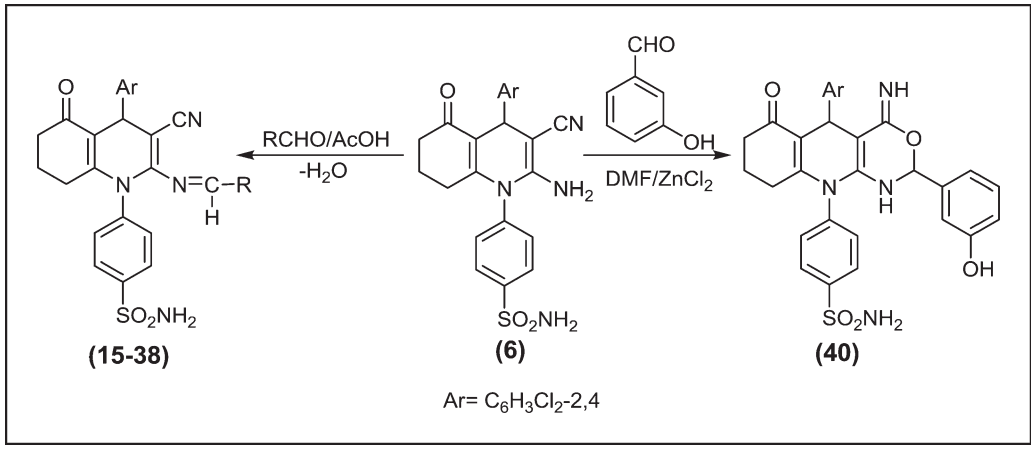
In Vitro Cytotoxic Evaluation of Some New Heterocyclic Sulfonamide Derivatives

Mostafa M. Ghorab,[a]* Mansour S. Al-Said,[a] and Ebaa M. El-Hossary[b]

[a]Medicinal, Aromatic and Poisonous Plants Research Center (MAPPRC), College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia
[b]Department of Drug Radiation Research, National Center for Radiation Research and Technology, Atomic Energy Authority, Cairo, Egypt
*E-mail: mmsghorab@yahoo.com

Received June 20, 2010
DOI 10.1002/jhet.619
Published online 22 February 2011 in Wiley Online Library (wileyonlinelibrary.com).



Sulfonamide-bearing compounds posses many types of biological activities and have been recently reported to show substantial antitumor activity *in vitro* and/or *in vivo*. There are a variety of mechanisms for the anticancer activity, and the most prominent mechanism is the inhibition of carbonic anhydrase isozymes. This work reports the synthesis of some new quinoline, pyrimido[4,5-*b*]quinoline and 3,1-oxazinoquinoline derivatives bearing a sulfonamide moiety. All the newly synthesized compounds were evaluated for their *in vitro* anticancer activity against Ehrlich ascites carcinoma cells. Compounds **10**, **13**, and **26** were the most active compounds with IC_{50} values of 6.1 μ*M*, 6.8 μ*M*, and 6.4 μ*M*, respectively, and exhibited better activities than the reference drug doxorubicin (IC_{50} = 68.1 μ*M*).

J. Heterocyclic Chem., **48**, 563 (2011).

INTRODUCTION

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

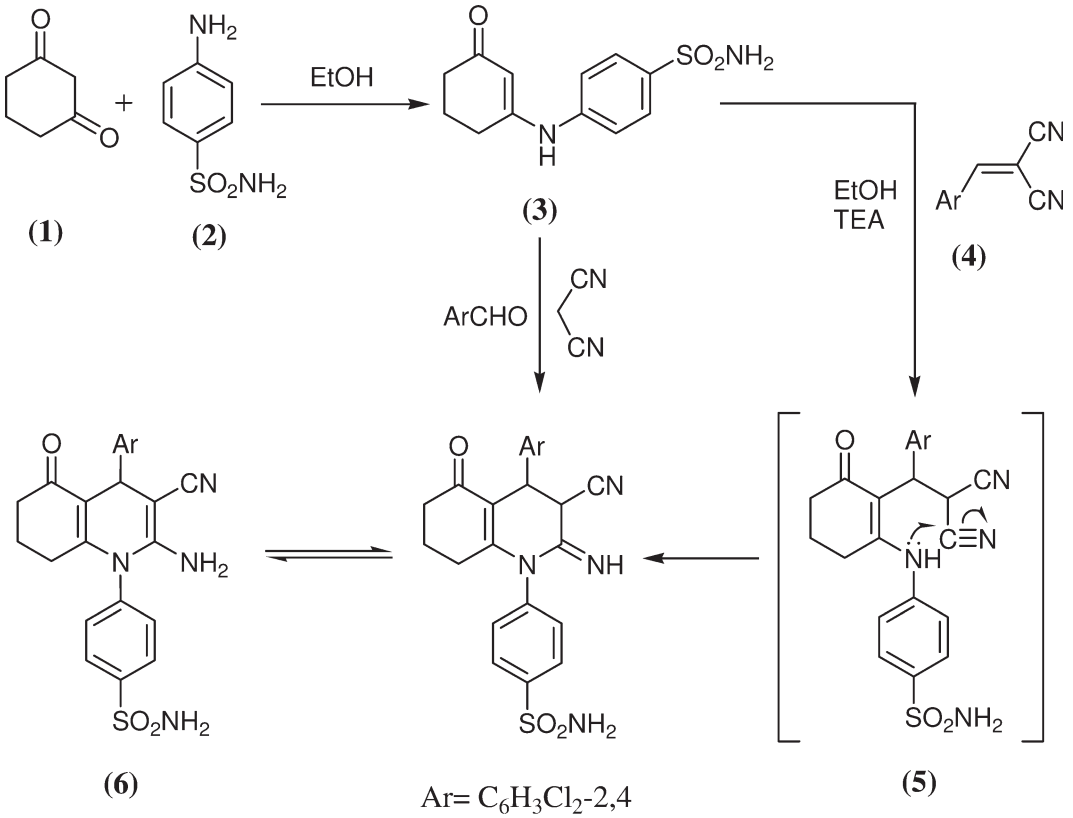
It has been known that aryl/heteroaryl sulfonamides may act as antitumor agents through a variety of mechanisms such as cell cycle perturbation in the G1 phase, disruption of microtubule assembly, angiogenesis inhibition, and functional suppression of the transcriptional activator NF-Y. Moreover, following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

On the other hand, quinoline derivatives are important biologically active compounds showing anticancer activity [17–19]. In the light of these facts, and as a continuation of our previous reported work [20,21], we planned to synthesize a novel series of quinoline and pyrimido[4,5-*b*]quinoline derivatives bearing a sulfonamide moiety, to study their structure activity relationship and hoping that the new compounds might show significant anticancer activity.

RESULTS AND DISCUSSION

Chemistry. Several compounds were designed with the aim of exploring their antitumor activity (Schemes 1–4). Enaminone **3** was obtained from condensation of 1,3-cyclohexandione **1** with sulfanilamide **2**. The structure of compound **3** was supported by elemental analysis and spectral data. IR spectrum of compound **3** revealed the presence of bands at 3354, 3263, and 3210 cm^{-1} (NH, NH_2), at 2940, 2870 cm^{-1} (CH aliph.), and 1612 cm^{-1} (C=O). Also, the ^{1}H-NMR spectrum in DMSO-d_6

Scheme 1



indicated the presence of a signal at 9.0 ppm which could be assigned to NH of enaminone **3**. Treatment of enaminone **3** with 2,4-dichlorobenzylidenemalononitrile **4** in the presence of a catalytic amount of triethylamine resulted in cycloaddition affording compound **6**, via the formation of the intermediate Michael type product **5**, followed by intramolecular cyclization (Scheme 1).

