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ARTICLE *in* EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY · SEPTEMBER 2010

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Original article

In vitro anticancer screening and radiosensitizing evaluation of some new quinolines and pyrimido[4,5-*b*]quinolines bearing a sulfonamide moiety

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ARTICLE INFO

Article history:
Received 26 October 2009
Received in revised form
6 May 2010
Accepted 7 May 2010
Available online 12 May 2010

Keywords:
Quinoline
Pyrimido[4,5-*b*]quinoline
Sulfonamide
Carbonic anhydrase II
Anticancer
γ-Radiation

ABSTRACT

Sulfonamide bearing compounds posses many types of biological activities and have recently been reported to show substantial antitumor activity *in vitro* and/or *in vivo*. There are a variety of mechanisms for the anticancer activity, and the most prominent mechanism is the inhibition of carbonic anhydrase (CA) isozymes. The present work reports the synthesis of twenty novel quinoline and pyrimido[4,5-*b*] quinoline derivatives bearing a sulfonamide moiety. The new synthesized compounds were designed in compliance with the general pharmacophoric requirements for CA inhibiting anticancer drugs, as this may play a role in their anticancer activity. All the newly synthesized compounds were evaluated for their *in vitro* anticancer activity against human breast cancer cell line (MCF7). Compounds **6**, **9** and **18** showed IC_{50} values (72.9 μM, 72.1 μM and 71.9 μM, respectively) comparable to that of the reference drug doxorubicin (IC_{50} = 71.8 μM). On the other hand, compound **8** exhibited better activity than doxorubicin with an IC_{50} value of 64.5 μM. Additionally, the most potent compounds **8** and **18** were evaluated for their ability to enhance the cell killing effect of γ-radiation.

1. Introduction

Sulfonamides posses many types of biological activities and many of them are widely used in therapy as antibacterial [1], hypoglycemic [2], diuretic [3,4], anti-carbonic anhydrase [3,5] and antithyroid agents [6]. Recently, a host of structurally novel sulfonamide derivatives have been reported to show substantial antitumor activity *in vitro* and/or *in vivo* [7–11].

It has been known that aryl/heteroaryl sulfonamides may act as antitumor agents through a variety of mechanisms such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y. Moreover, following an extensive evaluation, numerous sulfonamides were found to act as carbonic anhydrase (CA) inhibitors [12–15]. The most prominent mechanism was the inhibition of carbonic anhydrase isozymes (CA) [16].

In brief, the α-CAs are a family of metalloenzymes involved in the catalysis of an important physiological reaction, which is the hydration of carbon dioxide to bicarbonate and a proton ($CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$). At least 13 enzymatically active isoforms have been discovered in higher vertebrates [12–15]. CAs are involved in pH regulation, secretion of electrolytes, respiration [17,18], biosynthetic reactions which require CO_2/bicarbonate as substrate such as gluconeogenesis, lipogenesis, ureagenesis, and pyrimidines synthesis among others [19]. Other roles for these enzymes were highlighted, such as calcification and bone resorption [19].

On the other hand, quinoline derivatives are important biologically active compounds showing anticancer activity [20–22]. In the light of these facts, and as a continuation of our previous reported work [23,24], we planned to synthesize a novel series of quinoline and pyrimido[4,5-*b*]quinoline derivatives bearing a sulfonamide moiety, in order to study their structure activity relationship and hoping that the new compounds might show significant anticancer activity. Moreover, we also aimed to evaluate these new compounds for their *in vitro* anticancer activity in combination with γ-radiation, to evaluate their ability to enhance the cytotoxic activity of γ-radiation.

2. Results and discussion

A general pharmacophore (Fig. 1) for the compounds acting as carbonic anhydrase inhibitors has been reported by Thiry et al. [25], from the analysis of the CA active site and from the structure of inhibitors described in the literature [15].

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doi:10.1016/j.ejmech.2010.05.014

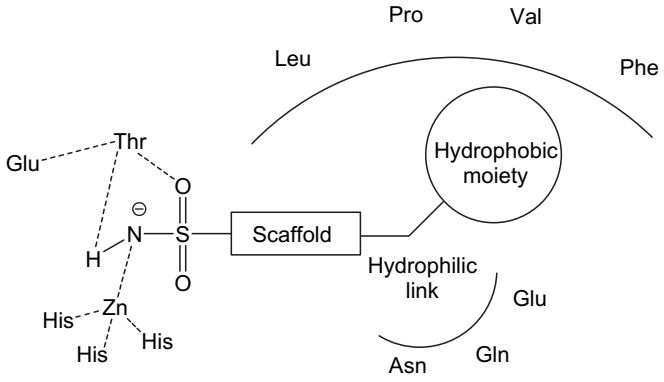


Fig. 1. Structural elements of CA inhibitors in the CA enzymatic active site.

This pharmacophore includes the structural elements that are required to be present in the compounds in order to act as CA inhibitors. This includes the presence of a sulfonamide moiety which coordinates with the zinc ion of the active site of the CA and the sulfonamide is attached to a scaffold, which is usually a benzene ring. The side chain might posses a hydrophilic link able to interact with the hydrophilic part of the active site and a hydrophobic moiety which can interact with the hydrophobic part of the CA active site.

Fig. 2 illustrates two representative examples of the newly synthesized compounds showing compliance with the above-mentioned pharmacophore model.

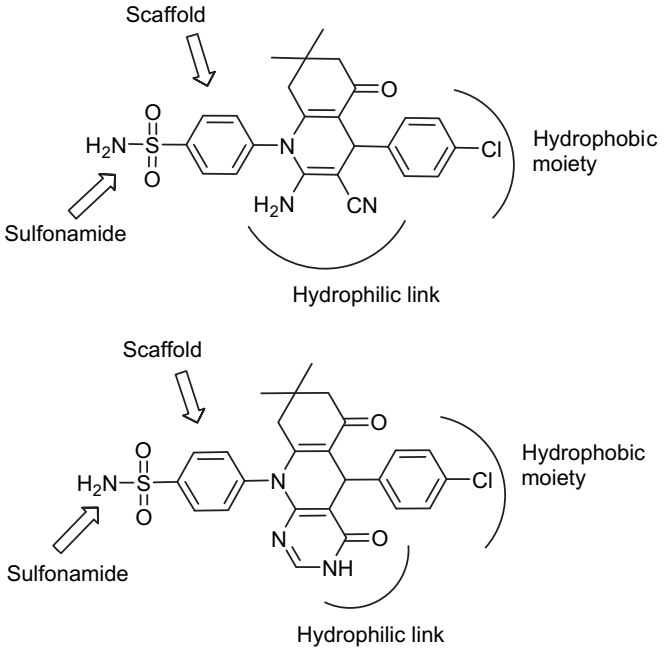


Fig. 2. Representative examples of the synthesized compounds showing the compliance with the general pharmacophore of sulfonamide compounds acting as CA inhibitors.

