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Original research paper

Anti-breast cancer activity of some novel quinoline derivatives

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To discover new bioactive lead compounds for medicinal purposes, 2-cyano-3-(4-substituted)-*N*-(quinolin-3-yl) acrylamide derivatives **2–24**, chromenes **25, 26** and benzochromenes **27, 28** were synthesized. The structures of the newly synthesized compounds were confirmed by elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectroscopies. In addition, the structure of compound **1** was confirmed through X-ray crystallography. All the newly synthesized compounds were evaluated for their cytotoxic activity against the breast cancer cell line MCF7. The corresponding 2-cyano-3-(4-hydroxy-3-methoxyphenyl)-*N*-(quinolin-3-yl) acrylamide (**15**), 3-oxo-*N*-(quinolin-3-yl)-3*H*-benzol[*f*] chromene-2-carboxamide (**27**), 2-cyano-3-(4-fluorophenyl-*N*-(quinolin-3-yl) acrylamide (**7**), 2-cyano-5-(4-(dimethylamino) phenyl)-*N*-(quinolin-3-yl) penta-2,4-dienamide (**19**) exhibited higher activity compared to doxorubicin (with IC_{50} value of 47.9 μmol L^{-1}) as a reference drug, with IC_{50} values of 29.8, 39.0, 40.0, 40.4 μmol L^{-1}, resp. Also, quinoline acrylamides containing 2,3,4-trimethoxyphenyl **17**, 2-chlorophenyl **10**, benzo[*d*][1,3]dioxol **12**, 2-methoxynaphthalen **22**, 2,4-dichlorophenyl **18** and quinoline carrying a chromene-3-carboxamide moiety **25** were nearly as active as doxorubicin, while quinoline acrylamides incorporating unsubstituted phenyl **2**, *p*-tolyl **3**, 2,4-dienamide **8**, 3-nitrophenyl **13**, 4-nitrophenyl **14**, 3,4-dimethoxyphenyl **16** and chromene **26** exhibited a moderate activity. In addition, quinoline with acetamide **1**, 4-hydroxyphenyl **4**, 4-dimethylaminophenyl **9**, 4-chlorophenyl **11**, 3-bromophenyl **20**, 4-bromophenyl **21** and 3-thienyl moiety **24** showed less activity than doxorubicin. On the other hand, quinoline having 2-methoxyphenyl **5**, 4-methoxyphenyl **6**, 4-methoxynaphthalene **23** and chromene-2-carboxamide **28** showed no activity.

Keywords: quinolineacrylamides, chromenes, benzochromenes, anti-breast cancer activity

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Several quinoline derivatives, isolated from natural sources or prepared synthetically, are important for medicinal chemistry and biomedical use. The bark of *Cinchona* plant containing quinine has been utilized to treat palpitations (1), fevers and tertians for more than 200 years. Quinidine, a diastereo isomer of quinine, was regarded in the early 20th century as the most potent antiarrhythmic compound isolated from the *Cinchona* plant (2). The quinoline skeleton is often used to design many synthetic compounds with diverse pharmacological properties, such as anti-inflammatory (3), antimicrobial (4), cytotoxic (5), antibacterial (6) and antitumor activity (7). In addition, quinoline derivatives find use in the synthesis of fungicides, virucides, biocides, alkaloids and flavoring agents (8, 9). Quinolines also act as carbonic anhydrase inhibitors (10, 11). On the other hand, various fused systems of quinolines were studied for their intercalative DNA binding properties. A literature survey reveals that the antitumor activity is due to the intercalation between the base pairs of DNA and interferences with the normal functioning of enzyme topoisomerase II, which is involved in the breaking and releasing of DNA strands (12). The antitumor drugs that intercalate DNA are of growing interest in the field of anticancer derivatives. On the other hand, doxorubicin, the reference drug used in this study, is a drug used in cancer chemotherapy. It is an anthracycline antibiotic and works by intercalating DNA and inhibiting of macromolecular biosynthesis. This inhibits the progression of the enzyme topoisomerase II, which relaxes super coils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, preventing the DNA double helix from being resealed and thereby stopping the process of replication. It is commonly used in the treatment of a wide range of cancers such as acute leukemia Hodgkin's disease and other lymphomas and cancers of the breast, adrenal cortex, endometrial, lung, ovary, and other sites. As a part of our ongoing research program directed towards developing new approaches to a variety of heterocyclic ring systems for anticancer activity, especially those containing nitrogen compounds (13–21), we herein report the utility of strategic starting material 3-aminoquinoline for the synthesis of target compounds.

EXPERIMENTAL

Melting points (uncorrected) were determined in an open capillary in a Gallenkamp melting point apparatus (Sanyo Gallenkamp, 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 and the spots were detected by ultraviolet light. 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 NMR. 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 values were within ±0.4 % of the theoretical values. All reagents used were of AR grade. The starting material 3-aminoquinoline was purchased from Sigma (USA) and was directly used for the preparation of target compounds.

Syntheses

*2-Cyano-*N*-(quinolin-3-yl) acetamide* (**1**). – A mixture of 3-aminoquinoline (1.44 g, 0.01 mol) and ethyl cyanoacetate (1.13 g, 0.01 mol) was fused at 220 °C for 2 h. The reaction

mixture was cooled and the obtained product was crystallized from ethanol to give **1** (Table I).

