FULL PAPER

Synthesis, Anticancer, and QSAR Studies of 2-Alkyl(aryl,hetaryl)quinazolin-4(3*H*)-thione's and [1,2,4]Triazolo[1,5-*c*]quinazoline-2-thione's Thioderivatives

by **Oleksii M. Antypenko**[a]), **Sergiy I. Kovalenko**[a]), **Oleksandr V. Karpenko**[b]), **Vladyslav O. Nikitin**[b]), and **Lyudmyla M. Antypenko***[a])

[a]) Organic and Bioorganic Chemistry Department, Zaporizhzhya State Medical University, 26, Mayakovsky Ave., Zaporizhzhya, 69035, Ukraine (phone: +380669658740; e-mail: antypenkol@gmail.com)
[b]) Enamine Ltd., 78, Chervonotkats'ka str., Kyiv, 02094, Ukraine

Considering the frightening high level of mortality from cancer, studies of anticancer agents are vital nowadays. The 24 thioderivatives of 2-alkyl(aryl)-quinazolin-4(3*H*)-thiones and 20 thioderivatives of [1,2,4]triazolo[1,5-*c*]quinazoline-2-thiones were synthesized and evaluated for preliminary *in vitro* anticancer activity with subsequent *in silico* QSAR analysis. The substance **18** had the best results inhibiting growth of eight cancer cell lines: CCRF-CEM of leukemia; SF-539, SNB-75, and U251 of CNS cancer; 786, RXF393, and UO-31 of renal cancer; and MDA-MB-231/ATCC of breast cancer (–31.50 – 47.41% of cell growth) with low procancer effect. Calculated QSAR-models for CCRF-CEM of leukemia, T-47D and HS 578T of breast cancer, and mean cell growth demonstrated good rate of anticancer activity prediction ($r^2 = 0.7 – 0.8$, $Q^2_{\mathrm{LOO}} = 0.5 – 0.7$).

Keywords: 2-Alkyl(aryl)-quinazolin-4(3*H*)-thiones, Anticancer, [1,2,4]triazolo[1,5-*c*]quinazoline-2-thiones, QSAR analysis, Structure–activity relationship.

Introduction

Lately, *Malvezzi et al.* [1] calculated that 1 359 100 Europeans were predicted to die of cancer in 2015, consisting of 766 200 men and 592 900 women, which projected the 7.5% decrease in rates for men and a 6% for women, compared with data in 2009. Considering these terrifying data, new anticancer agent search is of undoubtedly obligatoriness not only in Europe, but also all over the world.

The 4-anilinoquinazoline moiety is a known pharmacophore, which exhibits potent EGFR tyrosine kinase inhibitory activity of afatinib [2], erlotinib [3], and saracatinib [4] (*Fig. 1*). Moreover, *N*-{4-[(3-chlorophenyl)amino] quinazolin-6-yl}picolinamide showed anticancer properties at 2.9 μM against human c-Src kinases when compared with saracatinib [5]. Benzylideneamino **A** and 3-phenylthioureido **B** derivatives of 4-(3-*R*-3,4-dihydro-4-oxoquinazolin-2-ylamino)-*N*-(pyridin-2-yl)benzenesulfonamide had GI_{50} of 22.11 and 19.70 μM against human liver cell line HEPG2, respectively [6]. Moreover, 2-(3-benzyl-3,4-dihydro-6-iodo-4-oxoquinazolin-2-ylsulfanyl)acetohydrazide substituted with *N*-propanethione (**C**), *N*-benzyloxo (**D**), and cyclic piperazine-3,6-dione (**E**) fragment showed mean graph midpoint GI_{50} values of 12.8, 11.3, and 13.8 μM of nine subpanel anticancer cell lines (*Fig. 1*) [7]. Besides, *N*-(4-methoxyphenyl)-2-({4-[4-(*m*-tolyloxy) quinazolin-2-yl]phenyl}amino)acetamide (**F**) had GI_{50} of 45.6 μg/ml against prostate cancer PC3 cell line, as well as derivatives with electron-withdrawing groups – 4-NO_2 (**G**) and 4-Cl (**H**) displayed 55.6 μg/ml (*Fig. 1*) [8].

Furthermore, quinazoline condensed derivatives have also shown *in vitro* anticancer activity: 2-(methylsulfonyl)-4-(4-nitrobenzyl)-[1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one (**I**) had IC_{50} 1.29 μg/ml and 5-chloro-2-(methylsulfanyl)-[1,2,4]triazolo[1,5-*a*]quinazoline (**J**) had 2.93 μg/ml against medulloblastoma (Daoy) [9]. The latter one also had IC_{50} 3.88 μg/ml against melanoma (SK-MEL283) and 4.52 μg/ml against hepatocellular carcinoma (HepG2), and 2-(methylsulfanyl)-[1,2,4]triazolo[1,5-*a*]quinazoline-5(4*H*)-thione (**K**) had 5.53 μg/ml against medulloblastoma (Daoy), exceeding dasatinib (*Fig. 1*).

Considering patented anticancer activity mechanisms of quinazolines, they can be divided into seven major groups: p53 regulators, serine-threonine and tyrosine kinases, dual TK-histone deacetylases, and dehydrofolate reductase inhibitors, radioligands for imaging, and other target compounds [10]. For example, afatinib is a tyrosine kinase inhibitor (TKI) that also irreversibly inhibits epidermal (EGFR) and human epidermal growth factor receptors (HER2 and HER4) [2]. Another interesting anticancer target for analysis is Ser/Thr protein kinase CK2 (casein kinase II), a constitutively active serine/threonine kinase, that is involved in a variety of roles

DOI: 10.1002/hlca.201600062

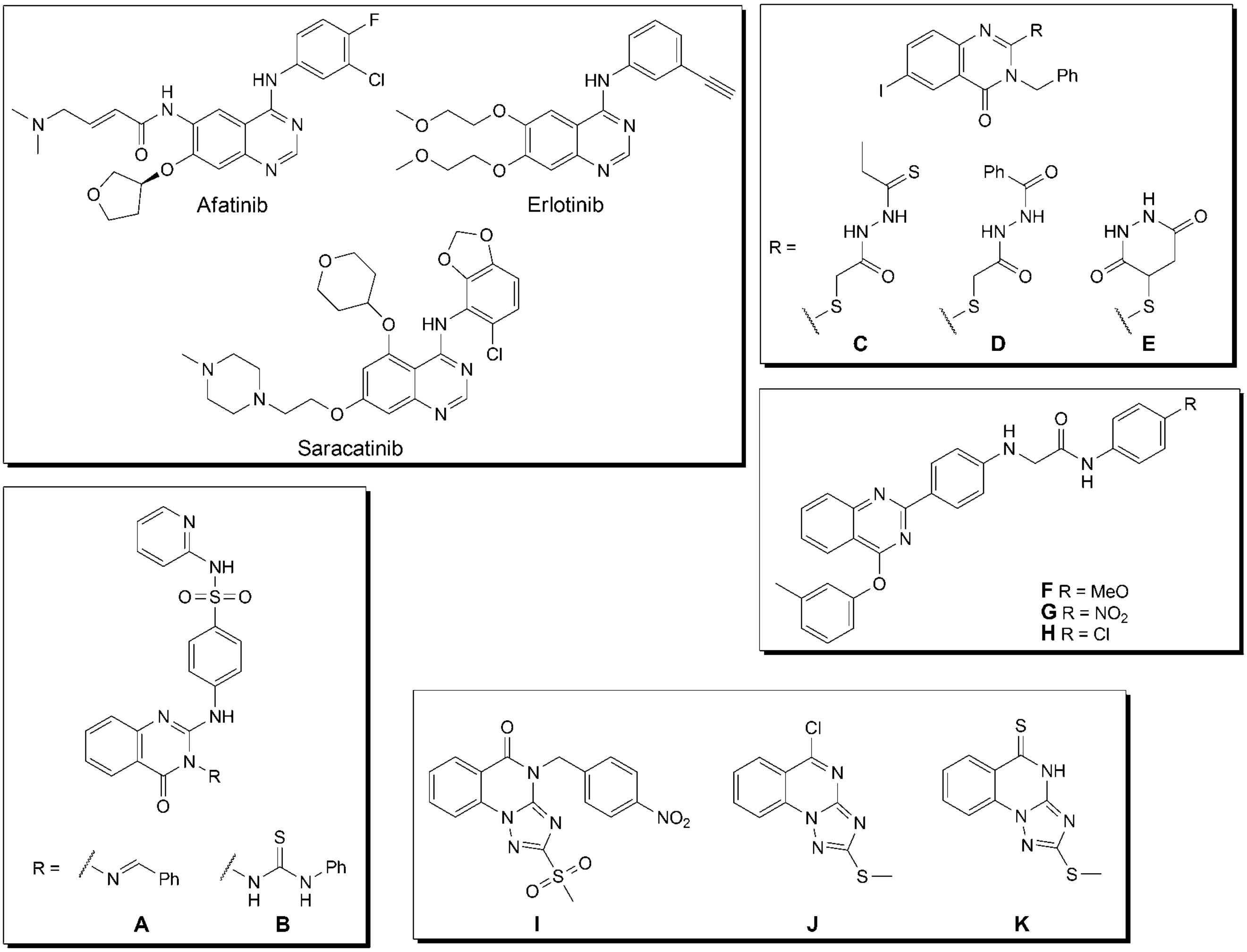


Fig. 1. Derivatives of quinazoline with anticancer properties.

essential for cellular homeostasis. It controls multiple processes that play important roles in the sensitivity of cancer to EGFR targeting medicines, including PI3K-Akt-mTOR signaling, Hsp90 activity, and inhibition of apoptosis [11].

