European Journal of Medicinal Chemistry 45 (2010) 738–744

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Novel quinolines and pyrimido[4,5-b]quinolines bearing biologically active sulfonamide moiety as a new class of antitumor agents

Saleh I. Alqasoumi [a], Areej M. Al-Taweel [b], Ahmed M. Alafeefy [c], Eman Noaman [d], Mostafa M. Ghorab [a,*]

[a] Medicinal, Aromatic and Poisonous Plants Research Center (MAPPRC), College of Pharmacy, King Saud University, P.O.Box 2457, Riyadh 11451, Saudi Arabia
[b] Pharmacognosy Department, College of Pharmacy, King Saud University, Saudi Arabia
[c] Medicinal Chemistry Department, College of Pharmacy, King Saud University, Saudi Arabia
[d] Radiation Biology Department, National Center for Radiation Research and Technology, Atomic Energy Authority, Nasr City, Cairo, Egypt

ARTICLE INFO

Article history:
Received 17 June 2009
Received in revised form
4 November 2009
Accepted 12 November 2009
Available online 18 November 2009

Keywords:
Quinoline
Pyrimidoquinoline
Sulfonamide
Antitumor activity

ABSTRACT

Some novel quinolines and pyrimido[4,5-b]quinolines have been synthesized. The structures of which were confirmed by elemental analyses and spectral data. All the target compounds were subjected to in-vitro antitumor activity against Ehrlich Ascites Carcinoma (EAC) cells. Compounds **24**, **19** and **12** showed higher activity with IC_{50} values (5.5, 6.9, 7 μg/ml) when compared with Doxorubicin as a reference drug (IC_{50} value 38 μg/ml).

1. Introduction

Quinoline derivatives were found to possess several pharmacological properties, including antibacterial [1–3] and anticancer [4–10] activities. Also, the chemistry of pyrimidine and fused pyrimidine derivatives has been of increasing interest, since many of these compounds exhibited several biological activities and useful application as antitumor [11–19], and antibacterial agents [20]. On the other hand, among the wide range of compounds tested as antitumor agents, sulfonamides have attracted great attention, as many sulfonamide derivatives were reported to have interesting antitumor activity [21–25]. Several mechanisms have been reported for the anticancer activity of the sulfonamide compounds and the most prominent of these mechanisms was through the inhibition of the carbonic anhydrase isozymes [26–29]. The mechanism of tumor inhibition by sulfonamide carbonic anhydrase (CA) inhibitor was suggested by Boyle and Chegwidden [30], that these compounds may reduce the provision of bicarbonate for the synthesis of nucleotides and other cell components such as membrane lipids. In continuation of our work it seemed of interest to design and synthesize some novel 4-(quinoline-1-yl)-benzenesulfonamide and pyrimido[4,5-b](quinoline-10-yl)benzenesulfonamide derivatives, bearing potentially active side chains, such as cyano [11], ureido, thioureido [13] and thione [18] as analogues of compound E7070 [29] (Fig. 1), to be evaluated as potential antitumor agents.

2. Results and discussion

2.1. Chemistry

In this investigation a series of new quinolines bearing sulfonamide moiety **6**–**11**, **18**, **21**–**24**, pyrimido[4,5-b]quinoline attached to sulfonamide moiety, **12**–**16**, **17**, **19** and **20** were designed, synthesized (Schemes 1–4) and biologically evaluated for their in-vitro antitumor activity. Thus, condensation of 1,3-cyclohexandione **1** with sulfanilamide **2** gave the corresponding enaminone **3**, which upon reaction with 2-(2,4-dichlorobenzylidene)- malononitrile **4**, in ethanol containing a catalytic amount of triethylamine, yielded 2-aminoquinoline-3-carbonitrile derivative **6**. The structure of the enaminone **3** was established by elemental analyses and spectral data. IR spectrum of compound **3** showed the presence of the characteristic bands for (NH, NH_2), (C═O) and (SO_2). Also, the ^1H NMR spectrum indicated the presence of a singlet at 9.0 ppm which could be assigned to NH of enaminone **3**. IR spectrum of compound **6** exhibited bands for (NH_2), (C═O), (SO_2) in addition to the

* Corresponding author. Tel.: +966 534292860; fax: +966 01 4670560.
E-mail address: mmsghorab@yahoo.com (M.M. Ghorab).

0223-5234/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.ejmech.2009.11.021

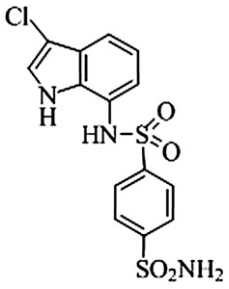
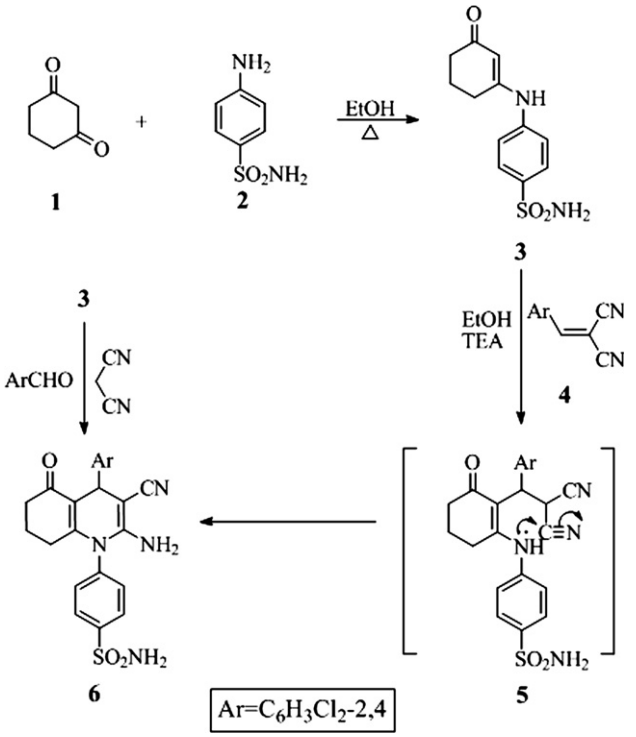


Fig. 1. Compound E7070, a sulfonamide compound in advanced clinical trials as anticancer agent.

