The Synthesis of 8-Hydroxyquinazoline Derivatives and Their Acid–Base Interactions

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The reaction of *N*-(2-R^1-oxyphenyl)benzimidoyl chlorides with cyanamide derivatives in the presence of titanium tetrachloride as a catalyst has yielded some new 4-amino-8-R^1-oxy-2-phenylquinazolines. pK_a values have been determined for these compounds and the influence of substituents at the basicity of the parent system has been discussed. Some investigations on the methyl-quinazolinyl ether cleavage in different medium have been done yielding the appropriate hydroxyquinazoline derivatives. In those cases when the deprotection of 4-amino-8-methoxy-2-phenylquinazoline was carried in aqueous acidic solutions, the formation of the hydrolysis products 3,4-dihydro-2-phenyl-4-quinazolone derivatives was observed as well.

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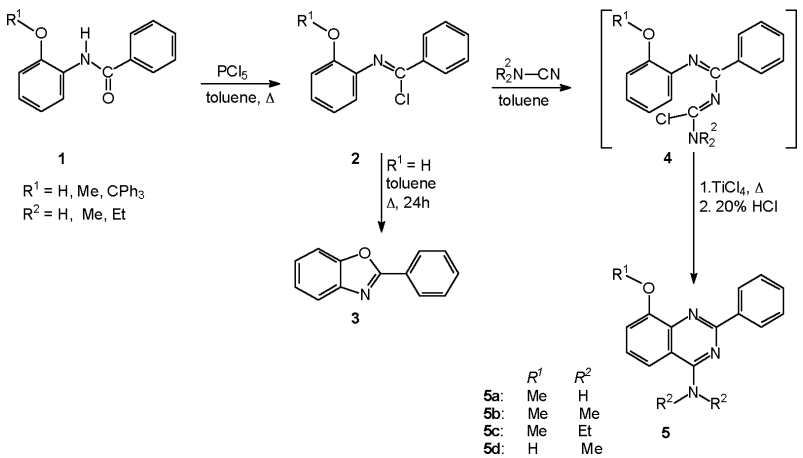
Quinazolines have been attracting attention for a few decades due to their wide range of biological activity [1]. Particular attention has been focused on amino, methoxy and hydroxy derivatives which display anti-malaria and anticance properties and are used to work in drugs against hypertension and to fight infections involving AIDS [2]. The topic of this study is the synthesis and basicity of 8-hydroxyquinazoline derivatives. Only a few 4-amino- and 2,4-diaminoquinazoline derivatives have been synthesized earlier from the original substituted benzamides or ureas using cyanamide derivatives and $TiCl_4$ in a several-step reactions [3-7]. We have tried to apply a similar procedure to the synthesis of 8-hydroxyquinazolines. Apart from all the aspects connected with the biological activity, such quinazolines have been the subject of detailed studies because they are analogues of 8-hydroxyquinoline. They form complexes with many cations (Cu^{+2}, Ni^{+2}, Zn^{+2}, Fe^{+2}, Mg^{+2}, Li^+ and others), which are used in the spectrophotometric determinations of the metals [8-10].

A group of 4-amino-8-hydroxy-2-phenylquinazoline derivatives (**5**) has been synthesized from well-known compounds: *N*-(2-hydroxyphenyl)benzamide and *N*-(2-methoxyphenyl)benzamide (Scheme 1). The synthesis involves conversion of *N*-(2-R^1-oxyphenyl)benzamide derivatives (**1**) to the appropriate benzimidoyl chlorides (**2**) in the reaction with PCl_5. Such chlorides obtained in almost quantitative yields react at room temperature with cyanamide derivatives (R^2 = H, Me, Et) yielding probably linear products [3] (**4**), which undergo cyclization to final 8-R^1-oxyquinazolines (**5**) with the use of a Lewis acid catalyst $TiCl_4$. After several hours of heating in toluene a highly stable quinazoline-$TiCl_4$ complex was isolated. The compound was broken up using concentrated acid solution (20% HCl), however, difficulties with the separation of the quinazoline from the post-reaction mixture adversely affect product yield (42-86%). Although the number of the obtained quinazolines is relatively small, one could observe a relationship between the basicity of the quinazoline and its yield. The stronger the acidity of the compound is, the lower yield is achieved during the acidic cleavage of the quinazoline-$TiCl_4$ complex.

