Acta Pharm. **65** (2015) 299–309
DOI: 10.1515/acph-2015-0021

Original research paper

Novel 4-aminoquinazoline derivatives as new leads for anticancer drug discovery

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A novel series of quinazoline derivatives **2**-**8**, **10**-**12** were designed and synthesized. Structures of the newly synthesized compounds were confirmed by elemental analyses, IR, ^{1}H and ^{13}C NMR spectral data. All the newly synthesized compounds were evaluated for *in vitro* cytotoxic activity against the breast cancer cell line MCF-7. Seven of the novel compounds exhibited higher activity than the reference drug doxorubicin. The corresponding compounds **3**, **4**, **5**, **8**, **10**, **11** and **12** exhibited higher activity with IC_{50} values from 22.75 to 43.44 μmol L^{-1}, compared to the reference drug doxorubicin with IC_{50} value of 47.90 μmol L^{-1}. Also, compounds **1**, **6**, and **9** are nearly as active as doxorubicin with IC_{50} values of 48.31, 48.90, and 48.91 μmol L^{-1}, respectively, while compounds **2** and **7** exhibited a moderate activity with IC_{50} values of 50.44 and 52.37 μmol L^{-1}. In addition, compound **13** showed no activity. Cytotoxic screening of the tested copmpounds offered an encouraging framework that may lead to the discovery of potent anti-breast cancer activity.

Keywords: 4-aminoquinazoline derivatives, synthesis, anti-breast cancer activity

Accepted February 16, 2015

A literature survey found that quinazoline derivatives are of considerable chemical and pharmacological importance as therapeutical agents (1-3). They are being extensively utilized as a drug-like scaffold in medicinal chemistry (4), especially as anticancer agents. Since a series of targeted anticancer agents such as nolatrexed **I** (5), GMC-5-193 **II** (6, 7), gefitinib **III** (8) and erlotinib **IV** (9) were reported for anticancer therapy, the 4-aminoquinazoline and 4-aminoquinoline skeletons are considered to be promising nuclea for anticancer drug development (10). As a result, a great number of novel 4-aminoquinazoline derivatives have been developed in succession (Fig. 1). On the other hand, the quinazoline ring system has been consistently regarded as a promising and privileged structural icon owing to its pharmacodynamics versatility in many of its synthetic derivatives as well as in several naturally occurring alkaloids isolated from animals, plants and mi-

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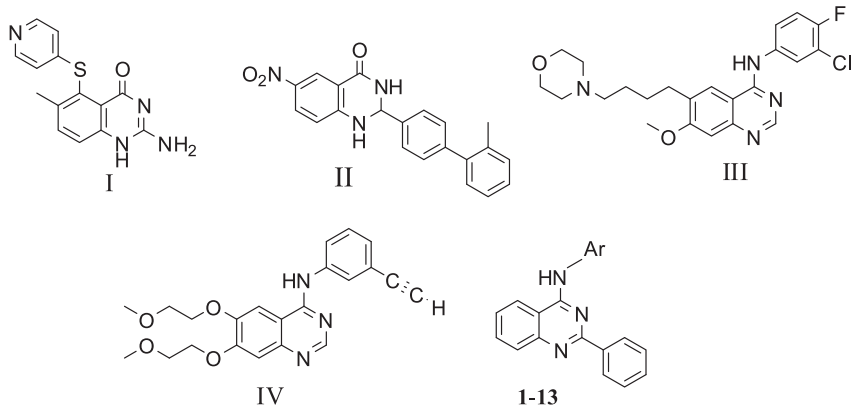


Fig. 1. Structures of bioactive derivatives **I-IV** and target compounds **1-13.**

croorganisms (11–13). In the light of these facts, and as a continuation of our previous reported work on the synthesis of novel anticancer agents (14–23), we planned to synthesize a novel series of 4-aminoquinazoline derivatives carrying biologically active moieties as analogues to bioactive compounds **I-IV**, hoping that the new compounds might show significant cytotoxic activity. Anticancer activity of the newly synthesized compounds was evaluated against the human breast cancer cell line MCF-7.

