Syntheses of Some 4-Anilinoquinazoline Derivatives

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Abstract: Some 4-*N*-(3′- or 4′-substituted-phenyl)amino-6,7-dimethoxyquinazolines and the corresponding unsubstituted compounds were synthesized from 2-amino-4,5-dimethoxybenzoic acid and the appropriate substituted anilines. Other related quinazolines or their synthetic intermediates were also obtained. A large number of the described quinazolines are new compounds, while the remaining were prepared by a more efficient procedure. The main goal for the synthesis of these compounds comes from the fact that the 4-anilinoquinazoline pharmacophore is an important unit, which is found among the ATP-competitive inhibitors of several protein kinase enzymes.

Key words: 4-anilinoquinazolines, quinazolinones, ATP-inhibitors

The epidermal growth factor (**EGF**) receptor is known to be overexpressed in a large percentage of human cancers,[1,2] including mammarian, ovarian, esophageal, head and neck, colorectal, prostate, etc.[2–4] The activation of the EGF receptor tyrosine kinase has been identified as a key initiating event for cell proliferation.[4] For these reasons, inhibitors of the EGF receptor tyrosine kinase are potentially useful as chemotherapeutic agents for the treatment of cancer.[3] However, protein tyrosine kinases are also important in many signaling pathways involved in normal cellular function.[3]

A number of reports[1–11] have shown that 4-anilinoquinazolines are potential and highly selective inhibitors of EGF receptor tyrosine kinase phosphorylation, resulting from competitive binding at the ATP site.[3–5] Thus, the syntheses of quinazolines have received much attention in recent years, and have been comprehensively reviewed.[6–13]

The first step for most synthetic routes leading to 4-*N*-phenylaminoquinazoline derivatives **A** (Figure 1) involves the addition of a one-carbon unit to anthranilic acid **B**, with subsequent ring-closure to 3*H*-quinazolin-4-one, **C**, an important intermediate, usually occurring in situ. Traditionally, formamide has been the reagent of choice for this reaction (*Niementowski* reaction), although better results are often obtained with other reagents such as formamidine acetate.[12]

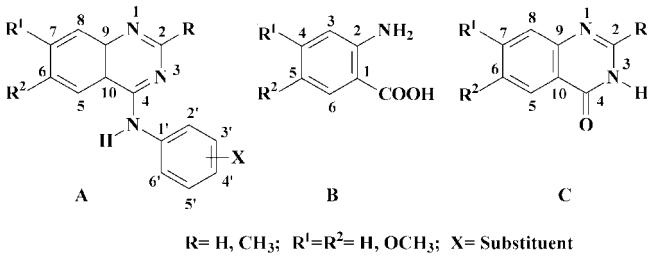

Figure 1 4-*N*-phenylaminoquinazoline derivatives (**A**), anthranilic acid (**B**), 3*H*-quinazolin-4-one and 3*H*-2-methylquinazolin-4-one, (**C**), and the corresponding dimethoxy derivatives.

The syntheses of some new 4-*N*-phenylaminoquinazoline derivatives, with and without a substituent at the 2-position, and of their synthetic intermediates, through known reactions or alternative approaches, are reported here.

2-Methyl-4-*N*-phenylaminoquinazoline (**6**) and its interesting intermediates **2**–**5** were synthesized through the method of Tomisek and Christensen[14] and alternative approaches,[15–18] as shown in Scheme 1.

In the first step of this sequence, 2-methyl-3,1-benzoxazin-4-one (**2**) was obtained by heating anthranilic acid (**1**) in anhydrous acetic anhydride at reflux temperature. The NMR spectrum (not shown here) revealed that a mixture of compound **2** (30%) and *N*-acetylanthranilic acid was formed. Actually, the literature[15,16] reports that compound **2** is very sensitive and it is easily hydrolyzed to *N*-acetylanthranilic acid.

Both components of this mixture react with NH_3 at room temperature to yield the *N*-acetylanthranilamide (**3**). Subsequent heating of compound **3** with NaOH solution led to a cyclodehydration giving the quinazolinone **4**.[16]

3*H*-2-Methyl-4-thioxoquinazoline (**5**) was synthesized from anthranilonitrile (**7**) and thiolacetic acid (Scheme 2),[17]since the described method from 3*H*-2-methyl-4-quinazolinone (**4**) and phosphorus pentasulfide did not result in the desired product (Scheme 1, step d). The last step of the synthetic pathway (Scheme 1, step e) for 2-methyl-4-*N*-phenylaminoquinazoline (**6**), through the reaction of compound **5** with aniline, did not lead to satisfactory results, as observed from the NMR spectrum of the crude reaction product. Compound **6** was obtained through an alternative route,[18] from 3*H*-2-methyl-4-quinazolinone (**4**), aniline, phosphorus pentoxide and *N*,*N*-dimethylcyclohexylamine, in a single step (Scheme 1, step f).

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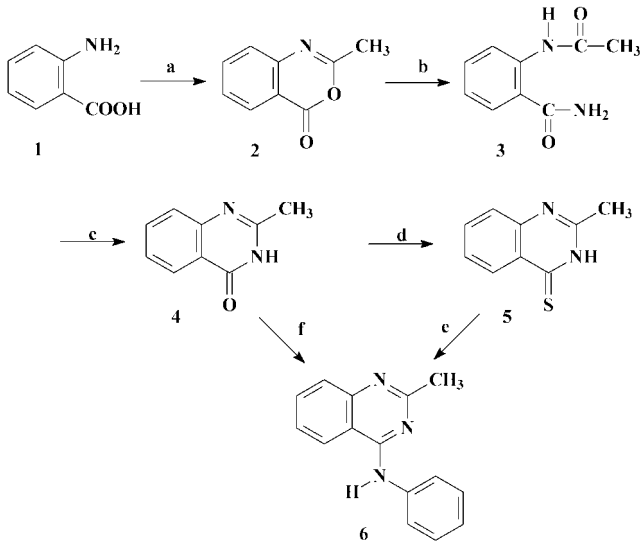
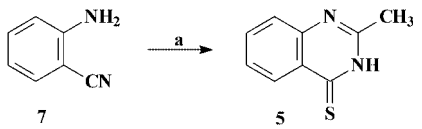
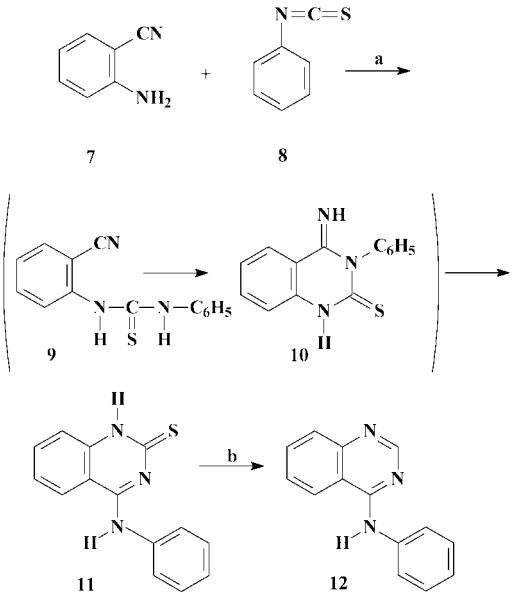


Scheme 1 (a) Ac_2O, reflux, 2 h; (b) NH_3, 4 h, r.t.; (c) 10% NaOH, then concd HCl until pH 8; (d) P_2S_5, xylene; (e) aniline, 130–160 °C, 4.5 h; (f) P_2O_5, *N*,*N*-dimethylcyclohexylamine, $C_6H_5NH_2 \cdot HCl$, 200 °C, 6 h.



