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ORIGINAL RESEARCH

Docking study, in vitro anticancer screening and radiosensitizing evaluation of some new fluorine-containing quinoline and pyrimidoquinoline derivatives bearing a sulfonamide moiety

Mostafa M. Ghorab · Fatma A. Ragab · Helmy I. Heiba · Reem K. Arafa · Ebaa M. El-Hossary

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Abstract The present work reports the synthesis of 20 novel fluorine-containing 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 carbonic anhydrase (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 **11** and **12** exhibited better activities than the reference drug doxorubicin ($IC_{50} = 71.8$ μM) with IC_{50} values of 52.6 μM and 67.3 μM, respectively. On the other hand, compounds **6**, **10**, and **13** showed IC_{50} values (71.8 μM, 69.8 μM, and 70.8 μM, respectively) comparable to that of the reference drug doxorubicin. In addition, docking of the synthesized compounds into human carbonic anhydrase isozyme II (hCA II) active site was performed in order to predict the affinity and the orientation of these compounds at the isozyme active site. Also, the most active compounds, **11** and **12**, were selected and evaluated for their ability to enhance the cell killing effect of γ-radiation.

Keywords Quinoline · Fluorine · Sulfonamide · Carbonic anhydrase II · Anticancer · γ-Radiation

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Introduction

Sulfonamides posses many types of biological activities and many of them are widely used in therapy as antibacterial (Drews, 2000), hypoglycemic (Boyd, 1988), diuretic (Supuran and Scozzafava, 2000; Maren, 1976), anti-carbonic anhydrase (Supuran and Scozzafava, 2000; Supuran and Scozzafava, 2001), and antithyroid (Thornber, 1979) agents. Recently, a host of structurally novel sulfonamide derivatives have been reported to show substantial antitumor activity in vitro and/or in vivo (Abbate *et al.*, 2004; Ghorab *et al.*, 2006; Ismail *et al.*, 2006; Rostom, 2006; Supuran *et al.*, 2004).

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, and the most prominent mechanism is the inhibition of carbonic anhydrase (CA) isozymes (Casini *et al.*, 2002).

In addition, quinoline and fused quinoline derivatives are known to possess several biological activities including anticancer activity (Gopal *et al.*, 2003; Kim *et al.*, 2005; Zhao *et al.*, 2005). Also, several reduced quinoline derivatives have shown significant anticancer activity (Liou *et al.*, 2008).

Also, the special properties of the fluorine atom, such as strong electronegativity, small size, and the low polarizability of the C–F bond, can have considerable impact on the behavior of a molecule in a biological environment (Bégué and Delpon, 2006). The incorporation of fluorine into a drug allows simultaneous modulation of electronic, lipophilic, and steric parameters, all of which can critically influence both the pharmacodynamic and pharmacokinetic properties of drugs. Bioisosteric substitution for hydrogen

by fluorine is, therefore, an important strategy for incorporation of a group capable of reinforcing drug–receptor interactions (electronic modulation), aiding translocation across lipid bilayers or absorption (lipophilic modulation) and inducing conformational change/blocking metabolism (steric parameters) (Ismail, 2002).

In the light of these facts, and as a continuation of our previous reported work (Ghorab *et al.*, 2007; Ghorab *et al.*, 2009), we report here the synthesis of some new fluorine-containing quinoline and pyrimido[4,5-*b*]quinoline derivatives (**6–25**) having a free sulfonamide moiety, where their design complies with the general pharmacophore of the sulfonamide CA inhibitors. The anticancer screening was done against a human breast cancer cell line (MCF7). We also aimed to evaluate the ability of these compounds to enhance the cell killing effect of γ-radiation.

Results and discussion

A general pharmacophore (Fig. 1) for the compounds acting as carbonic anhydrase inhibitors has been reported by Thiry *et al.* (2006), from the analysis of the CA active site and from the structure of inhibitors described in the literature (Supuran *et al.*, 2003).

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.

Figure 2 includes representative examples of the synthesized compounds, showing compliance to the above-mentioned pharmacophore, and the compounds were synthesized according to Schemes 1, 2, 3, 4, and 5.

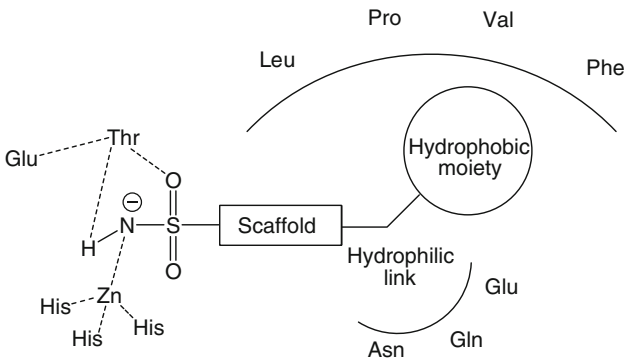


Fig. 1 Structural elements of CA inhibitors in the CA enzymatic active site

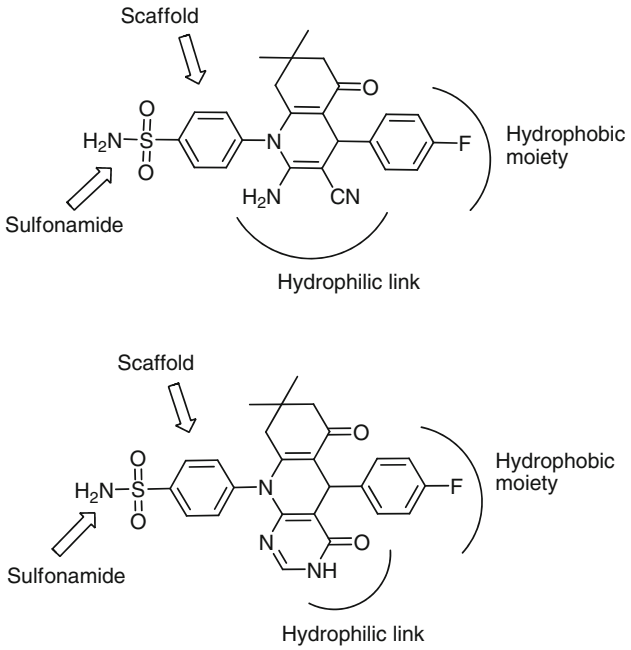


Fig. 2 Representative examples of the synthesized compounds complying with the general pharmacophore of sulfonamide compounds acting as CA inhibitors