Moreover, already reported 2-([1,2,4]triazolo[1,5-*c*]quinazolin-2-ylsulfanyl)-*N*-*m*-tolylacetamide was already proven as protein kinase CK2 inhibitor with 82% of remaining activity in the 33.3 μM concentration as well other derivative – ethyl 4-(2-([1,2,4]triazolo[1,5-*c*]quinazolin-2-yl-sulfanyl)acetamido)benzoate (76%) [12].

Therefore, the search of novel anticancer agents among thioderivatives of 2-alkyl(aryl)-quinazolin-4(3*H*)-thiones and [1,2,4]triazolo[1,5-*c*]quinazoline-2-thione with subsequent *in silico* QSAR analysis definitely seems to be promising.

Results and Discussion

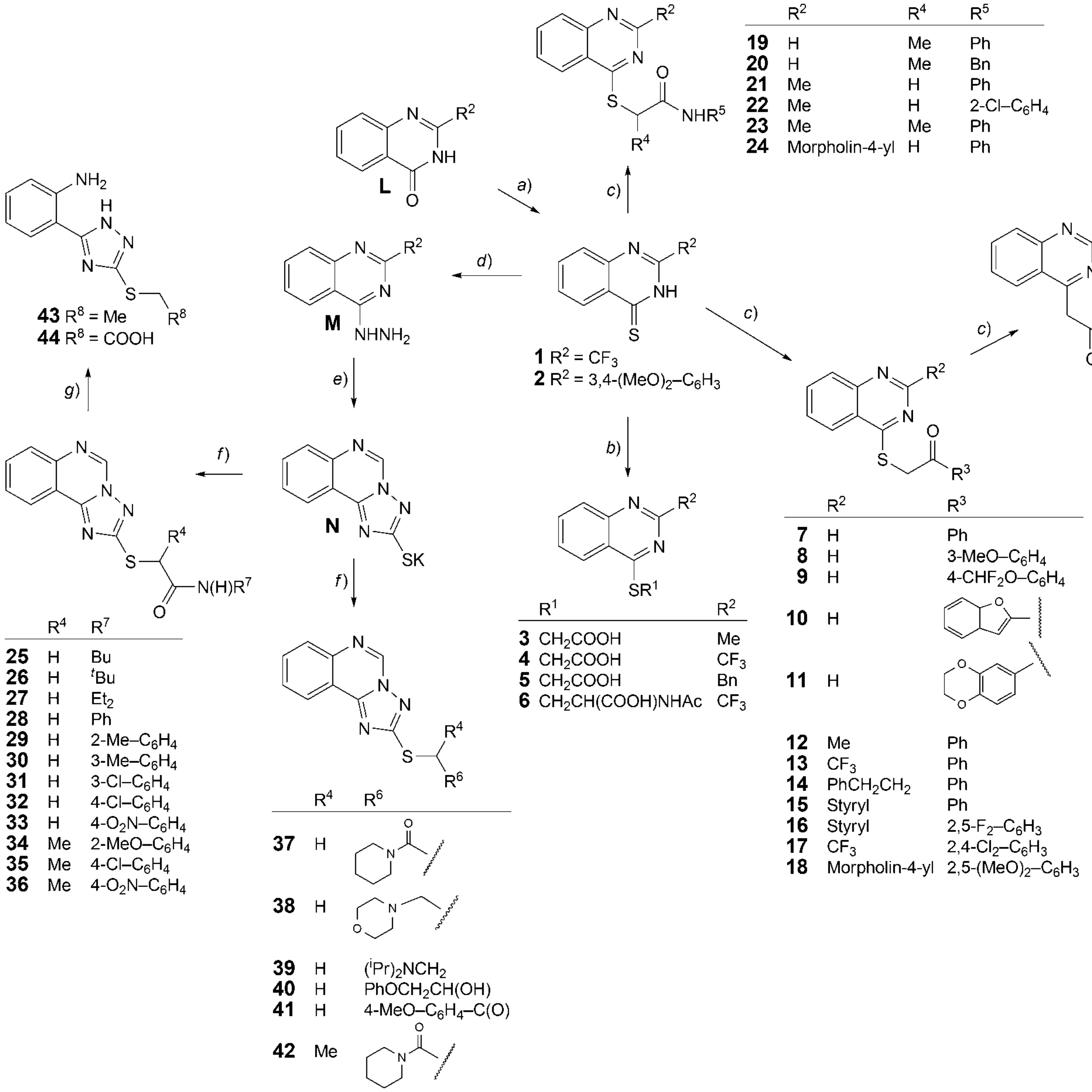
Among the main aims of this article was SAR analysis of anticancer activity of the quinazolin-4(3*H*)-thione's and [1,2,4]triazolo[1,5-*c*]quinazoline-2-thione's *S*-derivatives (**1** – **44**). Thus, summary of the already reported and several novel substances' synthetic routs were selected and presented in this article below (*Scheme*) [13 – 17].

The structures of all synthesized compounds were accurately evaluated by elemental analysis and their spectral data (IR, LC/MS, ^{1}H-NMR spectra).

Substances **1** and **2** were obtained by treatment of the quinazoline-4(3*H*)-one (**L**) with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphatane-2,4-disulfide (*Lawesson*'s reagent) or P_2S_5 in dioxane (*Scheme*) [13]. The corresponding substituted **3** – **24** were obtained by alkylation of **1** by proper halogen derivatives in MeOH with an equivalent amount of MeOK [13][14].

For 2-*R*-4(3*H*)quinazoline-4-thiones **1** and **2** alkylation, there were found some peculiarities, when refluxed with phenacylhalides in MeOH with MeONa for 5 – 10 min for Br derivatives and 10 – 25 min for Cl derivatives [14] (*Scheme*), namely, in some cases, 'sulfide compression', described by *Eschenmoser* [18], has occurred due to intermolecular attack of enol electron-deficient thioamide C-atoms, which initially lead to the formation of the corresponding thiirane, and then, after

Scheme. Synthetic routes of investigated derivatives.



	R^2	R^4	R^5
19	H	Me	Ph
20	H	Me	Bn
21	Me	H	Ph
22	Me	H	2-Cl–C_6H_4
23	Me	Me	Ph
24	Morpholin-4-yl	H	Ph

	R^1	R^2
3	CH_2COOH	Me
4	CH_2COOH	CF_3
5	CH_2COOH	Bn
6	$CH_2CH(COOH)NHAc$	CF_3

	R^2	R^3
7	H	Ph
8	H	3-MeO–C_6H_4
9	H	4-CHF_2O–C_6H_4
10	H	
11	H	
12	Me	Ph
13	CF_3	Ph
14	$PhCH_2CH_2$	Ph
15	Styryl	Ph
16	Styryl	2,5-F_2–C_6H_3
17	CF_3	2,4-Cl_2–C_6H_3
18	Morpholin-4-yl	2,5-$(MeO)_2$–C_6H_3

	R^4	R^7
25	H	Bu
26	H	^{t}Bu
27	H	Et_2
28	H	Ph
29	H	2-Me–C_6H_4
30	H	3-Me–C_6H_4
31	H	3-Cl–C_6H_4
32	H	4-Cl–C_6H_4
33	H	4-O_2N–C_6H_4
34	Me	2-MeO–C_6H_4
35	Me	4-Cl–C_6H_4
36	Me	4-O_2N–C_6H_4

