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Synthesis of 5-substituted 2-(4- or 3-methoxyphenyl)-4(1*H*)-quinolones

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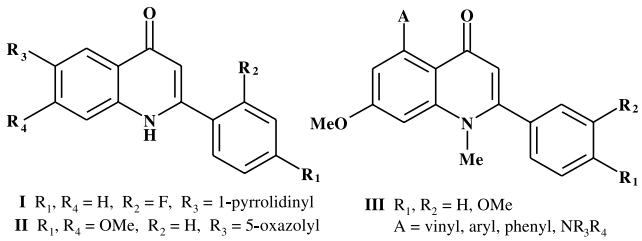
Abstract—5-Substituted 7-methoxy-2-(4- or 3-methoxyphenyl)-4(1*H*)-quinolones **8**–**17** have been synthesised in good yields from the corresponding 7-methoxy-2-(4- or 3-methoxyphenyl)-5-trifluoromethanesulfonate-4(1*H*)-quinolones **7** via palladium-mediated cross-coupling reactions or aromatic nucleophilic substitution (SN_{Ar}) reactions.

1. Introduction

Substituted 2-phenyl-4-quinolones displayed potent antitumor activity with effects similar to those observed with the antimitotic natural products colchicine, podophyllotoxin and combretastatin A-4.[1] Most notably, 2-(2-fluorophenyl)-6-(1-pyrrolidinyl)-4(1*H*)-quinolone **I** (Fig. 1) is a highly effective inhibitor of tubulin polymerisation (IC_{50}= 0.46 μM) and inhibits the growth of tumor cell lines at low concentrations.[2] Three-dimensional structure-activity relationship studies were also performed to predict novel inhibitors of tubulin polymerisation.[3] 2-Phenyl-4-quinolones were also described as topoisomerase inhibitors,[4] antiplatelet agents[5] or inosine 5′-monophosphate dehydrogenase type II inhibitors (IMPDH) such as 7-methoxy-2-(4-methoxyphenyl)-6-(5-oxazolyl)-4(1*H*)-quinolone **II**.[6] To our knowledge, no example of 5-C_{sp2}- or *N*-substituted 2-phenyl-4(1*H*)-quinolones has been mentioned in the literature.



I R_1, R_4 = H, R_2 = F, R_3 = 1-pyrrolidinyl
II R_1, R_4 = OMe, R_2 = H, R_3 = 5-oxazolyl

III R_1, R_2 = H, OMe
A = vinyl, aryl, phenyl, NR_3R_4

Figure 1.

In a previous patent,[7] we reported the syntheses of 5-substituted 3-(4-methoxyphenyl)-4(1*H*)-quinolones via either palladium-catalysed reactions or aromatic nucleophilic substitution reactions. According to the same approach, we have developed the syntheses of series of new 7-methoxy-2-phenyl-4(1*H*)-quinolones **III**.

2. Results and discussion

These syntheses, first, require the preparation of 5,7-dimethoxy-2-(4- or 3-methoxyphenyl)-4(1*H*)-quinolones **4**. Following the methodology described in the literature,[8] the 4-quinolone nucleus was obtained in two steps. A mixture of 3,5-dimethoxyaniline **1** and ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate **2a**[9] or ethyl 3-(3-methoxyphenyl)-3-oxo-propanoate **2b**[9] in ethanol was heated under reflux for 25 h in the presence of *p*-toluenesulfonic acid (*p*-TsOH) to give the enamino esters **3** in fair yields.[10] The synthesis of 4-quinolones **4** were achieved by simply heating **3** in xylene at 250°C in a sealed tube for 8 h. It should be noted that the increasing of the reaction time led directly to the 5-hydroxy derivative **5**. As described in Ref. 7, the methyl ether in 5-position was selectively cleaved in the presence of HBr 48% to afford **5** in 85–90% yield (Scheme 1).

Methylation of **5** with iodomethane in basic medium (K_2CO_3) in DMF at room temperature afforded **6** in good yield. Contrary to classical 2-phenyl-4-quinolone alkylation

Keywords: quinolones; Stille reaction; Suzuki reaction; SN_{Ar}; aminations.
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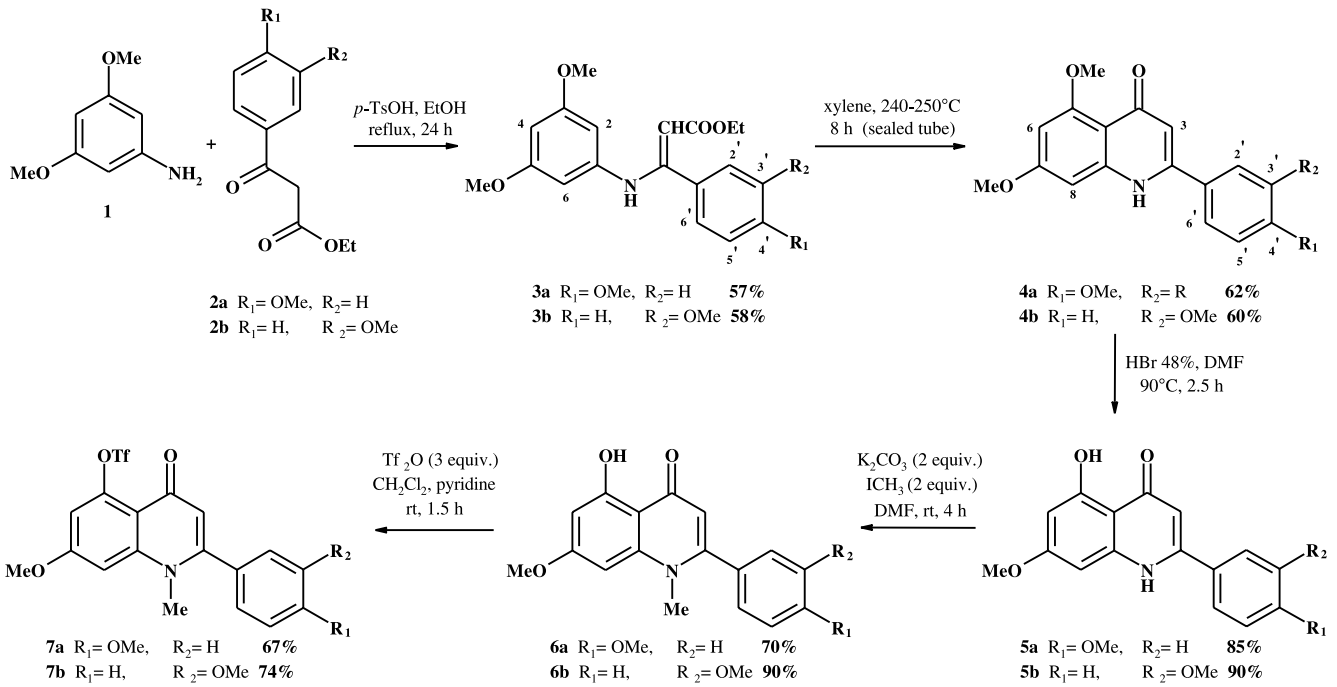
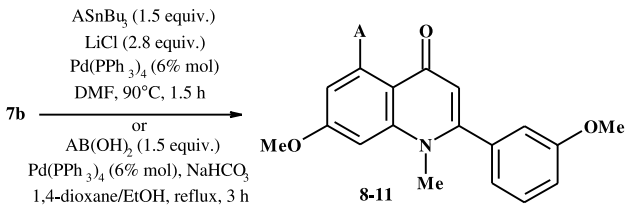