Scheme 2 (a) $H_3CC(O)SH$, 110–115 °C, 2 h.

A different synthetic approach to 4-anilinoquinazolines, starting from anthranilonitrile and phenyl isothiocyanate, has been described by Taylor and Ravindranathan[19] and is presented in Scheme 3. This route was followed for obtaining the quinazolines not bearing a substituent at the 2-position.



Scheme 3 (a) 100 °C, 12 h; (b) Raney nickel, MeOH, reflux, 6 h.

Taylor and Ravindranathan[19]reported that anthranilonitrile (**7**) reacts readily with isothiocyanate at 100 °C, in the absence of solvent, resulting in an exothermic reaction with the formation of 4-phenylaminoquinazoline-2(1*H*)-thione (**11**) in good yield (77.8%) (Scheme 3, step a). In the last step, desulfurization of **11** with Raney nickel in refluxing MeOH resulted in 4-anilinoquinazoline (**12**), in 90.2% yield (Scheme 3, step b). Thus, the reaction between **7** and **8** resulted in compound **11**, through consecutive steps, with cyclization of compound **9** to **10** and its 1,3-exoannular rearrangement.[20,21] This sequence of ring-opening and ring-closure required high temperatures, and it represents a pure thermal conversion of **10** to **11** (Scheme 3).[19]

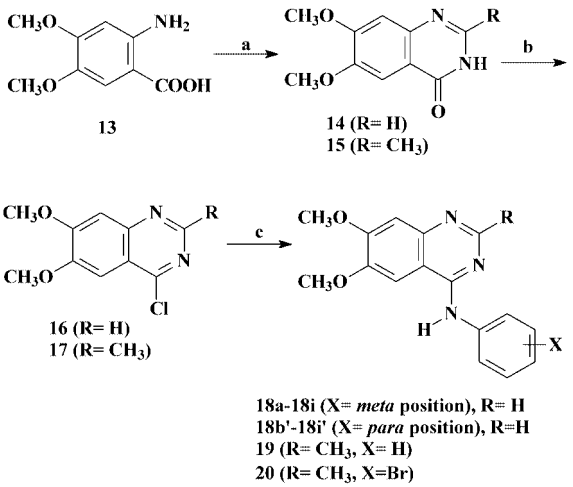
The preparation of compounds **18a–i** (*meta*-position), **18b′–i′** (*para*-position), **19** and **20** was performed following the synthetic strategy depicted on Scheme 4, based on the method described by Bridges et al.[7]

The cyclization of 4,5-dimethoxyanthranilic acid (**13**) with formamide, at a high temperature (165 °C), leads to 3*H*-6,7-dimethoxyquinazolin-4-one (**14**) in yields of only 19.2%. On the other hand, its reaction with formamidine acetate led to the subsequent in situ ring-closure to the quinazolinone precursor **14** in good yield (75.9%). To prepare the quinazolinone **15**, bearing a methyl substituent at the 2-position, in an excellent yield (99.1%), the amino acid **13** was heated with acetic anhydride. The excess of solvent was evaporated and the resulting solid was treated with NH_3 and 10% NaOH. The second step in the derivatization, involved conversion of the 3*H*-6,7-dimethoxyquinazolin-4-ones (**14** and **15**) to 4-chloro derivatives (**16** and **17**) with thionyl chloride containing a catalytic amount of DMF (yields of 79.1% and 90.6%, respectively). In the final step, compounds **18a–18i**, **18b′–18i′**, **19** and **20** were prepared by nucleophilic displacement of the chlorine of the 4-chloroquinazoline intermediate with substituted aniline derivatives by refluxing in *i*-PrOH. The yields ranged from 50.7–93.2%. The products were isolated as the hydrochloride salts by filtering directly from the reaction mixture.[7]

In conclusion, twenty two quinazoline derivatives were prepared by three synthetic pathways (Experimental section).[7,14,17–19] Two synthetic routes were used for preparation of compounds **5** (Scheme 2) and **6** (Scheme 1, step f) as the pathways suggested by Tomisek and Christensen[14] did not lead to satisfactory results.

The syntheses of ten compounds (**18b′**, **18d′**, **18e′**, **18f**, **18f′**, **18g′**, **18h**, **18h′**, **18i** and **18i′**) are reported for the first time. Preliminary experiments have shown that these compounds can exhibit cardiovascular activity[22] and it has also been reported that some quinazoline derivatives can be potential anticarcinogenic agents.[3] Therefore, a comprehensive study of their biological activities is under way.

Melting points were determined on an MQAPF-301 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-



Scheme 4 (a) For **14**: Formamidine acetate, 140 °C, 8 h or 165 ºC, formamide, 3 h; For **15**: (i) Acetic anhydride, reflux, 4 h, NH_3, 4 h, r.t., (ii) 10% NaOH; (b) $SOCl_2$, DMF, reflux, 2 h; (c) corresponding aniline, *i*-PrOH, reflux, 2 h.

1600 or FTIR 1605. ^{1}H NMR spectra were taken on Bruker AC300/P or Varian Gemini-300 spectrometers operating at 300 MHz, or on a Varian INOVA-500 spectrometer operating at 500 MHz. All NMR spectra were recorded at 21 °C in $(CD_3)_2SO$ and referenced to Me_4Si. Mass spectra were recorded on a VG Auto-Spec (Varian) spectrometer. Elemental analyses were obtained from a Perkin-Elmer (2400) analyzer.

2-Methyl-3,1-benzoxazin-4-one or Acylanthranil (2) (Scheme 1, step a); Typical Procedure

Method A

A stirred solution consisting of anthranilic acid (**1**) (20 g, 146 mmol) and anhyd Ac_2O (64.7 g, 60 mL, 634 mmol) was reacted at reflux temperature for 2 h, cooled to 0 °C and left in the refrigerator for 72–96 h. The precipitate was filtered to yield 2.90 g of a white solid, which was identified by its NMR spectrum as a mixture of 2-methyl-3,1-benzoxazin-4-one (**2**) and of *N*-acetylanthranilic acid; mp 77–80 °C (compared with data in refs.[15,16]).

Method B[16]

The reaction mixture was prepared according to Method A and heated at reflux for 2 h. Excess of Ac_2O was removed under vacuum in a rotary evaporator. The residue was distilled under vacuum and the fraction with a boiling range 125–135 °C at 4 Torr was collected as an oil, which turned to a white solid. The attempt to isolate the acylanthranil (**2**, cyclic compound) was not successful, and a mixture was obtained (3.20 g) which melted at 80–82 °C.[16]

Method C

The same procedure as Method B was carried out up to removal of Ac_2O. The resulting mixture of cyclic and acyclic compounds was then dried under vacuum to give 18 g of the same mixture as in Methods A and B. However, a better yield was obtained.