EXPERIMENTAL

Melting points (uncorrected) were determined in an open capillary on a Gallen Kamp melting point apparatus (Sanyo Gallen Kamp, UK). Precoated silica gel plates (Kieselgel 0.25 mm, 60 F254, Merck, Germany) were used for thin layer chromatography. A developing solvent system of chloroform/methanol (8:2) was used; the spots were detected by ultraviolet light and the purity of all synthesized compounds was > 95 %. IR spectra (KBr disc) were recorded using an FT-IR spectrophotometer (Perkin Elmer, USA). ^{1}H NMR spectra were scanned on a NMR spectrophotometer (Bruker AXS Inc., Switzerland) operating at 500 MHz for ^{1}H- and 125.76 MHz for ^{13}C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard, using DMSO-d_6 as a solvent. Elemental analyses were done on a model 2400 CHNSO analyser (Perkin Elmer, USA). All the values were within ± 0.4 % of the theoretical values. All reagents used were of AR grade. The starting material 4-chloro-2-phenylquinazoline was purchased from Sigma (USA) and was directly used for the preparation of target compounds.

Synthesis of quinazoline derivatives

N-*(3-ethylphenyl)-2-phenylquinazolin-4-amine (**1**) (24),* N-*(4-ethoxyphenyl)-2-phenylquinazolin-4-amine (**2**),* N-*(3,5-dimethoxyphenyl)-2-phenylquinazolin-4-amine (**3**), 2-phenyl*-N-*(3,4,5-trimethoxyphenyl)quinazolin-4-amine (**4**),* N-*(2-methyl-6-nitrophenyl)-2-phenyl-quinazolin-4-amine (**5**), 2-phenyl*-N-*(2,3,4-trichlorophenyl)quinazolin-4-amine (**6**), 2-phenyl*-N-*(2,4,5-trichlorophe-*

*nyl)quinazolin-4-amune (**7**), 2-phenyl-*N*-(2,4,6-trichlorophenyl)quinazolin-4-amine (**8**), N-(4-bromophenyl)-2-phenylquinazolin-4-amine (**9**) (25), N-(2,4-dichlorophenyl)-2-phenylquinazolin-4-amine (**10**), N-(adamantan-1-yl)-2-phenylquinazolin-4-amine (**11**), phenyl(4-(2-phenylquinazolin-4-yl-amino)phenyl)methanone (**12**), 2-((2-phenylquinazolin-4-yl)amino)anthracene-9,10-dione (**13**) (26). General procedure*. – A mixture of 4-chloro-2-phenylquinazoline (2.4 g, 0.01 mol) and substituted amine, namely 3-ethylaniline, 4-ethoxyaniline, 3,5-dimethoxyaniline, 3,4,5-trimethoxyaniline, 2-methyl-6-nitroaniline, 2,3,4-trichloroaniline, 2,4,5-trichloroaniline, 2,4,6--trichloroaniline, 4-bromoaniline, 2,4-dibromoaniline, 1-adamantylamine, 4-aminobenzophenone, 2-aminoanthraquinone (0.012 mol) in dimethylformamide (20 mL) was heated under reflux for 18 h. After cooling, the reaction mixture was poured into ice water. The obtained solid was recrystallized from dioxane to give compounds **1-13**, respectively.

Table I. Physical and analytical data of the synthesized compounds

Compd.	Formula (M_r)	M. p. (°C)	Yield (%)	Analysis (calcd. / found) (%)		
				C	H	N
1	$C_{22}H_{19}N_3$ (325.41)	106.7	88	81.20/81.49	5.89/5.61	12.91/12.69
2	$C_{22}H_{19N}N_3O$ (341.41)	168.2	91	77.40/77.09	5.61/5.33	12.31/12.56
3	$C_{22}H_{19}N_3O_2$ (357.41)	>360	69	73.93/73.65	5.36/5.08	11.76/11.99
4	$C_{23}H_{21}N_3O_3$ (387.43)	281.5	72	71.30/70.95	5.46/5.12	10.85/10.66
5	$C_{21}H_{16}N_4O_2$ (356.38)	105.6	81	70.77/70.39	4.53/4.28	15.72/15.48
6	$C_{20}H_{12}Cl_3N_3$ (401.69)	150.8	78	59.95/59.61	3.02/3.23	10.49/10.16
7	$C_{20}H_{12}Cl_3N_3$ (401.69)	93.6	86	59.95/60.18	3.02/3.33	10.49/10.81
8	$C_{20}H_{12}Cl_3N_3$ (401.69)	111.2	81	59.95/59.77	3.02/3.19	10.49/10.25
9	$C_{20}H_{14}BrN_3$ (376.04)	161.4	88	63.84/63.51	3.75/3.46	11.17/11.38
10	$C_{20}H_{13}Br_2N_3$ (455.15)	218.4	75	52.78/52.94	2.88/2.60	9.23/9.45
11	$C_{24}H_{25}N_3$ (355.48)	145.0	86	81.09/81.32	7.09/7.29	11.82/11.58
12	$C_{27}H_{19}N_3O$ (401.46)	148.4	79	80.78/80.49	4.77/4.96	10.47/10.17
13	$C_{28}H_{17}N_3O_2$ (427.45)	235.3	91	78.68/78.35	4.01/4.31	9.83/9.55

