AN APPROACH TO THE SYNTHESIS OF A PAPAVERINE ANALOGUE CONTAINING A QUINAZOLINE RING SYSTEM [1]

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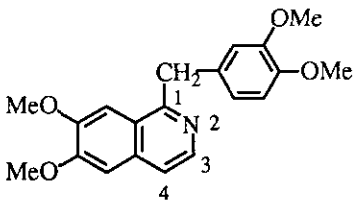
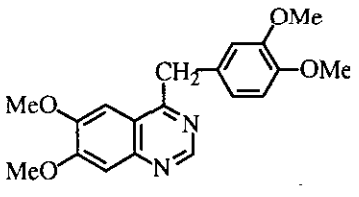
Abstract ——Synthesis of a papaverine analogue containing a quinazoline ring system (4-azapapaverine) was achieved. In the synthesis of 4-azapapaverine catalytic aroylation is a useful reaction. Preparation of several 4-aroyl-6,7-dimethoxyquinazolines was accomplished by aroylation.

A number of synthetic methods for papaverine have been reported because of interest in its biological activity.[2] Therefore, an approach to the synthesis of papaverine analogues having another ring system is an intriguing and inspiring investigation. The preparation of papaverine analogues possessing a quinazoline ring system (4-azapapaverine) using catalytic aroylation as a key reaction was interesting. As a part of our study, our purpose was the application of aroylation in organic synthesis. In this paper, we will describe a synthetic approach to 4-azapapaverine by nucleophilic aroylation involving the catalytic action of 1,3-dimethylimidazolium iodide (2).



Papaverine



4-Azapapaverine

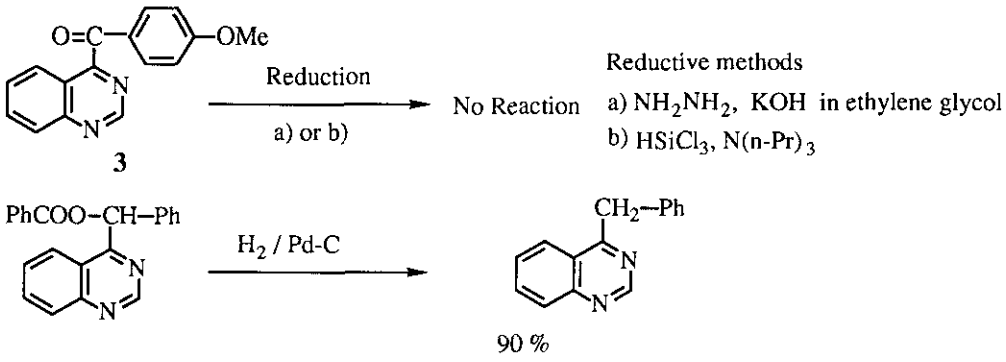
Scheme 1

In the literature, only one example of the synthesis of 4-azapapaverine can be found.[3] Namely, Kamath *et al.* reported that synthesis of 4-azapapaverine was established by ring-closure of a quinazoline ring at the final step in a long sequence in their synthetic program, though the procedure which built the quinazoline ring at the final step is unsuitable for the preparation of various 4-azapapaverine derivatives. We then

designed a synthetic route to 4-azapapaverine by production of a quinazoline ring at an earlier step followed by introduction of a 3,4-dimethoxybenzyl moiety onto the quinazoline ring.

In the previous paper,[4,5] we reported that an aromatic aldehyde in the presence of azolium salts acts as a nucleophilic reagent corresponding to a aroyl anion (Ar-$\bar{C}$O), resulting in the formation of a nucleophilically aroylated compound. We then applied this method to the preparation of 4-azapapaverine analogues using catalytic aroylation as a key reaction.