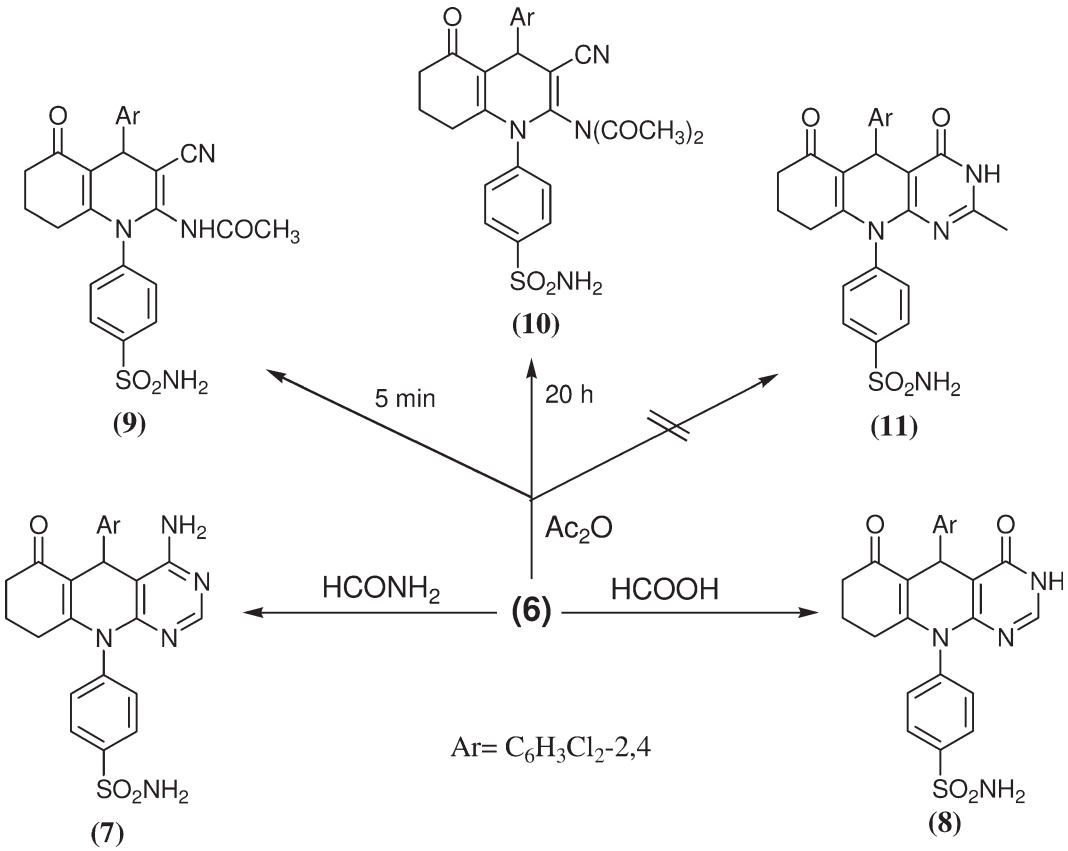
Compound **6** was unambiguously synthesized by another route involving one-pot condensation of the 2,4-dichlorobenzaldehyde, malononitrile, and enaminone **3** in a molar ratio (1:1:1) in refluxing ethanol containing triethylamine as catalyst. In this case, formation of compound **6** illustrated in terms of initial condensation of the aldehyde with malononitrile affording the activated arylidenemalononitrile **4**, followed by addition of the enaminone **3** to the arylidenemalononitrile **4**. IR spectrum of compound **6** revealed bands at 3464, 3347 cm^{-1} (NH_2), 2171 cm^{-1} (C≡N), 1634 cm^{-1} (C=O), 1374, 1189 cm^{-1} (SO_2). The mass spectrum of **6** revealed a molecular ion peak *m/z* at 489 (M^+, 1.8%), with a base peak *m/z* at 73 (100), (Scheme 1).

Interaction of compound **6** with formamide caused cyclization to give the pyrimidoquinoline derivative **7** (Scheme 2). Its IR spectrum exhibited the absence of C≡N band, which confirms the cyclization and the formation of the pyrimido[4,5-*b*]quinoline system. Refluxing compound **6** in formic acid caused cyclization via elimination of two moles of water to give the pyrimidoquinoline derivative **8**. Its IR spectrum showed the absence of C≡N band, which confirms the cyclization and the formation of pyrimido[4,5-*b*]quinoline system.

Reaction of compound **6** with acetic anhydride and/or trifluoroacetic anhydride for 5 min furnished the monoacyl derivative **9** and **12**, respectively. On the other hand, when compound **6** was reacted with acetic anhydride for long time (20 h), the corresponding diacetyl derivative **10** was obtained instead of the cyclic system pyrimidoquinoline derivative **11** on the basis of elemental analysis and IR spectrum which showed the presence of (C≡N) band. On the other hand, when compound **6** was reacted with trifluoroacetic anhydride for long time (20 h), the corresponding cyclic system pyrimidoquinoline derivative **13** was obtained instead of **14** on the basis of elemental analysis and IR spectrum which showed the disappearance of C≡N band (Scheme 3). IR spectra of compounds **9**, **10**, and **12** revealed the presence of C≡N band. ^{1}H-NMR spectrum of **10** showed a signal at 2.4 ppm for two acetyl groups.

The reactivity of compound **6** toward some carbonyl compounds in different conditions was also discussed. Thus, reaction of compound **6** with aromatic aldehydes in acetic acid yielded Schiff's bases **15–38**. The structures of compounds **15–38** were confirmed by elemental

Scheme 2



analyses, IR, ^{1}H-NMR, and mass spectral data (Scheme 4). IR spectra of compounds **15–38** exhibited the presence of C≡N band. Also, ^{1}H-NMR spectra of compounds **15–38** revealed the presence of signal for N=CH.

From the literature survey, it was found that $ZnCl_2$ is an effective catalyst in organic reactions for the preparation of 3,1-oxazine derivatives. The use of anhydrous $AlCl_3$, CuCl, $CuCl_2$, $TiCl_4$, and *p*-toluenesulfonic acid was much less effective [22]. Thus, interaction of compound **6** with 3-hydroxybenzaldehyde in dimethylformamide containing anhydrous $ZnCl_2$ yielded the corresponding 3,1-oxazinoquinoline derivative **40**. Its IR spectrum exhibited the absence of C≡N band and the presence of characteristic bands at 3365, 3270, and 3220 cm^{-1} (NH, NH_2), and 1640 cm^{-1} (C=O). ^{1}H-NMR spectrum of **40** revealed signals at 4.5 ppm for (CH pyridine), 6.1 ppm for (CH oxazine) and 8.1, 8.2 ppm for two NH groups. Its mass spectrum exhibited a molecular ion peak *m*/*z* at 611 with a base peak at 44 (100).