In vitro *anti-breast cancer activity*

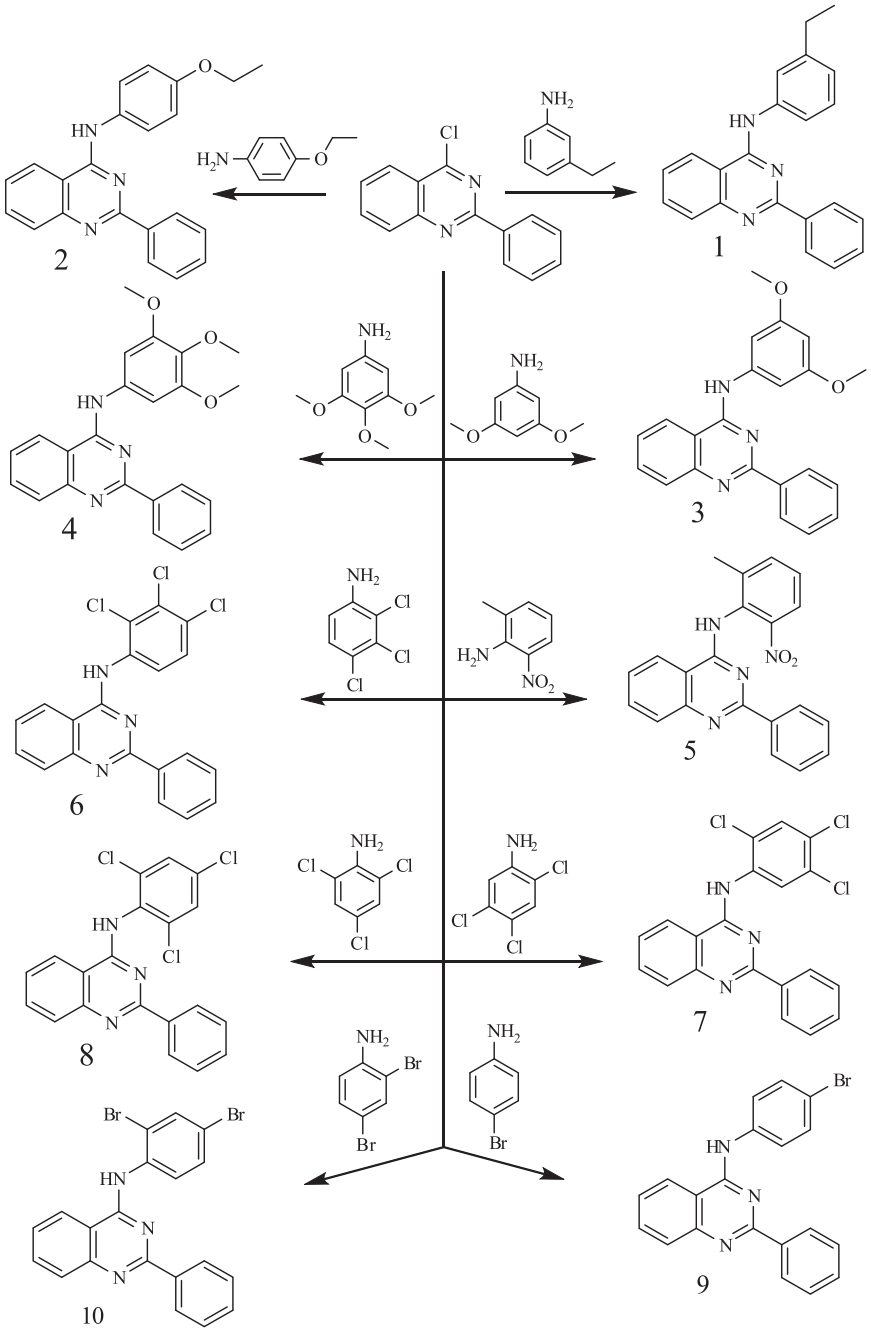
The cytotoxic activity *in vitro* of the newly synthesized compounds was measured using the sulforhodamine B stain (SRB) assay and the method of Skehan (29). The human breast cancer cell line MCF-7 (obtained from National Cancer Institute, Cairo, Egypt) was maintained at 37 °C in 5 % CO_2 as sub-confluent monolayers in 80-mL culture flasks (Nunclon, Sigma, USA) and were subcultured once or twice weekly in Dulbecco's modified of eagle's medium (Flow, Sigma, USA) supplemented with 5 % heat-inactivated fetal calf serum (FCS) and 1 mmol L^{-1} L-glutamine (Sigma, USA). During experiments, 50 μg mL^{-1} gentamicin (Sigma) was added to the culture medium. Passage levels were in the range of

