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Original article

Discovering some novel tetrahydroquinoline derivatives bearing the biologically active sulfonamide moiety as a new class of antitumor agents

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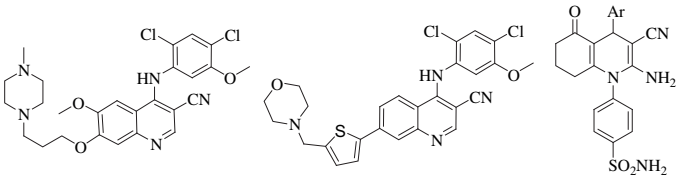
ABSTRACT

The present article describes the synthesis of some novel 4-(2-amino-3-cyano-4-(substituted-aryl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl)benzenesulfonamide (**23**–**41**) starting with 4-(3-oxo-cyclohex-1-enylamino)benzenesulfonamide (**3**). All the newly synthesized compounds were evaluated for their *in vitro* antitumor activity. Compounds **32**, **25**, **41**, **35**, **33**, and **37** with IC_{50} values (2.5, 3, 5, 10, 12, and 12.5 μg/mL) are more potent and efficacious than Doxorubicin (CAS-23214-92-8) as reference drug with (IC_{50} value = 37.5 μg/mL). Also, compounds **28**, **30**, **31**, and **34** (with IC_{50} values = 25 μg/mL) are nearly as active as Doxorubicin.

1. Introduction

Protein tyrosine kinases (TKs) play an important role in cell growth and differentiation. These enzymes catalyze the transfer of a phosphate group from **ATP** to a tyrosine residue on an appropriate substrate, thereby bringing about cell signaling events. Several nonreceptor **TKs** have been identified, among them the **Src** family of cytoplasmic protein **TKs** [1]. The **TK Src** has been implicated in several disease states, including cancer [2,3], osteoporosis [4], and stroke [5]. Therefore, inhibition of **Src** kinase could prove useful in the treatment of these and other diseases. A number of **Src** family kinase inhibitors have been reported in the literature, including 4-anilinoquinazolines [6], pyrazolo [3,4-*d*]- pyrimidines [7], pyrrolo[2,3-*d*]pyrimidines [8], pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones [9],1,6-naphthyridin-2(1*H*)-ones [10], and aminopyrido[2,3-*d*]pyrimidin-7-yl ureas [11]. A series of 4-anilino-3-quinolinecarbonitrile compounds has been reported to be potent inhibitors of **EGFr** [12], **Src** [13] and **MEK** [14] kinases. While earlier synthetic efforts were directed at 4-anilino-6,7-dialkoxy-3-quinolinecarbonitrile **Src** kinase inhibitors, such as compound **I** [15], recent efforts have focused on 4-anilino-7-thienyl-3-quinolinecarbonitriles (e.g., **II**) as potent **Src** kinase inhibitors [16]. Given the obvious importance of quinoline-3-carbonitrile as efficient **Src** kinase inhibitors, and as part of our research effort to explore the new antitumor heterocyclic compounds [17–24], we synthesized a novel series of tetrahydroquinoline-3-carbonitriles **23**–**41**, bearing the biologically active sulfonamide moiety at 1-position with substituted-aryl at the 4-position and free amino group at the 2-position as analogues of compounds **I** and **II**.



I **II** **23-41**

2. Results and discussion

2.1. Chemistry

The present work reports the possible utility of 4-(3-oxo-cyclohex-1-enylamino)-benzenesulfonamide **3** in the synthesis of 4-(quinolin-1-yl)benzenesulfonamide derivatives **23**–**41**. Enaminone **3** was obtained by condensation of cyclohexan-1,3-dione **1**

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with sulfanilamide **2** in ethanol (Scheme 1). The structure of compound **3** was confirmed by elemental analysis and spectral data. The IR spectrum of compound **3** revealed the presence of bands for NH, NH_2 at 3354, 3263 cm^{-1}, C═O at 1611 cm^{-1}, SO_2 at 1360, 1184 cm^{-1}. Also, the ^1H NMR spectrum in DMSO-d_6 indicated the presence of signal at 9.0 ppm which could be assigned to NH of the enaminone **3**.

Treating the enaminone, **3**, with arylidenemalononitriles, **4**–**22**, in the presence of catalytic amount of triethylamine as a base catalyst, yielded the corresponding tetrahydroquinolines **23**–**41** *via* the formation of the intermediate Michael type products, followed by intramolecular cyclization (Scheme 1).

