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SYNTHESIS AND ANTIVIRAL ACTIVITY OF [(9-R^1-10-R^2-3-R-2-OXO-2*H*-[1,2,4]-TRIAZINO[2,3-*c*]QUINAZOLIN-6-YL)THIO] ACETAMIDES DERIVATIVES WITH THE FRAGMENTS OF CARCASS AMINES

I.S.Nosulenko, O.Yu.Voskoboynik, G.G.Berest, S.L.Safronyuk*, S.I.Kovalenko, A.V.Katsev*, R.S.Sinyak, V.O.Palchikov**

Zaporizhzhia State Medical University,
26, Mayakovsky ave., 69035, Zaporizhzhia, Ukraine
* Crimean State Medical University
** Dnipropetrovsk National University named after Oles Honchar

Key words: 2-[(9-R^1-10-R^2-3-R-2-[(3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazoline-6-yl)thio]acetamides; carcass amines; viruses Flu A&B strain; antiviral activity

Alkylation of potassium 9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-thiolates by N-cycloalkyl-(cycloalkylaryl-)-2-chloracetamides and interaction of [(9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl) thio]acetic acids imidazolides and chloranhydrides with carcass amines yielded the corresponding amides. The structures of the compounds synthesized have been confirmed by ^{1}H, ^{13}C NMR, LC–MS and EI-MS analysis. The features of ^{1}H, ^{13}C NMR, LC–MS and EI-MS spectra have been described, and characteristic signals have been identified. The compounds synthesized have been studied for their antiviral activity. The results of the antiviral assay have shown that some compounds exhibit a moderate and high activity against the strains studied. The correlation between the structure and the antiviral action has been also discussed. According to the data obtained the conclusion can be made that the combination of carcass amine moieties with the fragment of little known [(9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]-triazino[2,3-c]quinazolin-6-yl)thio]acetic acid results in compounds with a high antiviral activity. High indicators of the antiviral activity of compounds 3.2 and 3.14 against Influenza Type A H3N2 allow to suppose the expediency of further chemical modification of [1,2,4]triazino[2,3-c]quinazoline directed to obtaining new antiviral agents.

СИНТЕЗ ТА АНТИВІРУСНА АКТИВНІСТЬ ПОХІДНИХ [(9-R^1-10-R^2-3-R-2-ОКСО-2H-[1,2,4]-ТРИАЗИНО[2,3-c] ХІНАЗОЛІН-6-ІЛ)ТІО]АЦЕТАМІДІВ З ФРАГМЕНТАМИ КАРКАСНИХ АМІНІВ
І.С.Носуленко, О.Ю.Воскобойнік, Г.Г.Берест, С.Л.Сафронюк, С.І.Коваленко, А.М.Кацев, Р.С.Синяк, В.О.Пальчиков
Ключові слова: *2-[(9-R^1-10-R^2-3-R-2-[(3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хіназолін-6-іл)тіо]ацетаміди; каркасні аміни; вірус штаму Flu A&B; антивірусна активність*
Алкілування калій 9-R^1-10-R^2-3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хіназолін-6-тіолатів N-циклоалкіл-(циклоалкіларил-)-2-хлорацетамідами та взаємодія імідазолідів та хлорангідридів [(9-R^1-10-R^2-3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хіназолін-6-іл)тіо]оцтових кислот з каркасними амінами призвели до утворення відповідних амідів. Структуру та чистоту синтезованих сполук встановлено за допомогою комплексу фізико-хімічних методів, зокрема ^{1}H, ^{13}C-NMR, LC–MS та EI-MS аналізом. Особливості ^{1}H, ^{13}C NMR, LC–MS та EI-MS спектрів були обговорені, також були ідентифіковані характеристичні сигнали. Синтезовані сполуки були досліджені на наявність антивірусної активності. Встановлено, що окремі представники синтезованих сполук виявляють помірну та високу антивірусну активність по відношенню до штамів, що досліджувались. Кореляція взаємозв'язків «будова-дія» була обговорена. Відповідно до одержаних даних ми зробили висновок, що комбінація залишку каркасних амінів з фрагментами маловідомих [(9-R^1-10-R^2-3-R-2-оксо-2H-[1,2,4]-триазино[2,3-c]хіназолін-6-іл)тіо]оцтових кислот дозволяє одержати сполуки зі значною антивірусною активністю. Високі індикатори антивірусної активності по відношенню до штаму Influenza Type A H3N2 сполук 3.2 та 3.14 дозволяють передбачити перспективність подальшої хімічної модифікації [1,2,4]триазино[2,3-c]хіназоліну з метою пошуку нових антивірусних агентів.