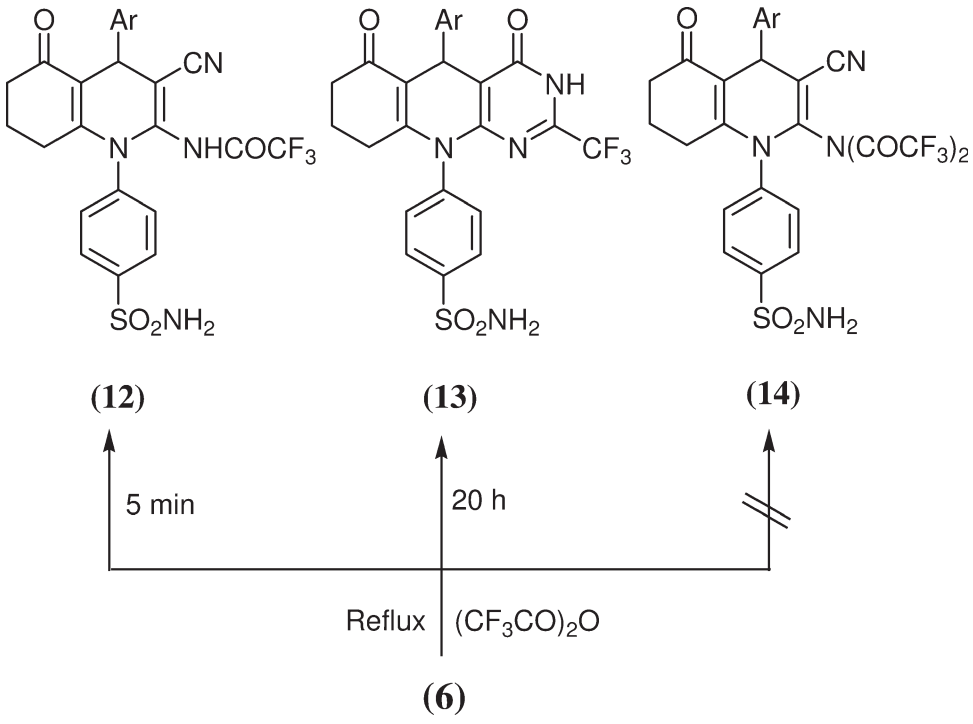
The formation of 3,1-oxazinoquinoline derivative **40** can be explained by (Scheme 4). The attack of the amino group of **6** onto the carbonyl carbon atom of 3-hydroxybenzaldehyde, gave intermediate **39** and the product **40** was obtained through subsequent cyclization by attack of the oxygen atom onto the nitrile group of **6** [23].

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

From these results (Table 1), it can be seen that the diacetyl quinoline derivative **10** (IC_{50} = 6.1 μ*M*), pyrimidoquinoline derivative **13** having trifluoromethyl at position-2 (IC_{50} = 6.8 μ*M*), compounds **7**, **8**, **9**, **20**, **22**, **25**, **26**, **28**, **29**, **31**, **33**, **34**, and **36** IC_{50} (19.3, 16, 23.5, 16.8, 16.5, 10.4, 6.4, 9.2, 8.9, 9.5, 22, 20.6, and 11.2 μ*M*) showed significant cytotoxic activities which were even higher than that of the reference drug doxorubicin (IC_{50} = 68.1 μ*M*).

Also, the diacetyl quinoline derivative **10** (IC_{50} = 6.1 μ*M*) is the most active compound compared with the other tested compounds and the reference drug Doxorubicin. In the meantime, the diacetyl quinoline derivative **10** is more active than the monoacetyl quinloine derivative **9** (IC_{50} = 23.5 μ*M*).

Scheme 3



Additionally, compound **26** bearing 3-nitrophenyl at position-2 (IC_{50} = 6.4 μ*M*) is the most potent compound in the Schiff's bases series and exhibited a higher activity than the 2-nitrophenyl derivative, **25** (IC_{50} = 10.4 μ*M*).

The pyrimidoquinoline derivative **13** having trifluoromethyl at position-2 (IC_{50} = 6.8 μ*M*) revealed higher activity than the pyrimidoquinoline derivative **7** containing the amino group at position-4 (IC_{50} = 19.3 μ*M*).

It was found that Schiff's base **34** carrying 2-furyl-5-methyl at position-2 (IC_{50} = 20.6 μ*M*) exhibited higher activity than the unsubstituted furan **33** at the same position (IC_{50} = 22 μ*M*).

On the other hand, it is clear from the results that the quinoline derivative **6** and Schiff's bases **16**, **23**, and **38** (IC_{50} = 51.1, 50.6, 50.7, and 53.6 μ*M*) are nearly as active as doxorubicin. Substituting Schiff's bases with phenyl **15**, 4-tolyl **17**, 4-methoxyphenyl **19**, 4-methoxynaphthyl **32**, and/or 3-pyridyl **37** exhibited a moderate activity but less than the reference drug doxorubicin. Finally, compounds **21**, **24**, **27**, and **35** showed no activity.

