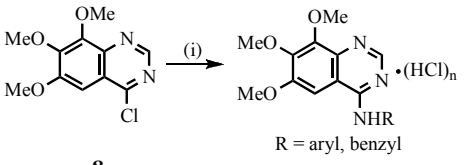
Microwave Assisted Synthesis of Novel 6,7,8-Trimethoxy *N*-Substituted-4-aminoquinazoline Compounds

Gang Liu,* Lin Sun, Chunping Liu, Chunnuan Ji, Quanwu Wen and Songmei Ma

School of Chemistry and Materials Science, Ludong University, Yantai 264025, P. R. of China

Received June 25, 2007



8 **9**

(i) aryl amines or benzyl amines, i-propanol, MW

A fast, efficient and convenient reaction of 6,7,8-trimethoxy-4-chloroquinazoline and aryl (or benzyl) amines was achieved under microwave irradiation in isopropyl alcohol, providing a simple method for synthesis of novel 6,7,8-trimethoxy *N*-substituted-4-aminoquinazoline compounds in good yield in short time. The title compounds were evaluated for their *in vitro* anti-proliferative activities against PC3 cell by MTT method.

J. Heterocyclic Chem., **45**, 759 (2008).

INTRODUCTION

In recent years, quinazoline compounds have been shown to possess biological activity in medicine and pesticide. As part our ongoing research program on heterocyclic compounds which may serve as leads for designing novel antitumor agents regarding PD153035 [4-(3-bromophenyl)amine-6,7-dimethoxyquinazoline] as the leading compound, we were particularly interested in 4-substituted quinazolines [1-3]. We considered the well known activity of the quinazoline nucleus in chemotherapy, where many of its substituted derivatives are effective antitumor agents [4-7]. Furthermore, more recent reported data has shown that a broad class of quinazolines also act as potent and highly selective inhibitors of epidermal growth factor receptor (EGFR) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) [8-10]; members of this class are expected to have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases [11,12]. In view of these facts, and in order to study the influence of 4-position and 8-position substituents on antitumor activity, we have now prepared a series of novel 6,7,8-trimethoxy-4-aryl(benzyl)aminoquinazolines starting from gallic acid of natural materials, in the hope of discovering more active ATP site inhibitors.

Microwave-assisted organic synthesis is a new and rapidly expanding area of synthetic organic chemistry [13-16]. This technique is based on the empirical observation that some organic reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. In the classical synthesis of these compounds [17,18], a mixture of 4-chloroquinazoline and amines are refluxed at 80°C for 4-12 hours in isopropyl alcohol. This method, however, involves long reaction times and complex handling and gives low yields of products. In this paper, we wish to report a rapid and convenient reaction using 6,7,8-trimethoxy-4-chloroquinazoline and aryl (or benzyl) amines for the synthesis of novel 6,7,8-trimethoxy *N*-substituted-4-aminoquinazoline compounds under microwave irradiation in short time in isopropyl alcohol (Scheme 1). The new method requires short reaction times, is very easy and mild and environmentally friendly. To the best of our knowledge, this is the first report of the rapid synthesis of novel 6,7,8-trimethoxy *N*-substituted-4-aminoquinazoline compounds under microwave irradiation.

RESULTS AND DISCUSSION

The reaction results with or without microwave irradiation are shown in Table 1. It can be seen that the presence of microwave irradiation both accelerated the reactions and gave higher yields. The reaction time for synthesis of compounds **9a**-**q** was shortened from 360 minutes to only 10 minutes with the one-step microwave-assisted procedure.

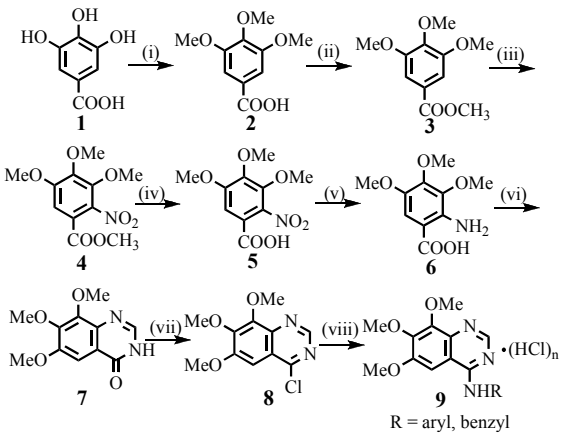
In order to optimize the reaction parameters, we selected compound **9b** for further study under different conditions. These results are shown in Table 2. Without microwave irradiation (Table 1) compound **9b** could be obtained in 47% after 360 minutes. When the reaction was carried out under microwave irradiation at 80°C for 5 minutes, the yield of **9b** was increased to 87%, and increased further to 97% when the reaction time was

extended to 10 minutes (Table 2, entries 1 and 2). However, no further improvement of the yield was noted when the reaction time was prolonged to 15 minutes (Table 2, entry 3). Consequently, we chose 10 minutes. as the optimum reaction time (Table 2, entry 2). As for the effect of the microwave power, it could be seen that when it was increased from 40 to 60, 80 and 100 W, the yields of **9b** were 76%, 97%, 99%, and 97%, respectively (Table 2, entries 2 and 4-6). Hence, it's better for the reaction to be carried out at 60 W or higher power settings than at 40 W. No improvement was observed under irradiation when the microwave power varied from 80 W to 100 W (Table 2, entries 5 and 6) and the yield even decreased a little, a fact we attribute to the formation of byproducts. When the reaction temperature was increased from 30°C to 50°C, 70°C or 80°C, **9b** was obtained in 46%, 84%, 91% and 99% yields respectively (Table 2, entry 2 and entries 7-9).