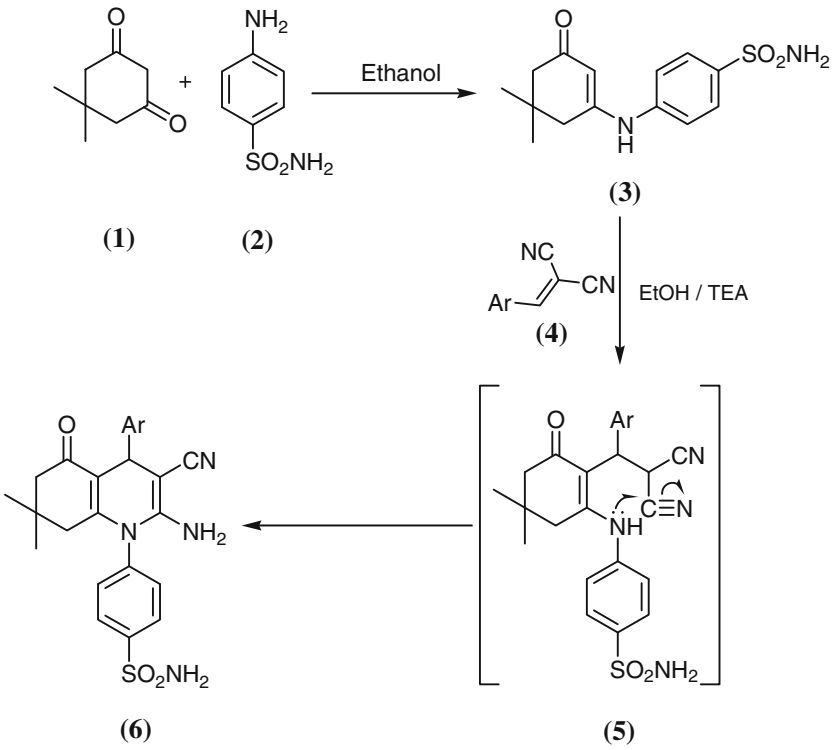
Synthesis

Enaminone **3** was obtained from condensation of 5,5-dimethyl-1,3-cyclohexandione **1** with sulfanilamide **2**. Treatment of enaminone **3** with 2-(4-fluorobenzylidene)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) (Ghorab *et al.*, 2007).

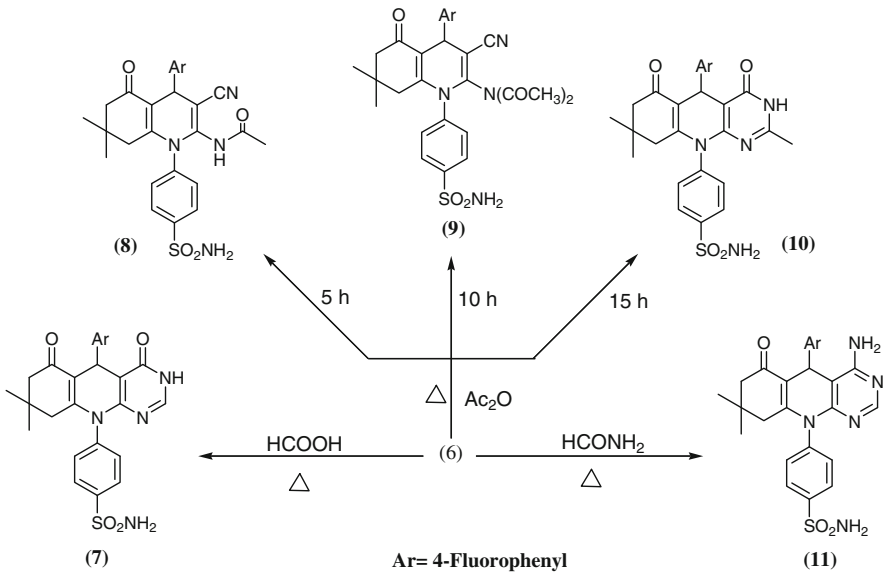
The pyrimido[4,5-*b*]quinoline derivative **7** was obtained by refluxing compound **6** in formic acid. When compound **6** was refluxed in acetic anhydride for 5 h and 10 h, the monoacetyl derivative **8** and the diacetyl derivative **9** were obtained, respectively. While refluxing compound **6** in acetic anhydride for 15 h 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 h, yielded the 2-chloromethyl-pyrimido[4,5-*b*]quinoline derivative **14**. Fusion of compound **6** with ethyl cyanoacetate

Scheme 1 Adopted synthetic pathway of compound **6**



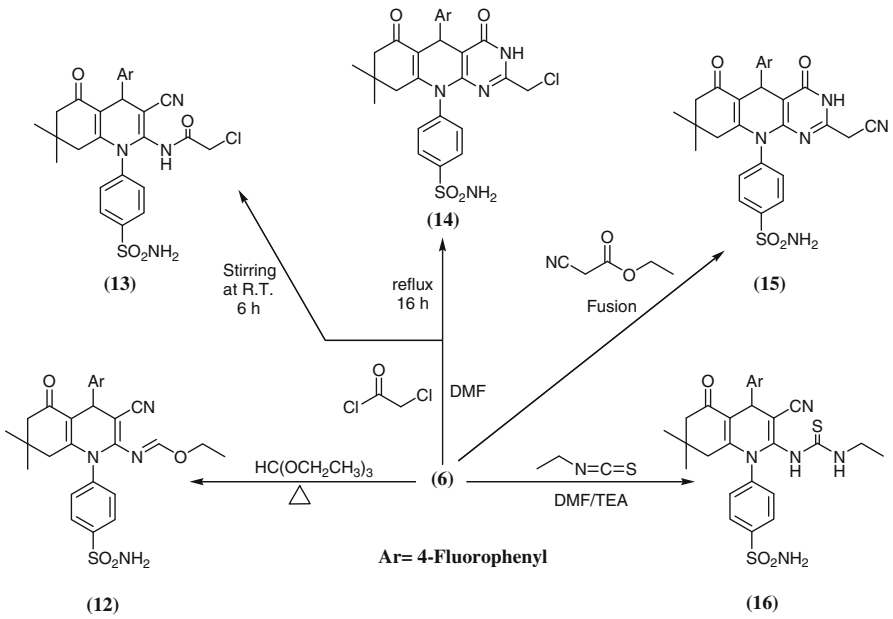
Scheme 2 Adopted synthetic pathways of compounds **7–11**



