

## First Functionalization by Metallation of the Benzene Moiety of Quinazolines. Diazines XIX.

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**Abstract:** The first lithiation on the benzene moiety of 4-substituted quinazolines has been highlighted. According to the nature and position of various directing groups, an exceptional regioselective metallation occurred at position C<sub>8</sub>, *peri* to the N-1 ring nitrogen. This method allows an easy access to a large range of new substituted quinazolines.  
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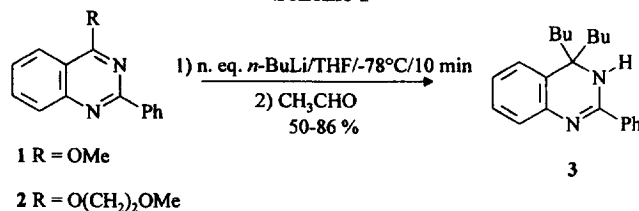
Directed *ortho*-lithiation of diazines has been recently developed. This technique is currently used to functionalize these heteroaromatic systems despite their high reactivity towards the competitive reaction of nucleophilic addition. In the field of benzodiazines, which are even more prone than diazines to undergo nucleophilic addition,<sup>1</sup> there are few papers dealing with the metallation of these compounds. The metallation of 2-substituted quinoxalines has been reported,<sup>1,2</sup> and more recently the *ortho*-directed metallation of cinnolines has been described,<sup>3</sup> opening a new route to *ortho*-disubstituted derivatives. With the quinazoline ring system, only lithiation of 3-acylamino-2-substituted-4(3*H*)-quinazolones and 2-alkyl- and 2-aryl-4(3*H*)-quinazolones has been reported.<sup>4,5</sup>

The synthesis of quinazoline derivatives is an interesting challenge since the quinazoline ring system provides the backbone for compounds having numerous pharmacological activities such as sedative, analgesic, diuretic, antihypertensive, antibiotic and antitumoral properties.

As a continuation of our studies on diazines<sup>6</sup> and benzodiazines,<sup>1-3</sup> we report here the direct lithiation and functionalization of 4-substituted quinazolines. It is of evidence that, for these compounds, the *ortho*-lithiation, which is induced by an *ortho*-directing group, would not occur, since there is a ring nitrogen atom at the *ortho* position. In this case, the lithiation would take place either at the C<sub>2</sub> position or on the benzene moiety.

In order to avoid the lithiation at the C<sub>2</sub> position, we have tested the metallation reaction with 4-methoxy-2-phenylquinazoline **1**. The phenyl group has been chosen because it undergoes a lithiation less easily than alkyl groups.<sup>7</sup> Concerning the methoxy group, it was observed that, during metallation of 1-methoxynaphthalene, under specific conditions, the methoxy group could induce a highly selective metallation at the C<sub>8</sub> position (*peri* to the methoxy).<sup>8</sup>

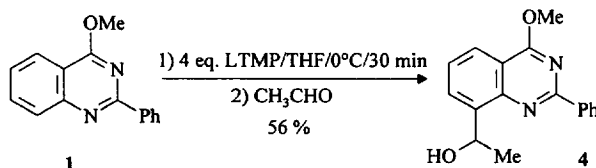
## Scheme 1



Reaction of **1** in anhydrous THF with 1,1 equivalent of *n*-butyllithium as metallating agent at -78°C for a short time (10 min), followed by reaction with acetaldehyde as the electrophile gave the addition compound **3** as sole product (50%). It could be assumed that a first nucleophilic attack by *n*-BuLi occurred at C<sub>4</sub>, followed by an elimination reaction, led to the aromatic 4-butyl-2-phenylquinazolinone. The latter underwent a nucleophilic addition affording **3**. An excess of *n*-BuLi (4 equivalents) provided **3** with a better yield (86%) (Scheme 1).

To avoid this competitive nucleophilic attack, the metallation was achieved by using lithium alkylamides which are less nucleophilic than alkyllithiums.

## Scheme 2



Treatment of **1** with an excess of lithium 2,2,6,6-tetramethylpiperidide (LTMP) (4 equivalents) at 0°C for 30 minutes followed by reaction with acetaldehyde led to the secondary alcohol **4** in moderate yield (56%) besides starting material (40 %) (Scheme 2). The compound **4** results from the lithiation on the benzene moiety. Determination of the site of lithiation has been achieved by NMR experimental methods such as nuclear Overhauser effect (nOe) and long range HETCOR.<sup>9</sup> Long range HETCOR spectrum of **4** revealed correlation between protons and carbons up to three bonds away, allowing unequivocal identification of the structure (Table 1).

	C <sub>4</sub>	C <sub>8</sub>	C <sub>9</sub>	C <sub>10</sub>
CH <sub>3</sub>		*		
OCH <sub>3</sub>	*			
H <sub>5</sub>	*		*	
H <sub>6</sub>		*		*
H <sub>7</sub>			*	

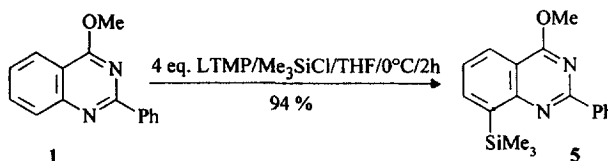
Table 1

*Selected correlations from the long range HETCOR spectrum of 4*

The structure of **4** was also confirmed by nOe effects between H<sub>5</sub> and the methoxy protons, H<sub>7</sub> and methyl and CH protons.

When the lithiation of **1** was performed under the experimental conditions of the "in situ trapping" method<sup>10</sup> at 0°C with 4 equivalents of LTMP for 2 hours and trimethylsilyl chloride as the electrophile, the 8-substituted quinazoline **5** was obtained as only product in very good yield (94 %).

Scheme 3



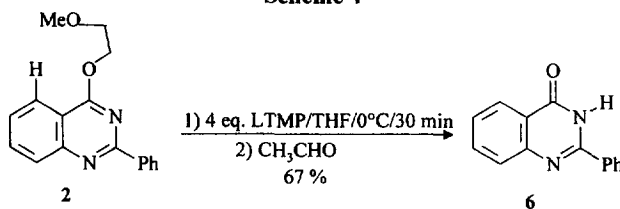
It can be noticed that the regioselective metallation was not induced by the methoxy group as it was for 1-methoxynaphthalene<sup>8</sup> but rather by the ring nitrogen atom.

Some years ago, such an unexpected lithiation *peri* to the ring nitrogen of quinoline has been reported during metallation of 4-pivaloylaminoquinoline,<sup>11</sup> and more recently during metallation of 4-chlorocinnoline.<sup>3</sup>

It would be interesting to observe if the replacement of the methoxy group by a more complexing group as the methoxyethoxy group (even if complexation with lithium alkylamides is weaker than the one with *n*-BuLi) could influence the site of metallation. Therefore, the metallation of 4-(2-methoxyethoxy)-2-phenylquinazoline **2** has also been tested.

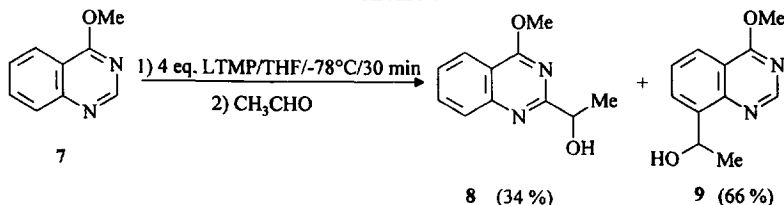
Reaction of **2** with 2.2 equivalents of *n*-BuLi under the previous conditions led to the addition compound **3** in 51 % yield (Scheme 1). With LTMP as metallating agent, no lithiation has been observed and 2-phenyl-4(3*H*)-quinazolinone **6** was obtained as sole product in 67 % yield with recovery of starting material (23 %) (Scheme 4).

Scheme 4



In order to test whether a competitive reactivity towards the metallation reaction could occur at the C<sub>2</sub> position or on the benzene moiety, the metallation of 4-methoxyquinazoline **7** has been performed using LTMP as metallating agent. A mixture of the secondary alcohols **8** and **9** was obtained (Scheme 5).

Scheme 5

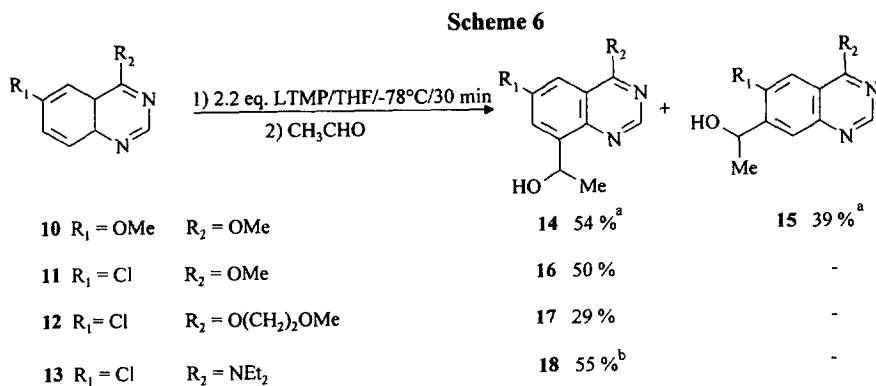


Metallation took place at the C<sub>8</sub> position on the benzene moiety affording the major product **9**, and at the C<sub>2</sub> position giving **8**.

One of our targets was the metallation at the C<sub>5</sub> position by assistance of a directing group placed on the pyrimidine moiety. However the results indicated a higher reactivity towards the metallation at the C<sub>8</sub> position rather than at the C<sub>2</sub> or C<sub>5</sub> positions. We then examined the influence of the nature and the position of various directing groups upon the regioselectivity.

It can be assumed that the presence of an *ortho*-directing group such as a methoxy group or a chlorine atom could favour the *ortho*-lithiation on the benzene moiety. However it can be asked if this favourable factor was strong enough to prevent lithiation at the C<sub>2</sub> position.

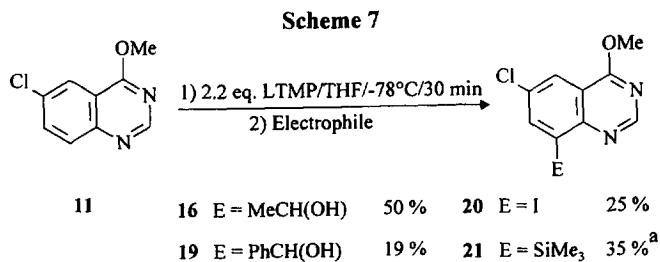
Various disubstituted quinazolines (**10-13**) have been synthesized. Reaction of the lithiated derivatives with acetaldehyde gave rise to the products **14-18** (Scheme 6).