The *N*-Aryl-substituted benzenesulfonamide decreased the nucleophilicity of the enaminone **3** towards 2-arylidenemalononitriles **4**–**22**. The base catalyst triethylamine was required to generate the anion of the enaminone **3**, thus facilitating the addition to the unsaturated nitriles **4**–**22**.

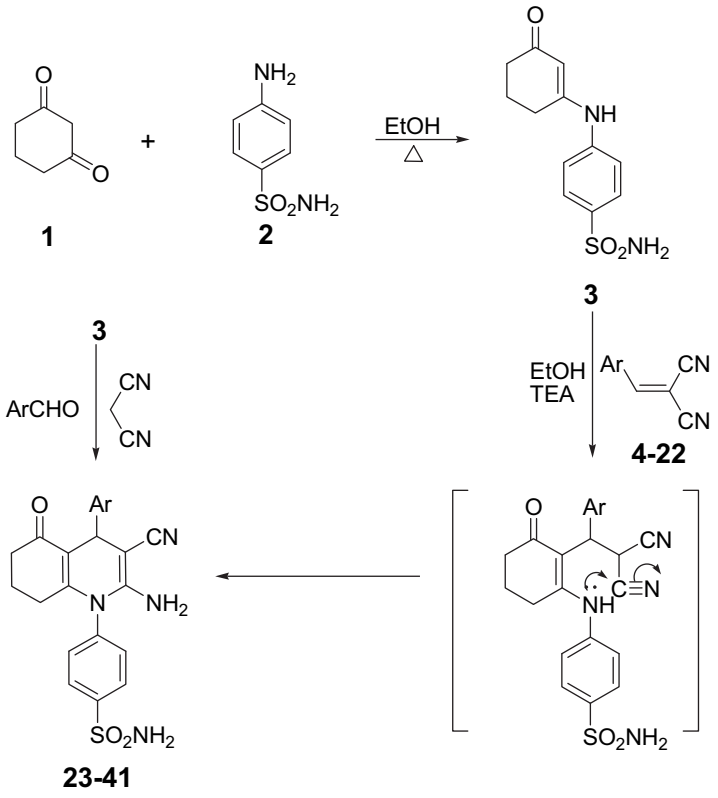
Compounds **23**–**41** were unambiguously synthesized by another route involving one-pot condensation of the aldehyde, malononitrile and enaminone **3** in a molar ratio of (1:1:1) in refluxing ethanol containing triethylamine as catalyst. In this case, formation of compounds **23**–**41** is illustrated in terms of initial condensation of the appropriate aldehyde with malononitrile affording the activated arylidenemalononitriles **4**–**22**, followed by addition of the enaminone **3** to arylidenemalononitriles **4**–**22**. The IR spectra of compounds **23**–**41** showed bands at 3472–3185 cm^{-1} due to (NH_2), 2227–2120 cm^{-1} (C≡N), 1647–1611 cm^{-1} (C═O), 1383–1140 cm^{-1} (SO_2).

2.2. 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 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 parent target molecule, containing both tetrahydroquinoline and sulfonamide moieties, was synthesized with amino group



23: Ar= -C_6H_5
24: **Ar**= -C_6H_4.CH_3-4.
25: **Ar**= -C_6H_4.OH-4.
26: **Ar**= CH=CH-C_6H_5.
27: **Ar**= -C_6H_4.OCH_3-2.
28: **Ar**= -C_6H_4.OCH_3-4..
29: **Ar**= piperonyl.
30: **Ar**= vanillyl.
31: **Ar**= -C_6H_4.NO_2-3.
32: **Ar**= -C_6H_4.NO_2-4.
33: Ar= -C_6H_2.$(OCH_3)_3$.2,4,5.
34: **Ar**= -C_6H_3.Cl_2.2,4.
35: **Ar**= -C_6H_3.OC_2H_5-3, OCH_3-4.
36: **Ar**= -$C_{10}H_6$.OH-2.
37: **Ar**= -$C_{10}H_6$.OCH_3-2.
38: **Ar**= -$C_{10}H_6$.OCH_3-4.
39: **Ar**= 2-furyl.
40: **Ar**= 2-furyl,CH_3-5.
41: **Ar**= 2-thienyl.

Scheme 1.

