734, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.49 (dd, J = 6.0, 12.0 Hz, 1H, $\underline{CH}Ar'$), 3.79 (s, 6H, OMe), 3.86–4.03 (m, 2H, CH_2NH), 4.21 (q, J = 6.0 Hz, 2H, $\underline{CH_2}CH_3$), 5.85 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 5.96 (t, J = 3.0 Hz, 1H, ArH4), 7.33–7.40 (m, 5H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.5 (Me), 47.2 (CHAr′), 51.3 (CH_2NH), 55.6 (2 × OMe), 61.5 (OCH_2), 90.4 (ArC), 92.3 (2 × ArC), 128.1 (ArC4′), 128.3 (ArC3′, ArC5′), 129.4 (ArC2′, ArC6′), 137.3 (ArC1′), 149.7 (ArC), 162.2 (ArC3, ArC5), 173.3 (C=O); HRMS (ESI) m/z Calcd for $C_{19}H_{24}NO_4$ $(M+H)^+$ 330.1705. Found 330.1693.

6.4.20. 2-(4-Bromophenyl)-3-((3,5-dimethoxyphenyl)(ethoxycarbonyl)amino)propanoic acid (11a)

Yellow oil (9 g, 95.5%); UV (MeOH): λ_{max} 203 (ε 73662 cm^{-1} - M^{-1}), 282 (1851) nm; IR (KBr): ν_{max} 2938, 1702, 1593, 1456, 1408, 1381, 1303, 1203, 1062, 1010, 928, 829, 767, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.62 (s, 6H, OMe), 3.94–4.08 (m, 4H, $\underline{CH_2}CH_3$ & CH_2N), 4.18 (dd, J = 6.0, 12.0 Hz, 1H, $\underline{CH}Ar'$), 5.98 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 6.23 (t, J = 3.0 Hz, 1H, ArH4), 7.08 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 7.34 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.9 (Me), 49.8 (CHAr′), 52.8 (CH_2N), 55.7 (2 × OMe), 62.4 (OCH_2), 99.7 (ArC), 106.0 (2 × ArC), 122.4 (ArC4′), 130.8 (ArC2′, ArC6′), 132.2 (ArC3′, ArC5′), 135.2 (ArC1′), 143.5 (ArC), 155.9 (C=O), 161.1 (2 × ArC), 177.1 (COOH); HRMS (ESI) m/z Calcd for $C_{20}H_{23}BrNO_6$ $(M+H)^+$ 452.0709. Found 452.0703.

6.4.21. 3-((3,5-Dimethoxyphenyl)(ethoxycarbonyl)amino)-2-(4-fluorophenyl)propanoic acid (11b)

Yellow oil (11 g, 94%); UV (MeOH): λ_{max} 203 (ε 62426 cm^{-1} - M^{-1}), 282 (587) nm; IR (KBr): ν_{max} 2940, 2842, 1703, 1593, 1509, 1459, 1409, 1306, 1222, 1203, 1062, 1035, 928, 833, 768, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.09 (t, J = 6.0 Hz, 3H, $\underline{CH_3}$-CH_2), 3.61 (s, 6H, OMe), 3.93–4.08 (m, 4H, $\underline{CH_2}CH_3$, CH_2N), 4.16 (dd, J = 6.0, 15.0 Hz, 1H, $\underline{CH}Ar'$), 6.00 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 6.23

(t, J = 3.0 Hz, 1H, ArH4), 6.88–6.93 (m, 2H, ArH3′, ArH5′), 7.15–7.20 (m, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.9 (Me), 49.7 (CHAr′), 52.9 (CH_2N), 55.7 (2 × OMe), 62.4 (OCH_2), 99.7 (ArC), 106.0 (2 × ArC), 115.8 (ArC3′), 116.1 (ArC5′), 130.6 (ArC2′), 130.7 (ArC6′), 131.8 (ArC1′), 131.9 (ArC4′), 143.5 (ArC), 155.9 (C=O), 161.1 (ArC), 161.2 (ArC), 178.0 (COOH); HRMS (ESI) m/z Calcd for $C_{20}H_{23}FNO_6$ $(M + H)^+$ 392.1509. Found 392.1502.

6.4.22. 3-((3,5-Dimethoxyphenyl)(ethoxycarbonyl)amino)-2-*p*-tolylpropanoic acid (11c)

Yellow oil (10.5 g, 94%); UV (MeOH): λ_{max} 204 (ε 46050 cm^{-1} M^{-1}); IR (KBr): ν_{max} 3352, 2971, 1693, 1594, 1513, 1473, 1446, 1427, 1328, 1295, 1269, 1200, 1155, 1064, 1043, 926, 820, 770, 730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J = 6.0 Hz, 3H, $\underline{CH_3}$-CH_2), 2.23 (s, 3H, MeAr′), 3.60 (s, 6H, OMe), 3.92–4.08 (m, 4H, $\underline{CH_2}$-CH_3, CH_2N), 4.19 (dd, J = 12.0, 18.0 Hz, 1H, $\underline{CH}$Ar′), 6.01 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 6.23 (t, J = 3.0 Hz, 1H, ArH4), 7.02 (d, J = 6.0 Hz, 2H, ArH3′, ArH5′), 7.08 (d, J = 6.0 Hz, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.9 (Me), 21.4 (MeAr′), 50.0 (CHAr′), 53.0 (CH_2N), 55.7 (2 × OMe), 62.3 (OCH_2), 99.8 (ArC), 106.0 (2 × ArC), 128.9 (ArC3′, ArC5′), 129.7 (ArC2′, ArC6′), 133.2 (ArC1′), 138.0 (ArC4′), 143.7 (ArC), 156.0 (C=O), 161.0 (2 × ArC), 178.2 (COOH); HRMS (ESI) m/z Calcd for $C_{21}H_{26}NO_6$ $(M+H)^+$ 388.1760. Found 388.1752.