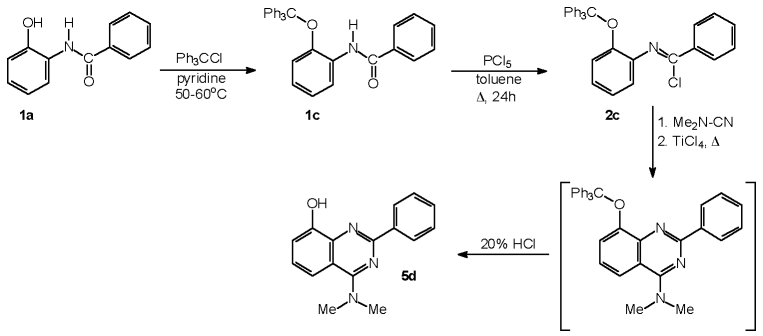
Unfortunately, the unsubstituted *N*-(2-hydroxyphenyl)-benzamide (R^1 = H) reacts with PCl_5 in anhydrous toluene yielding mainly 2-phenyl-1,3-benzoxazole [11]

Scheme 1



(**3**, Scheme 1). It was necessary to protect the hydroxy group in amide using trityl chloride [12] Ph_3CCl to avoid such side reaction and then transfer the protected amide into the benzimidoyl chloride and finally to quinazoline. We have not obtained the quinazoline with triphenylmethoxy group in the position 8 because the deprotection of such ether occurs during the cleavage of the quinazoline-catalyst complex in the acidic medium (Scheme 2).

Scheme 2



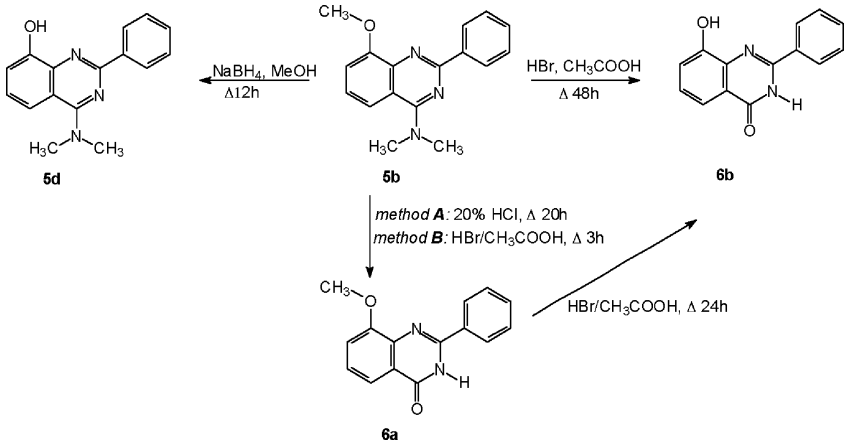
Studies of the methyl-quinazolinyl ether cleavage have been also carried out using some typical reagents suggested in those cases where the leaving group is methyl, CH_3. A selective cleavage of **5b** ether to the appropriate hydroxy derivative **5d** took place during heating with $NaBH_4$ in methanol (Scheme 3). We did not succeed with a more reactive system than the former one – $LiAlH_4$ in benzene [13]. Two 3,4-dihydro-2-phenyl-4-quinazolones (**6a**, **6b**) have been also obtained during the refluxing of **5b** compound with other suggested reagents such as aqueous HCl [14] or HBr in glacial acetic acid [15]. 4-*N,N*-Dimethylamino-8-methoxyquinazoline derivative **5b**, when heated both in a boiling aqueous HCl or HBr in glacial CH_3COOH undergoes mainly the hydrolysis [7,16,17] to the corresponding quinazolone **6a** without disturbing the methoxy group. This group was replaced by the hydroxy group in boiling HBr/CH_3COOH solution, thus forming **6b** quinazolone when the reaction time was adequately prolonged.

