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.\(^5\)

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 3H-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.\(^12\)

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, which included a cyclodehydration giving the quinazolinone 3, was formed. Actually, the literature\(^15,16\) reports that 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 2-acetylanthranilamide (3). Subsequent heating of compound 3 with NaOH solution led to a cyclodehydration giving the quinazolinone 4.\(^16\)

3H-2-Methyl-4-thioxoquinazoline (5) was synthesized from anthranilonitrile (7) and thialactonic acid (Scheme 2).\(^17\) Since the described method from 3H-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 3H-2-methyl-4-quinazolinone (4), aniline, phosphorus pentoxide and \(N,N\)-dimethylcyclohexylamine, in a single step (Scheme 1, step f).

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A different synthetic approach to 4-anilinoquinazolines, starting from anthranilonitrile and phenyl isothiocyanate, has been described by Taylor and Ravindranathan 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 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-phenylaminoquinozoline-2(1H)-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. This sequence of ring-opening and ring-closure required high temperatures, and it represents a pure thermal conversion of 10 to 11 (Scheme 3).

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

The cyclization of 4,5-dimethoxyanthranilic acid (13) with formamide, at a high temperature (165 °C), leads to 3H-6,7-dimethoxyquinozolin-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 NH3 and 10% NaOH. The second step in the derivatization, involved conversion of the 3H-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.

In conclusion, twenty two quinazoline derivatives were prepared by three synthetic pathways (Experimental section). 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 did not lead to satisfactory results.

The syntheses of ten compounds (18b′, 18d′, 18e′, 18f, 18g′, 18h′, 18i′, 18g and 18h′) are reported for the first time. Preliminary experiments have shown that these compounds can exhibit cardiovascular activity and it has also been reported that some quinazoline derivatives can be potential anticarcinogenic agents. 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-
A stirred solution consisting of antranilic 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 Ac₂O was removed under vacuum in a rotary evaporator. The resulting solid was placed in an Erlemeyer flask and then concd NH₃ (100 mL) was slowly added (exothermic reaction). The reaction mixture was kept at r.t. for 4 h. Afterwards, the crude material was washed under vacuum and, after recrystallization from ac 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), 3032 (aromatic CH), 2978 (CH), 1681 (C=O amide), 1615 (aromatic CN), 1421 (aromatic CC), 775 (CH) cm⁻¹.

¹¹H NMR [300 MHz, (CD₃)₂SO]: δ = 12.34 (s, 1 H, H-3), 6.40 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-5), 7.23 (td, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-6), 7.75 (td, J = 7.77 Hz, J = 1.6 Hz, 1 H, H-7), 5.90 (dd, J = 8.0 Hz, J = 1.0 Hz, 1 H, H-8), 2.38 (s, 3 H, H-11).

The mixture of 2-methyl-3,1-benzoxazin-4-one (10 g, 62.5 mmol), phosphorus pentasulfide (13.5 g, 61.0 mmol) and xylene (100 mL) was heated at reflux for 2 h. The excess Ac₂O was removed under vacuum in a rotary evaporator. The residue was distilled under vacuum and, after recrystallization from ac EtOH and drying under vacuum, the desired product was obtained as a yellow solid (15 g, 84.3 mmol, 57.7%); mp 187–189 °C.¹⁵,¹⁶

IR (KBr): 3414 (NH), 3032 (aromatic CH), 2978 (CH), 1681 (C=O amide), 1615 (aromatic CN), 1421 (aromatic CC), 775 (CH) cm⁻¹.

¹¹H NMR [300 MHz, (CD₃)₂SO]: δ = 12.34 (s, 1 H, H-3), 6.40 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-5), 7.23 (td, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-6), 7.75 (td, J = 7.77 Hz, J = 1.6 Hz, 1 H, H-7), 5.90 (dd, J = 8.0 Hz, J = 1.0 Hz, 1 H, H-8), 2.38 (s, 3 H, H-11).

Anal. Calcd for C₁₄H₁₁N₃O₂: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.60; H, 5.51; N, 15.55.

Method A

The reaction mixture was prepared according to Method A and heated at reflux for 2 h. Excess of Ac₂O 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 acylanilinamide (2, cyclic compound) was not successful, and a mixture was obtained (3.20 g) which melted at 80–82 °C.¹⁶

Scheme 4
(a) For 14: Formamidine acetate, 140 °C, 8 h or 165 °C, formamide, 3 h; for 15: (i) Acetic anhydride, reflux, 4 h, NH₃, 4 h, r.t., (ii) 10% NaOH; (b) SOCl₂, DMF, reflux, 2 h; (c) corresponding aniline, i-PrOH, reflux, 2 h.