General procedure for 2-cyano-3-phenyl-N-*(quinolin-3-yl) acrylamide* (**2**), *2-cyano*-N-*(quinolin-3-yl)-3*-p-*tolylacrylamide* (**3**), *cyano-3-(4-hydroxyphenyl)*-N-*(quinolin-3-yl) acrylamide* (**4**), *2-cyano-3-(2-methoxyphenyl)*-N-*(quinolin-3-yl) acrylamide* (**5**), *2-cyano-3-(4-methoxyphenyl)*-N-*(quinolin-3-yl) acrylamide* (**6**), *2-cyano-3-(4-fluorophenyl*-N-*(quinolin-3-yl) acrylamide* (**7**), *2-cyano-5-phenyl-* N-*(quinolin-3-yl) penta-2,4-dienamide* (**8**), *2-cyano-3-(4-(dimethylamino) phenyl)*-N-(*quinolin-3-yl) acrylamide* (**9**), *3-(2-chlorophenyl)-2-cyano*-N-*(quinolin-3-yl) acrylamide* (**10**), *3-(4-chlorophenyl)-2-cyano*-N-*(quinolin-3-yl) acrylamide* (**11**), *3-(benzo*[d] *[1,3] dioxol-5-yl)-2-cyano*-N-(*quinolin-3-yl) acrylamide* (**12**), *2-cyano-3-(3-nitrophenyl)*-N-(*quinolin-3-yl) acrylamide* (**13**), *2-cyano-3-(4-nitrophenyl)*-N-(*quinolin-3-yl) acrylamide* (**14**), *2-cyano-3-(4-hydroxy-3-methoxyphenyl*)-N-*(quinolin-3-yl) acrylamide* (**15**), *2-cyano-3-(3,4-dimethoxyphenyl*)-N-(*quinolin-3-yl) acrylamide* (**16**), *2-cyano*-N-*(quinolin-3-yl)-3-(2,3,4-trimethoxyphenyl) acrylamide* (**17**), *2-cyano-3-(2,4-dichorophenyl)*-N-*(quinolin-3-yl) acrylamide* (**18**), *2-cyano-5-(4-(dimethylamino) phenyl)*-N-(*quinolin-3-yl) penta-2,4-dienamide* (**19**), *3-(3-bromophenyl)-2-cyano*-N-(*quinolin-3-yl) acrylamide* (**20**), *3-(4-bromophenyl)-2-cyano*-N-*(quinolin-3-yl) acrylamide* (**21**), *2-cyano-3-(2-methoxynaphthalen-1-yl*)-N-(*quinolin-3-yl) acrylamide* (**22**), *2-cyano-3-(4-methoxynapthalen-1-yl*)-N-(*quinolin-3-yl) acrylamide* (**23**), *2-cyano*-N-*(quinolin-3-yl)-3-(thiophen-2-yl) acrylamide* (**24**) – A mixture of **1** (2.11 g, 0.01 mol) and appropriate aldehyde (0.01 mol) in absolute ethanol (20 mL) containing 3 drops of piperidine was refluxed for 8 h. The reaction mixture was cooled and poured into ice/water. The solid obtained was recrystallized from dioxane to give quinoline derivatives **2–24**, respectively (Table I).

General procedure for 2-oxo-N-*(quinolin-3-yl)-2*H-*chromene-3-carboxamide* (**25**) and *3-oxo*-N-*(quinolin-3-yl)-3H-benzol[f]chromene-2-carboxamide* (**27**) – To a solution of 1 (2.11 g, 0.01 mol) in acetic anhydride (20 mL), salicylaldehyde (1.22 g, 0.01 mol) or 2-hydroxy-1-naphthaldehyde (1.72 g, 0.01 mol) and fused sodium acetate (0.8 g, 0.01 mol) were added. The reaction mixture was refluxed for 2 h, cooled and the solid was filtered and crystallized from ethanol to give **25** and **27**, respectively (Table I).

General procedure for 2-imino-N-*(quinolin-3-yl)-2*H-*chromene-3-carboxamide* (**26**) and *3-imino*-N-*(quinolin-3-yl)-3*H-*benzol[f]chromene-2-carboxamide* (**28**) – A mixture of compound **1** (2.11 g, 0.01 mol), salicylaldehyde (1.22 g, 0.01 mol) or 2-hydroxy-1-naphthyladehyde (1.72 g, 0.01 mol) and anhydrous ammonium acetate (1.15 g, 0.015 mol) was refluxed in absolute ethanol (30 mL) for 2 h. The obtained solid was recrystallized from ethanol to give **27** and **29**, respectively (Table I).

In vitro *anti-breast cancer activity*

In vitro cytotoxic activity of the synthesized compounds was measured using the sulforhodamine B stain (SRB) assay after the method of Skehan (22). The human breast cancer cell line MCF7 was obtained from the National Cancer Institute (Cairo, Egypt). The cell lines were grown in RPMI 1640 medium containing 10 % fetal bovine serum (Lonza, Switzerland), 100 IU mL^{-1} penicillin, 100 mg mL^{-1} streptomycin and 2 mmol L^{-1} L-glutamine (Sigma, USA). Cells were plated in 96-multiwell plates (10^4 cells/well). After cell inoculation, the micro titer plates were incubated at 37 °C in 5 % CO_2, 95 % air and 100 % relative humidity for 24 h prior to addition of experimental drugs to allow attachment of cells to the plate wall. After 24 h, cell line was fixed *in situ* with TCA (trichloroacetic acid).

