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Design and synthesis of novel 7-aminoquinazoline derivatives: Antitumor and anticonvulsant activities

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ABSTRACT

A novel series of 7-substituted-4(3*H*)-quinazolinone were designed, synthesized and evaluated for their antitumor and anticonvulsant activity. Compound **7** revealed broad-spectrum antitumor effectiveness toward numerous cell lines that belong to different tumor subpanels, whereas compounds **9** and **18** possess selective activity toward leukemia cell lines. Additionally, compounds **3**, **15**, **16**, **18**, **19** and **20** showed advanced anticonvulsant activity as well as lower neurotoxicity than reference drugs. The achieved results proved that the distinctive compounds could be valuable as a model for future devise, acclimatization and investigation to construct more active analogues.

Cancer is continuing to be a major health problem in developing as well as developed countries.[1,2] Surpassing heart diseases, it is taking the position number one killer due to various worldwide factors. Although major advances have been made in the chemotherapeutic management of some patients, the continued commitment to the laborious task of discovering new anticancer agents remains critically important.

Quinazolines are considered to be an important chemical synthon of various physiological significance and pharmaceutical utility. They possess a variety of biological effects including antihypertensive,[3] antimicrobial,[4–6] antihyperlipidemic,[7,8] antioxidant,[9] anti-inflammatory,[10–12] anticonvulsant,[13–16] and anticancer activities.[17–19]

Interests in quinazolines as anticancer agents have further increased since the discovery of raltitrexed **I** and thymitaq **II** (Fig. 1), both compounds proved to be thymidylate synthase inhibitors.[20–22] Moreover, many quinazolines contributed to the quest for an ultimate antitumor chemotherapeutic agent.[17,18] Interestingly, it was reported that the sulfonamide, Schiff's base and amide functions were enhanced the antitumor activity of quinazoline core **III–VII** (Fig. 1).[18,19,23]

On the other hand, Epilepsy is one of the most common neurological disorders, affecting about 1% of the world's population. Much efforts devoted in the recent years for the development of novel therapeutics resulted in the availability of several newer drugs as promising anticonvulsants.[24,25] However, the currently available anticonvulsants are effective in reducing the severity and number of seizures in less than 70% of patients. Moreover, their usage is associated with undesirable numerous side effects.[26–29] Therefore, continued search for safer and more effective anticonvulsants is urgently necessary. Literature survey revealed that the presence of a methyl group at position 2 and a substituted aromatic ring at position 3 in a quinazoline nucleus are preferential requirement for the CNS depression and anticonvulsant activities[30] **VIII–XI** (Fig. 1).

The present study aimed to synthesize and evaluate the biological activity of some new quinazoline derivatives as potential anticonvulsant and anticancer agents, a new series of quinazoline compounds were designed, in such a way to accommodate an amino function group at position 7 that used to introduce amides, sulfonamides, biquinazoline and Schiff's base, the later compound was converted into phenylthiazolidin-4-one moiety (Fig. 1).

The designed target compounds were obtained as outlined in Schemes 1–3 starting with 4-nitroanthranilic acid.

Synthesis of 2-methyl-3-(2-methylphenyl)-7-amino-4(3*H*)-quinazolinone **(2)** as a key intermediate was achieved by the reaction of 4-nitroanthranilic acid with acetic anhydride followed by treatment with *o*-toludine in anhydrous pyridine. The latter compound