The antitumor activities *in vitro* of these compounds were evaluated against PC3 cell by MTT method. The results for title compounds **9a**-**q** and **8** are summarized in Table 3. Unfortunately, most of the test compounds exhibited less anticancer activity than the reference standard drug PD153035. It can be found from Table 3 that compounds **9b** (R=2-methoxydibenzofuran-3-yl), **9i** (R=3,4,5-trimethoxyphenyl), **9k** (R=3-nitrophenyl), **9p** (R=(*R*)-α-methylbenzylphenyl), and **8** (4-chloro-6,7,8-trimethoxyquinazoline) showed weak inhibitory activity against PC3 cell. When 4-position in quinazoline ring was substituted by different aryl moiety or benzyl moiety, the compounds generally have potential anticancer bioactivity, such as **9b**, **9i**, **9k** and **9p** with the inhibition of 50.0, 35.0, 37.2 and 35.5% in the concentration of 10 μM against PC3 cell.

Scheme 1

Reaction Route for Synthesis of 6,7,8-Trimethoxy *N*-Substituted-4-aminoquinazoline Compounds **9a-q**



Reagents and conditions: (i) $(CH_3O)_2SO_2$ / NaOH, N_2, reflux 3 hours, then con. HCl pH=7; (ii) CH_3OH / H_2SO_4, reflux 5 hours; (iii) fuming HNO_3 / CH_3COOH, 30-40°C, 2 hours; (iv) 0.8 *M* NaOH / EtOH, 45-50°C, 2 hours, then con. HCl pH=2-3; (v) $SnCl_2$ / HCl, 80°C, 20 minutes, then the solid added 10% K_2CO_3 pH=9-10, then the filter solution added CH_3COOH pH=2-3; (vi) $HCONH_2$, 130-140°C, 6 hours; (vii) $POCl_3$ / $PhN(CH_3)_2$, reflux 3 hours; (viii) aryl or benzyl amines, i-propanol, MW, 80 W, 80°C, 10 minutes.

In summary, this work presents a new method of the formation of novel 6,7,8-trimethoxy-4-aryl (benzyl)-aminoquinazolines **9a**-**q** under microwave irradiation and offers several advantages: faster reaction rates and excellent yields, while the classical method of formation of 6,7,8-trimethoxy-4-aryl(benzyl)aminoquinazolines involves long reaction times (6 hours). All compounds

Table 1

Yields and Reaction Conditions Used for the Microwave Assisted Synthesis of **9a-q**

Entry	Compound	R	n	Microwave Method [a]		Classical Method [b]	
				Irradiation Time (minutes)	Yield [c] (%)	Irradiation Time (minutes)	Yield [c] (%)
1	**9a**	4-bromophenyl	2	10	94	360	52
2	**9b**	2-methoxydibenzofuran-3-yl	2	10	99	360	47
3	**9c**	3-chlorophenyl	1	10	93	360	61
4	**9d**	3-bromophenyl	1	10	95	360	66
5	**9e**	3-fluorophenyl	1	10	85	360	60
6	**9f**	4-fluorophenyl	0	10	87	360	55
7	**9g**	2-fluorophenyl	0	10	89	360	64
8	**9h**	2-chloro-4-bromophenyl	1	10	91	360	66
9	**9i**	3,4,5-trimethoxyphenyl	1	10	90	360	64
10	**9j**	4-nitrophenyl	1	10	87	360	54
11	**9k**	3-nitrophenyl	1	10	84	360	35
12	**9l**	2-nitrophenyl	1	10	83	360	33
13	**9m**	4-chlorophenyl	2	10	92	360	42
14	**9n**	4-hydroxyphenyl	2	10	98	360	58
15	**9o**	benzyl	0	10	86	360	64
16	**9p**	(*R*)-α-methylbenzyl	0	10	81	360	49
17	**9q**	(*S*)-α-methylbenzyl	0	10	84	360	61

[a] Reaction conditions: **8** (3.0 mmoles), aryl (or benzyl) amines (3.0 mmoles), i-propanol (30 mL), MW 80 W (80°C), 10 minutes.
[b] Reaction conditions: **8** (3.0 mmoles), aryl (or benzyl) amines (3.0 mmoles), i-propanol (30 mL), heated with oil-bath at reflux

Table 2

Different Conditions Used for the Microwave Assisted Synthesis of **9b**

Entry	Irradiation time (minutes)	Power (Watt)	Reaction temperature (°C)	Yield [a] (%)
1	5	60	80	87
2	10	60	80	97
3	15	60	80	97
4	10	40	80	76
5	10	80	80	99
6	10	100	80	97
7	10	80	30	46
8	10	80	50	84
9	10	80	70	92

[a] Yields of isolated products. Each reaction was repeated three times and the result was averaged.

Table 3

Inhibition Activity of **9a**-**q** and **8** in the Concentration of 10 μ*M* Against PC3 Cancer Cell

Compound	Inhibition [a] (%)	Compound	Inhibition [a] (%)
9a	19.5± 1.8*	**9k**	37.2± 1.4*
9b	50.0± 4.3*	**9l**	22.8± 3.0*
9c	26.7± 3.2**	**9m**	19.4± 5.5*
9d	22.2± 3.4**	**9n**	25.0± 6.1**
9e	16.3± 2.4*	**9o**	9.3± 3.1*
9f	16.6± 1.9*	**9p**	35.5± 4.1*
9g	18.1± 5.3**	**9q**	-7.44± 4.2*
9h	11.5± 4.8**	**8**	71.3 ± 4.7**
9i	35.0± 3.3*	**PD153035** [b]	87.5± 1.8**
9j	34.5± 5.8**		

[a] Each value represents the mean ± SEM (n = 9). [b] the standard compound was made of comparison for activity. Significance levels *p < 0.1, **p < 0.05 as compared with the respective control.