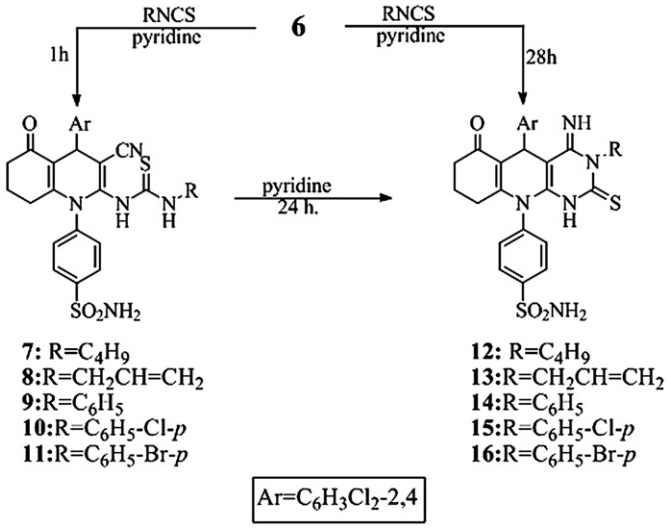
carbonitrile band. The mass spectrum of **6** revealed a molecular ion peak *m*/*z* at 489 [M^+] (1.8), with a base peak at 73 (100)

The behavior of compound **6** towards isothiocyanate was studied. Thus, nucleophilic reaction of compound **6** on the highly positive carbon of the isothiocyanate RNCS in dry pyridine for (2 h) yielded the corresponding thioureido derivatives **7**–**11** (Scheme2), while 24 h reaction time, furnished the cyclic system pyrimido[4,5-b]quinoline derivatives **12**–**16**, respectively. Structures of compounds **7**–**11** were confirmed on the basis of their IR spectra which showed the presence of (C≡N) band at 2164–2182 cm^{-1}. The structure of compounds **12**–**16** was established on the basis of elemental analyses, IR, ^1H NMR and mass spectral data. IR spectra of compounds **12**–**16** revealed the absence of (C≡N) and the presence of (C═S) bands at 1256–1270 cm^{-1}.

The target ring system **17** was synthesized by reaction of compound **6** with carbon disulfide in pyridine for long time (48 h) (Scheme 3). IR spectrum of compound **17** exhibited the absence of (C≡N) band. When compound **6** was allowed to react with urea in ethanolic sodium ethoxide, a product of the molecular formula $C_{23}H_{19}Cl_2N_5O_4S$ **18** is formed *via* the elimination of ammonia, based on the presence of (C≡N) absorption in the IR spectrum. Its IR spectrum showed bands for (NH, NH_2), (C≡N) and (2C═O). The



Scheme 1.



Scheme 2.

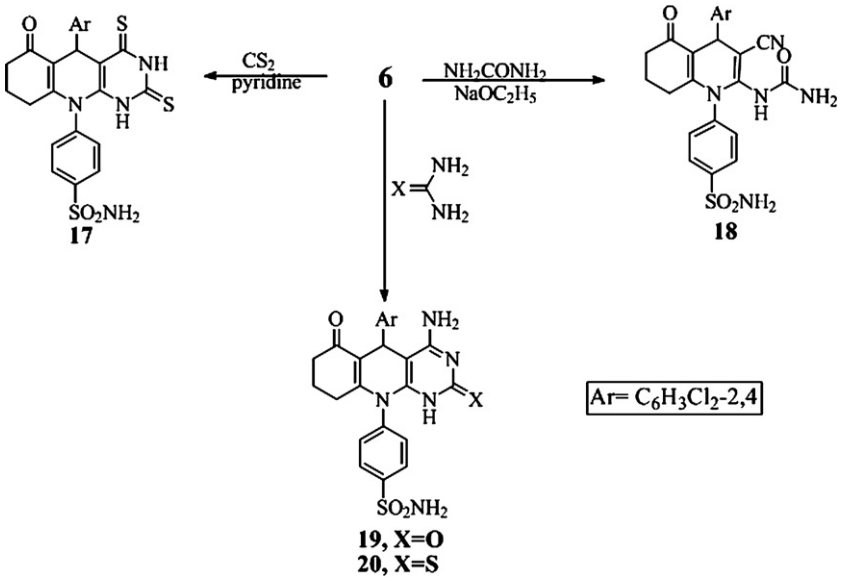
mass spectrum of compound **18** exhibited a molecular ion peak *m*/*z* at 532 [M^+] (2.8), with a base peak at 48 (100), while fusion of compound **6**, with urea and/or thiourea, furnished the condensed pyrimidoquinolines **19** and **20**, respectively. Products **19**, **20** were formed *via* the loss of an ammonia molecule, followed by an intramolecular addition to the cyano function to give the final isolated products **19** and **20**, respectively. IR spectra of **19** and **20** exhibited the disappearance of a band characteristic for the carbonitrile functional group and the presence of bands at 3420–3209 cm^{-1} (NH, NH_2). The mass spectrum of compound **19** revealed a molecular ion peak *m*/*z* at 532 [M^+] (2.5), with abase peak at 41 (100). The mass spectrum of compound **20** showed a molecular ion peak *m*/*z* at 548 [M^+] (2.4), with abase peak at 47 (100).

In addition, the behavior of compound **6** towards succinic anhydride under different conditions was studied. Thus, the reaction of compound **6** with succinic anhydride in boiling ethanol gave the acid derivative **21**. While carrying out the reaction under the condition of fusion, the pyrrolo derivative **22** was obtained (Scheme 4). The structure of compounds **21**, **22** was proved on the basis of elemental analyses and spectral data. IR spectrum of compound **21** revealed bands for (OH), (NH, NH_2), (C≡N) and (2C═O). ^1H NMR spectrum of **21** exhibited signals at 1.10–1.20 ppm for CH_2–CH_2, 8.90 ppm (OH). IR spectrum of compound **22** revealed the absence of OH band and presence of (NH_2), (C≡N) and (3C═O) bands. ^1H NMR spectrum showed signals at 1.10–1.40 ppm (CH_2–CH_2). Its mass spectrum revealed a molecular ion peak *m*/*z* at 571 [M^+] (4.2), with a base peak at 41 (100).

Finally, 2-arylsulfonylaminoquinoline derivatives **23** and **24** were obtained by refluxing compound **6** with 4-nitro and/or 4-bromobenzenesulfonyl chloride in dry pyridine. The structures of compounds **23** and **24** were confirmed by IR, ^1H NMR and mass spectral data. IR spectra revealed bands for (C≡N). ^1H NMR spectrum of **23** showed singlet at 8.30 ppm (NH). Mass spectrum of **23** showed a molecular ion peak *m*/*z* at 674 [M^+] (1.6), with a base peak at 40 (100). Mass spectrum of compound **24** revealed a molecular ion peak *m*/*z* at 708 [M^+] (3.1), with a base peak at 44 (100).

2.2. In-vitro antitumor activity

Doxorubicin, the reference drug used in this study is one of the most effective antitumor agents used to produce regressions in acute leukemia's, Hodgkin's disease, and other lymphomas. The relationship between survival ratio and drug concentration was



Scheme 3.

