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Novel Brominated Quinoline and Pyrimidoquinoline Derivatives as Potential Cytotoxic Agents with Synergistic Effects of γ-Radiation

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New quinoline derivatives **6**, **7** and **19**, pyrimidoquinoline derivatives **8-16** and triazolopyrimidoquinoline derivatives **17** and **18** bearing a bromo-substituent were synthesized starting from 3-(4-Bromophenylamino)-5,5-dimethylcyclohex-2-enone **3.** All the newly synthesized compounds were evaluated for their *in vitro* anticancer activity against human breast cancer cell line (MCF7). Compounds **9**, **11**, **17** and **18** showed IC_{50} values (36.4, 39.7, 39.02 and 36.4 μM, respectively) comparable to that of the reference drug doxorubicin (IC_{50} = 32.02 μM). On the other hand, compound **6**, **14** and **19** exhibited better activity than doxorubicin with IC_{50} values of 8.5, 23.5 and 23.7 μM. Additionally, the most potent compounds **6**, **14** and **19** were evaluated for their ability to enhance the cell killing effect of γ-radiation.

Key words: Quinoline, Pyrimidoquinoline, Triazolopyrimidoquinoline, Brominated, γ-Radiation

INTRODUCTION

Quinoline derivatives posses a wide range of biological activities including anti-inflammatory (El-Sayed et al., 2004), antileishmanial (Palit et al., 2009), antifungal (Kategaonkar et al., 2010), antituberculosis (Eswaran et al., 2010) and antimalarial activities (Joshi et al., 2005; Milner et al., 2010). Also, several novel quinoline derivatives have been reported to show substantial anticancer activities (Ferlin et al., 2001; Gopal et al., 2007; Kim et al., 2005; Zhao et al., 2005; Behforouz et al., 2007; Abouzid et al., 2008; Kemnitzer et al., 2008; Alqasoumi et al., 2010; Heiniger et al., 2010; Al-Ghamdi et al., 2012).

It has been known that quinoline derivatives may act as anticancer agents through a variety of mechanisms such as cell cycle arrest in the G2 phase (Kim et al., 2005), topoisomerase inhibition (Cheng et al., 2008), and inhibition of tubulin polymerization (Alqasoumi et al., 2009), and the most common mechanism was the inhibition of tyrosine kinase isozymes (Pannala et al., 2007; Mulvihill et al., 2008; Nishii et al., 2010; Ghorab et al., 2011).

The chemistry of pyrimidine and fused pyrimidine derivatives has been of increasing interest, since many of these compounds revealed several biological activities and useful applications as anticancer and antibacterial agents (Kamen et al., 2000; Chauhan et al., 2005; Amr et al., 2006; Cocco et al., 2006; Kashyap et al., 2011). Also, the therapeutic effects of 1,2,4-triazole ring has been studied for a number of pathological conditions which include anti-inflammatory and anticancer (Palaska et al., 2002; Dogan et al., 2005; Singhal et al., 2011).

All the synthesized compounds were designed to carry a bromophenyl moiety, as it has been reported that several 2-(bromophenyl)quinoline-carboxylic acid derivatives showed activity as synthase inhibitor AG337 in human colon, breast and ovarian cancers (Mani et al., 2004). It is also found that several bromophenylpyrimido[4,5-c]quinolin-1(2H)ones possessed *in vitro* cytotoxic activity against cancer cells (Metwally et al., 2010). On the other hand, it has been reported that 9-bromonoscapine is 10-15 fold more potent than

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its congener noscapine in hormone insensitive human breast cancer. Noscapine is a natural antitumor isoquinoline derivative that triggered apoptosis in many cancer types (Zhou et al., 2003; Mahmoudian, M. and Rahimi-Moghaddam, 2009).

We report here the synthesis of some new quinoline derivatives **6**, **7** and **19**, pyrimidoquinoline derivatives **8-16** and triazolopyrimidoquinoline derivatives **17** and **18**. The anticancer screening was done against a human breast cancer cell line (MCF7). We also aimed to evaluate the ability of the cell killing effect of γ-radiation to sensitize the *in vitro* cytotoxic activity of the most active compounds.

MATERIALS AND METHODS

Chemistry

Melting points are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific). Elemental analyses (C, H, N) were performed on Perkin Elmer 2400 analyser (Perkin-Elmer) at the Microanalytical Laboratories of the Faculty of Science, Cairo University. All compounds were within ± 0.4% of the theoretical values. Infrared spectra (KBr) were determined using Shimadzu IR-110 spectrophotometer (Shimadzu), ^{1}H-NMR spectra were carried out using BRUCKER proton NMR-Avance 300 (300, MHz) (Bruker), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard, mass spectra were recorded on a JEOL JMS AX-500 spectrometer (JEOL JMS), in electronic impact (EI). All reactions were monitored by thin layer chromatograph (TLC) using precoated Aluminium sheets Silica gel Merck 60 F254. Ethyl acetate-cyclohexane (2.5:7.5 mL) mixture was used as eluting solvent and TLC sheets were visualized by UV lamp (Merck).

3-(4-Bromophenylamino)-5,5-dimethylcyclohex-2-enone (3)

A mixture of 5,5-dimethylcyclohexane-1,3-dione **1** (1.4 g, 0.01 mol) and 4-bromoaniline **2** (1.7 g, 0.01 mol) in ethanol (20 mL) was refluxed for 5 h. The reaction mixture was cooled then poured onto cold water. The obtained solid was crystallized from dioxane to give **3**. IR (KBr cm^{-1}): 3203 (NH), 3099 (CH arom.), 2978, 2838 (CH aliph.), 1656 (C=O). ^{1}H-NMR (DMSO-d_6): δ 1.1 (s, 6H, $2CH_3$), 2.2, 2.4 (2s, 4H, $2CH_2$), 4.3 (s, 1H, NH), 5.5 (s, 1H, CH), 6.5 (d, 2H, 2CH, J = 6 Hz, Ph), 7.3 (d, 2H, 2CH, J = 6 Hz, Ph). Anal. Calcd. for $C_{14}H_{16}BrNO$: C, 57.16; H, 5.48; N, 4.76. Found: C, 57.56; H, 5.10; N, 4.36.

2-Amino-1-(4-bromophenyl)-7,7-dimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6)

A mixture of compound **3** (2.9 g, 0.01 mol) and 2-(4-methylbenzylidene)malononitrile **4** (1.6 g, 0.01 mol) in ethanol (20 mL) containing 3 drops of triethylamine was refluxed for 6 h. The reaction mixture was filtered while hot and the solid product was recrystallized from dioxane to give **6**. IR (KBr cm^{-1}): 3311, 3203 (NH_2), 3099 (CH arom.), 2978, 2838 (CH aliph.), 2179 (C≡N), 1656 (C=O). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 5.4 (s, 2H, NH_2 D_2O-exchangeable), 7.1-8.0 (m, 8H, Ar-H). MS, m/z (%): 462 [M$^+$] (20.36), 372 (100). Anal. Calcd. for $C_{25}H_{24}BrN_3O$: C, 64.94; H, 5.23; N, 9.09. Found: C, 64.54; H, 5.53; N, 9.45.