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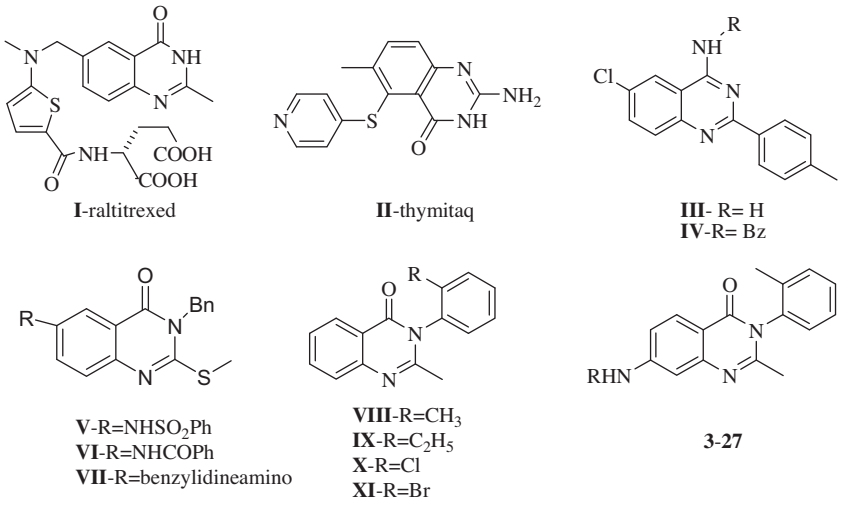
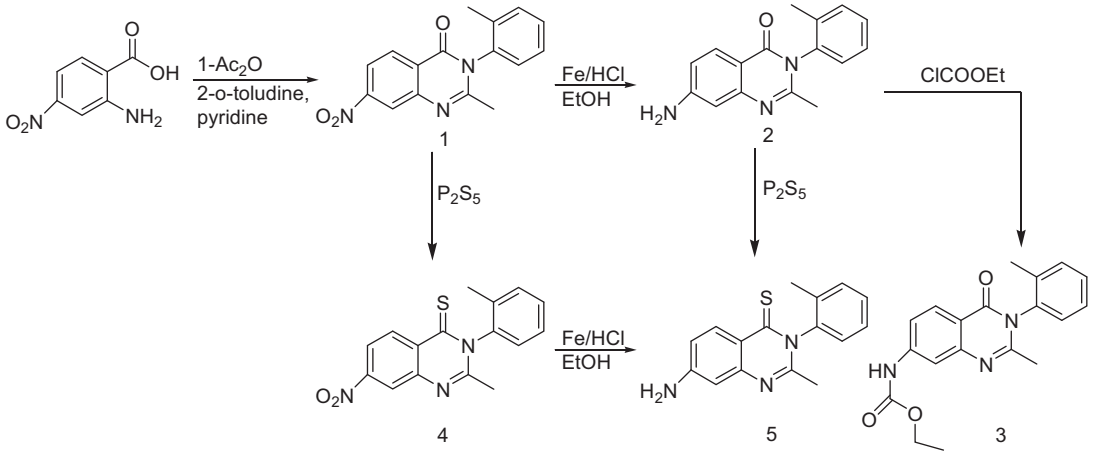
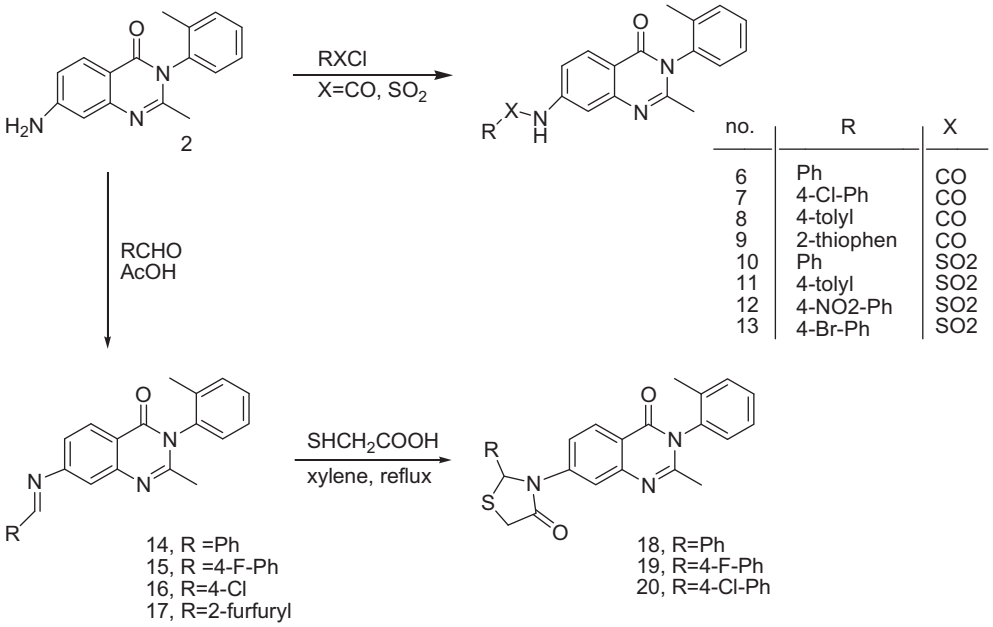


Figure 1. Reported and designed quinazolinones (**3**–**27**) as anticancer and CNS active agents.