	R^4	R^6
37	H	
38	H	
39	H	$(^iPr)_2NCH_2$
40	H	$PhOCH_2CH(OH)$
41	H	4-MeO–C_6H_4–C(O)
42	Me	

a) 2,4-Bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide or P_2S_5, dioxane, reflux, 2 h. *b*) $ClCH_2COOH$, MeOK, MeOH, reflux, 1 – 5 h; or proper halogen derivative, MeOK, MeOH, reflux, 2 h. *c*) Proper halogen derivative, MeOK, MeOH, r.t., 5 – 25 min. *d*) $NH_2NH_2 \cdot H_2O$, dioxane, reflux, 2 h. *e*) Potassium ethyl xanthogenate, ^{i}PrOH, reflux, 3 h. *f*) Proper halogen derivative, ^{i}PrOH, H_2O, reflux, 2 h; KOH, EtOH, amine · HCl, reflux, 3 h. *g*) conc. $HCl/H_2O/MeOH$ 1:5:5, reflux, 1 h.

the sulfur elimination, formed the ylidene ethanoles, whose structure were proved by NMR data [14]. For instance, comparing ^{1}H-NMR spectra of substance **10** and proper 1-(1-benzofuran-2-yl)-2-(quinazolin-4-yl)ethanone (**10a**), the two-H-atom *singlet* of the last CH_2 group was absent at 5.01 ppm and a one-H-atom *singlet* appeared at 6.99 ppm. Also, the significant increase in electron density of pyrimidine ring was noticed when the H-atom *singlet* in the second position of quinazoline was shifted at 1 ppm toward the strong field compared with S-containing derivatives.

Cyclization of 4-hydrazino-3*H*-quinazoline (**M**) with potassium ethyl xanthogenate in ^{i}PrOH lead to the formation of potassium [1,2,4]triazolo[1,5-*c*]quinazolin-2-ylthiolate (**N**), which consequently was alkylated with proper halogen derivatives to get **25** – **42** [15][16]. Alternatively, amides were formed by activation of the corresponding carboxylic acids with carbonyldiimidazole with further aminolysis.

The nucleophilic degradation of the pyrimidine ring of the proper compounds **25** – **36** by reflux with soln. of HCl resulted in 2-(3-(*R*-sulfanyl)-1*H*-1,2,4-triazol-5-yl)anilines **43** and **44** [17].

Biological Activity

Anticancer Preliminary in vitro *Testing.* All 44 compounds were selected by NCI Developmental Therapeutic Program according to their own internal demands to be studied *in vitro* for anticancer activity [19]. The human tumor cell lines were derived from nine different cancer types: leukemia, melanoma, lung, colon, CNS, ovarian, renal, prostate, and breast cancers. A single high dose was used (1.0 μM) in the full 60-cell panel. Results for each test agent were reported as the percent growth of the treated cells when compared with the untreated control cells (*Supplementary Information*). The activity of the compounds was measured according to a value of 100, which meant no cell growth (CG) inhibition. A value of 30 would mean 70% growth inhibition. A value of 0 meant no net growth over the course of the experiment. A value of −30 would mean 70% lethality. A value of −100 meant all cells were dead.

In the result, there were found 16 compounds possessing anticancer activity: **2** – **4**, **8** – **13**, **16**, **18**, **19**, **27**, **29**, **32**, and **37** (*Tables 1* and *2*), with subsequent structure–activity relationship analysis.

Thus, anticancer data of the 3-[(2-methylquinazolin-4-yl)sulfanyl]acetic acid (**3**) and 2-{[2-(trifluoromethyl)-quinazolin-4-yl]sulfanyl}acetic acid (**4**) showed that the presence of 2-CF_3 in the latter instead of 2-Me was vital to be selective against cell line UO-31 (17.01% of CG) of renal cancer for **4** or against HOP-62 of nonsmall cell lung cancer (16.71%) for **3**.

The presence of the MeO group in the Ph fragment was essential to enhance the inhibition of cancer cell lines proliferation by phenacyls **7** – **18**: 1-(3-methoxyphenyl)-2-(quinazolin-4-ylsulfanyl)ethanone (**8**) had lethal effect against HOP-62 of nonsmall cell lung cancer (−17.12%) and 786-0 of renal cancer (−52.80%, which was the best result among all compounds and cell lines), and 1-(2,5-dimethoxyphenyl)-2-(2-morpholinoquinazolin-4-ylsulfanyl)ethanone (**18**) – against SNB-75 of CNS cancer (−15.58%) and CCRF-CEM of leukemia (−31.50%). Also, 2-(3,4-dimethoxyphenyl)quinazoline-4(3*H*)-thione **2** had strong selective influence at the last mentioned cell line of leukemia (18.75%). It is notable that 2-(2-(morpholinomethyl)quinazolin-4-ylsulfanyl)-*N*-phenylacetamide (**24**) practically had no anticancer effect, which additionally proved obligatoriness of 2,5-dimethoxyphenyl radical presence into the structure to induct activity.

The colon, melanoma, and prostate cancers were practically insensitive to the synthesized substances. Only 1-(2,5-difluorophenyl)-2-(2-styrylquinazolin-4-ylsulfanyl)ethanone (**16**) inhibited growth of MDA-MB-435 of melanoma and HCT-116 of colon cancer, with 2,3-dihydrobenzo[*b*][1,4]-dioxin-6-yl derivative **11**, that also acted against the last cancer cell line.

Table 1. Cancer cells growth percentage [%] after addition of the most active compounds[a])

Type[b])	Cell line	Compound[c]) **3**	**8**	**11**	**12**	**13**	**16**	**18**	**27**	**32**
CNS	U251	–	–	–	–	–	–	42.07	–	–
	SNB–75	–	–	–	–	–	–	−15.58	–	–
	SF-295	–	–	44.78	–	–	–		–	–
	SF-539	–	–	–	–	–	–	16.34	–	–
NSCL	HOP-62	16.71	−17.12	39.65	–	–	39.92	–	23.47	3.37
R	786-0	–	−52.8	47.98	–	–	–	23.41	–	−42.37
	A498	–	–	–	–	–	–	–	–	–
	RXF 393	–	–	–	–	–	–	44.03	–	–
	UO-31	–	–	–	–		–	47.41	–	–
B	MDA-MB-468	–	–	–	–	18.03	–	–	–	–
	T-47D	–	–	–	–		–	–	–	–
	MCF7	–	–	–	–	41.38	–	–	–	–
	MDA-MB-231/ATCC	–	–	–	–	–	–	42.54	–	–
L	SR	40.46	–	–	25.84	43.93		–	32.79	
	HL-60(TB)	–	–	47.89	–	–	–	–	–	–
	RPMI-8226	–	–	49.69	23.47	–	–	–	–	–
	CCRF-CEM	–	–	51.55	–	–	–	−31.50	–	–
O	IGROV1	–	–	–	32.95	43.18	–	–	–	–
	NCI/ADR-RES	–	–	22.28	–	–	–	–	–	–
M	MDA-MB-435	–	–	–	–	–	33.12	–	–	–
Col	HCT-16	–	–	46.20	–	–	35.06	–	–	–

[a]) The results are given for the most active compounds inhibiting the growth in more than 52%. [b]) CNS, central nervous system cancer; R, renal cancer; NSCL, nonsmall cell lung cancer; Col, colon cancer; B, breast cancer; L, leukemia; O, ovarian cancer; M, melanoma. [c]) All other data are presented in the *Supplementary Material*. Compounds with strong inhibition against only one line were **2** – 18.75% (CCRF-CEM of L), **4** – 17.01% (OU-31 of R), **9** – 26.91% (SR of L), **10** – 49.25% (T-47D of B), **19** – 46.04% (MDA-MB-468 of B), **29** – 36.43% (A-498 of R) and **37** – 42.82% (RPMI-8226 of L).

Table 2. The best QSAR models' statistical characteristics

No.	Cell line[a])	L, CCRF-CEM	BC, T-47D	BC, HS 578T	Mean CG
Tr.	n[b])	34	35	30	36
	r^2	0.802	0.787	0.701	0.817
	RMSE	12.3146	7.325	9.886	3.290
	s	13.333	8.047	10.794	3.604
	F	29.311	21.475	15.270	26.853
	Q^2_{LOO}	0.698	0.701	0.517	0.764
Pr.	n	9	9	8	8
	r^2	0.699	0.7026	0.519	0.767
	RMSE	20.802	17.865	23.586	11.936

[a]) L, leukemia; BC, breast cancer. [b]) n, number of investigated compounds in set; RMSE, root mean square error; s, standard error; F, variance ratio, *Fisher* coefficient; Q^2_{LOO}, weighted correlation coefficient by leave-one out method.