Table I. Physical and analytical data of the newly synthesized compounds

Compd. No.	Formula (M_r)	M. p. (°C)	Yield (%)	Analysis (calcd/found) (%)		
				C	H	N
1	$C_{12}H_9N_3O$ (211.22)	220.4	92	68.24/68.51	4.29/4.08	19.89/19.59
2	$C_{19}H_{13}N_3O$ (299.33)	350.7	88	76.24/76.48	4.38/4.14	14.04/14.31
3	$C_{20}H_{15}N_3O$ (313.35)	309.6	78	76.66/76.34	4. 82/4.46	13.41/13.09
4	$C_{19}H_{13}N_3O_2$ (315.33)	302.1	85	72.37/72.69	4.16/4.39	13.33/13.12
5	$C_{20}H_{15}N_3O_2$ (329.35)	282.2	69	72.94/72.66	4.59/4.29	12.76/12.44
6	$C_{20}H_{15}N_3O_2$ (329.35)	245.9	84	72.94/72.61	4.59/4.29	12.76/12.99
7	$C_{19}H_{12}FN_3O$ (317.32)	296.5	86	71.92/72.23	3.81/3.49	13.24/13.56
8	$C_{21}H_{15}N_3O$ (325.36)	236.4	69	77.52/77.24	4.65/4.41	12.91/12.66
9	$C_{21}H_{18}N_4O$ (342.39)	287.9	77	73.67/73.36	5.30/5.55	16.36/16.09
10	$C_{19}H_{12}ClN_3O$ (333.77)	240.2	88	68.37/68.11	3.62/3.33	12.59/12.91
11	$C_{19}H_{12}ClN_3O$ (333.77)	313.7	89	68.37/68.03	3.62/3.31	12.59/12.88
12	$C_{20}H_{13}N_3O_3$ (343.34)	276.1	79	69.96/69.68	3.82/3.57	12.24/12.50
13	$C_{19}H_{12}N_4O_3$ (344.32)	238.0	77	66.28/66.51	3.51/3.22	16.27/16.01
14	$C_{19}H_{12}N_4O_3$ (344.32)	198.7	72	66.28/66.49	3.51/3.20	16.27/16.00
15	$C_{20}H_{15}N_3O_3$ (345.35)	304.5	66	69.56/69.77	4.38/4.12	12.17/12.44
16	$C_{21}H_{17}N_3O_3$ (359.38)	289.1	69	70.18/70.55	4.77/4.33	11.69/11.41
17	$C_{22}H_{19}N_3O_4$ (389.40)	180.7	68	67.86/67.50	4.92/4.68	10.79/10.45
18	$C_{19}H_{11}Cl_2N_3O$ (368.22)	312.1	90	61.98/61.68	3.01/3.29	11.41/11.72
19	$C_{23}H_{20}N_4O$ (368.43)	298.5	66	74.98/74.68	5.47/5.12	15.21/15.51
20	$C_{19}H_{12}BrN_3O$ (378.22)	312.6	77	60.34/60.66	3.20/3.00	11.11/11.39
21	$C_{19}H_{12}BrN_3O$ (378.22)	332.4	78	60.34/60.01	3.20/2.88	11.11/10.90
22	$C_{24}H_{17}N_3O_2$ (379.41)	117.4	81	75.97/75.69	4.52/4.21	11.08/11.31
23	$C_{24}H_{17}N_3O_2$ (379.41)	255.5	75	75.97/75.69	4.52/4.29	11.08/11.31
24	$C_{17}H_{11}N_3OS$ (305.35)	241.9	89	66.87/66.51	3.63/3.46	13.76/13.50
25	$C_{19}H_{12}N_2O_3$ (316.31)	>350	72	72.15/72.47	3.82/3.99	8.86/8.55
26	$C_{19}H_{13}N_3O_2$ (315.33)	195.6	69	72.37/72.62	4.16/4.44	13.33/13.00
27	$C_{23}H_{14}N_2O_3$ (366.37)	160.7	68	75.40/75.71	3.85/3.57	7.65/7.98
28	$C_{23}H_{15}N_3O_2$ (365.38)	270.2	59	75.60/75.28	4.14/4.39	11.50/11.81

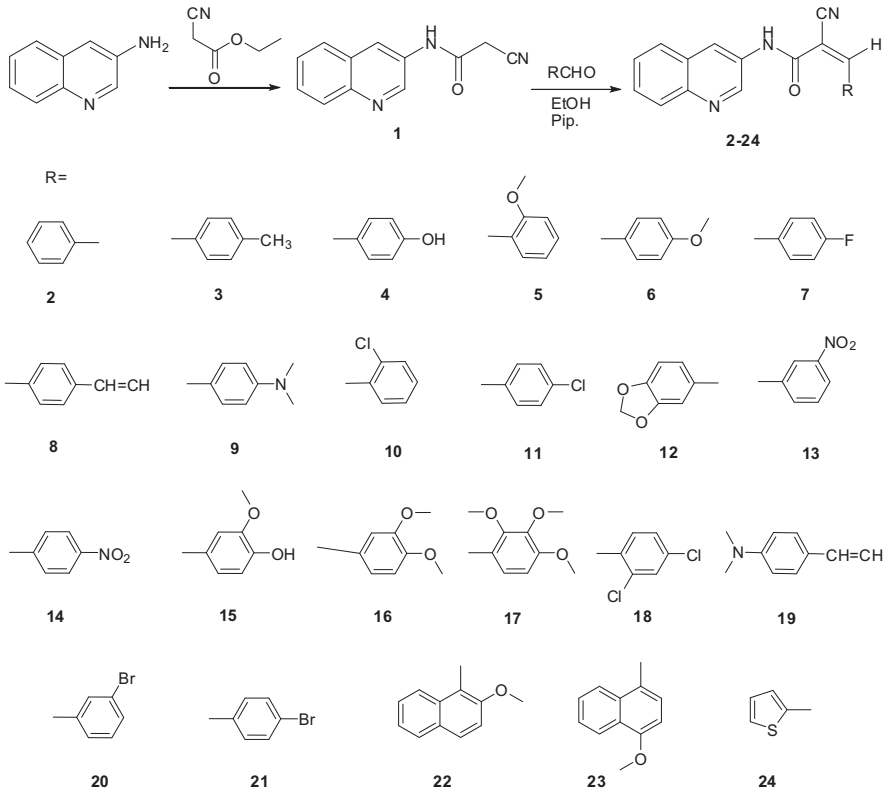
Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume and maintained in RPMI 1640 medium. Different concentrations of each test compound (5, 12.5, 25 and 50 μmol L^{-1}) were added to the cell monolayer. Triplicate wells were prepared for each individual dose. Monolayer cells were incubated with the compound(s) for 48 h at 37 °C and in an atmosphere of 5 % CO_2. After 48 h, cells were fixed *in situ* by gentle addition of 50 μL of cold 30 % (*m*/*V*) TCA (final concentration, 10 % TCA) and incubated for 60 min at 4 °C. The supernatant was discarded; the plates were washed five times

with tap water and air dried. Sulforhodamine B solution (50 μL) at 0.4 % (*m*/*V*) in 1 % acetic acid was added to each of the wells and plates were incubated for 20 min at room temperature. After staining, unbound dye was removed by four washes with 1 % acetic acid and the attached stain was recovered with Tris-EDTA buffer. Color intensity was measured using an ELISA reader (BMG Labtech, Germany). The relation between the surviving fraction and drug concentration was plotted to get the survival curve for the breast cancer cell line (MCF7) after specified time (22). The molar concentration required for 50 % inhibition of cell viability (IC_{50}) was calculated from the constructed dose-response curve using Prism software (Graphpad, Inc., USA) and compared with the reference drug doxorubicin. Results are given in Table III.