IR (KBr): 2960 (CH), 1758 (C=O acid), 1646 (C=O amide), 1053 (CO) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 8.09 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 1 H, H-5), 7.59 (td, ^3J = 8.2 Hz, ^4J = 1.5 Hz, 1 H, H-6), 7.91 (td, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-7), 7.59 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-8), 2.40 (s, 3 H, H-11).

N-Acetylanthranilamide (3) (Scheme 1, step b); Typical Procedure

A stirred solution consisting of anthranilic acid (20 g, 146 mmol) and anhyd acetic anhydride (64.7 g, 60 mL, 634 mmol) was heated at reflux temperature for 2 h. The excess Ac_2O was removed under vacuum in a rotary evaporator. The resulting solid was placed in an Erlenmeyer flask and then concd NH_3 (100 mL) was slowly added (exothermic reaction). The reaction mixture was kept at r.t. for 4 h. Afterwards, the crude material was filtered under vacuum and, after recrystallization from aq EtOH and drying under vacuum, the desired product was obtained as a white solid (15 g, 84.3 mmol, 57.7%); mp 187–189 °C.[15,16]

IR (KBr): 3414 (NH), 3034 (aromatic CH), 2977 (CH), 1659 (C=O amide), 1610 (NH of amide), 1469 (aromatic CC), 778 (CH) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 12.19 (s, 1 H, H-1), 3.40 (s, 2 H, H-3), 8.06 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-5), 7.43 (td, ^3J = 8.1 Hz, ^4J = 0.9 Hz, 1 H, H-6), 7.75 (td, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, H-7), 7.55 (dd, ^3J = 8.1 Hz, ^4J = 0.9 Hz, 1 H, H-8), 2.34 (s, 3 H, H-11).

3*H*-2-Methylquinazolin-4-one (4) (Scheme 1, step c)

To the mixture of 2-methyl-3,1-benzoxazin-4-one (**2**) and *N*-acetylanthranilic acid (3.50 g), concd NH_3 (20 mL) was added slowly. The mixture was kept at r.t. for 4 h. Then, 10 mL of 10% aq NaOH was added and the mixture was heated for 30 min. After solubilization had occurred, an excess of 10% aq NaOH (10 mL) was added. The pH was adjusted from 13 to 8 by the addition of concd HCl, leading to the precipitation of the desired quinazolinone, which was filtered and rinsed with water. Recrystallization from aq EtOH and drying under vacuum gave the product **4** (2.0 g, 12.0 mmol) as a white solid; mp 237–239 °C.[15]

IR (KBr): 3427 (NH), 3032 (aromatic CH), 2978 (CH), 1681 (C=O amide), 1615 (aromatic CN), 1421 (aromatic CC), 775 (CH) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 12.20 (s, 1 H, H-3), 8.06 (dd, ^3J = 8.0 Hz, ^4J = 1.6 Hz, 1 H, H-5), 7.44 (td, ^3J = 7.77 Hz, ^4J = 1.0 Hz, 1 H, H-6), 7.75 (td, ^3J = 7.77 Hz, and ^4J = 1.6 Hz, 1 H, H-7), 7.56 (dd, ^3J = 8.0 Hz, ^4J = 1.0 Hz, 1 H, H-8), 2.34 (s, 3 H, H-11).

Anal. Calcd for $C_9H_8N_2O.H_2O$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.60; H, 5.51; N, 15.55.

3*H*-4-Thioxo-2-methylquinazoline (5); Typical Procedure

Method A (Scheme 1, step d)[14]

A stirred mixture of 3*H*-2-methylquinazolin-4-one (**4**) (10 g, 62.5 mmol), phosphorus pentasulfide (13.5 g, 61.0 mmol) and xylene (100 mL) was heated at reflux for 4 h. The reaction mixture was washed with 100 mL of 10% aq NaOH, filtered under vacuum and the filtrate was turned slightly acidic with glacial HOAc. The precipitated pale yellow solid was collected by filtration, washed with water and dried under vacuum. Its NMR spectrum showed that neither the desired product nor a side product was formed; only starting material was recovered.

Method B (Scheme 2)[17]

The stirred mixture of anthranilonitrile (**7**) (1.50 g, 13.0 mmol) and thiolacetic acid (1.38 g, 1.30 mL, 10.1 mmol) was heated at 100–115 °C for 2 h. Afterwards, the reaction mixture was cooled in an ice bath and the crude product recrystallized from 50% aq EtOH. The desired compound was obtained as a yellow solid (0.99 g, 5.1 mmol, 40.2%); mp 215–217 °C.[17]

IR (KBr): 3427 (NH), 3052–3097 (aromatic CH), 2979 (CH), 1621–1613 (aromatic CN), 1237 (C=S), 761 (CH) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 13.80 (s, 1 H, H-3), 8.54 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, H-5), 7.54 (td, ^3J = 8.0 Hz, ^4J = 1.2 Hz, 1 H, H-6), 7.86 (td, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1 H, H-7), 7.63 (dd, ^3J = 7.7 Hz, ^4J = 1.2 Hz, 1 H, H-8), 2.47 (s, 3 H, H-11).

Anal. Calcd for $C_9H_8N_2S$: C, 61.34; H, 4.58; N, 15.90. Found: C, 60.26; H, 4.15; N, 15.94.

2-Methyl-4-*N*-phenylaminoquinazoline (6); Typical Procedure
Method A (Scheme 1, step e)[14]

3*H*-4-Thioxo-2-methylquinazoline (**5**) (0.50 g, 2.80 mmol) and aniline (4.10 g, 4 mL, 44.0 mmol) were mixed and heated for 4.5 h at 130–160 °C, when a clear solution was obtained. Brownish needles separated on cooling. Excess aniline was removed by washing with 10% aq NaOH solution (10 mL). The solid residue was filtered and washed with Et_2O. Only 50.4 mg of a solid that melted at 189–195° was obtained. By analyzing the ^1H and ^{13}C NMR spectra, we concluded that neither the desired nor any side-product was formed; just the starting materials were recovered.

Method B (Scheme 1, step f)[18]

A mixture of phosphorus pentoxide (7.10 g, 50.0 mmol), *N*,*N*-dimethylcyclohexylamine (5.09 g, 6 mL, 40.0 mmol), and of aniline hydrochloride (5.0 g, 38.6 mmol) was heated in an oil bath at 200 °C until a clear homogeneous mixture was obtained. Afterwards, 3*H*-2-methylquinazolin-4-one (**4**) was added and the reaction mixture was heated at 200 °C for 6 h with stirring. The mixture was allowed to cool to about 100 °C, and a 2 M aq NaOH solution (300 mL) was added. The stirring was continued for another 1 h at r.t. Then, the alkaline solution was extracted with CH_2Cl_2 (3 × 100 mL), and the extract was washed with water and dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The residue was recrystallized from 50% aq EtOH to give a dark yellow solid (0.70 g, 2.98 mmol, 23.8%); mp 163–165 °C.[23]

IR (KBr): 3432 (NH), 3055 (aromatic CH), 2922 (CH), 1620 (aromatic C=N), 1355 (aromatic CC), 747 (CH) cm^{-1}.