(a) carried out with 4 eq. LTMP  
(b) with recovery of starting material (15%)

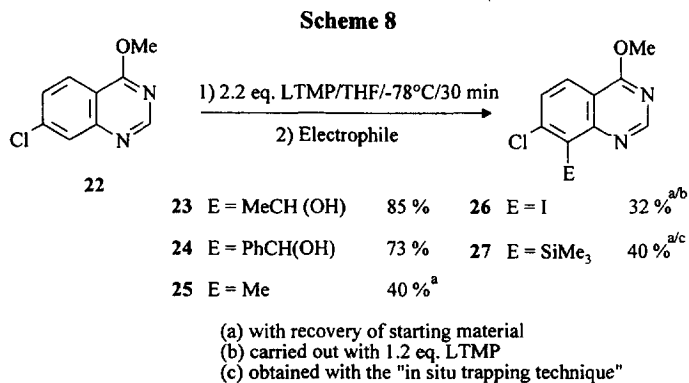
With 4,6-dimethoxyquinazoline **10**, a mixture of regioisomeric carbinols **14** and **15** was obtained. In this case, the metallation took place at C<sub>8</sub>, *peri* to the ring N-1 nitrogen atom and at C<sub>7</sub>, *ortho* to the methoxy group. With 6-chloro-4-substituted quinazolines (**11-13**) a regioselective metallation at the C<sub>8</sub> position has been observed in moderate yields (29-55 %).

Some other 8-substituted quinazoline derivatives were synthesized by metallation of **11** followed by reaction with various electrophiles (Scheme 7).



(a) obtained with the "in situ trapping technique"

From these results, it may be assumed that metallation of 7-chloro-4-methoxyquinazoline **22** would be completely regioselective at the C<sub>8</sub> position (Scheme 8). Actually, **22** underwent lithiation at this position and after reaction with various electrophiles afforded 8-substituted quinazoline derivatives in better yields than for **11**.

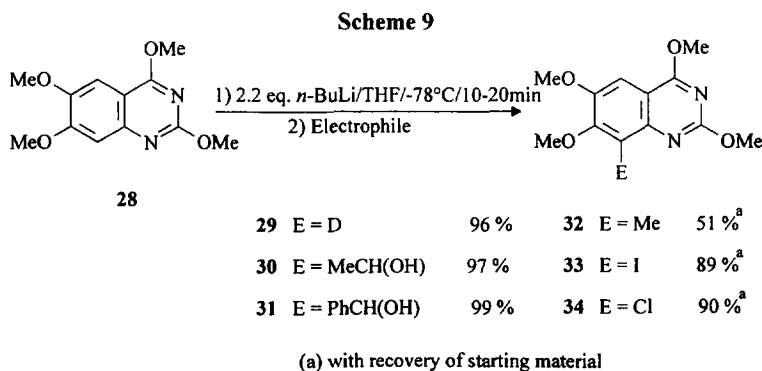


When methyl iodide was used as the electrophile, 7-chloro-8-ethyl-4-methoxyquinazoline was obtained in 8 % yield. This compound is the result of a further metallation of the methyl group of the compound **25**.

The metallation of 2,4,6,7-tetramethoxyquinazoline **28** has been performed. The presence of two methoxy groups at the C<sub>6</sub> and C<sub>7</sub> positions could favour metallation at C<sub>5</sub> and C<sub>8</sub>. When the metallation was achieved with LTMP as metallating agent at -78°C, followed by reaction with acetaldehyde, the secondary alcohol **30** was obtained in good yield (85 %).

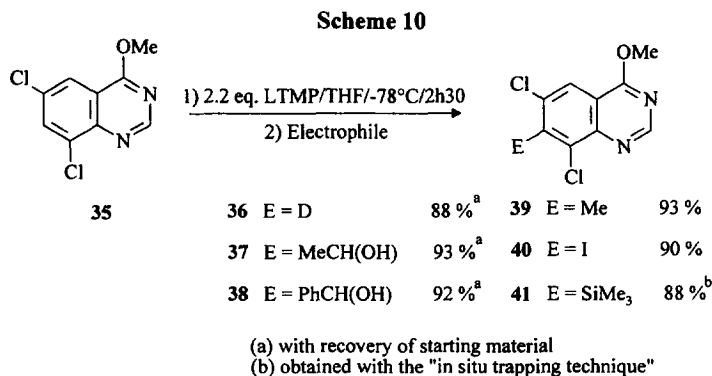
The high substitution pattern of quinazoline ring system with methoxy groups tends to increase the energy level of the LUMO  $\pi$  orbital, as confirmed by semi-empirical AM1 molecular orbital calculations.<sup>12</sup> Therefore, the compound **28** is less sensitive to nucleophilic additions. This fact prompted us to test *n*-BuLi as metallating agent.

Lithiation of **28** occurred rapidly with 2.2 equivalents of *n*-BuLi at -78°C to give lithiated reagent which was reacted with various electrophiles (Scheme 9).

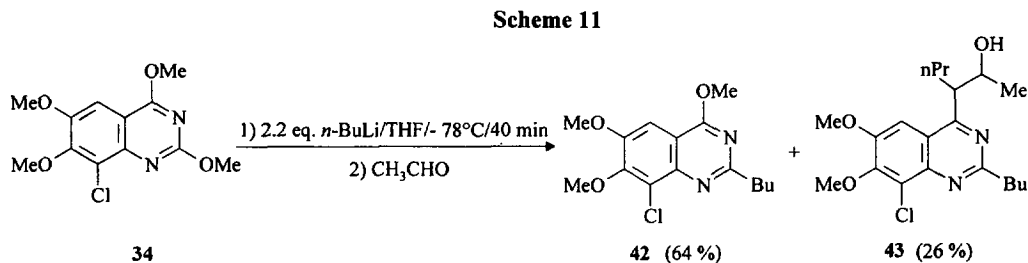


These results exhibit a high regioselectivity of the metallation at the C<sub>8</sub> position. Consequently, we wondered what kind of selectivity would be observed if the C<sub>8</sub> carbon was substituted. We then decided to prepare 6,8-dichloro-4-methoxyquinazoline **35**. In this case, the metallation could take place on two sites: either at C<sub>7</sub> between the chlorine atoms or at the *peri* position C<sub>5</sub>.

Treatment of **35** with LTMP, followed by reaction with various electrophiles afforded only 7-substituted quinazoline derivatives in very good yields (Scheme 10).



So, since the metallation at the C<sub>5</sub> position failed when another site could compete, it would be interesting to test the metallation reaction of a pentasubstituted quinazoline derivative, with only the C<sub>5</sub> position free. Therefore, 8-chloro-2,4,6,7-tetramethoxyquinazoline **34** was chosen, and metallation was tested with various metallating agents. Attempted lithiation with LTMP failed. The starting material was recovered at -78°C and at 0°C. Only traces of products resulting from metallation of the methoxy group were identified. Treatment of **34** with 2 equivalents of *n*-BuLi at -78°C for 40 minutes and reaction with acetaldehyde led to two compounds **42** and **43** (Scheme 11).

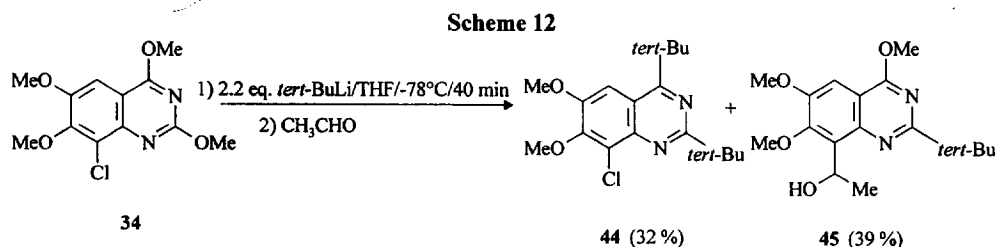


Their <sup>1</sup>H NMR spectra present respectively singlets at 7.23 and 7.15 ppm which were attributed to H<sub>5</sub>, thus indicating that no lithiation occurred on the benzene moiety.

The compound **42**, for which one methoxy group of the pyrimidine moiety has been substituted by a butyl group, was obtained in 64 % yield. The compound **43** with a molecular weight of 380 was obtained in 26 % yield and has a more complex structure : the two methoxy groups of the pyrimidine moiety have been substituted by a butyl group, then one of them has undergone lithiation on α-carbon. The lithiated derivative

reacted then with acetaldehyde to give the secondary alcohol **43**. NMR experiments have been performed in order to determine the structure of the compounds **42** and **43**. The structure of **43** was confirmed by a nOe effect between H<sub>5</sub> and a CH proton (CH(α) or CH(OH)) of the alkyl group. With **42**, no nOe effect between H<sub>5</sub> and the CH<sub>2</sub> (α) protons of the butyl group was observed. However, the long range HETCOR spectrum revealed a correlation between H<sub>5</sub> (7.23 ppm) and C<sub>4</sub> (168 ppm), and between C<sub>4</sub> and OCH<sub>3</sub> (4.17 ppm). These results are in favour of the presence of the butyl group at the C<sub>2</sub> position.

With *tert*-butyllithium as metallating agent, the results were somewhat different, since in this case no lithiation on α-carbon could occur. Lithiation of **34** with *tert*-BuLi and reaction with acetaldehyde gave rise to two compounds **44** and **45** with moderate yields (32-39 %) besides starting material (29 %) (Scheme 12).



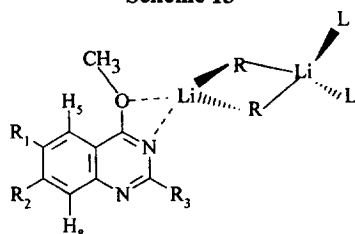
The compound **44** results from the replacement of the methoxy groups of the pyrimidine moiety by *tert*-butyl groups. The structure of the secondary alcohol **45** is more elaborate; only one methoxy group has been substituted by a *tert*-butyl group, whereas a very unexpected chlorine-lithium exchange gave a lithio derivative which reacted with acetaldehyde. Various nOe experiments were performed with **45** to determine its structure. However no significant effects have been observed. So by analogy with the structure of the compound **42**, it could be assumed that the *tert*-butyl group was at the C<sub>2</sub> position.

Using stronger bases such as the superbasic mixture of *n*-BuLi and potassium *tert*-butoxide led to the compound **42** in low yield (13 %) besides starting material (67 %).

In contrast with 1-methoxynaphthalene<sup>8</sup> and 1-naphthol<sup>13</sup>, all attempts to lithiate at the *peri* C<sub>5</sub> position have failed. This high inadequacy towards deprotonation by strong bases could not be explained by the net charges, since the net charge of H<sub>5</sub> of various quinazolines determined by AM1 calculations is equal or higher than the one of H<sub>8</sub>.<sup>12</sup>

The *peri* lithiation of 1-naphthol has been studied and explained by means of MNDO determined agostic parameters and proximity features.<sup>14,15</sup> According to these parameters, calculations revealed that the lowest transition state is related to a *peri* lithiation directed by an agostic activation of nearby *peri* hydrogen. With 4-methoxyquinazolines, it could be assumed that a complexation of the lithiated species occurred thanks to the oxygen of the methoxy group and the N-3 ring nitrogen (Scheme 13). In this case, the geometry of the mixed aggregate could be unsuitable for an agostic activation of the *peri* hydrogen H<sub>5</sub>. This fact could explain that lithiation occurred only at the C<sub>8</sub> position, *peri* to the N-1 ring nitrogen. As a matter of fact, the complexation of the lithiated species with the N-1 ring nitrogen is probably more favourable for an agostic activation of the *peri* hydrogen H<sub>8</sub>.