Ethyl N-1-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinolin-2-ylformimidate (7)

A solution of compound **6** (4.6 g, 0.01 mol) in triethylorthoformate (20 mL) was refluxed for 8 h. The reaction mixture was cooled and then poured onto ice water. The precipitated solid was filtered and recrystallized from ethanol to give **7**. IR (KBr cm^{-1}): 3099 (CH arom.), 2959, 2890 (CH aliph.), 2199 (C≡N), 1638 (C=O). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.1 (t, 3H, CH_3 ethyl), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 3.9 (q, 2H, CH_2 ethyl), 4.6 (s, 1H, CH), 7.1-7.8 (m, 8H, Ar-H), 8.1 (s, 1H, N=CH). Anal. Calcd. for $C_{28}H_{28}BrN_3O_2$: C, 64.48; H, 5.44; N, 8.11. Found: C, 64.44; H, 5.03; N, 8.55.

10-(4-Bromophenyl)-2-(4-chlorophenyl)-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-4,6(3H,5H)-dione (8)

A mixture of compound **6** (4.6 g, 0.01 mol) and 4-chlorobenzoyl chloride (1.7 g, 0.01 mol) in pyridine (20 mL) was refluxed for 8 h. The reaction mixture was cooled then poured onto ice cold water. The solid obtained was crystallized from dioxane to give **8**. IR (KBr cm^{-1}): 3310 (NH), 3017 (CH arom.), 2956, 2854 (CH aliph.), 1731, 1654 (2C=O), 1580 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.7, 0.9 (2s, 6H, $2CH_3$), 1.9-2.1 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.5 (s, 1H, CH), 7.1-7.9 (m, 12H, Ar-H), 8.0 (s, 1H, NH). MS, m/z (%): 600 [M$^+$] (0.75), 143 (100). Anal. Calcd. for $C_{32}H_{27}BrClN_3O_2$: C, 63.96; H, 4.53; N, 6.99. Found: C, 63.54; H, 4.25; N, 6.66.

4-Amino-10-(4-bromophenyl)-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(5H)-one (9)

A solution of compound **6** (4.6 g, 0.01 mol) in for-

mamide (20 mL) was refluxed for 5 h. The reaction mixture was cooled and poured onto ice cold water. The precipitated solid was filtered and crystallized from ethanol to give **9**. IR (KBr cm^{-1}): 3310, 3230 (NH_2), 3017 (CH arom.), 2952, 2897 (CH aliph.), 1635 (C=O), 1588 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 6.5-7.4 (m, 9H, Ar-H + CH pyrimidine), 7.7 (s, 2H, NH_2). MS, *m/z* (%): 489 [M^+] (20.36), 91 (100). Anal. Calcd. for $C_{26}H_{25}BrN_4O$: C, 63.81; H, 5.15; N, 11.45. Found: C, 63.42; H, 5.50; N, 11.80.

10-(4-Bromophenyl)-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-4,6(3H,5H)-dione (10)

A solution of **6** (4.6 g, 0.01 mol) in formic acid (15 mL) was refluxed for 5 h. The reaction mixture was cooled and poured onto ice cold water. The solid precipitate was filtered and crystallized from ethanol to give **10**. IR (KBr cm^{-1}): 3210 (NH), 3085 (CH arom.), 2951, 2863 (CH aliph), 1710, 1633 (2C=O), 1583 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 7.3-7.6 (m, 9H, Ar-H + CH pyimidine), 7.9 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ 22.6, 26.7 (2), 33.1, 41.6, 42.9, 54.4, 102.3, 112.7, 114.3, 119.1 (2), 128.6 (2), 129.1 (2), 134.5 (2), 137.2, 141.7, 143.2, 152.6, 153.0, 156.1, 163.7, 199.8. MS, *m/z* (%): 490 [M^+] (11.11), 55 (100). Anal. Calcd. for $C_{26}H_{24}BrN_3O_2$: C, 63.68; H, 4.93; N, 8.57. Found: C, 63.41; H, 4.72; N, 8.33.

10-(4-Bromophenyl)-2-(chloromethyl)-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinoline-4,6(3H,5H)-dione (11)

A mixture of compound **6** (4.6 g, 0.01 mol) and chloroacetyl chloride (1.3 g, 0.01 mol) in dimethylformamide (20 mL) was refluxed for 10 h. The reaction mixture was cooled and then poured onto ice cold water and the solid obtained was crystallized from dioxane to give **11**. IR, (KBr cm^{-1}): 3422 (NH), 3025 (CH arom.), 2950, 2880 (CH aliph.), 1672, 1663 (2C=O). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 5.1 (s, 2H, CH_2Cl), 7.3-7.9 (m, 8H, Ar-H), 8.2 (s, 1H, NH). MS, *m/z* (%): 538 [M^+] (1.05), 78 (100). Anal. Calcd. for $C_{27}H_{25}BrClN_3O_2$: C, 60.18; H, 4.68; N, 7.80. Found: C, 60.43; H, 4.42; N, 7.67.

Ethyl 2-(10-(4-bromophenyl)-8,8-dimethyl-4,6-dioxo-5-p-tolyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-3(4H,5H,10H)-yl)acetate (12)

A mixture of **10** (4.9 g, 0.01 mol), ethyl bromoacetate (1.6 g, 0.01 mol) and anhydrous potassium carbonate (2 g) in dry acetone (20 mL) was refluxed for 24 h. The reaction mixture was filtered and the filtrate was poured onto ice cold water. The precipitated solid was filtered and crystallized from dioxane to give **12**. IR (KBr cm^{-1}): 3091 (CH arom.), 2952, 2831 (CH aliph.), 1711, 1658, 1627 (3C=O), 1590 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.7 (2s, 6H, $2CH_3$), 1.1 (t, 3H, CH_3 ethyl), 1.7-1.9 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 3.8 (q, 2H, CH_2 ethyl), 4.1 (s, 1H, CH), 4.6 (s, 2H, CH_2CO), 6.8-7.2 (m, 9H, Ar-H + CH pyrimidine). Anal. Calcd. for $C_{30}H_{30}BrN_3O_4$: C, 62.50; H, 5.25; N, 7.29. Found: C, 62.90; H, 5.60; N, 7.60.