Condensation with triazole ring greatly weakened substances anticancer potential. Among alkylamides **25** – **27**, branching from Bu in **25** to ^{t}Bu for **26** lead to decrease in anticancer properties, and shortening to diethyl amide allowed substance **27** to inhibit HOP-62 of nonsmall cell lung cancer and SR of leukemia at the high level – 23.47% and 32.79% of CG, correspondingly.

Furthermore, one of the strongest effects was achieved by 2-([1,2,4]triazolo[1,5-*c*]quinazolin-2-ylsulfanyl)-*N*-(4-chlorophenyl)acetamide (**32**) with –42.37% rate of cell death against 786-0 of renal cancer and 96.63% inhibition of HOP-62 of nonsmall cell lung cancer. But acetamide **31**, which differed only by 3-chlorophenyl radical, practically, had no influence at the same cell lines.

Thus, not only the presence of the chlorine in the Ph fragment, but also its exact position in the ring was essential for activity. Comparing the results of acetamide **32** (amide of acetic acid) and **35** (amide of 2-propionic acid), the great decreasing effect of the small Me group was observed on the growth and proliferation of the cancer cells. The growth range for **32** was from –42.37 to 150.88% and for **35**, it decreased to 67.83 – 113.43%.

A similar correlation was detected for alicyclic piperidines: the absence of Me branching of **37** opposite to **42** initiated 42.28% of RPMI-8226 CG of leukemia, which was the better result, than 75.80%.

The *N*-phenyl-2-(2-methylquinazolin-4-ylsulfanyl)acetamide **21** and 2-propionamide **23** had similar principle in cancer cell lines inhibition, because the presence of the Me group in the chain of the carboxylic acid residue also decreased the minimum *CG* for the first amide, by small amount, from 52.08 to 64.41%, as well as the absence of the Me radical in the second position of the quinazoline core in **19** improved its activity to 46.04%.

Even for acetamide **33** and 2-propionamide **36**, the same correlation was observed: the first promoted growth at 112.98% of melanoma SK-MEL-28, but the second promoted its *CG* at 197.19%, which was the highest rate among all investigated substances.

By analyzing activities of substances **29** and **30**, it was found that the Me group in the second position of the Ph substituent was more preferable than in the third position, for cell line A498 of renal cancer inhibition indicating that even minimum differences in molecule mattered a lot.

Synthesis of the aliphatic alkylamine **39**, alicyclic amine **38**, alcohol **40**, aliphatic amide **42**, and phenacyl **41**, as well as nucleophilic degradation to 2-(3-(*R*-sulfanyl)-1*H*-1,2,4-triazol-5-yl)anilines **43** and **44** caused no possession of strong anticancer properties, but just stimulation of some cancer cell lines proliferation.

Summing up, the widest range of moderate activity was exhibited by 2-(2-*R*-quinazolin-4-ylsulfanyl)-1-phenylethanones **11** – **13**, **16**, and **18**, showing the importance of the second position substitution of their quinazolin-4(3*H*)-thione's ring by relatively small substituents or aliphatic heterocycle and the presence of electron-donating groups in the Ph residue.

Although, condensation of the triazole with quinazoline ring to [1,2,4]triazolo[1,5-*c*]quinazoline-2-thiones (**25** – **42**) lessened their anticancer activity range and level, surprisingly, acetamide **32** had lethal effect against line 786-0 of renal cancer. This fact once again reaffirmed that only *in vitro* results could show the real picture of biological activities.

Some of the proposed correlations were in accordance with those observed by *Patel* and co-authors that among *N*-Ph substituted quinazoline thioacetamide derivatives, MeO, NO_2, and Cl substituents had positive impact in the anticancer properties against human PC3 cells [8]. Still, the majority of substances had the best result against different cancer cell lines and, unfortunately, even promoted its growth (*Supplementary Information*). The strongest promotion of the cancer cell growth was detected for substances **44** (160%, presence of COOH group), **10** (164%, benzofuran-2-yl), **4** (170%, CF_3), **31** (171%, 3-ClPh), and **36** (197%, 4-NO_2Ph). Thus, these substances were not chosen to be investigated in five doses.

QSAR Studies. Molecular descriptors are digital values, which received the quantification of diverse structural and physicochemical characteristics of the molecule [20]. They could estimate that these attributes to establish the molecule biological activities, namely, anticancer properties in this case. The program QSARINS 2.2 calculated the best regression using descriptors obtained by Dragon 5.5 and MOPAC2012 [21 – 23]. Due to their very high quantity, genetic algorithm (GA) and multiple linear regression analysis (MLRA) were used.

Hence, all cancer cell lines were analyzed and upon their descriptors, 60 QSAR models were calculated. But only the four best equations were reported hereby: CCRF-CEM of leukemia, T-47D and HS 578T of breast cancer, and mean cell growth, relying on their highest squared regression (r^2) and weighted correlation coefficients by leave-one out method (Q^2_{LOO}; *Tables 2* and *3*).

When mean growth percent was used as single end point, the best r^2 (0.817) was found, still very close to all results. Then, simple (up to 4 – 5 descriptors in model), transparent, and thereby realistic QSAR models were proposed to avoid errors arising from overfitting of data (*i.e.*, inclusion of greater number of descriptor; *Table 3*).

Analyzing the QSAR models, among the essential descriptors were: RDF065e – weighted by atomic *Sanderson* electronegativities; RDF075m, RDF90m, RDF105m and RDF140m – weighted by mass, RDF125p – weighted by polarizability; piPC10 – molecular multiple path count of order 10; RSIpw3 and RSIpw5 – randic shape index; H7v – H autocorrelation of lag 7/weighted by *Van der Waals* volume; BEHe2 – highest eigenvalue n. 2 of *Burden* matrix/weighted by atomic *Sanderson* electronegativities; HATS4v – leverage-weighted autocorrelation of lag 4/weighted by *Van der Waals* volume; C-032 – atom-centered fragments X-CX-X; F07[O-S] – frequency of O-S at topological distance 7; D/Dr10 – distance/detour ring index of order 10; T(N..N) – sum of topological distances between N..N; MATS7v – Moran autocorrelation – lag 7/ weighted by atomic *Van der Waals* volumes; STD(O,O)- sum of topological distances between O..O [23].

The performance of all selected models had a little positive bias, due to conducted randomization according to the best r^2. The prediction of the anticancer activity by the calculated QSAR models showed their high accuracy. It was decided to add prediction of the mean cell growth data into the *Supplementary Information* and focused in the text at the exact cancer cell lines (*Table 4*).

Graphical representations of the experimental and calculated values of growth percent for all reported QSAR models are shown in *Fig. 2*.

Comparing *in vitro* experimental data with calculated data using models, the best predicted ones were found for substances **28** and **40** against CCRF-CEM cell line of leukemia (*Table 4*). The values differed only in 0.01 points for the last substance.

Also for cell line T-47D of breast cancer, the best prediction was achieved for compound **9** (distinction is 0.2 points). For cell line HS 578T of breast cancer, there were found more substances with closest results: **1**, **3**, **14**, and **25** with accuracy of the prediction in < 0.5 odds.

To propose the direction of the future modifications of the synthesized compounds, for example, against T-47D cell line of breast cancer, it was decided to create novel structures' base and calculate their anticancer activity using proposed QSAR model.

Thus, 177 compounds were drawn and their activity was predicted to establish structure–activity correlation (*Supplementary Information*, Table 2, WinRAR file).

In the result, considerable amount of proposed substances with better anticancer properties were derivatives of quinazolin-4(3*H*)-thione and condensation with triazole ring proved to worsen the cancer cells growth inhibition.

The summarized SAR to enhance or to reduce anticancer properties is shown in *Fig. 3*.

Therefore, it can be concluded that proposed QSAR models could be used for prediction of the anticancer properties of the consequently designed and synthesized compounds in the series of quinazolin-4(3*H*)-thione's and [1,2,4]triazolo[1,5-*c*]quinazoline-2-thione's derivatives to improve effectiveness of anticancer agents search.