Scheme 13



## CONCLUSION

Direct lithiation of the benzene moiety of various substituted quinazolines has been studied and performed. All attempts to functionalize the C<sub>5</sub> position *via* the metallation reaction have failed. However the unexpected reactivity towards lithiation of the C<sub>8</sub> position *peri* to the ring nitrogen has been highlighted. It may be noted that the presence of substituents on the benzene moiety could prevent the competitive lithiation at the C<sub>2</sub> position. On the other hand, substitution of the pyrimidine ring system by methoxy groups reduces the risk of nucleophilic additions, allowing the exceptional use of *n*-BuLi as metallating agent.

This regioselective lithiation provides an efficient process to access to a large range of new substituted quinazolines which could not be easily synthesized by other routes.

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in deuteriochloroform on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. The IR spectra were obtained as potassium bromide pellets with a Perkin Elmer FTIR 1650 spectrophotometer. Mass spectra were recorded at 70 eV (EI) on a JEOL JMS-AX 500 spectrometer.

Tetrahydrofuran was distilled from benzophenone/sodium and used immediately. Water content of the solvent was estimated by the modified Karl Fischer method (THF less than 50 ppm water). Metallations were performed under an argon atmosphere. Reagents were handled with syringes through septa. All reagents as well as 4-chloro-2-phenylquinazoline were of commercial quality and were purchased from Aldrich Chemical Co. or Acros.

4-Chloroquinazolines were synthesized according to the literature: 4,6-<sup>16</sup> and 4,7-dichloroquinazolines,<sup>17</sup> 4,6,8-trichloroquinazoline,<sup>18</sup> 2,4-dichloro-6,7-dimethoxyquinazoline,<sup>19</sup> 4-chloro-6-methoxyquinazoline<sup>20</sup> as well as 4-methoxyquinazoline 7.<sup>21</sup>

### General procedure for metallation A

A solution of *n*-butyllithium (1.6 M or 2.5 M in hexane) was added to cold (-50°C), stirred, anhydrous tetrahydrofuran (15 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine was added. The mixture was warmed to 0°C and it was allowed to stand at 0°C for 20 minutes. The mixture temperature was then carried to θ<sub>1</sub>. The quinazoline dissolved in 5 ml of tetrahydrofuran was added and the mixture was



stirred for a time  $t_1$  at  $\theta_1$ . The electrophile was introduced and stirring was continued for a time  $t_2$  at  $\theta_2$ . Hydrolysis was then carried out at  $\theta_2$  using a solution of 35% aqueous hydrochloric acid (2 ml), ethanol (3 ml) and tetrahydrofuran (5 ml) for  $\theta_2 = -78^\circ\text{C}$ . For a temperature equal or higher than  $0^\circ\text{C}$ , the hydrolysis solution was a mixture of water (2 ml) and ethanol (8 ml). The solution was warmed to room temperature, made slightly basic with a saturated sodium hydrogen carbonate solution. When the electrophile was iodine, the solution was decolorised with sodium thiosulphate and evaporated nearly to dryness. The residue was extracted with dichloromethane (3x15 ml). The organic extract was dried over magnesium sulphate and evaporated. The crude product was purified by column chromatography on silica gel or by sublimation.

#### **General procedure for metallation B : so-called "in situ trapping technique "**

A solution of *n*-butyllithium (1.6 M or 2.5 M in hexane) was added to cold ( $-50^\circ\text{C}$ ), stirred, anhydrous tetrahydrofuran (15 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine was added. The mixture was warmed to  $0^\circ\text{C}$  and it was allowed to stand at  $0^\circ\text{C}$  for 20 minutes. The mixture temperature was then carried to  $\theta$ . The quinazoline dissolved in 5 ml of tetrahydrofuran and trimethylsilyl chloride were simultaneously introduced and the mixture was stirred for a time  $t$  at  $\theta$ . The following steps are similar to metallation A.

#### **General procedure for metallation C**

A solution of *n*-butyllithium (1.6 M in hexane) or *tert*-butyllithium (1.7 M in pentane) was added slowly to the quinazoline dissolved in cold ( $-78^\circ\text{C}$ ), stirred, anhydrous tetrahydrofuran (15 ml) under an atmosphere of dry argon. The mixture was allowed to stand at  $-78^\circ\text{C}$  for  $t_1$ . The electrophile was introduced and stirring was continued for a time  $t_2$  at  $-78^\circ\text{C}$ . Hydrolysis and the following steps are similar to metallation A.

#### **General procedure for formation of 4-alkoxyquinazolines and 2,4-dialkoxyquinazolines**

A mixture of 4-chloroquinazoline (or 2,4-dichloroquinazoline) (1.0 g) in methanol or 2-methoxyethanol (30 ml) containing dissolved sodium metal (2-4 eq.) was refluxed for 2-5 h. The reaction was monitored by TLC. After cooling, the solvent was removed under reduced pressure. The residue was washed with 10 ml of water and extracted with dichloromethane (3x15 ml). The organic extract was dried over magnesium sulphate and evaporated to give crude 4-alkoxyquinazoline (or 2,4-dialkoxyquinazoline).

**4-methoxy-2-phenylquinazoline (1):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : dichloromethane) afforded 915 mg (93%) of **1** as a white solid, mp  $63-64^\circ\text{C}$ , Lit.<sup>22</sup> mp  $64^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.60 (m, 2H,  $2\text{H}_{\text{Ph}}$ ); 8.17 (dd,  $J_{5,6}=8\text{Hz}$  and  $J_{5,7}=1.3\text{Hz}$ , 1H,  $\text{H}_5$ ); 8.00 (dd,  $J_{8,7}=8.3\text{Hz}$  and  $J_{8,6}=1.3\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.83 (td,  $J=8\text{Hz}$  and  $1.3\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.51 (m, 4H,  $3\text{H}_{\text{Ph}} + \text{H}_6$ ); 4.30 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  166.8 ( $\text{C}_4$ ); 159.9 ( $\text{C}_2$ ); 151.7 ( $\text{C}_9$ ); 138.1 ( $\text{C}_{\text{Ph}}$ ); 133.4-123.4 ( $5\text{C}_{\text{Ph}} + \text{C}_{5,6,7,8}$ ); 115.2 ( $\text{C}_{10}$ ); 54 ( $\text{OCH}_3$ ); ir :  $\nu$  3000, 1619, 1576, 1556, 1503, 1490, 1450, 1375, 1350, 1331, 762, 706,  $675\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$  (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.50; H, 5.00; N, 11.75.

**4-(2-methoxyethoxy)-2-phenylquinazoline (2):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (8/2)) afforded 570 mg (50%) of **2** as a white solid, mp <50°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.58 (m, 2H,  $2\text{H}_{\text{Ph}}$ ); 8.22 (dd,  $J_{5,6}=8.2\text{Hz}$  and  $J_{5,7}=1.2\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.99 (dd,  $J_{8,7}=8.4\text{Hz}$  and  $J_{8,6}=1.2\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.83 (td,  $J=8.4\text{Hz}$  and  $1.2\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.51 (m, 4H,  $3\text{H}_{\text{Ph}}+\text{H}_6$ ); 4.89 (t,  $J=4.8\text{Hz}$ , 2H,  $\text{CH}_2$ ); 3.94 (t,  $J=4.8\text{Hz}$ , 2H,  $\text{CH}_2$ ); 3.51 (s, 3H,  $\text{OCH}_3$ ); ir :  $\nu$  3064, 2927, 2890, 1620, 1575, 1500, 1490, 1420, 1345, 1328, 768, 709,  $680\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$  (280.33): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.92; H, 5.98; N, 10.35.

**4,4-dibutyl-3,4-dihydro-2-phenylquinazoline (3):** metallation of **1** (120 mg, 0.51 mmol) according to the general procedure C with *n*-BuLi 2.5 M (4.1 eq., 0.84 ml),  $t_1 = 10$  min, followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (8/2)) 140 mg (86%) of **3** as a white solid, mp 154-155°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.85 (m, 2H,  $2\text{H}_{\text{Ph}}$ ); 7.47 (m, 3H,  $3\text{H}_{\text{Ph}}$ ); 7.21 (m, 2H,  $2\text{H}_{\text{Benz}}$ ); 7.05 (m, 2H,  $2\text{H}_{\text{Benz}}$ ); 4.90 (br, 1H, NH); 1.93-1.05 (m, 12H,  $6\times\text{CH}_2$ ); 0.83 (m, 6H,  $2\times\text{CH}_3$ ); MS :  $[\text{M}]^+$ , 320;  $[\text{M}-\text{C}_4\text{H}_9]^+$ , 263. Anal. Calcd for  $\text{C}_{22}\text{H}_{28}\text{N}_2$  (320.47): C, 81.14; H, 8.72; N, 9.39. Found: C, 80.88; H, 8.61; N, 9.74. Another fraction afforded 14 mg (12%) of starting material.

**8-(1-hydroxyethyl)-4-methoxy-2-phenylquinazoline (4):** metallation of **1** (130 mg, 0.55 mmol) according to the general procedure A with *n*-BuLi 2.5 M (4 eq., 0.88 ml), TMPH (4.1 eq., 0.38 ml),  $t_1 = 30$  min,  $\theta_1 = 0^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = 0^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : dichloromethane) 86 mg (56%) of **4** as a white solid, mp 82-83°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.53 (m, 2H,  $2\text{H}_{\text{Ph}}$ ); 8.03 (dd,  $J_{5,6}=8\text{Hz}$  and  $J_{5,7}=1.2\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.67 (dd,  $J_{7,6}=7\text{Hz}$  and  $J_{7,5}=1.2\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.50 (m, 3H,  $3\text{H}_{\text{Ph}}$ ); 7.43 (dd,  $J=7\text{Hz}$  and  $8\text{Hz}$ , 1H,  $\text{H}_6$ ); 5.96 (br, 1H, OH); 5.46 (q,  $J=6.6\text{Hz}$ , 1H, CH); 4.27 (s, 3H,  $\text{OCH}_3$ ); 1.77 (d,  $J=6.6\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  167.3 ( $\text{C}_4$ ); 158.5 ( $\text{C}_2$ ); 149.5 ( $\text{C}_9$ ); 140.9 ( $\text{C}_8$ ); 137.4 ( $\text{C}_{\text{Ph}}$ ); 130.8 ( $2\text{C}_{\text{Ph}}$ ); 130 ( $\text{C}_7$ ); 128.5 ( $3\text{C}_{\text{Ph}}$ ); 126.1 ( $\text{C}_6$ ); 122.3 ( $\text{C}_5$ ); 115.3 ( $\text{C}_{10}$ ); 69.6 (CH); 54.1 ( $\text{OCH}_3$ ); 23.9 ( $\text{CH}_3$ ); ir :  $\nu$  3363, 2919, 1616, 1566, 1488, 1450, 1375, 1349, 1201, 1019,  $763\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$  (280.33): C, 72.84; H, 5.75; N, 9.99. Found: C, 73.03; H, 5.74; N, 9.78. Another fraction afforded 52 mg (40%) of starting material.