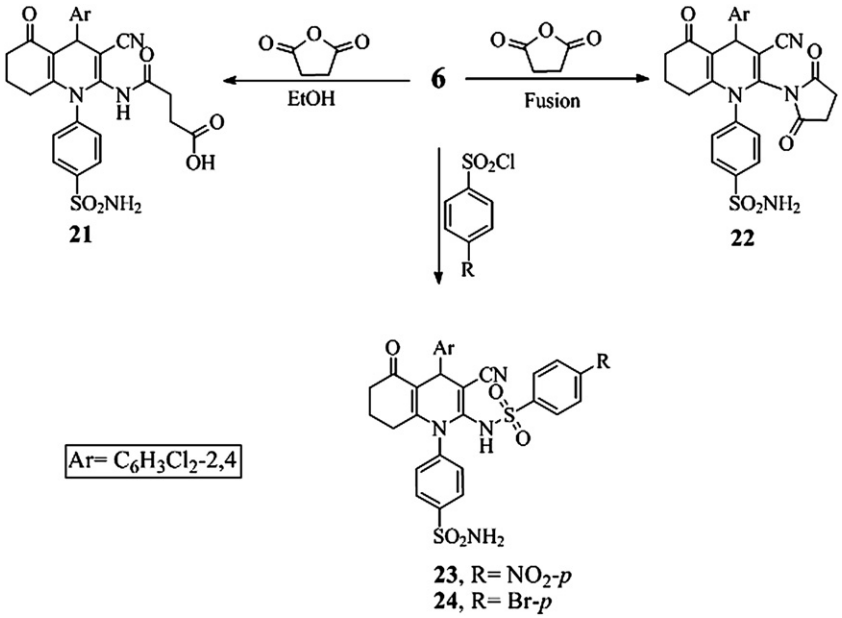
plotted to obtain the survival curve of Ehrlich Ascites Carcinoma (EAC) cells. The response parameter calculated was IC_{50} value (Table 1), which corresponds to the compound concentration causing 50% mortality in net cells.

2.2.1. Structure activity relationship

The cytotoxicity of nineteen compounds was examined on Ehrlich Ascites Carcinoma (EAC) cells. It is clear from the results, the comparison of cytotoxicity of the quinoline derivatives has shown that the cell killing potency follows the order quinoline having 4-bromobenzenesulfonamide **24** with (IC_{50} value = 5.5 μg/ml) > 4-chlorobenzenesulfonamide **23** with (IC_{50} value = 20 μg/ml) > quinoline derivative **6** bearing free amino group at position-2 with (IC_{50} value = 25 μg/ml).

Also, pyrimidoquinoline derivatives follows the order **19** > **12** > **15** > **20** with IC_{50} values (6.9, 7, 10, 25 μg/ml). The presence of 4-bromobenzenesulfonamide at position-2 of quinoline ring **24** with cyano group at position-3 increased the cytotoxic activity which showed the higher potency than the tested compounds and the reference drug Doxorubicin with (IC_{50} value = 38 μg/ml). These results revealed that the nature of substituent at C-2 of the quinoline ring by 4-bromobenzenesulfonamide has an important role on the cytotoxic activity and potency. On the other hand the cyclic system pyrimidoquinoline derivative **19** bearing urea moiety at position-2 with (IC_{50} value = 6.9 μg/ml) exhibited higher potency than the quinoline derivative **18** having urea moiety at position-2 with cyano group at position-3 with (IC_{50} value = 75 μg/ml). In addition it was found that the cyclic urea pyrimidoquinoline **19** revealed a higher potency than the cyclic thiourea **20** with (IC_{50} value = 25 μg/ml).

It is very clear from the results that the pyrimidoquinoline **12** bearing aliphatic butyl moiety at position-3 with (IC_{50} value = 7 μg/ml)



Scheme 4.

Table 1
In-vitro cytotoxic activity of the newly synthesized compounds **6**–**24**.

Compd. No.	Non-viable cells (%)[a]				IC_{50}[b] (μg/ml)
	Concentration (μg/ml)				
	100	50	25	10	
Doxorubicin	100	68 ± 3.3	32 ± 4.1	19 ± 1.8	38
6	95 ± 2.1	65 ± 2.2	50 ± 5.5	40 ± 2.4	25
7	40 ± 3.1	35 ± 3.2	30 ± 2.1	30 ± 2.6	>100[c]
8	40 ± 3.5	33 ± 5.1	30 ± 2.1	10 ± 1.2	>100[c]
9	95 ± 3.8	55 ± 2.4	50 ± 3.2	40 ± 2.1	25
10	100	100	60 ± 2.6	30 ± 1.6	40
11	90 ± 3.6	90 ± 4.7	50 ± 4.1	50 ± 2.1	25
12	80 ± 5.1	80 ± 3.2	70 ± 3.7	70 ± 4.1	7
13	75 ± 2.1	50 ± 3.2	40 ± 2.3	30 ± 2.1	50
14	60 ± 2.3	50 ± 3.3	30 ± 4.2	10 ± 1.1	50
15	95 ± 2.3	90 ± 5.3	60 ± 4.2	50 ± 3.2	10
16	70 ± 3.3	50 ± 5.2	30 ± 2.1	30 ± 3.9	50
17	57 ± 2.7	39 ± 3.7	30 ± 3.5	11 ± 1.6	>100[c]
18	60 ± 1.3	40 ± 3.8	35 ± 4.2	20 ± 2.1	75
19	100	90 ± 2.9	80 ± 5.1	80 ± 4.2	6.9
20	100	100	50 ± 2.8	30 ± 1.9	25
21	60 ± 2.3	50 ± 4.8	35 ± 2.4	20 ± 1.8	50
22	90 ± 3.5	70 ± 3.5	50 ± 4.3	20 ± 2.2	25
23	90 ± 4.5	85 ± 3.8	85 ± 3.4	50 ± 2.9	20
24	100	90 ± 2.9	90 ± 4.1	90 ± 2.1	5.5

[a] Mean of non-viable percentage of three repeated experiments.
[b] IC_{50} value: Corresponds to the compound concentration causing 50% mortality in net cells.
[c] Compounds with $IC_{50} > 100$ μg/ml are considered to be inactive.

is more active than the pyrimidoquinoline **15** carrying aromatic 4-chlorophenyl moiety at the same position with (IC_{50} value = 10 μg/ml).

According to these results it was found that quinoline derivative **10** having 4-chlorophenylthiourea at position-2 with cyano group at position-3 with (IC_{50} value = 40 μg/ml) is nearly as active as Doxorubicin as positive control. Finally, compounds **13**, **14**, **16**, **21**, and **18** exhibited a moderate activity, while compounds **7**, **8**, and **17** showed no activity.

3. Conclusions

We report here the synthesis of some new quinoline and pyrimidoquinoline derivatives containing biologically active sulfonamide moiety, it was clearly observed that quinolines with either 4-bromobenzenesulfonamide **24** or 4-chlorobenzenesulfonamide moiety **23** exhibited higher antitumor activity than the reference drug Doxorubicin. Also, pyrimidoquinoline derivatives **19**, **12**, **15**, and **20** revealed higher potency than the Doxorubicin. In the meantime compound **10** is nearly as active as Doxorubicin, while, compounds **13**, **14**, **16**, **21**, and **18** exhibited a moderate activity. On the other hand compounds **7**, **8**, and **17** showed no activity.