2.1. Chemistry

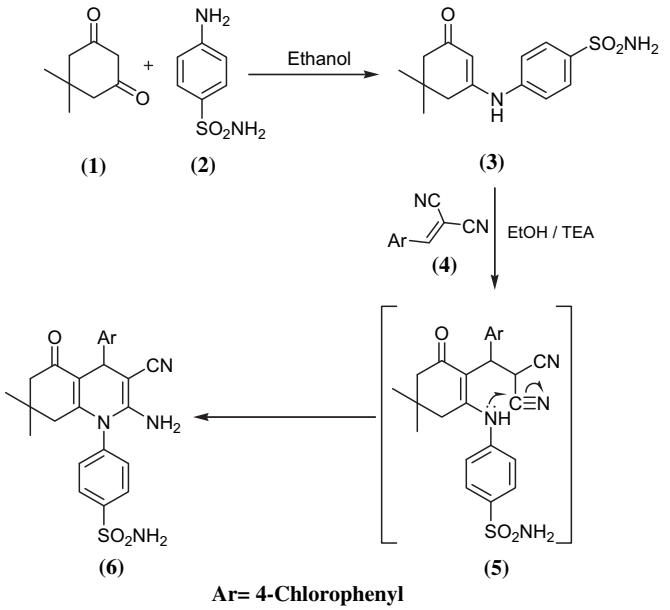
Enaminone **3** was obtained from condensation of 5,5-dimethyl-1,3-cyclohexandione **1** with sulfanilamide **2** [23]. Treatment of enaminone **3** with 2-(4-chlorobenzylidene)malononitrile **4** in ethanol containing a catalytic amount of triethylamine, as a base catalyst, yielded the corresponding hexahydroquinoline derivative **6**, via the formation of the intermediate Michael type product **5**, followed by intramolecular cyclization (Scheme 1).

The pyrimido[4,5-*b*]quinoline derivative **7** was obtained by refluxing compound **6** in formic acid. When compound **6** was refluxed in acetic anhydride for 5 hours and 10 hours, the mono-acetyl derivative **8** and the diacetyl derivative **9** were obtained, respectively. While refluxing compound **6** in acetic anhydride for 15 hours yielded the fused pyrimido[4,5-*b*]quinoline system **10**. Also, the pyrimido[4,5-*b*]quinoline derivative **11** was obtained by the reaction of compound **6** with formamide (Scheme 2).

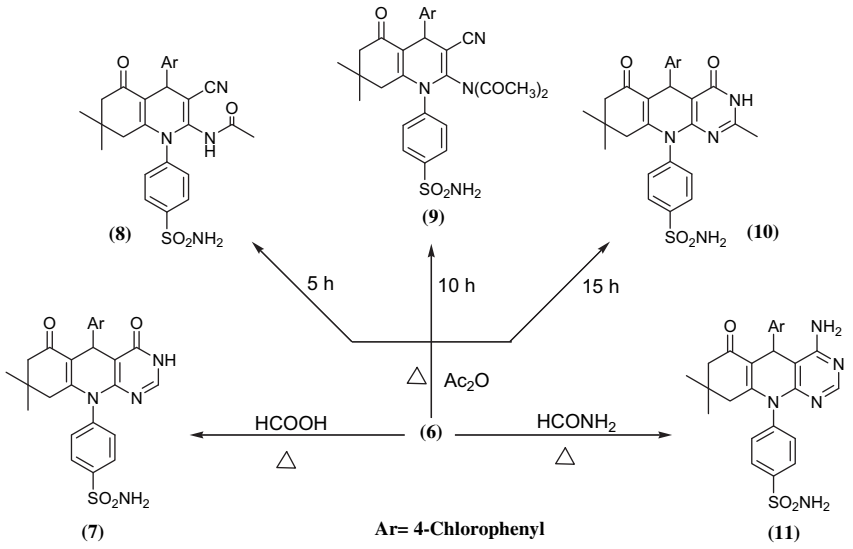
Treatment of compound **6** with triethylorthoformate in the presence of acetic anhydride yielded the quinoline derivative **12**. Reaction of compound **6** with chloroacetyl chloride at room temperature afforded the quinoline derivative **13**. While refluxing compound **6** with chloroacetyl chloride in dimethyl formamide for 16 hours, yielded the 2-chloromethyl-pyrimido[4,5-*b*]quinoline derivative **14**. Fusion of compound **6** with ethyl cyanoacetate yielded the corresponding 2-(cyanomethyl)-pyrimido[4,5-*b*]quinoline derivative **15**. The formation of compound **15** was assumed to proceed via elimination of 1 mol of ethanol followed by intramolecular cyclization. The thioureido derivative **16** was obtained by the reaction of compound **6** with ethyl isothiocyanate in dimethyl formamide containing a catalytic amount of triethylamine (Scheme 3).

Fusion of compound **6** with succinic anhydride yielded the 2,5-dioxopyrrolidinyl derivative **17**. Stirring of compound **6** in conc. H_2SO_4 caused partial hydrolysis of the cyano group yielding the carboxamide derivative **18**. Additionally, the imidazolyl derivative **19** was obtained by the treatment of compound **6** with ethylene diamine in the presence of carbon disulfide. The reaction proceeded via intramolecular cyclization through the elimination of 1 mole of ammonia. Also, the quinoline derivative **20** was obtained by the reaction of compound **6** with ethyl acetoacetate (Scheme 4).

Treatment of compound **7** with phosphorus pentasulfide in pyridine afforded the 4-thioxo-pyrimido[4,5-*b*]quinoline derivative **21**. While, the 4-chloro-pyrimido[4,5-*b*]quinoline derivative **22** was obtained by refluxing compound **7** in thionyl chloride for 2 h. Compound **23** was obtained by the treatment of compound **7** with ethyl bromoacetate in dry acetone in the presence of anhydrous



Scheme 1.