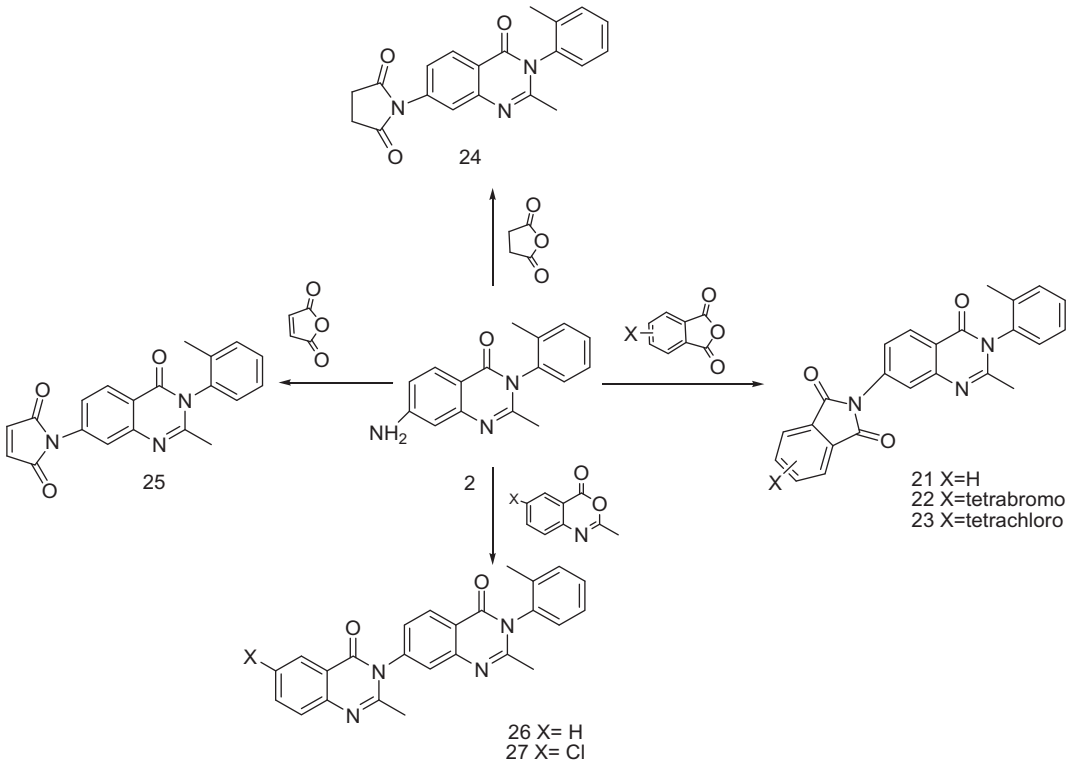


Scheme 1. Synthesis of 7-ethoxycarbonylamino-4(3*H*)-quinazolinone **3** and 7-substituted-4(3*H*)-quinazolinthione **4**–**5**.



no.	R	X
6	Ph	CO
7	4-Cl-Ph	CO
8	4-tolyl	CO
9	2-thiophen	CO
10	Ph	SO2
11	4-tolyl	SO2
12	4-NO2-Ph	SO2
13	4-Br-Ph	SO2

Scheme 2. Reactions of 7-amino-4(3*H*)-quinazolinone **2**.



Scheme 3. Synthesis of cyclic imides **21–25** and 4,4-biquinazolindione **26**–**27**.

was subjected to metal reduction by reaction with Fe/HCl in boiling ethanol.

Amino function of compound **2** was reacted with ethyl chloroformate in boiling pyridine to produce 2-methyl-3-(2-methylphenyl)-7-ethoxycarbonylamino-4(3*H*)-quinazolinone **(3)** in 84% yield**.** Thiation of compound **1** and **2** was accomplished by reaction with P_2S_5 in anhydrous xylene to give the corresponding 2-methyl-3-(2-methylphenyl)-7-nitro-4(3*H*)-quinazolinthione **(4)** and 2-methyl-3-(2-methylphenyl)-7-amino-4(3*H*)-quinazolinthione **(5),** in 81%, 53% yield, respectively. Compound **4** was subjected to metal reduction[16] using Fe/HCl in boiling ethanol to afford **5** in 50% yield (Scheme 1).

7-Amino-4(3*H*)-quinazolinone **2** was reacted with various acid chlorides and sulfonyl chlorides in dichloromethane in the presence of triethylamine at room temperature to furnish 7-(substituted carbonylamino)-4(3*H*)-quinazolinones **6**–**9** in 87–92% yield and 2-methyl-3-(2-methylphenyl)-7-(substituted sulfonylamino)-4(3*H*)-quinazolinones **10**–**13** in excellent yield. Schiff's base **14–17** was obtained in 60–66% yields, by reaction of **2** with various aldehyde in boiling methanol, compound **14–16** was subjected to cyclization via reaction with thioglycolic acid in anhydrous benzene to afford 2-phenylthiazolidin-4-ones **18–20** in 47–55% yields (Scheme 2).