СИНТЕЗ И ПРОТИВОВИРУСНАЯ АКТИВНОСТЬ ПРОИЗВОДНЫХ [(9-R^1-10-R^2-3-R-2-ОКСО-2H-[1,2,4]ТРИАЗИНО[2,3-c]ХИНАЗОЛИН-6-ИЛ)ТИО]АЦЕТАМИДОВ С ФРАГМЕНТАМИ КАРКАСНЫХ АМИНОВ
И.С.Носуленко, А.Ю.Воскобойник, Г.Г.Берест, С.Л.Сафронюк, С.И.Коваленко, А.М.Кацев, Р.С.Синяк, В.А.Пальчиков
Ключевые слова: *2-[(9-R^1-10-R^2-3-R-2-[(3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хиназолин-6-ил)тио]ацетамиды; каркасные амины; вирус штамма Flu A&B; противовирусная активность*
Алкилирование калий 9-R^1-10-R^2-3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хиназолин-6-тиолатов N-циклоалкил-(циклоалкиларил-)-2-хлорацетамидами и взаимодействие имидазолидов и хлорангидридов [(9-R^1-10-R^2-3-R-2-оксо-2H-[1,2,4]триазино[2,3-c]хиназолин-6-ил)тио]уксусных кислот с каркасными аминами ведет к образованию амидов. Структуру и чистоту синтезированных соединений установлено комплексом физико-химических методов, в частности, ^{1}H-, ^{13}C-NMR, LC–MS и EI-MS анализом. Также были описаны особенности ^{1}H-, ^{13}C-NMR, LC–MS и EI-MS спектров и идентифицированы характеристические

сигналы. Синтезированные соединения были исследованы на наличие противовирусной активности. Установлено, что отдельные представители класса синтезированных соединений проявляют умеренную или высокую противовирусную активность по отношению к изучаемым штаммам. Обсуждена корреляция «структура-действие». Согласно полученным данным можно сделать вывод, что комбинация структуры каркасных аминов с фрагментом малоизвестных [(9-R¹-10-R²-3-R-2-оксо-2H-[1,2,4]-триазино[2,3-c]хиназолин-6-ил)тио]уксусных кислот позволяет получить вещества с высокой противовирусной активностью. Высокие индикаторы противовирусной активности по отношению к штамму Influenza Type A H3N2 соединений 3.2 и 3.14 дают возможность прогнозировать перспективность дальнейшей химической модификации [1,2,4]триазино[2,3-c]хиназолина, направленной на получение новых противовирусных агентов.

Despite the fact of the centuries-old contact of mankind with influenza and significant breakthrough in studying and treating it and the similar (parainfluenza and rhinovirus) diseases during last decades there are a lot of unresolved problems in this field. So, according to statistical data, upper respiratory tract infections take a first place among infectious diseases by the level of morbidity. Virus infections in a season epidemic period strike about 20% of the population and more than five hundred thousand people die, as a result of complications. For prevention and treatment of infectious diseases caused by viruses different classes of compounds are used. Among antiviral drugs it should be mentioned vaccines, interferon, inductors of interferon, abnormal nucleosides, adamantine thiosemicarbasones derivatives and virucidal agents [1, 2]. At the same time, appearance of new high pathogenic strains, problems in antiepidemic control and decrease of the immunodefence level cause the necessity of searching new highly effective antiviral agents, which can affect both the cause and pathogenesis of the disease.