Scheme 2.

potassium carbonate. The 4-hydrazinyl derivative **24** and the 4-isothiocyanato derivative **25** were obtained by the reaction of the 4-chloro-pyrimido[4,5-*b*]quinoline derivative **22** with hydrazine hydrate and ammonium thiocyanate, respectively (Scheme 5).

2.2. In vitro anticancer screening

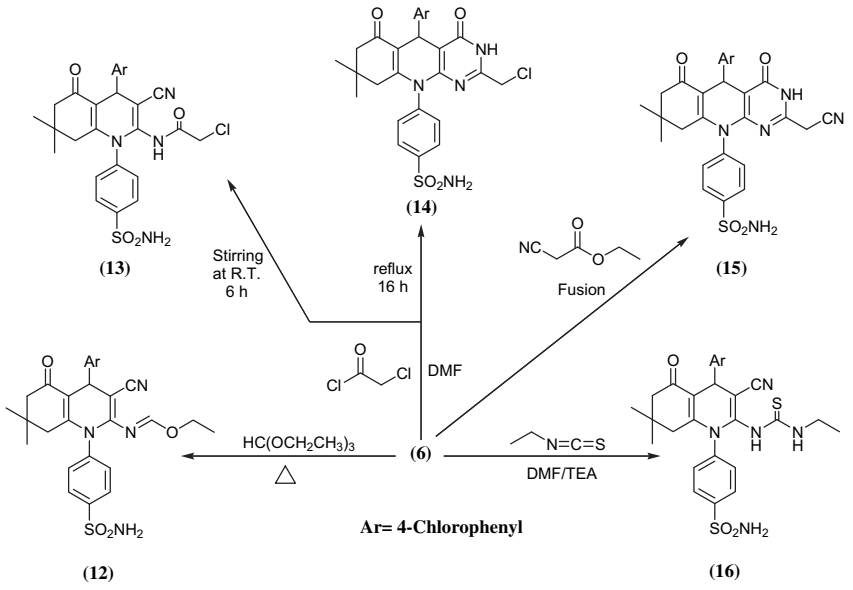
The newly synthesized compounds were evaluated for their *in vitro* cytotoxic activity against human breast cancer cell line, MCF7.

Doxorubicin which is one of the most effective anticancer agents was used as the reference drug in this study. The relationship between surviving fraction and drug concentration was plotted to obtain the survival curve of breast cancer cell line (MCF7). The response parameter calculated was the IC_{50} value, which corresponds to the concentration required for 50% inhibition of cell viability. Table 1 shows the *in vitro* cytotoxic activity of the synthesized compounds where some compounds exhibited significant activity compared to the reference drug.

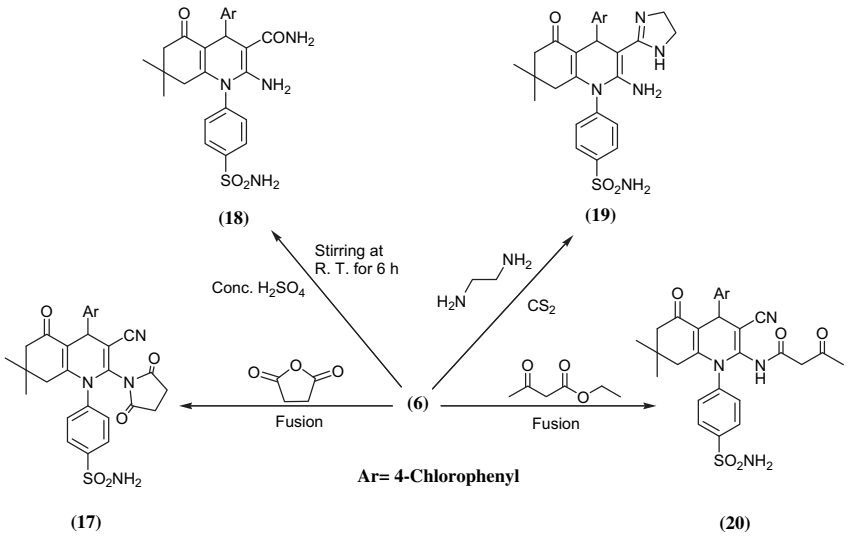
From the results in Table 1, it was found that the quinoline derivative **8** ($IC_{50} = 64.5$ μM) was the most potent compound in this screening, and exhibited a higher cytotoxic activity when compared with the reference drug doxorubicin ($IC_{50} = 71.8$ μM). Compounds **6**, **9** and **18** are nearly as active as doxorubicin, while compounds **7**, **10**–**13**, **16**, **17**, **22**, **24** and **25** showed lower IC_{50} values than that of the reference drug, ranging from 76–99.6 μM.

2.3. Radiosensitizing activity

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



Scheme 3.



Scheme 4.

radiotherapy and chemotherapy is required. The other idea is the enhancement of radiation effects.

Cytotoxic agents can enhance 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 [26].

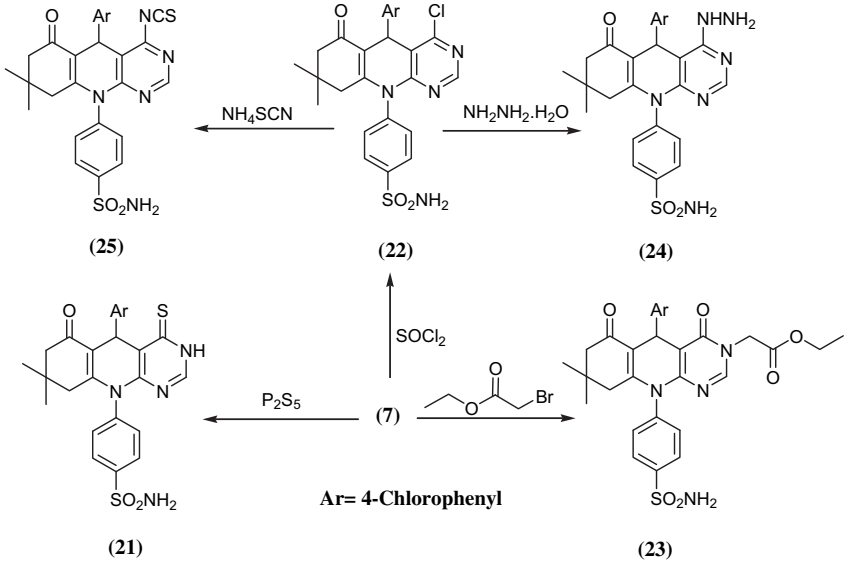
Consequently, the ability of the most two active compounds, compounds **8** and **18**, to enhance the cell killing effect of γ-irradiation was studied. From the results obtained in Table 1, compound **8** showed an *in vitro* cytotoxic activity with IC_{50} value of 64.5 μM, when the cells were subjected to different concentrations of the compound alone. While when the cells were subjected to the same concentrations of compound **8**, and irradiated with a single dose of γ-radiation at a dose level of 8 Gy, as shown in Table 2, the IC_{50} value was synergistically decreased to 33.1 μM (Fig. 3).