On the other hand, compound **2** was reacted with various anhydrides and 1,3-benzoxazine-4-one in boiling glacial acetic acid in the presence of anhydrous sodium acetate to give the corresponding imides **21–25** in 84–89% and 4,4-biquinazolindione **26**–**27** in 72–76% yield.

In vitro antitumor evaluation of the nine compounds indicated in (Tables 1) were selected by National Cancer Institute, Bethesda, Maryland, USA on the basis of degree of the structure variation and computer modeling techniques for evaluation of their anticancer activity. The selected compounds were subjected to in vitro anticancer assay against tumor cells in a full panel of 60-cell lines taken from nine different organs (lung, colon, breast, ovary, blood, kidney, skin, prostate and brain). The compounds were tested at a single dose concentration of 10 μM, and the percentages of growth inhibitions (GI %) over the 60 tested cell lines were determined.

The obtained results of the tested quinazoline derivatives showed potential pattern of selectivity, as well as broad-spectrum antitumor activity of compound **7**.

Regarding the activity toward individual cell lines; compounds **7**, **9**, **18**, **19** and **20** showed selective activity against leukemia MOLT-4 cell lines with GI values of 28.3%, 25.6%, 46.3%, 28.9% and 39.1%, respectively; while Non-Small Cell Lung EKVX and ovarian Cancer OVAR-4 proved to be selectively sensitive to **7** with GI value of 48.5% and 69.9%, respectively. Compounds **3** and **7** showed GI values of 41.6% and 56.4% against melanoma MDA-MB-435, while compounds **6** and **7** showed GI values of 26.6% and 24.4%, against colon KM12, 24.0%, 51.9% renal ACHN cancer cells and 27.9%, 71.0% against breast cancer T-47D, respectively. Compounds **7** and **18** showed GI values of 39.8% and 26.9% against prostate PC-3 and 71.0%, 25.8%, 24.7% GI values of breast-T-47D cancer cells, respectively. Compounds **3**, **6, 7** and **18** showed activity against CNS cancer SNB 75 with GI values of 21.3%, 21.2%, 21.2% and 19.5%, respectively. The percentages of growth inhibitions over the most sensitive 9-cell lines are shown in Figure 2.

Compound **20** demonstrated certain activity toward numerous cell lines that belong to different tumor subpanels such as UACC-62, SK-OV-3 and MDA-MB-231/ATCC with GI values 18%, 29.2% and 23.7%, respectively. Meanwhile, compound **9** and **18** showed a moderate activity against leukemia CCRF-CEM, HL-60TB, K-562, MOLTT-4, RPMI-8226, RPMI-8226 with GI values in percentages of (12.2, 31.1), (19.2, 32.7), (12.8, 37.6), (25.6, 46.3), (8.0, 21.4) and (21.0, 35.3), respectively.

In addition, compound **7** revealed effectiveness toward numerous cell lines that belong to different tumor subpanels such as CCRF-CEM, MALME-3M, SK-MEL-5 and UACC-62 cancer with GI values of 47.3%, 56.5%, 99.1% and 57.8%, respectively. Concurrently,

Table 1
Percentage growth inhibition (GI%) of in vitro subpanel tumor cell lines at 10 μM concentration