^1H NMR [300 MHz, $(CD_3)_2SO$]: δ = 8.54 (d, ^3J = 8.1 Hz, 1 H, H-5), 7.55 (t, ^3J = 7.6 Hz, 1 H, H-6), 7.81 (t, ^3J = 7.6 Hz, 1 H, H-7), 7.71 (d, ^3J = 8.0 Hz, 1 H, H-8), 2.53 (s, 3 H, H-11), 9.69 (s, 1 H, NH), 7.96 (d, ^3J = 7.8 Hz, 2 H, H-2′, H-6′), 7.40 (t, ^3J = 7.8 Hz, 2 H, H-3′, H-5′), 7.12 (t, ^3J = 7.3 Hz, 1 H, H-5′).

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 75.38, H, 5.27; N, 17.26.

4-*N*-Phenylaminoquinazoline-2-(1*H*)thione (11) (Scheme 3, step a)[19]

In a 100 mL round bottom flask, a stirred mixture of anthranilonitrile (**7**) (2.50 g, 21.0 mmol) and phenyl isothiocyanate (**8**) (4.95 g, 4.5 mL, 36.0 mmol) was heated at 100 °C for 12 h, whereupon an exothermic reaction took place within the first few minutes and the clear melt turned to an orange-red jelly. After heating for 12 h, the resulting yellow solid was removed from the flask and washed with Et_2O (4 × 10 mL) to remove unreacted starting materials. After filtration and drying under vacuum, the desired compound **11** was obtained (4.20 g, 17.0 mmol, 77.8%) as a yellow solid; mp 234–238 °C.[19]

^1H NMR [300 MHz, $(CD_3)_2SO$]: δ = 12.70 (s, 1 H, H-1), 8.40 (d, ^3J = 8.2 Hz, 1 H, H-5), 7.40 (t, ^3J = 8.0 Hz, 1 H, H-6), 7.70 (t, ^3J = 8.0 Hz, 1 H, H-7), 7.40 (d, ^3J = 7.9 Hz, 1 H, H-8), 10.0 (s, 1 H, NH), 7.80 (d, ^3J = 7.7 Hz, 2 H, H-2′, H-6′), 7.40 (t, ^3J = 7.6 Hz, 2 H, H-3′, H-5′), 7.20 (t, ^3J = 7.3 Hz, 1 H, H-5′).

IR (KBr): 3438 (NH), 3028 (aromatic CH), 1607 (C=N), 1353 (aromatic CC), 1189 (C=S), 756 (CH) cm^{-1}.

Anal. Calcd for $C_{14}H_{11}N_3S$: C, 66.38; H, 4.38; N, 16.59. Found: C, 65.22; H, 4.28; N, 16.13.

4-*N*-Phenylaminoquinazoline (12)[19] (Scheme 3, step b); Typical Procedure

A mechanically stirred mixture of 4-phenylaminoquinazoline-2-(1*H*)thione (**11**) (0.70 g, 2.17 mmol), Raney nickel (4.0 g) and MeOH (150 mL) was heated at reflux temperature for 6 h. Then, the reaction mixture was filtered to remove the Raney nickel and the solvent was evaporated under reduced pressure. The resulting solid was purified by recrystallization in MeOH to give the 4-*N*-phenylaminoquinazoline (**12**) (0.55 g, 2.50 mmol, 90.2%) as a pale yellow solid; mp 214–216 °C (Lit.[19] 220–221 °C).

IR (KBr): 3414 (NH), 3093 (aromatic CH), 1603 (C=N), 1356 (aromatic CC), 757 (CH) cm^{-1}.

^1H NMR [300 MHz, $(CD_3)_2SO$]: δ = 8.63 (s, 1 H, H-2), 8.61 (d, ^3J = 8.4 Hz, 1 H, H-5), 7.66 (t, ^3J = 8.1 Hz, 1 H, H-6), 7.90 (t, ^3J = 8.1 Hz, 1 H, H-7), 7.80 (d, ^3J = 8.1 Hz, 1 H, H-8), 9.84 (s, 1 H, NH), 7.90 (d, ^3J = 8.1 Hz, 2 H, H-2′, H-6′), 7.42 (t, ^3J = 8.1 Hz, 2 H, H-3′, H-5′), 7.18 (t, ^3J = 7.7 Hz, 1 H, H-5′).

3*H*-6,7-Dimethoxyquinazolin-4-one (14) (Scheme 4, step a); Typical Procedure
Method A[7]

The stirred mixture of 2-amino-4,5-dimethoxybenzoic acid (**13**) (1.0 g, 5.08 mmol) and formamide (2.27 g, 2 mL, 50.4 mmol) was heated at 165 °C for 3 h. After cooling, the resulting solid was filtered through a Büchner funnel and rinsed with water (3 × 10 mL). After drying under vacuum, the crude product was obtained (0.20 g, 0.97 mmol, 19.2%).

Method B[7]

2-Amino-4,5-dimethoxybenzoic acid (**13**) (1.0 g, 5.08 mmol) and formamidine acetate (4.50 g, 43.3 mmol) were intimately grounded together and then spread in an even layer around the bottom in a 50 mL round bottom flask. The mixture was heated to 140 °C in a silicone oil bath for 8 h. During heating a circular melting zone followed by resolidification passed from the borders to the center of the flask. The reaction mixture was allowed to cool and then sonicated with aq NaOH solution (0.33 M). After adjusting the pH to 8, the resulting purple-gray solid was collected by filtration, rinsed with water (3 × 10 mL), and dried under vacuum to give 3*H*-6,7-dimethoxyquinazolin-4-one (**14**) (0.79 g, 3.83 mmol, 75.9%); mp 296–298 °C.[7]

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 12.07 (s, 1 H, H-3), 8.00 (s, 1 H, H-2), 7.45 (s, 1 H, H-5), 7.14 (s, 1 H, H-8), 3.91 (s, 3 H, H-6a), 3.87 (s, 3 H, H-7a).

3*H*-6,7-Dimethoxy-2-methylquinazolin-4-one (15) (Scheme 4, step a); Typical Procedure

A suspension of 2-amino-4,5-dimethoxybenzoic acid (**13**) (1.0 g, 5.08 mmol) and anhyd Ac_2O (3.24 g, 3 mL, 31.7 mmol) was heated at reflux for 4 h. Excess of acetic anhydride was removed under vacuum in a rotary evaporator. The resulting solid was placed in an Erlenmeyer flask and then concd NH_3 (15 mL) was slowly added (exothermic reaction). The mixture was kept at r.t. for 4 h. Afterwards, 10% aq NaOH (10 mL) was added and the mixture was heated for 30 min. Afterwards, an excess of 10% aq NaOH was added. Using concd HCl, the mixture's pH was adjusted from 13 to 8. At this moment, precipitation of desired quinazolinone occurred. The product was filtered and rinsed with water, recrystallized from aq EtOH and dried under vacuum. This procedure gave product **15** (1.10g, 5.0 mmol, 99.1%) as a light pink solid; mp 237–239 °C.

IR (KBr): 3431 (NH), 3024 (CH), 2980 (CH), 1669 (C=O amide), 1613 (aromatic CN), 1487 (aromatic C=C), 1245 (COC), 861 (CH) cm^{-1}.

^1H NMR [300 MHz, $(CD_3)_2SO$]: δ = 12.09 (s, 1 H, H-3), 7.41 (s, 1 H, H-5), 7.07 (s, 1 H, H-8), 3.86 (s, 3 H, H-6a), 3.90 (s, 3 H, H-7a), 2.32 (s, 3 H, H-11).