6.4.23. 3-((3,5-Dimethoxyphenyl)(ethoxycarbonyl)amino)-2-(4-methoxyphenyl) propanoic acid (11d)

Yellow oil (8.9 g, 95%); UV (MeOH): λ_{max} 204 (ε 52217 cm^{-1} M^{-1}), 282 (1411) nm; IR (KBr): ν_{max} 2938, 2839, 1703, 1593, 1511, 1203, 1178, 1062, 1031, 769, 733, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.62 (s, 6H, OMe), 3.70 (s, 3H, OMe), 3.90–4.07 (m, 4H, $\underline{CH_2}CH_3$, CH_2N), 4.18 (dd, J = 6.0, 12 Hz, 1H, $\underline{CH}$Ar′), 6.02 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 6.24 (t, J = 3.0 Hz, 1H, ArH4), 6.75 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 7.12 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.9 (Me), 49.6 (CHAr′), 53.0 (CH_2N), 55.6 (OMe), 55.7 (2 × OMe), 62.3 (OCH_2), 99.8 (ArC), 106.0 (2 × ArC), 114.5 (ArC3′, ArC5′), 128.2 (ArC1′), 130.1 (ArC2′, ArC6′), 143.7 (ArC), 155.9 (C=O), 159.7 (ArC4′), 161.0 (ArC3, ArC5), 178.6 (COOH); HRMS (ESI) m/z Calcd for $C_{21}H_{26}NO_7$ $(M + H)^+$ 404.1709. Found 404.1700.

6.4.24. 3-((3,5-Dimethoxyphenyl)(ethoxycarbonyl)amino)-2-phenylpropanoic acid (11e)

Yellow oil (8.9 g, 96%); UV (MeOH): λ_{max} 204 (ε 63793 cm^{-1} M^{-1}), 282 (1149) nm; IR (KBr): ν_{max} 2939, 2841, 1703, 1593, 1455, 1248, 1203, 1062, 1033, 834, 765, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.60 (s, 6H, OMe), 3.96–4.08 (m, 4H, $\underline{CH_2}CH_3$, CH_2N), 4.21 (dd, J = 9.0, 15.0 Hz, 1H, $\underline{CH}$Ar′), 6.01 (d, J = 3.0 Hz, 2H, ArH2, ArH6), 6.23 (t, J = 3.0 Hz, 1H, ArH4), 7.19–7.23 (m, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.9 (Me), 50.5 (CHAr′), 53.0 (CH_2N), 55.7 (2 × OMe), 62.3 (OCH_2), 99.8 (ArC), 106.0 (2 × ArC), 128.3 (ArC1′), 129.0 (ArC3′, ArC5′), 129.1 (ArC2′, ArC6′), 136.2 (ArC4′), 143.7 (ArC), 156.0 (C=O), 161.0 (ArC3, ArC5), 178.0 (COOH); HRMS (ESI) m/z Calcd for $C_{20}H_{24}NO_6$ $(M + H)^+$ 374.1604. Found 374.1591.

6.4.25. Ethyl 3-(4-bromophenyl)-5,7-dimethoxy-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (12a)

White solid (1.2 g, 63.5%). Mp 136–138 °C; UV (MeOH): λ_{max} 202 (ε 39036 cm^{-1} M^{-1}), 230 (42813), 294 (25792) nm; IR (KBr): ν_{max} 3358, 2934, 1699, 1662, 1597, 1568, 1453, 1373, 1298, 1261, 1212, 1046, 1010, 951, 821, 766, 718, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.79 (dd, J = 6.0, 9.0 Hz, 1H, H3), 3.87 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.11–4.18 (m, 3H, $\underline{CH_2}CH_3$, H2a), 4.34 (dd, J = 6.0, 15.0 Hz, 1H, H2b), 6.29 (d, J = 3.0 Hz, 1H, ArH6), 6.94 (d, J = 3.0 Hz, 1H, ArH8), 7.05 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.42 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.2 (Me), 50.1 (CHAr′), 54.2 (CH_2N), 55.5 (OMe), 56.0 (OMe), 62.4 (OCH_2), 95.8 (ArC8), 100.3 (ArC6), 109.9 (ArC), 121.2 (ArC4′), 130.1 (ArC2′, ArC6′), 131.6 (ArC3′, ArC5′), 136.5 (ArC1′), 147.0 (ArC), 153.8 (COO), 164.4 (ArC5, ArC7), 191.7 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{21}BrNO_3$ $(M+H)^+$ 434.0705. Found 434.0698; Anal. Calcd for $C_{20}H_{20}BrNO_5$: C, 55.31; H, 4.64; N, 3.23. Found: C, 55.49; H, 4.61; N, 3.19.