Subpanel tumor cell lines	% Growth inhibition (GI%)[a]								
Compound	**3**	**5**	**6**	**7**	**9**	**10**	**18**	**19**	**20**
Leukemia									
CCRF-CEM	2.2	9.5	—	47.3	12.2	13.0	31.1	13.2	11.3
HL-60(TB)	—	—	6.0	35.5	19.2	4.0	32.7	7.0	6.0
K-562	6.2	—	9.0	44.2	12.8	10.0	37.6	10.0	8.4
MOLT-4	—	—	8.2	29.3	25.6	12.2	46.3	28.9	39.1
RPMI-8226	6.5	4.0	2.0	55.4	8.0	12.0	21.4	10.0	9.2
SR	24.1	—	3.5	26.3	21.0	—	35.3	4.0	—
Non-small cell lung cancer									
A549/ATCC	3.0	—	11.0	27.8	—	5.0	8.1	2.0	12.0
EKVX	11.6	15.2	11.1	48.5	11.0	14.3	12.8	—	4.0
HOP-62	—	5.5	5.0	3.0	—	—	—	—	—
NCI-H226	—	—	—	12.0	—	2.5	14.3	—	—
NCI-H23	—	—	—	35.7	—	5.2	4.4	—	—
NCI-H322M	—	11.1	—	6.0	—	—	—	—	—
NCI-H460	—	—	—	27.5	—	—	—	—	—
NCI-H522	—	4.0	—	nt	—	2.2	18.0	18.0	—
Colon cancer									
COLO 205	—	—	—	—	—	—	—	—	—
HCC-2998	—	16.6	—	19.1	—	4.0	—	—	—
HCT-116	—	—	3.2	25.2	—	4.0	16.0	—	—
HCT-15	6.4	2.5	3.7	36.3	—	—	13.3	5.0	—
HT29	7.8	—	—	38.1	11.0	3.0	—	3.0	—
KM12	12.0	8.3	26.6	24.4	—	—	15.5	4.0	—
SW-620	2.0	—	—	14.0	—	—	—	—	—
CNS cancer									
SF-268	—	10.6	—	32.3	—	—	14.2	—	—
SF-295	—	16.6	29.0	40.3	6.0	9.0	—	7.0	—
SF-539	17.2	2.0	10.0	31.8	—	4.0	—	—	5.0
SNB-19	5.7	2.0	14.0	24.2	—	4.0	9.7	—	—
SNB-75	21.3	15.5	21.2	21.2	—	14.8	19.5	8.5	7.6
U251	4.5	6.0	9.0	32.4	12.0	4.0	13.0	11.0	—
Melanoma									
LOX IMVI	—	—	—	31.6	4.2	—	—	5.0	—
MALME-3M	5.4	17.0	6.0	56.5	—	—	—	—	—
M14	—	4.0	12	32.3	—	—	—	—	—
MDA-MB-435	41.6	9.8	16.3	56.4	6.0	—	9.7	9.7	7.7
SK-MEL-28	1.72	—	—	20.4	—	2.4	5.0	11.0	—
SK-MEL-5	2.4	—	17.0	99.1	—	—	—	—	4.0
UACC-257	7.0	—	—	40.3	—	—	—	9.0	
UACC-62	15.8	9.0	23.0	57.8	8.0	9.0	—	14.0	18.0
Ovarian cancer									
IGROV1	—	—	—	21.4	—	—	—	—	—
OVCAR-3	3.8	—	—	41.1	—	—	—	—	5.2
OVCAR-4	—	—	17.3	69.9	—	—	3.0	—	5.0
OVCAR-5	3.2	10.0	12.0	24.1	—	—	—	—	—
OVCAR-8	—	—	−5.0	16.0	—	5.4	5.0	—	—
NCI/ADR-RES	—	—	—	17.6	—	—	—	—	—
SK-OV-3	—	5.0	—	16.8	—	—	—	3.0	29.2
Renal cancer									
786-0	—	—	—	32.4	—	—	3.0	—	—
A498	4.0	20.0	23.0	39.4	9.0	8.0	—	—	—
ACHN	4.0	—	24.0	52.0	—	—	—	3.0	3.5
CAKI-1	5.3	5.0	4.0	41.2	—	4.0	15.6	—	3.0
RXF 393	—	—	—	23.2	—	—	—	—	3.0
SN12C	—	—	15.0	32.4	—	—	3.0	—	5.0
TK-10	—	10.0	24.0	nt	—	—	—	—	—
UO-31	24.1	22.0	2.5	22.2	—	13.6	22.0	11.7	15.0
Prostate cancer									
PC-3	11.2	9.5	8.0	39.8	—	8.0	26.9	12.2	8.0
DU-145	—	—	—	12.4	—	—	—	—	—
Breast cancer									
MCF7	5.0	—	7.0	42.2	—	—	21.8	9.0	5.2
MDA-MB-231/ATCC	—	—	—	42.7	—	—	17.3	8.0	23.7
HS 578T	—	—	—	17.9	—	3.2	6.0	—	—
BT-549	3.5	8.0	18.0	nt	8.0	—	—	—	—
T-47D	—	11.0	28.0	71.0	7.8	—	25.8	—	4.0
MDA-MB-468	—	—	2.0	nt	—	—	25.8	2.5	—

nt = not tested; a = the showed growth inhibition percentages are measured at a single concentration of 10 μM % inhibition is calculated by simple abstraction of the % activity from 100.