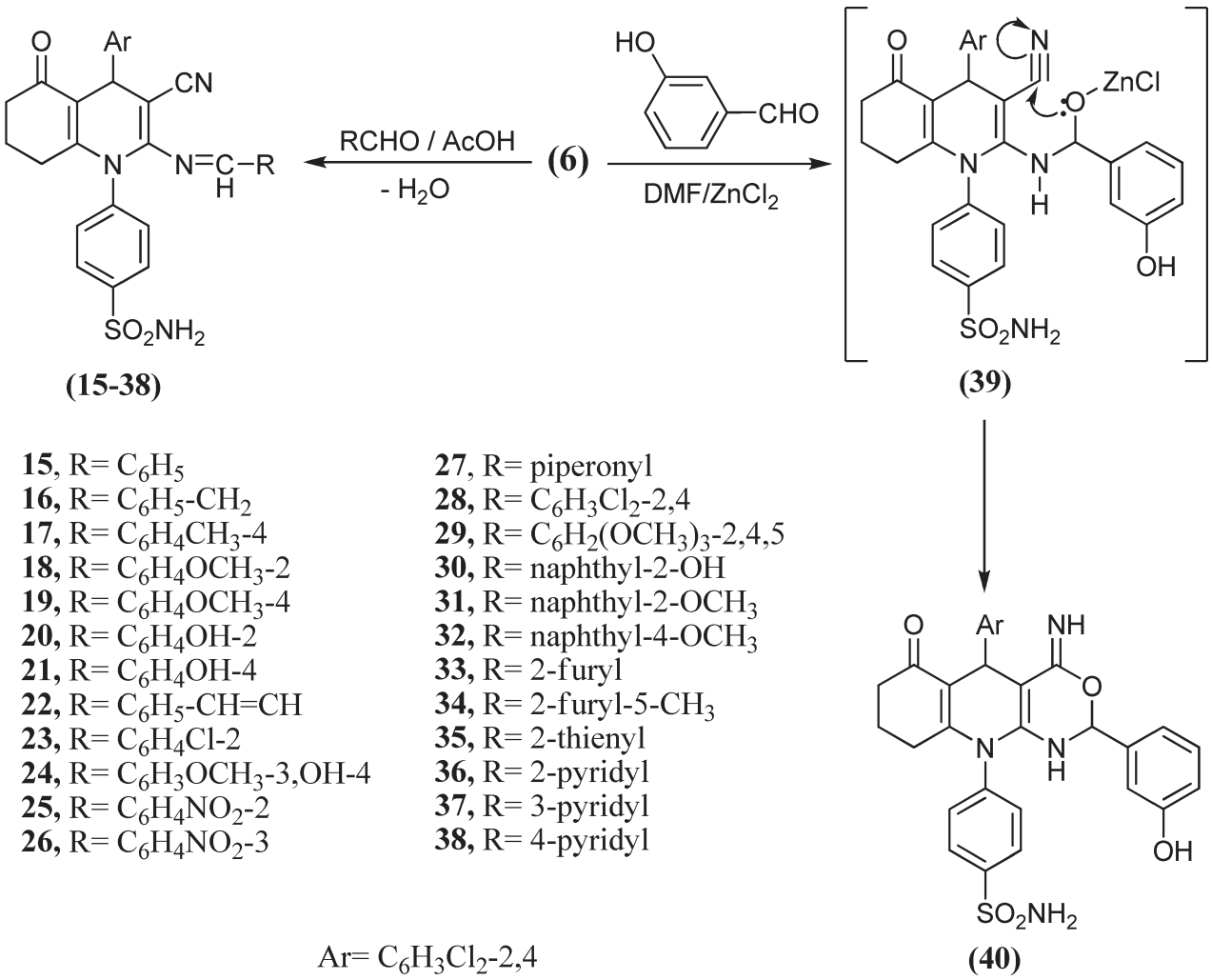
EXPERIMENTAL

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, 60G 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. Infrared spectra were recorded in KBr disks using IR-470 Shimadzu spectrometer (Shimadzu, Tokyo, Japan). ^{1}H-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-(3-Oxocyclohex-1-enylamino)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 and the obtained solid was crystallized from ethanol to give **3**. Yield, 92%; m.p. 236–238°C; IR (KBr, cm^{-1}): 3354, 3263, 3210 (NH, NH_2), 3032 (CH arom.), 2940, 2870 (CH aliph.), 1612 (C=O), 1360, 1184 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 1.05–1.9 (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). Anal. Calcd. for $C_{12}H_{14}N_2O_3S$ (266.32): C, 54.12; H, 5.30; N, 10.52. Found: C, 54.32; H, 5.53; N, 10.33.

4-(2-Amino-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 6. *Method A*. A mixture of enaminone **3** (2.66 g, 0.01 mol) and 2,4-dichlorobenzylidinemalononitrile **4** (2.23 g, 0.01 mol) in ethanol (20 mL) containing three drops of triethylamine was

Scheme 4



refluxed for 6 h. The reaction mixture was filtered while hot, and the solid obtained was crystallized from dioxane to give **6**.

Method B. A solution of enaminone **3** (2.66 g, 0.01 mol), 2,4-dichlorobenzaldehyde (1.75 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) in absolute ethanol (30 mL) containing three drops of triethylamine was refluxed for 6 h. The obtained solid after concentration was filtered and crystallized from ethanol to give **6**.

Yield, 90%; m.p. 291–293°C; IR (KBr, 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), 7.1–7.9 (m, 9H, Ar-H + SO_2NH_2). MS *m/z* (%): 489 [M^+] (1.8), 73 (100). Anal. Calcd. for $C_{22}H_{18}Cl_2N_4O_3S$ (489.37): C, 53.99; H, 3.71; N, 11.45. Found: C, 53.31; H, 3.95; N, 11.79.

4-(4-Amino-5-(2,4-dichlorophenyl)-6-oxo-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide 7. A solution of compound **6** (4.89 g, 0.01 mol) in formamide (20 mL) was refluxed for 6 h, the reaction mixture was cooled and then poured onto cold water, and the obtained solid was crystallized from dioxane to give **7**. Yield, 86%; m.p. > 320°C; IR (KBr, cm^{-1}): 3270, 3188 (NH_2), 3064 (CH arom.), 2957, 2880 (CH aliph.), 1640 (C=O), 1590 (C=N), 1380, 1158 (SO_2), 798 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.3–2.6 (m, 6H, $3CH_2$), 4.4 (s, 1H, CH), 6.7 (s, 2H, NH_2), 6.9–7.8 (m, 9H, Ar-H + SO_2NH_2). MS *m/z* (%): 516 [M^+] (4.1), 43 (100). Anal. Calcd. for $C_{23}H_{19}Cl_2N_5O_3S$ (516.40): C, 53.49; H, 3.71; N, 13.56. Found: C, 53.73; H, 3.52; N, 13.88.

4-(5-(2,4-Dichlorophenyl)-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide 8. A solution of compound **6** (4.89 g, 0.01 mol) in formic acid (20 mL) was refluxed for 5 h, the reaction mixture was cooled and then poured onto cold water, and the obtained solid was crystallized from dioxane to give **8**. Yield, 79%; m.p. 220–222°C; IR (KBr, cm^{-1}): 3300, 3271 (NH, NH_2), 3095 (CH arom.), 2955, 2860 (CH aliph.), 1710, 1654 (2C=O), 1625 (C=N), 1370, 1164 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.4–2.6 (m, 6H, $3CH_2$), 4.7 (s, 1H, CH), 7.1–7.9 (m, 10H, Ar-H + CH pyrimidine + SO_2NH_2), 8.4 (s, 1H, NH). MS *m/z* (%): 517 [M^+] (2.3), 44 (100). Anal. Calcd. for $C_{23}H_{18}Cl_2N_4O_4S$

Table 1

In Vitro cytotoxic activity of the newly synthesized compounds **6–40**.

Compound number	Nonviable cells (%) Concentration (μg/mL) 100	50	25	10	IC_{50}[a] (μg/mL)	IC_{50} (μ*M*)
6	95	65	50	40	25	51.1
7	80	70	60	50	10	19.3
8	100	100	80	40	8.3	16
9	100	60	40	30	12.5	23.5
10	100	95	90	85	3.5	6.1
12	10	6	5	0	>100[b]	–
13	95	95	90	80	4	6.8
15	95	95	25	25	50	86.6
16	100	100	80	40	30	50.6
17	80	60	20	20	43	72.7
18	100	100	20	2	37.5	61.7
19	60	50	40	30	50	82.3
20	80	80	70	50	10	16.8
21	10	6	7	0	>100[b]	–
22	90	80	60	50	10	16.5
23	90	80	40	30	31	50.7
24	45	30	20	10	>100[b]	–
25	85	80	75	70	6.5	10.4
26	100	90	80	80	4	6.4
27	60	10	10	10	>100[b]	–
28	100	95	80	80	6	9.2
29	100	90	90	80	6	8.9
30	30	10	5	0	>100[b]	–
31	99	95	80	60	6.3	9.5
32	95	95	50	0	60	91.3
33	95	90	60	40	12.5	22
34	95	80	60	40	12	20.6
35	20	10	0	0	>100[b]	–
36	80	75	70	70	6.5	11.2
37	80	60	20	20	43	74.3
38	90	80	40	30	31	53.6
40	95	95	20	20	60	98.1
Doxorubicin	100	68	30	24	37	68.1

[a] IC_{50} value: corresponds to the compound concentration causing 50% mortality in net cells.
[b] Compounds with $IC_{50} \geq 100$ μg/mL are considered to be inactive.

(517.38): C, 53.39; H, 3.51; N, 10.83. Found: C, 53.64; H, 3.80; N, 10.52.

N-(3-cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide 9. A solution of compound **6** (4.89 g, 0.01 mol) in acetic anhydride (20 mL) was refluxed for 5 min. The reaction mixture was then concentrated, and the solid separated was crystallized from acetic acid to give **9**. Yield, 88%; m.p. 266–268°C; IR (KBr, cm^{-1}): 3433, 3347, 3290 (NH, NH_2), 3080 (CH arom.), 2956, 2870 (CH aliph.), 2167 (C≡N), 1718, 1645 (2C=O), 1372, 1167 (SO_2), 707 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 2.1 (s, 3H, $COCH_3$), 5.0 (s, 1H, CH), 7.3–7.9 (m, 9H, Ar-H + SO_2NH_2), 11.9 (s, 1H, NH). Anal. Calcd. for $C_{24}H_{20}Cl_2N_4O_4S$ (531.41): C, 54.24; H, 3.79; N, 10.54. Found: C, 54.53; H, 3.51; N,10.79.