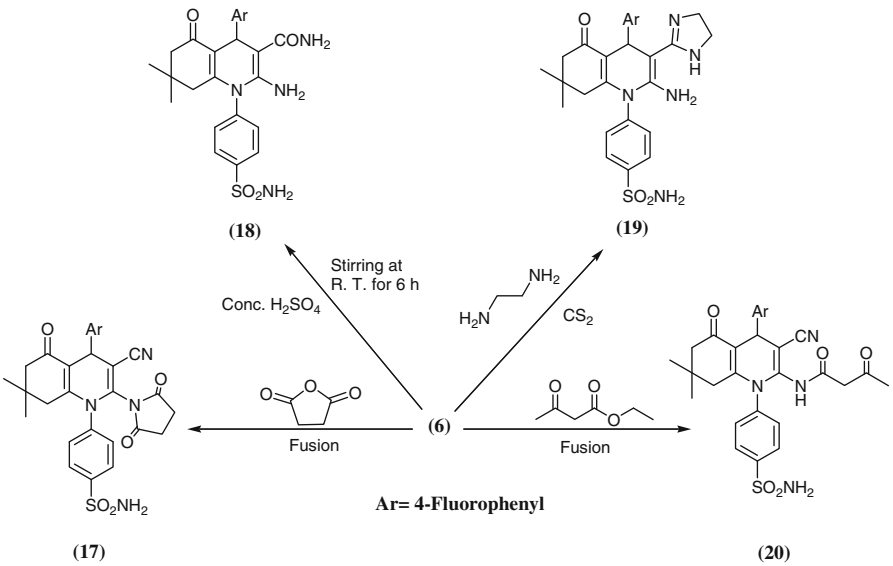
yielded the corresponding pyrimido[4,5-*b*]quinoline derivative **15**. The formation of compound **15** was assumed to proceed via elimination of 1 mol of ethanol followed by intramolecular cyclization. On the other hand, the thioureido derivative **16** was obtained by the reaction of compound **6** 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 concentrated 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 mol

Scheme 3 Adopted synthetic pathways of compounds **12–16**



Scheme 4 Adopted synthetic pathways of compounds **17–20**



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 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).

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 a 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.

Scheme 5 Adopted synthetic pathways of compounds **21–25**

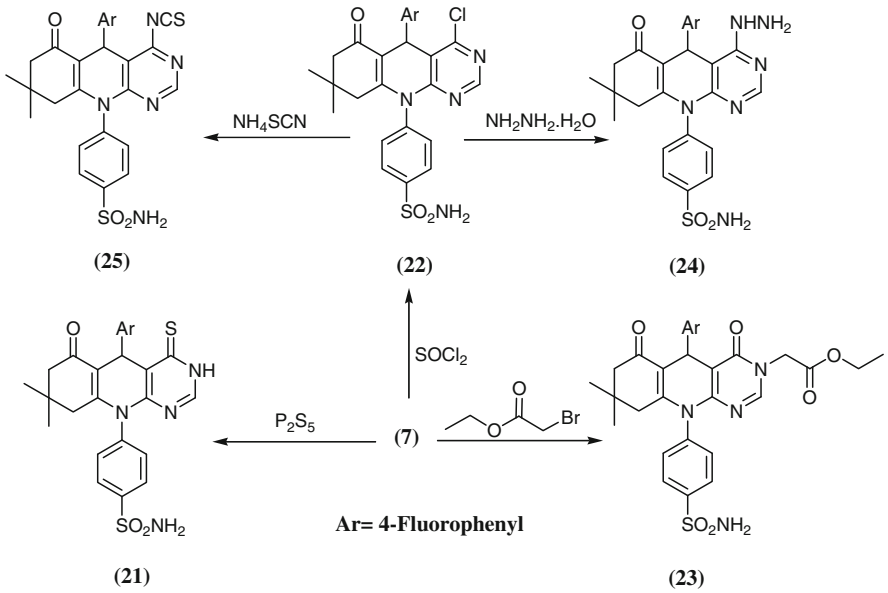


Table 1 In vitro anticancer screening of the synthesized compounds against human breast cell line (MCF7)

Compound	Compound concentration (μM)				IC_{50} (μM)
	10	25	50	100	
	Surviving fraction (means ± SE)[a]				
Doxorubicin	0.721 ± 0.02	0.546 ± 0.02	0.461 ± 0.01	0.494 ± 0.03	71.8
6	0.855 ± 0.01	0.562 ± 0.05	0.427 ± 0.01	0.482 ± 0.03	71.8
7	0.934 ± 0.03	0.757 ± 0.01	0.499 ± 0.01	0.447 ± 0.02	77.1
8	0.882 ± 0.01	0.763 ± 0.03	0.598 ± 0.01	0.483 ± 0.03	85.9
9	0.987 ± 0.01	0.733 ± 0.05	0.455 ± 0.01	0.498 ± 0.02	79.7
10	0.768 ± 0.01	0.654 ± 0.07	0.494 ± 0.03	0.425 ± 0.03	69.8
11	0.795 ± 0.03	0.448 ± 0.05	0.311 ± 0.01	0.381 ± 0.01	52.6
12	0.904 ± 0.06	0.620 ± 0.04	0.477 ± 0.05	0.401 ± 0.01	67.3
13	0.885 ± 0.02	0.700 ± 0.05	0.450 ± 0.06	0.430 ± 0.03	70.8
14	0.984 ± 0.02	0.770 ± 0.03	0.784 ± 0.05	0.768 ± 0.01	>100
15	0.976 ± 0.01	0.864 ± 0.01	0.662 ± 0.02	0.600 ± 0.02	>100
16	0.924 ± 0.01	0.852 ± 0.02	0.642 ± 0.04	0.609 ± 0.01	>100
17	0.933 ± 0.02	0.885 ± 0.02	0.678 ± 0.01	0.488 ± 0.02	94.1
18	0.906 ± 0.9	0.711 ± 0.01	0.409 ± 0.06	0.493 ± 0.01	75.2
19	0.873 ± 0.03	0.679 ± 0.01	0.423 ± 0.01	0.581 ± 0.02	87
20	0.919 ± 0.01	0.905 ± 0.01	0.760 ± 0.01	0.663 ± 0.06	>100
21	0.990 ± 0.01	0.901 ± 0.02	0.686 ± 0.06	0.608 ± 0.06	>100
22	0.909 ± 0.05	0.785 ± 0.02	0.635 ± 0.02	0.457 ± 0.02	85.6
23	0.969 ± 0.02	0.898 ± 0.01	0.686 ± 0.01	0.572 ± 0.02	>100
24	0.959 ± 0.01	0.652 ± 0.01	0.478 ± 0.04	0.518 ± 0.02	81.2
25	0.922 ± 0.01	0.755 ± 0.1	0.487 ± 0.01	0.534 ± 0.03	85.6