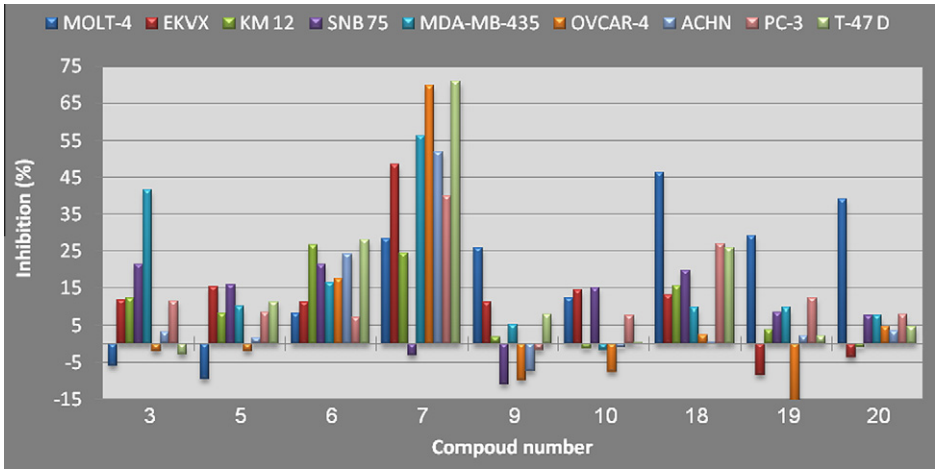


Figure 2. The percentages of growth inhibition of the nine selected compounds over the most sensitive tumor cell lines.

Table 2
Preliminary anticonvulsant activity of the new synthesized compounds (1.0 mmol/kg), valproate (1.5 mmol/kg) and methaqualone (1.4 mmol/kg)

Compound no.	PTZ (% of protection)	Strychnine (% of protection)	Picrotoxin (% of protection)	MES (% of protection)
Valproate	100	100	100	100
Methaqualone	100	0.0	50	100
3	100	0.0	100	100
6	33	0.0	0.0	33
7	0.0	0.0	0.0	50
11	66	0.0	0.0	0.0
14	0.0	0.0	0.0	50
15	100	0.0	75	100
16	100	0.0	50	100
17	0.0	0.0	0.0	50
18	100	0.0	50	100
19	100	0.0	75	100
20	100	0.0	75	100
25	0.0	0.0	0.0	33
26	0.0	0.0	0.0	100
27	33	0.0	0.0	50

PTZ = pentylenetetrazol, MES = maximal electroshock test.

Table 3
Comparison of the anticonvulsant activity (ED_{50}), acute neurotoxic effects (TD_{50}), median lethal dose (LD_{50}), therapeutic and protective indexes of the most promising anticonvulsant new synthesized compounds, valproate and methaqualone in mice

Compound no.	ED_{50} (mmol/kg)	TD_{50} (mmol/kg)	LD_{50} (mmol/kg)	Therapeutic index	Protective index
Valproate	1.50	2.70	3.00	2.00	1.80
Methaqualone	1.40	1.60	2.00	1.40	1.14
3	0.74	1.78	1.93	2.60	2.40
15	0.31	0.93	1.71	5.50	3.00
16	0.35	0.89	1.81	4.6	2.54
18	0.70	0.75	1.50	2.13	1.06
19	0.40	0.56	1.02	2.55	1.40
20	0.41	0.60	1.04	2.53	1.50

ED_{50} = median effective dose providing anticonvulsant protection in 50% of mice against pentylenetetrazole (PTZ) induced seizures.
TD_{50} = median toxic dose producing minimal neurological toxicity in 50% of mice subjected to the Chimney test.
LD_{50} = median lethal dose that causes 50% mortality in mice.
Therapeutic index = LD_{50}/ED_{50}.
Protective index = TD_{50}/ED_{50}.

compound **7** proved to inactive against different tumor subpanels such as HOP-92, NCI-H322M, SNB-75 and COLO 205.

With regard to antitumor activity; close examination of the data presented in Table 1 revealed that compound **7** is the most active member of this study, showing effectiveness toward numerous cell lines that belong to different tumor subpanels, while compounds **9** and **18** possess selective activity toward leukemia cell lines.