9a-**q** were fully characterized by spectroscopic methods. The title compounds **9a**-**q** showed weak inhibitory activity against PC3 cell.

EXPERIMENTAL

Melting points were determined on a XT-4 binocular microscope mp apparatus and were not corrected. IR spectra were recorded on a Bruker VECTOR22 spectrometer in potassium bromide disks. The ^{1}H nmr and ^{13}C nmr spectra (solvent DMSO-d_6) were measured on a Varian-Inova 500 MHz spectrometer at room temperature. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. D_2O exchange was used to confirm the assignment of the signals of NH protons. Elemental analysis was performed by an Elementar Vario-III CHN analyzer. Specific rotation was determined on a WZZ-2A automatic polarimeter. Microwave reactions were performed on a variable power Focused Microwave Synthesis, Discover™ LabMate equipped with a high sensitivity IR sensor for temperature control and measurement. Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purification. 3,4,5-trimethoxybenzoic acid (**2**) and methyl 3,4,5-trimethoxybenzoate (**3**) were prepared according to literature procedures [19-21]. Aryl amines and benzyl amines are commercially available.

Methyl 2-nitro-3,4,5-trimethoxybenzoate (4). A solution of methyl 3,4,5-trimethoxybenzoate (2.0 g, 8.8 mmoles) in acetyl hydrate (10 mL) at room temperature was carefully added fuming nitric acid (2.5 mL) during 30 minutes with stirring. After addition of acid, the solution was allowed to stir for 2 hours. The reaction mixture was then poured into ice water (60 mL). The solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol-water (2:1, V/V) to give **4** as pale yellow needles crystal; yield 25%; mp 62-63°C. ir (potassium bromide): 3013, 2963, 2847, 1719, 1580, 1497, 1545, 1344, 1233, 1113, 866 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 7.34 (s, 1H, PhH), 3.94-3.89 (3s, 9H, 3OCH$_3$), 3.83 (s, 3H, COOCH$_3$). ^{13}C nmr (DMSO-d_6): δ 163.3, 154.7, 146.2, 145.5, 139.6, 117.7, 109.2, 63.1, 61.6, 57.1, 53.7. *Anal.* Calcd for $C_{11}H_{13}NO_7$ (271.2): C, 48.71; H, 4.83; N, 5.16. Found: C, 48.57; H, 5.02; N, 4.91.

2-Nitro-3,4,5-trimethoxybenzoic acid (5). A solution of methyl 2-nitro-3,4,5-trimethoxybenzoate (14.0 g, 50 mmoles) in 0.8 *M* sodium hydroxide (120 mL, 100 mmoles) and 95% ethanol (60 mL) at 45-50°C in water bath for 2 hours with stirring. Then, the reaction mixture was cooled by ice-water and concentrated hydrochloric acid was added dropwise with stirring while maintaining the temperature at 20°C for the mixture pH 2-3. The solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol to give **5** as pale yellow needles crystal; yield 92%; mp 160-161°C. ir (potassium bromide): 3107, 2538, 2953, 2851, 1695, 1578, 1497, 1547, 1341, 1246, 1117, 725 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 7.32 (s, 1H, PhH), 3.93-3.88 (3s, 9H, 3OCH$_3$). ^{13}C nmr (DMSO-d_6): δ 164.1, 154.5, 145.8, 145.3, 139.8, 118.8, 109.3, 63.1, 61.5, 57.0. *Anal.* Calcd for $C_{10}H_{11}NO_7$ (257.2): C, 46.70; H, 4.31; N, 5.45. Found: C, 46.77; H, 4.14; N, 5.32.

2-Amino-3,4,5-trimethoxybenzoic acid (6). A mixture of powder stannum (5.3 g, 45 mmoles) and concentrated hydrochloric acid (18 mL) was stirred for 4-5 hours at room temperature, then added 2-nitro-3,4,5-trimethoxy-benzoic acid (2.6 g, 10 mmoles) to the solution. The reaction mixture was carefully heated to 80°C, while maintaining the temperature for 20 minutes. Then, concentrated hydrochloric acid (5 mL) was added into the reaction mixture, while maintaining the temperature for 10 minutes. The reaction mixture was cooled by ice-bath and stirred for 10 minutes. The precipitated complex stannic double salt was collected by filtration, washed with few concentrated hydrochloric acid. The white solid obtained was stirred with portions of 10% potassium carbonate solution until it dissolved with pH 9-10 and the mixture was alkaline, whereupon a grayish precipitate appeared and was removed by filter, washed with 10% potassium carbonate solution. The solution was neutralized with acetyl hydrate to pH 2-3 while maintaining the temperature blow 20°C. The white solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol-water (1:1, V:V) to give **6** as white needles crystal; yield 62%; mp 126-128°C. ir (potassium bromide): 3487, 3379, 3008, 1670, 1576, 1458, 1273, 1149, 744 cm^{-1}. ^{1}H nmr (DMSO-d_6): δ 7.07 (s, 1H, PhH), 3.82-3.70 (3s, 9H, 3OCH$_3$), 3.45 (s, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 169.4, 147.6, 142.9, 141.6, 140.4, 1109.3, 104.5, 60.9, 60.6, 56.6. *Anal.* Calcd for $C_{10}H_{13}NO_5$ (227.2): C, 52.86; H, 5.77; N, 6.16. Found: C, 52.74; H, 5.63; N, 6.02.