**4-methoxy-2-phenyl-8-trimethylsilylquinazoline (5):** metallation of **1** (131.5 mg, 0.56 mmol) according to the general procedure B with *n*-BuLi 2.5 M (4 eq., 0.88 ml), TMPH (4.1 eq., 0.38 ml), trimethylsilyl chloride (4 eq., 0.28 ml),  $t = 2$  h,  $\theta = 0^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether) 161 mg (94%) of **5** as a white solid, mp 134-135°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.71 (m, 2H,  $2\text{H}_{\text{Ph}}$ ); 8.19 (dd,  $J_{5,6}=8\text{Hz}$  and  $J_{5,7}=1.3\text{Hz}$ , 1H,  $\text{H}_5$ ); 8.00 (dd,  $J_{7,6}=7\text{Hz}$  and  $J_{7,5}=1.3\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.55 (m, 4H,  $3\text{H}_{\text{Ph}} + \text{H}_6$ ); 4.30 (s, 3H,  $\text{OCH}_3$ ); 0.58 (s, 9H,  $3\times\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ) :  $\delta$  167.2 ( $\text{C}_4$ ); 158.2 ( $\text{C}_2$ ); 155.8 ( $\text{C}_9$ ); 139.8 ( $\text{C}_8$  or  $\text{C}_{\text{Ph}}$ ); 139.4 ( $\text{C}_7$ ); 138.4 ( $\text{C}_{\text{Ph}}$  or  $\text{C}_8$ ); 130.1-124.2 ( $\text{C}_{5,6}$  and  $5\text{C}_{\text{Ph}}$ ); 114.4 ( $\text{C}_{10}$ ); 53.8 ( $\text{OCH}_3$ ); 0 ( $\text{Si}(\text{CH}_3)_3$ ); ir :  $\nu$  2946, 1604, 1577, 1556, 1483, 1366, 1136, 842, 766,  $709\text{ cm}^{-1}$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{20}\text{N}_2\text{OSi}$  (308.46): C, 70.09; H, 6.54; N, 9.08. Found: C, 70.31; H, 6.44; N, 8.95.

**2-phenyl-4(3H)quinazolone (6):** metallation of **2** (100 mg, 0.36 mmol) according to the general procedure A with *n*-BuLi 1.6 M (4 eq., 0.89 ml), TMPH (4.1 eq., 0.25 ml),  $t_1 = 30$  min,  $\theta_1 = 0^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = 0^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (8/2)) 53 mg (67%) of **6** as a white solid, mp  $240^\circ\text{C}$ , Lit.<sup>23,24</sup> mp  $238^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  11.4 (br, 1H, NH); 8.33 (m, 3H,  $2\text{H}_{\text{Ph}} + \text{H}_{\text{Benz}}$ ); 7.83 (m, 2H,  $2\text{H}_{\text{Benz}}$ ); 7.60 (m, 4H,  $3\text{H}_{\text{Ph}} + \text{H}_{\text{Benz}}$ ); MS :  $[\text{M}]^+$ , 222. Anal. Calcd for  $\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}$  (222.25): C, 75.66; H, 4.54; N, 12.60. Found: C, 75.98; H, 4.29; N, 12.41. Another fraction afforded 23 mg (23%) of starting material.

**2-(1-hydroxyethyl)-4-methoxyquinazoline (8) and 8-(1-hydroxyethyl)-4-methoxyquinazoline (9):**

metallation of **7** (100 mg, 0.63 mmol) according to the general procedure A with *n*-BuLi 1.6 M (4 eq., 1.6 ml), TMPH (4.1 eq., 0.43 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : dichloromethane/ethylacetate (8/2)) 44 mg (34%) of **8** as a colorless oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.13 (dd,  $J_{5,6}=8\text{Hz}$  and  $J_{5,7}=0.8\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.89 (dd,  $J_{8,7}=8.3\text{Hz}$  and  $J_{8,6}=1.4\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.81 (m,  $J_{7,8}=8.3\text{Hz}$ ,  $J_{7,6}=6.4\text{Hz}$  and  $J_{7,5}=0.8\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.52 (m,  $J_{6,5}=8\text{Hz}$ ,  $J_{6,7}=6.4\text{Hz}$  and  $J_{6,8}=1.4\text{Hz}$ , 1H,  $\text{H}_6$ ); 4.91 (q,  $J=6.6\text{Hz}$ , 1H, CH); 4.60 (br, 1H, OH); 4.18 (s, 3H,  $\text{OCH}_3$ ); 1.62 (d,  $J=6.6\text{Hz}$ , 3H,  $\text{CH}_3$ ); ir :  $\nu$  3400, 2930, 1574, 1501, 1376, 1099, 769  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$  (204.22): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.39; H, 6.11; N, 13.83.

Another fraction afforded 85 mg (66%) of **9** as a colorless oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.72 (s, 1H,  $\text{H}_2$ ); 8.01 (dd,  $J_{5,6}=8\text{Hz}$  and  $J_{5,7}=0.6\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.69 (dd,  $J_{7,6}=6.8\text{Hz}$  and  $J_{7,5}=1\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.46 (dd,  $J=6.8$  and  $8\text{Hz}$ , 1H,  $\text{H}_6$ ); 5.50 (br, 1H, OH); 5.39 (q,  $J=6.6\text{Hz}$ , 1H, CH); 4.14 (s, 3H,  $\text{OCH}_3$ ); 1.63 (d,  $J=6.6\text{Hz}$ , 3H,  $\text{CH}_3$ ); ir :  $\nu$  3436, 1576, 1494, 1359, 1019, 999, 767  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$  (204.22): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.77; H, 5.91; N, 13.65.

**4,6-dimethoxyquinazoline (10):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (4/6)) afforded 928 mg (95%) of **10** as a white solid, mp  $94-95^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.65 (s, 1H,  $\text{H}_2$ ); 7.78 (d,  $J_{8,7}=9\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.38 (dd,  $J=2.9\text{Hz}$  and  $9\text{Hz}$ , 1H,  $\text{H}_7$ ); 7.30 (d,  $J_{5,7}=2.9\text{Hz}$ , 1H,  $\text{H}_5$ ); 4.11 (s, 3H,  $\text{OCH}_3$ ); 3.86 (s, 3H,  $\text{OCH}_3$ ); ir :  $\nu$  1571, 1508, 1374, 1230, 832, 540  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$  (190.20): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.26; H, 5.31; N, 14.61.

**6-chloro-4-methoxyquinazoline (11):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : dichloromethane/ethylacetate (5/5)) afforded 938 mg (96%) of **11** as a white solid, mp  $110-111^\circ\text{C}$ ;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.79 (s, 1H,  $\text{H}_2$ ); 8.11 (d,  $J_{5,7}=2.3\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.86 (d,  $J_{8,7}=8.9\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.75 (dd,  $J=8.9\text{Hz}$  and  $2.3\text{Hz}$ , 1H,  $\text{H}_7$ ); 4.18 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  166 ( $\text{C}_4$ ); 154.3 ( $\text{C}_2$ ); 149 ( $\text{C}_9$ ); 134.1 ( $\text{C}_7$ ); 132.3 ( $\text{C}_6$ ); 129.1 ( $\text{C}_8$ ); 122.4 ( $\text{C}_5$ ); 117 ( $\text{C}_{10}$ ); 54.3 ( $\text{OCH}_3$ ); ir :  $\nu$  1571, 1497, 1459, 1371, 1109, 1068, 970, 830, 506  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_9\text{H}_7\text{ClN}_2\text{O}$  (194.62): C, 55.54; H, 3.63; N, 14.39. Found: C, 55.59; H, 3.58; N, 14.38.

**6-chloro-4-(2-methoxyethoxy)quinazoline (12):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) afforded 858 mg (72%) of **12** as a white solid, mp 72-73°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.78 (s, 1H, H<sub>2</sub>); 8.19 (d, J<sub>5,7</sub>=2.2Hz, 1H, H<sub>5</sub>); 7.88 (d, J<sub>8,7</sub>=8.9Hz, 1H, H<sub>8</sub>); 7.77 (dd, J=8.9Hz and 2.2Hz, 1H, H<sub>7</sub>); 4.75 (t, J=4.5Hz, 2H, CH<sub>2</sub>); 3.86 (t, J=4.5Hz, 2H, CH<sub>2</sub>); 3.48 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 165.6 (C<sub>4</sub>); 154.2 (C<sub>2</sub>); 149.2 (C<sub>9</sub>); 134.2 (C<sub>7</sub>); 132.4 (C<sub>6</sub>); 129.2 (C<sub>8</sub>); 122.6 (C<sub>5</sub>); 117 (C<sub>10</sub>); 70.2 (CH<sub>2</sub>); 66.2 (CH<sub>2</sub>); 58.9 (OCH<sub>3</sub>); ir : ν 1568, 1498, 1338, 1108, 1068, 864, 840, 506 cm<sup>-1</sup>. Anal. Calcd for C<sub>11</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub> (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.47; H, 4.37; N, 11.52.

**6-chloro-4-N,N-diethylaminoquinazoline (13):** to a solution of 4,6-dichloroquinazoline (300 mg, 1.51 mmol) dissolved in 15 ml of anhydrous tetrahydrofuran was added N,N-diethylamine (1.2 eq., 0.19 ml). The mixture was stirred for 25 h at room temperature, neutralized by addition of a saturated sodium hydrogen carbonate solution and evaporated. The residue was extracted with dichloromethane (3x15 ml). The organic extract was dried over magnesium sulphate and evaporated. Purification of the crude 4-aminoquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (4/6)) afforded 196 mg (55%) of **13** as a yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 8.53 (s, 1H, H<sub>2</sub>); 7.76 (d, J<sub>5,7</sub>=2.1Hz, 1H, H<sub>5</sub>); 7.68 (d, J<sub>8,7</sub>=8.9Hz, 1H, H<sub>8</sub>); 7.52 (dd, J=8.9Hz and 2.1Hz, 1H, H<sub>7</sub>); 3.63 (q, J=7Hz, 4H, 2xCH<sub>2</sub>); 1.31 (t, J=7Hz, 6H, 2xCH<sub>3</sub>); ir : ν 3330, 2970, 1563, 1527, 1345, 1099, 859, 836 cm<sup>-1</sup>. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>ClN<sub>3</sub> (235.72): C, 61.15; H, 5.99; N, 17.83. Found: C, 61.44; H, 6.03; N, 17.75.