10-(4-Bromophenyl)-8,8-dimethyl-4-thioxo-5-p-tolyl-3,4,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-6(5H)-one (13)

A mixture of **10** (4.9 g, 0.01 mol) and phosphorus pentasulphide (1.9 g, 0.01 mol) in xylene (20 mL) was refluxed for 8 h. The reaction mixture was evaporated and the solid obtained was filtered off and recrystallized from ethanol to give **13**. IR (KBr cm^{-1}): 3215 (NH), 3036 (CH arom.), 2959, 2871 (CH aliph.), 1638 (C=O), 1600 (C=N), 1239 (C=S). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 7.1-7.5 (m, 9H, Ar-H + CH pyimidine), 13.7 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6): δ 22.6, 24.8 (2), 34.7, 41.8, 47.9, 53.0, 111.4, 113.6, 115.2, 119.3 (2), 128.7 (2), 129.3 (2), 133.8, 134.2, 135.9, 140.8, 143.0, 153.4, 155.1, 157.7, 200.2, 203.6. MS, *m/z* (%): 506 [M^+] (8.09), 66 (100). Anal. Calcd. for $C_{26}H_{24}BrN_3OS$: C, 61.66; H, 4.78; N, 8.30. Found: C, 61.96; H, 4.48; N, 8.61.

10-(4-Bromophenyl)-4-chloro-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(5H)-one (14)

A mixture of **10** (4.9 g, 0.01 mol) and thionyl chlorid (1.2 g, 0.01 mol) in dry benzene (20 mL) was refluxed for 10 h. The reaction mixture was concentrated and the solid obtained was crystallized from dioxane to give **14**. IR (KBr cm^{-1}): 3030 (CH arom.), 2970, 2857 (CH aliph.), 1678 (C=O), 1589 (C=N), 816 (C-Cl). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 6.5-8.3 (m, 9H, Ar-H + CH pyimidine). MS, *m/z* (%): 508 [M^+] (13.69), 65 (100). Anal. Calcd. for $C_{26}H_{23}BrClN_3O$: C, 61.37; H, 4.56; N, 8.26. Found: C, 61.70; H, 4.15; N, 8.60.

10-(4-Bromophenyl)-4-isothiocyanato-8,8-dimethyl-5-p-tolyl-7,8,9,10-tetrahydropyrimido[4,5-b]quinolin-6(5H)-one (15)

A mixture of **14** (5 g, 0.01 mol) and ammonium

thiocyanate (0.76 g, 0.01 mol) in dry acetone (20 mL) was refluxed for 2 h. The reaction mixture was filtered while hot and the filtrate was poured onto ice cold water where a solid precipitate was formed. The precipitate was filtered and crystallized from ethanol to give **15**. IR (KBr cm^{-1}): 3017 (CH arom.), 2969, 2861 (CH aliph.), 2028 (N=C=S), 1670 (C=O), 1590 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 6.5-8.2 (m, 9H, Ar-H + CH pyimidine). MS, *m/z* (%): 531 [M^+] (1.01), 275 (100). Anal. Calcd. for $C_{27}H_{23}BrN_4OS$: C, 61.02; H, 4.36; N, 10.54. Found: C, 61.40; H, 4.70; N, 10.34.

3-Amino-10-(4-bromophenyl)-4-imino-8,8-dimethyl-5-p-tolyl-3,4,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-6(5H)-one (16)

A mixture of **7** (5.1 g, 0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol) in ethanol (20 mL) was stirred for 24 h at room temperature. The reaction mixture was poured onto ice cold water. The solid precipitate was filtered and crystallized from dioxane to give **16**. IR, (KBr cm^{-1}): 3340, 3292, 3150 (NH, NH_2), 3090 (CH arom.), 2977, 2856 (CH aliph.), 1715 (C=O), 1596 (C=N). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 2.5 (s, 1H, NH_2 D_2O-exchangeable), 4.6 (s, 1H, CH), 5.2 (s, 1H, NH), 7.1-8.1 (m, 9H, Ar-H + CH pyimidine). MS, *m/z* (%): 504 [M^+] (2.94), 379 (100). Anal. Calcd. for $C_{26}H_{26}BrN_5O$: C, 61.91; H, 5.20; N, 13.88. Found: C, 61.61; H, 5.55; N, 13.58.

7-(4-Bromophenyl)-9,9-dimethyl-12-(4-methylphenyl)-8,9,10,12-tetrahydro[1,2,4]triazolo[1',5':1,6]pyrimido[4,5-b]quinolin-11(7H)-one (17)

A solution of **16** (0.5 g, 0.01 mol) in formic acid (20 mL) was refluxed for 5 h. The reaction mixture was cooled and then poured onto ice cold water. The solid precipitate was filtered and crystallized from ethanol to give **17**. IR (KBr cm^{-1}): 3053 (CH arom.), 2955, 2846 (CH aliph.), 1690 (C=O). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 4.6 (s, 1H, CH), 6.5-8.3 (m, 10H, Ar-H + CH pyimidine + CH triazole). ^{13}C-NMR (DMSO-d_6): δ 23.9, 25.4 (2), 33.0, 38.8, 43.6, 54.1, 109.7, 115.3, 116.7, 119.2 (2), 119.9, 128.9 (2), 129.7 (2), 134.3, 135.9 (2), 137.6, 140.0, 146.1, 149.6, 153.8, 171.4, 201.2. MS, *m/z* (%): 514 [M^+] (28.13), 422 (100). Anal. Calcd. for $C_{27}H_{24}BrN_5O$: C, 63.04; H, 4.70; N, 13.61. Found: C, 63.44; H, 4.40; N, 13.31.

7-(4-Bromophenyl)-2,9,9-trimethyl-12-(4-methylphenyl)-8,9,10,12-tetrahydro[1,2,4]triazolo[1',5':1,6]pyrimido[4,5-b]quinolin-11(7H)-one (18)

A solution of **16** (0.5 g, 0.01 mol) in acetic anhydride (20 mL) was refluxed for 5 h. The reaction mixture was then concentrated, the solid separated was recrystallized from ethanol to give **18**. IR (KBr cm^{-1}): 3056 (CH arom.), 2957, 2866 (CH aliph.), 1632 (C=O). ^{1}H-NMR (DMSO-d_6): δ 0.6, 0.9 (2s, 6H, $2CH_3$), 1.9-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 2.4 (s, 3H, CH_3 triazole), 4.6 (s, 1H, CH), 6.5-8.2 (m, 9H, Ar-H + CH pyimidine). MS, *m/z* (%): 528 [M^+] (7.67), 438 (100). Anal. Calcd. for $C_{28}H_{26}BrN_5O$: C, 63.64; H, 4.96; N, 13.25. Found: C, 63.42; H, 4.67; N, 13.55.