6,7,8-Trimethoxyquinazlin-4-one (7). A solution of 2-amino-3,4,5-trimethoxybenzoic acid (1.1 g, 5 mmoles) and excess of formamide (2 mL) was stirred for 5 hours at 130-140°C. After the reaction was over, the suitable water was added dropwise to the reaction mixture to resolve the excess of formamide at 100°C. The gray solid obtained was collected by filtration, washed with water, dried and recrystallized from ethanol to give **7** as pale brown crystal; yield 25%; mp 220-222°C. ir (potassium bromide): 3304, 3163, 3009, 1665, 1613, 1474, 1287, 1126, 798 cm^{-1}. ^1H nmr (DMSO-d_6): δ 12.21 (s, 1H, NH), 8.01 (s, 1H, quinazolone H-2), 7.35 (s, 1H, quinazolone H-5), 3.95-3.88 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 160.6, 152.7, 148.3, 147.7, 143.3, 139.0, 119.2, 101.7, 62.4, 61.4, 56.4. *Anal.* Calcd for $C_{11}H_{12}N_2O_4$ (236.2): C, 55.93; H, 5.12; N, 11.86. Found: C, 56.18; H, 5.18; N, 12.04.

4-Chloro-6,7,8-trimethoxyquinazoline (8). A solution of 6,7,8-trimethoxyquinazolin-4-one (0.6 g, 2.5 mmoles) and four drops *N,N*-dimethylaniline in phosphorus oxychloride (25 mL) was heated at reflux for 3 hours. The phosphorus oxychloride was removed by distillation at reduced pressure and the residue was diluted with 20 mL chloroform and treated with 30 g ice-water. To the mixture was added saturated potassium carbonate with stirring until the mixture was pH 4-5. The organic layer was separated and the residue was extracted twice with 40 mL chloroform. The combined organic phases were dried (anhydrous magnesium sulfate), filtered, evaporated under reduced pressure, and recrystallized from petroleum ether (bp 60-90°C) to give **8** as pale gray solid; yield 63%; mp 101-103°C. ir (potassium bromide): 3099, 2945, 2845, 1603, 1468, 1246, 1136, 787 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.93 (s, 1H, quinazoline H-2), 7.29 (s, 1H, quinazoline H-5), 4.06-4.01 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.9, 154.3, 150.9, 148.1, 146.3, 142.7, 120.1, 98.6, 62.2, 61.1, 56.3. *Anal.* Calcd for $C_{11}H_{11}ClN_2O_3$ (254.7): C, 51.88; H, 4.35; N, 11.00. Found: C, 52.02; H, 4.21; N, 10.94.

4-(4-Bromophenyl)amine-6,7,8-trimethoxyquinazoline dihydrochloride (9a). A solution of **8** (0.71 g, 3.0 mmoles) and 4-bromoamine (0.52 g, 3.0 mmoles) in isopropyl alcohol (30 mL) was stirred for three minutes then the mixture was irradiated in the microwave oven at 80 W for 10 minutes. Upon completion of the reaction, as monitored by TLC, the solvent was removed under reduced pressure and the residue was washed with water, collected by filtration and purified by silicagel column chromatography (petroleum ether-ethyl acetate, 5:1 v:v) to give **9a** as pale yellow solid; yield 94%; mp170-173°C. ir (potassium bromide): 3011, 2947, 2847, 1628, 1489, 1288, 1128, 804 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.53 (s, 1H, NH), 8.76 (s, 1H, quinazoline H-2), 8.14 (s, 1H, quinazoline H-5), 7.71 (s, 4H, Ph-H), 4.05-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.9, 154.5, 149.6, 148.2, 142.1, 136.5, 132.2, 127.3, 109.9, 100.6, 62.7, 61.9, 57.8. *Anal.* Calcd for $C_{17}H_{16}BrN_3O_3\cdot 2HCl$ (463.1): C, 44.09; H, 3.92; N, 9.07. Found: C, 43.82; H, 4.18; N, 9.04.

4-(2-Methoxydibenzofuran-3-yl)amine-6,7,8-trimethoxyquinazoline dihydrochloride (9b). This compound was obtained as yellow solid; mp160-162°C. ir (potassium bromide): 3011, 2949, 2851, 1626, 1474, 1286, 1125, 764 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.45 (s, 1H, NH), 8.68 (s, 1H, quinazoline H-2), 8.22 (d, 1H, dibenzofurane H-5, J = 7.45 Hz), 8.09 (s, 1H, quinazoline H-5), 8.03 (s, 1H, dibenzofurane H-1), 7.88 (s, 1H, dibenzofura-ne H-4), 7.72 (d, 1H, dibenzofurane H-8, J = 7.45 Hz), 7.58-7.55 (m, 1H, dibenzofurane H-7), 7.47-7.45 (m, 1H, dibenzofurane H-6), 4.04-3.93 (3s, 12H, $4OCH_3$). ^{13}C nmr DMSO-d_6): δ 156.3, 154.0, 150.9, 148.9, 147.7, 145.3, 141.4, 127.7, 123.5, 123.3, 123.1, 121.3, 111.7, 111.4, 108.6, 103.6, 99.8, 62.0, 61.3, 56.9, 56.3. *Anal.* Calcd for $C_{25}H_{25}N_3O_5\cdot 2HCl$ (520.4): C, 57.70; H, 5.23; N, 8.07. Found: C, 57.60; H, 5.03; N, 8.16.

