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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel quinoline bearing sulfonamide derivatives and their cytotoxic activity against MCF7 cell line

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Abstract The present work reports the synthesis of novel 5-Oxo-5,6,7,8-tetrahydroquinoline and 2,5-dioxo-5,6,7,8-tetrahydroquinoline derivatives containing enaminone system and bearing a sulfonamide moiety. The newly synthesized compounds were designed in compliance with the general pharmacophoric requirements for carbonic anhydrase inhibiting anticancer drugs, as this may play a role in their anticancer activity. Twelve of the newly synthesized compounds were evaluated for their in vitro anticancer activity against human breast cancer cell line (MCF7). Compounds **5c**, **7**, **10**, and **12c** showed IC_{50} values (0.048, 0.040, 0.041, 0.044 μM, respectively) comparable to that of the reference drug doxorubicin ($IC_{50} = 0.04$ μM). On the other hand, compounds **12a**, **12d**, and **16b** exhibited better activity than doxorubicin with an IC_{50} values (0.025, 0.036, 0.015 μM, respectively).

Keywords Enaminones · 5,6,7,8-Tetrahydroquinolin · Sulphanilamid · Ultrasonic irradiation · CA inhibitors

Introduction

Recently, researchers have been showing great interest in the enaminone family of compounds. These compounds possess a great potential as multipurpose synthetic intermediate in organic synthesis, in heterocyclic synthesis (Michael et al. 1999) and as they showed a wide variety of medicinal effects such as cardiovascular effects (García et al. 2012), anti-inflammatory (El-Hashim et al. 2010), antiviral (El-Sabbagh and Rady 2009), antitussive (El-Hashim et al. 2001), antimicrobial (Abbas and Farghaly 2010), and anticonvulsant effects (Edafiogho et al. 2009; Eddington et al. 2000, 2002; Jackson et al. 2012).

On the other hand, quinoline and its derivatives are very much used in pharmaceuticals such as an anticancer agents (Creaven et al. 2010; Lu et al. 2010; Gao et al. 2010; Perin et al. 2011; Wang et al. 2012), antioxidant (Korrichi et al. 2009), antifungal (Creaven et al. 2010; Kouznetsov et al. 2012), anti-inflammatory (Ghodsi et al. 2010; Chen et al. 2011; Kumar et al. 2012), antibacterial (Garudachari et al. 2012), antimalarial (Pretorius et al. 2013), antiviral (Carta et al. 2011; Guo et al. 2011), and for depression of schizophrenia (Daniel 2007). Also, it was found that quinoline compounds containing enaminone moiety show more potent biological activities, especially as antiviral (Ahmed et al. 2010; Vandurm et al. 2009), antibacterial (Jayagobi et al. 2011), antitumor (Ghorab et al. 2009, 2010; Alqasoumi et al. 2009, 2010a, b; Al-Said et al. 2011), antimicrobial (Makawana et al. 2012), and hypotensive activity (El-Sabbagh et al. 2010).

Additionally, sulfonamides have attracted a great attention as antitumor agents since many of aryl/heteroaryl sulfonamides were reported to act as antitumor agents through a variety of mechanisms, as well as the most prominent

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mechanism was the inhibition of carbonic anhydrase isozyme (CA) (Ghorab et al. 2009, 2010; Al-Said et al. 2011).

In this respect, we reported here the preparation of some quinoline derivatives containing enaminone system and bearing sulfonamide moiety, then we had tested their in vitro growth inhibitory activities against human cultured breast carcinoma cell lines (MCF7) in comparison to doxorubicin (DOX) which is one of the most effective antitumor agents, hoping to obtain more active and less toxic anticancer agents.

Results/Discussion

A general pharmacophore (Fig. 1) for the compounds acting as CA 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 by 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 possess a hydrophilic link which is 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 (Ghorab et al. 2010). We have synthesized new compounds (Schemes 1–4), and two examples that showing their compliance with the above-mentioned pharmacophore model is represented in Fig. 2.

Chemistry

Synthesis of 5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl) benzenesulfonamide derivatives

Enaminone **3** was obtained from the condensation of 5,5-dimethyl-1,3-cyclohexandione **1** with sulfanilamide **2** in absolute ethanol under reflux for 3 h, (Ghorab et al. 2009), it was also obtained in 90% yield by using ultrasonic irradiation at 80 °C for 20 min. Treatment of enaminone **3** with different arylidene malononitrile derivatives **4a–c** in ethanol containing a catalytic amount of triethylamine, as a base catalyst, yielded the corresponding hexahydro quinoline derivative **5a–c** (Scheme 1). Compounds **5a–c** were also obtained by ultrasonic irradiation at 80 °C under the same condition in better yield. Table 1 shows a slight increase in the reaction yield in a relatively short reaction time in the presence of ultrasonic irradiation. These results confirm that ultrasonic irradiation played a crucial role in the enhancement of the rapid synthesis of hydro quinoline derivatives **5a–c**. The structures of these compounds were established

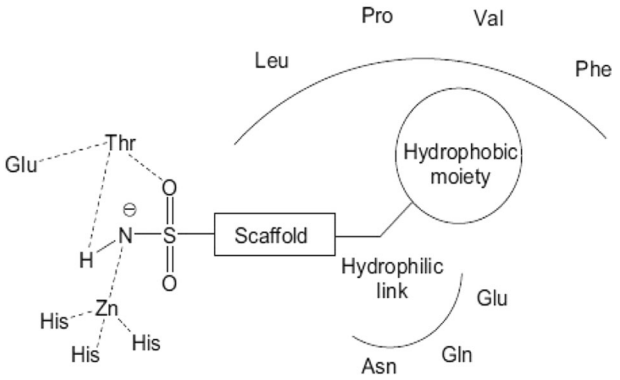


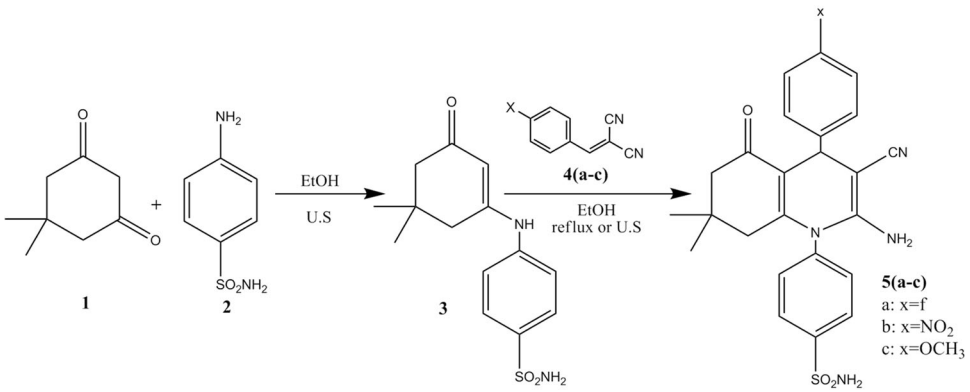
Fig. 1 Structural elements of CA inhibitors in the CA enzymatic active site