Scheme 1.

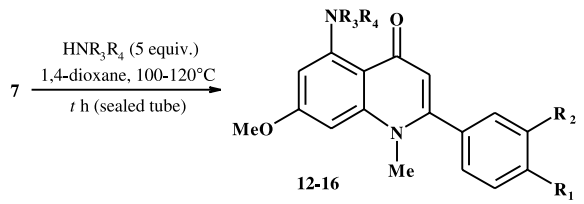
reaction in DMF,[1a,2,5,11] *N*-methyl compounds **6** were found the major products (*N*-methyl/*O*-methyl ratio: 9:1). The 4-quinolone structure was established from ^{13}C NMR chemical shift of methyl group and ^{1}H NMR chemical shift of proton in 3-position. Finally, triflates **7** were obtained by treatment of **6** with trifluoromethanesulfonic anhydride (3 equiv.) in the presence of pyridine in dichloromethane (Scheme 1).



Scheme 2.

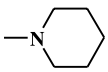
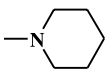
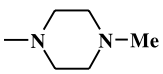
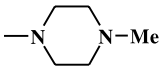
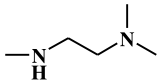
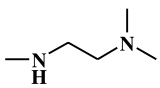
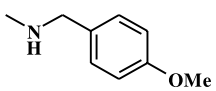
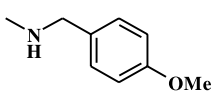
Table 1.

Compound	A	Yield (%)
8	CH_2=CH–	90
9		76
10		84
11		86



Scheme 3.

Table 2.

Compound	R_1	R_2	NR_3R_4	Yield (%)
12b	H	OMe		83
13a	OMe	H		82
13b	H	OMe		84
14a	OMe	H		90
14b	H	OMe		89
15a	OMe	H		79
15b	H	OMe		79
16a	OMe	H		82
16b	H	OMe		80

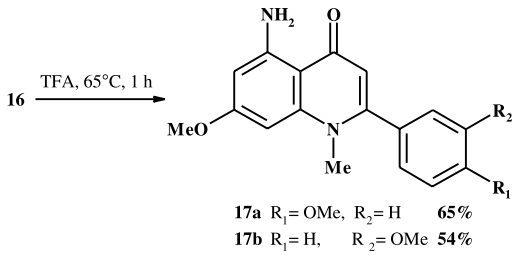
2.1. Palladium-mediated cross-coupling reactions

First family of compounds was obtained through Stille[12] or Suzuki reactions[13] on triflate **7b**. The latter were performed in classical conditions with freshly prepared tetrakis-(triphenylphosphine)palladium (6% mol) to led to the desired derivatives **8**–**11** (Scheme 2, Table 1). Coupling reaction between **7b** and commercially available vinyl-tributyltin (1.5 equiv.) afforded derivative **8** in good yield. 2-Thiophenyl, phenyl and 2-furanyl compounds **9**–**11** were prepared by reaction of **7b** with the corresponding boronic acids (1.5 equiv.) (Table 1).

2.2. Aromatic nucleophilic substitution

Similarly, amination reaction of **7a**–**b** with various amines was carried out in a sealed tube to afford **12**–**16** (Scheme 3). Optimal condition reactions were obtained with 5 equiv. of amine in 1,4-dioxane for *t* h depending of the amine used (see Section 3). The solution was heated in a range of 100–120°C. Thus, several amines such as pyrrolidine, piperidine, *N*-methylpiperazine, *N*,*N*-dimethylaminoethyl-amine and 4-methoxybenzylamine were introduced at the 5-position in good yields (Table 2).

Finally, the cleavage of the nitrogen-protecting group was performed on **16a**–**b** in the presence of trifluoroacetic acid at 65°C for 1 h to afford **17a**–**b** in fair yield (Scheme 4).



Scheme 4.

To conclude, we have described versatile syntheses of 5-substituted 2-(4-or 3-methoxyphenyl)-4-quinolones **8**–**17** from triflates **7** through palladium-mediated cross-coupling reactions or aromatic nucleophilic substitution (SN_{Ar}) reactions.