4-(3-Chlorophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9c). This compound was obtained as pale yellow solid; mp 172°C (dec.). ir (potassium bromide): 3013, 2947, 2847, 1628, 1487, 1288, 1126, 785 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.43 (s, 1H, NH), 8.81 (s, 1H, quinazoline H-2), 8.10 (s, 1H, quinazoline H-5), 7.90 (s, 1H, Ph-H-2), 7.71 (d, 1H, Ph-H-4, J = 9.15 Hz), 7.56-7.53 (m, 1H, Ph-H-5), 7.41 (d, 1H, Ph-H-6, J = 9.15 Hz), 4.05-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.4, 153.9, 149.2, 147.6, 138.1, 132.8, 130.4, 126.2, 124.2, 123.0, 109.3, 99.8, 62.0, 61.2, 57.1. *Anal.* Calcd for $C_{17}H_{16}ClN_3O_3\cdot HCl$ (382.2): C, 53.42; H, 4.48; N, 10.99. Found: C, 53.50; H, 4.57; N, 10.74.

4-(3-Bromophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9d). This compound was obtained as pale yellow solid; mp 180°C (dec.). ir (potassium bromide) ν: 3011, 2945, 2849, 1626, 1487, 1286, 1126, 787 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.62 (s, 1H, NH), 8.81 (s, 1H, quinazoline H-2), 8.20 (s, 1H, quinazoline H-5), 8.03 (s, 1H, Ph H-2), 7.77 (d, 1H, Ph-H-4, J = 8.0 Hz), 7.54 (d, 1H, Ph-H-6, J = 8.0 Hz), 7.49-7.46 (t, 1H, Ph-H-5, J = 4.0 Hz), 4.03-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.5, 154.0, 149.1, 147.7, 141.5, 138.8, 130.7, 129.1, 127.1, 123.6, 121.2, 109.3, 100.2, 62.1, 61.3, 57.2. *Anal.* Calcd for $C_{17}H_{16}BrN_3O_3\cdot HCl$ (426.7): C, 47.85; H, 4.02; N, 9.85. Found: C, 47.69; H, 4.25; N, 10.02.

4-(3-Fluorophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9e). This compound was obtained as pale yellow solid; mp 232-234°C. ir (potassium bromide): 3419, 3013, 2951, 2853, 1628, 1489, 1288, 1134 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.63 (s, 1H, NH), 8.81 (s, 1H, quinazoline H-2), 8.21 (s, 1H, quinazoline H-5), 7.73 (d, 1H, Ph-H-4, J = 10.9 Hz), 7.73 (d, 1H, Ph-H-6, J = 8.0 Hz), 7.57-7.54 (m, 1H, Ph-H-5), 7.20 (t, 1H, Ph-H-2, J = 4.0 Hz), 4.07-4.03 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 161.4, 159.0, 154.6, 149.7, 148.3, 131.0, 130.9, 121.1, 112.5, 112.3, 109.9, 100.7, 62.7, 61.9, 57.8. *Anal.* Calcd for $C_{17}H_{16}FN_3O_3\cdot HCl$ (365.8): C, 55.82; H, 4.68; N, 11.49. Found: C, 55.69; H, 4.72; N, 11.35.

4-(4-Fluorophenyl)amine-6,7,8-trimethoxyquinazoline (9f). This compound was obtained as pale yellow solid; mp 184-186°C. ir (potassium bromide): 3356, 3017, 2947, 2857, 1626, 1487, 1283, 1126, 789 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.61 (s, 1H, NH), 8.73 (s, 1H, quinazoline H-2), 8.17 (s, 1H, quinazoline H-5), 7.74-7.71 (m, 2H, Ph-H-3,5), 7.38-7.34 (m, 2H, Ph-H-2,6), 4.05-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 161.7, 159.8, 159.1, 154.5, 149.7, 148.1, 142.1, 133.3, 127.7, 127.6, 116.2, 116.1, 109.7, 100.7, 62.7, 61.8, 57.8. *Anal.* Calcd for $C_{17}H_{16}FN_3O_3$ (329.3): C, 62.00; H, 4.90; N, 12.76. Found: C, 61.85; H, 4.88; N, 12.63.

4-(2-Fluorophenyl)amine-6,7,8-trimethoxyquinazoline (9g). This compound was obtained as pale yellow solid; mp 194°C (dec.). ir (potassium bromide): 3364, 2945, 2855, 1630, 1487, 1258, 1126, 1011, 760 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.82 (s, 1H, NH), 8.72 (s, 1H, quinazoline H-2), 8.23 (s, 1H, quinazoline H-5), 7.56-7.36 (m, 4H, Ph-H-3,4,5,6), 4.06-4.03 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 159.3, 157.8, 155.9, 153.9, 149.2, 147.7, 141.7, 129.3, 128.6, 116.3, 116.2, 108.9, 100.2, 62.0, 61.2, 57.1. *Anal.* calcd for $C_{17}H_{17}ClFN_3O_3$ (329.3): C, 55.82; H, 4.68; N, 11.49. Found: C, 55.66; H, 4.86; N, 11.31.