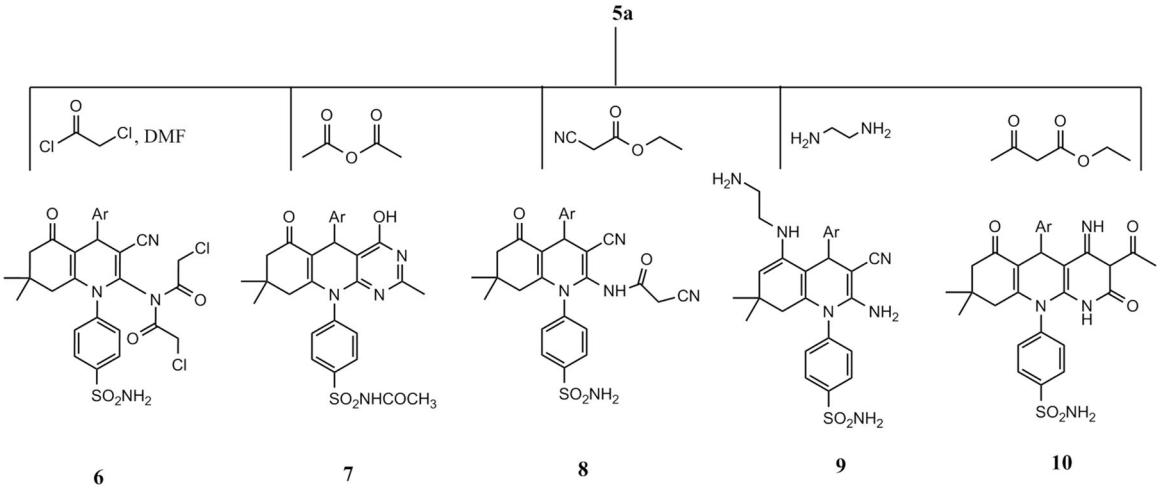
based on their elemental analysis and their spectral data. The fourier transform infrared spectroscopy (FTIR) spectra for compound **5a** revealed four bands at 3469, 3408, 3347, and 3334 cm^{-1} for two NH_2 groups, in addition to the absorption band at 2177 for C≡N, besides the characteristic bands for SO_2 group at 1357–1190 cm^{-1}. The ^1H nuclear magnetic resonance (NMR) spectrum of compound **5a** in (dimethyl sulfoxide (DMSO)-d_6) showed the two methyl groups as two singlet signals at δ_H 0.75 and 0.90 ppm, the two methylene proton appeared as a pair of singlet signal at δ_H 1.07 and 2.09 ppm, and C_4-H proton appeared as singlet signal at δ_H 4.45 ppm. Moreover, two singlet signals at δ_H 5.80 and 8.54 ppm for NH_2 and SO_2NH_2 groups, respectively, are exchangeable with D_2O, and the aromatic protons appear as a complex pattern from δ_H 6.89–8.06 ppm.

Moreover, refluxing of compound **5a** with chloroacetyl chloride in dimethylformamide (DMF) for 20 h yielded the quinoline derivative **6** (Scheme 2). The structure of the resulted compound was confirmed by elemental and spectral analysis. It's FTIR spectra showed absorption band at 2227 cm^{-1} C≡N, a band at 1653 cm^{-1} and a broadband appeared at 1699 cm^{-1} for 3C=O groups. ^1H NMR spectrum in (DMSO-d_6) for compound **6** showed the disappearance of NH_2 signals at δ_H 5.89 ppm and a new two singlet bands at δ_H 2.71 and 2.87 ppm for $2COCH_2Cl$.

When compound **5a** was refluxed in acetic anhydride for 1 h the fused pyrimido[4,5-b]quinoline system **7** was obtained in a good yield. The spectral and elemental data of compound **7** confirmed the assigned structures. The FTIR spectra of this particular sample show the disappearance of the cyano group band, while two bands at 1697 and 1669 cm^{-1} for 2C=O groups were recorded. On the other hand, it's ^1H NMR spectrum in (DMSO-d_6) showed singlet band at δ_H 1.89 ppm for 5H for $COCH_3$ and C_9-H_2, singlet band at δ_H 2.07 ppm for 5H for CH_3 at C_2 and C_7-H_2. Tow singlet bands at δ_H 10.37 and 11.95 ppm, which is corresponding to NH and OH, respectively were disappeared on adding D_2O (Scheme 2).

Scheme 1 Synthetic route to 5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)benzenesulfonamide derivatives variously substituted in the 4-position **5a–c**

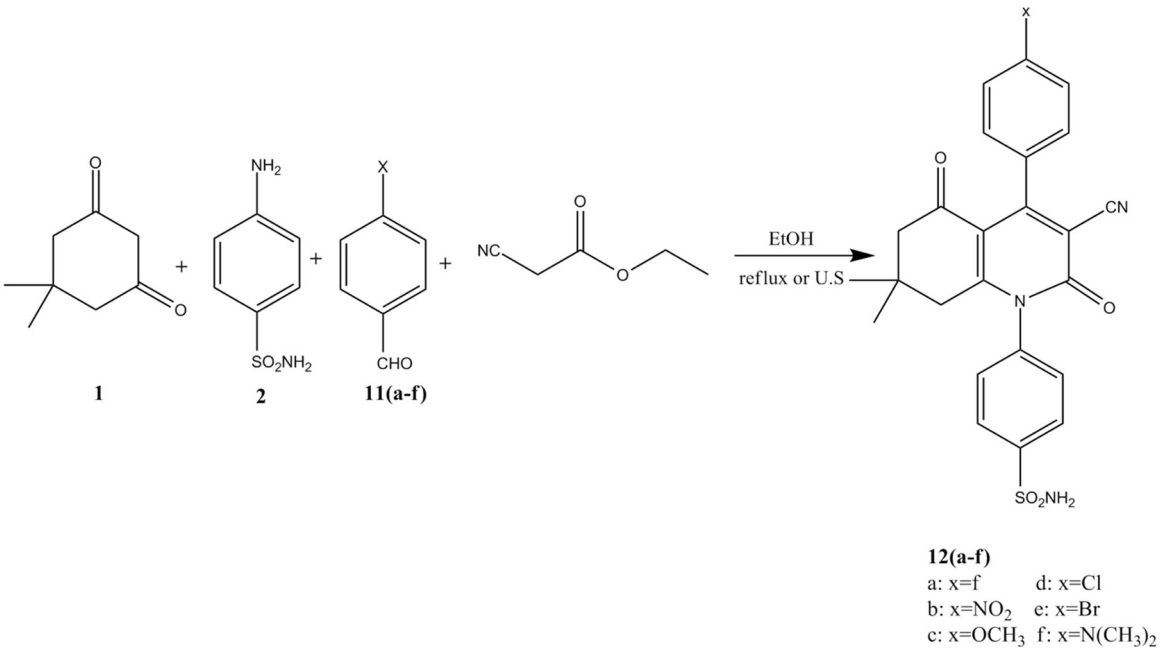




Scheme 2 Synthetic scheme and structure of the quinolines 6,8,9, pyrimido[4,5-b]quinoline derivative 7, and benzo[b][1,8] naphthyridine derivative **10**

In addition, the fusion of compound **5a** with ethyl cyanoacetate yielded the corresponding acetamide derivative **8** (Scheme 2). The structure of compound **8** was confirmed by elemental and spectral analysis. The FTIR showed bands at 3312, 3229, and 3123 cm^{-1} for NH and NH_2 groups. The new cyano groups at 2260 cm^{-1} were observed and two bands at 1743 and 1680 cm^{-1} for two C=O groups were recorded. ^1H NMR spectrum in (DMSO-d_6) showed the CH_2CN protons as singlet together with the C_4-H at δ_H 3.94 ppm, and NH proton appeared as singlet signal at δ_H 10.17 ppm which is disappeared on adding D_2O. In addition to that, 4-(2-amino-5-(2-aminoethylamino)-3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-7,8-dihydroquinolin-1(4*H*)-yl) benzenesulfonamide **9** was obtained by the treatment of compound **5a** with ethylenediamine in the presence of carbon disulfide (Scheme 2). The structure of compound **9** was proved on the basis of its spectral and elemental data. FTIR spectra showed a broadband from 3337–3193 cm^{-1} for NH and NH_2 groups, while C≡N appeared at 2201 cm^{-1}. ^1H NMR spectrum in (DMSO-d_6) showed singlet signal for C_8-H_2 at δ_H 1.88 ppm, two new singlet signals at δ_H 2.38 and 2.51 ppm for NH and NH_2 beside the original C_2-NH_2 at δ_H 5.77 ppm, and SO_2NH_2 at δ_H 8.30 ppm. On the other hand, the two methylene protons appeared as a pair of triplet bands at δ_H 3.63 and 3.81 ppm, while the C_6-H appeared with Ar–H in the range from δ_H 6.65 to 8.13 ppm.