Method B

The same procedure as Method A was carried out up to removal of Ac₂O. The resulting mixture of cyclic and acyclic compounds was then dried under vacuum to give 18 g of the same mixture as in Method B (Scheme 2) ¹⁷

To the mixture of 2-methyl-3,1-benzoxazin-4-one (10 g, 62.5 mmol), phosphorus pentasulfide (13.5 g, 61.0 mmol) and xylene (100 mL) was heated at reflux for 2 h. Afterwards, the crude mixture was washed under vacuum and, after recrystallization from ac 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), 3032 (aromatic CH), 2978 (CH), 1681 (C=O amide), 1615 (aromatic CN), 1421 (aromatic CC), 775 (CH) cm⁻¹.

¹¹H NMR [300 MHz, (CD₃)₂SO]: δ = 12.34 (s, 1 H, H-3), 6.40 (dd, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-5), 7.23 (td, J = 8.0 Hz, J = 1.6 Hz, 1 H, H-6), 7.75 (td, J = 7.77 Hz, J = 1.6 Hz, 1 H, H-7), 5.90 (dd, J = 8.0 Hz, J = 1.0 Hz, 1 H, H-8), 2.38 (s, 3 H, H-11).

2-Methyl-4-N-phenylaminoquinazoline (6); Typical Procedure Method A (Scheme 1, step e)\textsuperscript{14}

A mixture of phosphorus pentoxide (7.10 g, 50.0 mmol), aniline (4.10 g, 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 EtO\textsubscript{2}. Only 50.4 mg of a solid that melted at 189–195° was obtained. By analyzing the \textsuperscript{1}H and \textsuperscript{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)\textsuperscript{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, 3H-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\textsubscript{2}Cl\textsubscript{2} and this was washed with water and dried over MgSO\textsubscript{4}, filtered and concentrated to dryness under reduced pressure. The residue was recrystallized from 50% aq EtOH to give a dark yellow solid (0.70 g, 29.8 mmol, 23.8%). mp 163–165 °C. 23

A suspension of 2-amino-4,5-dimethoxybenzoic acid (1.0 g, 5.08 mmol, 19.2%). mp 163–165 °C. 23

Method A\textsuperscript{7}

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\textsuperscript{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 ground 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 cooled to room temperature and sonicated with aq NaOH solution. After adjusting the pH to 8, the resulting purple-gray solid was filtered, rinsed with water (3 × 10 mL), and dried under vacuum to give 3H-6,7-dimethoxyquinazolin-4-one (14) (0.79 g, 3.83 mmol, 75.9%); mp 296–298 °C.\textsuperscript{7}

Computer program: PROSPECTOR (UNICAMP Universidade Estadual de Campinas), Dot Ltd, Information. Copyrighted material.

1H NMR [300 MHz, (CD\textsubscript{3})\textsubscript{2}SO]: 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-6), 3.91 (s, 3 H, H-6a), 3.87 (s, 3 H, H-7a), 3.87 (s, 3 H, H-7a).

3H-6,7-Dimethoxyquinazolin-4-one (15) (Scheme 4, step a); Typical Procedure

A suspension of 2-aminoo-4,5-dimethoxybenzoic acid (13) (1.0 g, 5.08 mmol) and anhyd Ac\textsubscript{2}O (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\textsubscript{4}Cl (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): 3438 (NH), 3093 (aromatic CH), 1603 (C=N), 1487 (aromatic CN), 1302 (aromatic CC), 1189 (C=S), 756 (CH) cm\textsuperscript{-1}.

3H-6,7-Dimethoxyquinazolin-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 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%).
4-Chloro-6,7-dimethoxyquinazoline (16) (Scheme 4, step b); Typical Procedure
A suspension of 3H-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 CH₂Cl₂ and water (160 mL), placed in an ice bath, and washed aq sat. Na₂CO₃ (30 mL). Solid Na₂CO₃ was carefully added until the pH reached 7–8. Afterwards, the aq layer was extracted with CH₂Cl₂ (2 × 30 mL), and the combined organic phases were washed with brine (2 × 10 mL), dried over MgSO₄, 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.

IR (KBr): δ = 3412.3 (NH), 3062.1 (aromatic CH), 1634.8 (aromatic CN), 1235 (COC), 846 (CCl) cm⁻¹.