The structures of the new quinazolines (**5a-5d**) and quinazolones (**6a-6b**) were confirmed by means of elemental analyses and typical spectroscopic methods (MS, UV, ^1H-, ^{13}C-NMR).

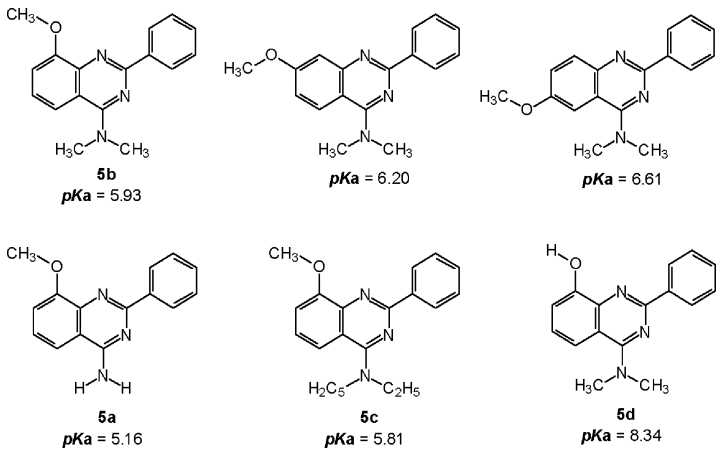
Considering the fact that the biological activity of compounds is also greatly dependent on their acid-base characteristics, the pK_a values of the synthesized compounds have been determined. The determination of the pK_a dissociation constants was performed according to the spectrophotometric method of Albert and Serjeant [18] in 50% aqueous-methanol solution (10^{-5}M, room temperature).

Our results show that the strongest base among the three derivatives of 8-methoxy-2-phenylquinazoline (**5a**, **5b**, **5c**) is the quinazoline **5b** with a strongly electron-donating dimethylamino group NMe_2 in the position 4 (Scheme 4). We have observed a lowering of the pK_a value in the case of **5c** with diethylamino group NEt_2. According to our earlier investigation [19] protonated quinazolines with strongly electron-donating substituents in the 4 position are stabilized by the resonance effect and a prevailing contribution in the resonance hybride has a *para-quinoid* form (**5c-1**, Scheme 5).

Scheme 3

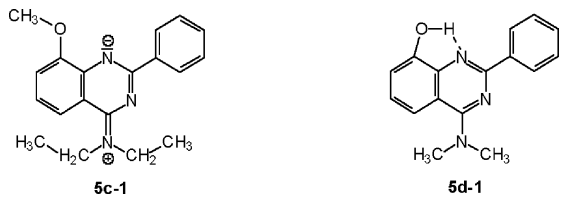


Scheme 4



That is why a bulky diethylamino group NEt_2 remains untwisted in the ring plane and its steric hindrance toward the addition of the proton increases. It is also worthwhile to consider the basicity of 4-(*N,N*-dimethylamino)-2-phenylquinazoline substituted differently with the methoxy group in the benzene fragment in different positions (6-methoxy-, 7-methoxy- and 8-methoxy isomers, Scheme 4). A steric effect of the untwisted bulky dimethylamino group in the 4 position causes a weakening of the C4-C4a bond and the electronic effects of the substituents in the benzene ring are mostly transfered *via* C8a-N1 bond [20]. Thus, the electron transfer in such quinazolines occurs in the same fashion as in substituted aniline. The strongest base in this group is 6-methoxy-4-(*N,N*-dimethylamino)-2-phenylquinazoline (*para* arrangement) which is attributed to the possibility of the electron coupling with the protonation centre (endocyclic nitrogen atoms N1, N3) [4]. No such coupling is observed in the case of the 7-methoxy derivative (*meta* arrangement). The 8-methoxy derivative **5c** has the lowest pK_a value. It should be noted that we have here the *ortho* arrangement where the equilibrium achieved between induction, resonance and steric effect is complex [20].

Scheme 5



A replacement of the methoxy group in the 8 position of the quinazoline with the hydroxy group drastically changes the character of the compound and leads to amphoteric properties. Such a quinazoline base **5d** is also a phenol and that is why its dissociation constant differs considerably from the pK_a of 8-methoxyquinazoline derivatives. The formation of the very stable *para-quinoid* form is limited here because of the hydrogen bonding [21] (**5d-1**, Scheme 5) which involves the N1 nitrogen atom and decreases the basicity.