Additionally, the octahydrobenzo[b][1,8] naphthyridine derivative **10** was obtained by the reaction of compound **5a** with ethyl acetoacetate (Scheme 2). The structure of the compound obtained was confirmed with their spectral and elemental analysis. The FTIR spectra of compound **10** showed NH and NH_2 absorption band at 3304, 3256, and 3225 cm^{-1}, and three absorption bands at 1713, 1660, and 1632 cm^{-1} for three different CO groups. ^1H NMR spectrum in (DMSO-d_6) of this compound revealed two singlet signals at δ_H 1.16 and 1.22 ppm due to $2CH_3$ group at C_8,



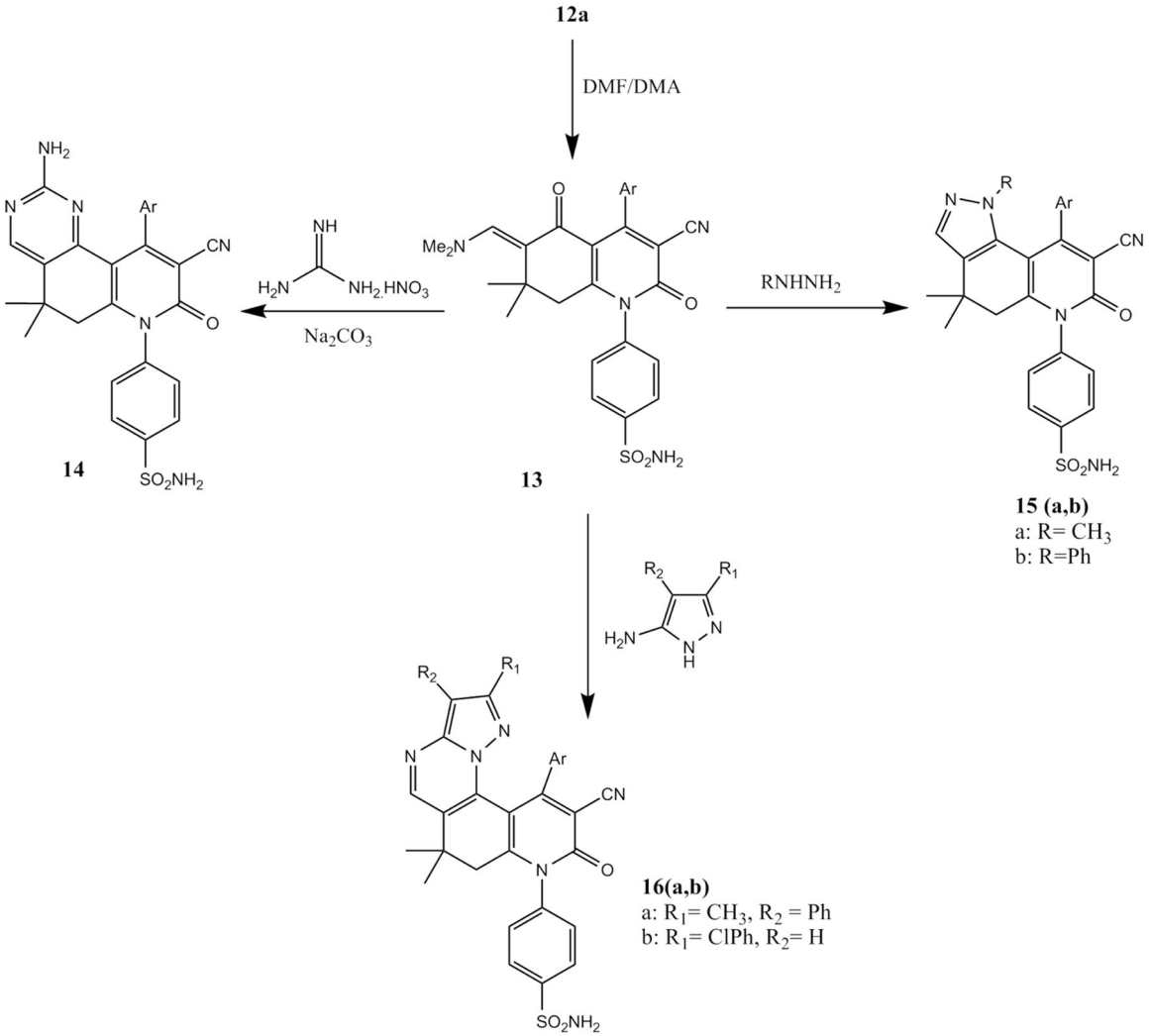
Scheme 3 Synthetic route to 2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide derivatives variously substituted in the 4-position **12a–f**

two singlet signals at δ_H 2.24 and 2.55 ppm for $2CH_2$ of C_9 and C_7, respectively. The new singlet signal at δ_H 2.35 ppm due to $COCH_3$, more over two singlet bands at δ_H 3.57 and 4.09 ppm for C_3-H and C_5-H, respectively. A singlet signal at δ_H 4.24 ppm due to NH proton at C_4, and a signal at δ_H 15.72 ppm for OH of the iminol structure **10b** (Fig. 3), which were disappeared on adding D_2O. In addition, a complex pattern appeared at δ_H 6.04–8.50 ppm due to aromatic protons together with SO_2NH_2 and endocyclic NH. The observed iminol structure may be attributed to the gain of energy enhanced by intramolecular hydrogen bonding and the rate at which this tautomer interconvert is slow compared with the inherent time scale of NMR spectroscopy.

Synthesis of 2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl) benzenesulfonamide derivatives

In one pot reaction, a mixture of diamidone **1**, sulfanilamide **2**, ethyl cyanoacetate, and benzaldehyde derivatives **11a–f**, were heated under reflux in the presence of ethanol to give the corresponding 2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide derivatives **12a–f** (Scheme 3). The same reaction was repeated by using ultrasonic irradiation instead of the conventional method, the same products **12a–f** as examined by thin layer chromatography (TLC) were obtained in shorter time and better yield (Table 2). The structures of the resulted compounds were proved by FTIR, ^{1}H NMR, ^{13}C NMR and elemental analysis. Compound **12a** as an example, it's FTIR spectra showed bands at 3372 and 3236 cm^{-1} for NH_2 group and a band at 2226 cm^{-1} for CN group, and two bands at 1715 and 1690 cm^{-1} for 2C=O groups. In addition ^{1}H NMR spectrum of compound **12a** in (DMSO-d_6) showed two singlet signals at δ_H 0.87 and 1.02 ppm for $2CH_3$ groups, pair of doublets bands at δ_H 2.03 and 2.23 ppm for C_6 protons and pair of doublet bands at δ_H 2.46 and 2.51 ppm of C_8 protons, a singlet band at δ_H 8.30 ppm for SO_2NH_2 group (exchangeable with D_2O), and the aromatic protons appear as complex pattern from δ_H 6.99–7.55 ppm.

Fusion of compound **12a** with dimethylformamide/dimethylacetal (DMF/DMA) in a sand bath for 6 h gave the corresponding enaminone **13** in 94% yield (Scheme 4). The structure of compound **13** is assigned based on the elemental analysis and spectral data. ^{1}H NMR spectrum in ($CDCl_3$) showed the absence of C_6 protons, a new two singlet signals at δ_H 3.04 and 3.15 ppm for $-N(CH_3)_2$, and a new singlet signal at δ_H 7.71 ppm for olefinic CH. Treatment of enaminone **13** with guanidine, (liberated in situ from guanidine nitrate in the presence of sodium carbonate) under fusion in a sand bath gave 4-(2-amino-9-cyano-10-(4-fluorophenyl)-5,5-dimethyl-8-oxo-5,6-dihydropyrido[2,3-h]quin-azolin-7(8*H*)-yl)benzenesulfonamide **14** in 97% yield. The structure of compound **14** is assigned based on its spectral and elemental analysis data. FTIR spectra for compound **14** showed two broadband peaks at 3351 and 3201 cm^{-1} for $2NH_2$ groups, and at 1666 cm^{-1} for CO group. ^{1}H NMR spectrum in (DMSO-d_6) showed the absence of $-N(CH_3)_2$ signals, and a new, D_2O exchangeable $-NH_2$ protons at δ_H 5.80 ppm. The C_4-H proton appears in a



Scheme 4 Synthetic scheme and structure of the pyrido[2,3-h]quinazoline derivative **14**, pyrazolo[3,4-f]quioline derivatives **15a**,**b**, and pyrazolo [1,5-a]pyrido[2,3-h]quinazoline derivatives **16a**,**b**

complex pattern with aromatic protons and $-SO_2NH_2$ protons in a range from δ_H 6.53–8.30 ppm.