Table 1
In vitro cytotoxic activity of the newly synthesized compounds **23**–**41**.

Compd. No.	Non-viable cells (%)[a]				IC_{50}[b] (μg/mL)
	Concentration (μg/mL)				
	100	50	25	10	
Doxorubicin	100	60	39	20	37.5
23	40	40	30	10	>100[c]
24	100	50	30	30	50
25	100	100	95	90	3
26	45	40	10	2	>100[c]
27	0	0	0	0	>100[c]
28	100	90	50	30	25
29	95	10	0	0	75
30	100	90	50	0	25
31	71	73	50	42	25
32	100	95	80	85	2.5
33	100	100	72	40	12
34	95	65	50	40	25
35	100	70	60	50	10
36	15	5	0	0	>100[c]
37	80	70	62	40	12.5
38	90	30	10	10	70
39	10	5	0	0	>100[c]
40	45	40	10	2	>100[c]
41	100	88	80	70	5

[a] Ehrlich Ascites Carcinoma (EAC) cells.
[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.

at position 2, and cyano group at position 3 in addition to several substituents at position 4, in order to study the structure–activity relationship of the newly synthesized compounds **23**–**41**. From these results, it was found that substitution with either 4-nitrophenyl **32**, 4-hydroxyphenyl **25**, 2-thienyl **41**, 3-ethoxy-4-methoxyphenyl **35**, trimethoxyphenyl **33** and 2-methoxynaphthyl **37** at position 4 (with IC_{50} values = 2.5, 3, 5, 10, 12, and 12.5 μg/mL) showed a significant cytotoxic activity which was even higher than that of reference drug Doxorubicin (CAS-23214-92-8) with IC_{50} value = 37.5 μg/mL. The substitution in *para* position was found to enhance the cytotoxic activity rather than in *ortho* or *meta* positions. These findings were clearly observed as the presence of 4-nitrophenyl **32** (IC_{50} value = 2.5 μg/mL), and 4-hydroxyphenyl **25** (IC_{50} value = 3 μg/mL) led to an increase in the antitumor activity where the percentage of non-viable cells were 85% and 90% respectively, at a concentration of 10 μg/mL. Compound **32** having *p*-nitrophenyl at position 4 is more active than compound **31** bearing *m*-nitrophenyl at the same position. Also, the presence of methoxy group at *ortho*-position **37** with (IC_{50} value = 12.5 μg/mL) is more active than compound **36** containing hydroxy group at the same position. On the other hand, it was found that compound **41** carrying 2-thienyl at position 4 enhances the cytotoxic activity rather the 2-furyl **39**. In addition compound having trimethoxy group **33** is more potent than compounds carrying only one methoxy group **27** and **28**.

It was very interesting to observe that compound **28** with 4-methoxyphenyl at position 4, compound **30** with 4-hydroxy-3-methoxyphenyl, compound **31** with 3-nitrophenyl and compound **34** with 2,4- dichlorophenyl (IC_{50} values = 25 μg/mL) are nearly as active as Doxorubicin as positive control, while compounds **24**, **29**, and **38** exhibited a moderate activity but less active than Doxorubicin.

It is clear from the present data that, the comparison of the cytotoxicity of tetrahydroquinoline derivatives against Ehrlich Ascites Carcinoma (EAC) cells (Table 1) has showed that the cell killing potency follows the order **32** > **25** > **41** > **33** > **37** > Doxorubicin. The presence of a cyano group at position 3 [12,25] in these compounds is supposed to enhance their antitumor activity.

3. Conclusions

The present data showed that, compounds combining tetrahydroquinoline and benzenesulfonamide moieties, exhibited promising *in vitro* cytotoxic activity against EAC cells, especially compounds **32** and **25** containing substituted phenyl with either NO_2 or OH groups in position 4. Compounds **32**, **25**, **41**, **35**, **33** and **37** exhibited the highest *in vitro* cytotoxic activity when compared with the other tested compounds and doxorubicin as a reference drug. Also, compounds **28**, **30**, **31** and **34** are nearly as active as doxorubicin.