Recent publication describe the strategies of antiviral drug creation based on chemical modification of aliphatic polycyclic systems (adamantane, norborane, bicyclo[2.2.0]hexane, bicyclo[2.2.1]heptane, pentacycloundecane, etc.) by introduction of pharmacophore groups or their combinations with cyclic, aromatic or heterocyclic fragments [2-7]. Following the strategy mentioned we decided to combine the carcass amine fragment with the planar [1,2,4]-riazino [2,3-c]quinazoline system, and it, in our opinion, yielded the compounds with a high antiviral activity. Our expectations also encouraged by the proved anticancer activity among substituted [1,2,4]-triazino[2,3-c]quinazolines [8, 9, 10].

So, our work was aimed at the synthesis of [9-R¹-10-R²-3-R-2-oxo-2H-[1,2,4]-triazino[2,3-c]quinazolin-6-yl)thio]acetamides with the fragments of carcass amines and evaluation of their antivirus activity against viruses Flu A&B.

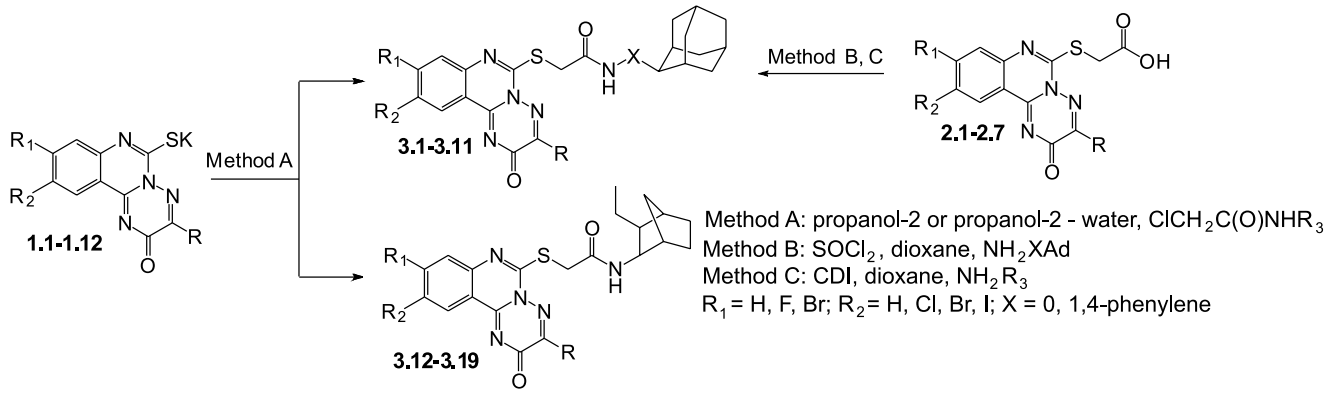
Results and Discussion

1. Chemistry

Synthesis of amides 3.1-3.18 was conducted by alkylation of potassium 9-R¹-10-R²-3-R-2-oxo-2*H*-[1,2,4] triazino-[2,3-*c*]-quinazolin-6-thiolates (1.1-1.11) by the corresponding chloracetamides in propanol-2 or propanol-2 – water mixture (Method A). The corresponded amides **3.1-3.10** were also synthesized by aminolysis of chloranhydrides (Method B) or imidazolides (Method C) of acids **2.1-2.11**. Our experiments showed that the reactivity of chloranhydrides and imidazolides generated *in situ* were enough for complete conversion of initial compounds into the corresponding amides. As specificity of methods B and C it is worth mentioning the necessity of using anhydrous solvents.

Purity of the compounds synthesized was determined by LC-MS (APCI) method, the structure was confirmed by elemental analysis, IR-, ^{1}H, ^{13}C and mass-spectra.