5–20 according to the original receipt. Cells were harvested from exponential phase cultures by trypsinisation, counted and plated in 96-well flat bottomed microliter plates (Greiner Labortechnik, Germany) (100 μL cell suspension containing 10^4 cells per well). Following plating and a 24-h recovery to allow cells to resume exponential growth, 100 μL of culture medium or culture medium containing the drug was added to the wells. Test compounds were dissolved in DMSO as a 0.1 mol L^{-1} stock solution (the final concentration of DMSO in culture medium was less than 0.1 %). Different concentrations of each test compound (5, 12, 25 and 50 μmol L^{-1}) were obtained by diluting with phosphate buffered saline (PBS), then added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37 °C and in an atmosphere of 5 % CO_2. Forty-eight hours after drug addition, cells were fixed with 50 % trichloroacetic acid at 4 °C (50 μL per well) for 1 h, washed with 1 % acetic acid and stained for 30 min with 50 μL of 0.4 % (*m*/*V*) SRB dissolved in 1 % acetic acid. Excess unbound dye was removed by four washes with 1 % acetic acid and the attached stain was recovered with Tris-EDTA buffer. Colour intensity was measured using an enzyme-linked immunosorbent assay ELISA reader. Optical density was read at 510 nm. The relation between the surviving fraction and drug concentration was plotted to get the survival curve for the breast cancer cell line MCF-7 after specified time (29). The molar concentration required for 50 % inhibition of cell viability (IC_{50}) was preliminarily calculated from the constructed dose-response curve using Prism software (Graphpad, Inc., USA) and the results are given in Table III.