4. Experimental

4.1. Chemistry

Melting points (°C, uncorrected) were determined in open capillaries on a Gallenkamp melting point apparatus (Sanyo Gallenkamp, Southborough, UK). 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. Infra red spectra were recorded in KBr discs 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, δppm) 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-Oxo-cyclohex-1-enylamino)benzenesulfonamide (**3**)

A mixture of cyclohexane-1,3-dione **1** (1.12 g, 0.01 mol) and sulfanilamide **2** (1.72 g, 0.01 mol) in ethanol (30 mL) was refluxed for 3 h. The reaction mixture was cooled and then poured onto cold water the obtained solid was crystallized from ethanol to give **3**. Yield, 92%; m.p. 236–238 °C; IR (KBr, cm^{-1}): 3354, 3263 (NH, NH_2), 3032 (CH arom.), 1611 (C═O), 1360, 1184 (SO_2). ^{1}H NMR: 1.05–1.9 [m, 6H, $3CH_2$ cyclo.], 5.5 [s, 1H, CH], 7.0–7.8 [m, 6H, Ar-H + SO_2NH_2], 9.0 [s, 1H, NH]. Anal.Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.32; H, 5.53; N, 10.33.

4.1.2. 4-[2-Amino-3-cyano-4-(substituted-aryl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**23**–**41**)

4.1.2.1. Method (A). A mixture of compound **3** (2.66 g, 0.01 mol) and the corresponding 2-arylidenemalononitrile derivatives **4**–**22** (0.01 mol) in ethanol (20 mL) containing 3 drops of triethylamine, was refluxed for 6 h. The reaction mixture was filtered while hot and the solid obtained was crystallized from dioxane to give **32**–**41**, respectively.

4.1.2.2. Method (B). A solution of enaminone **3** (2.66 g, 0.01 mol), the appropriate aldehyde (0.01 mol) and malononitrile (0.66 g, 0.01 mol) in absolute ethanol (30 mL) containing 3 drops of triethylamine, was refluxed for 5 h. The solid obtained after concentration and cooling, was filtered and crystallized from dioxane to give **23**–**41**, respectively (M.P., mixed M.P.).

4.1.3. 4-[2-Amino-3-cyano-4-phenyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**23**)

Yield, 90%; m.p. 246–248 °C; IR: 3354, 3263 (NH_2), 3029 (CH arom.), 2224 (C≡N), 1613 (C═O), 1390, 1140 (SO_2). ^{1}H NMR: 1.5–1.9

[m, 6H, $3CH_2$ cyclo.], 4.1 [s, 1H, CH], 5.3 [s, 2H, NH_2], 7.2–7.8 [m, 11H, Ar-H + SO_2NH_2]. MS, *m*/*z* (%): 420[M^+] (2), 73 (100). Anal.Calcd. for $C_{22}H_{20}N_4O_3S$: C, 62.84; H, 4.79; N, 13.32. Found: C, 62.48; H, 4.55; N, 13.61.

*4.1.4. 4-[2-Amino-3-cyano-4-p-tolyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)yl]benzenesulfonamide (**24**)*

Yield, 82%; m.p. 291–293 °C; IR: 3458, 3344, 3220 (NH_2), 3020 (CH arom.), 2940, 2850 (CH aliph.), 2169 (C≡N) 1634 (C═O), 1378, 1165 (SO_2). ^{1}H NMR: 1.6–1.8 [m, 6H, $3CH_2$ cyclo.], 2.2 [s, 3H, CH_3], 4.0 [s, 1H, CH], 5.4 [s, 2H, NH_2], 7.1–8.0 [m, 10H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{23}H_{22}N_4O_3S$: C, 63.58; H, 5.10; N, 12.89. Found: C, 63.37; H, 5.34; N, 12.63.

*4.1.5. 4-[2-Amino-3-cyano-4-p-hydroxyphenyl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**25**)*

Yield, 87%; m.p. 288–289 °C; IR: 3458 (OH), 3325, 3253 (NH_2), 2925, 2853 (CH aliph.), 2180 (C≡N) 1643 (C═O), 1375, 1163 (SO_2). ^{1}H NMR: 1.4–1.9 [m, 6H, $3CH_2$ cyclo.], 4.3 [s, 1H, CH], 5.5 [s, 2H, NH_2], 7.3–7.9 [m, 10H, Ar-H + SO_2NH_2], 10.8 [s, 1H, OH]. MS *m*/*z* (%): 436 [M^+] (7.5), 73 (100). Anal.Calcd. for $C_{22}H_{20}N_4O_4S$: C, 60.54; H, 4.62; N, 12.84. Found: C, 60.22; H, 4.35; N, 12.58.