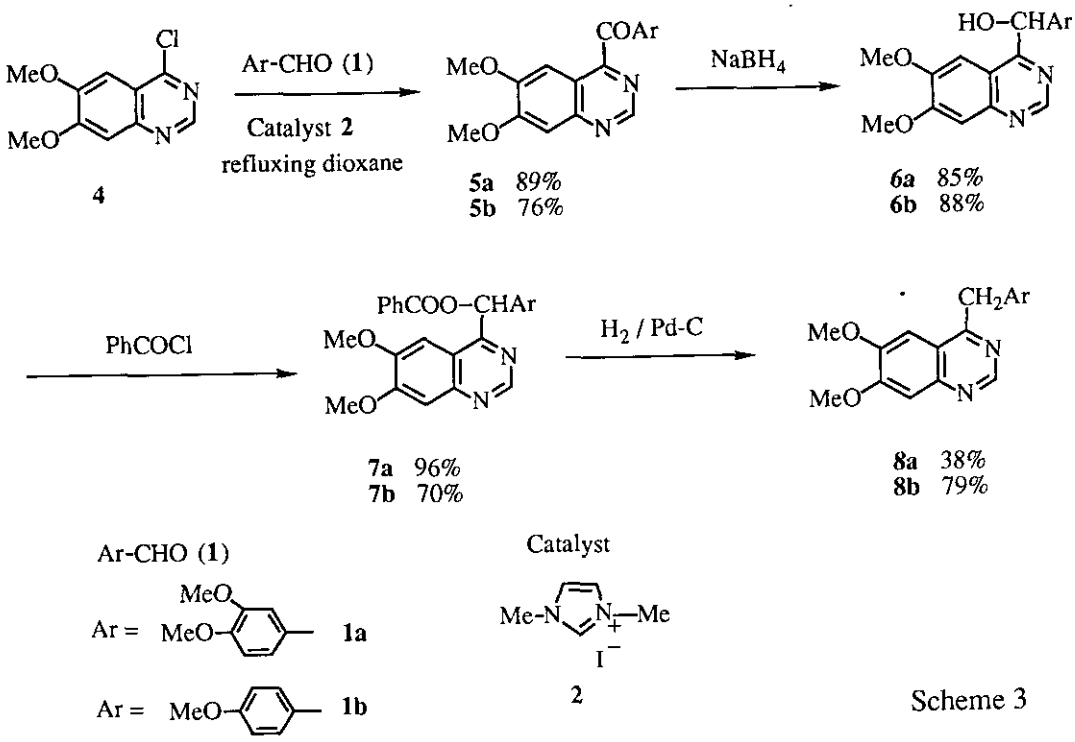
When 4-chloro-6,7-dimethoxyquinazoline[6] was treated with veratraldehyde (**1a**) in the presence of 1,3-dimethylimidazolium iodide (**2**) and sodium hydride in refluxing dioxane for 1 h, 4-(3,4-dimethoxybenzoyl)-6,7-dimethoxyquinazoline (**5a**) was obtained in 89% yield. Several attempts at the reduction of 4-(4-methoxybenzoyl)quinazoline (**3**), such as a Wolff-Kishner reduction[7] and reduction with trichlorosilane[8] were examined, but all were unsuccessful. Previously, we reported that 4-(α–benzoyloxybenzyl)quinazoline was easily reduced by hydrogen in the presence of palladium-carbon as a catalyst to give 4-benzylquinazoline in good yield.[9]



Scheme 2

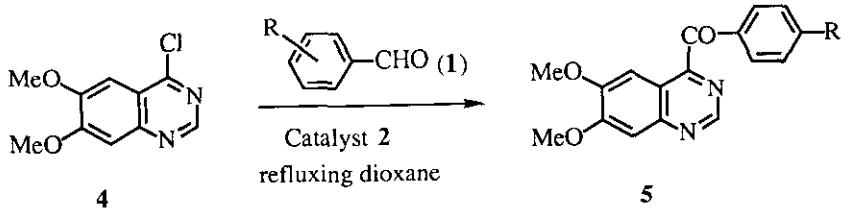
We utilized the reductive method to prepare 4-azapapaverine. Reduction of **5a** with sodium borohydride gave 4-(α-hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**6a**) in 85% yield. Benzoylation of **6a** treated with benzoyl chloride in pyridine gave 4-(α-benzoyloxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**7a**) in 96% yield. Finally, catalytic reduction of **7a** yielded 4-azapapaverine, 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**8a**), in 38% yield. We established the preparative method of 4-azapapaverine starting with 4-chloro-6,7-dimethoxyquinazoline (**4**) through four steps.

Under the same synthetic pathway, preparation of 4-(4-methoxybenzyl)-6,7-dimethoxyquinazoline (**8b**) which is analogous to 4-azapapaverine was achieved. The sequential reactions, catalytic aroylation, reduction with $NaBH_4$, benzoylation, and catalytic reduction, resulted in the formation of 4-(4-methoxybenzyl)-6,7-dimethoxyquinazoline in 37% overall yield. The synthetic route and the yields are shown in Scheme 3.



Scheme 3

In the synthetic program, catalytic aroylation is a key reaction. By aroylation of **4** with aromatic aldehydes (**1**) in the presence of **2**, the synthetic route to 4-aroyl-6,7-dimethoxyquinazolines (**5**) was established as shown in Scheme 4.