4-Chloro-6,7-dimethoxyquinazoline (16) (Scheme 4, step b); Typical Procedure

A suspension of 3*H*-6,7-dimethoxyquinazolin-4-one (**14**) (0.79 g, 3.83 mmol) in thionyl chloride (7 mL) containing 10 drops of DMF was stirred and heated under reflux for 3 h, when a clear solution was obtained. The reaction mixture was allowed to cool to r.t. Then, the residue was diluted with CH_2Cl_2 and water (160 mL), placed in an ice bath, and washed aq sat. Na_2CO_3 (30 mL). Solid Na_2CO_3 was carefully added until the pH reached 7–8. Afterwards, the aq layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic phases were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give 4-chloro-6,7-dimethoxyquinazoline (**16**) as a yellow solid (0.68 g, 3.03 mmol, 79.1%); mp 185–187 °C.[7]

IR (KBr): 2974.6 (CH), 1619.2 (aromatic CN) 1511(aromatic CC), 1232.8 (COC), 789.1 (CH), 872.2 (CCl) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.90 (s, 1 H, H-2), 7.39 (s, 1 H, H-5), 7.34 (s, 1 H, H-6), 4.08 (s, 6 H, H-6[a], H-7a).

4-Chloro-6,7-dimethoxy-2-methylquinazoline (17) (Scheme 4, step b); Typical Procedure

This compound was prepared in 90.6% yield (0.29 g, 1.21 mmol) from quinazolinone **15** (0.30 g, 1.36 mmol) and thionyl chloride (13.0 g, 8 mL, 109 mmol) according to the procedure used for the derivative **16**; mp 184–186 °C.[7]

IR (KBr): 3003 (aromatic CH), 2984 (CH), 1504 (aromatic CC), 1235 (COC), 846 (CCl) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 7.34 (s, 1 H, H-5), 7.25 (s, 1 H, H-8), 4.04 (s, 6 H, H-6a, H-7a) 2.79 (s, 3 H, H-11).

4-*N*-[3′- or 4′-(*R*)-Phenyl]amino-6,7-dimethoxyquinazoline Hydrochloride (18a–i and 18b′–i′) (Scheme 4, step c); General Procedure

Chloro displacement[7]

A mechanically stirred mixture of 4-chloro-6,7-dimethoxyquinazoline (**16**) (0.10 g, 0.445 mmol) and the corresponding aniline (5.5 mmol) in *i*-PrOH (10 mL) was heated at reflux for 2 h and then cooled to r.t. The yellow solid precipitate was filtered, washed with *i*-PrOH (2 × 50 mL) and dried under vacuum to give the desired compound. In most cases, the product was isolated as the hydrochloride salt, by filtering directly from the reaction mixture.

4-*N*-(Phenylamino)-6,7-dimethoxyquinazoline (18a)

Yield: 0.110 g (0.346 mmol, 78.6%); mp 268–270 °C.[7]

IR (KBr): 3417.6 (NH), 3062.1 (aromatic CH), 1634.8–1459.5 (aromatic CN), 1459.5 (aromatic CC), 1279.3 (COC), 866.9–748.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.46 (s, 1 H, NH), 8.80 (s, 1 H, H-2), 8.35 (s, 1 H, H-5), 7.70 (d, ^3J = 8.0 Hz, 2 H, H-2′, H-6′), 7.50 (t, ^3J = 8.0 Hz, 2 H, H-3′, H-5′), 7.38 (s, 1 H, H-8), 7.32 (t, ^3J = 8.5 Hz, 1 H, H-4′), 4.04 (s, 3 H, H-6a), 4.01 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 281.1 (84.2) [M^+·], 280.1 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{15}N_3O_2$·HCl: C, 60.48; H, 5.07; N, 13.22. Found: C, 60.48; H, 4.92; N, 13.16.

4-*N*-(3′-Fluoro-phenyl)amino-6,7-dimethoxyquinazoline (18b)

Yield: 0.100 g (0.298 mmol, 66.7%); mp 219–221 °C.[7]

IR (KBr): 3412.3 (NH), 3062.1 (aromatic CH), 1634.8 (aromatic CN), 1490.4 (aromatic C=C), 1279.3 (COC), 985.4 (CF), 872.4–774.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.51 (s, 1 H, NH), 8.86 (s, 1 H, H-2), 8.41 (s, 1 H, H-5), 7.74 (dt, $^3J_{HF}$ = 11.0 Hz, $^4J_{HH}$ = 2.0 Hz, 1 H, H-2′), 7.63 (ddd, ^3J = 8.1 Hz, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 7.52 (dt, $^3J_{HH}$ = 8.3 Hz, $^4J_{HF}$ = 6.7 Hz, 1 H, H-5′), 7.39 (s, 1 H, H-8), 7.15 (tdd, $^3J_{HH}$ = $^3J_{HF}$ = 8.6 Hz, $^4J_{HH}$ = 2.6 Hz, $^4J_{HH}$ = 1.0 Hz, 1 H, H-4′), 4.04 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 299.0 (91.4) [M^+·], 298.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2F$·HCl: C, 57.24; H, 4.50; N, 12.51. Found: C, 57.14; H, 4.38; N, 12.34.

4-*N*-(4′-Fluoro-phenyl)amino-6,7-dimethoxyquinazoline (18b′)

Yield: 0.098 g (0.292 mmol, 65.3%); mp 269–272 °C.

IR (KBr): 3417.6 (NH), 3031.2 (aromatic CH), 1634.8 (aromatic CN), 1511.1 (aromatic CN), 1284.3 (COC), 825.7 (CF), 774.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.56 (s, 1 H, NH), 8.79 (s, 1 H, H-2), 8.40 (s, 1 H, H-5), 7.75 (dd, ^3J = 9.0 Hz, $^4J_{HF}$ = 5.0 Hz, 2 H, H-2′, H-6′), 7.38 (s, 1 H, H-8), 7.32 (t, ^3J = 9.0 Hz, 2 H, H-3′, H-5′), 4.02 (s, 3 H, H-6a), 3.98 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 299.1 (92.0) [M^+·], 298.1 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2F$·HCl: C, 57.24; H, 4.50; N, 12.51. Found: C, 57.22; H, 4.41; N, 12.38.

4-*N*-(3′-Chloro-phenyl)amino-6,7-dimethoxyquinazoline (18c)

Yield: 0.113 g (0.321 mmol, 72.0%); mp 226–228 °C.[7]

IR (KBr): 3427.9 (NH), 3041.5 (aromatic CH), 1639.8 (aromatic CN), 1521.3 (aromatic CC), 1284.3 (COC), 990.7 (CCl), 877.3–774.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.60 (s, 1 H, NH), 8.88 (s, 1 H, H-2), 8.45 (s, 1 H, H-5), 7.93 (t, ^3J = 2.0 Hz, 1 H, H-2′), 7.77 (ddd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1 H, H-4′), 7.51 (t, ^3J = 8.0 Hz, 1 H, H-5′), 7.40 (s, 1 H, H-8), 7.37 (ddd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 4.04 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 315.0 (71.3) [M^+·], 314.0 (100) [M – H]$^+$ (100).