4-(2-Chloro-4-bromophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9h). This compound was obtained as white solid; mp 178°C (dec.). ir (potassium bromide): 3366, 3015, 2945, 2849, 1626, 1487, 1286, 1126 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.71 (s, 1H, quinazoline H-2), 8.04 (s, 1H, quinazoline H-5), 8.00 (d, 1H, Ph-H-3, J = 2.3 Hz), 7.74 (d, 1H, Ph-H-5, J = 8.6 Hz), 7.54 (d, 1H, Ph-H-6, J = 8.6 Hz), 4.03-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 164.8, 159.8, 154.7, 154.4, 153.3, 147.2, 138.8, 137.7, 137.5, 136.6, 126.4, 114.1, 105.1, 104.9, 67.4, 66.7, 62.3. *Anal.* Calcd for $C_{17}H_{15}BrClN_3O_3$·HCl (461.1): C, 44.28; H, 3.50; N, 9.11. Found: C, 43.96; H, 3.76; N, 9.01.

4-(3,4,5-Trimethoxyphenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9i). This compound was obtained as yellow solid; mp 195°C (dec.). ir (potassium bromide): 3419, 2947, 2839, 1634, 1456, 1285, 1130 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.52 (s, 1H, NH), 8.75 (s, 1H, quinazoline H-2), 8.17 (s, 1H, quinazoline H-5), 7.09 (s, 2H, Ph-H-1,6), 4.06-4.02 (3s, 9H, $3OCH_3$), 3.81 (s, 6H, Ph-3,5-$2CH_3$), 3.71 (s, 3H, Ph-4-CH_3). ^{13}C nmr (DMSO-d_6): δ 159.0, 154.5, 153.3, 149.6, 148.1, 136.6, 132.8, 109.7, 103.5, 100.8, 62.7, 61.2, 60.7, 57.8, 56.6. *Anal.* Calcd for $C_{20}H_{23}N_3O_6$·HCl (437.9): C, 54.86; H, 5.52; N, 9.60. Found: C, 54.67; H, 5.61; N, 9.55.

4-(4-Nitrophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9j). This compound was obtained as pale yellow solid; mp 212°C (dec.). ir (potassium bromide): 3366, 3011, 2951, 2839, 1628, 1514, 1487, 1340, 1285, 1130 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.21 (s, 1H, NH), 8.82 (s, 1H, quinazoline H-2), 8.36 (d, 2H, Ph-3,5-H, J = 8.6 Hz), 8.15 (d, 2H, Ph-2,6-H, J = 8.6 Hz), 8.06 (s, 1H, quinazoline H-5), 4.06-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 157.8, 153.6, 149.7, 147.4, 143.9, 124.4, 123.2, 110.5, 99.3, 62.0, 61.2, 56.9. *Anal.* Calcd for $C_{17}H_{16}N_4O_5$·HCl (392.8): C, 51.98; H, 4.36; N, 14.26. Found: C, 51.73; H, 4.52; N, 14.12.

4-(3-Nitrophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9k). This compound was obtained as pale yellow solid; mp 204-206°C. ir (potassium bromide): 3419, 3015, 2947, 2843, 1632, 1469, 1485, 1346, 1284, 1121 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.84 (s, 1H, NH), 8.86 (s, 1H, quinazoline H-2), 8.72 (s, 1H, Ph-2-H), 8.29 (d, 1H, Ph-4-H, J = 9.15 Hz), 8.26 (s, 1H, quinazoline H-5), 8.18 (d, 1H, Ph-6-H, J = 9.7 Hz), 7.82-7.79 (m, 1H, Ph-5-H), 4.08-4.03 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 159.1, 154.6, 149.8, 148.3, 142.3, 138.6, 131.2, 130.7, 121.3, 119.5, 110.1, 100.8, 62.7, 61.9, 57.9. *Anal.* Calcd for $C_{17}H_{16}N_4O_5$ ·HCl (392.8): C, 51.98; H, 4.36; N, 14.26. Found: C, 51.71; H, 4.55: N, 14.32.

4-(2-Nitrophenyl)amine-6,7,8-trimethoxyquinazoline hydrochloride (9l). This compound was obtained as white solid; mp 210°C (dec.). ir (potassium bromide): 3019, 2945, 2845, 1624, 1458, 1489, 1356, 1286, 1130, 793 cm^{-1}. ^1H nmr (DMSO-d_6): δ 12.01 (s, 1H, NH), 8.66 (s, 1H, quinazoline H-2), 8.18 (s, 1H, quinazoline H-5), 8.17 (d, 1H, Ph-3-H, J = 7.45 Hz), 7.90 (t, 1H, Ph-4-H, J = 9.15 Hz), 7.77 (d, 1H, Ph-6-H, J = 7.45 Hz), 7.65 (t, 1H, Ph-5-H, J = 7.75 Hz), 4.06-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.7, 153.9, 149.3, 147.8, 146.3, 144.8, 134.3, 128.9, 128.1, 125.2, 109.3, 99.9, 62.0, 61.2, 57.1. *Anal.* Calcd for $C_{17}H_{16}N_4O_5$·HCl (392.8): C, 51.98; H, 4.36; N, 14.26. Found: C, 52.18; H, 4.57; N, 14.29.

4-(4-Chlorophenyl)amine-6,7,8-trimethoxyquinazoline dihydrochloride (9m). This compound was obtained as pale yellow solid; mp 175°C (dec.). ir (potassium bromide): 3420, 3011, 2947, 2853, 1628, 1472, 1286, 1130, 806 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.57 (s, 1H, NH), 8.75 (s, 1H, quinazoline H-2), 8.23 (s, 1H, quinazoline H-5), 7.77 (d, 2H, Ph-3,5-H, J = 8.6 Hz), 7.57 (d, 2H, Ph-2,6-H, J = 8.6 Hz), 4.06-4.02 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.4, 153.7, 149.3, 147.5, 135.8, 128.6, 126.4, 109.9, 100.2, 62.0, 61.2, 57.2. *Anal.* Calcd for $C_{17}H_{16}ClN_3O_3$ ·2HCl (418.7): C, 48.77; H, 4.33; N, 10.04. Found: C, 48.53; H, 4.63; N 9.97.