Also, enaminone **13** undergo cyclo-condensation on treatment with hydrazine derivatives under reflux in a sand bath to afford compounds **15a**,**b** (Scheme 4). The structure of compounds **15a**,**b** were assigned depending on their spectral data and elemental analysis. FTIR spectra of compound **15a** showed a band at 1620 cm^{-1} for C=O. The ^1H NMR spectrum in ($CDCl_3$) for compound **15b** showed the disappearance of the $-N(CH_3)_2$ protons at δ_H 3.04 and 3.15 ppm, the ph-H and the CH of pyrazole ring appeared with the complex pattern from δ_H 6.64–8.09 ppm.

The behavior of 4-(3-cyano-6-((dimethylamino)methylene)-4-(4-fluorophenyl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl) benzenesulfonamide **13** toward some amino pyrazole derivatives was also investigated. Thus, when enaminone **13** was treated with amino pyrazole derivatives under fusion in the sand bath in the presence of catalytic amount of Triethylamine (TEA), it afforded the corresponding derivatives **16a**,**b** (Scheme 4). The structure of compounds **16a**,**b** was confirmed on the basis of their spectral data and elemental analysis. The ^1H NMR spectrum in ($CDCl_3$) of compound **16a** showed a new singlet signal at δ_H 2.67 ppm for C_2-CH_3, the phenyl protons appeared in the complex pattern with aromatic protons and SO_2NH_2 protons ranged from δ_H 7.17–8.00 ppm. The C_5 proton for the fused pyrazolo pyrido derivative appeared at δ_H 8.97 ppm.

In vitro cytotoxic screening

In the present work, 12 of the newly synthesized compounds (**5a**,**c**), (**7**), (**8**), (**10**), (**12a–d**), (**14**), (**15b**), (**16b**) were selected to evaluate their in vitro growth inhibitory

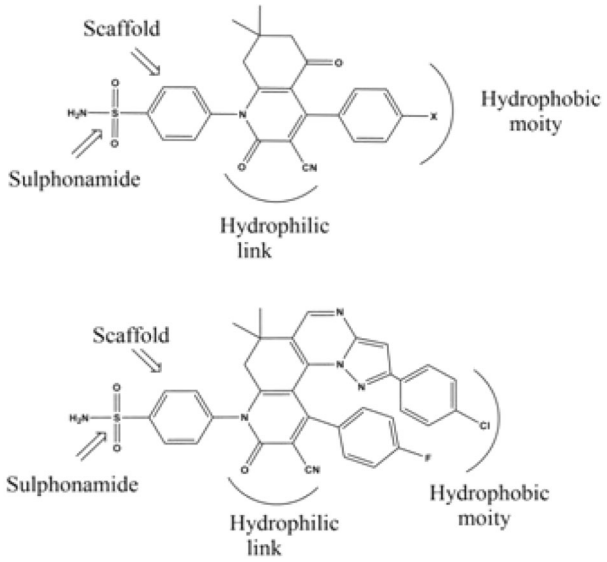


Fig. 2 Representative examples of the newly synthesized compounds

Table 1 Synthesis of hexahydro quinoline derivative **5a–c** under both ultrasonic irradiation and using the conventional method

Compounds	Ultrasonic irradiation		Conventional method	
	Time (min)	Yield (%)	Time (h)	Yield (%)
5a	30	62	6	60
5b	45	92	9	89
5c	60	93	14	89

activities against human cultured breast carcinoma cell lines (MCF7) in comparison to DOX, which is one of the most efficient antitumor agents. According to the resultant data presented in Table 3, which shows the in vitro cytotoxic activity of the selected synthesized compounds, some compounds exhibit significant activity compared to the reference drug. From the results in Table 3, it was found that the quinoline derivatives **12a**,**d** and **16b** ($IC_{50} = 0.036$, 0.025, 0.036, 0.015 µM, respectively) were the most potent compounds in this screening, and exhibited a higher cytotoxic activity when compared with the reference drug DOX ($IC_{50} = 0.04$ µM). Compounds **5c**, **7**, **10**, and **12c** ($IC_{50} =$ 0.048, 0.040, 0.041, 0.044 µM, respectively) were nearly as active as DOX, compounds **5a**, **8**, **12b**, **14**, and **15b** showed lower IC_{50} values than that of the reference drug, ranging from 0.055–0.088 µM.

Conclusion

In this work, we have synthesized novel quinoline derivatives containing enaminone system and bearing a sulfonamide moiety using both classical and sonicated methods. Selected examples of these newly synthesized compounds were investigated against their in vitro anticancer activity against human breast cancer cell line (MCF7). Some of these new compounds exhibited significant anticancer activity, when compared to DOX as a reference drug. Since it was reported that compounds bearing a free sulfonamide group may show potent CA inhibition activity, which is considered to be an interesting target for the design of anticancer agents, the results obtained from the anticancer screening may provide a suggestion that the synthesized compounds may act as CA inhibitors that could contribute to their anticancer activity.

Experimental section

General

All melting points (m.p.) were measured on a Mel-Temp apparatus and were uncorrected. TLC was performed on aluminum silica gel 60 F_{254} (E-Merk). The spots were detected by iodine and UV light absorption. Infrared spectra were recorded for the compounds in an FTIR, Perkin Elmr SP 100 Spectrometer. ^{1}H NMR and ^{13}C spectra were recorded on Burker WM 400 and 600 MHz spectrometer using TMS (0.00 ppm) or the signal of the deuterated solvent was used as internal standard. Reactions that carried out by ultrasonic irradiation was done using Daihan (Wiseclean, D-40 MHz) ultrasonic bath. Microanalysis was performed by Perkin Elmer elemental analyzer. Biological activity tests were performed at the National Cancer Institute, Cairo, Egypt.

Typical procedure for the reactions

*Synthesis of 4-(5,5-dimethyl-3-oxocyclohex-1-enylamino) benzenesulfonamide (**3**)*

Method A: silent reaction Prepared according to reported procedure (Ghorab et al. 2010).

Method B: sonicated reaction A mixture of diamidone **1** (0.14 g, 1 mmol) and sulfanilamide **2** (0.172 g, 1 mmol) in ethanol (7 ml) was sonicated at a frequency of 40 KHz for 20 min at 80 °C. Then the reaction mixture was cooled in ice bath and the collected mass was filtered off, dried, and crystallized from ethanol to give enaminone **3** as white crystals (0.265 g, 90% yield); m.p. 235–237 °C. FTIR, cm^{-1}: 3400, 3310, 3290 (NH, NH_2); 1630 (C=O); 1357–1150 (SO_2).

Fig. 3 Imine-iminol structures of compound **10**

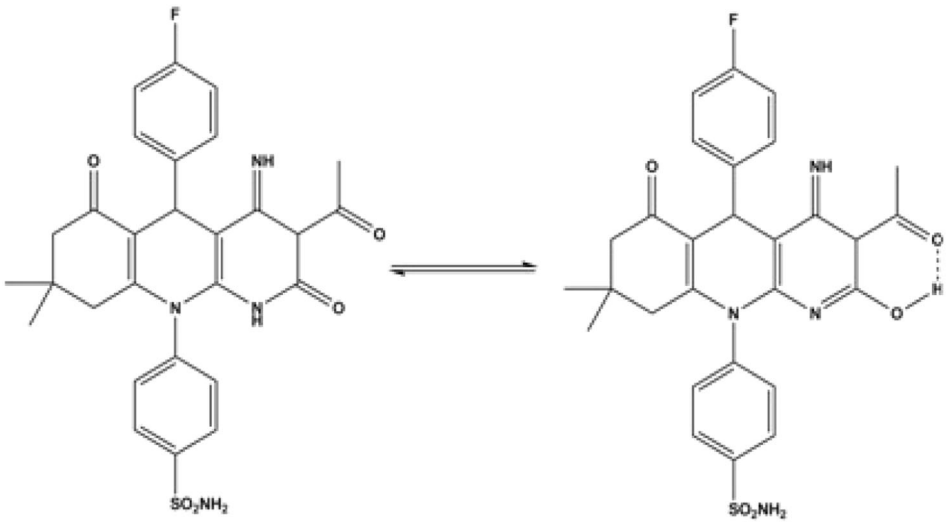


Table 2 Synthesis of benzenesulfonamide derivatives **12a–f** under both ultrasonic irradiation and using the conventional method