[a] Each value is the mean of three values ± standard error

From the results in Table 1, it was found that the pyrimido[4,5-*b*]quinoline derivative **11** (IC_{50} = 52.6 μM) and the quinoline derivative **12** (IC_{50} = 67.3 μM) were the most potent compounds in this screening, and exhibited higher cytotoxic activities when compared with the reference drug doxorubicin (IC_{50} = 71.8 μM). Compounds **6**, **10**, and **13** are nearly as active as doxorubicin, or slightly higher in activity. While compounds **7–9**, **17–19**, **22**, **24**, and **25** showed slightly lower IC_{50} values than that of the reference drug, ranging from 75.2 to 94.1 μM.

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 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).

Consequently, the ability of the most two active compounds, compounds **11** and **12**, to enhance the cell killing effect of γ-irradiation was studied. From the results obtained in Table 1, compound **11** showed an in vitro cytotoxic activity with IC_{50} value of 52.6 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 **11**, 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 28.5 μM (Fig. 3).

Similarly, compound **12** showed IC_{50} value of 67.3 μM when used alone, as shown in Table 1. The IC_{50} value was decreased to 36 μM, when the cells were treated with compound **12** in combination with γ-radiation (Fig. 4).

From these results, we can conclude that using a combination of compound **11** or **12** and ionizing radiation synergistically enhanced growth inhibition on breast cancer cells, compared with each agent alone.

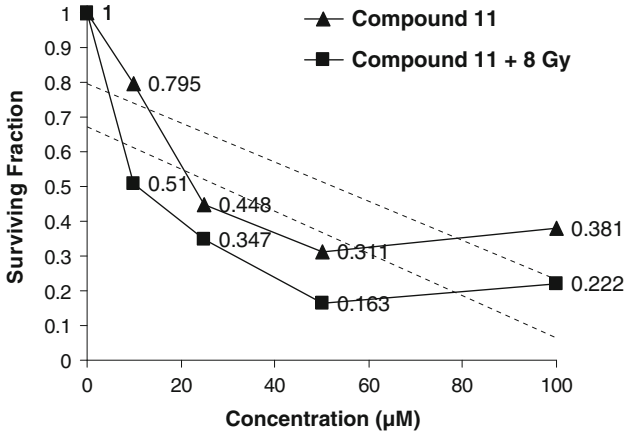


Fig. 3 Survival curve for MCF7 cell line for compound **11** alone and in combination with γ-irradiation (8 Gy)

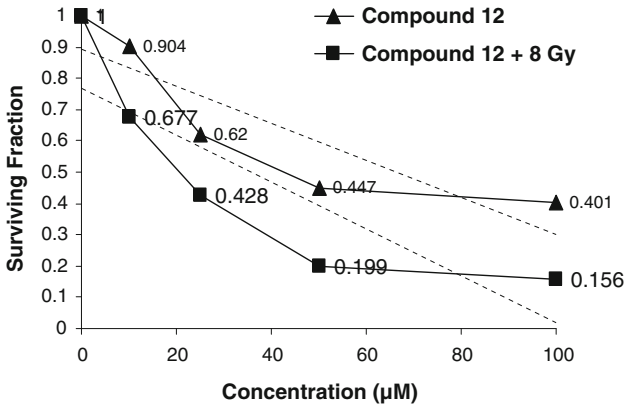


Fig. 4 Survival curve for MCF7 cell line for compound **12** alone and in combination with γ-irradiation (8 Gy)

Docking studies

Previous literature shows that carbonic anhydrase inhibition is one of the anticancer mechanisms of sulfonamides, and this was clearly showed by Abbate *et al.* (2004), who stated that the potent anticancer sulfonamide drug (E7070) (Fig. 5), currently undergoing clinical development for the treatment of several types of cancer, acts as a strong carbonic anhydrase inhibitor, and this may contribute at least in part, to its in vivo efficacy.

The X-ray crystal structure of the adduct of human carbonic anhydrase II (hCA II) with E7070 revealed

Table 2 In vitro anticancer screening of compounds **11** and **12** 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)[a]						
11	1.000	0.927 ± 0.02*	0.510 ± 0.04*	0.347 ± 0.01*	0.163 ± 0.01*	0.222 ± 0.01*	28.5
12	1.000	0.927 ± 0.02*	0.677 ± 0.02*	0.428 ± 0.01*	0.199 ± 0.01*	0.156 ± 0.01*	36

[a] Each value is the mean of three values ± standard error

* Significant difference from control group at $P < 0.001$

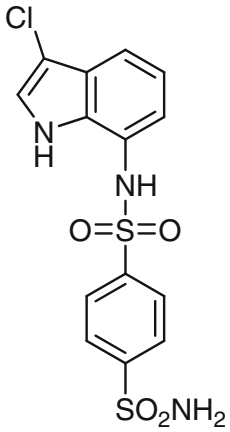


Fig. 5 E7070, a sulfonamide compound in advanced clinical trials as anticancer agent