EXPERIMENTAL

UV spectra were recorded on a Shimadzu UV-2102 spectrophotometer; basic medium: 0.05 *M* NaOH in 50% aqueous methanol solution, acidic medium: 0.05 *M* HCl in 50% aqueous methanol solution. Elemental analyses were carried out with a Perkin Elmer 240c analyser. The ^1H and ^{13}C nmr spectra were recorded on a Varian Inova 300 spectrometer in DMSO solution using TMS as internal standard. MS spectra were obtained with a Shimadzu QP-200 mass spectrometer. Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene-ethyl acetate-diethylamine mixture (6:2:1 v/v/v) as the mobile phase.

N-(2-Hydroxyphenyl)benzamide (**1a**).

A solution of 2-aminophenol (6.55 g, 0.06 mole) in pyridine (25 mL) and benzoic anhydride (15 g, 0.065 mol) was heated under reflux for about 1 hour. After cooling it was poured into ice water. The resulting precipitate was collected by filtration and crystallized from ethanol giving white crystals of **1a**; yield: 86%; mp: 169-171°C; lit. [22]: 173 °C, R_f: 0.17.

N-(2-Methoxyphenyl)benzamide (**1b**).

Benzoyl chloride (12.5 mL, 0.09 mole) was added dropwise with stirring to 2-methoxyaniline (10 g, 0.08 mol) in aqueous 10% NaOH solution (70 ml). After the addition of chloride was completed, the stirring was continued for about 1 hour. The crude product was collected by filtration and crystallized from ethanol giving yellow crystals of **1b**; yield: 71%; mp: 64-66°C; lit. [23]: 68-69 °C; R_f: 0.64.

N-[2-(Triphenylmethoxy)phenyl]benzamide (**1c**).

A solution of **1a** (7.1 g, 0.034 mole) in pyridine (50 mL) and trityl chloride (10.2 g, 0.037 mole) was gently heated at about 50 °C for 48 hours. Then it was left for crystallization

giving white crystals of **1c**; yield: 54%; mp: 77-80 °C; R_f: 0.61; ^{1}H nmr ($CDCl_3$, Me_4Si): δ 7.24-7.30 (m, 24 H_{arom}), 8.48 (s, 1 H, NH) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 256.4 (8.31), 215.0 (28.43) nm.

Anal. Calcd. for $C_{32}H_{25}NO_2$: C, 84.36; H, 5.54; N, 3.07. Found: C, 84.02; H, 5.40; N, 2.98.

General Procedure for the Preparation of *N*-(2-R^1-oxyphenyl)-benzimidoyl Chlorides (**2**).

N-(2-R^1-oxyphenyl)benzamide (**1**) (0.05 mole), anhydrous toluene (100 mL) and PCl_5 (11.5 g, 0.055 mole) were heated under reflux until the disappearance of the benzamide (TLC) was completed. Then the toluene and $POCl_3$ were removed using a rotary evaporator. The crude *N*-(2-R^1-oxyphenyl)benzimidoyl chloride (**2**) was pure enough to be used in the next step.

N-[2-(Triphenylmethoxy)phenyl]benzimidoyl Chloride (**2c**).

This compound was obtained as a brown-yellowish solid; yield: 64%; mp: 112-114 °C; R_f: 0.57; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) MeOH: 255.0 (12.81) nm.

Anal. Calcd. for $C_{32}H_{24}NOCl$: C, 81.59; H, 5.11; N, 2.95. Found: C, 81.32; H, 5.21; N, 2.99.

2-Phenyl-1,3-benzoxazole (**3**).

This compound was obtained as a yellowish solid; yield: 78%; mp: 100-101 °C; lit. [11]: 102 °C; R_f: 0.62; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 7.43 (d, *J* = 8.4, 1H, H-7), 7.45 (d, *J* = 8.4, 1H, H-4), 7.62-7.65 (m, 3H, H-3', H-4', H-5'), 7.81 (t, *J* = 8.4, 2H, H-5, H-6), 8.22 (d, *J* = 6.9, 2 H, H-2', H-6') ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 297.5 (19.70), 291.3 (20.70), 202.5 (2.86), basic: 300.2 (18.63), 292.5 (18.72), 238.8 (6.94) nm.