LC-MS-spectra (APCI) of compounds **3.1-3.19** are characterized by positive ions [M+1] and [M+3], the last one shows the "isotope profile" of sulfur [11]. Mass-spectra (EI) of compound **3.9** and **3.12** are characterized by the absence of molecular ions as a result of their low stability. The primary fragmentation



Scheme. Synthesis of N-(1-adamantyl-)-, N-(4-(1-adamantyl)phenyl-)-, N-(3-ethylbicyclo[2.2.1]heptan-2-yl-)-2-[(9-R¹-10-R²-3-R-2-oxo-2*H*-[1,2,4]-triazino[2,3-*c*]quinazolin-6-yl)thio]acetamides (**3.1**-**3.19**).

Table 1

Physicochemical properties of the compounds synthesized

Comp.	R	R_1	R_2	M.p., °C	Yields, %			Formula
					A	B	C	
3.1	CH_3	H	H	160-162	89.2	48.3	64.3	$C_{23}H_{25}N_5O_2S$
3.2	C_6H_5	H	H	214-216	91.3	56.3	77.4	$C_{28}H_{27}N_5O_2S$
3.3	4-$CH_3C_6H_4$	H	H	218-220	94.2	72.6		$C_{29}H_{29}N_5O_2S$
3.4	4-FC_6H_4	H	H	257-259	78.5		80.2	$C_{28}H_{26}FN_5O_2S$
3.5	C_6H_5	F	H	245-247	80.4		76.5	$C_{28}H_{26}FN_5O_2S$
3.6	4-FC_6H_4	F	H	282-284	32.4		73.9	$C_{28}H_{25}F_2N_5O_2S$
3.7	4-FC_6H_4	H	Cl	294-296	67.3	64.8		$C_{28}H_{25}ClFN_5O_2S$
3.8	CH_3	H	H	225-227	97.3	72.0	81.2	$C_{29}H_{29}N_5O_2S$
3.9	C_6H_5	H	H	314-318	94.5	78.4		$C_{34}H_{31}N_5O_2S$
3.10	4-$CH_3C_6H_4$	H	H	266-268	99.9		84.3	$C_{35}H_{33}N_5O_2S$
3.11	4-$CH_3OC_6H_4$	H	H	259-262	93.2	64.7		$C_{35}H_{33}N_5O_3S$
3.12	CH_3	H	H	217-219	84.6	36.9	81.3	$C_{22}H_{25}N_5O_2S$
3,13	4-$CH_3C_6H_4$	H	H	248-250	87.3	67.3		$C_{28}H_{29}N_5O_2S$
3.14	4-$CH_3OC_6H_4$	H	H	230-233	89.6		73.8	$C_{28}H_{29}N_5O_3S$
3.15	4-$CH_3OC_6H_4$	F	H	272-274	88.24	73.2		$C_{28}H_{28}FN_5O_3S$
3.16	4-FC_6H_4	F	H	264-266	42.72		68.2	$C_{27}H_{25}F_2N_5O_2S$
3.17	4-FC_6H_4	Br	H	284-286	78.79	73.9		$C_{27}H_{25}BrFN_5O_2S$
3.18	4-FC_6H_4	H	Br	264-266	66.67		73.5	$C_{27}H_{25}BrFN_5O_2S$
3.19	4-FC_6H_4	H	I	272-274	80.41		84.2	$C_{27}H_{25}FIN_5O_2S$

of a molecular ion is caused by cleavage of the amide bond (*m/z*=347 and 285) and degradation of *as*-triazinoquinazoline system on C(2) – C(3) and N(4) – N(5) (F_3 *m/z*=244) bonds, which have the highest intensity in spectra. Hereafter F_3eliminates parts of CO, SCH_2, CNO, which is typical for this class of heterocyclic compounds [11]. Fragment ions caused by the presence of the adamantane moiety are also observed in mass-spectra of compound **3.9** [12].