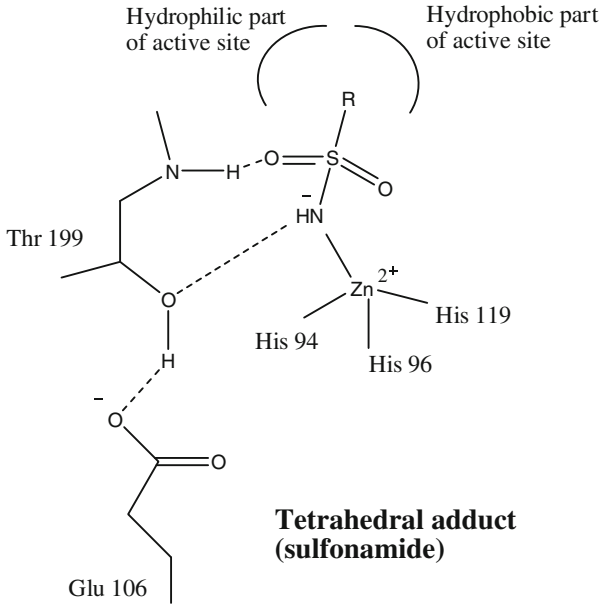


Fig. 6 CA inhibition mechanism by sulfonamides

similar interactions between the inhibitor and the active site as those reported by Supuran *et al*. These interactions are found to be common for the sulfonamide compounds which are CA inhibitors and include: (i) binding of the compounds to the Zn(II) ion by the sulfonamide moiety in a tetrahedral geometry which is a stable geometry for the metal ion; (ii) the nitrogen atom of the sulfonamide is coordinated to the Zn(II) ion of the enzyme; (iii) the amino acid Thr 199 participates in two hydrogen bonds, one with the NH moiety and the other with one of the oxygen atoms of the SO_2NH_2 (Fig. 6) (Supuran and Scozzafava, 2007; Pastorekova *et al.*, 2004).

Since the synthesized compounds are sulfonamide derivatives and their design complies with the general pharmacophore of sulfonamide CA inhibitors, it was interesting to perform docking studies on the synthesized compounds to hCA II and to compare their docking interactions with the previously reported interactions of E7070.

In order to validate our docking procedure, E7070 was docked into the active site of hCA II. The docking results clearly show that indeed, the compound exhibits similar interactions as those previously reported in the literature and stated above (Fig. 7).

Docking studies of all the newly synthesized compounds was performed, and it was found that they exhibit similar interactions to that previously reported for E7070 and stated above. Figure 8 shows the interaction map of the pyrimido[4,5-*b*]quinoline derivative **11** docked pose with nearby binding site amino acids of hCA II.

Finally, it can be concluded from our docking study that the synthesized compounds exhibit similar conformations and binding interactions with hCA II similar to those previously reported for other sulfonamide compounds that act as CA inhibitors. This suggests that the synthesized compounds might possibly act as CA inhibitors, and this may contribute at least in part, to their in vitro anticancer activity.

Conclusion

We report here the synthesis of new fluorine-containing quinolines and pyrimidoquinolines bearing a free sulfonamide moiety. Additionally, it was clearly observed that some of the synthesized compounds exhibited significant anticancer activities. 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 agents, docking study was performed which showed significantly similar binding interactions to hCA II compared to that of E7070. From the results obtained from the anticancer screening and the docking studies, it may be suggested that the anticancer activity may be in part due to the carbonic anhydrase inhibition. Moreover, the most two active compounds showed interesting radiosensitizing activity, when evaluated for their in vitro cytotoxic activity in combination with γ-irradiation.

Experimental

Synthesis

Melting points are uncorrected and were determined on a Stuart melting point apparatus (Stuart Scientific, Redhill,

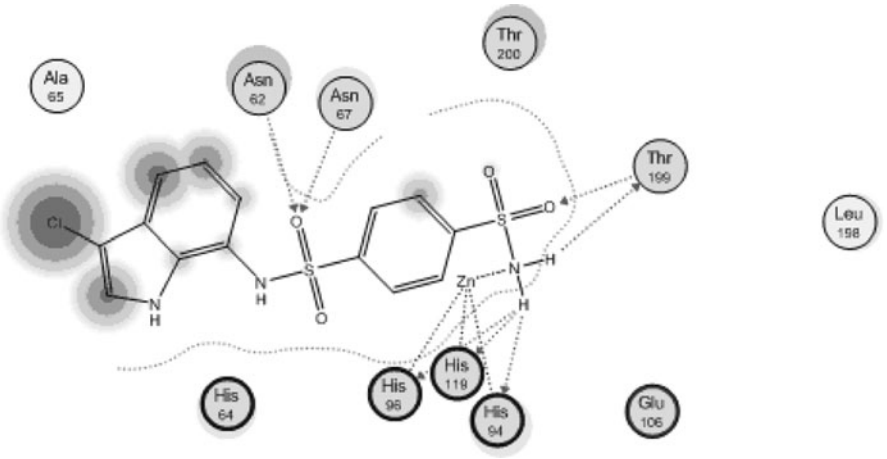


Fig. 7 Interaction map of E7070 with the active site of hCA II showing similar interactions as those previously reported

