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SYNTHESIS AND BIOLOGICAL ACTIVITY OF NOVEL N-SUBSTITUTED 4-AMINO-6,7,8-TRIMETHOXYQUIN-AZOLINE COMPOUNDS

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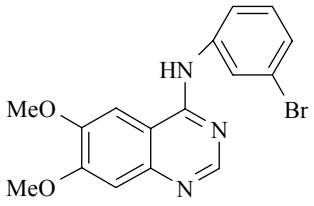
A series of N-substituted 4-amino-6,7,8-trimethoxyquinazoline derivatives has been synthesized from 4-chloro-6,7,8-trimethoxyquinazoline and aryl (or benzyl) amines using 2-propanol as a solvent. The starting material 4-chloro-6,7,8-trimethoxyquinazoline has been synthesized from natural gallic acid by a novel route. Their structures have been verified by elemental analysis and IR, ^{1}H, and ^{13}C NMR spectroscopy. The title compounds have been evaluated for their in vitro antiproliferative activities against some cancer cells by the MTT method. Unfortunately, most of the compounds tested have exhibited a weaker anticancer activity than the reference standard drug PD153035.

Keywords: gallic acid, quinazoline, anticancer.

Recently it has been shown that quinazoline compounds exhibit promising biological activity for medicinal or pesticidal use [1–5]. As part of our ongoing research program on heterocyclic compounds, which may serve as leads for designing novel antitumor referred to PD153035 as the leading compound, we were particularly interested in 4-substituted quinazolines [6–12]. We considered the well-known activity of the quinazoline nucleus in chemotherapy, where many of its substituted derivatives are effective antitumor agents [13-16].



PD153035

Furthermore, the more recent data reported that a broad class of quinazolines also acts as potent and highly selective inhibitors of epidermal growth factor receptor (EGFR) or epidermal growth factor receptor tyrosine kinase (EGFR-TK) [17–21]; the members of this class are expected to have great therapeutic potential in the treatment of malignant and nonmalignant epithelial diseases [22, 23]. In view of these facts and in order to

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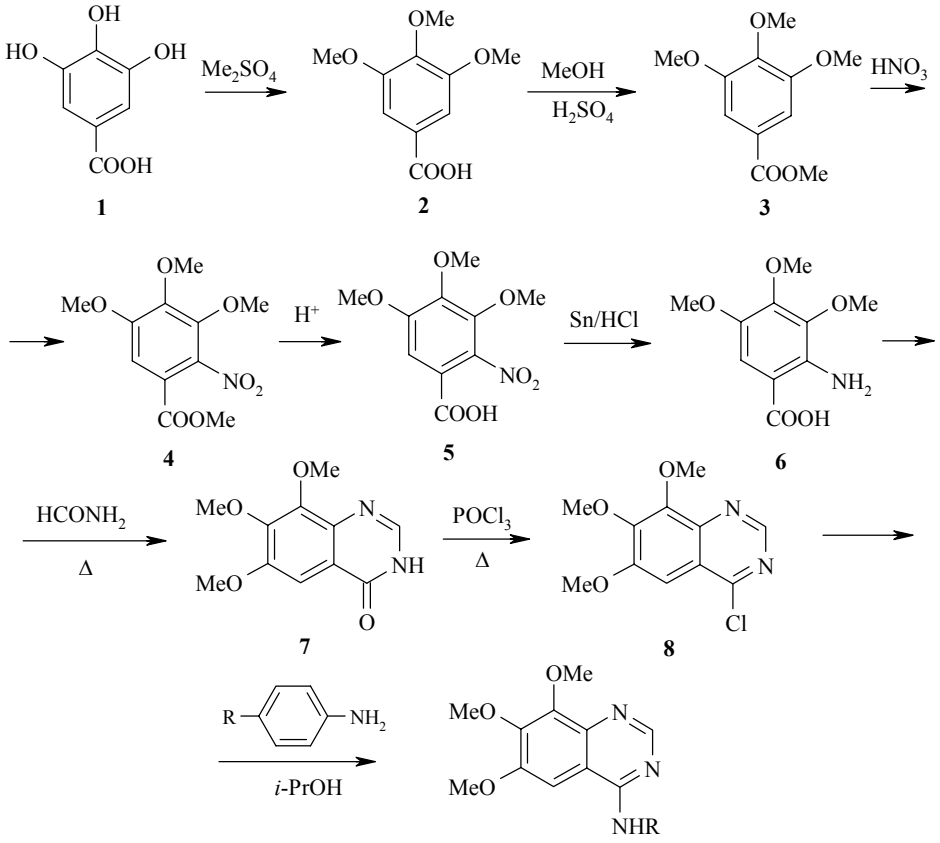
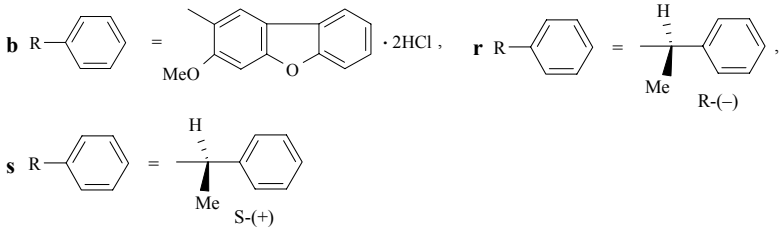
study the influence of position 4 and 8 substitution on antitumor activity, we have prepared a series of new 4-aryl(benzyl)amino-6,7,8-trimethoxyquinazolines from natural gallic acid hoping to discover more active ATP site inhibitors.

The synthetic route to the target compounds is shown in the Scheme:



9 a R = 4-Br·2HCl, **c** R = 3-Cl·HCl, **d** R = 3-Br, **e** R = 3-Br·HCl, **f** R = 3-F·HCl, **g** R = 3-F, **h** R = 4-F, **i** R = 2-F·HCl, **j** R = 2-Cl-4-Br·HCl, **k** R = 3,4,5-$(MeO)_3$·HCl, **l** R = 4-NO_2·HCl, **m** R = 3-NO_2·HCl, **n** R = 2-NO_2·HCl, **o** R = H, **p** R = 4-Cl·2HCl, **q** R = OH·2HCl,



To the best of our knowledge, this is the first report on the synthesis of N-substituted 4-amino-6,7,8-trimethoxyquinazoline compounds from natural gallic acid.