6.4.26. Ethyl 3-(4-fluorophenyl)-5,7-dimethoxy-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (12b)

White solid (1.2 g, 64%). Mp 70–72 °C; UV (MeOH): λ_{max} 294 (ε 22400 cm^{-1} M^{-1}) nm; IR (KBr): ν_{max} 2938, 1707, 1669, 1597, 1568, 1509, 1455, 1371, 1297, 1245, 1158, 1044, 955, 830, 761 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.75 (dd, J = 6.0, 9.0 Hz, 1H, H3), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.04-4.12 (m, 3H, $\underline{CH_2}CH_3$, H2a), 4.26 (dd, J = 6.0, 12.0 Hz, 1H, H2b), 6.23 (d, J = 3.0 Hz, 1H, ArH6), 6.88 (d, J = 3.0 Hz, 1H, ArH8), 6.92 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.06 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.7 (Me), 50.8 (CHAr′), 54.5 (CH_2N), 56.0 (OMe), 56.5 (OMe), 62.9 (OCH_2), 96.3 (ArC8), 100.8 (ArC6), 110.4 (ArC), 115.7 (ArC3′), 116.0 (ArC5′), 130.4 (ArC1′), 133.8 (ArC2′), 133.9 (ArC6′), 147.6 (ArC), 153.4 (COO), 164.0 (ArC4′), 164.8 (ArC5, ArC7), 192.6 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{21}FNO_5$ $(M+H)^+$ 374.1404. Found 374.1393.

6.4.27. Ethyl 5,7-dimethoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (12c)

White solid (1.1 g, 55%). Mp 104–106 °C; UV (MeOH): λ_{max} 201 (ε 28899 cm^{-1} M^{-1}), 239 (29474), 294 (20484) nm; IR (KBr): ν_{max} 2987, 2912, 2850, 1700, 1661, 1598, 1573, 1454, 1400, 1302, 1263, 1214, 1154, 1048, 1021, 952, 811, 763, 721 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 2.23 (s, 3H, MeAr′), 3.72 (dd, J = 6.0, 9.0 Hz, 1H, H3), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.03–4.10 (m, 3H, $\underline{CH_2}CH_3$, H2a), 4.27 (dd, J = 6.0 Hz, 15 Hz, 1H, H2b), 6.22 (d, J = 3.0 Hz, 1H, ArH6), 6.88 (d, J = 3.0 Hz, 1H, ArH8), 6.97–7.05 (m, 5H, ArH2′, ArH3′, ArH5′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.7 (Me), 21.4 (MeAr′), 50.9 (CHAr′), 55.0 (CH_2N), 56.0 (OMe), 56.5 (OMe), 62.8 (OCH_2), 96.3 (ArC8), 100.7 (ArC6), 110.7 (ArC), 128.7 (ArC3′, ArC5′), 129.7 (ArC2′, ArC6′), 135.0 (ArC1′), 137.2 (ArC4′), 147.7 (ArC), 154.4 (COO), 163.0 (ArC5), 164.6 (ArC7), 193.2 (C=O); HRMS (ESI) m/z Calcd for $C_{21}H_{24}NO_5$ $(M+H)^+$ 370.1654. Found 370.1642; Anal. Calcd for $C_{21}H_{23}NO_5$: C, 66.28; H, 6.28; N, 3.79. Found: C, 67.99; H, 6.26; N, 3.74.

6.4.28. Ethyl 5,7-dimethoxy-3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (12d)

White solid (1.2 g, 62%). Mp 108–110 °C; UV (MeOH): λ_{max} 201 (ε 29678 cm^{-1} M^{-1}), 229 (33704), 293 (19828) nm; IR (KBr): ν_{max} 2973, 2832, 1699, 1661, 1595, 1570, 1512, 1455, 1247, 1153, 1049, 1022, 855, 829, 808 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.75 (s, 3H, OMe), 3.79 (dd, J = 6.0, 9.0 Hz, 1H, H3), 3.86 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.09-4.17 (m, 3H, $\underline{CH_2}CH_3$, H2a), 4.32 (dd, J = 3.0, 12.0 Hz, 1H, H2b), 6.28 (d, J = 3.0 Hz, 1H, ArH6), 6.82 (d, J = 9.0 Hz, ArH2′, ArH6′), 6.94 (d, J = 3.0 Hz, 1H, ArH8), 7.08 (d, J = 9 Hz, 2H, ArH3′, ArH5′), ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.2 (Me), 50.4 (CHAr′), 54.0 (CH_2N), 55.1 (OMe), 55.5 (OMe), 56.0 (OMe), 62.3 (OCH_2), 95.8 (ArC6), 100.2 (ArC8), 110.1 (ArC), 114.0 (ArC3′, ArC5′), 129.4 (ArC2′, ArC6′), 129.6 (ArC1′), 147.1 (ArC), 153.9 (COO), 158.6 (ArC4′), 162.5 (ArC5), 164.1 (ArC7), 192.6 (C=O); HRMS (ESI) m/z Calcd for $C_{21}H_{24}NO_6$ $(M+H)^+$ 386.1604. Found 386.1592; Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63. Found: C, 65.41; H, 6.02; N, 3.68.