Two proton singlet of -SCH_2 group, which chemical shift depends on the electronodonor effect of the cycloalkyl fragment, is characteristic for amides **3.1-3.19**. Thus, for amides **3.1-3.7** and **3.12-3.19** this signal is observed at 4.00-3.93 ppm, whereas for amide **3.8-3.11** it is located at low field (4.25-4.21 ppm); this fact may be explained by introduction of the phenyl fragment between the amide group and the adamantine moiety. The chemical shift of a singlet signal caused by – C(O)NH-group also depends on the nature of a substituent. Thus, for amides with the adamantine fragment **3.1-3.7** the signal is observed at 7.88-7.68 ppm, for amides with 3-ethylbicycloheptyle fragment **3.12-3.19** it is at 8.18-8.05 ppm. At the same time in ^{1}H NMR – spectra of compounds, which contain 4-(1-adamantyl)phenyl fragment the signal of amide proton is observed at 10.40-10.36 ppm, it is characteristic for anilides [13]. In ^{1}H NMR-spectra of amides **3.1-3.11** in the high field two six-proton signals caused by protons at secondary carbon atoms are observed at 1.73-1.62 ppm (H-4′, 6′, 10′) and 1.98-1.84 ppm (H-2′, 8′, 9′). Three proton singlet at 2.05-2.01 ppm (H-3′, 5′, 7′) characterize protons located at tertiary carbon atoms of the adamantine fragment [13]. More intricate multiplicity is observed in ^{1}H NMR-spectra of amides **3.12-3.19**. Axial and equatorial protons of these compounds are caused the appearance of signal series at 1.51-0.92 ppm, 2.16-2.09 ppm, 2.67-2.60 ppm and 3.55-3.39 ppm [12]. All signals of the triazinoquinazoline system are also present in ^{1}H NMR-spectra of the compounds synthesized. The location and multiplicity of these signals are caused by the nature of the substituent in position 9 and 10.

^{13}C NMR-spectra of amides **3.1**, **3.3**, **3.12** correspond to the structure proposed and confirm S-regioselectivity of the reaction. The carbon atom of -SCH_2 group is observed at 36.79-35.78 ppm, signals of the secondary carbon atoms are at 36.49 ppm (4′, 6′, 10′) and 41.43 ppm (2′, 8′, 9′), signals of the tertiary ones (3′, 5′, 7′) – at 29,30-29.23 ppm [12]. Signals of aliphatic carbons of 3-ethylbicyclo[2.2.1]heptane moiety (**3.12**) are located in the high field and correspond to the structure of the compounds synthesized. Signals caused by deshielded carbons in position 2, 6 and amide carbon are also present in the low field of ^{13}C NMR-spectra of compounds **3.1**, **3.3**, **3.12**. The signals mentioned are observed at 155.20-155.16, 161.02-160.13 and 166.39-166.17 ppm, respectively.