Nineteen new N-substituted 4-amino-6,7,8-trimethoxyquinazoline compounds were synthesized referred to PD153035 as the leading compound.The structures of new compounds were confirmed by elemental analysis, IR, ^1H and ^{13}C NMR spectra.

TABLE 1. Inhibitory Activity of **9a-s** and **8** in a Concentration of 10 μM Against PC3 Cancer Cells

Compound	Inhibition*, %	Compound	Inhibition*, %
9a	19.5± 1.8	**9l**	34.5± 5.8
9b	50.0± 4.3	**9m**	37.2± 1.4
9c	26.7± 3.2	**9n**	22.8± 3.0
9d	17.0± 2.3	**9o**	9.3± 3.1
9e	22.2± 3.4	**9p**	19.4± 5.5
9f	16.3± 2.4	**9q**	25.0± 6.1
9g	12.1± 2.9	**9r**	35.5± 4.1
9h	16.6± 1.9	**9s**	–7.44± 4.2
9i	18.1± 5.3	**8**	71.3 ± 4.7
9j	11.5± 4.8	**PD153035*[2]**	87.5± 1.8
9k	35.0± 3.3		

* Each value represents the mean ± SEM (n = 9). Significance levels $p < 0.1$ (compounds **9a**, **b**, **d, f-h, k, m-p, r, s**), $p < 0.05$ (compounds **9c, e, i, j, l, q; 8, PD153035**) as compared with the respective control.
*[2] The standard compound was prepared for comparison of activity.

The *in vitro* antitumor activities of these compounds were evaluated against PC3, BGC823, and Bcap-37 cells by the MTT method. The results for title compounds **9a–s** and **8** against PC3 cells are summarized in Table 1.

Unfortunately, most of the test compounds exhibited less anticancer activity than the reference standard drug PD153035. The compounds **9b**, **k**, **m**, **r**, and **8** (4-chloro-6,7,8-trimethoxyquinazoline) showed weak inhibitory activity against PC3 cells. The data given in Table 1 indicate that the change of substituents of the quinazoline ring affects the antitumor activity. When the 6,7,8-position was substituted by the methoxy group, the compounds generally had less antitumor activities than 6,7-dimethoxy-substituted compounds. When position 4 in the quinazoline ring was substituted by a different aryl or benzyl moiety, the compounds generally had a potential anticancer activity, such as **9b**, **k**, **m,** and **r** with as inhibition of 50.0, 35.0, 37.2, and 35.5% against PC3 cells in the concentration of 10 μM. All the title compounds showed lower or no activities against Bcap-37 and BGC823 cells, the results of the antitumor activity against these cells were not listed.

The compounds **9d** and **9e** (R = 3-bromophenyl) differ from PD153035 only by the substituent in position 8, showing that introduction of an additional methoxy group lowers the activity against tumor cells PC3 (Table 1).

So, we can conclude that position 8 without substitution had a very important effect on antitumor activity. To the following research we should consider other positions, such as 2, 3, or 5.

The chiral compounds **9r** and **9s** exhibited a very different antitumor activity against PC3 cells (Table 1). (*R*)-4-(*α*-Methylbenzylphenyl)amino-6,7,8-trimethoxyquinazoline **9r** showed a weak inhibitory activity against PC3 cells (35.5% in a concentration of 10 μM), and (*S*)-4-(*α*-methylbenzylphenyl)amino-6,7,8-trimethoxy-quinazoline **9s** demonstrated no activity in the same concentration. In our following research, we can think of different chiral moieties in position 4.

In summary, N-substituted 4-amino-6,7,8-trimethoxyquinazoline derivatives **9a-s** were synthesized by a novel method from gallic acid. The compounds were evaluated for their *in vitro* antitumor activities against PC3, Bcap37, and BGC823 cells by the MTT method. Compounds **9b**, **k**, **m**, **r**, and **8** inhibited PC3 cells by 50.0, 35.0, 37.2, 35.5, and 71.3% in a concentration of 10 μM. Unfortunately, the other tested compounds exhibited low anticancer activity.

TABLE 2. Characteristics of Compounds **9a-s**

Compound*	Empirical formula	Found, % / Calculated, %			mp, °C	Yield*[2], %
		C	N	H		
9a	$C_{17}H_{16}BrN_3O_3 \cdot 2HCl$	43.82 / 44.09	4.18 / 3.92	9.04 / 9.07	170-173	51.7
9b	$C_{25}H_{25}N_3O_5 \cdot 2HCl$	57.60 / 57.70	5.03 / 5.23	8.16 / 8.07	160-162	46.8
9c	$C_{17}H_{16}ClN_3O_3 \cdot HCl$	53.50 / 53.42	4.57 / 4.48	10.74 / 10.99	172 (dec.)	61.2
9d	$C_{17}H_{16}BrN_3O_3$	52.21 / 52.32	4.35 / 4.13	10.98 / 10.77	126-127	19.9
9e	$C_{17}H_{16}BrN_3O_3 \cdot HCl$	47.69 / 47.85	4.25 / 4.02	10.02 / 9.85	180 (dec.)	65.6
9f	$C_{17}H_{16}FN_3O_3 \cdot HCl$	55.69 / 55.82	4.72 / 4.68	11.35 / 11.49	232-234	60.4
9g	$C_{17}H_{16}FN_3O_3$	61.97 / 62.00	4.85 / 4.90	12.59 / 12.76	252-254	36.1
9h	$C_{17}H_{16}FN_3O_3$	61.85 / 62.00	4.88 / 4.90	12.63 / 12.76	184-186	55.4
9i	$C_{17}H_{16}FN_3O_3 \cdot HCl$	55.66 / 55.82	4.86 / 4.68	11.31 / 11.49	194 (dec.)	63.8
9j	$C_{17}H_{15}BrClN_3O_3 \cdot HCl$	43.96 / 44.28	3.76 / 3.50	9.01 / 9.11	178 (dec.)	66.2
9k	$C_{20}H_{23}N_3O_6 \cdot HCl$	54.67 / 54.86	5.61 / 5.52	9.55 / 9.60	195 (dec.)	64.4
9l	$C_{17}H_{16}N_4O_5 \cdot HCl$	51.73 / 51.98	4.52 / 4.36	14.12 / 14.26	212 (dec.)	54.3
9m	$C_{17}H_{16}N_4O_5 \cdot HCl$	51.71 / 51.98	4.55 / 4.36	14.32 / 14.26	204-206	34.5
9n	$C_{17}H_{16}N_4O_5 \cdot HCl$	52.18 / 51.98	4.57 / 4.36	14.29 / 14.26	210 (dec.)	32.7
9o	$C_{18}H_{19}N_3O_3$	66.56 / 66.45	5.95 / 5.89	12.93 / 12.91	173-175	64.0
9p	$C_{17}H_{16}ClN_3O_3 \cdot 2HCl$	48.53 / 48.77	4.63 / 4.33	9.97 / 10.04	175 (dec.)	41.9
9q	$C_{17}H_{17}N_3O_4 \cdot 2HCl$	51.24 / 51.01	5.04 / 4.78	10.52 / 10.50	153 (dec.)	58.0
9r*[3]	$C_{19}H_{21}N_3O_3$	67.31 / 67.24	5.97 / 6.24	12.23 / 12.38	207-209	48.9
9s*[4]	$C_{19}H_{21}N_3O_3$	67.43 / 67.24	6.23 / 6.24	12.37 / 12.38	205-206	61.4