3. Experimental

3.1. General experimental procedures

Melting points were determined using a Büchi capillary instrument and are uncorrected. The infrared spectra of compounds were recorded on a Perkin–Elmer FTIR paragon 1000 spectrometer. NMR spectra were recorded at 300 K in $CDCl_3$ on a Bruker Avance DPX 250. Chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS). Mass spectra were recorded on Perkin–Elmer SCIEX API 300 using ionspray methodology. Thin-layer chromatography (TLC) was run on precoated silica gel plates (Merck $60F_{254}$) and the spots visualised using an ultraviolet lamp. Flash chromatography was carried out on column using flash silica gel 60 Merck (40–63 μm) using the indicated solvents (petroleum ether: boiling range 40–60°C). All reactions requiring anhydrous conditions were conducted in flame-dried apparatus. Stannane and boronic acids were purchased from Lancaster or Sigma-Aldrich.

3.1.1. Ethyl 3-(3,5-dimethoxyanilino)-3-(4-methoxyphenyl)-2-propenoate (3a). A mixture of 3,5-dimethoxyaniline **1** (2.07 g, 13.51 mmol), ethyl 3-(4-methoxyphenyl)-3-oxo-propanoate **2a** (1.00 g, 4.48 mmol) and *p*-toluenesulfonic acid (200 mg) in anhydrous ethanol (20 mL) was heated at reflux for 24 h. After cooling, the solvent was evaporated. The residue was diluted with dichloromethane, the organic phase was washed with water, then dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (eluent toluene) to give **3a** (916 mg, 57%) as an oil; IR (film) ν 3356 (NH), 1638 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7.0 Hz, CH_3), 3.56 (s, 6H, OCH_3), 3.79 (s, 3H, OCH_3), 4.20 (q, 2H, J=7.0 Hz, CH_2), 4.96 (s, 1H, =CH), 5.84 (d, 2H, J=2.0 Hz, H-2, H-6), 6.04 (t, 1H, J=2.0 Hz, H-4), 6.82 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.31 (d, 2H, J=8.8 Hz, H-2′, H-6′), 10.20 (broad s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.5 (CH_3), 55.1 ($2CH_3$), 55.3 (CH_3), 59.3 (CH_2), 91.0 (CH), 95.5 (CH), 100.3 (2CH), 113.8 (2CH), 128.4 (C), 129.5 (2CH), 142.4 (C), 158.6 (C), 160.6 (2C), 170.1 (CO). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.99; H, 6.65; N, 4.10; MS m/z 358 $(M+1)^+$.

3.1.2. Ethyl 3-(3,5-dimethoxyanilino)-3-(3-methoxyphenyl)-2-propenoate (3b). The same procedure applied to **2b** gave **3b** in 58% yield. Oil; IR (film) ν 3267 (NH), 1659 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.32 (t, 3H, J=7.0 Hz, CH_3), 3.56 (s, 6H, OCH_3), 3.72 (s, 3H, OCH_3), 4.21 (q, 2H, J=7.0 Hz, CH_2), 5.00 (s, 1H, =CH), 5.83 (d, 2H, J=2.1 Hz, H-2, H-6), 6.04 (t, 1H, J=2.1 Hz, H-4), 6.92 (m, 3H, H-2′, H-4′, H-6′), 7.19 (m, 1H, H-5′), 10.24 (broad s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 14.7 (CH_3), 55.3 ($2CH_3$), 55.5 (CH_3), 59.5 (CH_2), 91.6 (CH), 95.9 (CH), 100.3 (2CH), 113.4 (CH), 115.6 (CH), 120.7 (CH), 128.4 (CH), 129.7 (C), 137.7 (C), 142.2 (C), 158.6 (C), 160.8 (2C), 170.1 (CO). Anal. calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.55; H, 6.57; N, 3.77; MS m/z 358 $(M+1)^+$.

3.1.3. 5,7-Dimethoxy-2-(4-methoxyphenyl)-1,4-dihydro-4-quinolinone (4a). A mixture of **3a** (300 mg, 0.84 mmol) in xylene (8 mL) in a high-pressure reactor was heated at 240–250°C for 8 h. During the cooling, the final product **4a** precipitates in the medium. Filtration afforded 112 mg of desired compound **4a** as white solid. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (eluent CH_2Cl_2/MeOH 98:2) to give 50 mg (62% overall yield) of **4a**. Mp 225–226°C (xylene); IR (KBr) ν 3275 (NH), 1638 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.61 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 6.17 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.42 (s, 1H, H-3), 6.76 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.11 (d, 1H, J=2.0 Hz, H-6 or H-8), 7.77 (d, 2H, J=8.8 Hz, H-2′, H-6′), 11.70 (broad s, 1H, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 55.2 (OCH_3), 55.3 (OCH_3), 55.4 (OCH_3), 93.2 (CH), 95.3 (CH), 108.1 (CH), 110.3 (C), 114.1 (2CH), 126.3 (C), 128.7

(2CH), 146.0 (C), 149.9 (C), 160.2 (C), 161.1 (C), 162.5 (C), 177.4 (CO). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.13; H, 5.40; N, 4.25; MS *m/z* 312 $(M+1)^+$.

3.1.4. 5,7-Dimethoxy-2-(3-methoxyphenyl)-1,4-dihydro-4-quinolinone (4b). The same procedure was carried out with **3b** to afford **4b** in 60% yield. Mp 221–222°C (MeOH); IR (KBr) ν 3277 (NH), 1637 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.12 (s, 1H, H-3), 6.33 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.81 (d, 1H, J=2.0 Hz, H-6 or H-8), 7.10 (broad d, 1H, J=7.8 Hz, H-4′), 7.33–7.35 (m, 2H, H-2′, H-6′), 7.45 (t, 1H, J=7.8 Hz, H-5′), 11.12 (broad s, 1H, NH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 55.3 (OCH_3), 55.4 (OCH_3), 55.6 (OCH_3), 92.0 (CH), 94.5 (CH), 109.4 (CH), 110.5 (C), 112.3 (CH), 115.9 (CH), 119.2 (CH), 130.1 (CH), 135.1 (C), 144.7 (C), 147.1 (C), 159.5 (C), 160.8 (C), 162.0 (C), 176.5 (CO). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.77; H, 5.65; N, 4.61; MS *m/z* 312 $(M+1)^+$.