Conclusions

In the result of NCI anticancer preliminary screening of 44 2-alkyl(aryl,hetaryl)quinazolin-4(3*H*)-thione's and [1,2,4]triazolo[1,5-*c*]quinazoline-2-thione's thioderivatives, 16 substances were found to possess mild to strong anticancer activities. Among 60 studied types of cancer cell lines, 21 were sensitive to synthesized compounds. The cell line 786-0 of renal cancer had the highest rate of cell death: −52.8% for 1-(3-methoxyphenyl)-2-(quinazolin-4-ylsulfanyl)ethanone (**8**) and −42.37% for 2-([1,2,4]triazolo

Table 3. Calculated QSAR models for leukemia (L) and breast cancer (BC)

Cell line	Equation of growth inhibition
L, CCRF-CEM	17.782 (± 8.4423)*piPC10-2.8039 (± 0.6886)*RDF065e-297.024 (± 130.0034)*H7v-615.574 (± 399.6342)*path/walk3-Randicshapeindex(RSIpw3)+208.5102 (± 120.4788)
BC, T-47D	−77.8571 (± 30.7625)*BEHe2 + 2.2147 (± 1.5242)*RDF090m-3.4268 (± 1.9111)*RDF105 m-94.1573 (± 90.3526)*HATS4v+12.7357 (± 6.3241)*C-032 + 389.8157* (± 111.3616)
BC, HS 578T	11.9385 (± 4.0578)*RDF140m-5.6197 (± 3.4452)*RDF125p-16.4186 (± 12.3636)*F07[O-S]-1801.38 (± 783.495)*path/walk5-Randicshapeindex (RSIpw5)+290.8168 (± 78.6734)
Mean cell growth	−0.1802 (± 0.0456)*D/Dr10-0.0957 (± 0.0831)*T(N..N)-9.7387 (± 4.4643)*MATS7v+1.7553 (± 0.5924)*RDF075m-0.4213 (± 0.162)*STD(O,O)+103.9585 (± 4.3738)

Table 4. Experimental data of substances *in vitro* anticancer activity in comparison to QSAR models [%]

Compound	Leukemia, CCRF-CEM			Breast cancer, T-47D			Breast cancer, HS 578T		
	Status[a])	Exp.	Pr.	Status	Exp.	Pr.	Status	Exp.	Pr.
1	Pr.	102.64	93.89	Tr.	102.96	100.75	Tr.	**111.23**	**111.45**
2	Tr.	18.75	26.20	Tr.	92.97	89.97	Tr.	85.79	79.64
3	Tr.	85.20	98.56	Tr.	118.67	113.84	Tr.	**116.00**	**116.22**
4	Tr.	**102.67**[b])	**103.82**	Pr.	107.69	114.59	Tr.	**109.87**	**108.15**
5	Tr.	95.86	94.52	Tr.	101.89	86.37	Pr.	**103.99**	**104.67**
6	Pr.	97.58	94.82	Tr.	**104.21**	**103.37**	Tr.	107.62	114.87
7	Tr.	99.83	85.01	Tr.	84.12	78.02	Tr.	108.38	111.88
8	Tr.	109.17	76.48	Tr.	78.29	83.04	Tr.	121.92	111.94
9	Pr.	86.70	71.42	Tr.	**77.2**	**77.00**	Tr.	116.21	109.86
10	Tr.	78.61	67.37	Tr.	49.25	51.60	Tr.	103.72	88.61
11	Tr.	51.55	43.18	Tr.	59.52	71.90	Tr.	71.74	80.54
12	Tr.	77.69	72.34	Pr.	76.2	81.40	Tr.	81.03	103.50
13	Tr.	81.55	75.09	Tr.	72.32	80.74	Tr.	89.09	109.16
14	Tr.	78.08	71.90	Tr.	64.14	74.15	Tr.	**102.81**	**102.68**
15	Tr.	92.34	82.59	Tr.	90.99	84.22	Tr.	113.26	98.17
16	Tr.	70.27	79.38	Pr.	52.53	77.51	Tr.	97.53	93.66
17	Tr.	69.03	84.10	Tr.	**83.35**	**84.70**	Tr.	110.69	114.27
18	Tr.	–31.5	–20.68	Tr.	94.99	99.81	Tr.	70.86	74.56
19	Tr.	56.83	81.42	Tr.	76.18	71.62	Tr.	100.26	107.04
20	Pr.	93.09	85.31	Pr.	95.83	81.44	Tr.	104.2	104.86
21	Pr.	72.54	81.49	Tr.	67.20	71.50	Tr.	114.05	110.43
22	Tr.	82.06	72.60	Tr.	71.25	67.52	Tr.	89.08	86.24
23	Tr.	67.74	75.77	Tr.	65.92	70.95	Pr.	105.28	77.34
24	Pr.	94.56	61.66	Pr.	109.75	72.75	Tr.	82.25	104.23
25	Tr.	94.97	85.67	Tr.	91.71	113.13	Tr.	**105.38**	**115.98**
26	Pr.	99.68	127.94	Tr.	87.11	92.36	Tr.	106.78	103.93
27	Tr.	82.61	96.32	Tr.	110.68	108.05	Tr.	103.58	106.71
28	Tr.	**102.05**	**101.61**	Tr.	**84.07**	**85.28**	Tr.	92.55	84.52
29	Pr.	93.12	81.54	Tr.	91.78	96.53	–[c])	–	104.25
30	Tr.	**96.19**	**94.93**	Tr.	90.29	82.07	Tr.	169.10	157.59
31	Tr.	68.96	85.31	Pr.	89.9	71.25	Pr.	93.76	89.48
32	Tr.	111.89	99.19	Tr.	99.55	90.84	Tr.	116.00	98.13
33	Tr.	92.28	84.48	Pr.	84.91	94.34	Tr.	116.31	109.01
34	Tr.	88.74	79.68	Tr.	79.04	74.09	Pr.	**101.41**	**101.05**
35	–[c])	–	98.17	–	–	100.45	Tr.	84.60	89.37
36	Pr.	80.94	89.16	Tr.	82.27	85.68	Pr.	122.60	68.49
37	Tr.	79.81	106.65	Tr.	95.75	98.36	–	–	101.26
38	Tr.	129.37	111.76	Tr.	108.53	104.65	–	–	118.01
39	Tr.	92.41	94.82	Tr.	100.03	96.03	–	–	96.08
40	Tr.	**89.24**	**89.23**	Pr.	110.36	105.54	–	–	95.10
41	Tr.	89.64	97.79	Tr.	109.8	92.65	–	–	89.83
42	Tr.	**96.63**	**96.90**	Tr.	90.13	95.60	–	–	94.47
43	–	–	97.19	Tr.	**103.29**	**103.88**	Tr.	116.57	111.27
44	Tr.	99.25	108.52	Pr.	109.86	98.11	Pr.	130.27	119.54

[a]) Tr., Training set; Pr., prediction set. [b]) Bold values are the closest predicted results with < 1.5 digits difference. [c]) Substances have no experimental data at this cell line.

[1,5-*c*]quinazolin-2-ylsulfanyl)-*N*-(4-chlorophenyl)acetamide (**32**) influence. The cell line HOP-62 of nonsmall cell lung cancer had the widest range of effective substances against it: **3**, **8**, **11**, **16**, **27**, and **32**. 1-(2,5-Dimethoxyphenyl)-2-(2-morpholinoquinazolin-4-ylsulfanyl)ethanone (**18**) was the best one among all investigated compounds according to the results of the lethal effect and strong inhibition against eight cancer cell lines (CCRF-CEM of leukemia, SF-539, SNB-75, and U251 of CNS cancer; 786, RXF393, and UO-31 of renal cancer; and MDA-MB-231/ATCC of breast cancer (from –31.50 to 47.41%)). It is worth to mention its lowest cancer growth stimulation effect (105.44%). Besides, the widest range of moderate activity was shown by 1-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(quinazolin-4-ylsulfanyl)ethanone (**11**; 22.28 – 79.59%). SAR revealed that: *i*) introduction of MeO groups into the thioacetophenone substituent in the fourth position and morpholyl fragment into the second position of the quinazoline ring amplified its anticancer properties of series **1**; *ii*) replacement of small substituents in the second