6.4.29. Ethyl 5,7-dimethoxy-4-oxo-3-phenyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (12e)

Colourless oil (1.2 g, 63%); UV (MeOH): λ_{max} 203 (ε 25587 cm^{-1} M^{-1}), 238 (25694), 294 (17936) nm; IR (KBr): ν_{max} 2935, 1707, 1669, 1597, 1568, 1453, 1245, 1156, 1094, 1044, 829, 757, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.08 (t, J = 6.0 Hz, 3H, $\underline{CH_3}CH_2$), 3.77 (dd, J = 6.0, 9.0 Hz, 1H, H3), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.00–4.15 (m, 3H, $\underline{CH_2}CH_3$, H2a), 4.27 (dd, J = 6.0, 15.0 Hz, 1H, H2b), 6.23 (d, J = 3.0 Hz, 1H, ArH6), 6.88 (d, J = 3.0 Hz, 1H, ArH8), 7.08–7.22 (m, 5H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 14.7 (Me), 50.9 (CHAr′), 55.3 (CH_2N), 56.0 (OMe), 56.5 (OMe), 62.8 (OCH_2), 96.3 (ArC6), 100.8 (ArC8), 110.7 (ArC), 127.6 (ArC3′, ArC5′), 128.9 (ArC2′, ArC6′), 129.0 (ArC1′, ArC4′), 147.7 (ArC), 154.4 (COO), 163.0 (ArC5), 164.7 (ArC7), 193.0 (C=O); HRMS (ESI) m/z Calcd for $C_{20}H_{22}NO_5$ $(M+H)^+$ 356.1498. Found 356.1485.

6.4.30. 3-(4-Bromophenyl)-5,7-dimethoxy-2,3-dihydroquinolin-4(1*H*)-one (13a)

White crystals (0.65 g, 79.5%). Mp 212–214 °C; UV (MeOH): λ_{max} 203 (ε 32729 cm^{-1} M^{-1}), 220 (34958), 244 (31058), 291 (18105), 348 (3899) nm; IR (KBr): ν_{max} 3282, 2937, 2819, 1607, 1575, 1524, 1484, 1435, 1382, 1346, 1264, 1207, 1147, 1106, 1071, 1008, 983, 939, 765, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.61–3.71 (m, 3H, H2, H3), 3.78 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.66 (br s, 1H, NH), 5.70 (d, J = 3.0 Hz, 1H, ArH6), 5.81 (d, J = 3.0 Hz, 1H, ArH8), 7.13 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.40 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.2 (CH_2N), 52.3 (CHAr′), 55.2 (OMe), 55.7 (OMe), 89.7 (ArC6), 90.3 (ArC8), 104.0 (ArC), 120.9 (ArC4′), 130.1 (ArC2′, ArC6′), 131.4 (ArC3′, ArC5′), 136.9 (ArC1′), 154.6 (ArC), 163.5 (ArC5), 165.4 (ArC7), 190.0 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{17}BrNO_3$ $(M+H)^+$ 362.0392. Found 362.0382; Anal. Calcd for $C_{17}H_{16}BrNO_3$: C, 56.37; H, 4.45; N, 3.87. Found: C, 56.27; H, 4.34; N, 3.82.

6.4.31. 3-(4-Fluorophenyl)-5,7-dimethoxy-2,3-dihydroquinolin-4(1*H*)-one (13b)

White crystals (1.3 g, 80%). Mp 196–198 °C; UV (MeOH): λ_{max} 204 (ε 27980 cm^{-1} M^{-1}), 244 (28732), 291 (17440), 348 (4140) nm; IR (KBr): ν_{max} 3293, 2965, 2841, 1595, 1523, 1505, 1438, 1380, 1348, 1265, 1206, 1149, 1108, 1063, 985, 833, 790, 681 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.58–3.75 (m, 3H, H2, H3), 3.78 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.68 (br s, 1H, NH), 5.71 (d, J = 3.0 Hz, 1H, ArH6), 5.81 (d, J = 3.0 Hz, 1H, ArH8), 6.94–7.00 (m, 2H, ArH2′, ArH6′), 7.20-7.26 (m, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.5 (NCH_2), 52.2 (CHAr′), 55.2 (OMe), 55.7 (OMe), 89.7 (ArC6), 90.2 (ArC8), 104.1 (ArC), 115.0 (ArC3′), 115.2 (ArC5′), 129.9 (ArC2′), 130.0 (ArC6′), 133.6 (ArC1′), 154.7 (ArC), 160.2 (ArC4′), 163.5 (ArC5), 165.3 (ArC7), 190.4 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{17}FNO_3$ $(M+H)^+$ 302.1192. Found 302.1181; Anal. Calcd for $C_{17}H_{16}FNO_3$: C, 67.76; H, 5.35; N, 4.65. Found: C, 67.71; H, 5.54; N, 4.62.

6.4.32. 5,7-Dimethoxy-3-*p*-tolyl-2,3-dihydroquinolin-4(1*H*)-one (13c)

White crystals (0.7 g, 85%). Mp 150–152 °C; UV (MeOH): λ_{max} 218 (ε 30778 cm^{-1} M^{-1}), 244 (27803), 292 (16933), 368 (4118) nm; IR (KBr): ν_{max} 3286, 3000, 2929, 2821, 1629, 1607, 1530, 1439, 1383, 1348, 1261, 1206, 1154, 1106, 1096, 984, 813, 782, 676 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, MeAr′), 3.62–3.68 (m, 3H, H2, H3), 3.71 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.53 (br s, 1H, NH), 5.63 (d, J = 3.0 Hz, 1H, ArH6), 5.74 (d, J = 3.0 Hz, 1H, ArH8), 7.01–7.10 (m, 4H, ArH2′, ArH3′, ArH4′, ArH6′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.5 (MeAr′), 48.0 (CH_2N), 53.0 (CHAr′), 55.6 (OMe), 56.2 (OMe), 90.1 (ArC8), 90.7 (ArC6), 104.2 (ArC), 126.2 (ArC3′), 128.7 (ArC5′), 129.4 (ArC2′, ArC6′), 129.5 (ArC1′, ArC4′), 155.2 (ArC), 165.7 (ArC5, ArC7), 191.4 (C=O); HRMS (ESI) m/z Calcd for $C_{18}H_{20}NO_3$ $(M+H)^+$ 298.1443. Found 298.1434; Anal. Calcd for $C_{18}H_{19}NO_3$. 0.25MeOH: C, 71.78; H, 6.60; N, 4.59. Found: C, 71.88; H, 6.45; N, 4.60.