4. Experimental

4.1. Chemistry

Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkemp melting point apparatus (Sanyo Gallenkemp, Southborough, UK) and were uncorrected. Precoated silica gel plates (silica gel 0.25 mm, 60 G F254; Merck, Germany) were used for thin layer chromatography, dichloromethane/methanol (9.5:0.5) mixture was used as a developing solvent system and the spots were visualized by ultraviolet light and/or iodine. Infra red spectra were recorded in KBr discs using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). NMR spectra (in DMSO-d_6) were recorded on Bruker AC-300 Ultra Shield NMR spectrometer (Bruker, Flawil, Switzerland, δ ppm) at 300 MHz using TMS as internal Standard and peak multiplicities are designed as follows: s, singlet; d, doublet; t, triplet; m, multiplet. Electron impact Mass Spectra were recorded on a Shimadzu GC-MS-QP 5000 instrument (Shimadzu, Tokyo, Japan). Elemental analyses were performed on Carlo Erba 1108 Elemental Analyzer (Heraeus, Hanau, Germany).

4.1.1. 4-(3-Oxocyclohexenylamino)benzenesulfonamide (**3**)

A mixture of 1,3-cyclohexanedione **1** (1.12 g, 0.01 mol) and sulfanilamide **2** (1.72 g, 0.01 mol) in ethanol (30 ml) was refluxed for 5 h. The reaction mixture was cooled and then poured onto cold water, the obtained solid was crystallized from ethanol to give **3**: Yield, 88%; m.p. 236–238 °C; IR, cm^{-1}: 3354, 3263, 2210 (NH, NH_2), 3032 (CH arom.), 2940, 2870 (CH aliph.), 1611 (C═O), 1360, 1184 (SO_2). ^{1}H NMR (DMSO-d_6) δ: 1.0–2.2 [m, 6H, $3CH_2$], 5.5 [s, 1H, CH], 7.0–7.8 [m, 6H, Ar-H + SO_2NH_2], 9.0 [s, 1H, NH, D_2O-exchangable]. Anal. Calcd. For $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 53.81; H, 5.62; N, 10.23.

4.1.2. 4-[2-Amino-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydro quinolin-1(4H)-yl]benzenesulfonamide (**6**)

A mixture of enaminone **3** (2.66 g, 0.01 mol) and 2-(2,4-dichlorobenzylidine)malononitrile **4** (2.23 g, 0.01 mol) in ethanol (20 ml) containing 3 drops of triethy1amine was refluxed for 5 h. The reaction mixture was filtered while hot and the solid obtained was crystallized from dioxane to give **6**: Yield, 90%; m.p. 291–293 °C; IR, cm^{-1}: 3464, 3347 (NH_2), 3064 (CH arom.), 2957, 2860 (CH aliph.), 2171 (C≡N), 1634 (C═O), 1374, 1189 (SO_2), 706 (C–Cl). ^{1}H NMR (DMSO-d_6) δ: 1.8–2.2 [m, 6H, $3CH_2$], 4.9 [s, 1H, CH], 5.4 [s, 2H, NH_2, D_2O-exchangable], 7.1–8.0 [m, 9H, Ar-H + SO_2NH_2]. ^{13}C NMR (DMSO-d_6) δ: 21.9, 27.8, 34.8, 37.6, 58.6, 113.4, 116.5, 118.3 (C≡N), 128.2, 129.6, 130.9, 131.7, 132.8, 133.6, 136.7, 142.6, 145.9, 155.6, 167.8, 197.5 (C═O). MS, *m*/*z* (%): 489 [M^+] (1.8), 73 (100). Anal. Calcd. For $C_{22}H_{18}Cl_2N_4O_3S$: C, 53.99; H, 3.71; N, 11.45. Found: C, 54.33; H, 3.49; N, 11.10.

4.1.3. 4-[3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-2-(3-substituted-thioureido)-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzene sulfonamide **7**–**11**

A mixture of compound **6** (4.89 g, 0.01 mol) and the corresponding isothiocyanates (0.01 mol) in pyridine (20 ml) was refluxed for 1 h, the reaction mixture was cooled and then poured onto cold water, then acidified with dilute HCl. The solid obtained was crystallized from dioxane to give **7**–**11**, respectively.

4.1.3.1. 4-(2-(3-Butylthioureido)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**7**). **7**:

Yield, 87%; m.p. 284–286 °C; IR, cm^{-1}: 3432, 3347, 3236 (NH, NH_2), 3064 (CH arom.), 2957, 2866 (CH aliph.), 2164 (C≡N), 1646 (C═O), 1371, 1191 (SO_2), 1256 (C═S), 706 (C–Cl). ^{1}H NMR (DMSO-d_6) δ: 0.8 [t, 3H, CH_3], 1.3–1.8 [m, 6H, $3CH_2$], 1.9–2.4 [m, 6H, $3CH_2$ cyclo], 5.0 [s, 1H, CH], 7.3–7.9 [m, 9H, Ar-H + SO_2NH_2], 8.6 [s, 2H, 2NH, D_2O-exchangable]. MS, *m*/*z* (%): 604 [M^+] (0.62), 42 (100). Anal. Calcd. For $C_{27}H_{27}Cl_2N_5O_3S_2$: C, 53.64; H, 4.50; N, 11.58. Found: C, 53.46; H, 4.26; N, 11.77.

4.1.3.2. 4-(2-(3-Allylthioureido)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**8**). **8**:

Yield, 69%; m.p. 169–171 °C; IR, cm^{-1}: 3390, 3346, 3280 (NH, NH_2), 3100 (CH arom.), 2950, 2860 (CH aliph.), 2181 (C≡N), 1647 (C═O), 1372, 1192 (SO_2), 1267 (C═S), 707(C–Cl). ^{1}H NMR (DMSO-d_6) δ: 1.2–2.4 [m, 6H, $3CH_2$], 3.4 [d, 2H, NCH_2, J = 6.5 Hz], 4.3 [d, 2H, $CHCH_2$, J = 3.5 Hz], 4.9 [s, 1H, CH], 5.4 [s, 1H, C═CH], 7.3–8.0 [m, 9H, Ar-H + SO_2NH_2], 8.3, 9.2 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m*/*z* (%): 588 [M^+] (2.1), 45 (100). Anal. Calcd. For $C_{26}H_{23}Cl_2N_5O_3S_2$: C, 53.06; H, 3.94; N, 11.90. Found: C, 53.31; H, 4.29; N, 11.68.

*4.1.3.3. 4-(2-(3-Phenylthioureido)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**9**).* **9**: Yield, 74%; m.p. 165–167 °C; IR, cm^{-1}: 3370, 3345, 3180 (NH, NH_2), 3080 (CH arom.), 2949, 2880 (CH aliph.), 2180 (C≡N), 1646 (C=O), 1372, 1192 (SO_2), 1269 (C=S), 755 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.6–2.4 [m, 6H, $3CH_2$], 5.5 [s, 1H, CH], 7.2–7.8 [m, 14H, Ar-H + SO_2NH_2], 9.0 [s, 2H, 2NH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 21.7, 27.6, 35.6, 37.2, 58.0, 112.5, 117.9, 118.5 (C≡N), 125.9, 128.1, 129.4, 130.2, 131.3, 132.4, 133.1, 134.6, 137.5, 138.6, 143.0, 145.8, 155.3, 168.7, 179.4 (C=S), 198.9 (C=O). MS, *m/z* (%): 624 [M^+] (2.6), 43 (100). Anal. Calcd. For $C_{29}H_{23}Cl_2N_5O_3S_2$: C, 55.77; H, 3.71; N, 11.21. Found: C, 55.49; H, 3.50; N, 11.45.