N-acetyl-N-(3-cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)acetamide 10. A solution of compound **6** (4.89 g, 0.01 mol) in acetic anhydride (20 mL) was refluxed for 20 h. After cooling, the excess acetic anhydride was removed under reduced pressure. The obtained solid was crystallized from dioxane to give **10**. Yield, 76%; m.p. 300–302°C; IR (KBr, cm^{-1}): 3300, 3245 (NH_2), 2931, 2860 (CH aliph.), 2212 (C≡N), 1781, 1733, 1656 (3C=O), 1370, 1163 (SO_2), 715 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.6 (m, 6H, $3CH_2$), 2.4 (s, 6H, $2COCH_3$), 5.3 (s, 1H, CH), 7.3–8.0 (m, 9H, Ar-H + SO_2NH_2). Anal. Calcd. for $C_{26}H_{22}Cl_2N_4O_5S$ (573.45): C, 54.46; H, 3.87; N, 9.77. Found: C, 54.66; H, 3.57; N, 9.42.

N-(3-cyano-4-(2,4-dichlorophenyl)-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl)-2,2,2-trifluoroacetamide 12. A solution of compound **6** (4.89 g, 0.01 mol) in trifluoroacetic anhydride (20 mL) was refluxed for 5 min, the reaction mixture was then concentrated, and the solid separated was crystallized from dioxane to give **12**. Yield, 66%; m.p. 140–142°C; IR (KBr, cm^{-1}): 3320, 3266, 3105 (NH, NH_2), 2955, 2880 (CH aliph.), 2184 (C≡N), 1660, 1628 (2C=O), 1373, 1165 (SO_2), 733 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.6 (m, 6H, $3CH_2$), 4.7 (s, 1H, CH), 7.2–8.1 (m, 9H, Ar-H +

SO_2NH_2), 8.8 (s, 1H, NH). MS *m/z* (%): 585 [M^+] (2.6), 64 (100). Anal. Calcd. for $C_{24}H_{17}Cl_2F_3N_4O_4S$ (585.38): C, 49.24; H, 2.93; N, 9.57. Found: C, 49.60; H, 2.69; N, 9.34.

4-(4,6-Dioxo-5-[2,4–dichlorophenyl]-3,5,6,7,8,9-hexahydro-4H-2-trifluoromethyl-pyrimido[4,5-b]quinolin-10-yl)benzenesulfonamide 13. A solution of compound **6** (4.89 g, 0.01 mol) in trifluoroacetic anhydride (20 mL) was refluxed for 20 h. After cooling, the excess trifluoroacetic anhydride was removed under reduced pressure. The obtained solid was crystallized from dioxane to give **13**. Yield, 64%; m.p. 305–307°C; IR (KBr, cm^{-1}): 3410, 3367, 3273 (NH, NH_2), 2958, 2860 (CH aliph.), 1669, 1653 (2C=O), 1627 (C=N), 1372, 1166 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7–2.4 (m, 6H, $3CH_2$), 4.9 (s, 1H, CH), 7.0–7.9 (m, 9H Ar-H + SO_2NH_2), 11.7 (s, 1H, NH). MS *m/z* (%): 585 [M^+] (2.1), 46 (100). Anal. Calcd. for $C_{24}H_{17}Cl_2F_3N_4O_4S$ (585.38): C, 49.24; H, 2.93; N, 9.57. Found: C, 49.63; H, 3.14; N, 9.79.

4-(2-(Substitutedbenzylideneamino)-3-cyano-4-(2,4-dichlorophenyl)5-oxo-5,6,7,8,-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide) 15-38. A mixture of compound **6** (4.89 g, 0.01 mol) and the corresponding aromatic aldehyde (0.01 mol) in acetic acid (20 mL) was refluxed for 5 h, the reaction mixture was cooled and then poured onto cold water. The obtained solid was crystallized from dioxane to give **15–38**.

4-(2-(Benzylideneamino)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 15. Yield, 86%; m.p. 315–317°C; IR (KBr, cm^{-1}): 3366, 3275 (NH_2), 3100 (CH arom.), 2958, 2920 (CH aliph.), 2171 (C≡N), 1651 (C=O), 1626 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7–2.4 (m, 6H, $3CH_2$), 5.1 (s, 1H, CH), 7.0–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.1 (s, 1H, N=CH]. MS *m/z* (%): 577 [M^+] (4.9), 64 (100). Anal. Calcd. for $C_{29}H_{22}Cl_2N_4O_3S$ (576.08): C, 60.32; H, 3.84; N, 9.70. Found: C, 60.67; H, 3.59; N, 9.46.

4-(3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-2-(2-phenylethylideneamino)-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 16. Yield, 88%; m.p. 311–313°C; IR (KBr, cm^{-1}): 3365, 3273 (NH_2), 3102 (CH arom.), 2958, 2920 (CH aliph.), 2257 (C≡N), 1651 (C=O), 1626 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7–2.6 (m, 6H, $3CH_2$), 4.6 (s, 1H, CH), 5.2 (d, 2H, CH_2, J = 8.1 Hz), 7.3–8.0 (m, 14H Ar-H + SO_2NH_2), 7.6 (t, 1H, N=CH]. Anal. Calcd. for $C_{30}H_{24}Cl_2N_4O_3S$ (590.09): C, 60.92; H, 4.09; N, 9.47. Found: C, 60.74; H, 4.33; N, 9.68.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(4-methylbenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 17. Yield, 87%; m.p. 308–310°C; IR (KBr, cm^{-1}): 3365, 3272(NH_2), 3104 (CH arom.), 2959, 2929 (CH aliph.), 2170 (C≡N), 1651 (C=O), 1627(C=N), 1371, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.4–2.5 (m, 6H, $3CH_2$), 2.4 (s, 3H, CH_3), 5.1 (s, 1H, CH), 7.2–8.0 (m, 13H, Ar-H + SO_2NH_2), 12.0 (s, 1H, N=CH). Anal. Calcd. for $C_{30}H_{24}Cl_2N_4O_3S$ (590.09): C, 60.92; H, 4.09; N, 9.47. Found: C, 61.25; H, 3.84; N, 9.10.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(2-methoxybenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 18. Yield, 79%; m.p. 235–237°C; IR (KBr, cm^{-1}): 3363, 3180 (NH_2), 2955, 2880 (CH aliph.), 2182 (C≡N), 1651 (C=O), 1591 (C=N), 1371, 1164 (SO_2), 796 (CCl). ^{1}H-NMR (DMSO-d_6) δ: 1.4–2.5 (m, 6H, $3CH_2$), 3.8 (s, 3H, OCH_3), 5.1 (s, 1H, CH), 6.9–7.9 (m, 13H, Ar-H + SO_2NH_2), 10.4 (s, 1H, N=CH). Anal. Calcd. for $C_{30}H_{24}Cl_2N_4O_4S$ (606.09): C, 59.31; H, 3.98; N, 9.22. Found: C, 59.64; H, 3.71; N, 9.54.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(4-methoxybenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 19. Yield, 83%; m.p. 277–279°C; IR (KBr, cm^{-1}): 3380, 3310 (NH_2), 2960, 2870 (CH aliph.), 2210 (C≡N), 1660 (C=O), 1620 (C=N), 1380, 1180 (SO_2), 796 (CCl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 3.7 (s, 3H, OCH_3), 5.2 (s, 1H, CH), 7.1–7.9 (m, 13H, Ar-H + SO_2NH_2), 9.8 (s, 1H, N=CH). Anal. Calcd. for $C_{30}H_{24}Cl_2N_4O_4S$ (606.09): C, 59.31; H, 3.98; N, 9.22. Found: C, 59.50; H, 3.68; N, 8.90.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(2-hydroxybenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 20. Yield, 81%; m.p. 298–300°C; IR (KBr, cm^{-1}): 3366 (OH), 3272, 3105 (NH_2), 2957, 2929, 2865 (CH aliph.), 2171 (C≡N), 1650 (C=O), 1628 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 5.3 (s, 1H, CH), 7.1–7.8 (m, 13H, Ar-H + SO_2NH_2), 8.5 (s, 1H, N=CH), 10.8 (s, 1H, OH). MS *m/z* (%): 593 [M^+] (3.7), 56 (100). Anal. Calcd. for $C_{29}H_{22}Cl_2N_4O_4S$ (592.07): C, 58.69; H, 3.74; N, 9.44. Found: C, 58.45; H, 3.99; N, 9.15.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(4-hydroxybenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 21. Yield, 77%; m.p. 281–283°C; IR (KBr, cm^{-1}): 3420 (OH), 3366, 3273 (NH_2), 3100 (CH arom.), 2958, 2860 (CH aliph.), 2181 (C≡N), 1651 (C=O), 1628 (C=N), 1372, 1185 (SO_2), 795 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 5.4 (s, 1H, CH), 7.3–8.0 (m, 13H, Ar-H + SO_2NH_2), 8.4 (s, 1H, N=CH), 10.4 (s, 1H,OH). MS *m/z* (%): 593 [M^+] (1.25), 47 (100). Anal. Calcd. for $C_{29}H_{22}Cl_2N_4O_4S$ (592.07): C, 58.69; H, 3.74; N, 9.44. Found: C, 58.98; H, 3.51; N, 9.65.