3.1.5. 5-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-1,4-dihydro-4-quinolinone (5a). Compound **4a** (360 mg, 1.15 mmol), HBr 48% in water (0.50 mL) in DMF (10 mL) was stirred at 90°C for 2.5 h. After cooling, the solution was poured on ice. The precipitate was filtered and washed with water. The solid obtained was dried over P_2O_5 in vacuo to give **5a** (292 mg, 85%). Mp>270°C (EtOAc/petroleum ether); IR (KBr) ν 3307 (OH), 3260 (NH), 1657 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.17 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.27 (s, 1H, H-3), 6.66 (d, 1H, J=2.0 Hz, H-6 or H-8), 7.13 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.82 (d, 2H, J=8.8 Hz, H-2′, H-6′), 11.80 (broad s, 1H, NH), 14.77 (sharp s, 1H, OH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 55.4 (OCH_3), 55.5 (OCH_3), 90.4 (CH), 96.3 (CH), 104.4 (CH), 107.3 (C), 114.4 (2CH), 125.4 (C), 129.0 (2CH), 142.5 (C), 150.7 (C), 161.3 (C), 162.3 (C), 163.5 (C), 181.1 (CO). Anal. calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.95; H, 5.25; N, 4.62; MS *m/z* 298 $(M+1)^+$.

3.1.6. 5-Hydroxy-7-methoxy-2-(3-methoxyphenyl)-1,4-dihydro-4-quinolinone (5b). Following the procedure used for the preparation of **5a**, compound **5b** was obtained from **4b** in 90% yield. Mp 245–246°C (MeOH); IR (KBr) ν 3373 (OH), 3271 (NH), 1635 (CO) cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.19 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.34 (s, 1H, H-3), 6.68 (d, 1H, J=2.0 Hz, H-6 or H-8), 7.10 (broad d, 1H, J=7.9 Hz, H-4′), 7.37 (broad s, 1H, H-2′), 7.38 (d, 1H, J=7.9 Hz, H-6′), 7.50 (t, 1H, J=7.9 Hz, H-5′), 11.88 (broad s, 1H, NH), 14.67 (sharp s, 1H, OH); ^{13}C NMR (62.90 MHz, DMSO-d_6) δ 55.4 (OCH_3), 55.5 (OCH_3), 90.5 (CH), 96.5 (CH), 105.4 (CH), 107.5 (C), 112.8 (CH), 116.5 (CH), 119.6 (CH), 130.2 (CH), 134.8 (C), 142.5 (C), 150.8 (C), 159.5 (C), 162.3 (C), 163.6 (C), 181.3 (CO). Anal. calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.43; H, 4.88; N, 4.89; MS *m/z* 298 $(M+1)^+$.

3.1.7. 5-Hydroxy-7-methoxy-2-(4-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (6a). To a solution of **5a** (310 mg, 1.04 mmol) in DMF (10 mL) was added K_2CO_3 (288 mg, 2.08 mmol) then iodomethane (0.13 mL, 2.09 mmol). The final mixture was stirred at room temperature for 4 h. After evaporation of solvent, the residue was diluted with CH_2Cl_2, the organic phase was washed with water, then dried over $MgSO_4$, and concentrated in vacuo. The solid obtained was recrystallised from methanol to afford **6a** (227 mg, 70%). Mp 176–177°C (MeOH); IR (KBr) ν 1642 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.51 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.10 (s, 1H, H-3), 6.29 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.39 (d, 1H, J=2.0 Hz, H-6 or H-8), 7.01 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.32 (d, 2H, J=8.8 Hz, H-2′, H-6′), 15.02 (sharp s, 1H, OH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.0 (NCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 90.6 (CH), 96.3 (CH), 108.9 (C), 110.6 (CH), 114.4 (2CH), 127.8 (C), 130.1 (2CH), 144.1 (C), 155.3 (C), 160.8 (C), 164.5 (C), 164.7 (C), 180.9 (CO). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.27; H, 5.67; N, 4.47; MS *m/z* 312 $(M+1)^+$.

3.1.8. 5-Hydroxy-7-methoxy-2-(3-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (6b). The same procedure afforded **6b** in 90% yield. Mp 210–211°C (MeOH); IR (KBr) ν 1654 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.48 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.10 (s, 1H, H-3), 6.31 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.41 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.91 (d, 1H, J=1.8 Hz, H-2′), 6.95 (d, 1H, J=7.7 Hz, H-6′), 7.04 (dd, 1H, J=1.8, 7.7 Hz, H-4′), 7.41 (t, 1H, J=7.7 Hz, H-5′), 15.02 (sharp s, 1H, OH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 37.9 (NCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 90.7 (CH), 96.4 (CH), 109.0 (C), 110.4 (CH), 114.3 (CH), 115.4 (CH), 120.8 (CH), 130.2 (CH), 136.8 (C), 144.1 (C), 155.1 (C), 159.9 (C), 164.7 (C), 164.8 (C), 181.0 (CO). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.77; H, 5.55; N, 4.36; MS *m/z* 312 $(M+1)^+$.

3.1.9. 7-Methoxy-2-(4-methoxyphenyl)-1-methyl-5-trifluoromethanesufonate-1,4-dihydro-4-quinolinone (7a). To a solution of compound **6a** (590 mg, 1.90 mmol) and pyridine (0.46 mL, 5.64 mmol) in anhydrous dichloromethane (15 mL) at 0°C, was added a solution of trifluoromethanesulfonic anhydride (0.95 mL, 5.62 mmol) in anhydrous dichloromethane (5 mL). The mixture was stirred for 2 h at room temperature, then water was added and the mixture was extracted. The organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography (eluent CH_2Cl_2/MeOH 98:2) to afford **7a** (563 mg, 67%). Mp 183–185°C (MeOH); IR (KBr) ν 1619 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.76 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.13 (s, 1H, H-3), 6.71 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.88 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.99 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.30 (d, 2H, J=8.8 Hz, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.4 (NCH_3), 55.6 (OCH_3), 56.1 (OCH_3), 99.7 (CH), 106.2 (CH), 114.4 (2CH+C), 114.5 (CH), 118.9 (q, J=321 Hz, CF_3), 127.6 (C), 130.1 (2CH), 145.4 (C), 149.6 (C), 154.2 (C), 160.8 (C), 161.8 (C), 175.5. (CO). Anal. calcd for $C_{19}H_{16}F_3NO_6S$: C, 51.47; H, 3.64; N, 3.16. Found: C, 51.11; H, 3.54; N, 3.10; MS *m/z* 444 $(M+1)^+$.