4-(4-Hydroxyphenyl)amine-6,7,8-triethoxyquinazoline dihydrochloride (9n). This compound was obtained as pale yellow solid; mp 153°C (dec.). ir (potassium bromide): 3420, 3227, 3030, 2949, 2855, 1626, 1474, 1273, 1128 cm^{-1}. ^1H nmr (DMSO-d_6): δ 11.42 (s, 1H, NH), 9.75 (s, 1H, OH), 8.66 (s, 1H, quinazoline H-2), 8.15 (s, 1H, quinazoline H-5), 7.43 (d, 2H, Ph-3,5-H, J = 8.6 Hz), 6.87 (d, 2H, Ph-2,6-H, J = 8.6 Hz), 4.03-4.00 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 158.3, 156.1, 153.7, 149.1, 147.3,141.6, 127.6, 126.3, 115.2, 109.1, 100.2, 61.9, 61.2, 57.1. *Anal.* Calcd for $C_{17}H_{17}N_3O_4$·2HCl (400.3): C, 51.01; H, 4.78; N, 10.50. Found: C, 51.24; H, 5.04; N, 10.52.

4-Benzylamine-6,7,8-trimethoxyquinazoline (9o). This compound was obtained as white solid; mp 173-175°C. ir (potassium bromide): 3235, 3001, 2938, 2832, 1614, 1454, 1283, 1128, 800 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.60 (t, *J*=5.7 Hz, 1H, NH), 8.36 (s, 1H, quinazoline H-2), 7.54 (s, 1H, quinazoline H-5), 7.37-7.31 (m, 4H, Ph-H-2,3,5,6), 7.23 (t, 1H, Ph-4-H, J = 7.45 Hz), 4.79 (d, 2H, CH_2, J = 5.7 Hz), 3.97-3.87 (3s, 9H, $3OCH_3$). ^{13}C nmr (DMSO-d_6): δ 159.1, 153.1, 152.2, 147.6, 146.3, 140.9, 140.2, 128.8, 127.7, 127.3, 111.7, 98.5, 62.2, 61.4, 56.7, 42.1. *Anal.* Calcd for $C_{18}H_{19}N_3O_3$ (325.4): C, 66.45; H, 5.89; N, 12.91. Found: C, 66.56; H, 5.95; N, 12.93.

(*R*)-4-(α-Methylbenzylphenyl)amine-6,7,8-trimethoxyquinazoline (9p). This compound was obtained as white solid; mp 207-209°C; $[\alpha]^D_{22}$ -213.0 (*c* 0.01, EtOH). ir (potassium bromide): 3262, 3026, 2972, 2934, 2832, 1613, 1478, 1281, 1121, 702 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.31 (s, 1H, quinazoline H-2), 8.22 (d, 1H, NH, J = 7.45 Hz), 7.64 (s, 1H, quinazoline H-5), 7.42 (d, 2H, Ph-2,6-H, J = 7.45 Hz), 7.32 (t, 2H, Ph-3,5-H, J = 7.45 Hz), 7.21 (t, 1H, Ph-4-H, J = 7.45 Hz), 5.62 (p, 1H, CH, J = 7.45 Hz), 3.96-3.87 (3s, 9H, $3OCH_3$), 1.60 (d, 3H, CH_3, J = 7.45 Hz). ^{13}C nmr (DMSO-d_6): δ 158.3, 153.0, 152.2, 147.6, 146.3, 145.4, 140.9, 128.8, 127.1, 126.6, 111.6, 98.7, 62.2, 61.4, 56.9, 49.6, 22.9. *Anal.* Calcd for $C_{19}H_{21}N_3O_3$ (339.4): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.31; H, 5.97; N, 12.23.

(*S*)-4-(α-Methylbenzylphenyl)amine-6,7,8-trimethoxyquinazoline (9q). This compound was obtained as white solid; mp 205-206°C; $[\alpha]^D_{22}$ +208.0 (*c* 0.01, EtOH). ir (potassium bromide): 3242, 3028, 2972.3, 2936, 2832, 1613, 1478, 1312, 1130, 700 cm^{-1}. ^1H nmr (DMSO-d_6): δ 8.31 (s, 1H, quinazoline H-2), 8.22 (d, 1H, NH, J = 7.45 Hz), 7.64 (s, 1H, quinazoline H-5), 7.42 (d, 2H, Ph-2,6-H, J = 7.45 Hz), 7.32 (t, 2H, Ph-3,5-H, J = 7.45 Hz), 7.21 (t, 1H, Ph-4-H, J = 7.45 Hz), 5.62 (p, 1H, CH, J = 7.45 Hz), 3.96-3.87 (3s, 9H, $3OCH_3$), 1.60 (d, 3H, CH_3, J = 6.9 Hz). ^{13}C nmr (DMSO-d_6): δ 158.3, 153.0, 152.2, 147.6, 146.3, 145.4, 140.9, 128.8, 127.1, 126.6, 111.6, 98.7, 62.2, 61.4, 56.9, 49.6, 22.9. *Anal.* Calcd for $C_{19}H_{21}N_3O_3$ (339.4): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.43; H, 6.23; N, 12.37.