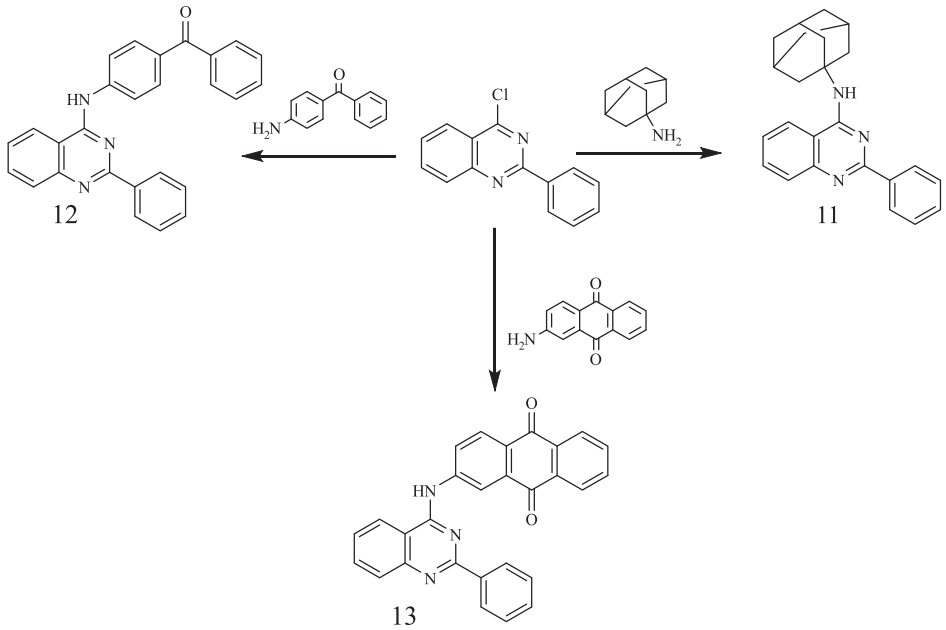
RESULTS AND DISCUSSION

Chemistry

The compounds were designed with the aim of exploring their anti-breast cancer activity. Thus, 4-aminoquinazoline derivatives **1-13** were synthesized starting from 4-chloro-2-phenylquinazoline as depicted in Schemes 1 and 2. Compounds **1-13** were obtained in good yield *via* reaction of 4-chloro-2-phenylquinazoline with different amines, as stated in Experimental. Interaction of 4-chloro-2-phenylquinazoline with different amines in dry dimethylformamide yielded the corresponding 4-aminoquinazoline derivatives **1-13**. All the synthesized compounds were established on the basis of elemental analyses, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. IR spectra of compounds **1-13** revealed the presence of bands characteristic of NH at 3423 to 3240 cm^{-1}, CH aromatic from 3098 to 3054 cm^{-1}, C=N from 1624 to 1560 cm^{-1}. ^{1}H NMR spectra of compounds **1-13** exhibited signals at 12.5–8.8 ppm attributed to NH group. ^{1}H NMR spectrum of compound **1** revealed a triplet at 1.2 ppm assigned to CH_3 group and at 2.7 ppm due to CH_2 group. Also, ^{1}H NMR spectrum of compound **2** showed a triplet at 1.3 ppm for CH_3, a quartet at 4.0 ppm for CH_2 group. ^{1}H NMR spectra of compounds **3** and **4** indicated the presence of 2 OCH_3 at 3.8 ppm for compound **3** and 3.7 and 3.8 ppm of 3 OCH_3 groups for compound **4**. In addition, ^{1}H NMR spectrum of compound **5** gave a singlet at 2.2 ppm assigned to CH_3 group. On the other hand, ^{1}H NMR spectrum of compound **11** revealed the presence of a multiple peer at 1.5–2.3 ppm for adamantane moiety. ^{13}C NMR spectrum of compound **12** showed a singlet at 195.1 ppm attributed to C=O group.



Scheme 1



Scheme 2

In vitro *anti-breast cancer activity and SAR*

Doxorubicin [CAS 23214-92-8], the reference drug used in this study an anthracycline antibiotic is commonly used in the treatment of a wide range of cancers such as acute leukemia's Hodgkin's disease and other lymphomas and cancers of the breast, adrenal cortex, endometrial, lung, ovary, and other sites. The relationship between the cell surviving fraction and drug concentration was plotted; the response parameters expressed was as IC_{50} value, which corresponds to the compound concentration that causes 50 % inhibition of cellular viability (Table III). From the results it was found that compounds **3**-**5**, **8**, **10**-**12** were the most potent compounds in the study with IC_{50} ranging from 22.75 to 46.40 μmol L^{-1} and exhibiting higher cytotoxic activity than with the reference drug doxorubicin as positive control (IC_{50} 47.90 μmol L^{-1}). Compounds **1**, **6**, and **9** were nearly as active as doxorubicin with IC_{50} values ranging from 48.31 to 48.91 μmol L^{-1}. A more close look into the structure activity relationship indicates that the 4-aminoquinazoline carrying 3,4-dimethoxyphenyl (**3**), 3,4,5-trimethoxyphenyl (**4**), 2-methyl-6-nitrophenyl (**5**), 2,4,6-trichlorophenyl (**8**), 2,4-dibromophenyl (**10**), adamantyl (**11**), and phenyl-methanone (**12**) moieties showed higher activities with IC_{50} than the reference drug (of 22.75, 31.47, 46.40, 26.13, 41.82, 35.83, 43.44 μmol L^{-1}, respectively. Addition of 3,4-dimethoxyaniline, 2,4,6-trichloroaniline, 3,4,5-trimethoxyaniline moieties was proven to be successful in the case of compounds, **3**, **8**, and **4**, which showed an increase in activity IC_{50} values of 22.75, 26.13, 31.47 μmol L^{-1}. Also, 4-aminoquinazoline having 3,4-dimethoxyphenyl moiety (**3**) with IC_{50} value of 22.75 μmol L^{-1} exhibited higher activity than **4** having 3,4,5-trimethoxyphenyl