Aldehyde **1**		Reaction time (min.)	**5**	Yield (%)
1c	(R = *p*-Cl)	30	**5c**	92
1d	(R = H)	40	**5d**	91
1e	(R = *p*-Me)	30	**5e**	79
1f	(R = 3,4-OCH_2O-)	60	**5f**	88

Scheme 4

We established a preparative method for 4-azapapaverine (a papaverine analogue possessing a quinazoline ring system) and its derivative using catalytic aroylation as a key reaction. In addition, several 4-aroyl-6,7-dimethoxylquinazolines were prepared.

EXPERIMENTAL

All melting points were uncorrected. Ir spectra were recorded on a JASCO A-102 diffraction grating IR spectrophotometer. ^{1}H-Nmr spectra were measured at 60 MHz on a HITACHI High Resolution NMR R-1100 Spectrometer. Chemical shifts are quoted in ppm with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in hertz (Hz). Column chromatography was carried out on SiO_2.

4-(3,4-Dimethoxybenzoyl)-6,7-dimethoxyquinazoline (5a). Sodium hydride (60 % in oil, 132 mg, 3.3 mmol) was added to a stirred solution of 4-chloro-6,7-dimethoxyquinazoline (**4**, 674 mg, 3 mmol), veratraldehyde (**1a**, 548 mg, 3.3 mmol), and 1,3-dimethylimidazolium iodide (**2**, 224 mg, 1mmol) in dioxane (20 ml), and the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature, poured into ice-H_2O, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction gave 4-(3,4-dimethoxybenzoyl)-6,7-dimethoxyquinazoline (**5a**) in 89% (945 mg) yield.
5a: Yellow needles (MeOH), mp 215 - 217 °C. *Anal.* Calcd for $C_{19}H_{18}N_2O_5$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.52; H, 5.03; N, 7.86. Ir (KBr) cm^{-1}: 1650 (CO). ^{1}H-Nmr ($CDCl_3$): 9.10 (1H, s, C^2-H), 7.59 (1H, d, *J* = 2), 7.18 - 7.47 (m, 4H), 6.78 (1H, d, *J* = 8), 4.02 (3H, s, OMe), 3.91 (6H, s, OMe x 2).

4-(α-Hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (6a). Sodium borohydride (76 mg, 2 mmol) was added to a stirred solution of 4-(3,4-dimethoxybenzoyl)-6,7-dimethoxyquinazoline (**5a**, 354 mg, 1 mmol) in 30 ml of benzene and 15 ml of MeOH, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, and the residue was poured into ice-H_2O. The solution was acidified with AcOH and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with benzene to give 4-(α-hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**6a**) in 85% (303 mg) yield.
6a: Colorless prisms (MeOH), mp 172 - 174 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.29; H, 5.65; N, 7.73. ^{1}H-Nmr ($CDCl_3$): 9.26 (1H, s, C^2-H), 7.38 (1H, s), 7.12 (1H, s), 6.90 (3H, br s), 6.21 (1H, s, CH), 4.02 (3H, s, OMe), 3.86 (6H, s, OMe x 2), 3.80 (3H, s, MeO).

4-(α-Benzoyloxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (7a). Benzoyl chloride (169 mg, 1.2 mmol) was added to a stirred solution of 4-(α-hydroxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**6a**, 356mg, 1mmol) in 20 ml of pyridine, and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated, and the residue was poured into ice-H_2O. The solution was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and

concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-(α-benzoyloxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**7a**) in 96% (442 mg) yield.

7a: Colorless prisms (MeOH), mp 131 - 134 °C. *Anal.* Calcd for $C_{26}H_{24}N_2O_6$: C, 67.82; H, 5.25; N, 6.08. Found: C, 68.22; H, 5.14; N, 6.13. Ir (KBr) cm^{-1}: 1715 (CO). ^{1}H-Nmr ($CDCl_3$): 9.17 (1H, s, C^2-H), 8.14 - 8.41 (2H, m), 6.84 - 7.60 (9H, m), 4.03 (3H, s, OMe), 3.93 (3H, s, OMe), 3.86 (3H, s, OMe), 3.83 (3H, s, OMe).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyquinazoline (8a) (4-Azapapaverine). A solution of 4-(α-benzoyloxy-3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**7a**, 460 mg, 1 mmol) in a mixture of benzene (5 ml) and MeOH (5 ml) in the presence of 5 % palladium-carbon (100 mg) was stirred under a H_2 stream for 20 h. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyquinazoline (**8a**) in 38% (129 mg) yield.