MTT Method. MTT assay against cancer cell proliferation [22]. All tested compounds were dissolved in DMSO (1–100 μM solution) and subsequently diluted in the culture medium before treatment of the cultured cells. Tested cells were plated in 96-well plates at a density 2×10^3 cells/well/100 μL of the proper culture medium and treated with the compounds at 1–100 μM for 72 hours. In parallel, the cells treated with 0.1% DMSO

served as control. An MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide] assay (Roche Molecular Biochemicals, 1465-007) was performed 30 hours later according to the instructions provided by Roche. This assay is based on the cellular cleavage of MTT into formazan which is soluble in cell culture medium. And the absorbance caused by formazan was measured at 595 nm with a microplate reader (Bio-Rad, model 680), which is directly proportional to the number of living cells in culture. Three types of cells were used in these assays, PC3 cell lines, provided by ATCC and cultivated in RPMI 1640 for PC3 supplemented with 10% fetal bovine serum. Tissue culture reagents were obtained from Gibco BRL.

REFERENCES

[1] Szczepankiewicz, W.; Suwinski J.; Bujok, R. *Tetrahedron* **2000**, *56*, 9343.

[2] Tobe, M.; Isobe, Y.; Tomizawa, H.; Nagasaki, T.; Obara, F.; Hayashi, H. *Bioorg. Med. Chem.* **2003**, *11*, 609.

[3] Liu, G.; Yang, S.; Song, B.-A.; Xue, W.; Hu D.-Y.; Jin, L.-H.; Lu, P. *Molecules* **2006**, *11*, 272.

[4] Rosowsky, A.; Papoulis, A. T.; Forsch, R. A.; Queener, S. F. *J. Med. Chem.* **1999**, *42*, 1007.

[5] Jackman, A. L.; Kimbell, R.; Brown, M.; Brunton, L.; Harrap, K. R.; Wardleworth J. M. ; Boyle, F. T. *Adv Exp Med Biol.* **1994**, *370*, 185.

[6] Gangjee, A.; Zaveri, N ; Kothare, M.; Queener, S. F. *J. Med. Chem.* **1995**, *38*, 3660.

[7] Griffin, R. J.; Srinivasan, S.; Bowman, K.; Calvert, A. H.; Curtin, N. J.; Newell, D. R.; Pemberton, L. C.; Golding, B. T. *J. Med. Chem.* **1998**, *41*, 5247.

[8] Smaill, J. B.; Rewcastle, G. W.; Loo, J. A.; Greis, K. D.; Chan, O. H.; Reyner, E. L.; Lipka, E.; Showalter, H. D. H.; Vincent, P. W.; Elliott, W. L.; Denny, W. A. *J. Med. Chem.* **2000**, *43*, 1380.

[9] Wissner, A.; Berger, D. M.; Boschelli, D. H.; Floyd, M. B. Jr.; Greenberger, L. M.;. Gruber, B. C.; Johnson, B.D.; Mamuya, N.; Nilakantan, R.; Reich, M. F.; Shen, R.; Tsou, H. R.; Upeslacis, E.; Wang, Y. F.; Wu, B.; Ye, F.; Zhang, N. *J. Med. Chem.* **2000**, *43*, 3244.

[10] Bridges, A. J.; Zhou, H.; Cody, D. R.; Rewcastle, G. W.; McMichael, A.; Showalter, H. D. H.; Fry, D. W.; Kraker, A. J.; Denny, W.A. *J. Med. Chem.* **1996**, *39*, 267.

[11] Discafani, C. M.; Carroll, M. L.; Floyd, M. B. Jr.; Hollander, I. J.; Husain, Z.; Johnson, B. D.; Kitchen, D.; May, M. K.; Malo, M. S.; Minnick, A. A. Jr.; Nilakantan, R.; Shen, R.; Wang, Y.-F.; Wissner, A.; Greenberger, L. M. *Biochem. Pharmacol.* **1999**, *57*, 917.

[12] Rewcastle, G. W.; Palmer, B. D.; Bridges, A. J.; Showalter, H. D. H.; Sun, L.; Nelson, J.; McMichael, A.; Kraker, A. J.; Fry, D. W.; Denny, W. A. *J. Med. Chem.* **1996**, *39*, 918.

[13] Caddick, S. *Tetrahedron* **1995**, *51*, 10403.

[14] Galema, S. A. *Chem. Soc. Rev.* **1997**, *26*, 223.

[15] Lidstrom, P.; Tierney, J.; Wathry, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

[16] Kuhnert, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 1863.

[17] Lee, J. Y.; Park, Y. K.; Seo, S. H.; So, I. S.; Chung, H.-K.; Yang, B. S.; Lee, S. J.; Park, H.; Lee, Y. S. *Arch. Pharm.* **2001**, *334*, 357.

[18] Lee, J. Y.; Lee, Y. S.; Park, H. K.; Seo, S. H.; Yang, B. S. U.S. Patent 2003,045,537, 2003; *Chem. Abstr.* **2003**, *138*, 122652c.

[19] Mauthner, F.; Clarker, H.-T. *Organic Synthesis Collection*, Gilman, H. Ed, Wiley, New York, 1941, Vol 1, pp 537.

[20] Kudryashova, N. I.; Davidenko, L. R.; Khromov-Borisov, N. V. *Zh. Obshch. Biol.* **1959**, *29*, 1885.

[21] Song, B. A.; Chen, C. J.; Yang, S.; Jin, L. H.; Xue, W.; Zhang, S. M.; Zou, Z. H.; Hu, D. Y. ; Liu, G.. *Acta Chim. Sinica* **2005**, *63*, 1720.

[22] Skehan, P.; Storeng, R.; Scadiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107.