*4.1.3.4. 4-(2-(3-(4-Chlorophenylthioureido)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl))benzenesulfonamide (**10**).* **10**: Yield, 81%; m.p. °C 152–154 °C; IR, cm^{-1}: 3360, 3316, 3260 (NH, NH_2), 3091 (CH arom.), 2950, 2870 (CH aliph.), 2182 (C≡N), 1647 (C=O), 1371, 1192 (SO_2), 1269 (C=S), 713 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.8–2.4 [m, 6H, $3CH_2$], 5.4 [s, 1H, CH], 6.9–7.9 [m, 13H, Ar-H + SO_2NH_2], 8.0, 9.2 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 658 [M^+] (1.4), 43 (100). Anal. Calcd. for $C_{29}H_{22}Cl_3N_5O_3S_2$: C, 52.85; H, 3.36; N, 10.63. Found: C, 52.61; H, 3.10; N, 10.92.

*4.1.3.5. 4-(2-(3-(4-Bromophenylthioureido)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl))benzenesulfonamide (**11**).* **11**: Yield, 65%; m.p. 176–178 °C; IR, cm^{-1}: 3390, 3368, 3210 (NH, NH_2), 3068 (CH arom.), 2940, 2870 (CH aliph.), 2182 (C≡N), 1628 (C=O), 1372, 1192 (SO_2), 1270 (C=S), 708 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.6–2.3 [m, 6H, $3CH_2$], 5.3 [s, 1H, CH], 7.4–8.1 [m, 13H, Ar-H + SO_2NH_2], 8.6, 9.0 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 703 [M^+] (4.2), 48 (100).Anal. Calcd. For $C_{29}H_{22}BrCl_2N_5O_3S_2$: C, 49.51; H, 3.15; N, 9.96. Found: C, 49.20; H, 3.48; N, 9.71.

*4.1.4. 4-[5-(2,4-Dichlorophenyl)-4-imino-6-oxo-3-substituted-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl]benzene- sulfonamide **12**–**16***

Method (*A*): A mixture of compound **6** (4.89 g, 0.01 mol) and the corresponding isothiocyanate (0.01 mol) in pyridine (20 ml) was refluxed for 28 h, the reaction mixture was cooled and then poured onto cold water, then acidified with dilute HCl. The solid obtained was crystallized from acetic acid to give **12**–**16**, respectively.

Method (*B*): A solution of compounds **7**–**11** (0.01 mol) in pyridine (10 ml) was refluxed for 24 h, the reaction mixture was cooled and then poured onto cold water, then acidified with dilute HCl. The solid obtained was crystallized from acetic acid to give **12**–**16**, respectively. (m.p and m.m.p.).

*4.1.4.1. 4-(3-(4-Butyl)-5-(2,4-dichlorophenyl)-4-imino-6-oxo-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide (**12**).* **12**: Yield 68%; m.p. 241–243 °C; IR, cm^{-1}: 3380, 3341, 3220 (NH, NH_2), 3060 (CH arom.), 2955, 2869 (CH aliph.), 1627 (C=O), 1368, 1188 (SO_2), 1265 (C=S), 763(C–Cl). ^1H NMR (DMSO-d_6) δ: 1.0 [t, 3H, CH_3], 1.2–1.7 [m, 4H, CH_2–CH_2], 1.8–2.4 [m, 6H, $3CH_2$ cyclo], 4.3 [s, 1H, CH], 5.1 [t, 2H, NCH_2], 7.5–8.1 [m, 9H, Ar-H + SO_2NH_2], 8.7, 9.0 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 703 [M^+] (4.2), 48 (100). Anal. Calcd. For $C_{27}H_{26}Cl_2N_5O_3S_2$: C, 53.73; H, 4.34; N, 11.60. Found: C, 53.48; H, 4.54; N, 11.87.

*4.1.4.2. -4-(3-(4-Allyl)-5-(2,4-dichlorophenyl)-4-imino-6-oxo-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide (**13**).* **13**: Yield 72%; m.p258–260 °C; IR, cm^{-1}: 3421, 3380, 3200 (NH, NH_2), 3068 (CH arom.), 2923, 2866 (CH aliph.), 1624 (C=O), 1370, 1188 (SO_2), 1289 (C=S), 720 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.0 [d, 2H, C=CH_2, $J = 1.9$ Hz], 2.1–2.9 [m, 6H, $3CH_2$ cyclo], 4.5 [s, 1H, CH], 5.1 [d, 2H, NCH_2, $J = 4.6$ Hz], 5.9–6.2 [m, 1H, =CH], 7.0–7.8 [m, 9H, Ar-H + SO_2NH_2], 8.2, 8.3 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 703 [M^+] (4.2), 48 (100). Anal. Calcd. For $C_{26}H_{23}Cl_2N_5O_3S_2$: C, 53.06; H, 3.94; N, 11.90. Found: C, 53.29; H, 3.73; N, 11.67.

*4.1.4.3. -4-(3-(4-Allyl)-5-(2,4-dichlorophenyl)-4-imino-6-oxo-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide (**14**).* **14**: Yield 83%; m.p. 270–272 °C; IR, cm^{-1}: 3390, 3325, 3260 (NH, NH_2), 3058 (CH arom.), 2926, 2889 (CH aliph.), 1626 (C=O), 1368, 1191 (SO_2), 1295 (C=S), 754 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.7–2.6 [m, 6H, $3CH_2$], 5.5 [s, 1H, CH], 7.1–7.8 [m, 14H, Ar-H + SO_2NH_2], 9.0 [2s, 2H, 2NH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 21.2, 26.8, 31.6, 37.8, 77.0, 112.6, 116.9 (C≡N), 125.9, 126.8, 129.7, 130.4, 131.2, 132.3, 133.5, 134.6, 135.8, 137.5, 143.7, 146.6, 155.6, 169.2, 185.2 (C=S), 199.4 (C=O). MS, *m/z* (%): 624 [M^+] (3.6), 64 (100). Anal. Calcd. For $C_{29}H_{23}Cl_2N_5O_3S_2$: C, 55.77; H, 3.71; N, 11.21. Found: C, 55.49; H, 3.92; N, 11.52.