* Physical state: pale yellow solid (compounds **9a, c–i, l–n, p, q**), yellow solid (compounds **9b, k**), white solid (compounds **9j, o, r, s**).
*[2] Yields of isolated products.
*[3] $[\alpha]^{D}_{22}$ -213° (c = 0.01 mol/l, EtOH).
*[4] $[\alpha]^{D}_{22}$ +208° (c = 0.01 mol/l, EtOH).

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial supplies without further purification. All melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and are not corrected. The IR spectra were recorded on a Bruker VECTOR22 spectrometer in KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer Varian-Inova 500 (500 and 125 MHz respectively) at room temperature in DMSO-d_6 using 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 automatically polarimeter (Beijing Tech Instrument Co., China). The following compounds were prepared as described in the literature: 3,4,5-trimethoxybenzoic acid (**2**): white solid, yield 81.4%; mp 159-161°C (lit. [24], mp 160-162°C); methyl 3,4,5-trimethoxybenzoate (**3**): white needles, yield 69.5%; mp 75-76°C (lit. [25], mp 82-84°C).

TABLE 3 IR Spectra of Compounds **9a-s**

Com-pound	IR, cm^{-1}	
	ν	δ_{Ar-H}
9a	3415.5 (N–H_2^+); 3010.9 (Ar–H); 2947.2 (*as*CH_3); 2847.0 (*s*CH_3); 1627.9-1489.1 (quinaz. skeleton vibr.); 1288.5 (*as*Ar–O–C); 1128.4 (*s*Ar–O–C)	804.3
9b	3416.3 (N–H_2^+);3010.9 (Ar–H); 2949.2 (*as*CH_3); 2850.8 (*s*CH_3); 1626.0-1473.6 (Ar skeleton vibr.); 1286.5 (*as*Ar–O–C); 1124.5 (*s*Ar–O–C)	763.8
9c	3418.6 (N–H_2^+); 3012.8 (Ar–H); 2947.2 (*as*CH_3); 2846.9 (*s*CH_3); 1627.9-1487.1 (quinaz. skeleton vibr.); 1288.5 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C)	785.0
9d	3307.9 (N–H); 3010.9 (Ar–H); 2941.4 (*as*CH_3); 2852.7 (*s*CH_3); 1627.9-1487.1 (quinaz. skeleton vibr.); 1288.5 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C)	788.9
9e	3419.8 (N–H_2^+); 3010.9 (Ar–H); 2945.3 (*as*CH_3); 2848.9 (*s*CH_3); 1626.0-1487.1 (quinaz. skeleton vibr.); 1286.5 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C)	786.9
9f	3414.2 (N–H_2^+); 3012.8 (Ar–H); 2951.1 (*as*CH_3); 2852.6 (*s*CH_3); 1627.9-1489.1 (Ar skeleton vibr.); 1288.5 (*as*Ar–O–C); 1134.1 (*s*Ar–O–C)	
9g	3369.4 (N–H); 3074.5 (Ar–H); 2933.7 (*as*CH_3); 2833.4 (*s*CH_3); 1618.3–1454.3 (Ar skeleton vibr.); 1271.1 (*as*Ar–O–C); 1118.7 (*s*Ar–O–C)	
9h	3356.1 (N–H); 3016.7 (Ar–H); 2947.2 (*as*CH_3); 2856.6 (*s*CH_3); 1626.0-1487.1 (quinaz. skeleton vibr.); 1282.7 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C)	788.9
9i	3363.9 (N–H_2^+); 2945.3 (*as*CH_3); 2854.7 (*s*CH_3); 1629.9-1487.1 (quinaz. skeleton vibr.); 1257.6 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C); 1010.7 (C–F)	759.9
9j	3365.8 (N–H_2^+); 3014.7 (Ar–H); 2945.3 (*as*CH_3); 2848.9 (*s*CH_3); 1626.0-1487.1 (Ar skeleton vibr.); 1286.5 (*as*Ar–O–C); 1126.4 (*s*Ar–O–C)	
9k	3419.8 (N–H_2^+); 2947.2 (*as*CH_3); 2839.2 (*s*CH_3); 1633.7-1456.3 (Ar skeleton vibr.); 1284.6 (*as*Ar–O–C); 1130.3 (*s*Ar–O–C)	
9l	3365.8 (N–H_2^+); 3010.9 (Ar–H); 2951.1 (*as*CH_3); 2839.0 (*s*CH_3); 1627.9-1514.1 (Ar skeleton vibr.); 1487.1 (*as*NO_2); 1340.5 (*s*NO_2); 1284.6 (*as*Ar–O–C); 1130.3 (*s*Ar–O–C)	
9m	3419.8 (N–H_2^+); 3014.7 (Ar–H); 2947.2 (*as*CH_3); 2843.1 (*s*CH_3); 1631.8-1469.8 (Ar skeleton vibr.); 1485.2 (*as*NO_2); 1346.3 (*s*NO_2); 1284.6 (*as*Ar–O–C); 1120.6 (*s*Ar–O–C)	
9n	3387.8 (N–H_2^+); 3018.6 (Ar–H); 2945.3 (*as*CH_3); 2845.0 (*s*CH_3); 1624.0-1458.2 (Ar skeleton vibr.); 1489.0 (*as*NO_2); 1355.9 (*s*NO_2); 1286.5 (*as*Ar–O–C); 1130.3 (*s*Ar–O–C)	792.7
9o	3234.6 (N–H); 3001.2 (Ar–H); 2937.6 (*as*CH_3); 2831.5 (*s*CH_3); 1614.4-1454.3 (Ar skeleton vibr.); 1282.7 (*as*Ar–O–C); 1128.4 (*s*Ar–O–C)	800.5
9p	3419.8 (N–H_2^+); 3010.9 (Ar–H); 2947.2 (*as*CH_3); 2852.7 (*s*CH_3); 1627.9-1471.7 (Ar skeleton vibr.); 1286.5 (*as*Ar–O–C); 1130.3 (*s*Ar–O–C)	806.3
9q	3419.8 (N–H_2^+); 3226.9 (O–H_2^+); 3030.2 (Ar–H); 2949.2 (*as*CH_3); 2854.7 (*s*CH_3); 1626.0-1473.6 (Ar skeleton vibr.); 1273.0 (*as*Ar–O–C); 1128.4 (*s*Ar–O–C)	
9r	3261.6 (N–H); 3026.3 (Ar–H); 2972.3, 2933.7 (*as*CH_3+CH_2); 2831.5 (*s*CH_3); 1612.5-1477.5 (Ar skeleton vibr.); 1280.7 (*as*Ar–O–C); 1120.6 (*s*Ar–O–C)	702.1
9s	3242.3 (N–H); 3028.2 (Ar–H); 2972.3, 2935.7 (*as*CH_3+CH_2); 2831.5 (*s*CH_3); 1612.5-1477.5 (Ar skeleton vibr.); 1311.6 (*as*Ar–O–C); 1130.3 (*s*Ar–O–C)	700.2