**8-(1-hydroxyethyl)-4,6-dimethoxyquinazoline (14) and 7-(1-hydroxyethyl)-4,6-dimethoxyquinazoline (15):** metallation of **10** (100 mg, 0.53 mmol) according to the general procedure A with *n*-BuLi 1.6 M (4 eq., 1.32 ml), TMPH (4.1 eq., 0.37 ml), t<sub>1</sub> = 30 min, θ<sub>1</sub> = -78°C, followed by reaction with acetaldehyde (2 ml), t<sub>2</sub> = 30 min, θ<sub>2</sub> = -78°C, gave after purification by column chromatography (silica, eluent : ethylacetate) 67 mg (54%) of **14** as a pale yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.64 (s, 1H, H<sub>2</sub>); 7.33 (d, J<sub>7,5</sub>=2.7Hz, 1H, H<sub>7</sub>); 7.25 (d, J<sub>5,7</sub>=2.7Hz, 1H, H<sub>5</sub>); 5.51 (br, 1H, OH); 5.36 (q, J=6.5Hz, 1H, CH); 4.16 (s, 3H, OCH<sub>3</sub>); 3.90 (s, 3H, OCH<sub>3</sub>); 1.65 (d, J=6.5Hz, 3H, CH<sub>3</sub>); ir : ν 3386, 2955, 1576, 1498, 1365, 1246, 1052, 999, 846, 808 cm<sup>-1</sup>. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> (234.25): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.20; H, 6.30; N, 11.61.

Another fraction afforded 48 mg (39%) of **15** as a white solid, mp 176-177°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.67 (s, 1H, H<sub>2</sub>); 8.02 (s, 1H, H<sub>8</sub>); 7.32 (s, 1H, H<sub>5</sub>); 5.24 (q, J=6.5Hz, 1H, CH); 4.16 (s, 3H, OCH<sub>3</sub>); 3.96 (s, 3H, OCH<sub>3</sub>); 3.60 (br, 1H, OH); 1.55 (d, J=6.5Hz, 3H, CH<sub>3</sub>); ir : ν 3277, 1571, 1497, 1379, 1230, 1101, 897, 792 cm<sup>-1</sup>. Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> (234.25): C, 61.53; H, 6.02; N, 11.96. Found: C, 61.24; H, 6.32; N, 11.67.

**6-chloro-8-(1-hydroxyethyl)-4-methoxyquinazoline (16):** metallation of **11** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.54 ml), TMPH (2.3 eq., 0.24 ml), t<sub>1</sub> = 30 min, θ<sub>1</sub> = -78°C, followed by reaction with acetaldehyde (2 ml), t<sub>2</sub> = 30 min, θ<sub>2</sub> = -78°C, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) 73 mg (50%) of **16** as a yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 8.73 (s, 1H, H<sub>2</sub>); 7.96 (d, J<sub>5,7</sub>=2.3Hz, 1H, H<sub>5</sub>); 7.66 (d, J<sub>7,5</sub>=2.3Hz, 1H, H<sub>7</sub>); 5.40 (q, J=6.5Hz, 1H, CH); 5.14 (br, 1H, OH); 4.16 (s, 3H, OCH<sub>3</sub>); 1.63 (d, J=6.5Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ 166.4 (C<sub>4</sub>); 153 (C<sub>2</sub>); 146.9 (C<sub>9</sub>); 143.6 (C<sub>8</sub>); 132.4 (C<sub>6</sub>); 130.6 (C<sub>7</sub>); 121.1 (C<sub>5</sub>); 117.2

(C<sub>10</sub>); 67.9 (CH); 54.4 (OCH<sub>3</sub>); 23.7 (CH<sub>3</sub>); ir :  $\nu$  3395, 2972, 1574, 1488, 1454, 1417, 1358, 1201, 1032, 1004, 921, 861, 814, 504 cm<sup>-1</sup>. Anal. Calcd for C<sub>11</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub> (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.27; H, 4.93; N, 11.48.

**6-chloro-8-(1-hydroxyethyl)-4-(2-methoxyethoxy)quinazoline (17):** metallation of **12** (130 mg, 0.55 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.48 ml), TMPH (2.3 eq., 0.21 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) 45 mg (29%) of **17** as a yellow solid, mp 89-90°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.76 (s, 1H, H<sub>2</sub>); 8.10 (d,  $J_{5,7}=2.4\text{Hz}$ , 1H, H<sub>5</sub>); 7.69 (d,  $J_{7,5}=2.4\text{Hz}$ , 1H, H<sub>7</sub>); 5.40 (q,  $J=6.6\text{Hz}$ , 1H, CH); 5.06 (br, 1H, OH); 4.75 (t,  $J=4.5\text{Hz}$ , 2H, CH<sub>2</sub>); 3.86 (t,  $J=4.5\text{Hz}$ , 2H, CH<sub>2</sub>); 3.47 (s, 3H, OCH<sub>3</sub>); 1.68 (d,  $J=6.6\text{Hz}$ , 3H, CH<sub>3</sub>); ir :  $\nu$  3436, 1570, 1484, 1339, 1031, 855, 812 cm<sup>-1</sup>. Anal. Calcd for C<sub>13</sub>H<sub>15</sub>ClN<sub>2</sub>O<sub>3</sub> (283.73): C, 55.23; H, 5.35; N, 9.91. Found: C, 55.12; H, 5.46; N, 9.68.

**6-chloro-4-*N,N*-diethylamino-8-(1-hydroxyethyl)quinazoline (18):** metallation of **13** (100 mg, 0.42 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.2 eq., 0.58 ml), TMPH (2.3 eq., 0.17 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (4/6)) 65 mg (55%) of **18** as a yellow oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.60 (s, 1H, H<sub>2</sub>); 7.74 (d,  $J_{5,7}=2.2\text{Hz}$ , 1H, H<sub>5</sub>); 7.53 (d,  $J_{7,5}=2.2\text{Hz}$ , 1H, H<sub>7</sub>); 5.90 (br, 1H, OH); 5.30 (q,  $J=6.5\text{Hz}$ , 1H, CH); 3.72 (q,  $J=7\text{Hz}$ , 4H, 2xCH<sub>2</sub>); 1.66 (d,  $J=6.5\text{Hz}$ , 3H, CH<sub>3</sub>); 1.39 (t,  $J=7\text{Hz}$ , 6H, 2xCH<sub>3</sub>); ir :  $\nu$  3374, 2972, 1570, 1520, 1344, 860, 811 cm<sup>-1</sup>. Anal. Calcd for C<sub>14</sub>H<sub>18</sub>ClN<sub>3</sub>O (279.77): C, 60.10; H, 6.48; N, 15.02. Found: C, 59.79; H, 6.81; N, 15.00. Another fraction afforded 15 mg (15%) of starting material.

**6-chloro-8-(hydroxyphenylmethyl)-4-methoxyquinazoline (19):** metallation of **11** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.54 ml), TMPH (2.3 eq., 0.24 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with benzaldehyde (2.2 eq., 0.14 ml),  $t_2 = 1$  h,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (8/2)) 35 mg (19%) of **19** as an orange solid, mp 143-144°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.78 (s, 1H, H<sub>2</sub>); 8.05 (d,  $J_{5,7}=2.4\text{Hz}$ , 1H, H<sub>5</sub>); 7.54 (d,  $J_{7,5}=2.4\text{Hz}$ , 1H, H<sub>7</sub>); 7.37 (m, 5H, 5H<sub>ph</sub>); 6.38 (s, 1H, CH); 5.9 (br, 1H, OH); 4.18 (s, 3H, OCH<sub>3</sub>); ir :  $\nu$  3356, 1566, 1496, 1381, 1197, 1007, 862, 814 cm<sup>-1</sup>. Anal. Calcd for C<sub>16</sub>H<sub>13</sub>ClN<sub>2</sub>O<sub>2</sub> (300.74): C, 63.90; H, 4.36; N, 9.31. Found: C, 63.89; H, 4.43; N, 9.25.

**6-chloro-8-iodo-4-methoxyquinazoline (20):** metallation of **11** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.54 ml), TMPH (2.3 eq., 0.24 ml),  $t_1 = 5$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with iodine (1.2 eq., 0.188 g),  $t_2 = 2$  h,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) and sublimation 50 mg (25%) of **20** as a pale yellow solid, mp 95-96°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  8.90 (s, 1H, H<sub>2</sub>); 8.35 (d,  $J_{5,7}=2.3\text{Hz}$ , 1H, H<sub>5</sub>); 8.15 (d,  $J_{7,5}=2.3\text{Hz}$ , 1H, H<sub>7</sub>); 4.21 (s, 3H, OCH<sub>3</sub>); ir :  $\nu$  1475, 1348, 978, 804, 790, 514 cm<sup>-1</sup>. Anal. Calcd for C<sub>9</sub>H<sub>6</sub>ClIN<sub>2</sub>O (320.52) : C, 33.73; H, 1.88; N, 8.74. Found: C, 34.03; H, 1.74; N, 8.43.

**6-chloro-4-methoxy-8-trimethylsilylquinazoline (21):** metallation of **11** (120 mg, 0.62 mmol) according to the general procedure B with *n*-BuLi 1.6 M (2.2 eq., 0.85 ml), TMPH (2.3 eq., 0.24 ml), trimethylsilyl chloride (2.2 eq., 0.17 ml),  $t = 2$  h,  $\theta = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) and sublimation 57 mg (35%) of **21** as a white solid, mp 114-115°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.80 (s, 1H,  $\text{H}_2$ ); 8.11 (d,  $J_{5,7}=2.4\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.84 (d,  $J_{7,5}=2.4\text{Hz}$ , 1H,  $\text{H}_7$ ); 4.16 (s, 3H,  $\text{OCH}_3$ ); 0.45 (s, 9H,  $3\times\text{CH}_3$ ); ir :  $\nu$  2956, 1560, 1479, 1337, 846  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{OSi}$  (266.81): C, 54.02; H, 5.67; N, 10.50. Found: C, 53.62; H, 6.06; N, 10.30.

**7-chloro-4-methoxyquinazoline (22):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : dichloromethane/ethylacetate (7/3)) afforded 930 mg (96%) of **22** as a white solid, mp 90-91°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.81 (s, 1H,  $\text{H}_2$ ); 8.12 (d,  $J_{5,8}=8.8\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.94 (d,  $J_{8,6}=2\text{Hz}$ , 1H,  $\text{H}_8$ ); 7.52 (dd,  $J=8.8\text{Hz}$  and  $2\text{Hz}$ , 1H,  $\text{H}_6$ ); 4.17 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  166.7 ( $\text{C}_4$ ); 155.3 ( $\text{C}_2$ ); 151.4 ( $\text{C}_9$ ); 139.4 ( $\text{C}_7$ ); 127.8, 126.8, 124.8 ( $\text{C}_{5,6,8}$ ); 114.8 ( $\text{C}_{10}$ ); 54.3 ( $\text{OCH}_3$ ); ir :  $\nu$  1614, 1569, 1490, 1386, 1097, 872, 784, 678  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_9\text{H}_7\text{ClN}_2\text{O}$  (194.62): C, 55.54; H, 3.63; N, 14.39. Found: C, 55.82; H, 3.48; N, 14.26.