N'-(1-(4-bromophenyl)-3-cyano-7,7-dimethyl-5-oxo-4-p-tolyl-1,4,5,6,7,8-hexahydroquinolin-2-yl)-N-(4-sulfamoylphenyl)formimidamide (19)

A mixture of **7** (5.1 g, 0.01 mol) and sulfanilamide (1.7 g, 0.01 mol) in ethanol (20 mL) was stirred at room temperature for 3 h. The reaction mixture was poured onto ice cold water. The solid precipitate was filtered and crystallized from ethanol to give **19**. IR (KBr cm^{-1}): 3344, 3250, 3160 (NH, NH_2), 3085 (CH arom.), 2951, 2850 (CH aliph.), 2202 (C≡N), 1641 (C=O). ^{1}H-NMR (DMSO-d_6): δ 0.7, 0.9 (2s, 6H, $2CH_3$), 2.1-2.2 (m, 4H, $2CH_2$), 2.3 (s, 3H, CH_3 tolyl), 3.8 (s, 1H, NH, D_2O-exchangeable), 4.5 (s, 1H, CH), 7.1-7.9 (m, 14H, Ar-H+SO_2NH_2), 8.1 (s, 1H, N=CH). Anal. Calcd. for $C_{32}H_{30}BrN_5O_3S$: C, 59.63; H, 4.69; N, 10.86. Found: C, 59.93; H, 4.39; N, 10.56.

***In vitro* anticancer screening**

The *in vitro* anticancer screening was done by the pharmacology unit at the National Cancer Institute, Cairo University using the human tumor breast cell line (MCF7). Irradiation was performed in the National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt using the gamma cell-40 (^{60}CO) source.

The cytotoxic activity was measured in vitro for the newly synthesized compounds using the Sulfo-Rhodamine-B stain (SRB) assay using the method of (Skehan et al., 1990). Cells were plated in 96-multiwell microtiter plate (10^4 cells/well) for 24 h before treatment with the compound(s) to allow attachment of cell to the wall of the plate. Test compounds were dissolved in DMSO and diluted with saline to the appropriate volume. Different concentrations of the compound under test (0, 1, 2.5, 5, and 10 μM/mL) 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 atmosphere of

5% CO_2. After 48 h, cells were fixed, washed, and stained for 30 min with 0.4% (wt/vol) SRB dissolved in 1% acetic acid. Excess unbounded dye was removed by four washes with 1% acetic acid, and attached stain was recovered with Tris EDTA buffer. Color intensity was measured in an ELISA reader. The relation between surviving fraction and drug concentration is plotted to get the survival curve for human breast tumor cell line after the specified time. The molar concentration required for 50% inhibition of cell viability (IC_{50}) was calculated and compared to the reference drug doxorubicin (CAS, 25316-40-9). The surviving fractions were expressed as means ± S.E. and the results are given in Table I.

Radiosensitizing evaluation

The most potent compounds resulted from the *in vitro* anticancer screening; the quinoline derivative **6**, the 4-chloro-pyrimidoquinoline derivative **14**, and the sulfamoylphenyl formimidamide derivative **19**, were selected to be evaluated again for their *in vitro* anticancer activity alone and in combination with γ-radiation. This study was conducted to evaluate the ability of the cell killing effect of γ-radiation to sensitize the *in vitro* cytotoxic activity of the most active compounds. Cells were subjected to a single dose of γ-radiation at a dose level of 8 Gy with a dose rate of 2 Gy/min. Irradition was performed in the National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt, using Gamma cell-40 (^{60}Co) source. The surviving fractions were expressed as means ± S.E. The results were analyzed using 1-way ANOVA test (Figs. 1A-C).

Molecular docking study

The most biologically active compounds were docked using MOE software based on the protein data bank file 1VR2 which contains crystal structure of the VEGFR2 kinase domain in complex with Vatalanib.

Validation of the docking protocol

To perform accurate validation of the docking protocol docking of the co-crystallized ligand should be carried out to study the scoring energy (s), root mean standard deviation (RMSD) and amino acid interactions. Docking was performed using London dG force and refinement of the results was done using Force field energy.

Preparing compounds for docking

Preparation of the synthesized compounds for docking was achieved via their 3D structure built by MOE. Certain procedures should be taken before docking which includes:

1. 3D protonation of the structures.
2. Running conformational analysis using systemic search.
3. Selecting the least energetic conformer.
4. Applying the same docking protocol used with co-crystallized legand.

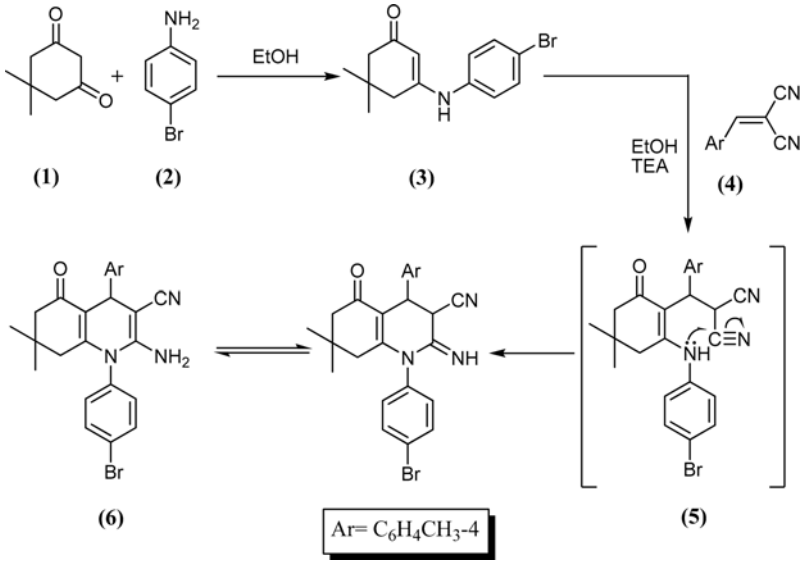
RESULTS AND DISCUSSION

Chemistry

From the literature survey, it was found that the bromine containing compounds exhibited known broad spectrum biological activities especially anticancer one (Zhou et al., 2003; Mahmoudian and Rahimi-Moghaddam, 2009).