8a: Pale yellow needles (petroleum benzin-benzene), mp 174 - 176 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 66.75; H, 5.88; N, 8.04. ^{1}H-Nmr ($CDCl_3$): 9.10 (1H, s, C^2-H), 7.30 (3H, br s), 6.81 (2H, s, C^5-H and C^8-H), 4.48 (2H, s, CH_2), 4.02 (3H, s, OMe), 3.93 (3H, s, OMe), 3.82 (3H, s, OMe), 3.79 (3H, s, OMe).

Reduction of 4-(4-Methoxybenzoyl)quinazoline (3) by Wolff-Kishner Reduction. A solution of 4-(4-methoxybenzoyl)quinazoline (**3**, 792 mg, 3 mmol), hydrazine hydrate (80 %, 0.5 ml), and potassium hydroxide (398 mg, 7.1 mmol) in 10 ml of ethylene glycol was heated at 140 °C for 5 h with stirring. The reaction mixture was cooled to room temperature, poured into ice-H_2O, and extracted with ether. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with benzene then $CHCl_3$. The fraction eluted with $CHCl_3$ recovered the ketone(**3**)in 23% (182 mg) yield.

Reduction of 4-(4-Methoxybenzoyl)quinazoline (3) with Trichlorosilane. A solution of 4-(4-methoxybenzoyl)quinazoline (**3**, 500mg, 1.9 mmol), tri(n-propyl)amine (360 μl, 1.89 mmol), and trichlorosilane (573 μl, 5.7 mmol) in 5 ml of acetonitrile was heated at 60 °C for 2 h. The reaction solution was concentrated, and the residue was examined by tlc on SiO_2 to give multiple spots. The purification was difficult.

4-(4-Methoxybenzoyl)-6,7-dimethoxyquinazoline (5b). Sodium hydride (60 % in oil, 132 mg, 3.3 mmol) was added to a stirred solution of 4-chloro-6,7-dimethoxyquinazoline (**4**, 674 mg, 3 mmol), 4-methoxybenzaldehyde (**1b**, 3.3 mmol), and 1,3-dimethylimidazolium iodide (**2**, 224 mg, 1mmol) in dioxane (20 ml), and the mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature, poured into ice-H_2O, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction gave 4-(4-

methoxybenzoyl)-6,7-dimethoxyquinazoline (**5b**) in 76% (739 mg) yield.

5b: Pale yellow needles (MeOH), mp 216 - 217 °C. *Anal.* Calcd for $C_{18}H_{16}N_2O_4$: C, 66.55; H, 4.97; N, 8.64. Found: C, 66.43; H, 4.84; N, 8.70. Ir (KBr) cm^{-1}: 1655 (CO). ^{1}H-Nmr ($CDCl_3$): 9.13 (1H, s, C^2-H), 7.92 (2H, d, J = 9), 7.30 (1H, d, C^5-H or C^8-H), 7.25 (1H, d, C^5-H or C^8-H), 6.88 (2H, d, J = 9),4.09 (3H, s, OMe), 3.96 (3H, s, OMe), 3.89 (3H, s, OMe).

4-(α-Hydroxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (6b). Sodium borohydride (76 mg, 2 mmol) was added to a stirred solution of 4-(4-methoxybenzoyl)-6,7-dimethoxyquinazoline (**5a**, 324 mg, 1 mmol) in 30 ml of benzene and 15 ml of MeOH, and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated, and the residue was poured into ice-H_2O. The solution was acidified with AcOH and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with benzene to give 4-(α-hydroxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (**6b**) in 88% (287 mg) yield.

6b: Yellowish needles (MeOH), mp 210 - 212 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.58. Found: C, 66.22; H, 5.35; N, 8.60. ^{1}H-Nmr ($CDCl_3$): 9.21 (1H, s, C^2-H), 6.79 - 7.50 (6H, m), 6.26 (1H, s, CH), 4.06 (3H, s, OMe), 3.90 (3H, s, OMe), 3.81 (3H, s, OMe), 3.00 (1H, br s, OH).

4-(α-Benzoyloxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (7b). Benzoyl chloride (169 mg, 1.2 mmol) was added to a solution of 4-(α-hydroxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (**6a**, 326 mg, 1mmol) in 20 ml of pyridine and the mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated, and the residue was poured into ice-H_2O. The mixture was extracted with $CHCl_3$. The extract was washed with H_2O, dried over Na_2SO_4, and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-(α-benzoyloxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (**7a**) in 70% (301 mg) yield.