**7-chloro-8-(1-hydroxyethyl)-4-methoxyquinazoline (23):** metallation of **22** (110 mg, 0.56 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.50 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) 114 mg (85%) of **23** as a white solid, mp 117-118°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.78 (s, 1H,  $\text{H}_2$ ); 8.00 (d,  $J_{5,6}=8.8\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.51 (d,  $J_{6,5}=8.8\text{Hz}$ , 1H,  $\text{H}_6$ ); 7.00 (d,  $J=10.7\text{Hz}$ , 1H, OH); 5.57 (qd,  $J=10.7\text{Hz}$  and  $J=6.7\text{Hz}$ , 1H, CH); 4.20 (s, 3H,  $\text{OCH}_3$ ); 1.67 (d,  $J=6.7\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  167.5 ( $\text{C}_4$ ); 153.2 ( $\text{C}_2$ ); 149.8 ( $\text{C}_9$ ); 137.7, 136.6 ( $\text{C}_{7,8}$ ); 128.7, 123 ( $\text{C}_{5,6}$ ); 115.6 ( $\text{C}_{10}$ ); 69.3 ( $\text{CH}$ ); 54.5 ( $\text{OCH}_3$ ); 24.5 ( $\text{CH}_3$ ); ir :  $\nu$  3313, 2972, 1603, 1577, 1490, 1438, 1394, 1348, 894, 796, 653  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{11}\text{ClN}_2\text{O}_2$  (238.67): C, 55.36; H, 4.65; N, 11.74. Found: C, 55.42; H, 4.89; N, 11.69.

**7-chloro-8-(hydroxyphenylmethyl)-4-methoxyquinazoline (24):** metallation of **22** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.2 eq., 0.85 ml), TMPH (2.3 eq., 0.24 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with benzaldehyde (2.2 eq., 0.14 ml),  $t_2 = 1$  h,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) 135 mg (73%) of **24** as a white solid, mp 159-160°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.74 (s, 1H,  $\text{H}_2$ ); 8.06 (d,  $J_{5,6}=8.8\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.59 (d,  $J_{6,5}=8.8\text{Hz}$ , 1H,  $\text{H}_6$ ); 7.48 (m, 3H,  $2\text{H}_{\text{Ph}} + \text{OH}$ ); 7.28 (m, 3H,  $3\text{H}_{\text{Ph}}$ ); 6.58 (d,  $J=11\text{Hz}$ , 1H, CH); 4.18 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  167.4 ( $\text{C}_4$ ); 153.6 ( $\text{C}_2$ ); 149.9 ( $\text{C}_9$ ); 143.5, 138, 135.9 ( $\text{C}_{7,8}$  and  $\text{C}_{\text{Ph}}$ ); 128.8-123.6 ( $\text{C}_{5,6}$  and  $5\text{C}_{\text{Ph}}$ ); 115.7 ( $\text{C}_{10}$ ); 73.9 ( $\text{CH}$ ); 54.5 ( $\text{OCH}_3$ ); ir :  $\nu$  3287, 3066  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{16}\text{H}_{13}\text{ClN}_2\text{O}_2$  (300.74): C, 63.90; H, 4.36; N, 9.31. Found: C, 63.87; H, 4.34; N, 9.35.

**7-chloro-4-methoxy-8-methylquinazoline (25):** metallation of **22** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.2 eq., 0.85 ml), TMPH (2.3 eq., 0.24 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with methyl iodide (2.2 eq., 85  $\mu\text{l}$ ),  $t_2 = 1$  h,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by

column chromatography (silica, eluent : dichloromethane/ethylacetate (8/2)) 51 mg (40%) of **25** as a yellow solid, mp 114-115°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.84 (s, 1H,  $\text{H}_2$ ); 7.94 (d,  $J_{5,6}$ =8.8Hz, 1H,  $\text{H}_5$ ); 7.51 (d,  $J_{6,5}$ =8.8Hz, 1H,  $\text{H}_6$ ); 4.17 (s, 3H,  $\text{OCH}_3$ ); 2.78 (s, 3H,  $\text{CH}_3$ ); ir :  $\nu$  1604, 1576, 1483, 1399, 1343, 1177, 1038, 786  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{10}\text{H}_9\text{ClN}_2\text{O}$  (208.65): C, 57.57; H, 4.35; N, 13.43. Found: C, 57.95; H, 4.27; N, 13.12.

Other fractions afforded 11 mg (8%) of 7-chloro-8-ethyl-4-methoxyquinazoline and 37 mg (31%) of starting material.

**7-chloro-8-iodo-4-methoxyquinazoline (26)**: metallation of **22** (120 mg, 0.62 mmol) according to the general procedure A with *n*-BuLi 1.6 M (1.2 eq., 0.46 ml), TMPH (1.3 eq., 0.15 ml),  $t_1 = 30$  min,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with iodine (1.3 eq., 0.204 g),  $t_2 = 2$  h,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) and sublimation 63 mg (32%) of **26** as a white solid, mp 153-154°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.91 (s, 1H,  $\text{H}_2$ ); 8.08 (d,  $J_{5,6}$ =8.8Hz, 1H,  $\text{H}_5$ ); 7.61 (d,  $J_{6,5}$ =8.8Hz, 1H,  $\text{H}_6$ ); 4.21 (s, 3H,  $\text{OCH}_3$ ); ir :  $\nu$  1480, 1377, 786, 547  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_9\text{H}_6\text{ClIN}_2\text{O}$  (320.52): C, 33.73; H, 1.88; N, 8.74. Found: C, 33.99; H, 1.73; N, 8.59.

Another fraction afforded 42 mg (35%) of starting material.

**7-chloro-4-methoxy-8-trimethylsilylquinazoline (27)**: metallation of **22** (120 mg, 0.62 mmol) according to the general procedure B with *n*-BuLi 1.6 M (2.2 eq., 0.85 ml), TMPH (2.3 eq., 0.24 ml), trimethylsilyl chloride (2.2 eq., 0.17 ml),  $t = 2$  h,  $\theta = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) and sublimation 66 mg (40%) of **27** as a white solid, mp 105-106°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.78 (s, 1H,  $\text{H}_2$ ); 8.05 (d,  $J_{5,6}$ =8.7Hz, 1H,  $\text{H}_5$ ); 7.46 (d,  $J_{6,5}$ =8.7Hz, 1H,  $\text{H}_6$ ); 4.16 (s, 3H,  $\text{OCH}_3$ ); 0.56 (s, 9H,  $3\times\text{CH}_3$ ); ir :  $\nu$  1576, 1482, 1375, 1127, 845  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{15}\text{ClN}_2\text{OSi}$  (266.81): C, 54.02; H, 5.67; N, 10.50. Found: C, 54.20; H, 5.97; N, 10.33. Another fraction afforded 66 mg (55%) of starting material.

**2,4,6,7-tetramethoxyquinazoline (28)**: purification of the crude 2,4-dialkoxyquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) afforded 682 mg (71%) of **28** as a white solid, mp 175-176°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.31 (s, 1H,  $\text{H}_5$ ); 7.10 (s, 1H,  $\text{H}_8$ ); 4.16 (s, 3H,  $\text{OCH}_3$ ); 4.07 (s, 3H,  $\text{OCH}_3$ ); 4.02 (s, 3H,  $\text{OCH}_3$ ); 3.98 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  167.2 ( $\text{C}_4$ ); 161 ( $\text{C}_2$ ); 154.9 ( $\text{C}_7$ ); 148.8 ( $\text{C}_9$ ); 146.9 ( $\text{C}_6$ ); 106.3 ( $\text{C}_{10}$ ); 105.1 ( $\text{C}_8$ ); 101.3 ( $\text{C}_5$ ); 55.6, 55.5, 54 ( $4\times\text{OCH}_3$ ); ir :  $\nu$  1593, 1483, 1314, 1244, 1210, 1074, 1007, 785  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_4$  (250.25): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.25; H, 5.80; N, 10.97.

**8-deuterio-2,4,6,7-tetramethoxyquinazoline (29)**: metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.55 ml),  $t_1 = 20$  min, followed by reaction with a mixture of EtOD/DCl (0.7 ml/0.3 ml),  $t_2 = 20$  min, gave after purification by column chromatography (silica, eluent : dichloromethane/ethylacetate (5/5)) 96 mg (96%) of **29** as a white solid, mp 172-173°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.29 (s, 1H,  $\text{H}_5$ ); 4.16 (s, 3H,  $\text{OCH}_3$ ); 4.08 (s, 3H,  $\text{OCH}_3$ ); 4.04 (s, 3H,  $\text{OCH}_3$ ); 3.98 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  167.7 ( $\text{C}_4$ ); 161.4 ( $\text{C}_2$ ); 155.3 ( $\text{C}_7$ ); 149.2, 147.3 ( $\text{C}_{6,9}$ ); 106.7 ( $\text{C}_{10}$ ); 105.3 (t,  $\text{C}_8$ ); 101.8

(C<sub>5</sub>); 56, 55.8, 54.3, 54 (4xOCH<sub>3</sub>); ir :  $\nu$  1594, 1476, 1314, 1214, 1044, 1000, 797 cm<sup>-1</sup>. Anal. Calcd for C<sub>12</sub>H<sub>13</sub>DN<sub>2</sub>O<sub>4</sub> (251.26): C, 57.36; H, 5.21; N, 11.15. Found: C, 57.53; H, 5.33; N, 10.91.

**8-(1-hydroxyethyl)-2,4,6,7-tetramethoxyquinazoline (30):** metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.55 ml), t<sub>1</sub> = 10 min, followed by reaction with acetaldehyde (2 ml), t<sub>2</sub> = 30 min, gave after purification by column chromatography (silica, eluent : dichloromethane/ethylacetate (5/5)) 114 mg (97%) of **30** as a white solid, mp 105-106°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.28 (s, 1H, H<sub>5</sub>); 6.49 (d, J=11Hz, 1H, OH); 5.46 (qd, J=11Hz and 6.6Hz, 1H, CH); 4.14 (s, 3H, OCH<sub>3</sub>); 4.03 (s, 3H, OCH<sub>3</sub>); 3.93 (s, 6H, 2xOCH<sub>3</sub>); 1.62 (d, J=6.6Hz, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  168.4 (C<sub>4</sub>); 159.8 (C<sub>2</sub>); 151.2, 150.4 (C<sub>6,7</sub>); 145.9 (C<sub>9</sub>); 131.1 (C<sub>8</sub>); 109.8 (C<sub>10</sub>); 101.8 (C<sub>5</sub>); 65.9 (CH); 61, 55.7, 54.6, 54.4 (4xOCH<sub>3</sub>); 25.1 (CH<sub>3</sub>); ir :  $\nu$  3355, 2974, 1584, 1466, 1261, 1042, 1002, 802 cm<sup>-1</sup>. Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub> (294.31): C, 57.14; H, 6.16; N, 9.52. Found: C, 57.38; H, 6.16; N, 9.31.