4-(3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-2-((E)-3-phenylallylideneamino)-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 22. Yield, 69%; m.p. 144–146°C; IR (KBr, cm^{-1}): 3360, 3280 (NH_2), 3056 (CH arom.), 2960, 2870 (CH aliph.), 2182 (C≡N), 1653 (C=O), 1590 (C=N), 1371, 1165 (SO_2), 751 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.4–2.6 (m, 6H, $3CH_2$), 5.1 (d, 1H, CH-4), 5.2–5.5 (m, 1H, CH), 6.9 (d, 1H, CH—Ph, J = 7.8 Hz), 7.0–7.9 (m, 14H, Ar-H + SO_2NH_2), 9.7 (d, 1H, N=CH, J = 7.6 Hz). Anal. Calcd. for $C_{31}H_{24}Cl_2N_4O_3S$ (602.09): C, 61.69; H, 4.01; N, 9.28. Found: C, 61.85; H, 3.77; N, 8.95.

4-(2-(2-Chlorobenzylideneamino)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 23. Yield, 70%; m.p. 273–275°C; IR (KBr, cm^{-1}): 3366, 3273 (NH_2), 3103 (CH arom.), 2958, 2929 (CH aliph.), 2171 (C≡N), 1696 (C=O), 1627 (C=N), 1372, 1185 (SO_2), 795 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 4.9 (s, 1H, CH), 7.3–7.9 (m, 13H, Ar-H + SO_2NH_2), 9.9 (s, 1H, N=CH). MS *m/z* (%): 611 [M^+] (2.3), 46 (100). Anal. Calcd. for $C_{29}H_{21}Cl_3N_4O_3S$ (610.04): C, 56.92; H, 3.46; N, 9.16. Found: C, 57.25; H, 3.76; N, 8.80.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(4-hydroxy-3-methoxybenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)-benzenesulfonamide 24. Yield, 78%; m.p. 260–262°C; IR (KBr, cm^{-1}): 3410 (OH), 3365, 3273 (NH_2), 3100 (CH arom.), 2956, 2860, (CH aliph.), 2181 (C≡N), 1651 (C=O), 1590 (C=N), 1371, 1165 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 3.8 (s, 3H, OCH_3), 5.1 (s, 1H, CH), 6.9–7.9 (m, 12H, Ar-H + SO_2NH_2), 9.7 (s, 1H,

N=CH), 11.8 (s, 1H, OH). Anal. Calcd. for $C_{30}H_{24}Cl_2N_4O_5S$ (623.51): C, 57.79; H, 3.88; N, 8.99. Found: C, 57.51; H, 3.58; N, 8.69.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(2-nitrobenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 25. Yield, 65%; m.p. 297–299°C; IR (KBr, cm^{-1}): 3366, 3273 (NH_2), 3100 (CH arom.), 2958, 2928 (CH aliph.), 2170 (C≡N), 1651 (C=O), 1628 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 5.1 (s, 1H, CH), 7.0–7.9 (m, 13H, Ar-H + SO_2NH_2), 9.2 (s, 1H, N=CH). MS *m/z* (%): 622 [M^+] (0.93), 46 (100). Anal. Calcd. for $C_{29}H_{21}Cl_2N_5O_5S$ (622.48): C, 55.96; H, 3.40; N, 11.25. Found: C, 56.31; H, 3.72; N, 11.58.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(3-nitrobenzylideneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 26. Yield, 73%; m.p. 259–261°C; IR (KBr, cm^{-1}): 3365, 3273 (NH_2), 3092 (CH arom.), 2957, 2860 (CH aliph.), 2182 (C≡N), 1648 (C=O), 1591 (C=N), 1371, 1165 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7–2.3 (m, 6H, $3CH_2$), 5.4 (s, 1H, CH), 6.9–8.0 (m, 13H, Ar-H + SO_2NH_2), 9.8 (s, 1H, N=CH). MS *m/z* (%): 622 [M^+] (0.82), 47 (100). Anal. Calcd. for $C_{29}H_{21}Cl_2N_5O_5S$ (622.48): C, 55.96; H, 3.40; N, 11.25. Found: C, 55.74; H, 3.11; N, 10.93.

4-(2-(Benzo[d][1,3]dioxol-5-ylmethyleneamino)-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 27.. Yield, 80%; m.p. 279–281°C; IR (KBr, cm^{-1}): 3367, 3273 (NH_2), 3102 (CH arom.), 2957, 2880 (CH aliph.), 2171 (C≡N), 1651 (C=O), 1628 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7–2.4 (m, 6H, $3CH_2$), 5.1 (s, 1H, CH), 6.1 (s, 2H, O—CH_2—O), 7.1–7.9 (m, 12H, Ar-H + SO_2NH_2), 9.8 (s, 1H, N=CH). Anal. Calcd. for $C_{30}H_{22}Cl_2N_4O_5S$ (621.49): C, 57.98; H, 3.57; N, 9.01. Found: C, 57.76; H, 3.88; N, 9.34.