Compounds	Ultrasonic irradiation		Conventional method	
	Time (min)	Yield (%)	Time (h)	Yield (%)
12a	10	85	3	72
12b	10	96	4	50
12c	50	95	30	80
12d	30	82	20	65
12e	20	70	16	40
12f	20	80	16	69

Table 3 The effect of some newly synthesized compounds against human breast carcinoma cell line (MCF7)

Compounds	IC_{50} (μM)
5a	0.088
5c	0.048
7	0.040
8	0.055
10	0.041
12a	0.025
12b	0.064
12c	0.044
12d	0.036
14	0.076
15b	0.087
16b	0.015
DOX	0.04

*Synthesis of 4-(2-amino-3-cyano-4-(aryl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl) benzenesulfonamide (**5a–c**)*

Method A: silent reaction A mixture of compound **3** (2.94 g, 10 mmol) and different arylidene malononitrile **4a–c** (10 mmol) in EtOH (20 ml) containing three drops of TEA was refluxed for 6–14 h (until disappearance of starting material as examined by TLC). The reaction mixture was filtered while hot and the solid obtained was filtered off and dried.

Method B: sonicated reaction A mixture of compound **3** (0.294 g, 1 mmol) and different arylidene malononitrile **4a–c** (1 mmol) in EtOH (7 ml) containing one drop of TEA was sonicated at a frequency of 40 KHz for 30–60 min at 80 °C. Then the reaction mixture was filtered and the collected mass was filtered off and dried.

4-(2-Amino-3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)benzenesulfonamide (**5a**): It was crystallized from ethanol as red crystals (0.29 g, 62% yield); m.p. 119–120 °C. FTIR, cm^{-1}: 3469, 3408, 3347, 3334 ($2NH_2$); 2177 (C≡N); 1630 (C=O); 1357–1190 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.75, 0.90 (6H, 2s, $2CH_3$); 1.07 (2H, s, C_8-H_2); 2.09 (2H, s, C_6-H_2); 4.45 (1H, s, C_4-H); 5.80 (2H, s, NH_2); 6.89–8.06 (8H, complex pattern, Ar–H); 8.54 (2H, s, SO_2NH_2). ^{13}C NMR (600 MHz, DMSO-d_6) δ_C: 15.00 ($2CH_3$); 18.00 (C_7); 57.00 (C_4); 79.00 (C_8); 81.22 (C_6); 81.24 (C_3); 112.47 (C_4'); 113.21, 128.06, 130.05, 160.2 (of p-flouro phenyl ring); 114.20, 127.45, 133.55, 133.62 (of p-SO_2NH_2 phenyl ring); 117.04 (CN); 160.20 (C_8'); 164.36 (C_2); 194.00 (C_5). Anal. calcd. for $C_{24}H_{23}FN_4O_3S$ (466.53): C, 62.09; H, 4.97; N, 12.01%. Found: C, 61.99; H, 4.85; N, 11.95%.

4-(2-Amino-3-cyano-4-(4-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)benzenesulfonamide (**5b**): It was crystallized from isopropanol to give dark

red crystals (0.45 g, 92% yield); m.p. 85–87 °C. FTIR, cm^{-1}: 3460, 3371, 3337, 3243 ($2NH_2$); 2190 (C≡N); 1679 (C=O); 1344–1190 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.70, 0.90 (6H, 2s, $2CH_3$); 1.35 (2H, s, C_8-H_2); 2.07 (2H, s, C_6-H_2); 4.37 (1H, s, C_4-H); 5.79 (2H, s, NH_2); 6.56–8.29 (8H, complex pattern, Ar–H); 8.34 (2H, s, SO_2NH_2). ^{13}C NMR (600 MHz, DMSO-d_6) δ_C: 30.67 ($2CH_3$); 45.69 (C_7); 52.92 (C_4); 58.00 (C_8); 61.66 (C_6); 79.00 (C_3); 112.39 (C_4'); 115.58, 129.98, 130.16, 134.13 (of p-SO_2NH_2 phenyl ring); 118.18 (CN); 123.63, 127.39, 142.93, 148.33 (of p-NO_2 phenyl ring) 151.89 (C_8'); 165.05 (C_2); 194.00 (C_5). Anal. calcd. for $C_{24}H_{23}N_5O_5S$ (493.14): C, 58.41; H, 4.70; N, 14.19%. Found: C, 58.49; H, 4.50; N, 14.13%.

4-(2-Amino-3-cyano-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4*H*)-yl)benzenesulfonamide (**5c**): It was crystallized from ethanol to give pale yellow crystals (0.45 g, 93% yield); m.p. 148–149 °C. FTIR, cm^{-1}: 3475, 3380, 3311, 3235 ($2NH_2$); 2218 (C≡N); 1623 (C=O); 1314–1149 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.93, 1.01 (6H, 2s, $2CH_3$); 2.06 (2H, s, C_8-H_2); 2.21 (2H, s, C_6-H_2); 3.69 (H, s, C_4-H); 3.87 (3H, s, O–CH_3); 5.79 (2H, s, NH_2); 6.56–7.97 (8H, complex pattern, Ar–H); 8.37 (2H, s, SO_2NH_2). Anal. calcd. for $C_{25}H_{26}N_4O_4S$ (478.17): C, 62.74; H, 5.48; N, 11.71%. Found: C, 62.94; H, 5.39; N, 11.64%.

*Synthesis of 2-chloro-*N*-(2-chloroacetyl)-*N*-(3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide (**6**)*

A mixture of compound **5a** (0.466 g, 1 mmol) and chloroacetyl chloride (0.08 ml, 1 mmol) in dimethyl formamide (20 ml) was refluxed for 1 h. The reaction mixture was poured onto cold water and the solid obtained was filtered off and dried. It was crystallized from ethanol to give brown crystals (0.28 g, 40% yield); m.p. 126–128 °C. FTIR, cm^{-1}: 3356, 3336 (NH_2); 2227 (C≡N); br. 1699, 1653 (3C=O); 1303–1150 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 1.07 (6H, s, $2CH_3$); 2.53 (2H, s, C_8-H_2); 3.22 (2H, s, C_6-H_2); 2.71, 2.87 (4H, 2s, $2COCH_2Cl$); 3.99 (1H, s, C_4-H); 6.56–7.93 (8H, complex pattern, Ar–H), 8.30 (2H, s, SO_2NH_2). Anal. calcd. for $C_{28}H_{25}Cl_2FN_4O_5S$ (618.09): C, 54.29; H, 4.07; N, 9.04%. Found: C, 54.34; H, 4.00; N, 8.71%.

*Synthesis of N-(4-(5-(4-fluorophenyl)-4-hydroxy-2,8,8-trimethyl-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl) phenylsulfonyl) acetamide (**7**)*

A solution of compound **5a** (0.466 g, 1 mmol) in acetic anhydride (20 ml) was refluxed for 1 h, the reaction mixture was then concentrated, the solid obtained was filtered off and dried. It was crystallized from methanol to give pale yellow crystals (0.48 g, 87% yield); m.p. 245–246 °C. FTIR, cm^{-1}: 3332, 3274 (NH, OH); 1697, 1669 (2C=O); 1371, 1156 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.75, 0.90 (6H, 2s, $2CH_3$); 1.89 (5H, s, C_9-H_2 and $COCH_3$), 2.07 (5H, s, C_7-H_2 and C_2-CH_3); 3.15 (1H, s, C_5-H); 7.16–8.54 (8H, m, Ar–H); 10.37 (1H, s, NH); 11.95 (1H, s, OH). Anal. calcd. for $C_{28}H_{27}FN_4O_5S$ (550.17): C, 61.08; H, 4.94; N, 10.18%. Found: C, 61.22; H, 5.01; N, 9.97%.