RESULTS AND DISCUSSION

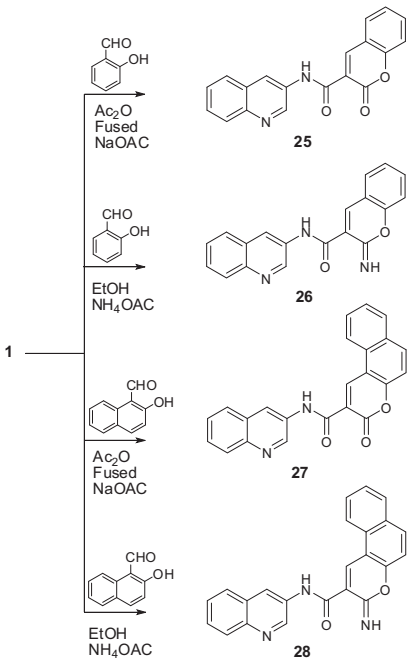
Chemistry

The designed target compounds are depicted in Schemes 1 and 2. In the present investigation, the strategic starting material, 2-cyano-*N*-(quinolin-3-yl) acetamide (**1**), was



Scheme 1

prepared in good yield *via* reaction of 3-aminoquinoline with ethyl cyanoacetate under fusion condition. The structure of compound **1** was proven on the basis of elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral data. In addition, the structure of compound **1** was confirmed by X-ray crystallography (23). IR spectrum showed characteristic bands at 3260 cm^{-1} (NH), 2201 cm^{-1} (C≡N), 1700 cm^{-1} (C=O), 1617 cm^{-1} (C=N). ^{1}H NMR spectrum of **1** reveled signals at 4.0 ppm assigned to the CH_2 group, 7.5 and 8.6 ppm due to 2CH quinoline, 10.8 ppm corresponding to the NH group. ^{13}C NMR spectrum of 1 exhibited a singlet at 161.9 ppm for (C=O) (Table II). Also, a novel series of potentially active quinoline incorporating cyanoacrylamide moieties (tyrphostin analogs) **2–24** were synthesized through reaction of compound **1** with various aldehydes in absolute ethanol containing a catalytic amount of piperidine (Scheme 1). The structures of compounds **2–24** were established on the basis of elemental analyses and spectral data. IR spectra revealed the presence of characteristic bands at 3426–3189 cm^{-1} (NH), 2222– 2170 cm^{-1} (C≡N), 1700–1657 cm^{-1} (C=O). ^{1}H NMR spectra of compounds **2–24** revealed the presence of a singlet at 9.0–8.0 ppm assigned to CH group and 11.1–10.0 ppm for NH group. Furthermore, Perkin reaction (24) was carried out by reaction of salicylaldehyde and/or 2-hydroxy-1-naphthaldehyde in acetic anhydride in the presence of sodium acetate to give the corresponding chromene-2-one **25** and benzochromene-2-one **27**, while conducting the same reaction in ethanol containing ammonium acetate furnished 2-iminochromene **26** and 2-iminobenzochromene **28** (Scheme 2). The structure of compounds **25–28** was supported of elemental analyses and spectral data. IR spectrum of **25** revealed bands at 3217 cm^{-1} (NH), 1711, 1668 cm^{-1} (2C=O). ^{1}H NMR spectrum of **25** showed a singlet at 8.8



Scheme 2

ppm, assigned to CH chromene and 10.4 ppm due to NH group. ^{13}C NMR spectrum showed signals at 160.8, 164.9 ppm assignable to 2C=O. IR spectrum of **26** revealed bands at 3261, 3216 cm^{-1} (NH), 1700 cm^{-1} (C=O). ^{1}H NMR spectrum revealed singlet at 12.6 ppm, assigned to the imino group. IR spectrum of **27** exhibited characteristic bands at 3323 cm^{-1} (NH), 1771, 1712 cm^{-1} (2C=O). ^{1}H NMR spectrum showed a singlet at 8.9 ppm, attributed to CH benzochromene. IR spectrum of **28** revealed bands at 3158, 3112 cm^{-1} (NH), 1685 cm^{-1} ((C=O), and ^{1}H NMR spectrum showed a singlet at 12.6 ppm corresponding to the imino group (Table II).