Anal. Calcd. for $C_{16}H_{14}N_3O_2Cl$.HCl: C, 54.56; H, 4.29; N, 11.93. Found: C, 54.43; H, 4.17; N, 11.27.

4-*N*-(4′-Chloro-phenyl)amino-6,7-dimethoxyquinazoline (18c′)[24]

Yield: 0.105 g (0.298 mmol, 66.9%); mp 282–284 °C.[21]

IR (KBr): 3397.0 (NH), 3041.5 (aromatic CH), 1634.8 (aromatic CN), 1516.3 (aromatic CC), 1243.1 (COC), 985.4 (CCl), 856.6–774.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.16 (s, 1 H, NH), 8.74 (s, 1 H, H-2), 8.28 (s, 1 H, H-5), 7.79 (d, ^3J = 8.5 Hz, 2 H, H-2′, H-6′), 7.50 (d, ^3J = 8.5 Hz, 2 H, H-3′, H-5′), 7.33 (s, 1 H, H-8), 4.00 (s, 3 H, H-6a), 3.97 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 315.0 (82.8) [M^+·], 314.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2Cl$·HCl: C, 54.56; H, 4.29; N, 11.93. Found: C, 54.77; H, 4.49; N, 11.27.

4-*N*-(3′-Bromo-phenyl)amino-6,7-dimethoxyquinazoline (18d)

Yield: 0.165 g (0.416 mmol, 93.2%); mp 263–265 °C.[7]

IR (KBr): 3417.6 (NH), 3031.2 (aromatic CH), 1639.8 (aromatic CN), 1521.3 (aromatic CC), 1279.3 (COC), 872.2–779.4 (CH), 600 (CBr) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.70 (s, 1 H, NH), 8.88 (s, 1 H, H-2), 8.45 (s, 1 H, H-5), 8.04 (t, ^4J = 2.0 Hz, 1 H, H-2′), 7.80 (ddd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1 H, H-4′), 7.49 (ddd, ^3J = 8.0 Hz, ^4J = 2.0 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 7.46 (t, ^3J = 8.0 Hz, 1 H, H-5′), 7.39 (s, 1 H, H-8), 4.03 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 359.0 (77.5) [M^+·], 360.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2Br.HCl$: C, 48.45; H, 3.81; N, 10.59. Found: C, 48.85; H, 3.54; N, 10.64.

4-*N*-(4′-Bromo-phenyl)amino-6,7-dimethoxyquinazoline (18d′)
Yield: 0.126 g (0.318 mmol, 71.2%); mp 277–279 °C.

IR (KBr): 3448.6 (NH), 3144.4 (aromatic CH), 1629.5 (aromatic CN), 1516.3 (aromatic CC), 1284.3 (COC), 866.9–774.4 (CH), 501.1 (CBr) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.19 (s, 1 H, NH), 8.88 (s, 1 H, H-2), 8.22 (s, 1 H, H-5), 7.70 (high s, 4 H, H-2′, H-3′, H-5′, H-6′), 7.32 (s, 1 H, H-8), 4.04 (s, 3 H, H-6a), 4.02 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 358.9 (81.1) [M^+·], 358.9 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2Br$·HCl: C, 48.45; H, 3.81; N, 10.59. Found: C, 48.38; H, 3.61; N, 10.54.

4-*N*-(3′-Iodo-phenyl)amino-6,7-dimethoxyquinazoline (18e)
Yield: 0.119 g (0.268 mmol, 60.4%); mp 218–220 °C.[7]

IR (KBr): 3417.6 (NH), 3025.9 (aromatic CH), 1629.5 (aromatic CN), 1516.3 (aromatic CC), 1279.3 (COC), 877.3–779.4 (CH), 600 (CI) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.50 (s, 1 H, NH), 8.85 (s, 1 H, H-2), 8.39 (s, 1 H, H-5), 8.15 (t, ^4J = 1.5 Hz, 1 H, H-2′), 7.81 (ddd, ^3J = 8.2 Hz, ^4J = 1.5 Hz, ^4J = 1.0 Hz, 1 H, H-4′), 7.70 (ddd, ^3J = 8.0 Hz, ^4J = 1.5 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 7.39 (s, 1 H, H-8), 7.27 (t, ^3J = 8.0 Hz, 1 H, H-5′), 4.03 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 406.9 (95.0) [M^+·], 405.9 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2I$·HCl: C, 43.31; H, 3.41; N, 9.47. Found: C, 43.26; H, 3.35; N, 9.26.

4-*N*-(4′-Iodo-phenyl)amino-6,7-dimethoxyquinazoline (18e′)
Yield: 0.121 g (0.273 mmol, 61.4%); mp 266–269 °C.

IR (KBr): 3397.0 (NH), 3031.2 (aromatic CH), 1634.8 (aromatic CN), 1516.3 (aromatic CC), 1289.6 (COC), 872.3–779.4 (CH), 501.1 (CI) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.50 (s, 1 H, NH), 8.83 (s, 1 H, H-2), 8.38 (s, 1 H, H-5), 7.82 (d, ^3J = 8.5 Hz, 2 H, H-3′, H-5′), 7.58 (d, ^3J = 8.5 Hz, 2 H, H-2′, H-6′), 7.37 (s, 1 H, H-8), 4.02 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 407.0 (100) [M^+·], 406.0 (93.2) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_3O_2I$·HCl: C, 43.31; H, 3.41; N, 9.47. Found: C, 43.44; H, 3.42; N, 9.28.

4-*N*-(3′-Methoxy-phenyl)amino-6,7-dimethoxyquinazoline (18f)
Yield: 0.094 g (0.270 mmol, 60.6%); mp 216–218 °C.

IR (KBr): 3438.3 (NH), 3005.3 (aromatic CH), 1634.8 (aromatic CN), 1495.7 (aromatic CC), 1279.3 (COC), 872.2–774.4 (CH) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.39 (s, 1 H, NH), 8.81 (s, 1 H, H-2), 8.37 (s, 1 H, H-5), 7.39 (s, 1 H, H-8), 7.39 (t, ^3J = 8.0 Hz, 1 H, H-5′), 7.35 (t, ^4J = 2.0 Hz, 1 H, H-2′), 7.31 (ddd, ^3J = 8.0 Hz, ^4J = 2. 0 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 6.90 (ddd, ^3J = 8.2 Hz, ^4J = 2.5 Hz, ^4J = 1.0 Hz, 1 H, H-4′), 4.03 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a), 3.80 (s, 3 H, H-7′).

MS (EI): *m*/*z* (%) = 311.0 (79.3) [M^+·], 310.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_3.HCl$: C, 58.71; H, 5.22; N, 12.08. Found: C, 58.52; H, 5.00; N, 12.17.

4-*N*-(4′-Methoxy-phenyl)amino-6,7-dimethoxyquina-zoline (18f′)
Yield: 0.101 g (0.291 mmol, 65.2%); mp 205–207 °C.

IR (KBr): 3403.2 (NH), 2948.6 (aromatic CH), 1634.8 (aromatic CN), 1516.3 (aromatic CC), 1243.1 (COC), 861.9–774.4 (CH) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.52 (s, 1 H, NH), 8.76 (s, 1 H, H-2), 8.38 (s, 1 H, H-5), 7.59 (d, ^3J = 9.0 Hz, 2 H, H-2′, H-6′), 7.38 (s, 1 H, H-8), 7.02 (d, ^3J = 9.5 Hz, 2 H, H-3′, H-5′), 4.01 (s, 3 H, H-6a), 3.97 (s, 3 H, H-7a), 3.80 (s, 3 H, H-7′).