*4.1.6. 4-[2-Amino-3-cyano-4-styryl-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**26**)*

Yield, 79%; m.p. 177–179 °C; IR: 3353, 3262, (NH_2), 3022 (CH arom.), 2940, 2860 (CH aliph.), 2227 (C≡N) 1611 (C═O), 1360, 1140 (SO_2). ^{1}H NMR: 1.9–2.4 [m, 6H, $3CH_2$ cyclo.], 4.0 [s, 1H, CH], 5.5 [s, 2H, NH_2], 7.3–7.8 [m, 11H, Ar-H + SO_2NH_2], 8.0, 8.2 [2d, 2H, CH═CH, J = 7.4, 7.2 Hz]. Anal.Calcd. for $C_{24}H_{22}N_4O_3S$: C, 64.56; H, 4.97; N, 12.55. Found: C, 64.36; H, 4.71; N, 12.23.

*4.1.7. 4-[2-Amino-3-cyano-4-(2-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**27**)*

Yield, 76%; m.p. 255–257 °C; IR: 3446, 3341, 3276 (NH_2), 3035 (CH arom.), 2175 (C≡N) 1653 (C═O), 1371, 1187 (SO_2). ^{1}H NMR: 1.9–2.2 [m, 6H, $3CH_2$ cyclo.], 3.7 [s, 3H, OCH_3], 4.4 [s, 1H, CH], 5.4 [s, 2H, NH_2], 7.2–7.9 [m, 10H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{23}H_{22}N_4O_4S$: C, 61.32; H, 4.92; N, 12.44. Found: C, 61.65; H, 4.74; N, 12.64.

*4.1.8. 4-[2-Amino-3-cyano-4-(4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**28**)*

Yield, 81%; m.p. 260–262 °C; IR: 3434, 3352, 3264 (NH_2), 3063 (CH arom.), 2940, 2850 (CH aliph.), 2176 (C≡N) 1644 (C═O), 1372, 1172 (SO_2). ^{1}H NMR: 1.6–2.2 [m, 6H, $3CH_2$ cyclo.], 3.5 [s, 3H, OCH_3], 4.3 [s, 1H, CH], 5.4 [s, 2H, NH_2], 7.1–8.0 [m, 10H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{23}H_{22}N_4O_4S$: C, 61.32; H, 4.92; N, 12.44. Found: C, 61.66; H, 4.69; N, 12.71.

*4.1.9. 4-[2-Amino-4-(benzo[d][1,3]dioxol-5-yl)-3-cyano-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**29**)*

Yield, 85%; m.p. 202–204 °C; IR: 3349, 3257, 3185 (NH_2), 3034 (CH arom.), 2978, 2947 (CH aliph.), 2222 (C≡N), 1611 (C═O), 1375, 1181 (SO_2). ^{1}H NMR: 1.3–2.2 [m, 6H, $3CH_2$ cyclo.], 4.0 [s, 2H, OCH_2O], 4.4 [s, 1H, CH], 5.5 [s, 2H, NH_2], 7.2–8.3 [m, 9H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{23}H_{20}N_4O_5S$: C, 59.47; H, 4.34; N, 12.06. Found: C, 59.61; H, 4.62; N, 12.34.

*4.1.10. 4-[2-Amino-3-cyano-4-(4-hydroxy-3-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**30**)*

Yield, 69%; m.p. 274–276 °C; IR: 3471 (OH), 3360, 3194 (NH_2), 3070 (CH arom.), 2978, 2947 (CH aliph.), 2148 (C≡N), 1647 (C═O), 1375, 1193 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 3.6 [s, 3H, OCH_3], 4.6 [s, 1H, CH], 5.6 [s, 2H, NH_2], 7.3–8.0 [m, 9H, Ar-H + SO_2NH_2], 9.0 [s, 1H, OH]. Anal.Calcd. for $C_{23}H_{22}N_4O_5S$: C, 59.22; H, 4.75; N, 12.01. Found: C, 59.50; H, 4.52; N, 12.32.

*4.1.11. 4-[2-Amino-3-cyano-4-(3-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**31**)*

Yield, 83%; m.p. 210–212 °C; IR: 3420, 3350, 3290 (NH_2), 3029 (CH arom.), 2950, 2860 (CH aliph.), 2173 (C≡N), 1647 (C═O), 1375, 1193 (SO_2). ^{1}H NMR: 1.6–2.2 [m, 6H, $3CH_2$ cyclo.], 4.4 [s, 1H, CH], 5.5 [s, 2H, NH_2], 7.1–7.8 [m, 10H, Ar-H + SO_2NH_2]. MS *m*/*z* (%): 465[M^+] (8.7), 207 (100). Anal.Calcd. for $C_{22}H_{19}N_5O_5S$: C, 56.77; H, 4.11; N, 15.05. Found: C, 56.48; H, 4.42; N, 15.37.