Table II. Spectral characterization of the newly synthesized compounds

Compd.	IR (ν_{max}, cm^{-1})	^{1}H NMR (DMSO-d_6) ^{13}C NMR (DMSO-d_6) (δ, ppm)	Mass (*m*/z, %)
1	3260 (NH), 3091 (CH arom.), 2957, 2927 (CH aliph.), 2201 (C≡N), 1700 (C=O), 1617 (C=N)	4.0 [s, 2H, CH_2], 7.5, 8.6 [2s, 2H, 2CH quinoline], 7.6-7.9 [m, 4H, Ar-H], 10.8 [s, 1H, NH, D_2O-exchangeable] 24.7, 115.6, 122.6, 123.8, 125.4, 126.3, 127.7, 128.5, 132.0, 144.1, 144.4, 161.9	211 [M$^+$] (9.4), 68 (100)
2	3216 (NH), 3100 (CH arom.), 2976, 2889 (CH aliph.), 2212 (C≡N), 1668 (C=O), 1586 (C=N)	7.0, 8.3 [2s, 2H, 2CH quinoline], 7.1- 8.1 [m, 9H, Ar-H], 8.9 [s, 1H, CH], 10.1 [s, 1H, NH, D_2O-exchangeable] 109.1, 113.6, 125.4, 125.8, 126.0, 126.8 (2), 127.2, 127.6, 127.9, 128.4 (2), 128.6, 135.5, 140.0 (2), 144.0, 148.0, 163.9	299 [M$^+$] (23.6), 78 (100)
3	3245 (NH), 3091 (CH arom.), 2926, 2861 (CH aliph.), 2200 (C≡N), 1659 (C=O), 1610 (C=N)	2.4 [s, 3H, CH_3], 7.0, 8.3 [2s, 2H, 2CH quinoline], 7.3- 8.0 [m, 8H, Ar-H], 8.7 [s, 1H, CH], 10.8 [s, 1H, NH, D_2O-exchangeable] 21.2, 105.4, 116.2, 124.2, 125.1, 125.8, 126.8 (2), 127.1, 127.5, 128.4 (2), 129.9, 132.0, 135.6, 137.0, 143.4, 144.0, 151.4, 163.9	313 [M$^+$] (17.9), 77 (100)
4	3320 (OH), 3189 (NH), 3065 (CH arom.), 2972, 2836 (CH aliph.), 2204 (C≡N), 1687 (C=O), 1607 (C=N)	6.9, 8.7 [2s, 2H, 2CH quinoline], 7.0- 8.0 [m, 8H, Ar-H], 8.2 [s, 1H, CH], 9.0 (s, 1H, OH, D_2O-exchangeable], 10.6 [s, 1H, NH, D_2O-exchangeable] 101.4, 116.3 (2), 116.8, 122.7, 124.0, 127.1, 127.5, 127.8 (2), 128.3, 128.5, 132.2, 133.1, 144.5, 145.4, 151.3, 161.7, 162.1	315 [M$^+$] (10.1), 78 (100)
5	3409 (NH), 3100 (CH arom.), 2966, 2878 (CH aliph.), 2217 (C≡N), 1682 (C=O), 1599 (C=N)	3.8 [s, 3H, OCH_3], 7.0, 8.6 [2s, 2H, 2CH quinoline], 7.2-8.0 [m, 8H, Ar-H], 8.4 [s, 1H, CH], 10.3 [s, 1H, NH, D_2O-exchangeable] 55.0, 103.8, 113.2, 113.9, 114.8, 120.6, 122.4, 123.6, 124.8, 126.6, 127.0, 128.1, 128.5, 128.8, 134.0, 136.7, 145.9, 154.1, 158.0, 165.7	329 [M$^+$] (29.4), 107 (100)
6	3324 (NH), 3055 (CH arom.), 2927, 2861 (CH aliph.), 2211 (C≡N), 1677 (C=O), 1605 (C=N)	3.8 [s, 3H, OCH_3], 7.1, 8.7 [2s, 2H, 2CH quinoline], 7.2-8.3 [m, 8H, Ar-H], 9.0 [s, 1H, CH], 10.7 [s, 1H, NH, D_2O-exchangeable]. 55.6, 102.9, 114.9 (2), 116.6, 124.1, 124.2, 127.1, 127.5, 127.8 (2), 128.3, 128.5, 132.1, 132.7, 144.5, 145.4, 151.0, 161.5, 162.9	329 [M$^+$] (31.5), 109(100)