* Quinaz. – quinazoline.

TABLE 4. ^{1}H NMR Spectra of Compounds **9a–s**

Com-pound	δ, ppm (*J*, Hz)*
9a	11.53 (1H, s, NH); 8.76 (1H, s, H-2 quinaz.); 8.14 (1H, s, H-5 quinaz.); 7.71 (4H, s, Ph); 4.05-4.02 (9H, 3s, 3OCH$_3$)
9b	11.45 (1H, s, NH); 8.68 (1H, s, H-2 quinaz.); 8.22 (1H, d, *J* = 7.45, H-5 DBF); 8.09 (1H, s, H-5 quinaz.); 8.03 (1H, s, H-1 DBF); 7.88 (1H, s, H-4 DBF); 7.72 (1H, d, *J* = 7.45, H-8 DBF); 7.58-7.55 (1H, m, H-7 DBF); 7.47-7.45 (1H, m, H-6 DBF); 4.04-3.93 (12H, 4s, 4OCH$_3$)
9c	11.43 (1H, s, NH); 8.81 (1H, s, H-2 quinaz.); 8.10 (1H, s, H-5 quinaz.); 7.90 (1H, s, H-2 Ph); 7.71 (1H, d, *J* = 9.15, H-4 Ph); 7.56-7.53 (1H, m, H-5 Ph); 7.41 (1H, d, *J* = 9.15, H-6 Ph); 4.05-4.02 (9H, 3s, 3OCH$_3$)
9d	11.51 (1H, s, NH); 8.81 (1H, s, H-2 quinaz.); 8.13 (1H, d, *J* = 4.0, H-2 Ph); 8.02 (1H, s, H-5 quinaz.); 7.76 (1H, d, *J* = 8.05, H-4 Ph); 7.54 (1H, d, *J* = 8.05, H-6 Ph); 7.48 (1H, t, *J* = 4.0, H-5 Ph); 4.05-4.02 (9H, 3s, 3OCH$_3$)
9e	11.62 (1H, s, NH); 8.81 (1H, s, H-2 quinaz.); 8.20 (1H, s, H-5 quinaz.); 8.03 (1H, s, H-2 Ph); 7.77 (1H, d, *J* = 8.0, H-4 Ph); 7.54 (1H, d, *J* = 8.0, H-6 Ph); 7.48 (1H, t, *J* = 4.0, H-5 Ph); 4.03-4.02 (9H, 3s, 3OCH$_3$)
9f	11.63 (1H, s, NH); 8.81 (1H, s, H-2 quinaz.); 8.21 (1H, s, H-5 quinaz.); 7.73 (1H, d, *J* = 10.9, H-4 Ph); 7.73 (1H, d, *J* = 8.0 Hz, H-6 Ph); 7.57-7.54 (1H, m, H-5 Ph); 7.20 (1H, t, *J* = 4.0, H-2 Ph); 4.07-4.03 (9H, 3s, 3OCH$_3$)
9g	9.69 (1H, s, NH); 8.56 (1H, s, H-2 quinaz.); 7.88 (1H, d, *J* = 12.05, H-4 Ph); 7.71 (1H, s, H-5 quinaz.); 7.63 (1H, d, *J* = 8.0, H-6 Ph); 7.44-7.43 (1H, m, H-5 Ph); 6.96 (1H, t, *J* = 4.0, H-2 Ph); 4.01-3.93 (9H, 3s, 3OCH$_3$)
9h	11.61 (1H, s, NH); 8.73 (1H, s, H-2 quinaz.); 8.17 (1H, s, H-5 quinaz.); 7.74-7.71 (2H, m, H-3,5 Ph); 7.38-7.34 (2H, m, H-2,6 Ph); 4.05-4.02 (9H, 3s, 3OCH$_3$)
9i	11.82 (1H, s, NH); 8.72 (1H, s, H-2 quinaz.); 8.23 (1H, s, H-5 quinaz.); 7.56-7.36 (4H, m, H-3,4,5,6 Ph); 4.06-4.03 (9H, 3s, 3OCH$_3$)
9j	8.71 (1H, s, H-2 quinaz.); 8.04 (1H, s, H- 5 quinaz.); 8.00 (1H, d, *J* = 2.3, H-3 Ph); 7.74 (1H, d, *J* = 8.6, H-5 Ph); 7.54 (1H, d, *J* = 8.6, H-6 Ph); 4.03-4.02 (9H, 3s, 3OCH$_3$)