Table II. Spectral characterization of the newly synthesized compounds

Compd.	IR (ν_{max}, cm^{-1})	^1H NMR (DMSO-d_6) ^{13}C NMR (DMSO-d_6) (δ, ppm)	Mass (*m*/*z*, %)
2	3414 (NH), 3065 (CH arom.), 2976, 2876 (CH aliph.), 1621, 1599 (2C=N)	1.3 [t, 3H, CH_3, J = 7.5 Hz], 4.0 [q, 2H, CH_2, J = 6.6 Hz], 7.0-8.5 [m, 13H, Ar-H], 9.7 [s, 1H, NH, D_2O exchangeable] 15.2, 63.8, 114.4(2), 114.6, 121.4(2), 124.5, 126.1(2), 128.3, 128.5, 128.8(2), 130.6, 132.5, 133.4, 138.9, 150.9, 155.4, 158.4, 159.6	341 [M^+] (43.8), 69 (100)
3	3411 (NH), 3090 (CH arom.), 2930, 2856 (CH aliph.), 1618, 1568 (2C=N)	3.8 [s, 6H, $2OCH_3$] 6.3-8.4 [m, 12H, Ar-H], 9.7 [s, 1H, NH, D_2O exchangeable]	357 [M^+] (47.4), 77 (100)
4	3413 (NH), 3089 (CH arom.), 2934, 2835 (CH aliph.), 1617, 1577 (2C=N).	3.7, 3.8 [2s, 9H, $3OCH_3$], 7.3-8.9 [m, 11H, Ar-H], 11.5 [s, 1H, NH, D_2O exchangeable] 56.5 (2), 60.7, 102.4 (2), 113.2, 121.1, 125.0 (2), 128.6 (2), 129.4, 129.6 (2), 132.2, 133.4, 133.8, 136.2, 141.0, 153.0 (2), 159.0, 163.4	387 [M^+] (11.5), 75 (100)
5	3371 (NH), 3055 (CH arom.), 2945, 2865 (CH aliph.), 1621, 1564 (2C=N).	2.2 [s, 3H, CH_3], 6.9-8.5 [m, 12H, Ar-H], 12.5 [s, 1H, NH, D_2O exchangeable] 13.8, 62.2, 102.6, 123.0, 127.1, 127.6, 128.9, 129.8, 130.1, 132.1, 133.3, 134.1, 135.2, 161.7, 190.2, 198.2	356 [M^+] (28.4), 68 (100)
6	3240 (NH), 3081 (CH arom.), 1594, 1569 (2 C=N), 815, 779 (3C-Cl).	6.8-8.8 [m, 11H, Ar-H], 10.1 [s, 1H, NH, D_2O exchangeable] 114.6 (2), 122.8, 124.1, 127.9 (2), 129.2 (2), 130.8 (3), 135.5 (3), 136.7 (3), 145.0, 161.1 (2)	401 [M^+] (39.6), 78(100)
7	3370 (NH), 3084 (CH arom.), 1611, 1560 (2 C=N), 867, 839 (3C-Cl).	6.6-8.0 [m, 11H, Ar-H], 11.0 [s, 1H, NH, D_2O exchangeable] 113.1 (2), 120.9, 122.8, 125.4 (2), 128.5 (2), 129.7 (3), 133.1 (3), 134.6 (3), 143.8, 160.6 (2)	401 [M^+] (34.9), 75 (100)
8	3423 (NH), 3063 (CH arom.), 1617, 1560, (2C=N), 854, 762 (3C-Cl)	7.3 -8.5 [m, 11H, Ar-H], 12.5 [s, 1H, NH, D_2O exchangeable] 114.8, 121.4, 124.8, 126.5 (2), 127.0, 127.9 (2), 128.3, 128.7 (2), 130.5 (2), 131.8, 132.8, 135.0, 138.8, 149.2, 152.7, 162.7	401 [M^+] (37.3), 74 (100)
10	3416 (NH), 3061 (CH arom.), 1602, 1560 (C=N).	7.4-8.4 [m, 12H, Ar-H], 12.5 [s, 1H, NH, D_20 exchangeable] 112.4, 117.2, 120.3, 121.3, 124.6, 125.8 (2), 126.8, 127.6, 128.6 (3), 130.6, 131.7, 132.2, 133.6, 148.7, 150.6, 161.9, 163.8	455 [M^+] (19.4), 162 (100)