Table II. continued

7	3294 (NH), 3045 (CH arom.), 2916, 2836 (CH aliph.), 2196 (C≡N), 1691 (C=O), 1605 (C=N)	7.0, 8.7 [2s, 2H, 2CH quinoline], 7.1- 8.0 [m, 8H, Ar-H], 8.2 [s, 1H, CH], 10.5 [s, 1H, NH, D_2O-exchangeable] 108.4, 114.6 (2), 116.7, 123.9, 124.2, 125.3, 126.8, 127.0 (2), 127.6, 128.5, 129.0, 135.2, 144.1, 145.0, 153.3, 162.3, 163.7	317 [M^+] (24.9), 93 (100)
8	3401 (NH), 3046 (CH arom.), 2928, 2861 (CH aliph.), 2192 (C≡N), 1689 (C=O), 1599 (C=N)	6.7, 8.0 [2d, 2H, PhCH = CH-CH, *J*= 7.6 Hz], 6.8- 6.9 [m, 1H, Ph-CH=CH-CH], 7.2, 8.6 [2s, 2H, 2CH quinoline], 7.3- 7.9 [m, 9H, Ar-H], 10.2 [s, 1H, NH, D_2O-exchangeable] 92.4, 113.2, 123.7, 124.5, 124.8, 125.6, 127.0 (2), 127.4, 127.8, 128.6, 128.9 (2), 130.2, 132.4, 133.8, 136.7, 136.9, 138.3, 144.2, 162.7	325 [M^+] (51.3), 98 (100)
9	3408 (NH), 3078 (CH arom.), 2971, 2836 (CH aliph.), 2219 (C≡N), 1700 (C=O), 1586 (C=N)	3.1 [s, 6H, $2CH_3$], 6.8, 8.6 [2s, 2H, 2CH quinoline], 7.0- 8.1 [m, 8H, Ar-H], 8.8 [s, 1H, CH], 10.4 [s, 1H, NH, D_2O-exchangeable] 40.1 (2), 108.3, 111.7 (2), 114.3, 123.8, 124.3, 124.8, 125.7, 127.0 (2), 127.6, 128.5 (2), 133.0, 140.1, 142.4, 145.5, 156.4, 162.7	342 [M^+] (12.6), 78(100)
10	3296 (NH), 3081 (CH arom.), 2937, 2861 (CH aliph.), 2170 (C≡N), 1699 (C=O), 1598 (C=N), 749 (C-Cl)	7.0, 8.7 [2s, 2H, 2CH quinoline], 8.6 [s, 1H, CH], 7.2- 8.1 [m, 8H, Ar-H], 10.3 [s, 1H, NH, D_2O-exchangeable] 107.8, 114.4, 123.2, 124.6, 124.9, 125.4, 127.1, 127.8, 128.5, 129.9, 129.7, 129.9, 130.7, 131.9, 135.7, 144.9 (2), 155.6, 160.1	334 [M^+] (11.2), 109 (100)
11	3217 (NH), 3056 (CH arom.), 2919, 2836 (CH aliph.), 2190 (C≡N), 1676 (C=O), 1608 (C=N), 745 (C-Cl)	6.9, 8.7 [2s, 2H, 2CH quinoline], 7.1- 8.1 [m, 8H, Ar-H], 8.4 [s, 1H, CH], 10.9 [s, 1H, NH, D_2O-exchangeable] 105.4, 113.6, 122.1, 123.6, 124.8, 127.1, 128.1 (2), 128.4, 128.6 (2), 129.1, 135.0 (2), 136.8, 140.6, 144.9, 151.4, 164.7	334 [M^+] (1.9), 93 (100)
12	3264 (NH), 3100 (CH arom.), 2956, 2861 (CH aliph.), 2186 (C≡N), 1675 (C=O), 1581 (C=N)	6.2 [s, 2H, O-CH_2-O], 7.1, 8.7 [2s, 2H, 2CH quinoline], 7.5- 8.0 [m, 7H, Ar-H], 8.6 [s, 1H, CH], 10.7 [s, 1H, NH, D_2O-exchangeable] 102.4, 107.9, 109.1, 116.5 (2), 121.3, 124.1, 125.8, 127.1, 127.5, 127.8, 128.3, 128.5, 132.1, 138.6, 144.5, 145.4, 148.1, 151.0, 161.4	343 [M^+] (6.4), 119(100)
13	3286 (NH), 3077 (CH arom.), 2961, 2881 (CH aliph.), 2210 (C≡N), 1678 (C=O), 1612 (C=N), 1527, 1367 (NO_2)	7.2, 8.7 [2s, 2H, 2CH quinoline], 7.3- 8.1 [m, 8H, Ar-H], 8.3 [s, 1H, CH], 10.1 [s, 1H, NH, D_2O-exchangeable] 102.8, 113.6, 119.7, 122.4, 125.1, 126.9 (2), 127.6, 128.4 (2), 129.8, 133.1, 134.6 (2), 141.3, 144.7, 147.2, 152.8, 161.7	334 [M^+] (10.8), 123 (100)
14	3380 (NH), 3065 (CH arom.), 2991, 2884 (CH aliph.), 2219 (C≡N), 1696 (C=O), 1601 (C=N), 1520, 1345 (NO_2)	7.0, 8.6 [2s, 2H, 2CH quinoline], 7.1- 8.0 [m, 8H, Ar-H], 8.2 [s, 1H, CH], 10.9 [s, 1H, NH, D_2O-exchangeable] 104.3, 116.6, 122.8 (2), 123.7, 126.9 (2), 127.8 (2), 128.0, 128.3, 128.8, 136.8, 142.1 (2), 146.4, 147.2, 156.7, 166.3. Anal. Calcd for $C_{19}H_{12}N_4O_3$ (344): C, 66.28; H, 3.51; N, 16.27	344 [M^+] (18.2), 103 (100)
15	3336 (OH), 3289 (NH), 3044 (CH arom.), 2972, 2856 (CH aliph.), 2220 (C≡N), 1671 (C=O), 1586 (C=N)	3.8 [s, 3H, OCH_3], 7.0, 8.8 [2s, 2H, 2CH quinoline], 7.5- 7.9 [m, 7H, Ar-H], 8.4 [s, 1H, CH], 9.4 [s, 1H, OH, D_2O-exchangeable], 11.1 [s, 1H, NH, D_2O-exchangeable] 55.5, 100.9, 113.3, 116.0, 116.8, 123.0, 124.2, 126.7, 128.0, 128.3, 128.6, 129.1, 130.8, 132.8 (2), 142.2, 147.8, 152.1, 152.2, 163.8	345 [M^+] (7.6), 118 (100)