The anticonvulsant activity and the acute neurotoxicity of the new synthesized compounds were evaluated by the use of standard techniques.[31,32] The preliminary screening was performed at 1.0 mmol/kg of all synthesized compounds (**3–27**) by using of pentylenetetrazole (PTZ), picrotoxin, and strychnine induced seizure and maximal electroshock seizure (MES) model of seizures. The MES test is associated with the electrical induction of the seizure, whereas PTZ, picrotoxin and strychnine methods involve a chemical induction to generate the convulsion.[32] The initial anticonvulsant evaluation showed that some of these compounds are inactive; however, compounds **3**, **6**, **11**, **15**, **16**, **18**, **19**, **20**,

and **27** were active against PTZ at 1.0 mmol/kg, among which compounds **3**, **15, 16**, **18**, **19** and **20** were presented 100% protection, compounds **11** was offered 66% protection, while compounds **6** and **27** proved 33% protection.

Compounds **3**, **6, 7, 14, 15**, **16**, **17, 18**, **19**, **20**, **25**, **26** and **27** exhibited anticonvulsant activity against MES-induced seizure at the dose of 1.0 mmol/kg. The most active of these compounds were **3**, **15**, **16**, **18**, **19**, **20** and **26** which showed 100% protection. The compounds **7**, **14, 17,** and **27** accessible anti-MES effect by 50%, while compound **6** and **25** revealed 33% protection.

The anticonvulsant activity against picrotoxin-induced seizure at the dose of 1.0 mmol/kg, the most active of these compounds was **3** which presented 100% protection, compounds **15**, **19** and **20** gave protection by 75%, while compound **16**, **18** exhibited 50% protection. Nevertheless, none of all synthesized compounds exhibited any potency towards anti-strychnine activity at the same dose levels (Table 2).

As a result of preliminary screening, the most active compounds **3**, **15, 16**, **18, 19** and **20** were subjected to further investigations at different doses for quantification of their anticonvulsant activity (indicated by ED_{50}) and neurotoxicity (indicated by TD_{50}) in mice (Table 3). The selected compounds **3**, **15, 16**, **18, 19** and **20** were displayed anticonvulsant activity against PTZ-induced seizure with ED_{50} values of 0.74, 0.31, 0.35, 0.70, 0.40 and 0.41 mmol/kg, respectively. Methaqualone and valproate were used as reference drugs and these compounds produced ED_{50} values of 1.40 and 1.5 mmol/kg, respectively. Interestingly, the ED_{50} values of the selected compounds were found to be smaller compared to the reference anticonvulsant drugs at the same molar doses (Table 3).

The protective index (TD_{50}/ED_{50}) is considered to be an index representing the margin of safety and tolerability between anticonvulsant doses and doses of anticonvulsant drugs exerting acute adverse effects (e.g., sedation, motor coordination impairment, ataxia or other neurotoxic manifestations).[33] Evaluation of the acute adverse effect profile (TD_{50}) of compounds **3, 15**, **16**, **18**, **19** and **20** revealed that these agents exerted low neurological deficit (Table 3). Almost the protective index values of the selected compounds (2.40, 3.00, 2.54, 1.06, 1.40 and 1.50) were higher than or equal to the reference drugs as compared to 1.14 for methaqualone and 1.80 for valproate. It is obvious that the protective index values for these selected compounds revealed a difference between the doses producing neurotoxic action (TD_{50}) and those exerting anti-PTZ (ED_{50}) actions in mice. The present results are in agreement with the results of the anticonvulsant study of 2-substituted 3-aryl-4(3*H*)-quinazolinones in mice[34] by Wolfe et al., Wolfe et al. reported that the series of 4(3*H*)-quinazolinones which possessing 3-*o*-tolyl and 3-*o*-chlorophenyl groups showed good protection against MES and PTZ induced seizures, combined with relatively low neurotoxicity after ip administration 4(3*H*)-quinazolinones in mice.

Compounds **3**, **15**, **16**, **18**, **19** and **20** revealed LD_{50} values of 1.93, 1.71, 1.81, 1.50, 1.02 and 1.04 with therapeutic index (LD_{50}/ED_{50}) values 2.60, 5.50, 4.60, 2.13, 2.55 and 2.53. It is worthwhile to note that the therapeutic index of the selected compounds was found to be higher as compared to the reference anticonvulsant drugs at the same molar doses (Table 3).