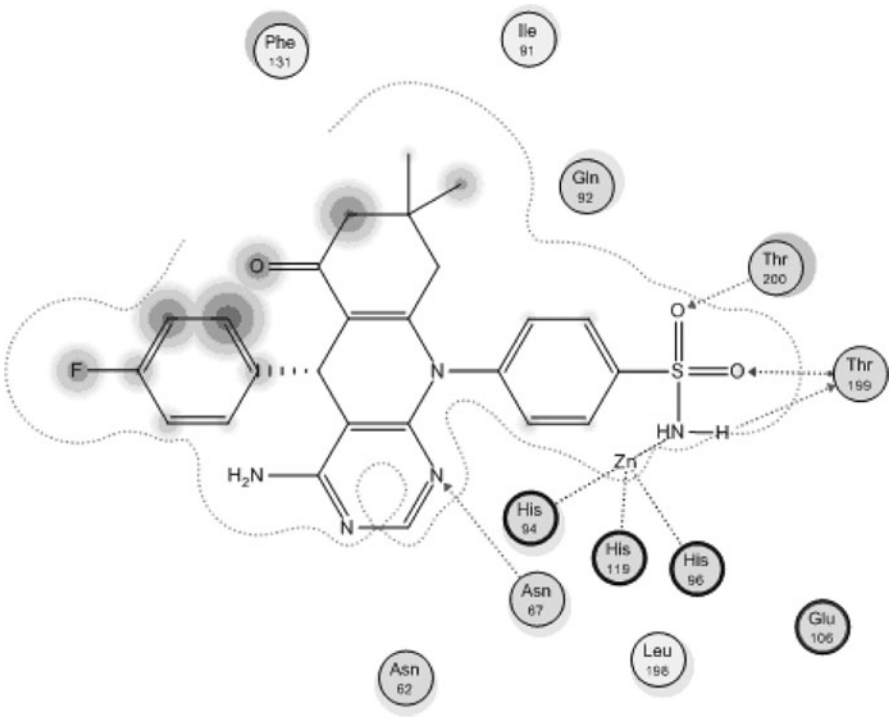


Fig. 8 Interaction map of compound **11** with the active site of hCA II showing similar interactions as those previously reported

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 Aluminum sheets Silica gel Merck 60 F254 and were visualized by UV lamp (Merck, Darmstadt, Germany).

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

Prepared according to the previously reported procedure (Supuran *et al.*, 2003).

*4-(2-Amino-3-cyano-4-(4-fluorophenyl)-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, 0.01 mol) and 2-(4-fluorobenzylidene)malononitrile **4** (1.72 g, 0.01 mol) in ethanol (20 ml) containing three 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 compound **6**: Yield, 86%; m.p. 282–284°C; IR, cm^{-1}: 3467, 3364, 3258 ($2NH_2$), 3068 ($CH_{arom.}$), 2954, 2882 ($CH_{aliph.}$), 2176 (C≡N), 1652 (C=O), 1325, 1153 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.7–2.3 [m, 4H, $2CH_2$], 4.4 [s, 1H, CH], 5.5 [s, 2H, NH_2, exchangeable with D_2O], 7.1–8.0 [m, 10H, Ar–H + SO_2NH_2, exchangeable with D_2O]. MS, *m/z* (%): 466 [M^+] (39.87), 371 (100). Anal. Calcd. For $C_{24}H_{23}FN_4O_3S$: C, 61.79; H, 4.97; N, 12.01. Found: C, 61.91; H, 4.73; N, 11.80.

*4-(5-(4-Fluorophenyl)-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** (0.466 g, 0.001 mol) 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, 79%; m.p. 168–170°C; IR, cm^{-1}: 3390, 3300, 3262 (NH, NH_2), 3082 ($CH_{arom.}$), 2959, 2883 ($CH_{aliph.}$), 1714, 1647 (2 C=O), 1602 (C=N), 1375, 1172 (SO_2). MS, *m/z* (%): 495 [M + 1] (0.16), 101 (100). Anal. Calcd. For $C_{25}H_{23}FN_4O_4S$: C, 60.72; H, 4.69; N, 11.33. Found: C, 60.82; H, 4.84; N, 11.49.

*N-(3-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide (**8**)*

A solution of compound **6** (0.466 g, 0.001 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 compound **8**: Yield, 97%; m.p. 150–152°C; IR, cm^{-1}: 3460, 3230, 3206 (NH, NH_2), 3057 ($CH_{arom.}$), 2957, 2876 ($CH_{aliph.}$), 2212 (C≡N), 1725, 1652 (2 C=O), 1364, 1164 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, CH_3], 1.5 [s, 3H, $COCH_3$], 1.8–2.2 [m, 4H, CH_2], 4.8 [s, 1H, CH], 7.1–8.0 [m, 10H, Ar–H + SO_2NH_2], 9.9 [s, 1H, NH]. MS, *m/z* (%): 510 [M + 2] (1.24), 90 (100). Anal. Calcd. For $C_{26}H_{25}FN_4O_4S$: C, 61.40; H, 4.95; N, 11.02. Found: C, 61.68; H, 5.11; N, 10.83.

*N-Acetyl-N-(3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide (**9**)*

A solution of compound **6** (0.466 g, 0.001 mol) 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, 89%; m.p. 178–180°C; IR, cm^{-1}: 3451, 3250, 3207 (NH, NH_2), 3060 ($CH_{arom.}$), 2959, 2876 ($CH_{aliph.}$), 2214 (C≡N), 1727, 1655 (3C=O), 1371, 1163 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.8–2.2 [m, 4H, $2CH_2$], 2.4 [s, 6H, $2COCH_3$], 4.8 [s, 1H, CH], 7.0–8.0 [m, 10H, Ar–H + SO_2NH_2]. Anal. Calcd. For $C_{28}H_{27}FN_4O_5S$: C, 61.08; H, 4.94; N, 10.18. Found: C, 61.25; H, 5.12; N, 10.39.

*4-(5-(4-Fluorophenyl)-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** (0.466 g, 0.001 mol) 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, 75%; m.p. 208–210°C; IR, cm^{-1}: 3471, 3300, 3205 (NH, NH_2), 3072 ($CH_{arom.}$), 2959, 2876 ($CH_{aliph.}$), 1720, 1656 (2C=O), 1591 (C=N), 1367, 1165 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.8 [2s, 6H, $2CH_3$], 1.8–2.2 [m, 4H, $2CH_2$], 2.4 [s, 3H, CH_3], 4.9 [s, 1H, CH], 7.0–8.0 [m, 11H, Ar–H + NH + SO_2NH_2]. MS, *m/z* (%):508 [M^+] (9.66), 456 (100). Anal. Calcd. For $C_{26}H_{25}FN_4O_4S$: C, 61.40; H, 4.95; N, 11.02. Found: C, 61.12; H, 4.81; N, 11.30.

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

A solution of compound **6** (0.466 g, 0.001 mol) 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, 45%; m.p. 140–142°C; IR, cm^{-1}: 3451, 3310, 3257 (NH_2), 3068 ($CH_{arom.}$), 2952, 2871 ($CH_{aliph.}$), 1640 (C=O), 1600 (C=N), 1330, 1157 (SO_2). MS, *m/z* (%): 494 [M + 1] (0.16), 90 (100). Anal. Calcd. For $C_{25}H_{24}FN_5O_3S$: C, 60.84; H, 4.90; N, 14.19. Found: C, 61.02; H, 4.73; N, 14.43.