*4.1.12. 4-[2-Amino-3-cyano-4-(4-nitrophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**32**)*

Yield, 82%; m.p. 287–288 °C; IR: 3472, 3361, (NH_2), 3070 (CH arom.), 2978, 2947 (CH aliph.), 2184 (C≡N), 1647 (C═O), 1375, 1193 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 4.6 [s, 1H, CH], 5.6 [s, 2H, NH_2], 7.5–8.0 [m, 10H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{22}H_{19}N_5O_5S$: C, 56.77; H, 4.11; N, 15.05. Found: C, 56.82; H, 4.30; N, 15.19.

*4.1.13. 4-[2-Amino-3-cyano-4-(2,4,5-trimethoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**33**)*

Yield, 86%; m.p. 149–151 °C; IR: 3390, 3358 (NH_2), 3083 (CH arom.), 2997, 2953 (CH aliph.), 2219 (C≡N) 1613 (C═O), 1341, 1193 (SO_2). ^{1}H NMR: 1.9–2.2 [m, 6H, $3CH_2$ cyclo.], 3.7, 3.92, 3.94 [3s, 9H, $3OCH_3$], 5.5 [s, 1H, CH], 6.7 [s, 2H, NH_2], 7.2–8.1 [m, 8H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{25}H_{26}N_4O_6S$: C, 58.81; H, 5.13; N, 10.97. Found: C, 58.54; H, 5.45; N, 11.25.

*4.1.14. 4-[2-Amino-3-cyano-4-(2,4-dichlorophenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**34**)*

Yield, 90%; m.p. 291–293 °C; IR: 3464, 3347 (NH_2), 3064 (CH arom.), 2957, 2860 (CH aliph.), 2171 (C≡N) 1634 (C═O), 1374, 1189 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 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 $C_{22}H_{18}Cl_2N_4O_3S$: C, 53.99; H, 3.71; N, 11.45. Found: C, 54.31; H, 3.95; N, 11.79.

*4.1.15. 4-[2-Amino-3-cyano-4-(3-ethoxy-4-methoxyphenyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**35**)*

Yield, 79%; m.p. 213–215 °C; IR: 3360, 3349, 3290 (NH_2), 3089 (CH arom.), 2965, 2850 (CH aliph.), 2176 (C≡N) 1654 (C═O), 1373, 1167 (SO_2). ^{1}H NMR: 1.0 [t, 3H, CH_3], 1.6–2.2 [m, 6H, $3CH_2$ cyclo.], 3.6 [s, 3H, OCH_3], 4.3 [s, 1H, CH], 4.6 [q, 2H, CH_2], 5.6 [s, 2H, NH_2], 7.2–8.1 [m, 9H, Ar-H + SO_2NH_2]. Anal.Calcd. for $C_{25}H_{26}N_4O_5S$: C, 60.71; H, 5.30; N, 11.33. Found: C, 60.47; H, 4.98; N, 11.56.

*4.1.16. 4-[2-Amino-3-cyano-4-(2-hydroxy-1-naphthyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**36**)*

Yield, 69%; m.p. >300 °C; IR: 3419 (OH), 3335, 3234 (NH_2), 3064 (CH arom.), 2950, 2840 (CH aliph.), 2210 (C≡N) 1638 (C═O), 1361, 1158 (SO_2). ^{1}H NMR: 1.7–2.2 [m, 6H, $3CH_2$ cyclo.], 4.4 [s, 1H, CH], 5.4 [s, 2H, NH_2], 7.2–7.9 [m, 12H, Ar-H + SO_2NH_2], 10.8 [s, 1H, OH]. MS *m*/*z* (%): 486 [M^+] (44.8), 73 (100). Anal.Calcd. for $C_{26}H_{22}N_4O_4S$: C, 64.18; H, 4.56; N, 11.52. Found: C, 64.49; H, 4.23; N, 11.19.