**8-(hydroxyphenylmethyl)-2,4,6,7-tetramethoxyquinazoline (31):** metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 2.5 M (2.2 eq., 0.35 ml), t<sub>1</sub> = 20 min, followed by reaction with benzaldehyde (2.2 eq., 89  $\mu$ l), t<sub>2</sub> = 1h30, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) 141 mg (99%) of **31** as a white solid, mp 193-194°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.47 (m, 2H, 2H<sub>Ph</sub>); 7.34 (s, 1H, H<sub>5</sub>); 7.30-7.16 (m, 3H, 3H<sub>Ph</sub>); 6.93 (d, J=11Hz, 1H, OH); 6.52 (d, J=11Hz, 1H, CH); 4.13 (s, 3H, OCH<sub>3</sub>); 3.97 (s, 3H, OCH<sub>3</sub>); 3.95 (s, 3H, OCH<sub>3</sub>); 3.93 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  168.5 (C<sub>4</sub>); 160.1 (C<sub>2</sub>); 152.1, 150.5, 146, 144.9 (C<sub>6,7,9</sub> and C<sub>Ph</sub>); 129.7 (C<sub>8</sub>); 127.9-125.7 (5C<sub>Ph</sub>); 110 (C<sub>10</sub>); 102.6 (C<sub>5</sub>); 70.6 (CH); 61.1, 55.8, 54.8, 54.5 (4xOCH<sub>3</sub>); ir :  $\nu$  3300, 1583, 1467, 1316, 1260, 1030, 703 cm<sup>-1</sup>. Anal. Calcd for C<sub>19</sub>H<sub>20</sub>N<sub>2</sub>O<sub>5</sub> (356.38): C, 64.04; H, 5.66; N, 7.86. Found: C, 63.80; H, 5.80; N, 7.61.

**8-methyl-2,4,6,7-tetramethoxyquinazoline (32):** metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 2.5 M (2.2 eq., 0.35 ml), t<sub>1</sub> = 20 min, followed by reaction with methyl iodide (2.2 eq., 55  $\mu$ l), t<sub>2</sub> = 1 h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) 54 mg (51%) of **32** as a beige solid, mp 116-117°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.22 (s, 1H, H<sub>5</sub>); 4.14 (s, 3H, OCH<sub>3</sub>); 4.06 (s, 3H, OCH<sub>3</sub>); 3.93 (s, 3H, OCH<sub>3</sub>); 3.89 (s, 3H, OCH<sub>3</sub>); 2.53 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  168.2 (C<sub>4</sub>); 160.3 (C<sub>2</sub>); 152.9, 150.3, 147.6 (C<sub>6,7,9</sub>); 127 (C<sub>8</sub>); 109.4 (C<sub>10</sub>); 100.2 (C<sub>5</sub>); 60.3, 55.5, 54.2 (4xOCH<sub>3</sub>); 9.9 (CH<sub>3</sub>); ir :  $\nu$  1596, 1460, 1256, 1074, 792 cm<sup>-1</sup>. Anal. Calcd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> (264.28): C, 59.08; H, 6.10; N, 10.60. Found: C, 59.43; H, 5.96; N, 10.39. Another fraction afforded 42 mg (42%) of starting material.

**8-iodo-2,4,6,7-tetramethoxyquinazoline (33):** metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.55 ml), t<sub>1</sub> = 20 min, followed by reaction with iodine (2 eq., 0.203 g), t<sub>2</sub> = 2 h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) 134 mg (89%) of **33** as a white solid, mp 150-151°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.34 (s, 1H, H<sub>5</sub>); 4.15 (s, 3H, OCH<sub>3</sub>); 4.12 (s, 3H, OCH<sub>3</sub>); 3.95 (s, 6H, 2xOCH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  168.6 (C<sub>4</sub>); 161.7 (C<sub>2</sub>); 156.2 (C<sub>7</sub>); 150.5, 148.2 (C<sub>6,9</sub>); 110 (C<sub>10</sub>); 103.6 (C<sub>5</sub>); 95.1 (C<sub>8</sub>); 60.5, 56, 54.8, 54.7 (4xOCH<sub>3</sub>);



ir :  $\nu$  1587, 1465, 1382, 1298, 1254, 1040, 1002, 791  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{13}\text{IN}_2\text{O}_4$  (376.15): C, 38.32; H, 3.48; N, 7.45. Found: C, 38.36; H, 3.48; N, 7.28. Another fraction afforded 9 mg (9%) of starting material.

**8-chloro-2,4,6,7-tetramethoxyquinazoline (34):** metallation of **28** (100 mg, 0.40 mmol) according to the general procedure C with *n*-BuLi 1.6 M (2 eq., 0.50 ml),  $t_1 = 20$  min, followed by reaction with hexachloroethane (1.1 eq., 105 mg),  $t_2 = 1$  h, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) 102 mg (90%) of **34** as a pale yellow solid, mp 154-155°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.18 (s, 1H,  $\text{H}_5$ ); 4.10 (s, 3H,  $\text{OCH}_3$ ); 4.07 (s, 3H,  $\text{OCH}_3$ ); 3.95 (s, 3H,  $\text{OCH}_3$ ); 3.90 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  168.2 ( $\text{C}_4$ ); 161.4 ( $\text{C}_2$ ); 151.9, 150.7 ( $\text{C}_{6,7}$ ); 145.3 ( $\text{C}_9$ ); 123.4 ( $\text{C}_8$ ); 109.9 ( $\text{C}_{10}$ ); 101.6 ( $\text{C}_5$ ); 60.8, 56, 54.6, 54.5 (4x $\text{OCH}_3$ ); ir :  $\nu$  2941, 1590, 1479, 1304, 1044, 1008, 975, 792  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{13}\text{ClN}_2\text{O}_4$  (284.70): C, 50.63; H, 4.60; N, 9.84. Found: C, 50.64; H, 4.54; N, 9.60. Another fraction afforded 6 mg (6%) of starting material.

**6,8-dichloro-4-methoxyquinazoline (35):** purification of the crude 4-alkoxyquinazoline by column chromatography (silica, eluent : petroleum ether/ethylacetate (8/2)) afforded 736 mg (75%) of **35** as a white solid, mp 155-156°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.91 (s, 1H,  $\text{H}_2$ ); 8.08 (d,  $J=2.2\text{Hz}$ , 1H,  $\text{H}_5$ ); 7.91 (d,  $J=2.2\text{Hz}$ , 1H,  $\text{H}_7$ ); 4.21 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  166.3 ( $\text{C}_4$ ); 154.9 ( $\text{C}_2$ ); 146 ( $\text{C}_9$ ); 133.8 ( $\text{C}_7$ ); 133.3, 132 ( $\text{C}_{6,8}$ ); 121.5 ( $\text{C}_5$ ); 117.9 ( $\text{C}_{10}$ ); 54.9 ( $\text{OCH}_3$ ); ir :  $\nu$  1570, 1483, 1360, 991, 880, 804  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_9\text{H}_6\text{Cl}_2\text{N}_2\text{O}$  (229.07): C, 47.19; H, 2.64; N, 12.23. Found: C, 47.39; H, 2.64; N, 12.02.

**7-deuterio-6,8-dichloro-4-methoxyquinazoline (36):** metallation of **35** (130 mg, 0.57 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.2 eq., 0.78 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 1\text{h}30$ ,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with a mixture of EtOD/DCl (0.7 ml/0.3 ml),  $t_2 = 20$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) 126 mg of a non separable mixture of **36** and **35** (proportion **36/35**: 92/8; yield : 88%/8%);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.91 (s, 1H,  $\text{H}_2$ ); 8.04 (s, 1H,  $\text{H}_5$ ); 4.20 (s, 3H,  $\text{OCH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  166.1 ( $\text{C}_4$ ); 154.8 ( $\text{C}_2$ ); 145.9 ( $\text{C}_9$ ); 133.6, 133.3, 131.8 ( $\text{C}_{6,8}$  and  $\text{C}_7(\text{t})$ ); 121.3 ( $\text{C}_5$ ); 117.7 ( $\text{C}_{10}$ ); 54.7 ( $\text{OCH}_3$ ).

**6,8-dichloro-7-(1-hydroxyethyl)-4-methoxyquinazoline (37):** metallation of **35** (130 mg, 0.57 mmol) according to the general procedure A with *n*-BuLi 1.6 M (2.2 eq., 0.78 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 1$  h,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (5/5)) 145 mg (93%) of **37** as a pale yellow solid, mp 62-63°C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  8.80 (s, 1H,  $\text{H}_2$ ); 7.95 (s, 1H,  $\text{H}_5$ ); 5.78 (qd,  $J=7\text{Hz}$  and 8.5Hz, 1H, CH); 4.14 (s, 3H,  $\text{OCH}_3$ ); 3.63 (d,  $J=8.5\text{Hz}$ , 1H, OH); 1.66 (d,  $J=7\text{Hz}$ , 3H,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  166.1 ( $\text{C}_4$ ); 155.1 ( $\text{C}_2$ ); 146.4, 144.1, 131.7 ( $\text{C}_{6,7,8,9}$ ); 123.2 ( $\text{C}_5$ ); 116.1 ( $\text{C}_{10}$ ); 68.5 (CH); 54.8 ( $\text{OCH}_3$ ); 20.8 ( $\text{CH}_3$ ); ir :  $\nu$  3421, 1569, 1480, 1373, 1119, 1003, 832, 804  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}_2$  (273.12): C, 48.37; H, 3.69; N, 10.26. Found: C, 48.48; H, 3.62; N, 9.90. Another fraction afforded 9 mg (7%) of starting material.