Similarly, compound **18** showed IC_{50} value of 71.9 μM when used alone, as shown in Table 1. The IC_{50} value was decreased to 44.4 μM, when the cells were treated with compound **18** in combination with γ-radiation (Fig. 4).

From these results, we can conclude that using the combination of compound **8** or **18** and ionizing radiation synergistically enhanced growth inhibition on breast cancer cells, compared with each agent alone.

3. Conclusion

The objective of the present study was to synthesize and investigate the anticancer activity of some new quinoline and pyrimidoquinoline derivatives bearing a free sulfonamide moiety. Some of these new compounds exhibited significant anticancer activity, when compared to doxorubicin as a reference drug. Since it was reported that compounds bearing a free sulfonamide group may exhibit potent carbonic anhydrase inhibition activity, which is considered to be an interesting target for the design of anticancer



Scheme 5.

Table 1
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 ± SE)[#]				
Doxorubicin	0.721 ± 0.02	0.546 ± 0.02	0.461 ± 0.01	0.494 ± 0.03	71.8
6	0.915 ± 0.04	0.612 ± 0.01	0.429 ± 0.04	0.484 ± 0.01	72.9
7	0.891 ± 0.03	0.676 ± 0.01	0.499 ± 0.01	0.468 ± 0.01	76.8
8	0.948 ± 0.01	0.779 ± 0.03	0.446 ± 0.01	0.324 ± 0.01	64.5
9	0.895 ± 0.04	0.773 ± 0.02	0.504 ± 0.01	0.414 ± 0.03	72.1
10	0.976 ± 0.02	0.721 ± 0.04	0.450 ± 0.05	0.557 ± 0.04	85.9
11	0.886 ± 0.02	0.612 ± 0.05	0.495 ± 0.03	0.602 ± 0.03	96.6
12	0.803 ± 0.04	0.551 ± 0.05	0.498 ± 0.04	0.607 ± 0.01	97.2
13	0.986 ± 0.01	0.736 ± 0.01	0.523 ± 0.04	0.502 ± 0.06	84.3
14	0.914 ± 0.03	0.775 ± 0.05	0.731 ± 0.05	0.625 ± 0.04	>100
15	0.971 ± 0.01	0.901 ± 0.01	0.774 ± 0.04	0.525 ± 0.01	>100
16	0.916 ± 0.01	0.837 ± 0.02	0.594 ± 0.06	0.561 ± 0.04	99.6
17	0.930 ± 0.02	0.813 ± 0.02	0.584 ± 0.02	0.549 ± 0.02	95.2
18	0.922 ± 0.02	0.662 ± 0.01	0.445 ± 0.01	0.452 ± 0.01	71.9
19	0.939 ± 0.01	0.763 ± 0.01	0.568 ± 0.03	0.621 ± 0.03	>100
20	0.897 ± 0.01	0.820 ± 0.03	0.648 ± 0.05	0.549 ± 0.06	>100
21	0.927 ± 0.03	0.910 ± 0.02	0.884 ± 0.04	0.814 ± 0.01	>100
22	0.843 ± 0.05	0.696 ± 0.03	0.476 ± 0.03	0.546 ± 0.05	86.5
23	0.954 ± 0.01	0.880 ± 0.01	0.653 ± 0.03	0.563 ± 0.03	>100
24	0.940 ± 0.02	0.788 ± 0.01	0.672 ± 0.03	0.358 ± 0.03	76
25	0.972 ± 0.01	0.721 ± 0.01	0.419 ± 0.01	0.515 ± 0.04	79.6

[#] Each value is the mean of three values ± Standard Error.

agents, the results obtained from the anticancer screening may give a suggestion that the synthesized compounds may act as carbonic anhydrase inhibitors and this may contribute in part to their anticancer activity. Moreover, the most two active compounds showed the ability to sensitize cancer cells to the lethal effects of ionizing radiation.

4. Experimental

4.1. Chemistry

Melting points are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill, UK). Elemental analysis (C, H, N) were performed on Perkin-Elmer 2400 analyser (Perkin-Elmer, Norwalk, CT, USA) at the microanalytical laboratories of the Faculty of Science, Cairo University. All compounds were within ±0.4% of the theoretical values. The IR spectra (KBr) were measured on Shimadzu IR 110 spectrophotometer (Shimadzu, Koyoto, Japan), ^{1}H NMR spectra were obtained on a Bruker proton NMR-Avance 300 (300 MHz) (Bruker, Munich, Germany), in DMSO-d_6 as a solvent, using tetramethylsilane (TMS) as internal standard. Mass spectra were run on HP Model MS-5988 (Hewlett Packard, Palo, Alto, California, USA). All reactions were monitored by thin layer chromatograph (TLC) using precoated Aluminium sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Darmstadt, Germany).

4.1.1. 4-(5,5-Dimethyl-3-oxocyclohex-1-enylamino) benzenesulfonamide (3)

Prepared according to the previously reported procedure [23].

4.1.2. 4-(2-Amino-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide **(6)**

A mixture of 4-(5,5-dimethyl-3-oxocyclohex-1-enylamino)benzenesulfonamide **3** (2.94 g, 10 mmol) and 2-(4-chlorobenzylidene) malononitrile **4** (1.88 g, 10 mmol) in EtOH (20 mL) containing 3 drops of triethylamine was refluxed for 6 h. The reaction mixture was filtered while hot and the solid obtained was recrystallized from dioxane to give **6**: Yield, 85%; m.p. 280–282 °C; IR, cm^{-1}: 3467, 3346, 3199 (2NH_2), 3065 (CH arom.), 2969, 2879 (CH aliph.), 2174 (C≡N), 1645 (C=O), 1374, 1162 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, 2CH_3], 1.6–2.3 [m, 4H, 2CH_2], 4.5 [s, 1H, CH], 5.5 [s, 2H, NH_2, exchangeable with D_2O], 7.3–8.0 [m, 10H, Ar-H + SO_2NH_2, exchangeable with D_2O]. ^{13}C NMR ($CDCl_3$) δ: 27.3, 33.4, 38.5, 43.3, 51.0, 57.9, 112.0, 117.1, 128.5, 130.4, 142.2, 143.9, 153.0, 167.5, 194.0. MS, m/z (%): 482 [M$^+$] (27.47), 371 (100). Anal. Calcd. For $C_{24}H_{23}ClN_4O_3S$: C, 59.68; H, 4.80; N, 11.60. Found: C, 59.92; H, 5.00; N, 11.33.