3.1.10. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-trifluoromethanesufonate-1,4-dihydro-4-quinolinone (7b). Following the procedure used for the preparation of **7a**, compound **7b** was obtained from **6b** in 74% yield. Mp 153–154°C (MeOH); IR (KBr) ν 3070 (OH), 1621 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.54 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.13 (s, 1H, H-3), 6.70 (d, 1H, J=1.8 Hz, H-6 or H-8), 6.90 (d, 1H, J=1.8 Hz, H-6 or H-8), 6.92–7.06 (m, 3H, H-2′, H-4′, H-6′), 7.39 (t, 1H, J=7.9 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.3 (NCH_3), 55.5 (OCH_3), 56.1 (OCH_3), 99.5 (CH), 106.4 (CH), 114.0 (CH), 114.2 (CH+C), 115.4 (CH), 119.0 (q, J= 321 Hz, CF_3), 120.7 (CH), 130.1 (CH), 136.4 (C), 145.2 (C), 149.4 (C), 154.0 (C), 159.8 (C), 161.8 (C), 175.4 (CO). Anal. calcd for $C_{19}H_{16}F_3NO_6S$: C, 51.47; H, 3.64; N, 3.16. Found: C, 51.77; H, 3.81; N, 2.97; MS m/z 444 $(M+1)^+$.

3.1.11. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-vinyl-1,4-dihydro-4-quinolinone (8). To a suspension of freshly prepared tetrakis(triphenylphosphine)palladium (16 mg, 0.01 mmol) and LiCl (28 mg, 0.70 mmol) in anhydrous DMF (2 mL) was added a solution of **7b** (104 mg, 0.23 mmol) and tributylvinyltin (0.1 mL, 0.34 mmol) in anhydrous DMF under argon. The final solution was stirred at 90°C for 1.5 h. The solvent was then removed in vacuo and the crude residue was purified by column chromatography (eluent CH_2Cl_2) to give **8** (68 mg, 90%) as a solid. Mp 176–177°C (EtOAc); IR (KBr) ν 1611 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.52 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.35 (dd, 1H, J=1.8, 10.8 Hz, CH_2=), 5.52 (dd, 1H, J=1.8, 17.3 Hz, CH_2=), 6.18 (s, 1H, H-3), 6.82 (d, 1H, J=2.2 Hz, H-6 or H-8), 6.92–7.03 (m, 4H, H-6 or H-8, H-2′, H-4′, H-6′), 7.39 (t, 1H, J=7.9 Hz, H-5′), 8.21 (dd, 1H, J=10.8, 17.3 Hz, =CH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.2 (NCH_3), 55.6 (OCH_3), 55.7 (OCH_3), 99.1 (CH), 111.0 (CH), 114.1 (CH), 114.3 (CH), 115.1 (CH), 115.2 (CH_2), 118.9 (CH), 121.0 (CH), 130.0 (CH), 137.2 (C), 139.4 (C), 143.8 (C), 145.2 (C), 153.1 (C), 159.8 (C), 161.8 (C), 179.1 (CO). Anal. calcd for $C_{20}H_{19}N_3O$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.90; H, 6.18; N, 4.56; MS m/z 322 $(M+1)^+$.

3.2. General procedure for Suzuki reaction

To a stirred solution of **7b** (100 mg, 0.22 mmol) in anhydrous 1,4-dioxane (5 mL) was added freshly prepared tetrakis(triphenylphosphine)palladium (15 mg, 0.01 mmol). The solution was stirred for 30 min at room temperature. Boronic acid (2-thiophenylboronic acid for **9**, phenylboronic acid for **10** and 2-furanylboronic acid for **11**, 0.33 mmol) diluted in ethanol (2 mL) was then added, followed immediately by saturated aqueous $NaHCO_3$ solution (2 mL). The heterogeneous solution was stirred at reflux for 3 h. Palladium catalyst was removed by filtration. Brine solution was then added, the two layers were separated and the aqueous phase was extracted with ethyl acetate (3×5 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated in vacuo. The crude residue was purified by column chromatography to give the desired compound.

3.2.1. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-(2-thienyl)-1,4-dihydro-4-quinolinone (9). Chromatography eluent: CH_2Cl_2/EtOAc 9:1; yield: 76%. Mp 205–206°C (EtOAc); IR (KBr) ν 1616 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.57 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.14 (s, 1H, H-3), 6.93–7.04 (m, 7H, H-6, H-8, H-2′, H-4′, H-6′, $2H_{Thien}$), 7.32 (dd, 1H, J=1.7, 4.5 Hz, H_{Thien}), 7.40 (t, 1H, J=8.0 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.3 (NCH_3), 55.6 (OCH_3), 55.8 (OCH_3), 100.2 (CH), 113.9 (CH), 114.4 (CH), 115.1 (CH), 116.3 (CH), 121.0 (CH), 125.1 (CH+C), 125.9 (CH), 126.3 (CH), 130.0 (CH), 137.1 (C), 138.0 (C), 144.1 (C), 145.3 (C), 153.2 (C), 159.8 (C), 161.0 (C), 176.9 (CO). Anal. calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.85; H, 5.21; N, 3.88; MS m/z 378 $(M+1)^+$.