General Procedure for the Preparation of 4-Amino-8-hydroxy-2-phenylquinazoline Derivatives (**5a-5d**).

The crude *N*-(2-R^1-oxyphenyl)benzimidoyl chloride (**2**) (0.05 mole), prepared from the appropriate *N*-(2-R^1-oxyphenyl)benzamide (**1**) was dissolved in the portion of anhydrous toluene (70 mL). Then cyanamide derivative (R^2 = H, Me, Et) (0.05 mole) in anhydrous diethyl ether (5 mL) was added there. The mixture was left for 1 hour, and then, $TiCl_4$ (5 mL, 0.05 mole) in anhydrous toluene (20 mL) was gradually added. The stirring was continued at 50 °C for about 3 hours. Solvents were removed using a rotary evaporator and the resulting gluey solid was washed with toluene and 20% aqueous HCl (100 mL) was added. After a rapid decomposition the mixture was extracted with chloroform. Purified and dried (calcium chloride) compounds (**5**) were crystallized from methanol or 2-propanol.

4-Amino-8-methoxy-2-phenylquinazoline (**5a**).

This compound was obtained as a white solid; yield: 54%; mp: 155-157 °C; R_f: 0.56; ^{1}H nmr ($CDCl_3$, Me_4Si): δ 3.75 (s, 2 H, NH_2), 3.84 (s, 3 H, OCH_3), 7.16 (d, *J* = 7.8, 1H, H-7), 7.24 (m, 1H, H-6), 7.40-7.50 (m, 3 H, H-3', H-4', H-5'), 7.64 (d, *J* = 8.4, 1 H, H-5), 8.29 (d, *J* = 7.8, 2 H, H-2', H-6') ppm; uv : λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 300.0 (17.30), 248.8 (14.33), 210.0 (26.67), basic: 289.0 (19.4), 235.4 (19.85) nm; ms: m/z (%) 51 (12), 63 (13), 77 (40), 92 (13), 104 (12), 105 (41), 167 (15), 195 (87), 210 (M^+, 100), 211 (19), 227 (12), 250 (15), 251 (25); pK_a = 5.16 ± 0.09 (λ_{anal} = 230.0 nm).

Anal. Calcd. for $C_{15}H_{13}N_3O$: C, 71.69; H, 5.22; N, 16.71. Found: C, 71.80; H, 5.31; N, 16.65.

4-(*N,N*-Dimethylamino)-8-methoxy-2-phenylquinazoline (**5b**).

This compound was obtained as a pink solid; yield: 86%; mp: 147-148 °C; R_f: 0.38; ^{1}H nmr ($CDCl_3$, Me_4Si): δ 3.39 (s, 6 H, $N(CH_3)_2$), 4.06 (s, 3 H, OCH_3), 7.06 (d, *J* = 7.5, 1 H, H-7), 7.27 (dd, *J* = 7.5 and 8.1, 1 H, H-6), 7.42-7.50 (m, 3 H, H-3', H-4', H-5'), 7.63 (d, *J* = 8.1, 1 H, H-5), 8.60 (d, *J* = 8.1, 2 H, H-2', H-6') ppm; ^{13}C nmr: δ 37.3 ($N(CH_3)_2$), 51.7 (OCH_3), 106.0 (C-4a), 111.1 (C-5), 112.7 (C-6), 119.3 (C-8), 123.6 (C-3', C-5'), 124.0 (C-2', C-6'), 125.4 (C-4'), 134.3 (C-7), 140.4 (C-1'), 150.7 (C-8a), 154.1 (C-2), 159.6 (C-4) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 335.4 (10.10), 271.0 (36.84), 203.2 (29.01), basic: 331.8 (15.48), 257.6 (38.28), 214.8 (15.27) nm; ms: m/z (%) 77 (11), 205 (13), 235 (20), 249 (26), 250 (29), 278 (M^+, 100), 279 (94), 280 (18); pK_a = 5.93 ± 0.12 (λ_{anal} = 332.6 nm).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.14; N, 15.03. Found: C, 72.90; H, 6.12; N, 14.96.