9k	11.52 (1H, s, NH); 8.75 (s, 1H, H-2 quinaz.); 8.17 (1H, s, H-5 quinaz.); 7.09 (2H, s, H-1,6 Ph); 4.06-4.02 (9H, 3s, 3OCH$_3$); 3.81 (6H, s, 3,5-2CH$_3$ phenyl); 3.71 (3H, s, 4-CH$_3$ phenyl)
9l	11.21 (1H, s, NH); 8.82 (1H, s, H-2 quinaz.); 8.36 (2H, d, *J* = 8.6, 3,5-H Ph); 8.15 (2H, d, *J* = 8.6, 2,6-H Ph); 8.06 (1H, s, H-5 quinaz.); 4.06-4.02 (9H, 3s, 3OCH$_3$)
9m	11.84 (1H, s, NH); 8.86 (1H, s, H-2 quinaz.); 8.72 (1H, s, H-2 Ph); 8.29 (1H, d, *J* = 9.15, H-4 Ph); 8.26 (1H, s, H-5 quinaz.); 8.18 (1H, d, *J* = 9.7, H-6 Ph); 7.82-7.79 (1H, m, H-5 Ph); 4.08-4.03 (9H, 3s, 3OCH$_3$)
9n	12.01 (1H, s, NH); 8.66 (1H, s, H-2 quinaz.); 8.18 (1H, s, H-5 quinaz.); 8.17 (1H, d, *J* = 7.45, H-3 Ph); 7.90 (1H, t, *J* = 9.15, H-4 Ph); 7.77 (1H, d, *J* = 7.45, H-6 Ph); 7.65 (1H, t, *J* = 7.75, H-5 Ph); 4.06-4.02 (9H, 3s, 3OCH$_3$)
9o	8.60 (1H, t, *J* = 5.7, NH); 8.36 (1H, s, H-2 quinaz.); 7.54 (1H, s, H-5 quinaz.); 7.37-7.31 (4H, m, H-2,3,5,6 Ph); 7.23 (1H, t, *J* = 7.45, H-4 Ph); 4.79 (2H, d, *J* = 5.7, CH$_2$); 3.97-3.87 (9H, 3s, 3OCH$_3$)
9p	11.57 (1H, s, NH); 8.75 (1H, s, H-2 quinaz.); 8.23 (1H, s, H-5 quinaz.); 7.77 (2H, d, *J* = 8.6, H-3,5 Ph); 7.57 (2H, d, *J* = 8.6, H-2,6 Ph); 4.06-4.02 (9H, 3s, 3OCH$_3$)
9q	11.42 (1H, s, NH); 9.75 (1H, s, OH); 8.66 (1H, s, H-2 quinaz.); 8.15 (1H, s, H-5 quinaz.); 7.43 (2H, d, *J* = 8.6, H-3,5 Ph); 6.87 (2H, d, *J* = 8.6, H-2,6 Ph); 4.03-4.00 (9H, 3s, 3OCH$_3$)
9r	8.31 (1H, s, H-2 quinaz.); 8.22 (1H, d, *J* = 7.45, NH); 7.64 (1H, s, H-5 quinaz.); 7.42 (2H, d, *J* = 7.45, Ph H-2,6); 7.32 (2H, t, *J* = 7.45, H-3,5 Ph); 7.21 (1H, t, *J* = 7.45, H-4 Ph); 5.62 (1H, p, *J* = 7.45, CH); 3.96-3.87 (9H, 3s, 3OCH$_3$); 1.60 (3H, d, *J* = 7.45, CH$_3$)
9s	8.31 (1H, s, H-2 quinaz.); 8.22 (1H, d, *J* = 7.45, NH); 7.64 (1H, s, H-5 quinaz); 7.42 (2H, d, *J* = 7.45, H-2,6 Ph); 7.32 (2H, t, *J* = 7.45, H-3,5 Ph); 7.21 (1H, t, *J* = 7.45, H-4 Ph); 5.62 (1H, p, *J* = 7.45, CH); 3.96-3.87 (9H, 3s, 3OCH$_3$); 1.60 (3H, d, *J* = 6.9, CH$_3$)