Table II. continued

16	3392 (NH), 3062 (CH arom.), 2931, 2846 (CH aliph.), 2210 (C≡N), 1683 (C=O), 1589 (C=N)	3.7, 3.8 [2s, 6H, $2OCH_3$], 7.0, 8.6 [2s, 2H, 2CH quinoline], 7.2- 7.9 [m, 7H, Ar-H], 8.4 [s, 1H, CH], 10.9 [s, 1H, NH, D_2O-exchangeable] 56.3 (2), 109.3, 111.7, 112.2 (2), 119.2, 122.4, 123.5, 127.1, 127.5, 128.1, 128.7, 129.4, 134.9, 137.3, 144.6, 148.9, 149.0, 151.5, 165.4	359 [M^+] (68.3), 78 (100)
17	3314 (NH), 3061 (CH arom.), 2972, 2855 (CH aliph.), 2215 (C≡N), 1673 (C=O), 1599 (C=N)	3.68, 3.72 [2s, 9H, $3OCH_3$], 7.1, 8.6 [2s, 2H, 2CH quinoline], 7.2- 8.0 [m, 6H, Ar-H], 8.5 [s, 1H, CH], 10.2 [s, 1H, NH, D_2O-exchangeable] 55.6, 60.2, 60.8, 105.3, 106.4, 107.6, 114.8, 119.1, 122.6, 124.4, 125.2, 127.1, 127.8, 128.4, 135.1, 138.5, 138.8, 142.6, 148.7, 151.6, 152.0, 162.6	389 [M^+] (36.9), 164 (100)
18	3426 (NH), 3100 (CH arom.), 2970, 2850 (CH aliph.), 1688 (C=O), 1629 (C=N), 747 (C-Cl)	7.2, 8.7 [2s, 2H, 2CH quinoline], 7.3- 8.1 [m, 7H, Ar-H], 8.5 [s, 1H, CH], 10.5 [s, 1H, NH, D_2O-exchangeable] 105.1, 112.6, 122.8, 125.1, 125.8, 125.9, 126.3, 126.9, 127.4, 128.2, 129.7, 131.6, 133.6 (2), 141.2 (2), 142.1, 152.7, 160.2	368 [M^+] (111.6), 146 (100)
19	3337 (NH), 3061 (CH arom.), 2971, 2836 (CH aliph.), 2201 (C≡N), 1676 (C=O), 1592 (C=N)	3.1 [s, 6H, $2CH_3$], 6.6, 8.0 [2d, 2H, = CH-CH = CHph; *J* = 7.3 Hz], 6.8 [m, 1H, CH-CH = CH-Ph], 7.0, 8.5 [2s, 2H, 2CH quinoline], 7.2- 7.9 [m, 8H, Ar-H], 10.8 [s, 1H, NH, D_2O-exchangeable] 42.3 (2), 94.6, 112.8 (2), 114.6, 123.1, 123.8, 124.6, 124.9, 125.7, 126.4 (2), 127.0, 127.6, 128.3, 129.8, 130.9, 135.4, 138.2, 141.6, 147.5, 162.9	368 [M^+] (16.4), 141 (100)
20	3213 (NH), 3067 (CH arom.), 2971, 2839 (CH aliph.), 2217 (C≡N), 1657 (C=O), 1607 (C=N)	6.9, 8.7 [2s, 2H, 2CH quinoline], 7.0- 8.1 [m, 8H, Ar-H], 8.3 [s, 1H, CH], 10.0 [s, 1H, NH, D_2O-exchangeable] 103.7, 114.2, 121.2, 124.4, 124.7, 125.3, 126.9, 127.3, 127.8, 128.1, 129.0, 129.4, 131.0, 135.1 (2), 143.0, 144.1, 148.2, 163.5	378 [M^+] (3.6), 155 (100)
21	3361 (NH), 3056 (CH arom.), 2956, 2886 (CH aliph.), 2222 (C≡N), 1670 (C=O), 1599 (C=N)	7.3, 8.7 [2s, 2H, 2CH quinoline], 7.4- 8.1 [m, 8H, Ar-H], 8.5 [s, 1H, CH], 10.9 [s, 1H, NH, D_2O-exchangeable] 108.4, 118.1, 121.1, 122.3, 125.2, 126.6, 127.1, 127.6, 128.0 (2), 128.9, 130.9 (2), 132.5, 135.2, 139.7, 144.1, 157.3, 163.7	378 [M^+] (1.8), 81(100)
22	3249 (NH), 3060 (CH arom.), 2935, 2862 (CH aliph.), 2193 (C≡N), 1669 (C=O), 1612 (C=N)	3.9 [s, 3H, OCH_3], 7.4, 8.7 [2s, 2H, 2CH quinoline], 7.5- 8.1 [m, 10H, Ar-H], 8.3 [s, 1H, CH], 10.7 [s, 1H, NH, D_2O-exchangeable] 56.8, 104.3, 113.4, 114.2, 115.4, 123.3, 123.6, 123.8, 124.3, 124.5, 126.7, 127.1, 127.6, 127.8, 128.1, 128.4, 129.7, 130.6, 137.9, 144.6, 145.5, 147.4, 155.4, 164.0	379 [M^+] (19.7), 157 (100)
23	3376 (NH), 3100 (CH arom.), 2938, 2866 (CH aliph.), 2211 (C≡N), 1691 (C=O), 1601 (C=N)	4.1 [s, 3H, OCH_3], 7.2, 8.7 [2s, 2H, 2CH quinoline], 7.6- 8.0 [m, 10H, Ar-H], 8.3 [s, 1H, CH], 10.9 [s, 1H, NH, D_2O-exchangeable] 56.2, 104.5, 107.2, 116.5, 121.0, 122.3, 123.6, 124.1, 124.7 (2), 126.3, 127.1, 127.6, 127.8, 128.2, 128.3, 128.5, 129.4, 132.1, 144.6, 145.5, 148.5, 158.5, 161.4	379 [M^+] (4.9), 149 (100)

Table II. continued

24	3302 (NH), 3076 (CH arom.), 2970, 2846 (CH aliph.), 2210 (C≡N), 1678 (C=O), 1608 (C=N)	7.3, 8.7 [2s, 2H, 2CH quinoline], 7.4- 8.1 [m, 7H, Ar-H], 8.6 [s, 1H, CH], 10.7 [s, 1H, NH, D_2O-exchangeable] 116.2 (2), 124.2 (2), 127.1, 127.5, 127.8, 128.3, 128.5, 128.7, 132.1, 135.7, 138.2, 144.4, 144.5, 160.9 (2)	305 [M^+] (1.7), 83 (100)
25	3217 (NH), 3100 (CH arom.), 1711, 1668 (2C=O), 1618 (C=N)	7.0, 8.6 [2s, 2H, 2CH quinoline], 7.2- 8.1 [m, 8H, Ar-H], 8.8 [s, 1H, CH chromene], 10.4 [s, 1H, NH, D_2O-exchangeable] 113.6, 119.9, 121.2, 122.6, 124.3, 124.8, 125.7, 125.9, 126.4, 127.8 (2), 128.6, 135.3, 137.6, 141.2, 142.5, 151.6, 160.8, 164.9	316 [M^+] (34.8), 142 (100)
26	3261, 3216 (NH), 3054 (CH arom.), 1700 (C=O), 1606 (C=N)	7.0, 8.6 [2s, 2H, 2CH quinoline], 7.2- 8.0 [m, 8H, Ar-H], 9.1 [s, 1H, CH chromene], 10.2 [s, 1H, NHCO, D_2O-exchangeable], 12.6 [s, 1H, NH imino, D_2O-exchangeable] 116.7, 117.1, 119.0, 119.4, 124.9, 127.2, 127.9, 128.2, 128.7, 129.1, 129.2, 132.4, 133.7, 136.3, 141.7, 146.6, 160.1, 165.2, 191.7	315 [M^+] (13.0), 169 (100)
27	3323 (NH), 3100 (CH arom.), 1771, 1712 (2C=O), 1598 (C=N)	7.2, 8.3 [2s, 2H, 2CH quinoline], 7.3- 8.1 [m, 10H, Ar-H], 8.9 [s, 1H, CH benzochromene], 10.4 [s, 1H, NH, D_2O-exchangeable] 115.5, 116.4, 116.8, 120.8, 120.9, 122.1, 124.2, 125.1, 125.9, 126.5, 127.3, 127.5, 128.6, 129.5, 130.2, 131.6, 136.6 (2), 146.9 (2), 153.1, 163.4, 168.4	366 [M^+] (75.4), 194 (100)
28	3158, 3112 (NH), 3100 (CH arom.), 1685 (C=O), 1628 (C=N)	7.1, 8.6 [2s, 2H, 2CH quinoline], 7.3- 8.1 [m, 10H, Ar-H], 8.7 [s, 1H, CH benzochromene], 10.6 [s, 1H, NH, D_2O-exchangeable], 12.6 [s, 1H, NH imino D_2O-exchangeable] 116.9, 117.3, 119.5, 121.4, 122.6, 123.5, 124.2, 124.8, 125.7, 126.1, 126.8, 127.3, 127.6, 128.2, 128.9, 129.7, 130.2, 135.0, 138.1, 142.7, 152.6, 163.1, 164.6	365 [M^+] (68.3), 101 (100)