*Synthesis of 2-cyano-*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 mixture of compound **5a** (0.466 g, 1 mmol) and ethyl cyanoacetate (10 ml) was refluxed together for 5 h. The formed solid mass was filtered off and dried. It was crystallized from methanol to give brown crystals (0.49 g, 92% yield); m.p. 227–228.5 °C. FTIR, cm^{-1}: 3312, 3229, 3123 (NH_2, NH); 2260 (C≡N); 1743, 1680 (2C=O); 1360–1150 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.75, 0.90 (6H, 2s, $2CH_3$); 1.20 (2H, s, C_8-H_2); 2.06 (2H, s, C_6-H_2); 3.98 (3H, s, CH_2CN and C_4-H); 7.27–7.78 (8H, complex pattern, Ar–H); 8.29 (2H, s, SO_2NH_2); 10.50 (1H, s, NH). ^{13}C NMR (600 MHz, DMSO-d_6:$CDCL_3$) δ_C: 23.00 ($\underline{CH_2}CN$); 26.93 ($2CH_3$); 59.49 (C_7); 60.74 (C_4); 63.3 (C_8); 66.91 (C_6); 68.08 (C_3); 112.00 (C_4'); 114.80, 138.84, 130.00, 161.04 (p-F phenyl ring); 119.21, 130.20, 130.60, 141.24 (P-SO_2NH_2 phenyl ring); 126.97 (CH-$\underline{CN}$); 152.00 (C_8'); 156.00 (C_2); 172.43 (NHCO); 195 (C_5). Anal. calcd. for $C_{27}H_{24}FN_5O_4S$ (533.15): C, 60.78; H, 4.53; N, 13.13%. Found: C, 60.90; H, 4.32; N, 13.02%.

*Synthesis of 4-(2-amino-5-(2-aminoethylamino)-3-cyano-4-(4-fluorophenyl)-7,7-dimethyl-7,8-dihydroquinolin-1(4H)-yl)benzenesulfonamide (**9**)*

A mixture of compound **5a** (0.466 g, 1 mmol) and ethylenediamine (7 ml) was refluxed in carbon disulfide (7 ml) for 3 h. The reaction mixture was cooled and then poured onto cold water. The solid obtained was filtered off and dried. It was washed with ethyl acetate, crystallized from ethanol to give brown crystals (0.234 g, 46% yield); m.p. 159–161 °C. FTIR, cm^{-1}: 3337–3193 (NH, NH_2); 2201 (C≡N); 1324–1190 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 1.04 (6H, s, $2CH_3$); 1.88 (2H, s, C_8-H_2); 2.38, 2.51 (3H, 2s, NH and NH_2); 3.63, 3.81 (4H, 2t, $2CH_2$); 4.30 (1H, s, C_4-H), 5.77 (2H, s, C_2-NH_2); 6.56–8.13 (9H, complex pattern, Ar–H and C_6-H); 8.3 (2H, s, SO_2NH_2). Anal. calcd. for $C_{26}H_{29}FN_6O_2S$ (508.21): C, 61.40; H, 5.75; N, 16.52%. Found: C, 61.54; H, 5.40; N, 16.28%.

*Synthesis of 4-(3-acetyl-5-(4-fluorophenyl)-4-imino-8,8-dimethyl-2,6-dioxo-1,2,3,4,6,7,8,9-octahydrobenzo[b][1,8] naphthyridin-10(5H)-yl)benzenesulfonamide (**10**)*

A mixture of compound **5a** (0.466 g, 1 mmol) and ethyl acetoacetate (10 ml) was refluxed together for 5 h. The formed solid mass was filtered off and dried. It was washed by ethylacetate, crystallized from toluene to give black crystals (0.38 g, 70% yield); m.p. 130–132 °C. FTIR, cm^{-1}: 3304, 3256, 3225 (2NH, NH_2); 1713, 1660, 1632 (3C=O); 1349–1198 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 1.16, 1.22 (6H, 2s, $2CH_3$); 2.24 (2H, s, C_9-H_2); 2.55 (2H, s, C_7-H_2); 2.35 (3H, s, $COCH_3$); 3.57 (1H, s, C_3-H); 4.09 (1H, s, C_5-H); 4.24 (1H, s, C_4-NH); 6.04–8.50 (9H, complex pattern, Ar–H and endocyclic NH and SO_2NH_2); 15.72 (1H, s, OH of the iminol structure). Anal. calcd. for $C_{28}H_{27}FN_4O_5S$ (550.17): C, 61.08; H, 4.94; N, 10.18%. Found: C, 61.27; H, 5.03; N, 10.21%.

*Synthesis of 4-(3-cyano-4-(aryl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin 1(2H)-yl) benzenesulfonamide (**12a–f**)*

Method A: silent reaction A mixture of diamidone **1** (0.14 g, 1 mmol) with sulfanilamide **2** (0.172 g, 1 mmol), different aromatic aldehydes **11a–f** (1 mmol) and ethyl cyanoacetate (0.12 ml, 1 mmol) in ethanol (10 ml) was refluxed for 3–30 h, the obtained solid filtered off and dried.

Method B: sonicated reaction A mixture of diamidone **1** (0.14 g, 1 mmol) with sulfanilamide **2** (0.172 g, 1 mmol), different aromatic aldehydes **11a–f** (1 mmol) and with ethyl cyanoacetate (0.12 ml, 1 mmol) in ethanol (10 ml) was sonicated at a frequency of 40 KHz for 10–50 min at 80 °C. Then the collected mass was filtered off and dried.

4-(3-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12a**): It was crystallized from ethanol to give colorless crystals (0.395 g, 85% yield); m.p. 149–150 °C. FTIR, cm^{-1}: 3372, 3236 (NH_2); 2226 (C≡N); 1715, 1690 (2C=O); 1305–1145 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.87, 1.02 (6H, 2s, $2CH_3$); 2.03, 2.23 (2H, 2d, C_6-H_2); 2.46, 2.51 (2H, 2d, C_8-H_2); 6.99–7.55 (8H, complex pattern, Ar–H); 8.30 (2H, s, SO_2NH_2). ^{13}C (600MHz, DMSO-d_6) δ_C: 26.45, 28.57 ($2CH_3$); 31.85 (C_7); 32.69 (C_8); 49.9 (C_6); 112 (C_4'); 114.26, 129.35, 162.12 (of p-flouro phenyl ring); 114.4 (C_3); 115.3 (CN); 126.00, 129.41, 142.51, 142.53 (of p-SO_2NH_2 phenyl ring); 159.59 (C_8'); 161.19 (C_2); 167.87 (C_4); 195.83 (C_5). Anal. calcd. for $C_{24}H_{20}FN_3O_4S$ (465.12): C, 61.92; H, 4.33; N, 9.03%. Found: C, 62.03; H, 4.18; N, 8.95%.

4-(3-Cyano-7,7-dimethyl-4-(4-nitrophenyl)-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12b**): It was crystallized from ethanol to give pale yellow crystals (0.472 g, 96% yield); m.p. 165.5–167 °C. FTIR, cm^{-1}: 3459, 3342 (NH_2); 2224 (C≡N); 1716, 1615 (2C=O); 1505 (NO_2 arom.); 1344–1190 (SO_2). ^1H NMR (600 MHz, $CDCL_3$) δ_H: 1.20, 1.34 (6H, s, $2CH_3$); 1.42 (2H, s, C_6-H_2); 1.52 (2H, s, C_8-H_2); 6.80–8.36 (10H, complex pattern, Ar–H and SO_2NH_2). ^{13}C (600 MHz, $CDCl_3$) δ_C: 14.11 ($2CH_3$); 20.00 (C_7); 63.37 (C_6 and C_8); 107.38 (C_4'); 114.00 (C_3); 114.54 (CN); 123.80, 129.00, 131.52, 149.00 (of p-SO_2NH_2 phenyl ring); 124.00, 131.90, 136.90, 149.72 (of p-NO_2 phenyl ring); 151.50 (C_8'); 151.75 (C_2); 161.40 (C_4); 194.00 (C_5). Anal. calcd. for $C_{24}H_{20}N_4O_6S$ (492.11): C, 58.53; H, 4.09; N, 11.38%. Found: C, 58.59; H, 4.02; N, 11.23%.