MS (EI): *m*/*z* (%) = 311.1 (100) [M^+·], 310.1 (64.9) [M – H]$^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_3$·HCl: C, 58.71; H, 5.22; N, 12.08. Found: C, 58.68; H, 5.03; N, 12.10.

4-*N*-(3′-Methyl-phenyl)amino-6,7-dimethoxyquinazoline (18g)[11]
Yield: 0.075 g (0.226 mmol, 50.7%); mp 221–223 °C.[11]

IR (KBr): 3417.6 (NH), 3007.6 (aromatic CH), 1634.8 (aromatic CN), 1511.0 (aromatic CC), 1279.3 (COC), 775.0 (CH) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.24 (s, 1 H, NH), 8.78 (s, 1 H, H-2), 8.29 (s, 1 H, H-5), 7.50 (signal superposition, 2 H, H-2′, H-5′), 7.36 (signal superposition, 2 H, H-8, H-6′), 7.14 (d, ^3J = 8.0 Hz, 1 H, H-4′), 4.02 (s, 3 H, H-6a), 3.99 (s, 3 H, H-7a), 2.37 (s, 3 H, H-7′).

MS (EI): *m*/*z* (%) = 295.0 (87.4) [M^+·], 294.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_2$·HCl: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.96; H, 5.55; N, 12.96.

4-*N*-(4′-Methyl-phenyl)amino-6,7-dimethoxyquinazoline (18g′)
Yield: 0.096 g (0.290 mmol, 64.9%); mp 227–229 °C.

IR (KBr): 3418.6 (NH), 2948.6 (CH), 1634.8 (aromatic CN), 1506.0 (aromatic CC), 1279.3 (COC), 866.9–779.4 (CH) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.26 (s, 1 H, NH), 8.75 (s, 1 H, H-2), 8.30 (s, 1 H, H-5), 7.57 (d, ^3J = 8.3 Hz, 2 H, H-2′, H-6′), 7.36 (s, 1 H, H-8), 7.28 (d, ^3J = 8.3 Hz, 2 H, H-3′, H-5′), 4.01 (s, 3 H, H-6a), 3.98 (s, 3 H, H-7a), 2.35 (s, 3 H, H-7′).

MS(EI): *m*/*z* (%) = 295.1 (85.1) [M^+·], 294.1 (100) [M – H]$^+$.

Anal. Calcd for $C_{17}H_{17}N_3O_2$·HCl: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.27; H, 5.53; N, 12.42.

4-*N*-(3′-Acetyl-phenyl)amino-6,7-dimethoxyquinazoline (18h)
Yield: 0.097 g (0.270 mmol, 60.6%); mp 219–221 °C.

IR (KBr): 3427.9 (NH), 3036.2 (aromatic CH), 1681.1 (C=O), 1634.8 (aromatic CN), 1516.3 (aromatic CC), 1279.3 (COC), 882.5–779.4 (CH) cm^{-1}.

^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.49 (s, 1 H, NH), 8.79 (s, 1 H, H-2), 8.45 (s, 1 H, H-5), 8.34 (t, ^4J = 2.0 Hz, 1 H, H-2′), 8.10 (ddd, ^3J = 8.1 Hz, ^4J = 2.1 Hz, ^4J = 1.1 Hz, 1 H, H-6′), 7.87 (ddd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, ^4J = 1.1 Hz, 1 H, H-4′), 7.62 (t, ^3J = 8.0 Hz, 1 H, H-5′), 7.42 (s, 1 H, H-8), 4.05 (s, 3 H, H-6a), 3.99 (s, 3 H, H-7a), 2.63 (s, 3 H, H-8′).

MS (EI): *m*/*z* (%) = 323.0 (83.9) [M^+·], 322.0 (100) [M – H]$^+$.

Anal. Calcd for $C_{18}H_{17}N_3O_3$·HCl: C, 60.09; H, 5.04; N, 11.68. Found: C, 59.07; H, 4.69; N, 11.72.

4-*N*-(4′-Acetyl-phenyl)amino-6,7-dimethoxyquinazoline (18h′)
Yield: 0.110 g (0.306 mmol, 68.7%); mp 218–220 °C.

IR (KBr): 3412.3 (NH), 2995.2 (aromatic CH), 1670.8 (C=O), 1634.8 (aromatic CN), 1516.3 (aromatic CC), 1279.3 (COC), 872.2–779.4 (CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.33 (s, 1 H, NH), 8.84 (s, 1 H, H-2), 8.35 (s, 1 H, H-5), 8.03 (d, ^3J = 9.0 Hz, 2 H, H-3′, H-5′), 7.98 (d, ^3J = 9.0 Hz, 2 H, H-2′, H-6′), 7.36 (s, 1 H, H-8), 4.03 (s, 3 H, H-6a), 3.98 (s, 3 H, H-7a), 2.60 (s, 3 H, H-8′).

MS (EI): *m*/*z* (%) = 323.1 (73.0) [M^+·], 322.1 (100) [M – H]$^+$.

Anal. Calcd for $C_{18}H_{17}N_3O_3$.HCl: C, 60.09; H, 5.04; N, 11.68. Found: C, 59.07; H, 4.67; N, 11.73.

4-*N*-(3′-Nitro-phenyl)amino-6,7-dimethoxyquinazoline (18i)
Yield :0.093 g (0.256 mmol, 57.8%); mp 279–281 °C.

IR (KBr): 3443.3 (NH), 3025.9 (aromatic CH), 1634.8 (aromatic CN), 1511.0 (aromatic CC), 1531.7 (NO_2), 1284.3 (COC), 872.2–733.1 (=CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 11.10 (s, 1 H, NH), 8.82 (s, 1 H, H-2), 8.76 (t, ^4J = 2.0 Hz, 1 H, H-2′), 8.34 (s, 1 H, H-5), 8.33 (ddd, ^3J = 8.0 Hz, ^4J = 2.2 Hz, ^4J = 1.0 Hz, 1 H, H-4′), 8.07 (ddd, ^3J = 8.2 Hz, ^4J = 2.2 Hz, ^4J = 1.0 Hz, 1 H, H-6′), 7.74 (t, ^3J = 8.5 Hz, 1 H, H-5′), 7.31 (s, 1 H, H-8), 4.04 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 326.0 (100) [M^+·], 325.0 (83.5) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_4O_4$.HCl: C, 52.97; H, 4.17; N, 15.44. Found: C, 52.68; H, 4.04; N, 15.04.

4-*N*-(4′-Nitro-phenyl)amino-6,7-dimethoxyquinazoline (18i′)
Yield: 0.121 g (0.334 mmol, 75.1%); mp 228–230 °C.

IR (KBr): 3427.9 (NH), 3118.7 (aromatic CH), 1634.8 (aromatic CN), 1511.0 (aromatic CC), 1572.9 (NO_2), 1279.3 (COC), 866.9–779.4 (=CH) cm^{-1}.