*4.1.4.4. 4-(3-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-4-imino-6-oxo-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl)-benzene-sulfonamide (**15**).* **15**: Yield 86%; m.p. 297–299 °C; IR, cm^{-1}: 3410, 3391, 3210 (NH, NH_2), 3080 (CH arom.), 2940, 2860 (CH aliph.), 1636 (C=O), 1368, 1163 (SO_2), 1271 (C=S), 711 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.6–2.7 [m, 6H, $3CH_2$], 5.7 [s, 1H, CH], 7.0–7.7 [m, 13H, Ar-H + SO_2NH_2], 8.7, 8.9 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 658 [M^+] (1.6), 64 (100). Anal. Calcd. For $C_{29}H_{22}Cl_3N_5O_3S_2$: C, 52.85; H, 3.36; N, 10.63. Found: C, 52.58; H, 3.65; N, 10.41.

*4.1.4.5. -4-(3-(4-Bromophenyl)-5-(2,4-dichlorophenyl)-4-imino-6-oxo-2-thioxo-1,2,3,4,6,7,8,9-octahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzene-sulfonamide (**16**).* **16**: Yield 82%; m.p. 315–317 °C; IR, cm^{-1}: 3420, 3385, 3300 (NH, NH_2), 3060 (CH arom.), 2925, 2860 (CH aliph.), 1630 (C=O), 1368, 1190 (SO_2), 1271 (C=S), 742 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.2–2.4 [m, 6H, $3CH_2$], 5.1 [s, 1H, CH], 6.9–7.8 [m, 13H, Ar-H + SO_2NH_2], 8.4, 8.8 [2s, 2H, 2NH, D_2O-exchangable]. MS, *m/z* (%): 703 [M^+] (1.2), 78 (100). Anal. Calcd. For $C_{29}H_{22}BrCl_2N_5O_3S_2$: C, 49.51; H, 3.15; N, 9.96. Found: C, 49.26; H, 3.51; N, 9.69.

*4.1.5. 4-(5-(2,4-dichlorophenyl)-6-oxo-2,4-dithioxo-1,2,3,4,6,7,8,9-octahydro- pyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide (**17**)*

A mixture of compound **6** (4.89 g, 0.01 mol) and carbon disulfide (3 ml) in dry pyridine (10 ml) was refluxed for 48 h. After cooling, the reaction mixture was poured onto ice-water and acidified with dilute HCl, the obtained solid was crystallized from ethanol–dimethylformamide (1:1) to give **17**.

17: Yield 62%; m.p. 310–312 °C; IR, cm^{-1}: 3365, 3272, 3205 (NH, NH_2), 3098 (CH arom.), 2927, 2880 (CH aliph.), 1653 (C=O), 1371, 1164 (SO_2), 756 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.7–2.6 [m, 6H, $3CH_2$], 5.6 [s, 1H, CH], 6.8–7.9 [m, 9H, Ar-H + SO_2NH_2], 8.8, 9.3 [2s, 2H, 2NH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 20.9, 26.8, 36.7, 39.6, 91.0, 112.7, 115.6, 126.7, 128.8, 130.6, 131.5, 132.39, 133.0, 135.8, 142.7, 145.6, 154.2, 162.3, 184.6 (C=S), 196.1 (C=S), 199.7 (C=O). MS, *m/z* (%): 565 [M^+] (4.2), 44 (100). Anal. Calcd. For $C_{23}H_{18}Cl_2N_4O_3S_3$: C, 48.85; H, 3.21; N, 9.91. Found: C, 48.56; H, 3.52; N, 9.61.

*4.1.6. 4-[3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-2-ureido-5,6,7,8-tetrahydro- quinolin-1(4H)-yl]benzenesulfonamide (**18**)*

A mixture of compound **6** (4.89 g, 0.01 mol) and urea (0.9 g, 0.015 mol) in ethanol (20 ml) containing sodium ethoxide (0.5 g) was refluxed for 4 h., the reaction mixture was cooled acidified

with dilute HCl. The separated crystals were crystallized from dioxane to give **18**.

18: Yield 79%; m.p. 318–320 °C; IR, cm^{-1}: 3366, 3273, 3209 (NH, NH_2), 3105 (CH arom.), 2958, 2866 (CH aliph.), 2170 (C≡N), 1696, 1651 (2C═O), 1627 (C═N), 1372, 1185 (SO_2), 795 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.7–2.9 [m, 6H, $3CH_2$], 5.4 [s, 1H, CH], 6.8 [s, 2H, NH_2, D_2O-exchangable], 7.0–8.0 [m, 9H, Ar-H + SO_2NH_2], 9.1 [s, 1H, NH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 22.0, 27.8, 35.2, 38.4, 61.5, 113.6, 115.9, 117.6 (C≡N), 126.6, 128.7, 130.4, 131.5, 133.7, 136.7, 142.7, 145.4, 150.6, 155.0, 156.3, 198.4 (C═O). MS, *m*/*z* (%): 532 [M^+] (2.8), 48 (100). Anal. Calcd. For $C_{23}H_{19}Cl_2N_5O_4S$: C, 51.89; H, 3.60; N, 13.15. Found: C, 52.08; H, 3.77; N, 12.85.

*4.1.7. 4-[4-Amino-5-(2,4-dichlorophenyl)-2,6-dioxo-1,2,6,7,8,9-hexahydro-pyrimido[4,5-b]quinolin-10(5H)-yl]benzenesulfonamide (**19**) and 4-[4-amino-5-(2,4-dichlorophenyl)-6-oxo-2-thioxo-1,2,6,7,8,9-hexahydro-pyrimido[4,5-b]quinolin-10(5H)-yl]benzenesulfonamide (**20**)*

A mixture of compound **6** (4.89 g, 0.01 mol) and urea or thiourea (0.015 mol) was fused together at 250 °C for 15 min, the formed mass was then triturated with ethanol and the separated solid was crystallized from ethanol–dimethylformamide (1:1) to give **19** and **20**, respectively.

19: Yield 65%; m.p. 252–254 °C; IR, cm^{-1}: 3320, 3209, 3190 (NH, NH_2), 3084 (CH arom.), 2920, 2830 (CH aliph.), 1700, 1630 (2C═O), 1399, 1157 (SO_2), 789 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.6–2.9 [m, 6H, $3CH_2$], 5.2 [s, 1H, CH], 6.9 [s, 2H, NH_2, D_2O-exchangable], 7.2–8.1 [m, 9H, Ar-H + SO_2NH_2], 8.9 [s, 1H, NH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 20.0, 26.1, 30.4, 37.1, 78.1, 112.6, 114.2, 126.5, 129.3, 130.4, 131.7, 133.0, 134.5, 136.8, 142.6, 143.2, 145.6, 154.8, 163.1, 165.4, 197.4 (C═O). MS, *m*/*z* (%): 532 [M^+] (2.5), 41 (100). Anal. Calcd. For $C_{23}H_{19}Cl_2N_5O_4S$: C, 51.89; H, 3.60; N, 13.15. Found: C, 52.16; H, 3.90; N, 13.34.