6.4.33. 5,7-Dimethoxy-3-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (13d)

White crystals (0.6 g, 76.5%). Mp 150–152 °C; UV (MeOH): λ_{max} 203 (ε 26296 cm^{-1} M^{-1}), 221 (28718), 245 (26837), 290 (14900), 358 (4102) nm; IR (KBr): ν_{max} 3269, 2971, 2941, 1600, 1578, 1507, 1437, 1382, 1348, 1206, 1103, 1031, 983, 818, 724, 687 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.59–3.71 (m, 3H, H2, H3), 3.75 (s, 6H, OMe), 3.80 (s, 3H, OMe), 4.75 (br s, 1H, NH), 5.69 (d, J = 3.0 Hz, 1H, ArH6), 5.79 (d, J = 3.0 Hz, 1H, ArH8), 6.81 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.17 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.5 (CH_2N), 52.1 (CHAr′), 55.1 (2 × OMe), 55.7 (OMe), 89.5 (ArC8), 90.2 (ArC6), 104.1 (ArC), 113.5 (ArC3′), 113.7 (ArC5′), 129.3 (ArC2′, ArC6′), 130.0 (ArC1′), 154.8 (ArC), 163.4 (ArC4′), 165.2 (ArC5, ArC7), 191.0 (C=O); HRMS (ESI) m/z Calcd for $C_{18}H_{20}NO_4$ $(M + H)^+$ 314.1392. Found 314.1381; Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.82; H, 6.16; N, 4.50.

6.4.34. 5,7-Dimethoxy-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (13e)

White crystals (0.8 g, 85%). Mp 160–162 °C; UV (MeOH): λ_{max} 203 (ε 37345 cm^{-1} M^{-1}), 244 (31681), 291 (19115), 348 (4070) nm; IR (KBr): ν_{max} 3277, 3056, 2970, 1629, 1607, 1579, 1525, 1436, 1262, 1242, 1152, 1107, 985, 936, 852, 817, 782, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.60–3.70 (m, 3H, H2, H3), 3.72 (s, 3H, OMe), 3.76 (s, 3H, OMe), 4.55 (br s, 1H, NH), 5.64 (d, J = 3.0 Hz, 1H, ArH6), 5.75 (d, J = 3.0 Hz, 1H, ArH8), 7.14–7.22 (m, 5H, Ph); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.2 (CH_2N), 52.3 (CHAr′), 55.4 (OMe), 55.6 (OMe), 88.7 (ArC8), 90.3 (ArC6), 103.2 (ArC), 126.4 (ArC3′), 126.9 (ArC5′), 128.2 (ArC2′), 128.5 (ArC6′), 128.6 (ArC4′), 139.3 (ArC1′), 155.7 (ArC), 163.1 (ArC), 164.9 (ArC), 189.5 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{18}NO_3$ $(M+H)^+$ 284.1287. Found 284.1277; Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.95; H, 6.12; N, 5.00.

6.4.35. 3-(4-Bromophenyl)-5,7-dihydroxy-2,3-dihydroquinolin-4(1*H*)-one (14a)

Yellow solid (0.1 g, 48%). Mp 164–166 °C; UV (MeOH): λ_{max} 203 (ε 34785 cm^{-1} M^{-1}), 244 (25000), 299 (13365) nm; IR (KBr): ν_{max} 3401, 3316, 2920, 2855, 1635, 1590, 1515, 1440, 1379, 1263, 1239, 1157, 1126, 1093, 1040, 858, 817, 807, 757, 720, 656 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62–3.86 (m, 3H, H2, H3), 5.33 (s, 1H, OH), 5.64 (d, J = 2.1 Hz, 1H, ArH6), 5.76 (d, J = 2.1 Hz, 1H, ArH8), 7.18 (d, J = 8.1 Hz, 2H, ArH2′, ArH6′), 7.50 (d, J = 8.4 Hz, 2H, ArH3′, ArH5′), 12.56 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 46.8 (CH_2N), 50.5 (CHAr′), 91.1 (ArC8), 92.2 (ArC6), 101.0 (ArC), 120.5 (ArC4′), 130.4 (ArC3′), 130.7 (ArC5′), 130.9 (ArC2′), 131.3 (ArC6′), 137.6 (ArC1′), 154.7 (ArC), 165.7 (ArC5), 166.0 (ArC7), 196.4 (C=O); HRMS (ESI) m/z Calcd for $C_{15}H_{13}BrNO_3$ $(M+H)^+$ 334.0079. Found 334.0069.