^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 10.70 (s, 1 H, NH), 8.78 (s, 1 H, H-2), 8.32 (d, ^3J = 9.0 Hz, 2 H, H-3′, H-5'), 8.18 (d, ^3J = 9.0 Hz, 2 H, H-2′, H-6′), 8.11 (s, 1 H, H-5), 7.31 (s, 1 H, H-8), 4.02 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a).

MS (EI): *m*/*z* (%) = 326.1 (86.9) [M^+·], 325.1 (100) [M – H]$^+$.

Anal. Calcd for $C_{16}H_{14}N_4O_4$.HCl: C, 52.97; H, 4.17; N, 15.44. Found: C, 52.76; H, 4.10; N, 14.98.

4-*N*-(Phenylamino)-6,7-dimethoxy-2-methyl-quinazoline (19) (Scheme 4, step c); Typical Procedure
The same procedure as that for the syntheses of compounds **18a**–**i** and **18b′**–**i′**, was followed for the reaction of the chloro-derivative **17** (0.50 g, 2.10 mmol) with aniline (1.58 g, 1 mL, 11.0 mmol) yielding compound **19** as a light yellow solid (0.30 g, 1.02 mmol, 48.4%); mp 268–270 °C.

IR (KBr): 3436 (NH), 3057 (aromatic CH), 2965 (CH), 1638 (aromatic CN), 1561 (aromatic CC), 1224 (COC), 773 (CH) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 11.18 (s, 1 H, NH), 8.26 (s, 1 H, H-5), 7.29 (s, 1 H, H-8), 7.74 (d, ^3J = 8.4 Hz, 2 H, H-2′, H-6′), 7.50 (t, ^3J = 7.7 Hz, 2 H, H-3′, H-5′), 7.31 (t, ^3J = 7.7 Hz, 1 H, H-4′), 3.99 (s, 3 H, H-6a), 4.00 (s, 3 H, H-7a), 2.60 (s, 3 H, H-11).

4-*N*-(3′-Bromo-phenyl)amino-6,7-dimethoxy-2-methylquinazoline (20) (Scheme 4, step c); Typical Procedure
The same procedure as that for the syntheses of compounds **18a**–**i** and **18b′**–**i′**, was also followed for the reaction of the chloro-derivative **17** (0.40 g, 1.68 mmol) and 3-bromoaniline (0.79 g, 0.5 mL, 4.59 mmol), yielding compound **20** as a yellow solid (0.50 g, 1.34 mmol, 79.4%); mp 263–265 °C.[7]

IR (KBr): 3415 (NH), 3029 (aromatic CH), 2997 (CH), 1634 (aromatic CN), 1561 (aromatic CC), 1217 (COC), 868 (CBr), 777 (CH) cm^{-1}.

^{1}H NMR [300 MHz, $(CD_3)_2SO$]: δ = 9.51 (s, 1 H, N-H), 7.83 (s, 1 H, H-5), 7.16 (s, 1 H, H-8), 8.21 (t, ^4J = 1.8 Hz, 1 H, H-2′), 7.99 (dd, ^3J = 8.1 Hz, ^4J = 1.1 Hz, 1 H, H-6′), 7.36 (t, ^3J = 8.1 Hz, 1 H, H-5′), 7.27 (dd, ^3J = 8.8 Hz, ^4J = 1.8 Hz, 1 H, H-4′) 3.96 (s, 3 H, H-6a), 3.92 (s, 3 H, H-7a), 2.55 (s, 3 H, H-11).

Anal. Calcd for $C_{17}H_{16}N_3O_2Br$·HCl: C, 49.72; H, 4.17; N, 10.23. Found: C, 49.67; H, 4.12; N, 10.12.

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References

(1) Palmer, B. D.; Trumpp-Kallmeyer, S.; Fry, D. W.; Nelson, J. M.; Showalter, H. D. H.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 1519.
(2) Thompson, A. M.; Murray, D. K.; Elliot, W. L.; Fry, D. W.; Nelson, J. A.; Showalter, H. D. H.; Roberts, B. J.; Vincent, P. W.; Denny, W. A. *J. Med. Chem.* **1997**, *40*, 3915.
(3) Fry, D. W.; Kraber, A. J.; McMichael, A.; Ambroso, L. A.; Nelson, J. M.; Leopold, W. R.; Connors, R. W.; Bridges, A. J. *Science* **1994**, *265*, 1093.
(4) Baselga, J.; Averbuch, S. D. *Drugs* **2000**, *60*, 33.
(5) Ciardiello, F. *Drugs* **2000**, *60*, 25.
(6) Rewcastle, G. W.; Denny, W. A.; Bridges, A. J.; Zhou, H.; Cody, D. R.; McMichael, A.; Fry, D. W. *J. Med. Chem.* **1995**, *38*, 3482.
(7) Bridges, A. J.; Zhou, H.; Cody, D. R.; Rewcastle, G. W.; McMichael, A.; Fry, D. W.; Denny, W. A. *J. Med. Chem.* **1996**, *39*, 267.
(8) Rewcastle, G. W.; Murray, D. K.; Elliot, W. L.; Fry, D. W.; Howard, C. T.; Nelson, J. A.; Roberts, B. J.; Vincent, P. W.; Showalter, H. D. H.; Winters, R. T.; Denny, W. A. *J. Med. Chem.* **1998**, *41*, 742.
(9) Fry, D. W. *Pharmacol. Ther.* **1999**, *82*, 207.
(10) Levitzki, A. *Pharmacol. Ther.* **1999**, *82*, 231.
(11) Fry, D. W. *Annu. Rep. Med. Chem.* **1996**, *31*, 151.
(12) Rewcastle, G. W.; Denny, W. A.; Showalter, H. D. H. *Curr. Org. Chem.* **2000**, *4*, 679.
(13) Szczepankiewicz, W.; Suwiski, J.; Bujok, R. *Tetrahedron* **2000**, *56*, 9343.
(14) Tomisek, A. J.; Christensen, B. E. *J. Am. Chem. Soc.* **1948**, *70*, 2423.
(15) Zentmyer, D. T.; Wagner, E. C. *J. Org. Chem.* **1949**, *14*, 967.
(16) Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12.
(17) Yale, H. L. *J. Am. Chem. Soc.* **1955**, *75*, 675.
(18) Girgis, N. S.; Mϕller, J.; Pedersen, E. B. *Chem. Scrip.* **1986**, *26*, 617.
(19) Taylor, E. C.; Ravindranathan, R. V. *J. Org. Chem.* **1962**, *27*, 2622.
(20) Loakes, D.; Brown, D. M.; Salisbury, S. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1333.
(21) Veldhuyzen, W. F.; Shallop, A. J.; Jones, R. A.; Rokita, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 11126.
(22) Franchini, K., Faculty of Medical Sciences, State University of Campinas, personal communication.
(23) Nishikawa, S.; Maki, S.; Nishikimi, Y.; Kumazawa, Z.; Kashimura, N. *Biosci. Biotech. Biochem.* **1994**, *58*, 1709.
(24) Hennequin, L. F.; Thomas, A. P.; Johnstone, C.; Stokes, E. S. E.; Plé, P. A.; Lohmann, J. J. M.; Ogilvie, D. J.; Dukes, M.; Wedge, S. R.; Curwen, J. O.; Kendrew, J.; Brempt, C. L. *J. Med. Chem.* **1999**, *42*, 5369.