4-(*N,N*-Diethylamino)-8-methoxy-2-phenylquinazoline (**5c**).

This compound was obtained in 77% yield; mp: 142-145 °C; R_f: 0.42; ^{1}H nmr ($CDCl_3$, Me_4Si): δ 1.44 (t, *J* = 7.8, 6 H, $N(CH_2CH_3)_2$), 3.70 (q, *J* = 7.8, 4 H, $N(CH_2CH_3)_2$), 4.05 (3 H, s, OCH_3), 7.05 (d, *J* = 7.8, 1 H, H-7), 7.28 (m, 1 H, H-6), 7.38-7.50 (m, 3 H, H-3', H-4', H-5'), 7.55 (d, *J* = 9.0, 1 H, H-5), 8.58 (d, *J* = 7.5, 2 H, H-2', H-6') ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 271.8 (8.96), 212.6 (21.18), basic: 232.4 (11.23) nm; ms: m/z (%) 72 (10), 77 (28), 105 (41), 178 (12), 195 (18), 210 (M^+, 100), 211 (17), 278 (15), 306 (13), 307 (32), 308 (12); pK_a = 5.81 ± 0.10 (λ_{anal} = 230.8 nm).

Anal. Calcd. for $C_{19}H_{21}N_3O$: C, 74.23; H, 6.89; N, 13.66. Found: C, 74.28; H, 6.80; N, 13.61.

4-(*N,N*-Dimethylamino)-8-hydroxy-2-phenylquinazoline (**5d**).

This compound was obtained in 42% yield; mp: 165-167 °C; R_f: 0.38; ^{1}H nmr ($CDCl_3$, Me_4Si): δ 3.26 (s, 6 H, $N(CH_3)_2$), 7.01 (d, *J* = 7.8, 1H, H-7), 7.15 (d, *J* = 7.8, 1H, H-5), 7.24-7.32 (m, 3 H, H-3', H-4', H-5'), 7.66 (dd, *J* = 7.8 and 7.8, 1 H, H-6), 8.75 (d, *J* = 7.8, 2H, H-2', H-6') 11.30 (s, 1H, OH) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 348 (5.00), 294.8 (4.33), 275.0 (10.09), 265.4 (9.70), 213.1 (14.65), basic: 338 (3.33), 264.8 (13.92), 239.2 (17.72) nm; ms: m/z (%) 51 (23), 72 (23), 78 (83), 79 (13), 93 (36), 94 (15), 119 (49), 120 (22), 121 (23), 146 (17), 148 (18), 161 (21), 164 (40), 175 (10), 190 (M^+, 100), 191 (19), 265 (36); pK_a = 8.34 ± 0.05 (λ_{anal} = 267.4 nm).

Anal. Calcd. for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.71; N, 15.83. Found: C, 72.25; H, 5.57; N, 15.91.

Quinazoline **5d** was also Obtained by Another Method.

8-Methoxy-4-(*N,N*-dimethylamino)-2-phenyl-quinazoline (**5b**) (0.5 g, 1.79 mmole) was dissolved in methanol (20 mL) and $NaBH_4$ (0.139 g, 3.67 mmole) was added there. The mixture was stirred at 40 °C for 12 hours. Then it was cooled down and acidified with 5% aqueous HCl solution. A white precipitate was crystallized from ethanol giving quinazoline **5d** (yield: 84%).

Preparation of 3,4-Dihydro-8-methoxy-2-phenyl-4-quinazolone (**6a**).

Method A.

8-Methoxy-4-(*N,N*-dimethylamino)-2-phenylquinazoline (**5 b**) (0.45 g, 1.61 mmole) was dissolved in the 20% aqueous HCl (10 mL). The mixture was kept under reflux for 20 hours until the

disappearance of starting quinazoline was complete. Then it was cooled down yielding a white precipitate **6a** that was was crystallized from acetone (yield: 74%).