Enaminone **3** was obtained from condensation of 5,5-dimethylcyclohexane-1,3-dione **1** with 4-bromoaniline **2**. The structure of compound **3** was established by elemental analysis and spectral data. IR spectrum of compound **3** showed the presence of bands at 3203 cm^{-1} (NH), 3099 cm^{-1} (CH arom.), 2978 and 2838 cm^{-1} (CH aliph.), 1656 cm^{-1} (C=O). Also, the ^{1}H-NMR spectrum in (DMSO-d_6) indicated the presence of a singlet at 4.3 ppm which could be assigned to NH of enaminone **3**. Treatment of enaminone **3** with 2-(4-methylbenzylidene)malononitrile **4** in ethanol containing a catalytic amount of triethylamine, as catalyst, yielded the corresponding hexahydroquinoline derivative **6** via the formation of the intermediate Michael type product **5** followed by intramolecular cyclization. IR spectrum of compound **6** showed bands at 3311, 3203 cm^{-1} (NH_2), 2179 cm^{-1} (C≡N), 1656 cm^{-1} (C=O). The mass spectrum of compound **6** exhibited a molecular ion peak m/z at 462 (M^+, 20.36%), with a base peak m/z at 372 (Scheme 1).

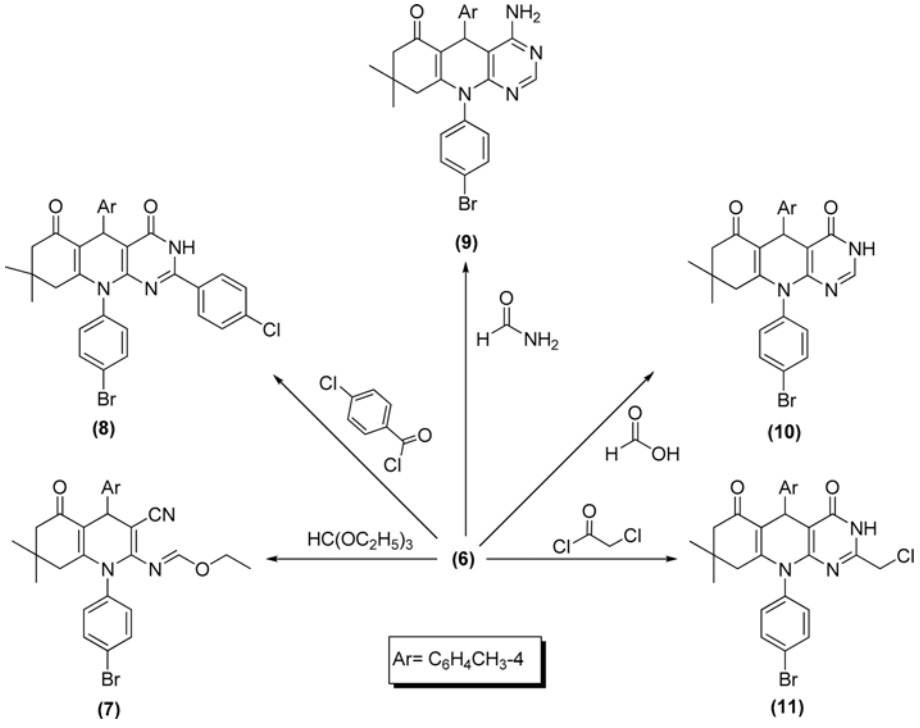
Treatment of compound **6** with triethylorthoformate afforded the formimidate derivative **7**. The formation of compound **7** was supported from its microanalytical and spectral data. IR spectrum exhibited the absence of the band corresponding to the (NH_2) and the presence of band at 2199 cm^{-1} corresponding to the cyano group. Also, the ^{1}H-NMR spectrum for compound **7** in DMSO-d_6 showed the presence of a triplet at 1.1 ppm for the CH_3 and a quartet at 3.9 ppm of CH_2 of the ethyl group. Refluxing compound **6** with 4-chlorobenzoyl chloride in pyridine yielded the corresponding 2-(4-chlorophenyl)pyrimidoquinoline derivative **8**. IR spectrum of compound **8** showed absence of the (C≡N) band and presence of (2C=O) bands at 1731, 1654 cm^{-1}. Heating of compound **6** with formamide yielded the 4-aminopyrimidoquinoline derivative **9** which exhibited the absence of (C≡N) band in IR spectrum to confirm



Scheme 1. Formation of hexahydroquinolinecarbonitrile derivative **6**.

cyclization. The pyrimidoquinoline derivative **10** was obtained by refluxing compound **6** in formic acid. This reaction proceeded via condensation followed by elimination of two moles of water. IR spectrum of compound **10** showed bands at 1710, 1633 cm^{-1} for (2C=O). Reaction of compound **6** with chloroacetyl chloride in DMF, intramolecular cyclization took place gaving the 2-chloromethylpyrimidoquinoline derivative **11**. Structure of compound **11** was supported by elemental analysis and spectral data. IR spectrum showed absence of band corresponding to cyano group and presence of bands at 1672, 1663 cm^{-1} for (2C=O) (Scheme 2).

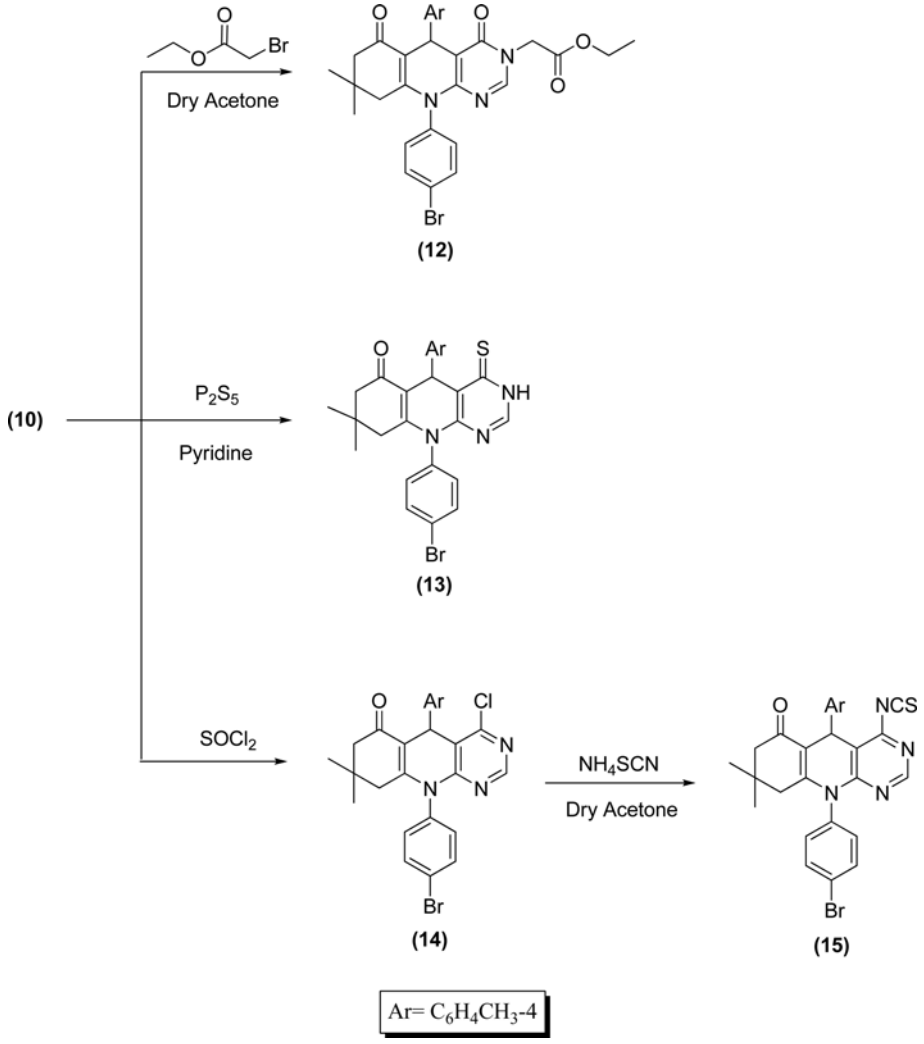
Reaction of compound **10** with ethyl bromoacetate in dry acetone in the presence of anhydrous potassium carbonate yielded the corresponding ester derivative **12**. IR spectrum of compound **12** exhibited the presence of bands at 1711, 1658, 1627 cm^{-1} for (3C=O). Also, the ^{1}H-NMR spectrum for compound **12** in (DMSO-d_6)