3.2.2. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-phenyl-1,4-dihydro-4-quinolinone (10). Chromatography eluent CH_2Cl_2/EtOAc 8:2; yield: 84%. Mp 206–207°C (EtOAc); IR (KBr) ν 1615 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.54 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.07 (s, 1H, H-3), 6.78 (d, 1H, J=2.3 Hz, H-6 or H-8), 6.90 (d, 1H, J=2.3 Hz, H-6 or H-8), 6.93–7.02 (m, 3H, H-2′, H-4′, H-6′), 7.28–7.41 (m, 6H, H-5′, $5H_{Phen}$); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.0 (CH_3), 55.5 (CH_3), 55.7 (CH_3), 99.1 (CH), 113.9 (CH), 114.3 (CH), 114.8 (CH), 114.9 (CH), 118.7 (C), 120.9 (C), 126.5 (CH), 127.3 (2CH), 128.2 (2CH), 129.9 (CH), 137.2 (C), 143.3 (C), 145.2 (C), 146.0 (C), 153.1 (C), 159.7 (C), 161.1 (C), 177.3 (CO). Anal. calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.34; H, 5.67; N, 3.90; MS m/z 372 $(M+1)^+$.

3.2.3. 5-(2-Furanyl)-7-methoxy-2-(3-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (11). Chromatography eluent CH_2Cl_2/EtOAc 7:3; yield: 86%. Mp 181–182°C (EtOAc); IR (KBr) ν 1618 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.55 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.17 (s, 1H, H-3), 6.51 (dd, 1H, J=1.8, 3.1 Hz, H_{Furan}), 6.55 (d, 1H, J=2.3 Hz, H-6 or H-8), 6.93–7.05 (m, 5H, H-6 or H-8, H-2′, H-4′, H-6′, H_{Furan}), 7.40 (t, 1H, J=8.0 Hz, H-5′), 7.54 (broad s, 1H, H_{Furan}); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 55.6 (CH_3), 55.8 (CH_3), 100.3 (CH), 108.2 (CH), 111.0 (CH), 114.0 (CH), 114.4 (CH), 114.7 (CH), 115.1 (CH), 119.3 (CH), 121.0 (CH), 130.0 (CH), 133.7 (C), 137.2 (C), 142.1 (C), 145.3 (C), 153.1 (C), 154.2 (C), 159.8 (C), 161.4 (C), 177.0 (CO). Anal. calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 72.81; H, 5.47; N, 3.73; MS m/z 362 $(M+1)^+$.

3.3. General procedure of nucleophilic aromatic substitution

A mixture of triflate **7** (200 mg, 0.45 mmol) and amine (2.20 mmol) in anhydrous 1,4-dioxane (4 mL) was heated at 100–120°C for t h. After cooling, the solvent was evaporated. The crude residue was purified by column chromatography to afford the desired compounds.

3.3.1. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-pyrrolidino-1,4-dihydro-4-quinolinone (12b). Amine: pyrrolidine; t=12 h; chromatography eluent: petroleum ether/EtOAc 1:9; yield 83%. Mp 155–156°C (EtOAc); IR (KBr) ν 1617 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95–2.00 (m, 4H, CH_2), 3.42–3.47 (m, 4H, CH_2), 3.45 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.10 (s, 1H, H-3),

6.28 (d, 1H, J=1.8 Hz, H-6 or H-8), 6.34 (broad s, 1H, H-6 or H-8), 6.94–7.03 (m, 3H, H-2′, H-4′, H-6′), 7.38 (t, 1H, J=7.8 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 25.8 ($2CH_2$), 38.1 (CH_3), 52.7 ($2CH_2$), 55.6 ($2CH_3$), 89.5 (CH), 94.8 (CH), 111.3 (CH), 113.1 (CH), 114.2 (CH), 115.1 (CH), 121.0 (CH), 129.9 (C), 137.4 (C), 146.6 (C), 151.2 (C), 151.8 (C), 159.8 (C), 162.7 (C), 177.3 (CO). Anal. calcd for $C_{22}H_{24}N_2O_3$: C, 72.51; H, 6.64; N, 7.69. Found: C, 72.68; H, 6.77; N, 7.80; MS m/z 365 $(M+1)^+$.

3.3.2. 7-Methoxy-2-(4-methoxyphenyl)-1-methyl-5-piperidino-1,4-dihydro-4-quinolinone (13a). Amine: piperidine; t=6 h; chromatography eluent: petroleum ether/EtOAc 1:9; yield: 82%. Mp 190–191°C (EtOAc/petroleum ether); IR (KBr) ν 1633 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50–1.65 (m, 2H, CH_2), 1.70–1.95 (m, 4H, CH_2), 2.90–3.20 (m, 4H, CH_2), 3.48 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.08 (s, 1H, H-3), 6.42 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.50 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.97 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.31 (d, 2H, J=8.8 Hz, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 24.5 (CH_2), 26.2 ($2CH_2$), 38.5 (CH_3), 54.7 ($2CH_2$), 55.4 (CH_3), 55.5 (CH_3), 92.4 (CH), 100.2 (CH), 114.2 (2CH+C), 114.4 (CH), 128.4 (C), 130.1 (2CH), 147.3 (C), 151.7 (C), 156.0 (C), 160.4 (C), 162.5 (C), 177.3 (CO). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.67; H, 6.85; N, 7.37; MS m/z 379 $(M+1)^+$.

3.3.3. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-piperidino-1,4-dihydro-4-quinolinone (13b). Amine: piperidine; t=6 h; chromatography eluent: petroleum ether/EtOAc 1:9; yield: 84%. Mp 171–172°C (EtOAc); IR (KBr) ν 1621 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.60–1.90 (m, 2H, CH_2), 1.90–2.00 (m, 4H, CH_2), 3.10–3.40 (m, 4H, CH_2), 3.50 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.13 (s, 1H, H-3), 6.47 (broad s, 1H, H-6 or H-8), 6.93 (d, 1H, J=1.8 Hz, H-6 or H-8), 6.94–7.05 (m, 3H, H-2′, H-4′, H-6′), 7.40 (t, 1H, J=7.8 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 23.5 (CH_2), 25.9 ($2CH_2$), 38.7 (CH_3), 55.0 ($2CH_2$), 55.6 ($2CH_3$), 89.5 (CH), 94.8 (CH), 111.3 (CH), 113.4 (CH), 114.3 (CH), 115.4 (CH), 120.9 (CH), 130.1 (C), 136.8 (C), 146.6 (C), 151.2 (C), 153.2 (C), 159.9 (C), 163.1 (C), 177.5 (CO). Anal. calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 73.12; H, 7.05; N, 7.33; MS m/z 379 $(M+1)^+$.