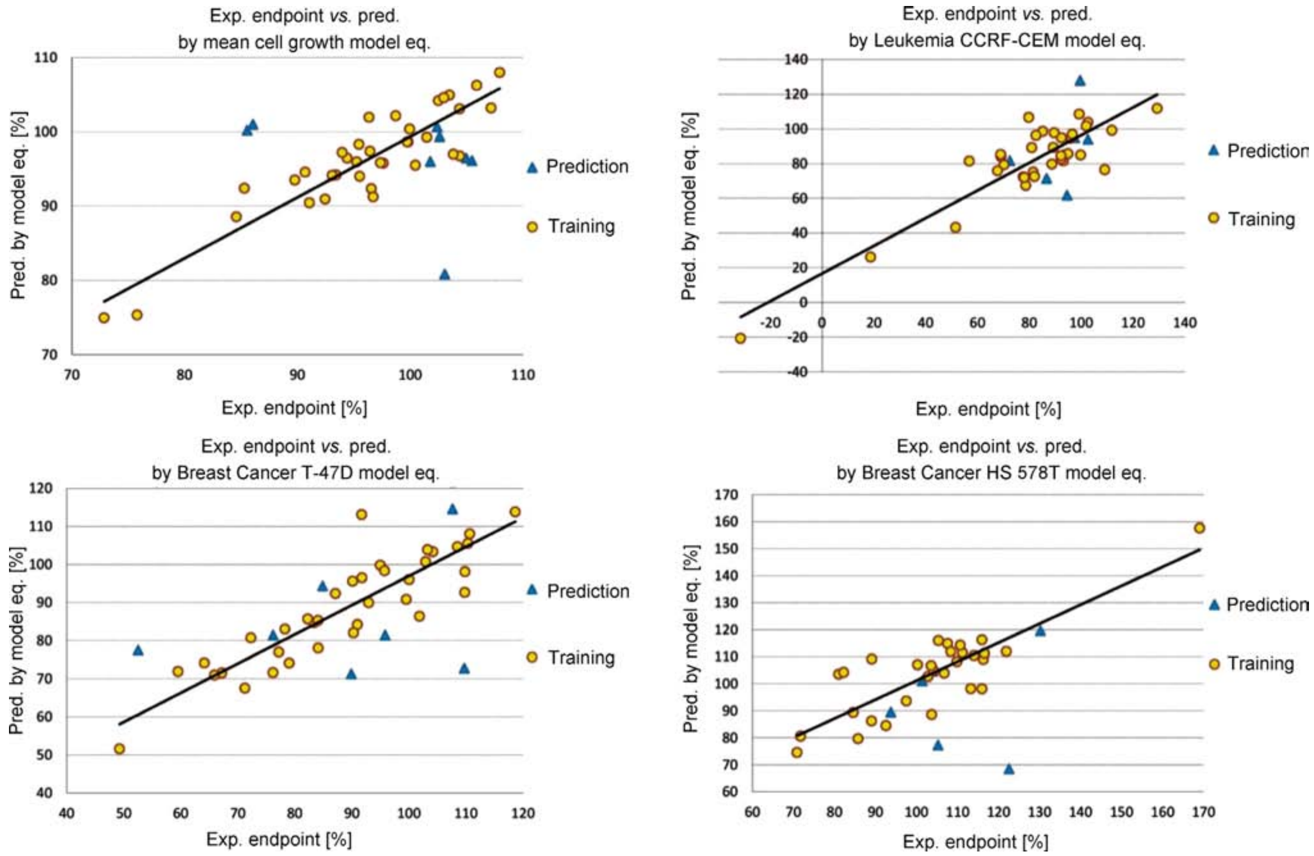


Fig. 2. Correlation graphs of predicted *vs.* experimental growth percentage for model equations.

position of the quinazoline ring was more effective, than changing radicals in the Ph ring for substances **7** – **18**; *iii*) condensation of quinazoline with 1,2,4-triazole ring for series **2** highly narrowed the types and level of cell lines inhibition; *iv*) branching of the thioalkyl residue lead to procancer effect; and *v*) cell line HOP-62 of nonsmall cell lung cancer, 786-0 of renal cancer, and SR, RPMI-8226, and CCRF-CEM of leukemia were the most sensitive to synthesized compounds. The calculated four best QSAR models for CCRF-CEM of leukemia, T-47D and HS 578T of breast cancer, and mean cell growth predicted anticancer data with satisfactory accuracy. Hence, the directions of the purposeful modification in the series of 2-alkyl(aryl)-quinazolin-4(3*H*)-thione's and [1,2,4]triazolo[1,5-*c*]quinazoline-2-thione's thioderivatives were found, and would be consequently done along with the multitarget QSAR method to derive predictive anticancer models as an alternative to represent selection among triazolo-, tetrazolo-, triazino, and uncondensed quinazolines.

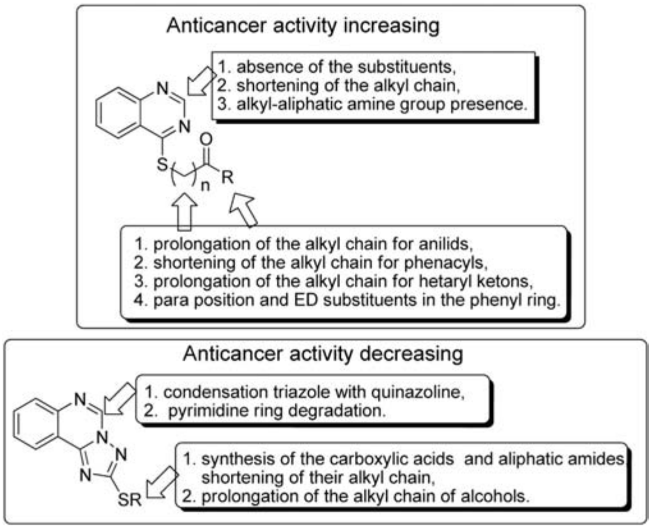


Fig. 3. Necessary modifications need to be done to improve anticancer activity against T-47D cell line of breast cancer for the investigated compounds according to the proposed QSAR model.

The authors gratefully acknowledge team of the Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD, USA, for *in vitro* evaluation of anticancer activity.

Supporting Information

Supporting Information for this article is available on the WWW under http://dx.doi.org/10.1002/hlca.201600062.

Experimental Part

Chemistry

M.p.: determined in open capillary tubes in a *Thiele*'s apparatus (Staffordshire, UK); uncorrected. UV Spectra: *Analytic Jena* UV/VIS spectrophotometer *Specord 200* (Jena, Germany). IR Spectra (4000 – 600 cm^{-1}): *Bruker ALPHA* (Ettingen, Germany) FT-IR spectrometer using a module for measuring attenuated total reflection (ATR); $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra (400 MHz and 500 MHz): *Varian-Mercury 400* and *Bruker Avance DRX-500* spectrometers in (D_6)DMSO soln.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. LC/MS: chromatography/mass spectrometric system which consists of HPLC *Agilent 1100 Series* (Palo Alto, CA, USA) equipped with diode-matrix and mass-selective detector *Agilent LC/MSD SL* (atmospheric pressure chemical ionization – APCI; Palo Alto, CA, USA). ESI-MS Spectra: *Varian 1200l* instrument at 70 eV. The purity of all obtained compounds was checked by ^1H-NMR and LC/MS.

Starting substances (**L**, **M**, **N**), **1** – **5** [13], **7** – **12**, **15**, **16**, **19** – **24** [14], **43**, **44** [15], **25** – **37**, **42** [16], and **40**, **41** [17] were already synthesized and reported. Other starting materials and solvents were obtained from commercially available sources and used without additional purification.

Procedure to Obtain Substances **6**, **13**, **14**, **17**, *and* **18**. To a soln. of 0.23 g (0.01 mol) of metallic Na in 25 ml of MeOH was added 0.01 mol of 2-*R*-quinazolin-4-(3*H*)-thione. After the dissolution, the mixture was cooled to 5 – 15°, and 0.01 mol of appropriate halogen derivative was added, heated until a neutral pH. A small amount of H_2O was poured and cooled. The precipitate was filtered out, washed with H_2O, and recrystallized from $^iPrOH/H_2O$ 3:1 soln.