6.4.36. 5,7-dihydroxy-3-(*p*-tolyl)-2,3-dihydroquinolin-4(1*H*)-one (14c)

Yellow solid (0.1 g, 45.5%). Mp 184–186 °C; UV (MeOH): λ_{max} 299 (ε 24899 cm^{-1} M^{-1}), 374 (2288) nm; IR (KBr): ν_{max} 3323, 2919, 1638, 1588, 1514, 1445, 1379, 1348, 1264, 1158, 1127, 1040, 814 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 3H, MeAr′), 3.63–3.81 (m, 3H, H2, H3), 4.61 (br s, 1H, NH), 5.58 (d, J = 3.0 Hz, 1H, ArH6), 5.72 (d, J = 3.0 Hz, 1H, ArH8), 7.15–7.23 (m, 5H, ArH2′, ArH3′, ArH5′, ArH6′, OH), 12.68 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.1 (Me), 47.9 (CH_2N), 51.2 (CHAr′), 91.6 (ArC8), 93.5

(ArC6), 102.0 (ArC), 128.4 (ArC2′), 128.7 (ArC6′), 129.1 (ArC3′), 129.4 (ArC5′), 133.9 (ArC1′), 137.3 (ArC4′), 153.9 (ArC), 164.7 (ArC5), 165.5 (ArC7), 197.4 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{15}NO_3Na$ $(M+Na)^+$ 292.0950. Found 292.0942.

6.4.37. 5,7-Dihydroxy-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one(14e)

Yellow solid (0.1 g, 44.5%). Mp 198–200 °C; UV (MeOH): λ_{max} 205 (ε 43422 cm^{-1} M^{-1}), 225 (35632), 242 (36398), 298 (26947), 368 (6002) nm; IR (KBr): ν_{max} 3415, 3393, 3298, 1633, 1592, 1513, 1263, 1175, 855, 802, 695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.50–3.55 (m, 2H, H2), 3.80 (dd, J = 6.0, 9.0 Hz, 1H, H3), 5.45 (d, J = 3.0 Hz, 1H, ArH6), 5.61 (d, J = 3.0 Hz, 1H, ArH8), 7.07 (br s, 1H, NH), 7.21–7.33 (m, 5H, Ph), 10.23 (s, 1H, OH), 12.64 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 46.6 (CH_2N), 50.5 (CHAr′), 91.1 (ArC), 92.0 (ArC), 100.7 (ArC), 127.3 (ArC4′), 128.7 (ArC3′, ArC5′), 128.9 (ArC2′, ArC6′), 138.4 (ArC1′), 155.0 (ArC), 165.0 (ArC5), 166.4 (ArC7), 197.0 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{15}H_{14}NO_3$ $(M+H)^+$ 256.0974. Found 256.0964.

6.4.38. 3-(4-Bromophenyl)-5-hydroxy-7-methoxyquinolin-4(1*H*)-one (15a)

Yellow solid (0.15 g, 89.5%). Mp > 300 °C; UV (1% CF_3COOH/MeOH): λ_{max} 202 (ε 37593 cm^{-1} M^{-1}), 233 (38445), 269 (52183), 319 (14376) nm; IR (KBr): ν_{max} 3479, 3211, 3111, 2924, 1643, 1587, 1562, 1200, 1157, 1075, 1062, 718, 704, 692 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.82 (s, 3H, OMe), 6.21 (d, J = 1.9 Hz, 1H, ArH6), 6.45 (d, J = 1.9 Hz, 1H, ArH8), 7.58 (d, J = 8.7 Hz, 2H, ArH2′, ArH6′), 7.80 (d, J = 8.3 Hz, 2H, ArH3′, ArH5′), 8.19 (s, 1H, H2), 14.78 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.8 (OMe), 90.2 (ArC6), 97.0 (ArC8), 108.6 (ArC), 117.1 (ArC), 120.1 (Ar′C4), 130.8 (ArC2′, ArC6′), 131.2 (ArC3′, ArC5′), 134.2 (ArC2), 139.7 (ArC1′), 141.8 (ArC), 163.3 (ArC5), 164.0 (ArC7), 179.1 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{13}BrNO_3$ $(M+H)^+$ 346.0079. Found 346.0067.

6.4.39. 3-(4-Fluorophenyl)-5-hydroxy-7-methoxyquinolin-4(1*H*)-one (15b)

Yellow solid (0.15 g, 86%). Mp 240–242 °C; UV (MeOH): λ_{max} 201 (ε 27213 cm^{-1} M^{-1}), 264 (53891), 316 (13012) nm; IR (KBr): ν_{max} 3209, 3092, 2960, 1661, 1554, 1512, 1447, 1271, 1202, 1165, 1087, 1068, 795, 780, 718, 657 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, OMe), 6.25 (d, J = 2.3 Hz, 1H, ArH6), 6.50 (d, J = 2.3 Hz, ArH8), 7.28 (m, 2H, ArH3′, ArH5′), 7.77 (m, 2H, ArH2′, ArH6′), 8.21 (s, 1H, H2), 12.37 (br s, 1H, NH), 14.90 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.8 (OMe), 90.1 (ArC6), 96.9 (ArC8), 108.7 (ArC), 115.0 (ArC3′), 115.2 (ArC5′), 117.5 (ArC), 130.7 (ArC2′, ArC6′), 130.8 (ArC), 139.6 (ArC2), 141.9 (ArC1′), 163.3 (ArC5, ArC4′), 163.9 (ArC7), 179.3 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{13}FNO_3$ $(M+H)^+$ 286.0879. Found 286.0870.