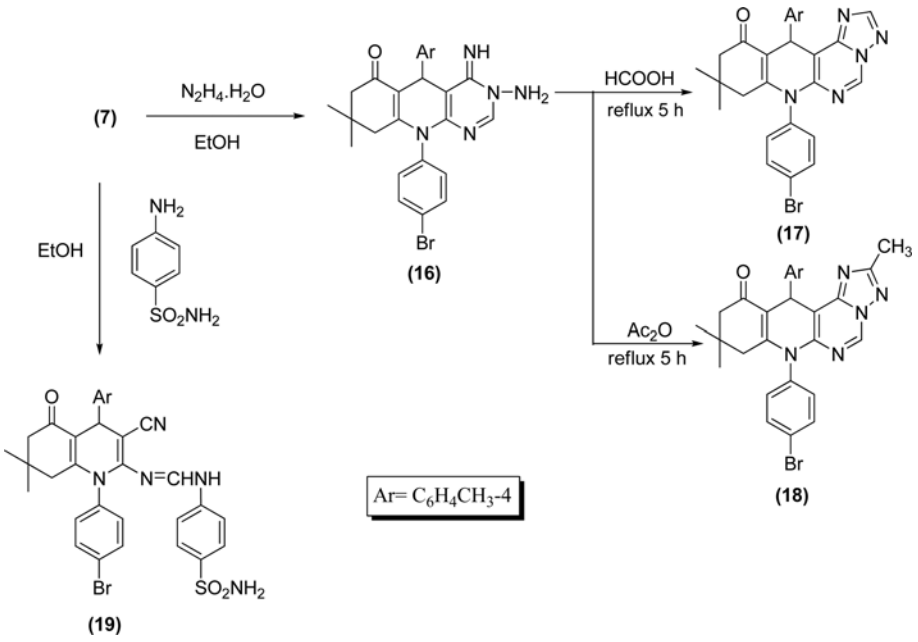
Scheme 2. Synthesis of quinoline and pyrimidoquinoline derivatives.

showed the presence of significant triplet at 1.1 ppm for the CH_3 and quartet at 3.8 ppm of CH_2 of the ethyl group. Thionation of compound **10** with phosphorus penta-sulfide in xylene afforded the corresponding 4-thioxo-pyrimidoquinoline derivative **13**. IR spectrum of compound **13** showed bands at 1638 cm^{-1} (C=O) and 1239 cm^{-1} (C=S). While, treatment of compound **10** with thionyl chloride afforded the 4-chloro-pyrimidoquinoline derivative **14**. The mass spectrum of compound **14** exhibited a molecular ion peak *m/z* at 508 (M^+, 13.69%), with a base peak m/z at 65. Finally, the 4-isothiocyanatopyrimidoquinoline derivative **15** was obtained by refluxing compound **14** with ammonium thiocyanate in dry acetone. IR spectrum of compound **15** afforded the presence of band at 2028 cm^{-1} for (N=C=S) (Scheme 3).

Reaction of compound **9** with hydrazine hydrate in ethanol at room temperature yielded the corresponding N-aminopyrimidoquinoline derivative **16**. IR spectrum showed absence of band corresponding to (C≡N) and presence of bands at 3340, 3292, 3150 corresponding to (NH, NH_2). The mass spectrum of compound **16** exhibited a molecular ion peak m/z at 504 (M^+, 2.94%), with a base peak *m/z* at 379. When compound **16** was refluxed with formic acid the corresponding triazolo-pyrimidoquinoline derivative **17** was formed via intramolecular cyclization. IR spectrum of compound **17** revealed the absence of bands corresponding to (NH, NH_2). Similarly, the corresponding 2-methyl-triazolo-pyrimidoquinoline derivative **18** was obtained when compound **16** was refluxed with acetic anhydride. Mass spectrum of compound **18** exhibited a molecular ion peak m/z at 528 (M^+, 7.67%), with a base peak *m/z* at 438. Interaction of compound **7** with sulfanilamide at room temperature in ethanol, the N-(4-sulfamoyl-phenyl)formimidamide derivative **19** was obtained. IR spectrum of compound **16** exhibited bands at 3344, 3250, 3160 corresponding to (NH, NH_2). ^{1}H-NMR



Scheme 3. Formation of pyrimidoquinoline derivatives.



Scheme 4. Formation of triazolopyrimidoquinoline and sulfonamide derivatives.

spectrum for compound **19** in (DMSO-d_6) showed the absence of triplet and quartet corresponding to ethyl group, and revealed presence of singlet at 3.8 of (NH) exchangeable with D_2O (Scheme 4).

In vitro anticancer screening

From results in Table I, it was observed that the quinoline derivative **6** (IC_{50} = 8.5 μM), 4-chloro-pyrimidoquinoline derivative **14** (IC_{50} = 23.5 μM) and sulfamoylphenyl formimidamide derivative **19** (IC_{50} = 23.7 μM) exhibited better activity than the reference drug doxorubicin (IC_{50} = 32.02 μM). While Compounds **9**, **11, 17** and **18** showed IC_{50} values (36.4, 39.7, 39.02 and 36.4 μM, respectively) are nearly as active as doxorubicin as positive control. While the other compounds showed IC_{50} values lower than that of the reference drug doxorubicin ranging from 42.9-53 μM.