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 (13.0 g, 8 mL, 109 mmol) according to the procedure used for the derivative 16; mp 184–186 °C.

IR (KBr): 3003 (aromatic CH), 2984 (CH), 1504 (aromatic CC), 1232 (COC), 983 (CCl), 877–774.4 (CH) cm⁻¹.

4-(N-[3'- or 4'-R)-Phenyl]-amino-6,7-dimethoxyquinazoline Hydrochloride (18a-i and 18b-f) (Scheme 4, step c); General Procedure
Chloro displacement
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.

IR (KBr): 3417.6 (NH), 3041.5 (aromatic CH), 1639.8 (aromatic CN), 1521.3 (aromatic CC), 1284.3 (COC), 990.7 (CCl), 877–774.4 (CH) cm⁻¹.

4-(N-[3'- or 4'-R)-Phenyl]-amino-6,7-dimethoxyquinazoline (18b-i and 18b-f) (Scheme 4, step c); General Procedure
Chloro displacement
This compound was prepared in 90.6% yield (0.29 g, 1.21 mmol) from quinazolinone (13.0 g, 8 mL, 109 mmol) according to the procedure used for the derivative 16; mp 184–186 °C.

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4-(N-[3'- or 4'-R)-Phenyl]-amino-6,7-dimethoxyquinazoline (18b-i and 18b-f) (Scheme 4, step c); General Procedure
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This compound was prepared in 90.6% yield (0.29 g, 1.21 mmol) from quinazolinone (13.0 g, 8 mL, 109 mmol) according to the procedure used for the derivative 16; mp 184–186 °C.

IR (KBr): 3003 (aromatic CH), 2984 (CH), 1504 (aromatic CC), 1232 (COC), 983 (CCl), 877–774.4 (CH) cm⁻¹.
Anal. Calcd for C₁₇H₁₇N₃O₂·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, (CD₃)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-6a), 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]⁺.

4-N-(3'-Iodo-phenyl)amino-6,7-dimethoxyquinazoline (18e)
Yield: 0.119 g (0.268 mmol, 60.4%); mp 218–220 °C.
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, (CD₃)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, J = 1.5 Hz, 1 H, H-2'), 7.81 (dd, J = 8.2 Hz, J = 1.5 Hz, J = 1.0 Hz, 1 H, H-4'), 7.70 (dd, J = 8.0 Hz, J = 1.5 Hz, J = 1.0 Hz, 1 H, H-6'), 7.39 (s, 1 H, H-8), 7.27 (t, J = 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]⁺.

4-N-(4'-Iodo-phenyl)amino-6,7-dimethoxyquinazoline (18f)
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), 1289.0 (COC), 872.2–774.4 (CH), 501.1 (Cl) cm⁻¹.

1H NMR [500 MHz, (CD₃)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, J = 8.5 Hz, 2 H, H-3', H-5'), 7.58 (d, J = 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 C₁₆H₁₄N₃O₂I·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 (18h)
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, (CD₃)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), 7.29 (t, J = 8.0 Hz, 1 H, H-5'), 7.35 (t, J = 2.0 Hz, 1 H, H-4'), 7.31 (dd, J = 8.0 Hz, J = 2.0 Hz, J = 1.0 Hz, 1 H, H-6'), 6.90 (dd, J = 8.2 Hz, J = 2.5 Hz, J = 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 (%) = 310.0 (79.3) [M⁺], 310.0 (100) [M – H]⁺.
Anal. Calcd for C₁₇H₁₄N₂O₃·HCl: C, 58.71; H, 5.22; N, 12.08. Found: C, 58.52; H, 5.00; N, 12.17.
The same procedure as that for the syntheses of compounds N4-(3)-Bromo-phenylamino-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–f, was also followed for the reaction of the chloro-derivative 17 (0.50 g, 2.10 mmol) with anilines (1.58 g, 1.10 mmol) yielding compound 19 as a light yellow solid (0.30 g, 1.02 mmol, 48.4%); mp 268–270 °C.

IR (KBr): 3427.9 (NH), 3118.7 (aromatic CH), 1634.8 (aromatic CN), 1561 (aromatic CC), 1224 (COC), 773 (CH) cm−1.


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References

(4) Basela, J.; Averbuch, S. D. Drugs 2000, 60, 33.
(14) Tomisek, A. J.; Christensen, B. E. J. Am. Chem. Soc. 1948, 70, 2423.
(22) Franchini, K., Faculty of Medical Sciences, State University of Campinas, personal communication.