6.4.40. 5-Hydroxy-7-methoxy-3-(*p*-tolyl)quinolin-4(1*H*)-one (15c)

Yellow solid (0.8 g, 86%). Mp > 300 °C; UV (1% CF_3COOH/MeOH): λ_{max} 266 (ε 86250 cm^{-1} M^{-1}), 316 (13125) nm; IR (KBr): ν_{max} 3444, 2919, 1660, 1552, 1446, 1291, 1197, 1158, 1071, 1028, 774, 701, 658 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.35 (s, 3H, MeAr′), 3.84 (s, 3H, OMe), 6.21 (d, J = 3.0 Hz, 1H, ArH6), 6.46 (d, J = 3.0 Hz, 1H, ArH8), 7.22 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 7.59 (d, J = 9.0 Hz, 2H, Ar′H2, ArH6′), 8.12 (s, 1H, H2), 12.27 (br s, 1H, NH), 14.99 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-*d6*): δ 21.1 (MeAr′), 55.7 (OMe), 90.0 (ArC6), 96.8 (ArC8), 108.7 (ArC), 118.5 (ArC), 128.7 (ArC3′, ArC5′), 128.9 (ArC2′, ArC6′), 132.0 (ArC1′), 136.2 (ArC2), 139.2 (ArC4′), 141.8 (ArC), 163.4 (ArC5), 163.8 (ArC7), 179.4 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{17}H_{16}NO_3$ $(M+H)^+$ 282.1130. Found 282.1122.

6.4.41. 5-Hydroxy-7-methoxy-3-(4-methoxyphenyl)quinolin-4(1*H*)-one (15d)

Yellow solid (0.75 g, 81.5%). Mp 232–234 °C[19], 236–237 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 3.78 (s, 3H, OMe), 3.81 (s, 3H, OMe), 6.18 (d, J = 2.2 Hz, 1H, ArH6), 6.42 (d, J = 2.2 Hz, 1H, ArH8), 6.96 (d, J = 8.7 Hz, 2H, ArH2′, ArH6′), 7.61 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 8.07 (s, 1H, H2), 12.23 (s, 1H, NH), 14.98 (s, 1H, OH).

6.4.42. 5-Hydroxy-7-methoxy-3-phenylquinolin-4(1*H*)-one (15e)

Yellow solid (0.8 g, 84%). Mp 240–242 °C; UV (1% CF_3COOH/MeOH): λ_{max} 203 (ε 44866 cm^{-1} M^{-1}), 230 (38877), 265 (54973), 316 (13743) nm; IR (KBr): ν_{max} 3261, 3163, 3113, 2948, 2919, 2849, 1655, 1558, 1443, 1271, 1202, 1160, 1072, 1032, 795, 702 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.88 (s, 3H, OMe), 6.26 (d, J = 2.1 Hz, 1H, ArH6), 6.50 (d, J = 2.4 Hz, 1H, ArH8), 7.36–7.49 (m, 3H, Ph), 7.72–7.75 (m, 2H, Ph), 8.20 (s, 1H, H2), 12.33 (br s, 1H, NH), 14.88 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.9 (OMe), 90.2 (ArC6), 96.9 (ArC8), 111.9 (ArC), 118.6 (ArC3), 127.1 (ArC4′), 128.4 (ArC2′, ArC6′), 129.0 (ArC3′, ArC5′), 135.2 (ArC2), 139.8 (ArC1′), 142.0 (ArC), 163.5 (ArC5), 164.0 (ArC7), 179.4 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{14}NO_3$ $(M+H)^+$ 268.0974. Found 268.0965.

6.4.43. 3-(3-Bromophenyl)-5-hydroxy-7-methoxyquinolin-4(1*H*)-one (15f)

Yellow solid (0.2 g, 79.5%). Mp 254–256 °C; UV (1% CF_3COOH/MeOH): λ_{max} 202 (ε 59302 cm^{-1} M^{-1}), 234 (54534), 269 (65697), 320 (20581) nm; IR (KBr): ν_{max} 3457, 3211, 3092, 2963, 1656, 1555, 1439, 1281, 1200, 1162, 1062, 1027, 774, 713, 686 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.87 (s, 3H, OMe), 6.28 (d, J = 2.3 Hz, 1H, ArH6), 6.51 (d, J = 2.3 Hz, 1H, ArH8), 7.42 (t, J = 7.5 Hz, 1H, ArH6′), 7.53 (m, 1H, ArH5′), 7.74 (m, 1H, ArH4′), 8.00 (t, J = 1.9 Hz, 1H, ArH2′), 8.28 (s, 1H, H2), 14.80 (s, 1H, OH); ^{13}C NMR (75.6 MHz, DMSO-d_6): δ 55.8 (OMe), 90.4 (ArC6), 97.1 (ArC8), 108.6 (ArC), 116.7 (ArC), 121.6 (ArC3′) 127.6 (ArC6′), 129.7 (ArC5′), 130.5 (ArC2′), 131.2 (ArC4′), 137.5 (ArC1′), 140.2 (ArC2), 141.9 (ArC), 163.3 (ArC5), 164.0 (ArC7), 179.1 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{13}BrNO_3$ $(M+H)^+$ 346.0079. Found 346.0073.

6.4.44. 3-(4-Bromophenyl)-5-hydroxy-7-methoxy-2,3-dihydroquinolin-4(1*H*)-one (16a)

Yellow solid (0.2 g, 73.5%). Mp 142–144 °C; UV (MeOH): λ_{max} 203 (ε 29213 cm^{-1} M^{-1}), 225 (27959), 242 (27437), 297 (17131), 368 (3690) nm; IR (KBr): ν_{max} 3360, 2838, 1633, 1568, 1511, 1487, 1370, 1347, 1291, 1208, 1190, 1096, 1011, 821, 795, 755, 663 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.62–3.73 (m, 2H, CH_2N), 3.78 (s, 3H, OMe), 3.80 (dd, J = 3.0 Hz, 9.0 Hz, 1H, CHAr′), 4.59 (br s, 1H, NH), 5.65 (d, J = 3.0 Hz, 1H, ArH6), 5.84 (d, J = 3.0 Hz, 1H, ArH8), 7.14 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.46 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 12.51 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.6 (CH_2N), 51.0 (CHAr′), 55.3 (OMe), 90.4 (ArC8), 91.8 (ArC6), 102.0 (ArC), 121.5 (ArC4′), 130.2 (ArC2′, ArC6′), 131.8 (ArC3′, ArC5′), 135.9 (ArC4′), 153.2 (ArC), 165.5 (ArC5), 167.7 (ArC7), 196.3 (C=O); HRMS (ESI) *m*/*z* Calcd for $C_{16}H_{14}BrNO_3Na$ $(M+Na)^+$ 370.0055. Found 370.0043.