4.1.3. 4-(5-(4-Chlorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide **(7)**

A solution of compound **6** (0.482 g, 1 mmol) in formic acid (30 mL) was refluxed for 5 h, the reaction mixture was cooled and then poured onto cold water, the obtained solid was recrystallized from dioxane to give compound **7**: Yield, 78%; m.p. 162–164 °C; IR, cm^{-1}: 3390, 3359, 3263 (NH, NH_2), 3072 (CH arom.), 2960, 2885 (CH aliph.), 1708, 1644 (2 C=O), 1627 (C=N), 1372, 1165 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.9, 1.0 [2s, 6H, 2CH_3], 1.9–2.3 [m, 4H, 2CH_2], 4.6 [s, 1H, CH], 7.3–7.6 [m, 10H, Ar-H + SO_2NH_2], 7.9 [s, 1H, NH], 8.0 [s, 1H, CH=N]. MS, m/z (%): 495 [M-CH_3] (2.25), 483 (100). Anal. Calcd. For $C_{25}H_{23}ClN_4O_4S$: C, 58.76; H, 4.54; N, 10.96. Found: C, 58.94; H, 4.38; N, 11.18.

4.1.4. N-(4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide **(8)**

A solution of compound **6** (0.482 g, 1 mmol) 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 compound **8**: Yield, 82%; m.p. 149–151 °C; IR, cm^{-1}: 3453, 3231, 3208 (NH, NH_2), 3050 (CH arom.), 2955, 2875 (CH aliph.), 2213 (C≡N), 1720, 1649 (2 C=O), 1371, 1163 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.8, 0.9 [2s, 6H, 2CH_3], 1.5 [s, 3H, $COCH_3$], 1.9–2.2 [m, 4H, 2CH_2], 4.8 [s, 1H, CH], 7.3–8.0 [m, 8H, Ar-H + SO_2NH_2], 9.9 [s, 1H, NH]. Anal. Calcd. For $C_{26}H_{25}ClN_4O_4S$: C, 59.48; H, 4.80; N, 10.67. Found: C, 59.31; H, 5.05; N, 10.49.

4.1.5. N-acetyl-N-(4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl) acetamide **(9)**

A solution of compound **6** (0.482 g, 1 mmol) in acetic anhydride (20 mL) was refluxed for 10 h, the reaction mixture was then concentrated, the solid separated was recrystallized from ethanol to give compound **9**: Yield, 91%; m.p. 182–184 °C; IR, cm^{-1}: 3447, 3260, 3212 (NH, NH_2), 3098 (CH arom.), 2959, 2873 (CH aliph.), 2213 (C≡N), 1728, 1655 (3C=O), 1370, 1164 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, 2CH_3], 1.8–2.3 [m, 4H, 2CH_2], 2.4 [s, 6H, 2$COCH_3$], 4.8 [s, 1H, CH], 7.2–8.0 [m, 10H, Ar-H + SO_2NH_2]. MS, m/z (%): 566 [M-1] (0.27), 90 (100). Anal. Calcd. For $C_{28}H_{27}ClN_4O_5S$: C, 59.31; H, 4.80; N, 9.88. Found: C, 59.52; H, 4.58; N, 10.07.

4.1.6. 4-(5-(4-Chlorophenyl)-2,8,8-trimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide **(10)**

A solution of compound **6** (0.482 g, 1 mmol) in acetic anhydride (20 mL) was refluxed for 15 h, the reaction mixture was then concentrated, the solid separated was recrystallized from ethanol to give compound **10**: Yield, 65%; m.p. 212–214 °C; IR, cm^{-1}: 3466, 3290, 3200 (NH, NH_2), 3062 (CH arom.), 2959, 2874 (CH aliph.), 1724, 1656 (2 C=O), 1595 (C=N), 1370–1163 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, 2CH_3], 1.9–2.2 [m, 4H, 2CH_2], 2.4 [s, 3H, CH_3], 4.9 [s, 1H, CH], 7.3–8.0 [m, 11H, Ar-H + NH + SO_2NH_2]. Anal. Calcd. For $C_{26}H_{25}ClN_4O_4S$: C, 59.48; H, 4.80; N, 10.67. Found: C, 59.68; H, 4.66; N, 10.91.

Table 2
In vitro anticancer screening of compounds **8** and **18** 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 ± SE)[#]						
8	1.000	0.927 ± 0.02*	0.427 ± 0.02*	0.503 ± 0.02*	0.310 ± 0.01*	0.137 ± 0.01*	33.1
18	1.000	0.927 ± 0.02*	0.653 ± 0.02*	0.517 ± 0.02*	0.281 ± 0.01*	0.282 ± 0.01*	44.4

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

*4.1.7. 4-(4-Amino-5-(4-chlorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide **(11)***

A solution of compound **6** (0.482 g, 1 mmol) in formamide (30 mL) was refluxed for 5 h, the reaction mixture was cooled and then poured onto cold water, the obtained solid was recrystallized from dioxane to give compound **11**. Yield, 49%; m.p. 149–151 °C; IR, cm^{-1}: 3421, 3338, 3263 (NH_2), 3052 (CH arom.), 2952, 2862 (CH aliph.), 1645 (C=O), 1598 (C=N), 1376, 1155 (SO_2). MS, m/z (%): 510 [M^+] (0.46), 87 (100). Anal. Calcd. For $C_{25}H_{24}ClN_5O_3S$: C, 58.88; H, 4.74; N, 13.73. Found: C, 59.11; H, 4.59; N, 13.92.