20: Yield 67%; m.p. >320 °C; IR, cm^{-1}: 3420, 3380, 3310 (NH, NH_2), 2950, 2882 (CH aliph.), 1653 (C═O), 1636 (C═N), 1390, 1160 (SO_2), 750 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.4–2.6 [m, 6H, $3CH_2$], 5.7 [s, 1H, CH], 6.7 [s, 2H, NH_2, D_2O-exchangable], 7.2–8.1 [m, 9H, Ar-H + SO_2NH_2], 9.4 [s, 1H, NH, D_2O-exchangable]. MS, *m*/*z* (%): 548 [M^+] (2.4), 47 (100). Anal. Calcd. For $C_{23}H_{19}Cl_2N_5O_3S_2$: C, 50.37; H, 3.49; N, 12.77. Found: C, 50.63; H, 3.78; N, 12.49.

*4.1.8. 4-[3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoyl-phenyl)-1,4,5,6,7,8-hexahydroquinolin-2-ylamino]-4-oxobutanoic acid (**21**)*

A mixture of compound **6** (4.89 g, 0.01 mol) and succinic anhydride (1.5 g 0.015 mol) in ethanol (30 ml) was refluxed for 6 h, the reaction mixture was concentrated and the solid obtained was crystallized from dioxane to give **21**: Yield 77%; m.p. 302–304 °C; IR, cm^{-1}: 3463 (OH), 3347, 3310, 3230 (NH, NH_2), 3064 (CH arom.), 2940, 2866 (CH aliph.), 2171 (C≡N), 1650, 1634 (3C═O), 1374, 1189 (SO_2), 706 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.1–1.2 [m, 4H, CH_2CH_2], 1.4–2.7 [m, 6H, $3CH_2$ cyclo], 5.0 [s, 1H, CH], 7.3–7.9 [m, 9H, Ar-H + SO_2NH_2], 8.0 [s, 1H, NH, D_2O-exchangable], 8.9 [s, 1H, OH, D_2O-exchangable]. ^{13}C NMR (DMSO-d_6) δ: 21.5, 27.6, 32.4, 33.1, 34.5, 37.6, 60.8, 111.6, 115.5, 117.9 (C≡N), 127.5, 129.3, 130.5, 131.6, 133.2, 134.3, 136.9, 142.4, 145.2, 154.9, 157.0, 171.6 (C═O), 178.0 (C═O), 199.5 (C═O). Anal. Calcd. For $C_{26}H_{22}Cl_2N_4O_6S$: C, 52.98; H, 3.76; N, 9.50. Found: C, 52.69; H, 3.47; N, 9.77.

*4.1.9. 4-[3-Cyano-4-(2,4-dichlorophenyl)-2-(2,5-dioxopyrrolidin-1-yl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzene-sulfonamide (**22**)*

A mixture of compound **6** (4.89 g, 0.01 mol) and succinic anhydride (1.5 g, 0.015 mol) was fused together in an oil bath at 250 °C for 20 min, the fused mass was triturated with ethanol and the formed crystals were collected and crystallized from ethanol/dimethylformamide (1:1) to give **22**: Yield 66%; m.p. 195–197 °C; IR, cm^{-1}: 3380, 3290 (NH_2), 3088 (CH arom.), 2943, 2886 (CH aliph.), 2213 (C≡N), 1783, 1733, 1654 (3C═O), 1368, 1189 (SO_2), 760 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.1–1.4 [m, 4H, $2CH_2$], 1.8–2.7 [m, 6H, $3CH_2$ cyclo], 5.3 [s, 1H, CH], 7.2–7.9 [m, 9H, Ar-H + SO_2NH_2]. ^{13}C NMR (DMSO-d_6) δ: 20.5, 26.6, 28.9, 34.4, 37.1, 60.7, 112.6, 115.9, 117.9 (C≡N), 128.5, 129.3, 131.7, 133.9, 136.3, 143.0, 145.9, 154.5, 155.1, 177.2 (2C═O), 199.4 (C═O). MS, *m*/*z* (%): 571 [M^+] (4.2), 41 (100). Anal. Calcd. For $C_{26}H_{20}Cl_2N_4O_5S$: C, 54.65; H, 3.53; N, 9.80. Found: C, 54.41; H, 3.84; N, 9.65.

*4.1.10. 4-Nitro-N-(3-cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoyl phenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)benzenesulfonamide (**23**), 4-bromo-N-(3-cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoyl phenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl) benzenesulfonamide (**24**)*

A mixture of compound 6 (4.89 g, 0.01 mol) and 4-nitro or 4-bromo-benzenesulfonylchloride (0.01 mol) in dry pyridine (10 ml) was refluxed for 8 h, the reaction mixture was cooled and poured onto ice-water, then acidified with dilute HCl, the obtained solid was crystallized from dioxane to give **23** and **24**, respectively.

23: Yield 89%; m.p. 177–179 °C; IR, cm^{-1}: 3370, 3351, 3260 (NH, NH_2), 3093 (CH arom.), 2940, 2886 (CH aliph.), 2180 (C≡N), 1647 (C═O), 1372, 1192 (SO_2), 742 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.7–2.9 [m, 6H, $3CH_2$], 5.6 [s, 1H, CH], 7.3–8.2 [m, 13H, Ar-H + SO_2NH_2], 8.3 [s, 1H, NH, D_2O-exchangable]. MS, *m*/*z* (%): 674 [M^+] (1.6), 40 (100). Anal. Calcd. For $C_{28}H_{21}Cl_2N_5O_7S_2$: C, 49.86; H, 3.14; N, 10.38. Found: C, 49.52; H, 3.47; N, 10.61.

24: Yield 87%; m.p. 308–310 °C; IR, cm^{-1}: 3390, 3349, 3210 (NH, NH_2), 3089 (CH arom.), 2952, 2860 (CH aliph.), 2182 (C≡N), 1647 (C═O), 1372, 1192 (SO_2), 708 (C–Cl). ^1H NMR (DMSO-d_6) δ: 1.6–2.6 [m, 6H, $3CH_2$], 5.2 [s, 1H, CH], 6.9–7.8 [m, 13H, Ar-H + SO_2NH_2], 8.6 [s, 1H, NH, D_2O-exchangable]. MS, *m*/*z* (%): 708 [M^+] (3.1), 44 (100). Anal. Calcd. For $C_{28}H_{21}BrCl_2N_4O_5S_2$: C, 47.47; H, 2.99; N, 7.91. Found: C, 47.71; H, 2.69; N, 7.73.

4.2. Biological testing

4.2.1. Animals, chemicals and facilities

Ehrlich Ascites Carcinoma cells (EAC) was maintained in female Swiss albino mice weighing 25–30 g (the holding company for biological products and vaccines, VACSERA, Cairo, Egypt) were housed at a constant temperature (24 ± 2 °C) with alternating 12-h light and dark cycles and fed standard laboratory food (Milad CO., Cairo, Egypt) and water *ad libitum*. All chemicals and reagents were of the highest grade commercially available. Facilities including animal house, biochemical equipments have been made available by the National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority (AEA), Cairo, Egypt. Animal care and handling was done according to the guidelines set by the world health organization, Geneva, Switzerland and approved from the committee for animals care at NCRRT, AEA.