2-Acetamido-3-{[2-(trifluoromethyl)quinazolin-4-yl]sulfanyl}propanoic Acid (**6**). Yield: 73%. M.p. 178 – 180°. IR: 3389, 2992, 2886, 2828, 1914, 1721, 1606, 1566, 1529, 1487, 1438, 1412, 1390, 1351, 1308, 1290, 1260, 1246, 1226, 1205, 1165, 1136, 1110, 1045, 1017, 999, 983, 931, 881, 849, 837, 794, 766, 755, 734, 693, 631. ^1H-NMR (400 MHz, (D_6)DMSO + CCl_4): 12.96 (br. *s*, COOH); 8.48 (*d*, *J* = 8.2, 1 H, H–C(5q)); 8.21 (*t*, *J* = 8.3, 1 H, H–C(7q)); 8.11 (*d*, *J* = 8.3, 1 H, H–C(8q)); 7.89 (*t*, *J* = 5.6, 1 H, H–C(6q)); 4.70 (*q*, *J* = 8.5, 1 H, CH_2CH); 4.05 (*dd*, *J* = 13.6, 4.4, 1 H, NH); 3.52 (*dd*, *J* = 13.4, 9.0, 2 H, SCH_2); 1.81 (*s*, Me). LC/MS: 360 ($[M + H]^+$). Anal. calc. for $C_{14}H_{12}F_3N_3O_3S$: C 46.80, H 3.37, N 11.69, O 13.36; found: C 46.84, H 3.34, N 11.73, O 13.33.

1-Phenyl-2-{[2-(trifluoromethyl)quinazolin-4-yl]sulfanyl}ethanone (**13**). Yield: 76%. M.p. 132 – 134°. IR: 3062, 3040, 2988, 2934, 1746, 1697, 1613, 1593, 1565, 1552, 1486, 1450, 1388, 1348, 1322, 1291, 1262, 1247, 1196, 1140, 1108, 1022, 999, 985, 938, 881, 866, 847, 778, 764, 757, 747, 730, 688, 644, 627. ^1H-NMR (500 MHz, $CDCl_3$): 8.33 (*d*, *J* = 8.2, 1 H, H–C(5)); 8.22 – 8.04 (*m*, 4 H, H–C(7), C(8), Ph(2,6); 7.92 (*t*, *J* = 7.1, 1 H, H–C(3)); 7.69 (*t*, *J* = 7.2, 1 H, Ph(5)); 7.58 (*t*, *J* = 7.6, 2 H, H–C(6), Ph(4); 5.07 (*s*, 2 H, SCH_2). LC/MS: 349 ($[M + H]^+$). Anal. calc. for $C_{17}H_{11}F_3N_2OS$: C 58.62, H 3.18, N 8.04, O 4.59; found: C 58.66, H 3.14,
N 8.08, O 4.53.

1-Phenyl-2-{[2-(2-phenylethyl)quinazolin-4-yl]sulfanyl}ethanone (**14**). Yield: 68%. M.p. 92 – 94°. IR: 3060, 3025, 2978, 2903, 1697, 1613, 1596, 1561, 1548, 1483, 1449, 1372, 1341, 1322, 1291, 1252, 1202, 1151, 1111, 1074, 1028, 990, 936, 905, 879, 867, 844, 760, 739, 690, 646, 620. LC/MS: 385 ($[M + H]^+$). Anal. calc. for $C_{24}H_{20}N_2OS$: C 74.97, H 5.24, N 7.29, O 4.16; found: C 74.99, H 5.21, N 7.33, O 4.12.

1-(2,4-Dichlorophenyl)-2-{[2-(trifluoromethyl)quinazolin-4-yl]sulfanyl}ethanone (**17**). Yield: 78%. M.p. 164 – 166°. IR: 2995, 2943, 2886, 1709, 1584, 1566, 1552, 1487, 1463, 1380, 1349, 1287, 1262, 1246, 1185, 1163, 1145, 1109, 1061, 1002, 983, 958, 882, 870, 850, 819, 800, 773, 755, 732, 705, 689, 627. LC/MS: 418 ($[M + H]^+$). Anal. calc. for $C_{17}H_9Cl_2F_3N_2OS$: C 48.94, H 2.17, N 6.71, O 3.83; found: C 48.91, H 2.19, N 6.68, O 3.86.

1-(2,5-Dimethoxyphenyl)-2-{[2-(morpholin-4-yl)quinazolin-4-yl]sulfanyl}ethanone (**18**). Yield: 75%. M.p. 172 – 174°. IR: 3011, 2987, 2944, 2896, 2859, 1658, 1613, 1554, 1497, 1478, 1452, 1427, 1412, 1368, 1349, 1327, 1291, 1279, 1255, 1240, 1224, 1162, 1114, 1070, 1048, 1029, 1014, 995, 979, 928, 888, 863, 842, 816, 786, 753, 726, 713, 653, 638. ^1H-NMR (400 MHz, (D_6)DMSO + CCl_4): 7.88 (*d*, *J* = 7.9, 1 H, H–C(5)); 7.70 (*t*, *J* = 7.0, 1 H, H–C(7)); 7.46 (*d*, *J* = 8.1, 1 H, H–C(8)); 7.26 (*t*, *J* = 7.4, 1 H, H–C(6)); 7.17 – 7.23 (*m*, 2 H, Ph(3,4)); 7.13 (*s*, 1 H, Ph(2)); 4.77 (*s*, 2 H, SCH_2); 3.89 – 3.94 (*m*, 2 H, OCH_2); 3.70 – 3.75 (*m*, 2 H, OCH_2); 3.60 (*s*, Me); 3.52 (*s*, Me); 3.30 – 3.36 (*m*, 4 H, $N(CH_2)_2$). LC/MS: 426 ($[M + H]^+$). Anal. calc. for $C_{22}H_{23}N_3O_4S$: C 62.10, H 5.45, N 9.88, O 15.04; found: C 62.13, H 5.42, N 9.91, O 15.01.

Procedure to Obtain Substances **38** *and* **39**. To a soln. of 0.34 g (0.006 mol) KOH in 15 ml of EtOH was added proper amine hydrochloride (0.006 mol) and 1.22 g (0.005 mol) of potassium [1,2,4]triazolo[1,5-*c*]quinazoline-2-thiolate. The mixture was refluxed for 3 h and then cooled down. Then, 30 ml of H_2O was added, oil was extracted with $CHCl_3$, and recrystallized from $^iPrOH/H_2O$ 3:1 soln.

2-{[2-(Morpholin-4-yl)ethyl]sulfanyl}[1,2,4]triazolo[1,5-*c*]quinazoline (**38**). Yield: 41%. M.p. 126 – 128°. IR: 3396, 3061, 2966, 2924, 2871, 2850, 2792, 1621, 1602, 1516, 1475, 1454, 1393, 1383, 1369, 1350, 1300, 1264, 1242, 1198, 1158, 1105, 1088, 1066, 1008, 982, 959, 912, 898, 869, 805, 768, 745, 714, 641.^1H-NMR: 9.50 (*s*, 1 H, H–C(5)); 8.41 (*d*, 1 H, *J* = 8.0, H–C(10)); 8.06 (*d*, 1 H, *J* = 7.8, H–C(7)); 7.94 (*t*, 1 H, *J* = 8.0, H–C(8)); 7.82 (*t*, 1 H, *J* = 8.0, H–C(9)); 3.42 (*t*, 2 H, *J* = 7.0, SCH_2); 3.04 – 2.98 (*m*, 4 H, $O(CH_2)_2$); 2.65 (*q*, 2 H, *J* = 7.8, $SCH_2–CH_2$); 1.32 – 1.27

(*m*, 4 H, $(CH_2)_2N$). LC/MS: 316 ($[M + H]^+$). Anal. calc. for $C_{15}H_{17}N_5OS$: C 57.12, H 5.43, N 22.21, O 5.07; found: C 57.16, H 5.41, N 22.23, O 5.04.

***N*-(1-methylethyl)-*N*-[2-([1,2,4]triazolo[1,5-*c*]quinazolin-2-ylthio)ethyl] propan-2-amine** (**39**). Yield: 69%. M.p. 82 – 84°. IR: 3055, 2957, 2868, 2836, 1622, 1608, 510, 1475, 1453, 1385, 1361, 1305, 1288, 1251, 1234, 1212, 1196, 1159, 1122, 1107, 1068, 1034, 972, 958, 925, 900, 867, 782, 766, 726, 714, 683, 640. ^{1}H-NMR: 9.53 (*s*, 1 H, H–C(5)); 8.40 (*d*, *J* = 8.0, 1 H, H–C(10)); 8.04 (*d*, *J* = 7.8, 1 H, H–C(7)); 7.95 (*t*, *J* = 8.0, 1 H, H–C(8)); 7.82 (*t*, *J* = 8.0, 1 H, H–C(9)); 3.43 (*t*, *J* = 8.0, 2 H, SCH_2); 2.88 – 2.84 (*m*, 2 H, NCH_2); 0.97 – 1.10 (*m*, 4 Me). LC/MS: 330 ($[M + H]^+$). Anal. calc. for $C_{17}H_{23}N_4S$: C 61.97, H 7.04, N 21.26, S 9.73; found: C 61.95, H 7.06, N 21.24, S 9.75.