6.4.45. 5-Hydroxy-7-methoxy-3-(*p*-tolyl)-2,3-dihydroquinolin-4(1*H*)-one (16c)

Yellow solid (0.2 g, 68%). Mp 134–136 °C; UV (MeOH): λ_{max} 297 (ε 14979 cm^{-1} M^{-1}) nm; IR (KBr): ν_{max} 3348, 2975, 2925, 2838, 1638, 1567, 1514, 1377, 1348, 1290, 1156, 1094, 1030, 852, 817, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, MeAr′), 3.59–3.64 (m, 2H, H2), 3.72 (s, 3H, OMe), 3.74 (dd, J = 6.0, 9.0 Hz, 1H, H3), 4.47 (br s, 1H, NH), 5.57 (d, J = 3.0 Hz, 1H, ArH6), 5.76 (d, J = 3.0 Hz, 1H, ArH8), 7.08 (s, 4H, ArH2′, ArH3′, ArH5′, ArH6′)

12.56 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 21.1 (Me), 48.0 (CH_2N), 51.3 (CHAr′), 55.4 (OMe), 90.4 (ArC8), 91.7 (ArC6), 102.3 (ArC), 128.4 (ArC2′, ArC6′), 129.4 (ArC3′), 129.5 (ArC5′), 133.9 (ArC1′), 137.3 (ArC4′), 153.3 (ArC), 165.6 (ArC), 167.5 (ArC), 197.4 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{17}NO_3Na$ $(M+Na)^+$ 306.1106. Found 306.1098.

6.4.46. 5-Hydroxy-7-methoxy-3-(4-methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (16d)

Yellow solid (0.2 g, 78%). Mp 144–146 °C; UV (MeOH): λ_{max} 201 (ε 30988 cm^{-1} M^{-1}), 225 (31736), 296 (18113), 368 (2994) nm; IR (KBr): ν_{max} 3370, 2978, 2938, 2842, 1640, 1597, 1511, 1380, 1236, 1157, 1017, 816, 796, 755, 655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64–3.70 (m, 2H, H2), 3.78 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.80 (dd, J = 6.0, 9.0 Hz, 1H, H3), 4.56 (br s, 1H, NH), 5.64 (d, J = 3.0 Hz, 1H, ArH6), 5.83 (d, J = 3.0 Hz, 1H, ArH8), 6.89 (d, J = 9.0 Hz, 2H, ArH2′, ArH6′), 7.19 (d, J = 9.0 Hz, 2H, ArH3′, ArH5′), 12.63 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.9 (CH_2N), 50.8 (CHAr′), 55.2 (OMe), 55.3 (OMe), 90.3 (ArC8), 91.6 (ArC6), 102.1 (ArC), 114.1 (ArC3′, ArC5′), 128.9 (ArC2′, ArC6′), 129.4 (ArC1′), 153.2 (ArC), 158.9 (ArC4′), 165.5 (ArC5), 167.5 (ArC7), 197.4 (C=O); HRMS (ESI) m/z Calcd for $C_{17}H_{17}NO_4Na$ $(M+Na)^+$ 300.1055. Found 300.1043.

6.4.47. 5-Hydroxy-7-methoxy-3-phenyl-2,3-dihydroquinolin-4(1*H*)-one (16e)

Yellow solid (0.2 g, 80.5%). Mp 146–148 °C; UV (MeOH): λ_{max} 205 (ε 28744 cm^{-1} M^{-1}), 243 (28879), 297 (18074), 368 (3668) nm; IR (KBr): ν_{max} 3312, 2977, 2870, 1638, 1568, 1531, 1386, 1267, 1193, 1231, 1136, 806, 756, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67–3.73 (m, 2H, H2), 3.79 (s, 3H, OMe), 3.85 (dd, J = 3.0, 9.0 Hz, 1H, H3), 4.57 (br s, 1H, NH), 5.65 (d, J = 3.0 Hz, 1H, ArH6), 5.84 (d, J = 3.0 Hz, 1H, ArH8), 7.25–7.35 (m, 5H, Ph), 12.61 (s, 1H, OH); ^{13}C NMR (75.6 MHz, $CDCl_3$): δ 47.8 (CH_2N), 51.6 (CHAr′), 55.3 (OMe), 90.3 (ArC8), 91.7 (ArC6), 102.2 (ArC), 127.5 (ArC3′, ArC5′), 128.4 (ArC2′, ArC6′), 128.6 (ArC1′, ArC4′), 153.2 (ArC), 165.4 (ArC5), 167.5 (ArC7), 197.5 (C=O); HRMS (ESI) m/z Calcd for $C_{16}H_{15}NO_3Na$ $(M+Na)^+$ 292.0950. Found 292.0942.

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