*4.1.8. Ethyl N-4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-ylformimidate **(12)***

A solution of compound **6** (0.482 g, 1 mmol) in triethylorthoformate (30 mL) containing 3 drops of acetic anhydride was refluxed for 8 h, the reaction mixture was cooled and then poured onto cold water, the obtained solid was recrystallized from methanol to give compound **12**. Yield, 98%; m.p. 154–156 °C; IR, cm^{-1}: 3354, 3251 (NH_2), 3071 (CH arom.), 2966, 2886 (CH aliph.), 2194 (C≡N), 1642 (C=O), 1590 (C=N), 1378, 1175 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.8, 0.9 [2s, 6H, $2CH_3$], 1.2 [t, 3H, CH_3 ethyl], 1.9–2.2 [m, 4H, $2CH_2$], 4.3 [q, 2H, CH_2 ethyl], 4.6 [s, 1H, CH], 7.4–8.0 [m, 10H, Ar-H + SO_2NH_2], 8.7 [s, 1H, N=CH]. ^{13}C NMR ($CDCl_3$) δ: 15.2, 27.4, 33.2, 39.9, 44.0, 51.9, 63.5, 76.6, 112.1, 117.2, 128.9, 131.1, 142.9, 153.5, 155.7, 161.6, 194.2. MS, m/z (%): 539 [M^+] (0.52), 90 (100). Anal. Calcd. For $C_{27}H_{27}ClN_4O_4S$: C, 60.16; H, 5.05; N, 10.39. Found: C, 59.95; H, 5.12; N, 10.59.

*4.1.9. 2-Chloro-N-(4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl) acetamide **(13)***

A mixture of compound **6** (0.482 g, 1 mmol) and chloroacetyl chloride (0.112 g, 1 mmol) in Dimethyl formamide (20 mL) was stirred at room temperature for 6 h. The reaction mixture was poured onto cold water and the solid obtained was recrystallized from dioxane to give compound **13**: Yield, 91%; m.p. 164–166 °C; IR, cm^{-1}: 3371, 3300, 3251 (NH, NH_2), 3096 (CH aliph.), 2959, 2882 (CH aliph.), 2213 (C≡N), 1705, 1644 (2 C=O), 1371, 1162 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.8–2.2 [m, 4H, $2CH_2$], 4.2 [s, 1H, CH], 4.7 [s, 2H, CH_2Cl], 7.4–7.9 [m, 10H, Ar-H + SO_2NH_2], 10.2 [s, 1H, NH]. MS, m/z (%): 559 [M^+] (1.43), 63 (100). Anal. Calcd. For $C_{26}H_{24}Cl_2N_4O_4S$: C, 55.82; H, 4.32; N, 10.01. Found: C, 55.92; H, 4.60; N, 9.80.

*4.1.10. 4-(2-(Chloromethyl)-5-(4-chlorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl) benzenesulfonamide **(14)***

A mixture of compound **6** (0.482 g, 1 mmol) and chloroacetyl chloride (0.112 g, 1 mmol) in Dimethyl formamide (20 mL) was refluxed for 16 h. The reaction mixture was cooled and then poured onto cold water and the solid obtained was recrystallized from dioxane to give compound **14**: Yield, 64%; m.p. >300 °C; IR, cm^{-1}: 3460, 3359, 3249 (NH, NH_2), 3063 (CH arom.), 2939, 2879 (CH aliph.), 1671, 1648 (2 C=O), 1572 (C=N), 1395, 1156 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.8, 0.9 [2s, 6H, $2CH_3$], 1.9–2.2 [m, 4H, $2CH_2$], 4.6 [s, 1H, CH], 5.1 [s, 2H, CH_2Cl], 7.3–7.9 [m, 10H, Ar-H + SO_2NH_2], 8.2 [s, 1H, NH]. Anal. Calcd. For $C_{26}H_{24}Cl_2N_4O_4S$: C, 55.82; H, 4.32; N, 10.01. Found: C, 56.01; H, 4.19; N, 9.78.

*4.1.11. 4-(5-(4-Chlorophenyl)-2-(cyanomethyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl) benzenesulfonamide **(15)***

A mixture of compound **6** (0.482 g, 1 mmol) and ethyl cyanoacetate (10 mL) was refluxed together for 5 h. The formed solid mass was collected and recrystallized from dioxane to give compound **15:** Yield, 82%; m.p. >300 °C; IR, cm^{-1}: 3370, 3255, 3208 (NH, NH_2), 3038 (CH arom.), 2962, 2890 (CH aliph.), 2214 (C≡N), 1686, 1645 (2 C=O), 1621 (C=N), 1365, 1159 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.8, 0.9 [2s, 6H, $2CH_3$], 1.9, 2.2 [2s, 4H, $2CH_2$], 4.1 [s, 1H, CH], 4.7 [s, 2H, CH_2CN], 7.3-8.0 [m, 9H, Ar-H + NH], 12.5 [s, 2H, SO_2NH_2]. Anal.

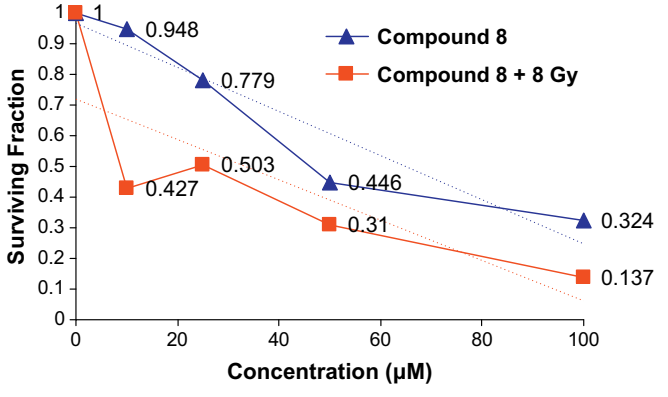


Fig. 3. Survival curve for MCF7 cell line for compound **8** alone or in combination with γ-irradiation (8 Gy).

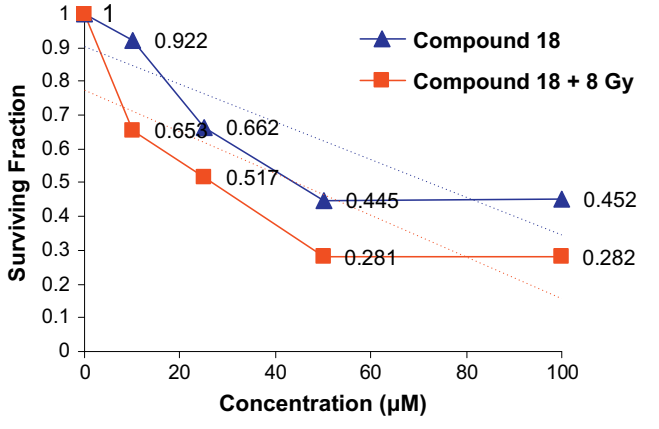


Fig. 4. Survival curve for MCF7 cell line for compound **18** alone or in combination with γ-irradiation (8 Gy).