* Quinaz. – quinazoline; DBF – dibenzofuran.

TABLE 5. ^{13}C NMR Spectra of Compounds **9a-s**

Compound	δ, ppm
1	2
9a	158.9 (C-2 quinaz.); 154.5 (C-6 quinaz.); 149.6 (C-9 quinaz.); 148.2 (C-7 quinaz.); 142.1 (C-8 quinaz.); 136.5 (quinaz. C-10); 132.2 (2C, C-3,5 Ph); 127.3 (2C, C-2,6 Ph); 109.9 (C-4 Ph); 100.6 (C-5 quinaz.); 62.7, 61.9, 57.8 (3C, 6,7,8-site OCH_3 quinaz.)
9b	156.3 (C-2 quinaz.); 154.0 (C-6 quinaz.); 150.9 (C-9 quinaz.); 148.9 (C-7 quinaz.); 147.7 (C-13 DBF); 145.3 (C-2 DBF); 141.4 (C-8 quinaz.); 127.7 (C-11 DBF); 123.5 (C-12 DBF); 123.3 (C-7 DBF); 123.1 (C-6 DBF); 121.3 (C-5 DBF); 111.7 (C-10 quinaz.); 111.4 (C-8 DBF); 108.6 (C-4 DBF); 103.6 (C-1 DBF); 99.8 (C-5 quinaz.); 62.0, 61.3, 56.9 (3C, 6,7,8-site OCH_3 quinaz.); 56.3 (2-site OCH_3 DBF)
9c	158.4 (C-2 quinaz.); 153.9 (C-6 quinaz.); 149.2 (C-9 quinaz.); 147.6 (C-7 quinaz.); 138.1 (C-8 quinaz.); 132.8 (C-3 Ph); 130.4 (C-5 Ph); 126.2 (C-4 Ph); 124.2 (C-2 Ph); 123.0 (C-6 Ph); 109.3 (C-10 quinaz.); 99.8 (C-5 quinaz.); 62.0, 61.2, 57.1 (3C, 6,7,8-site OCH_3 quinaz.)
9d	159.0 (C-2 quinaz.); 154.5 (C-6 quinaz.); 149.8 (C-9 quinaz.); 148.2 (C-7 quinaz.); 138.8 (C-8 quinaz.); 131.3 (C-3 Ph); 129.7 (C-5 Ph); 127.7 (C-4 Ph); 124.1 (C-2 Ph); 121.8 (C-6 Ph); 109.9 (C-10 quinaz.); 100.6 (C-5 quinaz.); 62.7, 61.9, 57.7 (3C, 6,7,8-site OCH_3 quinaz.)
9e	158.5 (C-2 quinaz.); 154.0 (C-6 quinaz.); 149.1 (C-1 Ph); 147.7 (C-9 quinaz.); 141.5 (C-7 quinaz.); 138.8 (C-8 quinaz.); 130.7 (C-5 Ph); 129.1 (C-3 Ph); 127.1 (C-4 Ph); 123.6 (C-2 Ph); 121.2 (C-6 Ph); 109.3 (C-10 quinaz.); 100.2 (C-5 quinaz.); 62.1, 61.3, 57.2 (3C, 6,7,8-site OCH_3 quinaz.)
9f	161.4 (C-2 quinaz.); 159.0 (C-6 quinaz.); 154.6 (C-9 quinaz.); 149.7 (C-7 quinaz.); 148.3 (C-8 quinaz.); 131.0 (C-3 Ph); 130.9 (C-5 Ph); 121.1 (C-4 Ph); 112.5 (C-2 Ph); 112.3 (C-6 Ph); 109.9 (C-10 quinaz.); 100.7 (C-5 quinaz.); 62.7, 61.9, 57.8 (3C, 6,7,8-site OCH_3 quinaz.)
9g	162.7 (C-2 quinaz.); 160.7 (C-6 quinaz.); 156.1 (C-9 quinaz.); 151.4 (C-7 quinaz.); 146.0 (C-8 quinaz.); 129.7 (C-3 Ph); 129.6 (C-5 Ph); 117.4 (C-4 Ph); 111.1 (C-2 Ph); 109.6 (C-6 Ph); 108.4 (C-10 quinaz.); 97.6 (C-5 quinaz.); 61.6, 60.7, 56.2 (3C, 6,7,8-site OCH_3 quinaz.)
9h	161.7 (C-2 quinaz.); 159.8 (C-6 quinaz.); 159.1 (C-1 Ph); 154.5 (C-9 quinaz.); 149.7 (C-7 quinaz.); 148.1 (C-8 quinaz.); 142.1 (C-4 Ph); 133.3 (C-1 Ph); 127.7, 127.6 (2C, C-2,6 Ph); 116.2, 116.1 (2C, C-3,5 Ph); 109.7 (C-10 quinaz.); 100.7 (C-5 quinaz.); 62.7, 61.8, 57.8 (3C, 6,7,8-site OCH_3 quinaz.)
9i	159.3 (C-2 quinaz.); 157.8 (C-6 quinaz.); 155.9 (C-9 quinaz.); 153.9 (C-7 quinaz.); 149.2 (C-2 Ph); 147.7 (C-8 quinaz.); 141.7 (C-1 Ph); 129.3 (C-5 Ph); 128.6 (C-4 Ph); 116.3 (C-6 Ph); 116.2 (C-3 Ph); 108.9 (C-10 quinaz.); 100.2 (C-5 quinaz.); 62.0, 61.2, 57.1 (3C, 6,7,8-site OCH_3 quinaz.)
9j	164.8 (C-4 quinaz.); 159.8 (C-2 quinaz.); 154.7 (C-7 quinaz.); 154.4 (C-8 quinaz.); 153.3 (C-6 quinaz.); 147.2 (C-1 Ph); 138.8 (C-9 quinaz.); 137.7 (C-3 Ph); 137.5 (C-5 Ph); 136.6 (C-2 Ph); 126.4 (C-6 Ph); 114.1 (C-4 Ph); 105.1 (C-10 quinaz.); 104.9 (C-5 quinaz.); 67.4, 66.7, 62.3 (3C, 6,7,8-site OCH_3 quinaz.)
9k	159.0 (C-2 quinaz.); 154.5 (C-6 quinaz.); 153.3 (2C, C-3,5 Ph); 149.6 (C-9 quinaz.); 148.1 (C-7 quinaz.); 136.6 (C-8 quinaz.); 132.8 (C-4 Ph); 109.7 (C-10 quinaz.); 103.5 (2C, C-2,6 Ph); 100.8 (C-5 quinaz.); 62.7, 61.2, 60.7 (3C, 6,7,8-site OCH_3 quinaz.); 57.8 (4-site OCH_3 Ph); 56.6 (2C, 3,5-site OCH_3 Ph)
9l	157.8 (C-2 quinaz.); 153.6 (C-6 quinaz.); 149.7 (C-9 quinaz.); 147.4 (C-7 quinaz.); 143.9 (C-4 Ph); 124.4 (2C, 3,5-C Ph); 123,2 (2C, C-2,6 Ph); 110.5 (C-10 quinaz.); 99.3 (C-5 quinaz.); 62.0, 61.2, 56.9 (3C, 6,7,8-site OCH_3 quinaz.)
9m	159.1 (C-2 quinaz.); 154.6 (C-6 quinaz.); 149.8 (C-3 Ph); 148.3 (C-9 quinaz.); 142.3 (C-7 quinaz.); 138.6 (C-8 quinaz.); 131.2 (C-5 Ph); 130.7 (C-6 Ph); 121.3 (C-4 Ph); 119.5 (C-2 Ph); 110.1 (C-10 quinaz.); 100.8 (C-5 quinaz.); 62.7, 61.9, 57.9 (3C, 6,7,8-site OCH_3 quinaz.)
9n	158.7 (C-2 quinaz.); 153.9 (C-6 quinaz.); 149.3 (C-9 quinaz.); 147.8 (C-7 quinaz.); 146.3 (C-8 quinaz.); 144.8 (C-5 Ph); 134.3 (C-2 Ph); 128.9 (C-3 Ph); 128.1 (C-4 Ph); 125.2 (C-6 Ph); 109.3 (C-10 quinaz.); 99.9 (C-5 quinaz.); 62.0, 61.2, 57.1 (3C, 6,7,8-site OCH_3 quinaz.)

TABLE 5. (continued)