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

A solution of compound **6** (0.466 g, 0.001 mol) in triethylorthoformate (30 ml) containing three 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, 97%; m.p. 164–166°C; IR, cm^{-1}: 3364, 3258

(NH_2), 3065 ($CH_{arom.}$), 2953, 2895 ($CH_{aliph.}$), 2195 (C≡N), 1650 (C=O), 1585 (C=N), 1373, 1159 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 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], 7.1–8.0 [m, 10H, Ar–H + SO_2NH_2], 8.7 [s, 1H, N=CH]. Anal. Calcd. For $C_{27}H_{27}FN_4O_4S$: C, 62.05; H, 5.21; N, 10.72. Found: C, 61.81; H, 5.00; N, 11.01.

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

A mixture of compound **6** (0.466 g, 0.001 mol) and chloroacetyl chloride (0.112 g, 0.001 mol) 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, 95%; m.p. 172–174°C; IR, cm^{-1}: 3375, 3304, 3252 (NH, NH_2), 3096 ($CH_{aliph.}$), 2960, 2884 ($CH_{aliph.}$), 2213 (C≡N), 1705, 1649 (2C=O), 1365, 1172 (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], 7.1–7.9 [m, 10H, Ar–H + SO_2NH_2], 10.2 [s, 1H, NH]. MS, *m/z* (%): 543 [M^+] (14.63), 464 (100). Anal. Calcd. For $C_{26}H_{24}ClFN_4O_4S$: C, 57.51; H, 4.45; N, 10.32. Found: C, 57.78; H, 4.22; N, 10.53.

*4-(2-(Chloromethyl)-5-(4-fluorophenyl)-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** (0.466 g, 0.001 mol) and chloroacetyl chloride (0.112 g, 0.001 mol) 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, 84%; m.p. >300°C; IR, cm^{-1}: 3472, 3407, 3255 (NH, NH_2), 3064 ($CH_{arom.}$), 2940, 2879 ($CH_{aliph.}$), 1672, 1649 (2C=O), 1595 (C=N), 1381, 1146 (SO_2). MS, *m/z* (%): 542 [M − 1] (4.31), 232 (100). Anal. Calcd. For $C_{26}H_{24}ClFN_4O_4S$: C, 57.51; H, 4.45; N, 10.32. Found: C, 57.34; H, 4.61; N, 10.50.

*4-(2-(Cyanomethyl)-5-(4-fluorophenyl)-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** (0.466 g, 0.001 mol) 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, 95%; m.p. >300°C; IR, cm^{-1}: 3356, 3260, 3227 (NH, NH_2), 3040 ($CH_{arom.}$), 2958, 2880 ($CH_{aliph.}$), 2216 (C≡N), 1677, 1645 (2C=O), 1620 (C=N), 1370, 1161 (SO_2). MS, *m/z* (%): 534 [M + 1] (4.90), 97 (100). Anal. Calcd. For $C_{27}H_{24}FN_5O_4S$: C, 60.78; H, 4.53; N, 13.13. Found: C, 60.95; H, 4.30; N, 12.91.

*4-(3-Cyano-2-(3-ethylthioureido)-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**16**)*

A mixture of compound **6** (0.466 g, 0.001 mol) and ethyl isothiocyanate (0.086 g, 0.001 mol) in dimethyl formamide (20 ml) containing three drops of triethylamine was refluxed for 10 h. The reaction mixture was cooled and then poured onto cold water, and the solid obtained was recrystallized from ethanol to give compound **16**: Yield, 95%; m.p. 180–182°C; IR, cm^{-1}: 3410, 3346, 3280 (NH, NH_2), 3095 ($CH_{arom.}$), 2967, 2874 ($CH_{aliph.}$), 2183 (C≡N), 1646 (C=O), 1257 (C=S), 1369, 1137 (SO_2). ^{1}H 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]. Anal. Calcd. For $C_{27}H_{28}FN_5O_3S_2$: C, 58.57; H, 5.10; N, 12.65. Found: C, 58.32; H, 4.86; N, 12.41.

*4-(3-Cyano-2-(2,5-dioxopyrrolidin-1-yl)-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**17**)*

A mixture of compound **6** (0.466 g, 0.001 mol) and succinic anhydride (0.15 g, 0.0015 mol) 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, 46%; m.p. 196–198°C; IR, cm^{-1}: 3362, 3257 (NH_2), 3072 ($CH_{arom.}$), 2959, 2892 ($CH_{aliph.}$), 2214 (C≡N), 1734, 1658 (3C=O), 1368, 1163 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.9–2.2 [m, 4H, $2CH_2$], 4.8 [s, 1H, CH], 5.2 [t, 4H, $2CH_2$ pyrrolidine], 7.0–8.0 [m, 10H, Ar–H + SO_2NH_2]. Anal. Calcd. For $C_{28}H_{25}FN_4O_5S$: C, 61.30; H, 4.59; N, 10.21. Found: C, 61.57; H, 4.39; N, 10.33.

*2-Amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxamide (**18**)*

A solution of compound **6** (0.466 g, 0.001 mol) in concentrated 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, 75%; m.p. 210–212°C; IR, cm^{-1}: 3400, 3310, 3251 (NH_2), 3090 ($CH_{arom.}$), 2962, 2885 ($CH_{aliph.}$), 1685, 1642 (2C=O), 1376, 1165 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.8–2.2 [m, 4H, $2CH_2$], 4.6 [s, 1H, CH], 4.8 [s, 2H, NH_2], 6.3 [s, 2H, $CONH_2$], 7.0–8.0 [m, 10H, Ar–H + SO_2NH_2]. Anal. Calcd. For $C_{24}H_{25}FN_4O_4S$: C, 59.49; H, 5.20; N, 11.56. Found: C, 59.65; H, 5.00; N, 11.31.

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

A mixture of compound **6** (0.466 g, 0.001 mol) 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, 35%; m.p. 188–190°C; IR, cm^{-1}: 3401, 3333, 3217 (NH, NH_2), 3047 ($CH_{arom.}$), 2926, 2862 ($CH_{aliph.}$), 1643 (C=O), 1579 (C=N), 1345, 1164 (SO_2). MS, *m/z* (%): 508 [M − 1] (1.23), 90 (100). Anal. Calcd. For $C_{26}H_{28}FN_5O_3S$: C, 61.28; H, 5.54; N, 13.74. Found: C, 61.03; H, 5.74; N, 13.90.