4.2.2. Antitumor activity [31]

Ehrlich Ascites Carcinoma cells (EAC) were obtained by needle aspiration of ascetic fluid from preinoculated mice; under aseptic conditions. Tumor cells suspension (2.5×10^6 per ml) was prepared in RPMI-1640 media. Tested compounds were prepared with various dilutions by dissolving: 100, 50, 25 & 10 μg of the tested compounds in DMSO (1 ml).

In a set of sterile test tubes 0.8 ml RPMI-1640 media containing (glutamine, fetal calf serum as nutrient, streptomycin and penicillin), 0.1 ml each of the tested compounds (corresponding to 100, 50, 25, 10 μg) were mixed then 0.1 ml of tumor cell suspension

(2×10^6) was added. The test tubes were incubated at 37 °C for 2 h. Trypan blue exclusion test was carried out to calculate the percentage of non-viable cells after 2 h of incubation [32].

The total number of cells/ml will be determined using the following calculations:

$$\text{Cells/ml} = \text{average cells count per 5 squares} \times \text{dilution factor} \times 10^4.$$

$$\text{Total cells} = \text{cells/ml} \times \text{the original volume of fluid from which the cellsample was removed.}$$

$$\%\ \text{cell non-viability} = \frac{\text{total non-viable cells (stained)}}{\text{total cells}} \times 100$$

The results of in-vitro cytotoxic activity experiments are presented in Table 1.

References

[1] S.M. Abdel-Gawad, M.S.A. El-Gaby, H.I. Heiba, H.M. Ali, M.M. Ghorab, J. Chin. Chem. Soc. 52 (2005) 1227–1236.
[2] M.S.A. El-Gaby, S.M. Abdel-Gawad, M.M. Ghorab, H.I. Heiba, H.M. Ali, Phosphorus, Sulfur, Silicon 181 (2006) 279–297.
[3] M.M. Ghorab, S.G. Abdel-Hamide, H.A. Farrag, Acta Pol. Pharm. Drug Res. 58 (3) (2001) 175–184.
[4] M.M. Ghorab, F.A. Ragab, E. Noaman, H.I. Heiba, S.A. Aboulmagd, Arzneimittelforschung 59 (2) (2009) 96–103.
[5] Y.L. Chen, C.J. Huang, Z.Y. Huang, C.H. Tseng, F.S. Chang, S.H. Yang, S.R. Lin, C.C. Tzeng, Bioorg. Med. Chem. 14 (9) (2006) 3098–3105.
[6] Y.L. Zhao, Y.L. Chen, F.S. Chang, C.C. Tzeng, Eur. J. Med. Chem. 40 (8) (2005) 792–797.
[7] Y.L. Chen, H.M. Hung, C.M. Lu, K.C. Li, C.C. Tzeng, Eur. J. Med. Chem. 40 (8) (2005) 792–797.
[8] S.Y. Li, Y.L. Chen, C. Wang, C.C. Tzeng, Bioorg. Med. Chem. 14 (22) (2006) 7370–7376.
[9] C.H. Tseng, Y.L. Chen, P.J. Lu, C.N. Yang, C.C. Tzeng, Bioorg. Med. Chem. 16 (6) (2008) 3153–3162.
[10] Y.L. Chen, I.L. Chen, T.C. Wang, C.H. Han, C.C. Tzeng, Eur. J. Med. Chem. 40 (2005) 928–934.
[11] M.M. Ghorab, E. Noaman, M.M.F. Ismail, H.I. Heiba, Y.A. Amar, M.Y. Sayed, Arzneimittelforschung 56 (6) (2006) 405–413.
[12] M.M. Ghorab, F.A. Ragab, E. Noaman, H.I. Heiba, M. Galal, Arzneimittelforschung 56 (7) (2006) 553–560.
[13] D.A. Abou El Ella, M.M. Ghorab, E. Noaman, H.I. Heiba, A.I. Khalil, Bioorg. Med. Chem. 16 (5) (2008) 2391–2402.
[14] M.M. Ghorab, A.N. Osman, E. Noaman, H.I. Heiba, N.H. Zaher, Phosphorus, Sulfur, Silicon 181 (2006) 1935–1950.
[15] M.M. Ghorab, A.N. Osman, E. Noaman, H.I. Heiba, N.H. Zaher, Phosphorus, Sulfur, Silicon 181 (2006) 1983–1996.
[16] H.I. Heiba, F.A. Ragab, E. Noaman, M.M. Ghorab, M. Galal, Arzneimittelforschung 56 (8) (2006) 593–599.
[17] M.M. Ghorab, Phosphorus, Sulfur, Silicon 165 (2000) 221–235.
[18] M.M. Ghorab, S.B. El-Sayed, H.M. Saker, M.M. Abd Rabo, Arzneimittelforschung 56 (9) (2006) 665–670.
[19] M.M. Ghorab, S.G. Abdel-Hamide, M.M. Abou Zeid, Phosphorus, Sulfur, Silicon 112 (1996) 7–17.
[20] M.M. Ghorab, S.G. Abdel-Hamide, M.S.A. El-Gaby, Acta Pharm. 49 (1999) 1–10.
[21] M.M. Ghorab, Z.H. Ismail, S.M. Abdel-Gawad, A. Abdel-Aziem, Heteroat. Chem. 15 (2004) 57–62.
[22] S.A. Rostom, Bioorg. Med. Chem. 14 (19) (2006) 6475–6485.
[23] C.T. Supuran, A. Casini, A. Mastrolorenzo, A. Scozzafava, Mini-Rev. Med. Chem. 4 (6) (2004) 625–632.
[24] F. Abbate, A. Casini, T. Owa, A. Scozzafava, C.T. Supuran, Bioorg. Med. Chem. Lett. 14 (1) (2004) 217–223.
[25] A. Casini, A. Scozzafava, A. Mastrolorenzo, C.T. Supuran, Curr. Cancer Drug Targets 2 (1) (2002) 55–75.
[26] A.J. Kivela, J. Kivela, J. Saarnio, S. Parkkila, World J. Gastroenterol. 11 (2005) 155–163.
[27] C.T. Supuran, Nat. Rev. Drug Discov. 7 (2008) 168–181.
[28] C.T. Supuran, A. Scozzafava, Bioorg. Med. Chem. 15 (2007) 4336–4350.
[29] A. Bertucci, A. Innocenti, D. Zoccola, A. Scozzafava, S. Tambutté, C.T. Supuran, Bioorg. Med. Chem. 17 (14) (2009) 5054–5058.
[30] N.A. Boyle, W.R. Chegwidden, G.M. Blackburn, Org. Biomol. Chem. 3 (2) (2005) 222–224.
[31] P.U. Devi, F.E. Solomon, A.C. Sharada, Plumbagin. Pharm. Biol. 37 (3) (1999) 231–236.
[32] D.J. Brusick, Human Press Inc., Clifton, New Yersey, 1984, pp. 265–276.