1	2
9o	159.1 (C-4 quinaz); 153.1 (C-2 quinaz.); 152.2 (C-6 quinaz.); 147.6 (C-1 Ph); 146.3 (C-9 quinaz.); 140.9 (C-7 quinaz.); 140.2 (C-8 quinaz.); 128.8 (2C, C-3,5 Ph); 127.7 (2C, C-2,6 Ph); 127.3 (C-4 Ph); 111.7 (C-10 quinaz.); 98.5 (C-5 quinaz.); 62.2, 61.4, 56.7 (3C, 6,7,8-site OCH_3 quinaz.); 42.1 (CH_2)
9p	158.4 (C-2 quinaz.); 153.7 (C-6 quinaz.); 149.3 (C-9 quinaz.); 147.5 (C-7 quinaz.); 135.8 (C-4 Ph); 128.6 (2C, C-3,5 Ph); 126.4 (2C, C-2,6 Ph); 109.9 (C-10 quinaz.); 100.2 (C-5 quinaz.); 62.0, 61.2, 57.2 (3C, 6,7,8-site OCH_3 quinaz.)
9q	158.3 (C-2 quinaz.); 156.1 (C-6 quinaz.); 153.7 (C-9 quinaz.); 149.1 (C-7 quinaz.); 147.3 (C-8 quinaz.);141.6 (C-4 Ph); 127.6 (C-1 Ph); 126.3 (2C, C-3,5 Ph); 115.2 (2C, C-2,6 Ph); 109.1 (C-10 quinaz.); 100.2 (C-5 quinaz.); 61.9, 61.2, 57.1 (3C, 6,7,8-site OCH_3 quinaz.)
9r	158.3 (C-4 quinaz.); 153.0 (C-2 quinaz.); 152.2 (C-6 quinaz.); 147.6 (C-1 Ph); 146.3 (C-9 quinaz.); 145.4 (C-7 quinaz.); 140.9 (C-8 quinaz.); 128.8 (2C, C-3,5 Ph); 127.1 (C-4 Ph); 126.6 (2C, C-2,6 Ph); 111.6 (C-10 quinaz.); 98.7 (C-5 quinaz.); 62.2, 61.4, 56.9 (3C, 6,7,8-site OCH_3 quinaz.); 49.6 (CH); 22.9 (CH_3)
9s	158.3 (C-4 quinaz.); 153.0 (C-2 quinaz.); 152.2 (C-6 quinaz.); 147.6 (C-1 Ph); 146.3 (C-9 quinaz.); 145.4 (C-7 quinaz.); 140.9 (C-8 quinaz.); 128.8 (2C, C-3,5 Ph); 127.1 (C-4 Ph); 126.6 (2C, C-2,6 Ph); 111.6 (C-10 quinaz.); 98.7 (C-5 quinaz.); 62.2, 61.4, 56.9 (3C, 6,7,8-site OCH_3 quinaz.); 49.6 (CH); 22.9 (CH_3)

Methyl 3,4,5-Trimethoxy-2-nitrobenzoate (**4**). To a stirred solution of methyl 3,4,5-trimethoxybenzoate (2.0 g, 8.8 mmol) in AcOH (10 ml) at room temperature was carefully added fuming HNO_3 (2.5 ml) during 30 min. After addition of the acid, the solution stirred for 1-2 h. The reaction mixture was then poured into ice water (60 ml). The solid obtained was filtered off, washed with water, dried, and recrystallized from EtOH–H_2O (2:1, v:v). Pale yellow needles, yield 25.4%; mp 62-63°C. IR spectrum, ν [δ], cm^{-1}: 012.8 (Ph–H), 2962.7 (*as*CH_3), 2846.9 (*s*CH_3), 1718.6 (C=O), 1579.7–1496.8 (Ph skeleton vibration), 1544.9 (*as*NO_2), 1344.4 (*s*NO_2), 1232.5 (*as*Ph–O–C), 1112.9 (*s*Ph–O–C), [866.0 (Ar–H)]. ^{1}H NMR, δ, ppm: 7.34 (1H, s, PhH); 3.94-3.89 (9H, 3s, 3OCH_3); 3.83 (3H, s, $COOCH_3$). ^{13}C NMR, δ, ppm: 163.3 (C=O), 154.7 (C-5 Ph), 146.2 (C-3 Ph), 145.5 (C-4 Ph), 139.6 (C-2 Ph), 117.7 (C-1 Ph), 109.2 (C-6 Ph), 63.1 (4-OCH_3), 61.6 (5-OCH_3), 57.1 (3-OCH_3), 53.7 ($COOCH_3$). Found, %: C 48.57; H 5.02; N 4.91. $C_{11}H_{13}NO_7$. Calculated, %: C 48.71; H 4.83; N 5.16.

3,4,5-Trimethoxy-2-nitrobenzoic Acid (**5**). A stirred solution of methyl 3,4,5-trimethoxy-2-nitrobenzoate (14.0 g, 50 mmol) in 0.8 mol/l NaOH (120 ml, 100 mmol) and 95% EtOH (60 ml) was heated at 45-50°C in a water bath for 2 h. 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 filtered off, washed with water, dried, and recrystallized from EtOH. Pale yellow needles, yield 92.3%; mp 160-161°C. IR spectrum, ν [δ], cm^{-1}: 3107.3-2538.3 (OH+Ph–H), 2953.0 (*as*CH_3), 2850.8 (*s*CH_3), 1695.4 (C=O), 1577.8-1496.8 (Ph skeleton vibration), 1546.9 (*as*NO_2), 1340.5 (*s*NO_2), 1246.0 (*as*Ph–O–C), 1116.8 (*s*Ph–O–C), [725.2 (Ar–H)]. ^{1}H NMR, δ, ppm: 7.32 (1H, s, PhH); 3.93–3.88 (9H, 3s, 3OCH_3). ^{13}C NMR, δ, ppm: 164.1 (C=O), 154.5 (C-5 Ph), 145.8 (C-3 Ph), 145.3 (C-4), 139.8 (C-2 Ph), 118.8 (C-1 Ph), 109.3 (C-6 Ph), 63.1 (4- OCH_3), 61.5 (5-OCH_3), 57.0 (3-OCH_3). Found, %: C 46.77; H 4.14; N 5.32. $C_{10}H_{11}NO_7$. Calculated, %: C 46.70; H 4.31; N 5.45.

2-Amino-3,4,5-trimethoxybenzoic Acid (**6**). A mixture of powder Sn (5.3 g, 45 mmol) and concentrated hydrochloric acid (18 ml) was stirred for 4-5 h at room temperature, and 3,4,5-trimethoxy-2-nitrobenzoic acid (2.6 g, 10 mmol) was added to the solution. The reaction mixture was carefully heated to 80°C in a water bath while maintaining the temperature for 20 min. Then concentrated hydrochloric acid (5 ml) was added into the reaction mixture while maintaining the temperature for 10 min. The reaction mixture was cooled by ice bath and stirred for 10 min. The precipitated complex stannic double salt was filtered off and washed with a little concentrated hydrochloric acid. The white solid obtained was stirred with portions of 10% K_2CO_3 solution until