3.3.4. 7-Methoxy-2-(4-methoxyphenyl)-1-methyl-5-(1-methylpiperazino)-1,4-dihydro-4-quinolinone (14a). Amine: *N*-methylpiperazine; t=6 h; chromatography eluent: CH_2Cl_2/MeOH 98:2; yield: 90%. Mp 188–189°C (EtOAc/petroleum ether); IR (KBr) ν 1618 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.36 (s, 3H, NCH_3), 2.70–2.80 (m, 4H, CH_2), 3.10–3.20 (m, 4H, CH_2), 3.46 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.05 (s, 1H, H-3), 6.41 (s, 2H, H-6, H-8), 6.95 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.29 (d, 2H, J=8.8 Hz, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.5 (CH_3), 46.1 (CH_3), 52.9 ($2CH_2$), 55.3 ($2CH_2$), 55.4 (CH_3), 55.5 (CH_3), 92.4 (CH), 100.1 (CH), 114.1 (2CH), 114.5 (C+CH), 128.2 (C), 130.1 (2CH), 147.4 (C), 151.7 (C), 155.1 (C), 160.4 (C), 162.4 (C), 177.0 (CO). Anal. calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 69.98; H, 6.78; N, 10.52; MS m/z 394 $(M+1)^+$.

3.3.5. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-(1-methylpiperazino)-1,4-dihydro-4-quinolinone (14b). Amine: *N*-methylpiperazine; t=6 h; chromatography eluent: CH_2Cl_2/MeOH 98:2; yield: 89%. Mp 196–197°C (EtOAc/petroleum ether); IR (KBr) ν 1623 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.40 (s, 3H, NCH_3), 2.75–2.80 (m, 4H, CH_2), 3.15–3.25 (m, 4H, CH_2), 3.49 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.11 (s, 1H, H-3), 6.46 (s, 2H, H-6, H-8), 6.92 (d, 1H, J=1.9 Hz, H-2′), 6.95–7.02 (m, 2H, H-4′, H-6′), 7.38 (t, 1H, J=7.8 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.5 (CH_3), 46.2 (CH_3), 52.9 ($2CH_2$), 55.3 ($2CH_2$), 55.4 (CH_3), 55.5 (CH_3), 92.4 (CH), 100.2 (CH), 114.3 (CH), 114.5 (CH), 114.6 (C), 115.4 (CH), 121.0 (CH), 129.9 (CH), 137.3 (C), 147.3 (C), 151.7 (C), 155.3 (C), 159.8 (C), 162.5 (C), 177.1 (CO). Anal. calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.34; H, 7.06; N, 10.79; MS m/z 394 $(M+1)^+$.

3.3.6. 7-Methoxy-2-(4-methoxyphenyl)-1-methyl-5-(dimethylaminoethylamino)-1,4-dihydro-4-quinolinone (15a). Amine: *N*,*N*-dimethylaminoethylamine; t=48 h; chromatography eluent: CH_2Cl_2/MeOH 95:5; yield: 79%. Mp 130–131°C (EtOAc/petroleum ether); IR (KBr) ν 1626 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.33 (s, 6H, CH_3), 2.66 (t, 2H, J=7.0 Hz, CH_2), 3.31 (broad q, J=7.0 Hz, CH_2), 3.42 (s, 3H, NCH_3), 3.87 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 5.94 (d, 1H, J=2.2 Hz, H-6 or H-8), 5.97 (d, 1H, J=2.2 Hz, H-6 or H-8), 6.02 (s, 1H, H-3), 6.98 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.30 (d, 2H, J=8.8 Hz, H-2′, H-6′), 10.48 (broad t, 1H, J=7.0 Hz, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 41.3 (CH_2), 45.8 ($2CH_3$), 55.2 (CH_3), 55.5 (CH_3), 58.0 (CH_2), 86.2 (CH), 88.4 (CH), 107.7 (C), 112.9 (CH), 114.2 (2CH), 128.4 (C), 130.0 (2CH), 146.4 (C), 152.5 (C), 153.4 (C), 160.4 (C), 164.0 (C), 180.2 (CO). Anal. calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.54; H, 6.94; N, 10.88; MS m/z 382 $(M+1)^+$.

3.3.7. 7-Methoxy-2-(3-methoxyphenyl)-1-methyl-5-(dimethylaminoethylamino)-1,4-dihydro-4-quinolinone (15b). Amine: *N*,*N*-dimethylaminoethylamine; t=60 h; chromatography eluent: CH_2Cl_2/MeOH 95:5; yield: 79%. Mp 121–122°C (EtOAc); IR (KBr) ν 1628 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.34 (s, 6H, NCH_3), 2.67 (t, 2H, J=7.0 Hz, CH_2), 3.32 (broad q, 2H, J=7.0 Hz, CH_2), 3.41 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.95 (d, 1H, J=2.2 Hz, H-6 or H-8), 5.98 (d, 1H, J=2.2 Hz, H-6 or H-8), 6.04 (s, 1H, H-3), 6.90–7.02 (m, 3H, H-2′, H-4′, H-6′), 7.38 (t, 1H, J=7.8 Hz, H-5′), 10.50 (broad t, 1H, J=7.0 Hz, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 41.3 (CH_2), 45.8 ($2CH_3$), 55.3 (CH_3), 55.5 (CH_3), 58.0 (CH_2), 86.2 (CH), 88.5 (CH), 107.8 (C), 112.7 (CH), 114.3 (CH), 115.0 (CH), 121.0 (CH), 129.9 (CH), 137.4 (C), 146.3 (C), 152.5 (C), 153.5 (C), 159.8 (C), 164.1 (C), 180.2 (CO). Anal. calcd for $C_{22}H_{27}N_3O_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 68.94; H, 6.97; N, 10.93; MS m/z 382 $(M+1)^+$.