Table I. *In vitro* anticancer screening of the synthesized compounds against human breast cell line (MCF7)

Compound	Compound concentration (μM)				IC_{50} (μM)
	10	25	50	100	
	Surviving fraction (Means ± S.E.)[#]				
Doxorubicin	0.451 ± 0.02	0.352 ± 0.02	0.290 ± 0.01	0.280 ± 0.03	32.02
6	0.276 ± 0.01	0.130 ± 0.03	0.176 ± 0.01	0.143 ± 0.01	8.5
7	0.904 ± 0.03	0.685 ± 0.01	0.355 ± 0.01	0.209 ± 0.01	53
8	0.807 ± 0.08	0.723 ± 0.03	0.293 ± 0.01	0.133 ± 0.01	47.3
9	0.792 ± 0.03	0.361 ± 0.01	0.145 ± 0.01	0.174 ± 0.01	36.4
10	0.967 ± 0.01	0.515 ± 0.01	0.185 ± 0.02	0.123 ± 0.01	43.1
11	0.659 ± 0.01	0.569 ± 0.01	0.137 ± 0.01	0.233 ± 0.01	39.7
12	0.920 ± 0.02	0.417 ± 0.01	0.272 ± 0.02	0.146 ± 0.01	42.9
13	0.851 ± 0.01	0.719 ± 0.01	0.340 ± 0.01	0.115 ± 0.01	48.8
14	0.582 ± 0.01	0.161 ± 0.01	0.134 ± 0.01	0.206 ± 0.01	23.5
15	0.584 ± 0.01	0.346 ± 0.03	0.083 ± 0.01	0.178 ± 0.02	28
16	0.209 ± 0.01	0.119 ± 0.01	0.088 ± 0.01	0.078 ± 0.01	27.19
17	0.780 ± 0.01	0.487 ± 0.09	0.112 ± 0.01	0.203 ± 0.01	39.02
18	0.740 ± 0.06	0.442 ± 0.01	0.102 ± 0.01	0.203 ± 0.01	36.4
19	0.514 ± 0.01	0.277 ± 0.01	0.092 ± 0.01	0.194 ± 0.01	23.7

[#]Each value is the mean of three values ± S.E.

Table II. *In vitro* anticancer screening of compounds **6, 14, 15** and **19** against human breast cell line (MCF7) in combination with γ-radiation

Compd.No.	Control	Irradiated (8 Gy)	Compound concentration (μM) + Irradiation (8 Gy)				IC_{50} (μM)
			10	25	50	100	
	Surviving fraction (Means ± S.E.)[#]						
6	1.000	0.927 ± 0.02*	0.147 ± 0.01*	0.082 ± 0.04*	0.036 ± 0.01*	0.021 ± 0.01*	1.57
14	1.000	0.927 ± 0.02*	0.146 ± 0.01*	0.085 ± 0.01*	0.018 ± 0.01*	0.016 ± 0.01*	1.68
19	1.000	0.927 ± 0.02*	0.165 ± 0.02*	0.127 ± 0.01*	0.039 ± 0.01*	0.025 ± 0.01*	1.31

[#]Each value is the mean of three values ± S.E.; *Significant difference from control group at $p < 0.001$.

Radiosensitizing evaluation

The rationale for combining chemotherapy and radiotherapy is based mainly on two ideas, one being spatial cooperation, which is effective if chemotherapy is sufficiently active to eradicate subclinical metastases and if the primary local tumor is effectively treated by radiotherapy. In this regard, no interaction between radiotherapy and chemotherapy is required. The other idea is the enhancement of radiation effects by direct enhancement of the initial radiation damage by incorporating drugs into DNA, inhibiting cellular repair, accumulating cells in a radiosensitive phase or eliminating radioresistant phase cells, eliminating hypoxic cells, or inhibiting the accelerated repopulation of tumor cells. Virtually, all chemotherapeutic agents have the ability to sensitize cancer cells to the lethal effects of ionizing radiation (Nishimura, 2004).

From the results obtained in Table I, compound **6** showed an *in vitro* cytotoxic activity with IC_{50} value of 8.5 μM, when the cells were subjected to different concentrations of the compound alone. While when the cells were subjected to the same concentrations of compound **6**, and irradiated with a single dose of γ-radiation at a dose level of 8 Gy. The IC_{50} value was synergistically decreased to 1.57 μM. Similarly, compounds **14** and **19** showed IC_{50} values of 23.5 and 23.7 μM respectively, when used alone. The IC_{50} values were decreased to 1.68 and 1.31 μM respectively after irradiation (Figs. 1A-C).

Molecular docking study

Vatalnib which is a known VEGFR2 inhibitor was the reference drug for docking on the active site of VEGFR2. Vatalanib interacted with Cys A919 with one hydrogen bond 2.7 A° and with Lys A868 with arene cation interaction as shown in Figs. 2(A-B). Docking results for the most biologically active compounds and Vatalnib were summarized in Table II.

From Table II we can conclude the following:

1. All compounds were fit in the active site of VGEFR2 with good to moderate scoring energy compared to Vatalanib but Compound **19** was fit in the active

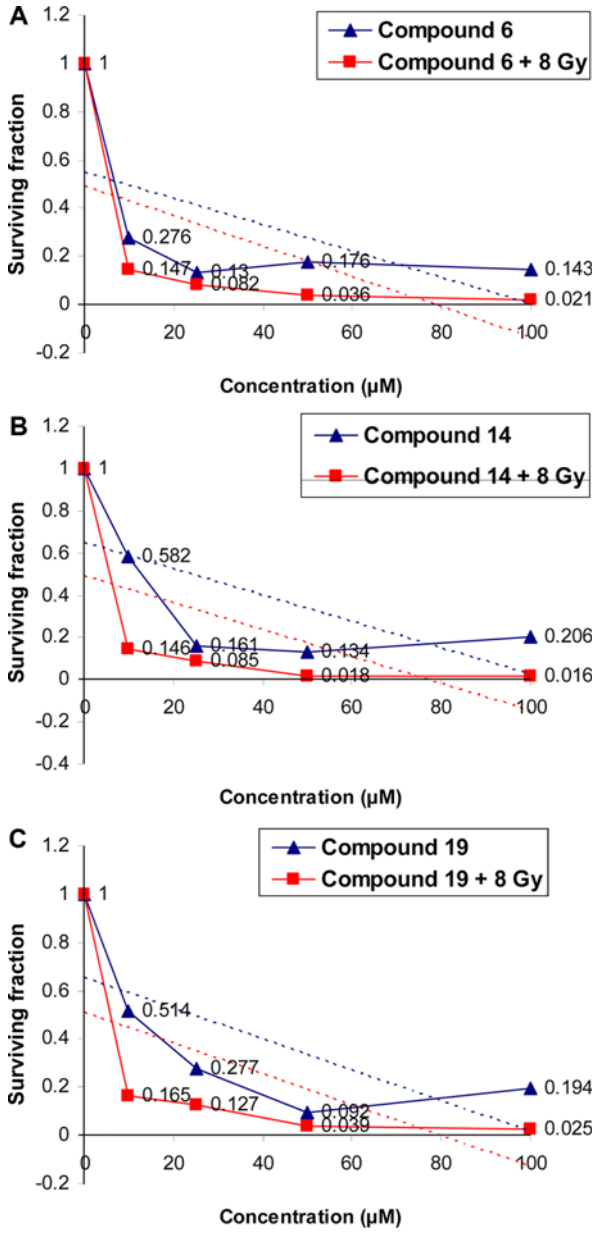


Fig. 1. Survival curve for MCF7 cell line for: (**A**) compound **6** alone and in combination with γ-irradiation (8 Gy), (**B**) compound **14** alone or in combination with γ-irradiation (8 Gy), and (**C**) compound **19** alone and in combination with γ-irradiation (8 Gy).