it dissolved with pH 9-10 and the mixture was alkaline, whereupon a grayish precipitate appeared. It was removed by filter and washed with 10% K_2CO_3 solution. The solution was neutralized with acetic acid to pH 2-3 while maintaining the temperature below 20°C. The white solid obtained was filtered off, washed with water, dried, and recrystallized from EtOH-H_2O (1:1, v:v). White needles, yield 61.7%; mp 126-128°C. IR spectrum, ν [δ], cm^{-1}: 3487.3, 3379.3 (NH_2), 3200-2400 (O–H+Ph–H+*as*CH_3+*s*CH_3), 1670.4 (C=O), 1575.8-1458.2 (Ph skeleton vibration), 1273.0 (*as*Ph–O–C), 1149.6 (*s*Ph–O–C), 744.5 (Ar–H). ^{1}H NMR, δ, ppm: 7.07 (1H, s, PhH); 3.82-3.70 (9H, 3s, 3OCH_3); 3.45 (1H, s, NH). ^{13}C NMR, δ, ppm: 169.4 (C=O), 147.6 (C-5 Ph), 142.9 (C-3 Ph), 141.6 (C-4 Ph), 140.4 (C-2 Ph), 1109.3 (C-1 Ph), 104.5 (C-6 Ph), 60.9 (4-OCH_3), 60.6 (5-OCH_3), 56.6 (3-OCH_3). Found, %: C 52.74; H 5.63; N 6.02. $C_{10}H_{13}NO_5$. Calculated, %: C 52.86; H 5.77; N 6.16.

6,7,8-Trimethoxyquinazolin-4-one (**7**). A mixture of 2-amino-3,4,5-trimethoxybenzoic acid (1.1 g, 5 mmol) and excess of formamide (4 ml) was stirred at 130–140°C for 5 h. After the reaction was over, a suitable amount of water was added dropwise to the reaction mixture to dissolve the excess of formamide at 100°C. The gray solid obtained was filtered off, washed with water, dried, and recrystallized from EtOH. Pale brown crystal, yield 55.4%; mp 220-222°C. IR spectrum, ν[δ], cm^{-1}: 3304.1 (NH), 3163.3 (OH), 3200-2400 (O–H+Ar–H+*as*CH_3+*s*CH_3), 1664.6 (C=O), 1612.5-1473.6 (quinazolone skeleton vibration), 1286.5 (*as*Ar–O–C), 1126.4 (*s*Ar–O–C), [798.5 (Ar–H)]. ^{1}H NMR, δ, ppm: 12.21 (1H, s, NH); 8.01 (1H, s, H-2 quinazolone); 7.35 (1H, s, H-5 quinazolone); 3.95–3.88 (9H, 3s, 3OCH_3). ^{13}C NMR, δ, ppm: 160.6 (C=O), 152.7 (C-2 quinazolone), 148.3 (C-6 quinazolone), 147.7 (C-8 quinazolone), 143.3 (C-7 quinazolone), 139.0 (C-9 quinazolone), 119.2 (C-10 quinazolone), 101.7 (C-5 quinazolone), 62.4, 61.4, 56.4 (3C, 6,7,8-OCH_3 quinazolone). Found, %: C 56.18; H 5.18; N 12.04. $C_{11}H_{12}N_2O_4$. Calculated, %: C 55.93; H 5.12; N 11.86.

4-Chloro-6,7,8-trimethoxyquinazoline (**8**). A solution of 6,7,8-trimethoxyquinazolin-4-one (0.6 g, 2.5 mmol) and four drops of N,N-dimethylaniline in $POCl_3$ (25 ml) was heated at reflux for 3 h. $POCl_3$ was removed by distillation at reduced pressure and the residue was diluted with 20 ml $CHCl_3$ and treated with 30 g ice-water. To the mixture was added saturated potassium carbonate solution with stirring until the mixture acquired pH 4-5. The organic layer was separated and the residue was extracted twice with 40 ml $CHCl_3$, dried by $MgSO_4$, concentrated by distillation, and recrystallized from petroleum ether (bp 60–90°C). Pale gray solid, yield 62.5%; mp 101-103°C. IR spectrum, ν [δ], cm^{-1}: 3099.6 (Ar–H), 2945.3 (*as*CH_3), 2845.0 (*s*CH_3), 1602.9-1467.8 (quinazoline skeleton vibration), 1246.0 (*as*Ar–O–C), 1136.1 (*s*Ar–O–C), [786.9 (Ar–H)]. ^{1}H NMR, δ, ppm: 8.93 (1H, s, H-2 quinaz.); 7.29 (1H, s, H-5 quinaz.); 4.06-4.01 (9H, 3s, 3OCH_3). ^{13}C NMR, δ, ppm: 158.9 (C-2 quinaz.), 154.3 (C-4 quinaz.), 150.9 (C-6 quinaz.), 148.1 (C-9 quinaz.), 146.3 (C-7 quinaz.), 142.7 (C-8 quinaz.), 120.1 (C-10 quinaz.), 98.6 (C-5 quinaz.), 62.2, 61.1, 56.3 (3C, 6,7,8-OCH_3 quinaz.). Found, %: C 52.02; H 4.21; N 10.94. $C_{11}H_{12}N_2O_4$. Calculated, %: C 51.88; H 4.35; N 11.00.

N-Substituted 4-amino-6,7,8-trimethoxyquinazoline 9a-s (Tables 2-5). A solution of 4-chloro-6,7,8-trimethoxyquinazoline (3.0 mmol) and aryl (or benzyl) amines (3.0 mmol) in *i*-PrOH (30 ml) was stirred under reflux for 4-12 h. Upon completion of the reaction, as monitored by TLC, the solid was filtered off, washed with 2-propanol, dried, and recrystallized from EtOH–H_2O to give the title compounds. Most of them were hydrochlorides. If not more solid appeared after the reaction was complete, the solvent was removed under reduced pressure and the residue was washed with cool water, filtered off, and purified by silica gel column chromatography (petroleum ether–ethyl acetate, 5:1, v:v) to give the title compounds. Most of them were free organic bases. So, sometimes we could get both bases and their hydrochlorides in the same reaction.

MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay of cancer cell proliferation [26]. All tested compounds were dissolved in DMSO (1-100 μM solution) and subsequently diluted in the culture medium before treatment of the cultured cells. The 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 h. In parallel, the cells treated with 0.1% DMSO served as a control. The MTT assay (Roche Molecular Biochemicals, 1465-007) was performed 30 h 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. 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 (prostate cancer), BGC 823 (human gastric cancer), and Bcap37 (breast cancer) cell lines, provided by ATCC and cultivated in RPMI 1640 (for PC3, BGC823, and Bcap37) supplemented with 10% fetal bovine serum. Tissue culture reagents were obtained from Gibco BRL.

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