3.3.8. 7-Methoxy-5-(4-methoxybenzylamino)-2-(4-methoxyphenyl)-1-méthyl-1,4-dihydro-4-quinolinone (16a). Amine: 4-methoxybenzylamine; t=16 h; chromatography eluent: CH_2Cl_2/EtOAc 9:1; yield: 82%. Mp 148–150°C (EtOAc/petroleum ether); IR (KBr) ν 1623 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.43 (s, 3H, NCH_3), 3.79 (s, 6H,

OCH_3), 3.87 (s, 3H, OCH_3), 4.40 (d, 2H, J=5.5 Hz, CH_2), 5.89 (d, 1H, J=2.0 Hz, H-6 or H-8), 5.99 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.05 (s, 1H, H-3), 6.86 (d, 2H, J=8.8 Hz, $2H_{Phen}$), 6.98 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.29–7.35 (m, 4H, H-2′, H-6′, $2H_{Phen}$), 10.88 (t, 1H, J=5.5 Hz, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 46.6 (CH_2), 55.2 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 86.6 (CH), 89.4 (CH), 107.9 (C), 112.9 (CH), 114.1 (2CH), 114.2 (2CH), 128.4 (2CH), 130.1 (2CH), 131.0 (C), 146.4 (C), 152.6 (C), 153.4 (C), 158.7 (C), 160.5 (C), 163.9 (C), 180.3 (CO). Anal. calcd for $C_{26}H_{26}N_2O_4$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.33; H, 5.90; N, 6.55; MS m/z 431 $(M+1)^+$.

3.3.9. 7-Methoxy-5-(4-methoxybenzylamino)-2-(3-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (16b). Amine: 4-methoxybenzylamine; t=16 h; chromatography eluent: CH_2Cl_2/EtOAc 9:1; yield: 80%. Mp 181–182°C (EtOAc); IR (KBr) ν 1630 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (s, 3H, NCH_3), 3.79 (s, 6H, OCH_3), 3.85 (s, 3H, OCH_3), 4.40 (d, 2H, J=5.5 Hz, CH_2), 5.89 (d, 1H, J=2.0 Hz, H-6 or H-8), 5.99 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.06 (s, 1H, H-3), 6.86 (d, 2H, J=8.8 Hz, $2H_{Phen}$), 6.90–7.02 (m, 3H, H-2′, H-4′, H-6′), 7.33 (d, 2H, J=8.8 Hz, $2H_{Phen}$), 7.38 (t, 1H, J=8.0 Hz, H-5′), 10.88 (t, 1H, J=5.5 Hz, NH); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 46.6 (CH_2), 55.2 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 86.5 (CH), 89.5 (CH), 108.0 (C), 112.7 (CH), 114.1 (2CH), 114.3 (CH), 115.0 (CH), 121.0 (CH), 128.4 (2CH), 130.0 (CH), 130.9 (C), 137.4 (C), 146.2 (C), 152.5 (C), 153.4 (C), 158.7 (C), 159.8 (C), 163.9 (C), 180.3 (CO). Anal. calcd for $C_{26}H_{26}N_2O_4$C, 72.54; H, 6.09; N, 6.51. Found: C, 72.81; H, 5.99; N, 6.61; MS m/z 431 $(M+1)^+$.

3.3.10. 5-Amino-7-methoxy-2-(4-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (17a). A solution of **16a** (100 mg, 0.23 mmol) in trifluoroacetic acid (3 mL) was stirred at 65°C for 1 h. Acid was removed under reduced pressure. The residue was diluted in ethyl acetate, washed with 10% NaOH solution. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The solid obtained was recrystallised from ethyl acetate to give **17a** (46 mg, 65%) as a solid. Mp 198–200°C (EtOAc); IR (KBr) ν 3377 broad s (NH_2), 1624 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.41 (s, 3H, NCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.99 (d, 1H, J=2.2 Hz, H-6 or H-8), 6.01 (s, 1H, H-3), 6.06 (d, 1H, J=2.2 Hz, H-6 or H-8), 6.97 (d, 2H, J=8.8 Hz, H-3′, H-5′), 7.11 (broad s, 2H, NH_2), 7.31 (d, 2H, J=8.8 Hz, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.1 (CH_3), 55.4 (CH_3), 55.5 (CH_3), 88.5 (CH), 93.6 (CH), 108.2 (C), 112.7 (CH), 114.2 (2CH), 128.5 (C), 130.1 (2CH), 146.2 (C), 153.2 (2C), 160.5 (C), 163.4 (C), 180.5 (CO). Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.87; H, 5.66; N, 8.88; MS m/z 311 $(M+1)^+$.

3.3.11. 5-Amino-7-methoxy-2-(3-methoxyphenyl)-1-methyl-1,4-dihydro-4-quinolinone (17b). Following the procedure used for the preparation of **17a**, compound **17b** was obtained from **16b** in 54% yield. Mp 182–183°C (EtOAc); IR (KBr) ν 3432, 3362 (NH_2), 1627 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.40 (s, 3H, NCH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.00 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.03 (s 1H, H-3), 6.06 (d, 1H, J=2.0 Hz, H-6 or H-8), 6.90–7.07 (m, 5H, H-2′, H-4′, H-6′+NH_2), 7.38 (t, 1H, J=7.9 Hz, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$) δ 38.0 (CH_3), 55.4 (CH_3), 55.6 (CH_3), 88.5 (CH), 93.7 (CH), 108.2 (C), 112.5 (CH), 114.2 (CH), 115.1 (CH), 121.0 (CH), 130.0 (CH), 137.4 (C), 146.1 (C), 153.1 (C), 153.2 (C), 159.8 (C), 163.5 (C), 180.5 (CO). Anal. calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 70.02; H, 5.92; N, 8.97; MS m/z 311 $(M+1)^+$.

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