**6,8-dichloro-7-(hydroxyphenylmethyl)-4-methoxyquinazoline (38):** metallation of **35** (130 mg, 0.57 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.50 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 1\text{h}30$ ,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with benzaldehyde (2.2 eq., 0.13 ml),  $t_2 = 2\text{ h}$ ,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) 175 mg (92%) of **38** as a white solid, mp 181-182°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.92 (s, 1H, H<sub>2</sub>); 8.14 (s, 1H, H<sub>5</sub>); 7.31 (m, 5H, 5H<sub>Ph</sub>); 6.92 (d, J=10Hz, 1H, CH); 4.21 (s, 3H, OCH<sub>3</sub>); 3.85 (d, J=10Hz, 1H, OH);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  166.3 (C<sub>4</sub>); 155.4 (C<sub>2</sub>); 146.9 (C<sub>9</sub>); 143.2, 140.4 (C<sub>6,8</sub>); 133.4 (C<sub>7</sub>); 132.7 (C<sub>Ph</sub>); 128.3-125.2 (5C<sub>Ph</sub>); 123.5 (C<sub>5</sub>); 116.8 (C<sub>10</sub>); 72.9 (CH); 54.9 (OCH<sub>3</sub>); ir :  $\nu$  3386, 1568, 1478, 1374, 1013, 728  $\text{cm}^{-1}$ . Anal. Calcd for C<sub>16</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> (335.2): C, 57.33; H, 3.61; N, 8.36. Found: C, 57.50; H, 3.75; N, 7.98. Another fraction afforded 10 mg (8%) of starting material.

**6,8-dichloro-4-methoxy-7-methylquinazoline (39):** metallation of **35** (130 mg, 0.57 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.50 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 1\text{h}30$ ,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with methyl iodide (2.2 eq., 80  $\mu\text{l}$ ),  $t_2 = 1\text{ h}$ ,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) 129 mg (93%) of **39** as a white solid, mp 157-158°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.81 (s, 1H, H<sub>2</sub>); 7.96 (s, 1H, H<sub>5</sub>); 4.14 (s, 3H, OCH<sub>3</sub>); 2.63 (s, 3H, CH<sub>3</sub>);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  166.1 (C<sub>4</sub>); 154.8 (C<sub>2</sub>); 146 (C<sub>9</sub>); 140.4, 133.6, 132.5 (C<sub>6,7,8</sub>); 121.1 (C<sub>5</sub>); 115.5 (C<sub>10</sub>); 54.6 (OCH<sub>3</sub>); 18.7 (CH<sub>3</sub>); ir : 1470, 1370, 960, 879, 804  $\text{cm}^{-1}$ . Anal. Calcd for C<sub>10</sub>H<sub>8</sub>Cl<sub>2</sub>N<sub>2</sub>O (243.10): C, 49.41; H, 3.31; N, 11.52. Found: C, 49.48; H, 3.07; N, 11.28.

**6,8-dichloro-7-iodo-4-methoxyquinazoline (40):** metallation of **35** (130 mg, 0.57 mmol) according to the general procedure A with *n*-BuLi 2.5 M (2.2 eq., 0.50 ml), TMPH (2.3 eq., 0.22 ml),  $t_1 = 1\text{h}30$ ,  $\theta_1 = -78^\circ\text{C}$ , followed by reaction with iodine (1.2 eq., 0.173 g),  $t_2 = 2\text{ h}$ ,  $\theta_2 = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (7/3)) 182 mg (90%) of **40** as a white solid, mp 203-204°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.85 (s, 1H, H<sub>2</sub>); 8.17 (s, 1H, H<sub>5</sub>); 4.19 (s, 3H, OCH<sub>3</sub>);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  166.5 (C<sub>4</sub>); 155.6 (C<sub>2</sub>); 145.5 (C<sub>9</sub>); 139.5 (C<sub>8</sub>); 137.3 (C<sub>6</sub>); 120.8 (C<sub>5</sub>); 117.1 (C<sub>10</sub>); 111.9 (C<sub>7</sub>); 55 (OCH<sub>3</sub>); ir :  $\nu$  1466, 1354, 1128, 991, 801, 528  $\text{cm}^{-1}$ . Anal. Calcd for C<sub>9</sub>H<sub>5</sub>Cl<sub>2</sub>IN<sub>2</sub>O (354.87): C, 30.46; H, 1.42; N, 7.89. Found: C, 30.74; H, 1.32; N, 7.70.

**6,8-dichloro-4-methoxy-7-trimethylsilylquinazoline (41):** metallation of **35** (100 mg, 0.44 mmol) according to the general procedure B with *n*-BuLi 1.6 M (2.2 eq., 0.60 ml), TMPH (2.3 eq., 0.17 ml), trimethylsilyl chloride (2.2 eq., 122  $\mu\text{l}$ ),  $t = 2\text{ h}$ ,  $\theta = -78^\circ\text{C}$ , gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (9/1)) and sublimation 115 mg (88%) of **41** as a white solid, mp 128-129°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  8.87 (s, 1H, H<sub>2</sub>); 8.00 (s, 1H, H<sub>5</sub>); 4.17 (s, 3H, OCH<sub>3</sub>); 0.58 (s, 9H, 3xCH<sub>3</sub>); ir :  $\nu$  1473, 1352, 1247, 1008, 846, 804, 536  $\text{cm}^{-1}$ . Anal. Calcd for C<sub>12</sub>H<sub>14</sub>Cl<sub>2</sub>N<sub>2</sub>OSi (301.25): C, 47.85; H, 4.68; N, 9.30. Found: C, 47.84; H, 4.62; N, 9.08.

**2-*n*-butyl-8-chloro-4,6,7-trimethoxyquinazoline (42) and 2-*n*-butyl-8-chloro-4-(1-(1-hydroxyethyl)-butyl)-6,7-dimethoxyquinazoline (43):** metallation of **34** (104 mg, 0.37 mmol) according to the general procedure C with *n*-BuLi 1.6 M (2.2 eq., 0.50 ml),  $t_1 = 40\text{ min}$ , followed by reaction with acetaldehyde (2

ml),  $t_2 = 30$  min, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (6/4)) 73 mg (64%) of **42** as a beige solid, mp 120-121°C;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.23 (s, 1H, H<sub>5</sub>); 4.17 (s, 3H, OCH<sub>3</sub>); 4.13 (s, 3H, OCH<sub>3</sub>); 3.92 (s, 3H, OCH<sub>3</sub>); 2.99 (t, J=7Hz, 2H, CH<sub>2</sub>); 1.51 (m, 4H, 2xCH<sub>2</sub>); 0.95 (t, J=7Hz, 3H, CH<sub>3</sub>); ir :  $\nu$  2959, 1588, 1453, 1383, 1285, 1080, 1032, 792  $\text{cm}^{-1}$ . MS:  $[\text{M Cl}(35)]^+$ , 310;  $[\text{M Cl}(37)]^+$ , 312;  $[\text{M}-\text{C}_4\text{H}_9]^+$ , 253;  $[\text{M}-\text{CH}_3\text{O}]^+$ , 279. Anal. Calcd for  $\text{C}_{15}\text{H}_{19}\text{ClN}_2\text{O}_3$  (310.78): C, 57.97; H, 6.16; N, 9.01. Found: C, 57.60; H, 6.36; N, 9.28.

Another fraction afforded 37 mg (26%) of **43** as a pale yellow oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.15 (s, 1H, H<sub>5</sub>); 4.27 (m, 1H, CH); 4.15 (m, 4H, OCH<sub>3</sub> + OH); 3.96 (s, 3H, OCH<sub>3</sub>); 3.52 (m, 1H, CH); 3.03 (t, J=7Hz, 2H, CH<sub>2</sub>); 1.93 (m, 2H, CH<sub>2</sub>); 1.47 (m, 4H, 2xCH<sub>2</sub>); 1.22 (m, 2H, CH<sub>2</sub>); 1.17 (d, J=6.4Hz, 3H, CH<sub>3</sub>); 0.97 (t, J=7.7Hz, 3H, CH<sub>3</sub>); 0.88 (t, J=7Hz, 3H, CH<sub>3</sub>); ir :  $\nu$  3407, 2957, 1572, 1459, 1371, 1268, 1205, 756  $\text{cm}^{-1}$ . MS:  $[\text{M}]^+$ , 380;  $[\text{M}-\text{CH}_3]^+$ , 365;  $[\text{M}-\text{C}_3\text{H}_6]^+$ , 338;  $[\text{M}-\text{CH}_3\text{O}]^+$ , 307;  $[\text{M}-\text{C}_2\text{H}_4\text{O}]^+$ , 294;  $[\text{M}-\text{C}_4\text{H}_9]^+$ , 281;  $[\text{M}-\text{C}_4\text{H}_9]^+$ , 251. Anal. Calcd for  $\text{C}_{20}\text{H}_{29}\text{ClN}_2\text{O}_3$  (380.91): C, 63.06; H, 7.67; N, 7.35. Found: C, 63.33; H, 8.02; N, 7.40.

**2,4-di-tert-butyl-8-chloro-6,7-dimethoxyquinazoline (44) and 2-tert-butyl-8-(1-hydroxyethyl)-4,6,7-trimethoxyquinazoline (45)**: metallation of **34** (100 mg, 0.35 mmol) according to the general procedure C with *tert*-BuLi 1.7 M (2.2 eq., 0.48 ml),  $t_1 = 40$  min, followed by reaction with acetaldehyde (2 ml),  $t_2 = 30$  min, gave after purification by column chromatography (silica, eluent : petroleum ether/ethylacetate (8.5/1.5)) 38 mg (32%) of **44** as a colorless oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.57 (s, 1H, H<sub>5</sub>); 4.15 (s, 3H, OCH<sub>3</sub>); 3.96 (s, 3H, OCH<sub>3</sub>); 1.69 (s, 9H, 3xCH<sub>3</sub>); 1.63 (s, 9H, 3xCH<sub>3</sub>); ir :  $\nu$  2953, 2568, 1446, 1368, 1340, 1283, 1216, 1061, 1040, 842, 807  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{18}\text{H}_{25}\text{ClN}_2\text{O}_2$  (336.86): C, 64.18; H, 7.48; N, 8.32. Found: C, 64.07; H, 7.67; N, 8.09.

Another fraction afforded 44 mg (39%) of **45** as a colorless oil;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  7.24 (s, 1H, H<sub>5</sub>); 6.81 (d, J=11Hz, 1H, OH); 5.90 (qd, J=11Hz and 6.6Hz, 1H, CH); 4.16 (s, 3H, OCH<sub>3</sub>); 4.06 (s, 3H, OCH<sub>3</sub>); 3.85 (s, 3H, OCH<sub>3</sub>); 1.76 (d, J=6.6Hz, 3H, CH<sub>3</sub>); 1.61 (s, 9H, 3xCH<sub>3</sub>); ir :  $\nu$  3416, 2952, 1587, 1567, 1382, 1292, 1254, 1231, 1071, 804  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{24}\text{N}_2\text{O}_4$  (320.39): C, 63.73; H, 8.74; N, 7.55. Found: C, 63.67; H, 8.83; N, 7.52. Another fraction afforded 29 mg (29%) of starting material.

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Compound	H <sub>5</sub>	H <sub>8</sub>	LUMO
1	+ 0.151	+ 0.153	- 0.750
7	+ 0.151	+ 0.155	- 0.595
10	+ 0.168	+ 0.156	- 0.610
11	+ 0.166	+ 0.160	- 0.820
13	+ 0.163	+ 0.159	- 0.831
22	+ 0.158	+ 0.169	- 0.820
28	+ 0.160	+ 0.161	- 0.530

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