11	3382 (NH), 3065 (CH arom.), 2904, 2844 (CH aliph.), 1618, 1562 (2C=N).	1.5-2.3 [m, 15, 6 CH2 + 3 CH adamantyl], 7.2-8.5 [m, 9H, Ar-H], 8.8 [s, 1H, NH, D_2O exchangeable] 13.8, 55.2, 55.3, 62.9, 110.7, 111.5, 115.8, 116.3, 119.0, 123.7 (2), 127.8, 128.4 (2), 140.0, 140.9, 144.2, 150.1, 152.8, 163.1	355 [M^+] 61.9), 69 (100)
12	3331 (NH), 3060 (CH arom.), 1672, (C=O), 1622, 1601 (2C=N).	6.6-8.6 [m, 18H, Ar-H]. 10.2 [s, 1H, NH, D_2O exchangeable] 113.2 (2), 114.6, 123.6, 124.7 (2), 126.5, 127.9 (3), 128.2, 128.9 (2), 129.0 (2), 130.8 (3), 131.6, 132.6, 133.2, 138.2, 144.4, 149.2, 151.1, 162.7, 195.1	401 [M^+] (9.4), 75(100)

Compounds **1**, **9** and **13** already reported (24–26).

Table III. In vitro *cytotoxic activity of the synthesized compounds against human breast cancer cell line MCF-7*

Compound	IC_{50} μg mL^{-1}	IC_{50} μmol L^{-1}
1	15.70	48.31
2	17.20	50.44
3	8.12	22.75
4	12.18	31.47
5	16.52	46.40
6	19.61	48.90
7	21.00	52.37
8	10.48	26.13
9	18.39	48.91
10	19.03	41.82
11	12.72	35.83
12	17.42	43.44
13	NA	NA
Doxorubicin	26.30	47.90

NA – No activity observed under the experimental conditions.

moiety with IC_{50} value of 31.47 μmol L^{-1}. Compound **8** with 2,4,6-trichlorophenyl moiety was found to be more active than compound **4** with 3,4,5-trimethoxyphenyl moiety. On the other hand, the chlorine atoms at position 2,4,6 in compound **8** make it more active than when in position 2,3,4 in compound **6** and 2,4,5 in compound **7**. The presence of dibromophenyl in compound **10** enhanced the anti-breast cancer activity more than the corre-

sponding monobromophenyl in compound **9**. Compounds **1**, **6** and **9** with IC_{50} values of 48.31, 48.90, 48.91 μmol L^{-1} are nearly as active as doxorubicin, while compounds **2** and **7** were less active than the positive control. Finally, compound **13** showed no activity. Comparison of the cytotoxicity of 4-aminoquinazoline derivatives against the breast cancer cell line MCF-7 (Table III) has shown that the activity follows the order **3** > **8** > **4** > **11** > **10** > **12** > **5** > doxorubicin > **1** > **6** > **9** > **2** > **7**. These results indicate the possible use of the newly synthesized 4-aminoquinazoline derivatives carrying 3,4-dimethoxyphenyl **3**, 2,4,6-trichlorophenyl- (**8**), 3,4,5-trimethoxyphenyl (**4**), adamantly (**11**), 2,4-dibromophenyl (**10**), phenyl-methanone (**12**) and 2-methyl-6-nitrophenyl (**5**) for the treatment of breast tumors.

CONCLUSIONS

In conclusion, we have synthesized several new 4-aminoquinazoline derivatives. The synthesized compounds showed anticancer activity against the human breast cancer cell line MCF-7 higher or comparable activity to that of doxorubicin. We may conclude from the structure-activity relationships that the introduction of 4-amino-3,4-dimethoxyphenyl is associated with enhanced anticancer activity, giving the most potent compound **3** in this study. Combination of 4-aminoquinazoline with 2,4,6-trichlorophenyl moiety in compound **8** increased the activity also. It was found that quinazolin-4-amine derivatives **3**, **4**, **5**, **8**, **10**, **11** and phenyl-methanone **12** were more potent than the reference drug. In addition, compounds **1**, **6**, and **9** were nearly as active as doxorubicin, while compounds **2** and **7** were less potent and compound **13** showed no activity.

Acknowledgments. – The authors would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project No. RGP-VPP- 302.

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