In vitro *anti-breast cancer activity*

The relationship between the surviving fraction and drug concentration was plotted; the response parameter calculated was IC_{50} value, which corresponds to the compound concentration that causes 50 % inhibition of cellular viability (Table III). From Table III we can see that the tested compounds **15**, **27**, **7**, **19** were found to be more potent than doxorubicin as reference drug (IC_{50} = 47.9 μmol L^{-1}) on the MCF7 cell line. The most potent compounds in this study are compound **15** bearing 4-hydroxyl,3-methoxyphenyl moiety (IC_{50} = 29.8 μmol L^{-1}), benzochromene-2-one derivative **27** (IC_{50} = 39.0 μmol L^{-1}), 4-fluorophenyl **7** (IC_{50} = 40.0 μmol L^{-1}), styrylphenyl derivative **19** (IC_{50} = 40.4 μmol L^{-1}). On the other hand, 2,3,4-trimethoxyphenyl **17** (IC_{50} = 49.8 μmol L^{-1}), 2-chlorophenyl **10** (IC_{50} = 53.5 μmol L^{-1}), pipronyl derivative **12** (IC_{50} = 57.1 μmol L^{-1}), 2-methoxy-naphthyl **22** (IC_{50} value= 57.5 μmol L^{-1}), 2,4-dichlorophenyl **18** (IC_{50} value = 57.6 μmol L^{-1}) and chromene-2-one **25** (IC_{50} value =

Table III. In vitro *cytotoxic activity of the newly synthesized compounds* ***1–28*** *against the human breast cancer cell line (MCF7)*

Compound	IC_{50} (μg mL^{-1})	IC_{50} (μmol L^{-1})
1	22.7	107.5
2	23.7	79.2
3	23.3	74.4
4	29.5	93.6
5	NA	NA
6	NA	NA
7	12.7	40.0
8	20.7	63.6
9	33.4	97.6
10	17.9	53.5
11	40.6	121.5
12	19.6	57.1
13	21.8	65.2
14	21.7	63.0
15	10.3	29.8
16	23.2	64.6
17	19.4	49.8
18	21.2	57.6
19	14.9	40.4
20	41.0	108.4
21	42.0	111.1
22	21.8	57.5
23	NA	NA
24	41.3	135.4
25	18.7	59.1
26	22.1	70.1
27	14.3	39.0
28	NA	NA
Doxorubicin	26.3	47.9

NA – No activity observed under the adopted experimental conditions.

59.1 μmol L^{-1}) were found to be nearly as potent as doxorubicin. In addition, acrylamide derivatives **2, 3, 8, 13, 14, 16** and imino-chromene exhibited moderate activity (IC_{50} = 79.2, 74.4, 63.6, 65.2, 63.0, 64.6, 70.1 μmol L^{-1}, resp). It was found that the least potent compounds were **1, 4, 9, 11, 20, 21** and **24** (IC_{50} values = 107.5, 93.6, 97.6, 121.5, 108.4, 111.1, 135.4 μmol L^{-1}). Finally, compounds **5, 6, 23** and **28** showed no activity against the breast cancer cell line

MCF7. These results attract attention due to the possible use of the newly synthesized acrylamide derivatives carrying 4-hydroxy-3-methoxyphenyl (**15**), benzochromene-2-one (**27**) and acrylamide bearing 4-fluorophenyl (**7**) and styrylphenyl (**10**) for treatment of breast tumors.

CONCLUSIONS

In this work, we report the synthesis of a novel series of quinolines bearing a biologically active acrylamide **1–24**, chromene-2-one **25,** chromene-2-imino **26**, benzochromene--2-one **27** and benzochromene-2-imino **28** moieties through simple and convenient routes. The new derivatives were evaluated for their anticancer activity against a human tumor breast cancer cell line (MCF7). It was found that the most potent compounds in this study were the corresponding 2-cyano-3-(4-hydroxy-3-methoxyphenyl)-N-(quinolin-3-yl) acrylamide (**15**), 3-oxo-N-(quinolin-3-yl)-3H-benzol[*f*]chromene-2-carboxamide (**27**), 2-cyano-3-(4-fluorophenyl-N-(quinolin-3-yl) acrylamide (**7**), 2-cyano-5-(4-(dimethylamino) phenyl)-N-(quinolin-3-yl) penta-2,4-dienamide (**19**) compared to doxorubicin as a positive control.

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