Calcd. For $C_{27}H_{24}ClN_5O_4S$: C, 58.96; H, 4.40; N, 12.73. Found: C, 59.13; H, 4.19; N, 13.02.

4.1.12. 4-(4-(4-Chlorophenyl)-3-cyano-2-(3-ethylthioureido)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl) benzenesulfonamide (16)

A mixture of compound **6** (0.482 g, 1 mmol) and ethyl isothiocyanate (0.086 g, 1 mmol) in dimethyl formamide (20 mL) containing 3 drops of triethylamine was refluxed for 10 h. The reaction mixture was cooled and then poured onto cold water, the solid obtained was recrystallized from ethanol to give compound **16**: Yield, 94%; m.p. 182–184 °C; IR, cm^{-1}: 3412, 3347, 3281 (NH, NH_2), 3097 (CH arom.), 2963, 2878 (CH aliph.), 2181 (C≡N), 1645 (C=O), 1256 (C=S), 1369, 1136 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.2 [t, 3H, CH_3 ethyl], 1.8–2.2 [m, 4H, $2CH_2$], 3.2 [q, 2H, CH_2 ethyl], 4.4 [s, 1H, CH], 7.2–7.8 [m, 10H, Ar-H + SO_2NH_2], 8.2, 9.0 [2s, 2H, 2NH]. MS, m/z (%): 570 [M^+] (0.7), 78 (100). Anal. Calcd. For $C_{27}H_{28}ClN_5O_3S_2$: C, 56.88; H, 4.95; N, 12.28. Found: C, 56.68; H, 4.75; N, 12.51.

4.1.13. 4-(4-(4-Chlorophenyl)-3-cyano-2-(2,5-dioxopyrrolidin-1-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl) benzenesulfonamide (17)

A mixture of compound **6** (0.482 g, 1 mmol) and succinic anhydride (0.15 g, 1.5 mmol) was fused together in an oil bath at 250 °C for 15 min, the fused mass was dissolved in dimethyl formamide and poured onto cold water, the solid obtained was recrystallized from ethanol to give compound **17**: Yield, 55%; m.p. 194–196 °C; IR, cm^{-1}: 3360, 3249 (NH_2), 3070 (CH arom.), 2959, 2876 (CH aliph.), 2213 (C≡N), 1734, 1655 (3C=O), 1369, 1165 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.8 [2s, 6H, $2CH_3$], 1.9–2.2 [m, 4H, $2CH_2$], 4.8 [s, 1H, CH], 5.1 [t, 4H, $2CH_2$ pyrrolidine], 7.0–8.0 [m, 10H, Ar-H + SO_2NH_2]. MS, m/z (%): 564 [M-1] (0.6), 78 (100). Anal. Calcd. For $C_{28}H_{25}ClN_4O_5S$: C, 59.52; H, 4.46; N, 9.92. Found: C, 59.35; H, 4.71; N, 9.62.

4.1.14. 2-Amino-4-(4-chlorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (18)

A solution of compound **6** (0.482 g, 1 mmol) in conc. H_2SO_4 (10 mL) was stirred for 6 h at room temperature, then the reaction mixture was poured onto cold water. The obtained solid was recrystallized from ethanol to give **18**: Yield, 72%; m.p. 256–258 °C; IR, cm^{-1}: 3444, 3339, 3240 (NH_2), 3069 (CH arom.), 2961, 2884 (CH aliph.), 1706, 1677 (2 C=O), 1376, 1165 (SO_2). MS, m/z (%): 501 [M^+] (1.41), 458 (100). Anal. Calcd. For $C_{24}H_{25}ClN_4O_4S$: C, 57.54; H, 5.03; N, 11.18. Found: C, 57.70; H, 4.81; N, 11.44.

4.1.15. 4-(2-Amino-4-(4-chlorophenyl)-3-(4,5-dihydro-1H-imidazol-2-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (19)

A mixture of compound **6** (0.482 g, 1 mmol) and ethylene diamine (7 mL) was refluxed in carbon disulfide (7 mL) for 6 h. The reaction mixture was cooled and then poured onto cold water. The solid obtained was recrystallized from dioxane to give compound **19**: Yield, 44%; m.p. 184–186 °C; IR, cm^{-1}: 3400, 3319, 3200 (NH, NH_2), 3048 (CH arom.), 2930, 2867 (CH aliph.), 1643 (C=O), 1591 (C=N), 1346, 1166 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.9, 1.0 [2s, 6H, $2CH_3$], 1.9–2.2 [m, 4H, $2CH_2$], 4.5 [s, 1H, CH], 5.6 [s, 2H, NH_2], 6.4–6.6 [m, 4H, $2CH_2$ imidazole], 7.1–8.0 [m, 10H, Ar-H + SO_2NH_2], 8.3 [t, 1H, NH]. Anal. Calcd. For $C_{26}H_{28}ClN_5O_3S$: C, 59.36; H, 5.36; N, 13.31. Found: C, 59.18; H, 5.55; N, 13.50.

4.1.16. N-(4-(4-chlorophenyl)-3-cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)-3-oxobutanamide (20)

A mixture of compound **6** (0.482 g, 1 mmol) and ethyl acetoacetate (10 mL) was refluxed together for 5 h. The formed solid mass was collected and recrystallized from dioxane to give compound **20:** Yield, 90%; m.p. 138–140 °C; IR, cm^{-1}: 3366, 3307, 3253 (NH, NH_2), 3095 (CH arom.), 2961, 2896 (CH aliph.), 2183 (C≡N), 1727, 1702, 1644 (C=O), 1338, 1166 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.9–2.1 [m, 4H, $2CH_2$], 2.2 [s, 3H, $COCH_3$], 4.5 [s, 1H, CH], 4.8 [s, 1H, $COCH_2$], 7.2–8.0 [m, 10H, Ar-H + SO_2NH_2], 10.1 [s, 1H, NH]. Anal. Calcd. For $C_{28}H_{27}ClN_4O_5S$: C, 59.31; H, 4.80; N, 9.88. Found: C, 59.52; H, 4.66; N, 9.58.