*4.1.17. 4-[2-Amino-3-cyano-4-(2-methoxy-1-naphthyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**37**)*

Yield, 66%; m.p. 228–230 °C; IR: 3339, 3255, 3186 (NH_2), 3106 (CH arom.), 2949, 2830 (CH aliph.), 2120 (C≡N) 1611 (C═O), 1361, 1183 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 3.6 [s, 3H, OCH_3], 5.5 [s, 1H, CH], 7.3–7.8 [m, 14H, Ar-H + NH_2 + SO_2NH_2]. Anal.Calcd. for $C_{27}H_{24}N_4O_4S$: C, 64.78; H, 4.83; N, 11.19. Found: C, 64.49; H, 4.57; N, 10.87.

*4.1.18. 4-[2-Amino-3-cyano-4-(4-methoxy-1-naphthyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**38**)*

Yield, 71%; m.p. >300 °C; IR: 3441, 3350, 3239, 3188 (NH_2), 3106 (CH arom.), 2949, 2830 (CH aliph.), 2214 (C≡N) 1640 (C═O), 1383, 1157 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 3.5 [s, 3H, OCH_3], 5.5 [s, 1H, CH], 7.2–8.4 [m, 14H, Ar-H + NH_2 + SO_2NH_2]. Anal.Calcd. for $C_{27}H_{24}N_4O_4S$: C, 64.78; H, 4.83; N, 11.19. Found: C, 64.53; H, 4.62; N, 11.26.

*4.1.19. 4-[2-Amino-3-cyano-4-(2-furyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**39**)*

Yield, 84%; m.p. 198–199 °C; IR: 3354, 3262 (NH_2), 3034 (CH arom.), 2950, 2840 (CH aliph.), 2224 (C≡N), 1611 (C═O), 1360, 1184 (SO_2). ^{1}H NMR: 1.6–2.2 [m, 6H, $3CH_2$ cyclo.], 4.4 [s, 1H, CH], 5.4 [s, 2H, NH_2], 7.2–8.2 [m, 9H, Ar-H + SO_2NH_2]; MS *m*/*z* (%): 410 [M^+] (2.1), 207 (100). Anal.Calcd. for $C_{20}H_{18}N_4O_4S$: C, 58.53 H, 4.42; N, 13.65. Found: C, 58.87; H, 4.11; N, 13.98.

*4.1.20. 4-[2-Amino-3-cyano-4-(5-methyl-2-furyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**40**)*

Yield, 89%; m.p. 296–298 °C; IR: 3355, 3263 (NH_2), 3034 (CH arom.), 2923, 2860 (CH aliph.), 2207 (C≡N) 1611 (C═O), 1360, 1184 (SO_2). ^{1}H NMR: 1.8–2.2 [m, 6H, $3CH_2$ cyclo.], 2.5 [s, 3H, CH_3], 5.4 [s, 1H, CH], 7.2–7.8 [m, 10H, Ar-H + NH_2 + SO_2NH_2]. Anal.Calcd. for $C_{21}H_{20}N_4O_4S$: C, 59.42 H, 4.75; N, 13.20. Found: C, 59.10; H, 5.09; N, 12.88.

*4.1.21. 4-[2-Amino-3-cyano-4-(2-thienyl)-5-oxo-5,6,7,8-tetrahydroquinolin-1(4H)-yl]benzenesulfonamide (**41**)*

Yield, 83%; m.p. 234–236 °C; IR: 3354, 3262 (NH_2), 3033 (CH arom.), 2950, 2840 (CH aliph.), 2223 (C≡N) 1612 (C═O), 1360, 1184 (SO_2). ^{1}H NMR: 1.7–2.2 [m, 6H, $3CH_2$ cyclo.], 4.6 [s, 1H, CH], 5.6 [s, 2H, NH_2] 7.2–8.1 [m, 9H, Ar-H + SO_2NH_2]. MS *m*/*z* (%): 425 [$M^+ - 1$] (1.5), 73 (100). Anal.Calcd. for $C_{20}H_{18}N_4O_3S_2$: C, 56.32 H, 4.25; N, 13.14. Found: C, 56.07; H, 4.53; N, 12.80.

4.2. Biological testing

4.2.1. Animals, chemicals and facilities

Ehrlich ascites carcinoma (EAC) cells were 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 [26]

Ehrlich Ascites Carcinoma (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 & 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, 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 [27]. The results of *in vitro* cytotoxic activity experiments are presented in Table 1.

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