4-(3-Cyano-2-(2,4-dichlorobenzylideneamino)-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 28. Yield, 82%; m.p. 75–77°C; IR (KBr, cm^{-1}): 3421, 3280 (NH_2), 3087 (CH arom.), 2970, 2870 (CH aliph.), 2183 (C≡N), 1686 (C=O), 1636 (C=N), 1373, 1198 (SO_2), 759 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.7—2.4 (m, 6H, $3CH_2$), 5.2 (s, 1H, CH), 6.9–8.0 (m, 12H, Ar-H + SO_2NH_2), 9.8 (s, 1H, N=CH). MS *m/z* (%): 646 [M^+] (4.5), 46 (100). Anal. Calcd. for $C_{29}H_{20}Cl_4N_4O_3S$ (646.37): C, 53.89; H, 3.12; N, 8.67. Found: C, 53.61; H, 3.49; N, 8.90.

4-(3-Cyano-4-(2,4-dichlorophenyl)-5-oxo-2-(2,4,5-trimethoxybenzylideneamino)-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 29. Yield, 76%; m.p. 200–202°C; IR (KBr, cm^{-1}): 3468, 3351 (NH_2), 2929, 2890 (CH aliph.), 2182 (C≡N), 1648 (C=O), 1590 (C=N), 1373, 1190 (SO_2), 758 (CCl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.5 (m, 6H, $3CH_2$), 3.6, 3.8, 3.9 (3s, 9H, $3OCH_3$), 5.0 (s, 1H, CH), 7.1–8.1 (m, 11H, Ar-H + SO_2NH_2), 9.3 (s, 1H, N=CH). Anal. Calcd. for $C_{32}H_{28}Cl_2N_4O_6S$ (667.56): C, 57.57; H, 4.23; N, 8.39. Found: C, 57.29; H, 4.55; N, 8.64.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-((2-hydroxynaphthalen-1-yl)methyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 30. Yield, 78%; m.p. 201–203°C; IR (KBr, cm^{-1}): 3410 (OH), 3368, 3310 (NH_2), 3090 (CH arom.), 2928, 2860 (CH aliph.), 2181 (C≡N), 1636 (C=O), 1593 (C=N), 1372, 1163 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 4.6 (s, 1H, CH), 7.0–8.1 (m, 15H, Ar-H + SO_2NH_2), 8.9 (s, 1H, N=CH), 9.7 (s, 1H, OH). MS *m/z* (%): 643 [M^+] (2.3), 64 (100). Anal. Calcd. for $C_{33}H_{24}Cl_2N_4O_4S$ (643.54): C, 61.59; H, 3.76; N, 8.71. Found: C, 61.28; H, 3.92; N, 8.46.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-((2-methoxynaphthalen-1-yl)methyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 31. Yield, 66%; m.p. 108–110°C; IR (KBr, cm^{-1}): 3300, 3255 (NH_2), 3085 (CH arom.), 2944, 2885 (CH aliph.), 2182 (C≡N), 1665 (C=O), 1619 (C=N), 1369, 1152 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 3.9 (s, 3H, OCH_3), 5.1 (s, 1H, CH), 7.3–8.2 (m, 15H, Ar-H + SO_2NH_2), 10.8 (s, 1H, N=CH). Anal. Calcd. for $C_{34}H_{26}Cl_2N_4O_4S$ (657.57): C, 62.10; H, 3.99; N, 8.52. Found: C, 61.85; H, 4.25; N, 8.70.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-((4-methoxynaphthalen-1-yl)methyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 32. Yield, 71%; m.p. 142–144°C; IR (KBr, cm^{-1}): 3335, 3300 (NH_2), 3090 (CH arom.), 2940, 2870 (CH aliph.), 2181 (C≡N), 1676 (C=O), 1647 (C=N), 1370, 1190 (SO_2), 766 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 3.9 (s, 3H, OCH_3), 5.0 (s, 1H, CH), 7.0–8.3 (m, 15H, Ar-H + SO_2NH_2), 10.1 (s, 1H, N=CH). Anal. Calcd. for $C_{34}H_{26}Cl_2N_4O_4S$ (657.57): C, 62.10; H, 3.99; N, 8.52. Found: C, 62.47; H, 4.28; N, 8.77.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(furan-2-ylmethyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 33. Yield, 78%; m.p. 268–270°C; IR (KBr, cm^{-1}): 3366, 3272 (NH_2), 3079 (CH arom.), 2956, 2866 (CH aliph.), 2181 (C≡N), 1651 (C=O), 1627 (C=N), 1371, 1165 (SO_2), 795 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 5.1 (s, 1H, CH), 7.1–8.2 (m, 12H, Ar-H + SO_2NH_2), 9.8 (s, 1H, N=CH). MS *m/z* (%): 567 [M^+] (4.4), 48 (100). Anal. Calcd. for $C_{27}H_{20}Cl_2N_4O_4S$ (567.44): C, 57.15; H, 3.55; N, 9.87. Found: C, 57.44; H, 3.81; N, 10.16.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-((5-methylfuran-2-yl)-methylene amino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)-benzenesulfonamide 34.. Yield, 81%; m.p. 264–266°C; IR (KBr, cm^{-1}): 3367, 3273 (NH_2), 3100 (CH arom.), 2957, 2866 (CH aliph.), 2181 (C≡N), 1699 (C=O), 1628 (C=N), 1321, 1166 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 2.3 (s, 3H, CH_3), 5.1 (s, 1H, CH), 6.3 (d, 2H, CH furan, J = 8.3 Hz), 7.3–7.9 (m, 9H, Ar-H + SO_2NH_2), 11.9 (s, 1H, N=CH). Anal. Calcd. for $C_{28}H_{22}Cl_2N_4O_4S$ (581.47): C, 57.84; H, 3.81; N, 9.64. Found: C, 58.09; H, 3.57; N, 9.92.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(thiophene-2-ylmethyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 35. Yield, 77%; m.p. 262–264°C; IR (KBr, cm^{-1}): 3365, 3272 (NH_2), 3099 (CH arom.), 2957, 2880 (CH aliph.), 2181 (C≡N), 1651 (C=O), 1591 (C=N), 1371, 1165 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 5.2 (s, 1H, CH), 7.0–8.1 (m, 13H, Ar-H + SO_2NH_2 + N=CH). MS *m/z* (%): 583 [M^+] (4.1), 45 (100). Anal. Calcd. for $C_{27}H_{20}Cl_2N_4O_3S_2$ (583.51): C, 55.58; H, 3.45; N, 9.60. Found: C, 55.92; H, 3.67; N, 9.39.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(pyridine-2-ylmethyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 36. Yield, 73%; m.p. 200–202°C; IR (KBr, cm^{-1}): 3361, 3310 (NH_2), 3092 (CH arom.), 2954, 2860 (CH aliph.), 2182 (C≡N), 1652 (C=O), 1590 (C=N), 1371, 1165 (SO_2), 795 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.3 (m, 6H, $3CH_2$), 4.9 (s, 1H, CH), 6.9–8.6 (m, 14H, Ar-H + SO_2NH_2 +

N=CH). MS *m/z* (%): 578 [M^+] (2.7), 44 (100). Anal. Calcd. for $C_{28}H_{21}Cl_2N_5O_3S$ (578.47): C, 58.14; H, 3.66; N, 12.11. Found: C, 57.91; H, 3.91; N, 12.36.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(pyridine-3-ylmethyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 37. Yield, 76%; m.p. 299–301°C; IR (KBr, cm^{-1}): 3365, 3272 (NH_2), 3103 (CH arom.), 2958, 2929 (CH aliph.), 2171 (C≡N), 1697 (C=O), 1627 (C=N), 1372, 1185 (SO_2), 796 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.8–2.4 (m, 6H, $3CH_2$), 5.0 (s, 1H, CH), 6.9–9.3 (m, 14H, Ar-H + SO_2NH_2 + N=CH). MS *m/z* (%): 578 [M^+] (3.3), 46 (100). Anal. Calcd. for $C_{28}H_{21}Cl_2N_5O_3S$ (578.47): C, 58.14; H, 3.66; N, 12.11. Found: C, 58.46; H, 3.39; N, 11.86.