Anticancer Activity

Primary anticancer assay was performed against human tumor cell lines panel derived from nine neoplastic diseases, in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, Bethesda [19]. The human tumor cell lines of the cancer screening panel were grown in RPMI 1640 medium containing 5% fetal bovine serum and 2 mM L-glutamine. For a typical screening experiment, cells were inoculated in 96-well microtiter plates in 100 ml assay volume, at plating densities ranging from 5000 to 40 000 cell/well. After cell inoculation, the microtiter plates were incubated at 37°, under an atmosphere of 5:95 CO_2/air (*v*/*v*) at 100% relative humidity, for 24 h prior to addition of drugs under assessment. Following drug addition (1 μM), the plates were incubated for an additional 48 h, under the same conditions. Sulforhodamine B (SRB) soln. (100 μl, 0 – 4% *w*/*v* in 1% aq. AcOH) was added to each well and plates were incubated for 10 min at r.t. The percentage growth was evaluated spectrophotometrically *vs.* controls not treated with test agents.

QSAR Modeling

First, all structures were built by MarvinSketch 6.3.0 (MarvinSketch version: 6.3.0, *ChemAxon*, Cambridge, MA, USA). Then, they were preliminary optimized by program HyperChem 8.0.8 using molecular mechanical MM+ algorithm combined with semiempirical PM3 molecular modeling method with a maximum number of cycles and Polak-Ribiere (Conjugate Gradient) algorithm. Molecular mechanics has been used to produce more realistic geometry values for the majority of org. molecules owing to the fact of being highly parameterized. The next step was a reoptimization of the MM+ optimized structures by applying semiempirical PM3 molecular modeling method. Obtained files were further used for calculations.

Descriptors were calculated using Dragon 5.5 (> 1500 descriptors) (DRAGON 5.5 for Windows, *TALETE SRL*, Milano, Italy). The definition of all used molecular descriptors and the calculation procedures were summarized elsewhere [21 – 23]. Optimized structures were also used for calculation of additional important quantum-chemical parameters (final heat of formation, total energy, electronic energy, core–core repulsion, ionization potential, HOMO, and LUMO), that were also used as descriptors. MOPAC2012 was used to do such computation (MOPAC2009 for CAChe, *Stewart Computational Chemistry*, Oregon, LLC, USA). The correlation coefficients for all pair of descriptor variables used in the models were evaluated to identify highly correlated descriptors in order to detect redundancy in the data set. Hence, descriptors with constant variables and near-constant variables were excluded from the further consideration ($r \geq 0.95$).

The genetic algorithm (GA) and multiple linear regression analysis (MLRA) were used to select the descriptors and to generate the correlation models that relate the structural features to the cell growth percent of different cancer cell lines. The combination of the GA-MLRA technique was applied to obtain the best QSAR models using the QSARINS 2.2. The latter program split compounds data as the following: random selection of 20% of compounds for prediction set and 80% for training set. For each obtained model, such random selection was different.

Calculation of QSAR models was conducted separately for each of 60 cell lines. Growth percent according to the NCI protocol was not converted to any other value; it was used in original version to built models. Some cell lines were given the value of −999, which means, that they were not tested.

The amount of generation algorithm setup was set until four descriptors, and generation per size was established to the value of 3000, and the division into training and test sets was performed automatically at a ratio of 80 – 20 percent relatively. Models, which showed statistical significance according to the parameters at a higher level ($r^2 \geq 0.5$), were selected for a more thorough rendering. For these lines, the following options were given: the amount of generation algorithm setup was set until seven descriptors, and generation per size was established to the value of 10 000. Substances were spited into training and test sets and the division, was made such, as to establish equal distribution of substances of high and moderate percentage of inhibition of cell growth.

REFERENCES

[1] M. Malvezzi, P. Bertuccio, T. Rosso, M. Rota, F. Levi, C. La Vecchia, E. Negri, *Ann. Oncol.* **2015**, *26*, 779.

[2] J. Bliesath, N. Huser, M. Omori, D. Bunag, C. Proffitt, N. Streiner, C. Ho, A. Siddiqui-Jain, S. E. O'Brien, J. K. C. Lim, D. M. Ryckman, K. Anderes, W. G. Rice, D. Drygin, *Cancer Lett.* **2012**, *322*, 113.

[3] A. Aleksic, V. MacLaren, *Lung Cancer* **2014**, *83*, S9.

[4] M. A. Gubens, M. Burns, S. M. Perkins, M. S. Pedro-Salcedo, S. K. Althouse, P. J. Loehrer, H. A. Wakelee, *Lung Cancer* **2015**, *89*, 57.

[5] F. Fang, D. D. Li, J. R. Li, J. Sun, Q. R. Du, H. B. Gong, H. L. Zhu, *RSC Adv.* **2013**, *3*, 26230.

[6] M. M. Ghorab, F. A. Ragab, H. I. Heiba, A. A. Bayomi, *J. Heterocycl. Chem.* **2014**, *51*, E255.

[7] A. A. Khalil, S. G. A. Hamide, A. M. Al-Obaid, H. I. El-Subbagh, *Arch. Pharm. (Weinheim, Ger.)* **2003**, *336*, 95.

[8] A. B. Patel, K. H. Chikhalia, P. Kumari, *Res. Chem. Intermed.* **2015**, *41*, 4439.

[9] R. Al-Salahi, M. Marzouk, A. E. Ashour, I. Alswaidan, *Asian J. Chem.* **2014**, *26*, 2173.

[10] G. Marzaro, A. Guiotto, A. Chilin, *Exp. Opin. Ther. Pat.* **2012**, *22*, 223.

[11] S. Kumar, R. Agrawal, *Recent Pat. Anticancer Drug Discov.* **2014**, *9*, 382.

[12] S. A. Starosyla, M. V. Protopopov, O. I. Voskoboinik, I. S. Nosulenko, L. M. Antypenko, O. M. Antypenko, I. M. Fesun, S. I. Kovalenko, S. M. Yarmoluk, *Ukrain. Bioorg. Acta* **2014**, *1*, 12. (http://www.bioorganica.org.ua/UBAdenovo/vol_12_1.htm)

[13] L. Antypenko, S. Kovalenko, Y. Posylkina, V. Nikitin, N. Fedyunina, V. Ivchuk, *J. Enzyme Inhibit. Med. Chem.* **2015**, *1*.

[14] V. A. Nikitin, S. I. Kovalenko, I. F. Belenichev, Y. M. Maksimov, N. O. Vrynchanu, *Pharmacology* **2006**, *1*, 122. (http://farmacomua.narod.ru/Arx1_2_2006/1_2_2006.htm)

[15] L. Antipenko, A. Karpenko, S. Kovalenko, A. Katsev, E. Komarovska-Porokhnyavets, V. Novikov, A. Chekotilo, *Chem. Pharm. Bull.* **2009**, *57*, 580.

[16] L. N. Antipenko, A. V. Karpenko, S. I. Kovalenko, A. M. Katsev, E. Z. Komarovska-Porokhnyavets, V. P. Novikov, *Arch. Pharm. (Weinheim, Ger.)* **2009**, *342*, 651.

[17] L. M. Antypenko, S. I. Kovalenko, O. V. Karpenko, A. M. Katsev, V. P. Novikov, N. S. Fedyunina, *Curr. Comput. Aided Drug Des.* **2015**, *12*, 29.

[18] M. Roth, P. Dubs, E. Götschi, A. Eschenmoser, *Helv. Chim. Acta* **1971**, *54*, 710.

[19] M. R. Boyd, 'The NCI In Vitro Anticancer Drug Discovery Screen', Anticancer Drug Development Guide Humana Press, 1997, p. 23.

[20] J. Kirchmair, A. H. Göller, D. Lang, J. Kunze, B. Testa, I. D. Wilson, R. C. Glen, G. Schneider, *Nat. Rev. Drug Discov.* **2015**, *14*, 387.

[21] P. Gramatica, N. Chirico, E. Papa, S. Cassani, S. Kovarich, *J. Comput. Chem.* **2013**, *34*, 2121.

[22] P. Gramatica, S. Cassani, N. Chirico, *J. Comput. Chem.* **2014**, *35*, 1036.

[23] R. Todeschini, V. Consonni, 'Handbook of Molecular Descriptors', Eds. R. Mannhold, H. Kubinyi, H. Timmerman, Wiley-VCH, Weinheim, New York, 2000.

Received March 12, 2016
Accepted May 18, 2016