*N-(3-cyano-4-(4-fluorophenyl)-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** (0.466 g, 0.001 mol) 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, 76%; m.p. 158–160°C; IR, cm^{-1}: 3410, 3321, 3260 (NH, NH_2), 3072 ($CH_{arom.}$), 2959, 2872 ($CH_{aliph.}$), 2182 (C≡N), 1725, 1709, 1646 (3C=O), 1372, 1165 (SO_2). ^1H NMR (DMSO-d_6) δ: 0.7, 0.9 [2s, 6H, $2CH_3$], 1.9–2.1 [m, 4H, $2CH_2$], 2.3 [s, 3H, $COCH_3$], 4.5 [s, 1H, CH], 4.8 [s, 1H, $COCH_2$], 7.1–7.9 [m, 10H, Ar–H + SO_2NH_2], 10.1 [s, 1H, NH]. MS, *m/z* (%): 552 [M + 2] (0.80), 78 (100). Anal. Calcd. For $C_{28}H_{27}FN_4O_5S$: C, 61.08; H, 4.94; N, 10.18. Found: C, 61.29; H, 5.13; N, 9.92.

*4-(5-(4-Fluorophenyl)-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** (0.494 g, 0.001 mol) and phosphorus pentasulfide (0.22 g, 0.001 mol) in pyridine (20 ml) was refluxed for 8 h, the reaction mixture was cooled and then poured onto cold water, then acidified with diluted HCl. The solid obtained was recrystallized from ethanol to give compound **21**: Yield, 55%; m.p. 190–192°C; IR, cm^{-1}: 3390, 3329, 3258 (NH, NH_2), 3075 ($CH_{arom.}$), 2960, 2875 ($CH_{aliph.}$), 1663 (C=O), 1626 (C=N), 1256 (C=S), 1374, 1164 (SO_2). MS, *m/z* (%): 510 [M^+] (0.25), 100 (100). Anal. Calcd. For $C_{25}H_{23}FN_4O_3S_2$: C, 58.81; H, 4.54; N, 10.97. Found: C, 59.04; H, 4.38; N, 10.71.

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

A solution of compound **7** (0.494 g, 0.001 mol) 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, 96%; m.p. 226–228°C; IR, cm^{-1}: 3346, 3260 (NH_2), 3084 ($CH_{arom.}$), 2981, 2883 ($CH_{aliph.}$), 1671 (C=O), 1600, 1570 (C=N), 1340, 1162 (SO_2). MS, *m/z* (%): 513 [M^+] (4.77), 100 (100). Anal. Calcd. For $C_{25}H_{22}ClFN_4O_3S$: C, 58.53; H, 4.32; N, 10.92. Found: C, 58.71; H, 4.10; N, 11.16.

*Ethyl 2-(5-(4-fluorophenyl)-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** (0.494 g, 0.001 mol), ethyl bromoacetate (0.167 g, 0.001 mol) 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, 94%; m.p. 90–92°C; IR, cm^{-1}: 3367, 3288 (NH_2), 3090 ($CH_{arom.}$), 2965, 2883 ($CH_{aliph.}$), 1736, 1643 (C=O), 1600 (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, 1H, CH], 4.6 [s, 2H, CH_2CO], 7.1–7.9 [m, 10H, Ar–H + SO_2NH_2], 8.0 [s, 1H, N=CH]. Anal. Calcd. For $C_{29}H_{29}FN_4O_6S$: C, 59.99; H, 5.03; N, 9.65. Found: C, 60.23; H, 4.79; N, 9.90.

*4-(5-(4-Fluorophenyl)-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** (0.513 g, 0.001 mol) 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, 72%; m.p. 150–152°C; IR, cm^{-1}: 3360, 3325, 3260 (NH, NH_2), 3080 ($CH_{arom.}$), 2967, 2872 ($CH_{aliph.}$), 1653 (C=O), 1596 (C=N), 1335, 1160 (SO_2). MS, *m/z* (%): 511 [M + 2] (26.47), 120 (100). Anal.

Calcd. For $C_{25}H_{25}FN_6O_3S$: C, 59.04; H, 4.95; N, 16.52. Found: C, 59.29; H, 4.78; N, 16.73.

*4-(5-(4-Fluorophenyl)-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** (0.513 g, 0.001 mol) and ammonium thiocyanate (0.076 g, 0.001 mol) 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, 54%; m.p. 198–200°C; IR, cm^{-1}: 3341, 3262 (NH_2), 3083 ($CH_{arom.}$), 2977, 2873 ($CH_{aliph.}$), 2019 (N=C=S), 1669 (C=O), 1612 (C=N), 1341, 1163 (SO_2). MS, *m/z* (%): 536 [M + 1] (0.25), 87 (100). Anal. Calcd. For $C_{26}H_{22}FN_5O_3S_2$: C, 58.30; H, 4.14; N, 13.08. Found: C, 58.51; H, 4.32; N, 12.80.

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*. (1990). 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.

Radiosensitizing activity

The most potent compounds resulted from the in vitro anticancer screening; the pyrimido[4,5-*b*]quinoline derivative **11** and the quinoline derivative **12**, 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.

Docking studies

All molecular modeling calculations and docking studies were performed using "Molecular Operating Environment (MOE) version 2007.09".

The ligand was drawn on ChemDraw and imported in MOE. The structure was subjected to energy minimization using MMFF94x forcefield and the partial charges were computed using the same forcefield.

The X-ray crystallographic structure of hCA II complexed with N-(2,3,4,5,6-pentafluoro-benzyl)-4-sulfomyl-benzamide (1G54) was obtained from the Protein Data Bank. The enzyme was prepared for the docking studies where: (i) the ligand molecule was removed from the enzyme active site; (ii) hydrogen atoms were added to the structure with their standard geometry; (iii) partial charges were computed using Amber99 forcefield.

Docking calculations were done using Alpha triangle placement method and poses were prioritized by affinity dG scoring method.

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