4-(3-Cyano-4-(2,4-dichlorophenyl)-2-(pyridine-4-ylmethyleneamino)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide 38. Yield, 69%; m.p. 304–306°C; IR (KBr, cm^{-1}): 3365, 3272 (NH_2), 3103 (CH arom.), 2958, 2929 (CH aliph.), 2171 (C≡N), 1651 (C=O), 1627 (C=N), 1372, 1185 (SO_2), 795 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.6–2.4 (m, 6H, $3CH_2$), 4.8 (s, 1H, CH), 6.9–8.8 (m, 14H, Ar-H + SO_2NH_2 + N=CH). MS *m/z* (%): 578 [M^+] (4.2), 46 (100). Anal. Calcd. for $C_{28}H_{21}Cl_2N_5O_3S$ (578.47): C, 58.14; H, 3.66; N, 12.11. Found: C, 57.96; H, 3.94; N, 11.83.

4-(5-(2,4-Dichlorophenyl)-2-(3-hydroxyphenyl)-4-imino-6-oxo-1,2,6,7,8,9-hexahydro-4H-[1,3]oxazino[4,5-b]quinolin-10(5H)-yl)benzenesulfonamide 40. A solution of dimethylformamide (20 mL) and anhydrous zinc chloride (1.36 g, 0.01 mol) were added to compound **6** (4.89 g, 0.01 mol) and 3-hydroxybenzaldehyede (1.12 g, 0.01 mol). The reaction mixture was heated at reflux for 4 h. After completion of the reaction as indicated by TLC, the cooled reaction mixture was quenched with water (20 mL) and the precipitate was separated by filtration. The filtration residue was dispersed into water and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the product was isolated by column chromatography (200–300 mesh silica gel, ethyl acetate-petroleum ether = 1:2). Yield, 72%; m.p. >320°C; IR (KBr, cm^{-1}): 3430 (OH), 3365, 3270 (NH, NH_2), 1640 (C=O), 1590 (C=N), 1371, 1161 (SO_2), 711 (C—Cl). ^{1}H-NMR (DMSO-d_6) δ: 1.4–2.4 (m, 6H, $3CH_2$), 4.5 (s, 1H, CH), 5.5 (d, 1H, CH—O, J = 7.7 Hz), 6.8 (s, 1H, =NH), 7.0–7.9 (m, 13H, Ar-H + SO_2NH_2), 8.1 (s, 1H, NH), 12.2 (s, 1H, OH). ^{13}C-NMR (DMSO) δ: 21.9, 28.4, 31.2, 36.2, 70.8, 82.9, 111.8, 112.0, 114.3, 115.6, 120.1, 127.1, 129.3, 129.9, 130.2, 130.7, 132.8, 134.6, 139.7, 141.6, 144.6, 152.8, 156.1, 159.7, 163.9, 198.4. Anal. Calcd. for $C_{29}H_{24}Cl_2N_4O_5S$ (611.50): C, 56.96; H, 3.96; N, 9.16. Found: C, 57.21; H, 4.29; N, 8.86.

***In vitro* anticancer activity.** 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°C ± 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, Genneva, Switherland and approved from the committee for animals care at NCRRT, AEA.

EAC cells 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 RBMI-1640 media. Tested compounds were prepared with various dilutions by dissolving: 100, 50, 25, and 10 μg of the tested compounds in DMSO (1 mL).

In a set of sterile test tubes 0.8 mL RBMI-1640 media containing (glutamine, fetal calf serum as nutrient, streptomycin, and penicillin), 0.1 mL of each of the tested compounds (corresponding to 100, 50, 25, and 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 nonviable cells after 2 h of incubation [22]. The results of *in vitro* cytotoxic activity experiments are presented in Table 1.

REFERENCES AND NOTES

[1] Drews, J. Science 2000, 287, 1960.

[2] Boyd, A. E., III.Diabetes 1988, 37, 847.

[3] Supuran, C. T.; Scozzafava, A. Expert Opin Ther Pat 2000, 10, 575.

[4] Maren, T. H. Annu Rev Pharmacol Toxicol 1976, 16, 309.

[5] Supuran, C. T.; Scozzafava, A. Curr Med Chem Immunol Endocr Metab Agents 2001, 1, 61.

[6] Thornber, C. W. Chem Soc Rev 1979, 8, 563.

[7] Abbate, F.; Casini, A.; Owa, T.; Scozzafava, A.; Supuran, C. T. Bioorg Med Chem Lett 2004, 14, 217.

[8] Ghorab, M. M.; Noaman, E.; Ismail, M. M.; Heiba, H. I.; Ammar, Y. A.; Sayed, M. Y. Arzneimittelforschung 2006, 56, 405.

[9] Ismail, M. M.; Ghorab, M. M.; Noaman, E.; Ammar, Y. A.; Heiba, H. I.; Sayed, M. Y. Arzneimittelforschung 2006, 56, 301.

[10] Rostom, S. A. Bioorg Med Chem 2006, 14, 6475.

[11] Supuran, C. T.; Casini, A.; Mastrolorenzo, A.; Scozzafava, A. Mini Rev Med Chem 2004, 4, 625.

[12] Kivela, A. J.; Kivela, J.; Saarnio, J.; Parkkila, S. World J Gastroenterol 2005, 11, 155.

[13] Supuran, C. T. Nat Rev Drug Discov 2008, 7, 168.

[14] Supuran, C. T.; Scozzafava, A. Bioorg Med Chem 2007, 15, 4336.

[15] Supuran, C. T.; Scozzafava, A.; Casini, A. Med Res Rev 2003, 23, 146.

[16] Casini, A.; Scozzafava, A.; Mastrolorenzo, A.; Supuran, C. T. Curr Cancer Drug Targets 2002, 2, 55.

[17] Gopal, M.; Shenoy, S.; Doddamani, L. S. J Photochem Photobiol B 2003, 72, 69.

[18] Kim, Y. H.; Shin, K. J.; Lee, T. G.; Kim, E.; Lee, M. S.; Ryu, S. H.; Suh, P. G. Biochem Pharmacol 2005, 69, 1333.

[19] Zhao, Y. L.; Chen, Y. L.; Chang, F. S.; Tzeng, C. C. Eur J Med Chem 2005, 40, 792.

[20] Ghorab, M. M.; Ragab, F. A.; Noaman, E.; Heiba, H. I.; El-Hossary, E. M. Arzneimittelforschung 2007, 57, 795.

[21] Ghorab, M. M.; Ragab, F. A.; Hamed, M. M. Eur J Med Chem 2009, 44, 4211.

[22] Brusick, D. J. In Carcinogenesis and Mutagenesis Testing; Douglas, J. F., Ed.; Human Press Inc.: Clifton, New Jersey, 1984; p 265.

[23] Shuling, M. A.; Jiarong, L. I.; Yongjiang, S.; Jianmin, Z.; Xiaofan, Z.; Xiquan, Y.; Lijun, Z.; Lijum, W.; Zhiming, Z. Tetrahedron 2006, 62, 7999.