Method B.

8-Methoxy-4-(*N,N*-dimethylamino)-2-phenylquinazoline (**5b**) (0.45 g, 1.61 mmole) was dissolved in a mixture of glacial CH_3COOH (7 mL) and 45% HBr (10 mL). The solution was kept under reflux for 3 hours until the disappearance of starting quinazoline was complete. Then it was cooled down and alkalized with 20% aqueous NaOH solution yielding a white precipitate **6a** which was crystallized from acetone (yield: 82%); mp: 260-262 °C; R_f: 0.07; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 3.96 (s, 3 H, OCH_3), 4.20 (br, 1 H, NH), 7.39 (d, *J* = 7.8, 1 H, H-7), 7.46 (dd, *J* = 7.8 and 7.8, 1 H, H-6), 7.52-7.60 (m, 3 H, H-3', H-4', H-5'), 7.71 (d, *J* = 7.8, 1 H, H-5), 8.16 (d, *J* = 7.5, 2 H, H-2', H-6') ppm; ^{13}C nmr: δ 56.0 (OCH_3), 115.2 (C-4a), 116.8 (C-8), 121.8 (C-5), 126.9 (C-6), 127.7 (C-2', C-6'), 128.4 (C-3', C-5'), 131.2 (C-4'), 132.5 (C-7), 138.6 (C-1'), 151.2 (C-8a), 154.3 (C-2), 161.9 (C-4) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 327.0 (10.15), 251.0 (23.00), 202.4 (27.88), basic: 316.0 (12.70), 249.0 (32.92), 212.8 (44.55) nm; ms: m/z (%) 77 (17), 104 (12), 194 (11), 222 (34), 223 (43), 251 (100), 252 (M^+, 86), 253 (16).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.10. Found: C, 71.37; H, 4.75; N, 11.15.

Preparation of 3,4-Dihydro-8-hydroxy-2-phenyl-4-quinazolone (**6b**).

4-(*N,N*-Dimethylamino)-8-methoxy-2-phenylquinazoline (**5b**) (0.40 g, 1.43 mmole) was dissolved in a mixture of glacial acetic acid (10 mL) and 45% HBr (10 mL). The solution was kept under reflux for 48 hours until the disappearance of starting quinazoline was complete. Then it was cooled down, poured into water (150 mL) and alkalized with 20% aqueous NaOH solution yielding a white precipitate **6b** (yield: 97%).

Such derivative was also obtained by heating of 3,4-dihydro-8-methoxy-2-phenyl-4-quinazolone (**6a**) (0.4 g, 1.58 mmole) with the mixture of glacial acetic acid (10 mL) and 45% HBr (10 mL) in the similar manner (yield: 95%); mp: 295-297°C; R_f: 0.02; ^{1}H nmr (DMSO-d_6, Me_4Si): δ 4.65 (br, 1 H, NH), 7.23 (d, *J* = 7.8, 1H, H-7), 7.34 (dd, *J* = 7.8 and 7.8, 1 H, H-6), 7.50-7.62 (m, 4 H, H-3', H-4', H-5', H-5), 8.42 (d, *J* = 7.8, 2H, H-2', H-6'), 11.50 (s, 1 H, OH) ppm; ^{13}C nmr: δ 115.7 (C-4a), 118.2 (C-8), 121.7 (C-5), 127.0 (C-6), 128.0 (C-2', C-6'), 128.4 (C-3', C-5'), 131.2 (C-4'), 132.7 (C-7), 137.7 (C-1'), 150.6 (C-8a), 153.0 (C-2), 162.5 (C-4) ppm; uv: λ_{max} ($\varepsilon \cdot 10^{-3}$) acidic: 328.2 (9.42), 252.0 (23.85), 203.4 (26.84), basic: 341.6 (9.53), 238.6 (28.77), 214.2 (38.60), 205.2 (16.18) nm; ms: m/z (%) 63 (16), 77 (12), 104 (21), 105 (11), 107 (39), 135 (12), 238 (M^+, 100), 239 (18).

Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.57; H, 4.24; N, 11.75. Found: C, 70.80; H, 4.32; N, 11.68.

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