The results of the seizure induction screening methods in the current study showed that some new quinazolines were effective in controlling the seizures induced by PTZ, picrotoxin and MES but failed to control those induced by strychnine, this effect is similar to that of 4(3*H*)-quinazolinones, which have anticonvulsant effects on seizures induced by PTZ, picrotoxin and MES but are ineffective against strychnine-induced seizures in mice.[34]

It has been reported that the convulsants induce seizures by inhibiting γ-aminobutyric acid (GABA) neurotransmission (such as PTZ), $GABA_A$-antagonist GABAA receptor agonist by increasing chloride influx via brain chloride channel (such as picrotoxin) or directly antagonizes the inhibitory spinal reflexes of glycine (such as strychnine).[35–37] Generally, in the MES test, one can determine the anti-seizure effects of agents or drugs that suppress tonic–clonic seizures by suggesting that those compounds possess the ability to prevent the spread of seizure discharge throughout neuronal tissues and to raise seizure threshold.[33]

On account of their partial effectiveness, it is difficult to report that our synthesized compounds as having anticonvulsant effects via influencing glycine neurotransmission. However, most of our new compounds can control the seizures induced by PTZ, MES and picrotoxin, this might suggest that these compounds exhibit a broad spectrum of anticonvulsant activity in animal models of partial and generalized epilepsy via GABA activation. In addition, more detailed study on the GABA pathways and the neurotransmitter levels might be interesting and might provide more insights for the anticonvulsant effects of these new 4(3*H*)-quinazolines against convalsants induced seizures, which will be considered extensively in our future study. However, at present some of the new synthesized compounds have relatively potent anticonvulsant effects combined with relatively low neurotoxicity.

Structure activity correlation, based on the number of cell lines proved sensitive toward each of the synthesized individual compounds, revealed that, the presence of electron withdrawing group at aromatic ring of 7-phenylcarbonylamino-4(3*H*)-quinazolinone enhance the antitumor activity as compared with unsubstituted phenyl or heterocyclic ring, for examples 7-[4-chlorophenylcarbonylamino]-4(3*H*)-quinazolinone **7** is extra forceful than 7-[phenylcarbonylamino]-4(3*H*)-quinazolinone **6** or 7-[thiophen-2-carbonylamino]-4(3*H*)-quinazolinone **9**. The presence of electron withdrawing group at aromatic ring of 2-(2-flourophenyl)]-thiazolidin-4-one reduce the antitumor activity match up to unsubstituted phenyl ring, such as compound **18** more active than **19.**

The anticonvulsant activity correlation of the newly synthesized compounds revealed that compounds having hydrazones or 2-phenylthiazolidin-4-ones fragments at position 7 possess significant anticonvulsant activity such as compounds **14–20**. Compounds containing hydrazones moieties such as **14**–**17** were potent as compared to the parent amine **2**. It is clear that the presence of electron withdrawing group at aromatic ring of Schiff's base enhance the activity compared with unsubstituted phenyl ring, or heterocyclic ring, for examples compound **15** and **16** are more active than compounds **14** and **17.**

Attractively, cyclization of Schiff's base **14–16** into phenylthiazolidin-4-one **18**–**20** improves the anticonvulsant activity. On the other hand, replacement of hydrazones or phenylthiazolidin-4-one moieties into carbonylamino or sulfonylamino fragment in position 7 dramatically reduces the anticonvulsant activity. Meanwhile, the presence of electron withdrawing group at aromatic ring slightly enhance the activity compared with unsubstituted or electron donating group in phenyl ring, for examples compound **8** more active than **6** as well as compound **11** more active than **10**, **12** and **13**. Furthermore, the presence of cyclic amide at position 7 eliminates the activity, for instance compounds **21**–**25**.

More interestingly, the presence of ethoxycarbonylamino fragment absolutely increases the anticonvulsant activity like compound **3**. The obtained new findings point to the hydrazones, 2-phenylthiazolidin-4-ones or ethoxycarbonylamino moieties at position 7 are important for the anticonvulsant activity, so further investigations of structural features are required for anticonvulsant activity and probably the pharmacokinetic profile of these compounds.3.

In conclusion, new derivative of 7-substituted-4(3*H*)-quinazolinones were synthesized and evaluated for their antitumor and anticonvulsant activity. The results of this study demonstrated that compound **7**, is broad-spectrum antitumor showing effectiveness

toward numerous cell lines that belong to different tumor subpanels, whereas compounds **9** and **18** possess selective activity toward leukemia cell lines.

Additionally, compounds **3**, **15**, **16**, **18**, **19** and **20** showed advanced anticonvulsant activity as well as lower toxicity than methaqualone and valproate reference drugs. The obtained results showed that certain compounds could be useful as a template for future design, modification and investigation to produce more active analogues.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.071.

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