4-(3-Cyano-4-(4-methoxyphenyl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12c**): It was crystallized from ethanol to give pale yellow crystals (0.453 g, 95% yield); m.p. 136–138 °C. FTIR, cm^{-1}: 3461, 3315 (NH_2); 2264 (C≡N); 1687, 1624 (2C=O); 1299–1144 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.88, 1.01 (6H, 2s, $2CH_3$); 2.02, 2.22 (2H, 2d, C_6-H_2); 2.42, 2.53 (2H, 2d, C_8-H_2) 3.66 (3H, s, OCH_3); 5.78–7.47 (10H, complex pattern, Ar–H and SO_2NH_2). ^{13}C NMR (600 MHz, DMSO-d_6) δ_C: 26.46 ($2CH_3$); 28.63 (C_7); 31.85 (C_8); 32.31 (C_6); 54.86 (OCH_3); 112.41 (C_4'); 113.06, 127.38, 129.98, 161.91 (of p-OCH_3 phenyl ring); 115.70 (C_3 and CN); 127.00, 128.56, 138.46, 151.88 (of p-SO_2NH_2 phenyl ring); 157.29 (C_8'); 159.04 (C_2); 168.04 (C_4); 195.91 (C_5). Anal. calcd. for $C_{25}H_{23}N_3O_5S$ (477.14): C, 62.88; H, 4.85; N, 8.80%. Found: C, 63.01; H, 4.72; N, 8.69%.

4-(4-(4-Chlorophenyl)-3-cyano-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12d**): It was crystallized from ethanol to give white crystals (0.381 g, 82% yield); m.p. 145–147 °C. FTIR, cm^{-1}: 3476, 3371 (NH_2); 2265 (C≡N); 1745, 1687 (2C=O); 1369–1143 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 0.87, 1.01 (6H, 2s, $2CH_3$); 2.02, 2.23 (2H, 2d, C_6-H_2); 2.42, 2.51 (2H, 2d, C_8-H_2); 5.79–7.56 (10H, complex pattern, Ar–H and SO_2NH_2). ^{13}C NMR (600 MHz, DMSO-d_6) δ_C: 26.53 ($2CH_3$); 28.65 (C_7); 31.39 (C_8); 33.03 (C_6); 112.49 (C_4'); 115.10 (C_3 and CN); 127.46, 129.63, 145.43, 162.39 (of p-SO_2NH_2 phenyl ring); 127.72, 130.05, 130.34 (of p-chlorophenyl ring); 151.96 (C_8'); 159.16 (C_2); 167.91 (C_4); 195.99 (C_5). Anal. calcd. for $C_{24}H_{20}ClN_3O_4S$ (481.09): C, 59.81; H, 4.18; N, 8.72%. Found: C, 59.92; H, 3.99; N, 8.65%.

4-(4-(4-Bromophenyl)-3-cyano-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12e**): It was crystallized from ethanol to give yellow crystals (0.367 g, 70% yield); m.p. 213–215 °C. FTIR, cm^{-1}: 3333, 3233 (NH_2); 2263 (C≡N); 1743, 1682 (2C=O); 1369–1149 (SO_2). ^1H NMR (600 MHz, DMSO-d_6) δ_H: 1.04 (6H, s, $2CH_3$); 1.10, 1.2 (2H, 2d, C_6-H_2); 2.00,

2.1 (2H, 2d, C_8-H_2); 6.70–7.78 (10H, complex pattern, Ar–H and SO_2NH_2). Anal. calcd. for $C_{24}H_{20}BrN_3O_4S$ (525.04): C, 54.76; H, 3.83; N, 7.98%. Found: C, 54.95; H, 3.80; N, 8.01%.

4-(3-Cyano-4-(4-(dimethylamino)phenyl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2*H*)-yl)benzenesulfonamide (**12f**): It was washed by petroleum ether to give yellow crystals (0.39 g, 80% yield); m.p. 122–123 °C. FTIR, cm^{-1}: 3400, 3373 (NH_2); 2208 (C≡N); 1699, 1593 (2C=O); 1274, 1227 (SO_2). ^{1}H NMR (600 MHz, DMSO-d_6) δ_H: 0.90, 1.08 (6H, 2s, $2CH_3$); 1.19, 1.33 (2H, 2d, C_6-H_2); 2.15, 2.20 (2H, 2d, C_8-H_2); 3.45 (6H, s, $N(CH_3)_2$); 6.59–8.1 (10H, complex pattern, Ar–H and SO_2NH_2).^{13}C NMR (600 MHz, DMSO-d_6) δ_C: 27.57, 29.09 ($2CH_3$); 30.94 (C_7); 32.72 (C_8); 40.67 ($N(CH_3)_2$); 50.76 (C_6); 81.45, 117.22, 128.76, 158.20 (of p-$N(CH_3)_2$ phenyl ring); 112.30 (C_4'); 113.01 (C_3 and CN); 114.01, 128.65, 134.27, 148.79 (of p-SO_2NH_2 phenyl ring); 161.01 (C_8'); 162.87 (C_2); 169.34 (C_4); 196.58 (C_5). Anal.calcd. for $C_{26}H_{26}N_4O_4S$ (490.17): C, 63.66; H, 5.34; N, 11.42%. Found: C, 63.80; H, 5.16; N, 11.24%.

*Synthesis of 4-(3-cyano-6-((dimethylamino) methylene)-4-(4-fluorophenyl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl) benzenesulfonamide (**13**)*

A mixture of **12a** (4.65 g, 10 mmol) and DMF/DMA (2 ml, 16.7 mmol) was fused together for 6 h at 100 °C. The obtained solid by cooling was crystallized from ethanol to give yellow crystals (0.48 g, 94% yield); m.p. 238–239 °C. FTIR, cm^{-1}: 3387, 3347 (NH_2); 2206 (C≡N); 1666, 1625 (2C=O); 1337–1153 (SO_2). ^{1}H NMR (600 MHz, $CDCL_3$) δ_H: 1.09, 1.63 (6H, 2s, $2CH_3$); 2.48 (2H, s, C_8-H_2); 3.04, 3.15 (6H, 2s, $N(CH_3)_2$); 7.71 (1H, s, olifinic H); 6.80–8.60 (10H, complex pattern, Ar–H and SO_2NH_2). ^{13}C (600 MHz, $CDCL_3$) δ_C: 28.55 (C_7); 30.94 ($2CH_3$); 35.63 (C_8); 41.59 ($N(CH_3)_2$); 108.00 (C_3 and C_4'); 109.65 (CN); 113.93, 119.70, 196.40 (of p-flouro phenyl ring); 117.75, 127.90, 139.89, 141.28 (of p-SO_2NH_2 phenyl ring); 128.67 (C_6); 149.61 ($CHN(CH_3)_2$); 158.86 (C_2); 159.10 (C_8'); 200.56 (C_4); 207.03 (C_5). Anal. calcd. for $C_{27}H_{25}FN_4O_4S$ (520.16): C, 62.29; H, 4.84; N, 10.76%. Found: C, 62.41; H, 4.81; N, 10.55%.

*Synthesis of 4-(2-amino-9-cyano-10-(4-fluorophenyl)-5,5-dimethyl-8-oxo-5,6-dihydropyrido[2,3-h]quinazolin-7(8H)-yl)benzenesulfonamide (**14**)*

A mixture of enaminone **13** (0.52 g, 1 mmol) and guanidine nitrate (0.122 g, 1 mmol) and sodium carbonate (0.12 g, 1 mmol) were fused at 180 °C for 2 h. The obtained solid on cooling was crystallized from chloroform to give brown crystals (0.5 g, 97% yield); m.p. 112–114 °C. FTIR, cm^{-1}: 3351–3201 ($2NH_2$); 2226 (C≡N); 1666 (C=O); 1336–1219 (SO_2). ^{1}H NMR (600 MHz, DMSO-d_6) δ_H: 0.98, 1.04 (6H, 2s, $2CH_3$); 2.92 (2H, s. C_6-H_2); 5.80 (2H, s, NH_2); 6.53–8.30 (11H, complex pattern, Ar–H and C_4-H and SO_2NH_2). Anal. calcd. for $C_{26}H_{21}FN_6O_3S$ (516.14): C, 60.45; H, 4.10; N, 16.27%. Found: C, 60.49; H, 4.01; N, 16.17%.