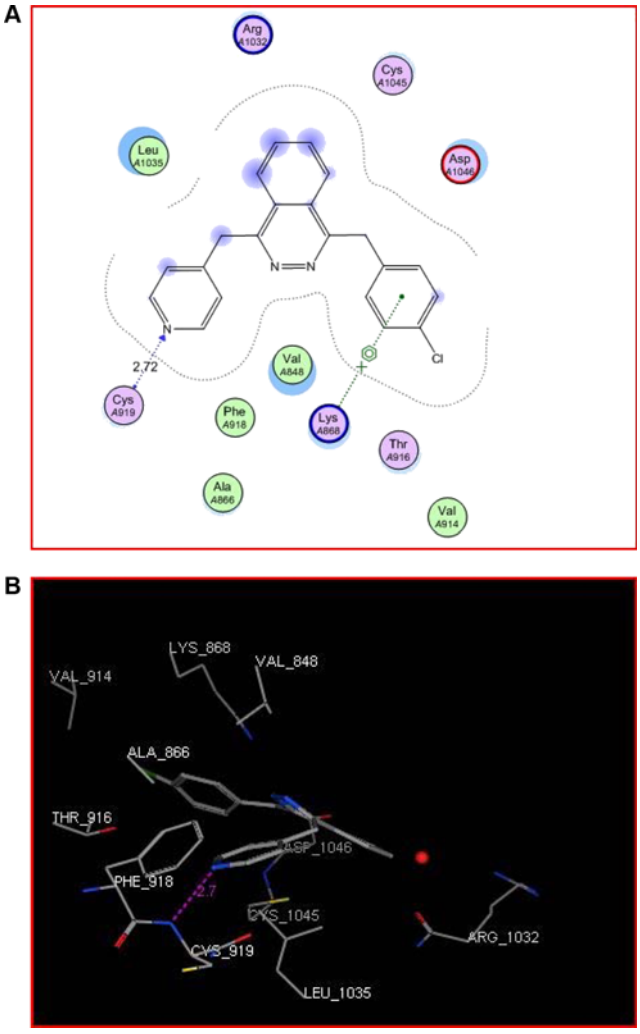


Fig. 2. Vatalnib in the active site of VEGFR2, 2D (**A**) and 3D (**B**).

Table III. Results of docking of the most three biologically active compounds and Vatalanib on the active site of VEGFR2a

Compound No.	(S) in Kcal/mole
Vatalanib	17.2652
6	6.2635
14	13.1624
19	13.7245

site of VGEFR2 with scoring energy comprable to Vatalnib.

2. Since compound **19** showed scoring energy comprable to Vatalanib, it was interesting to study its amino acid interaction in the active site of VGEFR2. Compound **19** interact with two amino acids, Lys A838 with one hydrogen bond 2.78 A°, and Cys A919 with one hydrogen bond 3.01 A° as shown in Figs. 3(A-B).

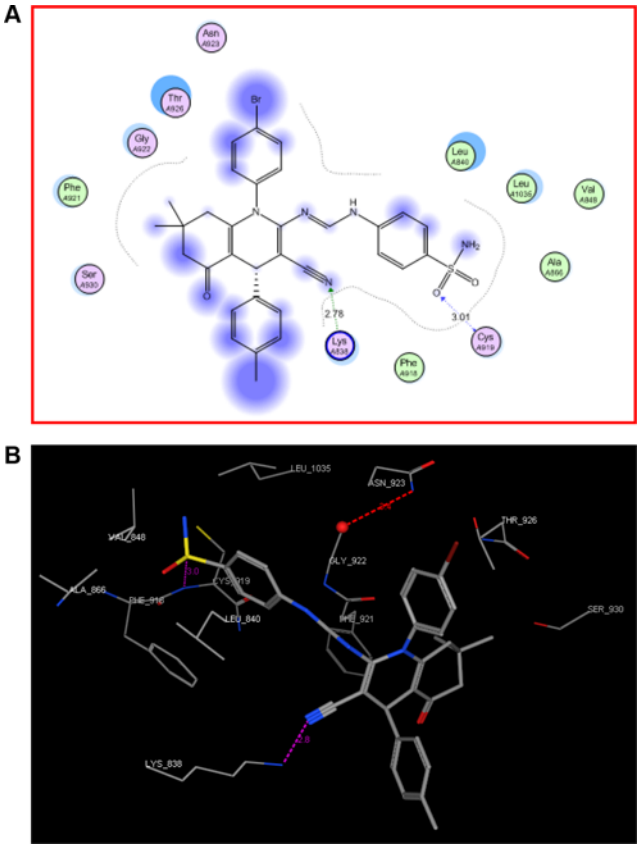


Fig. 3. Compound **19** in the active site of VGEFR2, 2D (**A**) and 3D (**B**).

3. The objective of the present study was to synthesize and investigate the anticancer activity of some novel quinoline **6**, **7**, **19**, pyrimidoquinoline **8-16** and triazolopyrimidoquinoline derivatives **17**, **18** against human breast cancer cell line (MCF7). Quinoline derivative **6**, 4-chloro-pyrimidoquinoline **14** and sulfamoylphenyl formimidamide **19** exhibited significant anticancer activity, when compared to doxorubicin as a reference drug. Additionally, pyrimidoquinolines **9**, **11** and triazolopyrimidoquinolines **17**, **18** showed IC_{50} values (36.4, 39.7 and 39.02, 36.4 μM, respectively) comparable to that of the reference drug doxorubicin. Moreover, the most three active compounds **6**, **14** and **19** showed the ability to sensitize cancer cells to the lethal effects of ionizing radiation. Also, compound **19** exhibited high cytotoxic activity and a binding mode comparable to Vatalanib (reported vascular endothelial growth factor receptor tyrosine kinase inhibitor VEGFRTKI) and this may contribute at least to its anticancer activity.

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