7a: Colorless needles (MeOH), mp 156 - 158 °C. *Anal.* Calcd for $C_{25}H_{22}N_2O_5$: C, 69.75; H, 5.15; N, 6.51. Found: C, 69.73; H, 5.15; N,6.31. Ir (KBr) cm^{-1}: 1700 (CO). ^{1}H-Nmr ($CDCl_3$): 9.05 (1H, s, C^2-H), 8.00 - 8.23 (2H, m), 7.30 - 7.60 (7H, m), 7.23 (1H, s, C^5-H or C^8-H), 6.90 (1H, s, C^5-H or C^8-H), 6.73 (1H, s, CH), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.73 (3H, s, OMe).

4-(4-Methoxybenzyl)-6,7-dimethoxyquinazoline (8b). A solution of 4-(α-benzoyloxy-4-methoxybenzyl)-6,7-dimethoxyquinazoline (**7b**, 430 mg, 1 mmol) in a mixture of benzene (5 ml) and MeOH (5 ml) in the presence of 5 % palladium-carbon (100 mg) was stirred under a H_2 stream for 20 h. The catalyst was filtered off and the filtrate was concentrated. The residue was dissolved in $CHCl_3$. The solution was washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The fraction eluted with $CHCl_3$ gave 4-(4-methoxybenzyl)-6,7-dimethoxyquinazoline (**8b**) in 79% (245 mg) yield.

8b: Colorless prisms (MeOH), mp 134 - 135 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.88; H, 5.85; N,9.03. ^{1}H-Nmr ($CDCl_3$): 9.04 (1H, s, C^2-H), 6.69 - 7.29 (6H, m), 4.40 (2H, s, CH_2), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.69 (3H, s, OMe).

Preparation of 4- Aroyl-6,7-dimethoxyquinazolines, General Procedure. Sodium hydride (60% in oil, 132 mg, 3.3 mmol) was added to a stirred solution of 4-chloro-6,7-dimethoxyquinazoline (**4**, 674 mg, 3 mmol), arenecarbaldehyde (**1**, 3.3 mmol), and 1,3-dimethylimidazolium iodide (**2**, 224 mg, 1mmol) in dioxane (20 ml), and the mixture was refluxed with stirring (see Scheme 4). The reaction mixture was cooled to room temperature, poured into ice-H_2O, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated. The residue was passed through a column of SiO_2 with $CHCl_3$. The first fraction gave 4-aroyl-6,7-dimethoxyquinazoline (**5**).

4-(4-Chlorobenzoyl)-6,7-dimethoxyquinazoline (5c). Slightly yellow needles (MeOH). mp 221 - 222 °C. *Anal.* Calcd for $C_{17}H_{13}N_2O_3Cl$: C, 62.11; H, 3.99; N, 8.52. Found: C, 61.84; H, 3.80; N, 8.42. Ir (KBr) cm^{-1}: 1670 (CO). ^{1}H-Nmr ($CDCl_3$): 9.12 (1H, s, C^2-H), 7.90 (2H, d, J = 7), 7.40 (2H, d, J = 7), 7.35 (2H, s, C^5-*H and* C^8-H), 4.05 (3H, s, OMe), 3.95 (3H, s, OMe).

4-Benzoyl-6,7-dimethoxyquinazoline (5d). Yellowish needles (MeOH), mp 171 - 172 °C. *Anal.* Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.50; H, 4.60; N, 9.52. Ir (KBr) cm^{-1}: 1670 (CO). ^{1}H-Nmr ($CDCl_3$): 9.10 (1H, s, C^2-H), 7.74 - 8.00 (2H, m), 7.19 - 7.50 (5H, m), 4.01 (3H, s, OMe), 3.89 (3H, s, OMe).

4-(4-Methylbenzoyl)-6,7-dimethoxyquinazoline (5e). Yellowish needles (MeOH), mp 200 - 201 °C. *Anal.* Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.20; H, 5.10; N, 9.05. Ir (KBr) cm^{-1}: 1665 (CO). ^{1}H-Nmr ($CDCl_3$): 9.12 (1H, s, C^2-H), 7.80 (2H, d, J = 8), 7.20 (2H, d, J = 8), 7.30 (2H, s, C^5-H and C^8-H), 4.05 (3H, s, OMe), 3.92 (3H, s, OMe).

4-(3,4-Methylenedioxybenzoyl)-6,7-dimethoxyquinazoline (5f). Pale yellow powder (MeOH), mp 254 - 255 °C *Anal.* Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.61; H, 3.91; N, 8.16. Ir (KBr) cm^{-1}: 1655 (CO). ^{1}H-Nmr ($CDCl_3$): 9.11 (1H, s, C^2-H), 6.70 - 7.45 (5H, m, aromatic H), 6.00 (2H, s, CH_2), 4.03 (3H, s, OMe), 3.89 (3H, s, OMe).

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