*Synthesis of 4-(8-cyano-9-(4-fluorophenyl)-4,4-trimethyl-7-oxo-4,5-dihydro-1H-pyrazolo[3,4-f]quinolin-6(7H)-yl) benzenesulfonamide derivatives (**15a,b**)*

General method A mixture of enaminone **13** (1 g, 2 mmol) and hydrazine derivatives (2 mmol) were fused together for 2–4 h, the residue obtained was crystallized.

4-(8-Cyano-9-(4-fluorophenyl)-1,4,4-trimethyl-7-oxo-4,5-dihydro-1*H*-pyrazolo[3,4-f]quinolin-6(7*H*)-yl)benzenesulfonamide (**15a**): It was crystallized from ethanol to give brown crystals (0.417 g, 83% yield); m.p. 101–103 °C. FTIR, cm^{-1}: 3323, 3270 (NH_2); 2353 (C≡N); 1620 (C=O); 1220–1155 (SO_2). ^{1}H NMR (600 MHz, $CDCl_3$) δ_H: 1.10, 1.20 (6H, 2s, $2CH_3$); 2.17 (2H, s, C_5-H_2); 3.80 (3H, s, NCH_3); 6.7–8.01 (11H, complex pattern, Ar–H and SO_2NH_2). Anal. calcd. for $C_{26}H_{22}FN_5O_3S$ (503.14): C, 62.02; H, 4.40; N, 13.91%. Found: C, 62.22; H, 4.35; N, 13.74%.

4-(8-Cyano-9-(4-fluorophenyl)-4,4-dimethyl-7-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazolo[3,4-f]quinolin-6(7*H*)-yl) benzenesulfonamide (**15b**): It was crystallized from dioxane to give brown crystals (0.45 g, 80% yield); m.p. 141–142 °C. FTIR, cm^{-1}: 3450, 3348 (NH_2); 2202 (C≡N); 1620 (C=O); 1340–1180 (SO_2). ^{1}H NMR (600 MHz, $CDCL_3$) δ_H: 1.24 (6H, s, $2CH_3$); 2.17 (2H, s, C_5-H_2); 6.64–8.09 (16H, complex pattern, Ar–H and SO_2NH_2). Anal. calcd. for $C_{31}H_{24}FN_5O_3S$ (565.16): C, 65.83; H, 4.28; N, 12.38%. Found: C, 66.03; H, 4.08; N, 12.22%.

*Synthesis of 4-(10-Cyano-11-(4-fluorophenyl)-6,6-dimethyl-9-oxo-6,7-dihydropyrazolo[1,5-a]pyrido[2,3-h]quinazolin-8(9H)-yl) benzenesulfonamide derivatives (**16a,b**)*

General method A mixture of enaminone **13** (0.52 g, 1 mmol) and amino pyrazole derivatives (1 mmol), and few drops from TEA was fused together at 130 °C for 5 h. The obtained mass was crystallized.

4-(10-Cyano-11-(4-fluorophenyl)-2,6,6-trimethyl-9-oxo-3-phenyl-6,7-dihydropyrazolo[1,5-a]pyrido[2,3-h]quinazolin-8(9*H*)-yl) benzenesulfonamide (**16a**): It was crystallized from toluene to give brown crystals (0.49 g, 79% yield); m.p. 226–227 °C. FTIR, cm^{-1}: 3480, 3397 (NH_2); 2197 (C≡N); 1663 (C=O); 1221, 1159 (SO_2). ^{1}H NMR (600 MHz, $CDCL_3$) δ_H: 1.24 (6H, s, $2CH_3$); 2.59 (2H, s, C_7-H_2); 2.67 (3H, s, C_2-CH_3); 7.17–8.00 (15H, complex pattern,

Ar–H and SO_2NH_2); 8.97 (1H, s, C_5-H). ^{13}C NMR (600 MHz, $CDCL_3$) δ_C: 14.00 (CH_3 at C_2); 29.27 ($2CH_3$ at C_6); 40.84 (C_6); 50.70 (C_7); 112.18 (C_{11}'); 113.2 80 (C_{10}); 114.78; 128.63, 128.72, 162.56 (of p-flouro phenyl ring); 115.39, 129.03, 131.24, 147.04 (of p-SO_2NH_2 phenyl ring); 115.75 (CN); 116.37 (C_3); 127.04, 128.87, 129.10, 131.10 (of phenyl at C_3); 129.80 (C_3'); 129.9 (C_5'); 146.41 (C_2); 151.00 (C_7'); 151.72 (C_5); 156.62 (C_9); 159.00 (C_{11}''); 194.4 (C_{11}). Anal. calcd. for $C_{35}H_{27}FN_6O_3S$ (630.18): C, 66.65; H, 4.32; N, 13.33%. Found: C, 66.76; H, 4.21; N, 13.17%.

4-(2-(4-Chlorophenyl)-10-cyano-11-(4-fluorophenyl)-6,6-dimethyl-9-oxo-6,7-dihydropyrazolo[1,5-a]pyrido[2,3-h]quinazolin-8(9*H*)-yl)benzenesulfonamide (**16b**): The obtained mass was crystallized from ethanol to give brown crystals (0.47 g, 72% yield); m.p. 117–118 °C. FTIR, cm^{-1}: 3336, 3254 (NH_2); 2263 (C≡N); 1652 (C=O); 1221, 1159 (SO_2). ^1H NMR (600 MHz, $CDCL_3$) δ_H: 1.16, 1.17 (6H, 2s, $2CH_3$); 2.60 (2H, s, C_7-H_2); 6.64 (C_3-H); 6.84–8.10 (14H, complex pattern, Ar–H and SO_2NH_2); 8.98 (C_5-H). ^{13}C NMR (600 MHz, $CDCL_3$) δ_C: 27.62 ($2CH_3$); 37.31 (C_6); 50.52 (C_7); 95.97 (C_3); 113.49 (C_{11}'); 114.01 (C_{10}); 114.79 (CN); 115.64, 127.73, 128.02, 147.32 (of p-flouro phenyl ring); 116.37, 128.38, 128.93, 129.17 (of p-SO_2NH_2 phenyl ring); 128.17, 128.22, 128.50, 128.63 (of p-chloro phenyl ring); 128.63 (C_5'); 129.52 (C_7'); 129.90 (C_3'); 130.19 (C_2); 130.92 (C_5); 158.72 (C_9); 169.00 (C_{11}''); 170.00 (C_{11}). Anal. calcd. for $C_{34}H_{24}ClFN_6O_3S$ (650.13): C, 62.72; H, 3.72; N, 12.91%. Found: C, 62.93; H, 3.56; N, 12.83%.

In vitro cytotoxic screening

Twelve analogs (**5a**,**c**), (**7**), (**8**), (**10**), (**12a–d**), (**14**), (**15b**), (**16b**) were selected as representative examples to evaluate their in vitro inhibitory effects against cellular proliferation in human cultured breast carcinoma cell line using DOX as a reference drug. Breast cancer cell lines (MCF7) were obtained from Cell Bank in National Cancer Institute, Cairo, Egypt. The potential cytotoxicity of the selected newly synthesized derivatives was done by SRB using the method of (Skehan et al. 1990) as follows: Cells were plated in a 96-multiwell plate (104 cells/well) for 24 h before treatment with compounds to allow attachment of the cell to the wall of the plate. Different concentrations of the compound under test (5, 12.5, 25, and 50 µg/ml) were added to the cell monolayer triplicate wells which were prepared for each individual dose. Monolayer cells were incubated with the compounds for 48 h at 37 °C and in an atmosphere of 5% CO_2. After 48 h, cells were fixed, washed, and stained with Sulpho-Rhodamine-B stain. Excess stain was washed with acetic acid and attached stain was recovered with Tris-EDTA buffer. Color intensity was measured in an ELISA reader. Measurements were done six times and averaged. The relation between surviving fraction and drug concentration is plotted to get the survival curve of each tumor cell line after the specified compound.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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