4.1.17. 4-(5-(4-Chlorophenyl)-8,8-dimethyl-6-oxo-4-thioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl) benzenesulfonamide (21)

A mixture of compound **7** (0.51 g, 1 mmol) and phosphorus pentasulfide (0.22 g, 1 mmol) in pyridine (20 mL) was refluxed for 8 h, the reaction mixture was cooled and then poured onto cold water, then acidified with dil HCl. The solid obtained was recrystallized from ethanol to give compound **21**: Yield, 81%; m.p. 182–184 °C; IR, cm^{-1}: 3384, 3317, 3255 (NH, NH_2), 3074 (CH arom.), 2959, 2875 (CH aliph.), 1660 (C=O), 1252 (C=S), 1374, 1165 (SO_2). MS, m/z (%): 527 [M^+] (0.21), 458 (100). Anal. Calcd. For $C_{25}H_{23}ClN_4O_3S_2$: C, 56.97; H, 4.40; N, 10.63. Found: C, 56.80; H, 4.58; N, 10.89.

4.1.18. 4-(4-Chloro-5-(4-chlorophenyl)-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide (22)

A solution of compound **7** (0.51 g, 1 mmol) in thionyl chloride (10 mL) was refluxed for 2 h, the thionyl chloride was then removed by distillation, the obtained solid was washed twice with benzene and recrystallized from dioxane to give compound **22**: Yield, 98%; m.p. 228–230 °C; IR, cm^{-1}: 3345, 3260 (NH_2), 3090 (CH arom.), 2979, 2883 (CH aliph.), 1673 (C=O), 1339, 1162 (SO_2). MS, m/z (%): 531 [M+2] (0.8), 87 (100). Anal. Calcd. For $C_{25}H_{22}Cl_2N_4O_3S$: C, 56.71; H, 4.19; N, 10.58. Found: C, 56.92; H, 4.38; N, 10.79.

4.1.19. Ethyl 2-(5-(4-chlorophenyl)-8,8-dimethyl-4,6-dioxo-10-(4-sulfamoylphenyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-3(4H,5H,10H)-yl)acetate (23)

A mixture of compound **7** (0.51 g, 1 mmol), ethyl bromoacetate (0.167 g, 1 mmol) and anhydrous potassium carbonate (1.5 g) was refluxed in dry acetone for 24 h. The reaction mixture was filtered while hot, and the filtrate was cooled then poured onto cold water. The solid obtained was recrystallized from ethanol to give compound **23**: Yield, 85%; m.p. 88–90 °C; IR, cm^{-1}: 3438, 3360 (NH_2), 3092 (CH arom.), 2963, 2890 (CH aliph.), 1738, 1642 (C=O), 1602 (C=N), 1364, 1168 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.9, 1.0 [2s, 6H, $2CH_3$], 1.3 [t, 3H, CH_3 ethyl], 1.9–2.2 [m, 4H, $2CH_2$], 4.1 [q, 2H, CH_2 ethyl], 4.2 [s, 2H, CH_2CO], 4.7 [s, 1H, CH], 7.1–7.9 [m, 10H, Ar-H + SO_2NH_2], 8.0 [s, 1H, N=CH]. Anal. Calcd. For $C_{29}H_{29}ClN_4O_6S$: C, 58.34; H, 4.90; N, 9.38. Found: C, 58.60; H, 5.06; N, 9.09.

4.1.20. 4-(5-(4-Chlorophenyl)-4-hydrazinyl-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl) benzenesulfonamide (24)

A mixture of compound **22** (0.529 g, 1 mmol) and hydrazine hydrate (0.1 mol) was refluxed in ethanol for 5 h. The reaction mixture was cooled and poured onto cold water. The solid obtained was recrystallized from dioxane to give compound **24**: Yield, 69%; m.p. 170–172 °C; IR, cm^{-1}: 3359, 3322, 3253 (NH, NH_2), 3092 (CH arom.), 2968, 2890 (CH aliph.), 1655 (C=O), 1590 (C=N), 1334, 1160 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.9, 1.0 [2s, 6H, $2CH_3$], 1.9–2.2 [m, 4H, $2CH_2$], 4.5 [s, 1H, CH], 6.4 [s, 2H, NH_2], 7.1–7.9 [m, 10H, Ar-H + SO_2NH_2], 8.0 [s, 1H, NH], 8.3 [s, 1H, N=CH]. Anal. Calcd. For $C_{25}H_{25}ClN_6O_3S$: C, 57.19; H, 4.80; N, 16.01. Found: C, 57.47; H, 4.51; N, 16.23.

*4.1.21. 4-(5-(4-Chlorophenyl)-4-isothiocyanato-8,8-dimethyl-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl) benzenesulfonamide **(25)***

A mixture of compound **22** (0.529 g, 1 mmol) and Ammonium thiocyanate (0.076 g, 1 mmol) was refluxed in dry acetone for 1 h. The reaction mixture was cooled and poured onto cold water. The solid obtained was recrystallized from ethanol to give compound **25**: Yield, 52%; m.p. 200–202 °C; IR, cm^{-1}: 3345, 3200 (NH_2), 3094 (CH arom.), 2976, 2883 (CH aliph.), 2023 (N=C=S), 1666 (C=O), 1610 (C=N), 1341, 1163 (SO_2). MS, m/z (%): 553 [M+1] (0.85), 90 (100). Anal. Calcd. For $C_{26}H_{22}ClN_5O_3S_2$: C, 56.57; H, 4.02; N, 12.69. Found: C, 56.71; H, 4.30; N, 12.48.

4.2. In vitro anticancer screening

Human tumor breast cell line (MCF7) was used in this study. 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. [27]. The *in vitro* anticancer screening was done by the pharmacology unit at the National Cancer Institute, Cairo University.

Cells were plated in 96-multiwell 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 dimethyl sulfoxide. Different concentrations of the compound under test (10, 25, 50, and 100 μM) were added to the cell monolayer. Triplicate wells were prepared for each individual concentration. 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 unbound 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 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 ± standard error and the results are given in Table 1.

4.3. Radiosensitizing activity

The most potent compounds resulted from the *in vitro* anticancer screening; the quinoline derivatives **8** and **18**, 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 these compounds to enhance the cell killing effect of γ-radiation.

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. Irradiation was performed in the National Cancer Institute, Cairo University, using Gamma cell-40 (^{60}Co) source.

The surviving fractions were expressed as means ± standard error. The results were analyzed using 1-way ANOVA test and given in Table 2.

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