Table 2

Results of the antiviral activity (Flu A H3N2) for the compounds studied

Comp.	Conc. Range (μg/mL)	Assay	Virus	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
3.1	0.1-100	PV	Flu A H3N2	32	–	32	1	–
	0.1-100	PNR	Flu A H3N2	3.0	–	3.6	1.2	–
3.2	0.1-100	PV	Flu A H3N2	3.2	–	>100	>31	–
	0.1-100	PNR	Flu A H3N2	4.1	–	>100	>24	–
	0.032-100	SV	Flu A H3N2	6.5	–	>100	>15	–
	0.032-100	SNR	Flu A H3N2	12	–	>100	>8.3	–
	0.032-100	TNR	Flu A H3N2	12	–	>100	>8.3	–
	0.032-100	TVYR/NR	Flu A H3N2	-	45	>100	-	>2.2
3.3	0.1-100	PV	Flu A H3N2	32	–	>100	>3.1	–
	0.1-100	PNR	Flu A H3N2	27	–	>100	>3.7	–
3.8	0.1-100	PV	Flu A H3N2	15	–	28	1.9	–
	0.1-100	PNR	Flu A H3N2	25	–	33	1.3	–
3.9	0.1-100	PV	Flu A H3N2	32	–	32	1	–
	0.1-100	PNR	Flu A H3N2	31	–	>100	>3.2	–
3.10	0.1-100	PV	Flu A H3N2	60	–	>100	>1.7	–
	0.1-100	PNR	Flu A H3N2	65	–	>100	>1.5	–
3.11	0.1-100	PV	Flu A H3N2	>19	–	19	0	–
	0.1-100	PNR	Flu A H3N2	31	–	78	2.5	–
3.12	0.1-100	PV	Flu A H3N2	32	–	32	1	–
	0.1-100	PNR	Flu A H3N2	33	–	>100	>3	–
3.13	0.1-100	PV	Flu A H3N2	32	–	>100	>3.1	–
	0.1-100	PNR	Flu A H3N2	33	–	85	2.6	–
3.14	0.1-100	PV	Flu A H3N2	4.2	–	>100	>24	–
	0.1-100	PNR	Flu A H3N2	3.1	–	43	14	–
	0.032-100	SV	Flu A H3N2	18	–	52	2.9	–
	0.032-100	SNR	Flu A H3N2	25	–	88	3.5	–
Ribavirin	0.1-100	PV	Flu A H3N2	12	–	>100	>8.3	–
	0.1-100	PNR	Flu A H3N2	11	–	>100	>9.1	–
	0.032-100	SV	Flu A H3N2	5.5	–	>100	>18	–
	0.032-100	SNR	Flu A H3N2	7.1	–	>100	>14	–
	0.032-100	TNR	Flu A H3N2	7.1	–	>100	>14	–
	0.032-100	TVYR/NR	Flu A H3N2	-	2.3	>100	-	>43

* The table presents the results of the antiviral activity compounds against strains for which the selectivity index $SI_{50} \geq 1$.

2. Evaluation of the antiviral activity

The antiviral activity of substances **3.1-3.19** was determined against respiratory viruses using standard AACF screening assay protocols [16-17]. The research was conducted on the most virulent and pathogenic strains for human Flu A H1N1, Flu A H5N1, Flu A H3N2 and less genetically various strain Flu B.

The results of preliminary tests for PV (inhibition of the viral cytopathic effect) and PNR (increase in NR dye uptake) showed that amides **3.1-3.7** with the adamantine moiety were effective against *Influenza Type A H3N2* (Tab. 2). Thus, N-(1-adamantyl-)-2-[(3-methyl-2-oxo-2*H*-[1,2,4]-triazino[2,3-*c*]quinazolin-6-yl)thio]acetamide (**3.1**) in these tests exhibited a moderate antiviral activity (EC_{50} 32 and 3 μg/ml, respectively) and was inferior comparing to Ribavirin (EC_{50} 12 and 11 μg/ml, respectively). The chemical modification of a molecule by introduction of the phenyl fragment in position 3 of 1,2,4-triazino[2,3-*c*] quinazoline system (compound **3.2**) led to increase of the antiviral activity. Thus, compound **3.2** possessed the lowest virus-inhibiting concentration (EC_{50}=3.1 and 4.2 μg/ml, respectively) in the tests mentioned and the high selectivity index (SI_{50}>31). Substitution of the phenyl fragment by 4-methylphenyl (**3.3**), 4-fluorophenyl (**3.4**) moieties and introduction of fluorine in position 9 (**3.6**) or chlorine (**3.7**) in position 10 did not lead to increase of the activity (SI_{50}>1).

Table 3

Results of the antiviral activity (Flu A H5N1) for the compounds studied

Comp.	Conc. Range (μg/mL)	Assay	Virus	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
3.2	0.1-100	PV	Flu A H5N1	3.6	–	>100	>18	–
	0.1-100	PNR	Flu A H5N1	3.3	–	>100	>30	–
	0.032-100	PV	Flu A H5N1	4.3	–	>100	>47	–
	0.032-100	PNR	Flu A H5N1	9.7	–	>100	>21	–
	0.064-200	SV	Flu A H5N1	4.1	–	>100	>49	–
	0.064-200	SNR	Flu A H5N1	5.5	–	>100	>36	–
	0.064-200	TNR	Flu A H5N1	5.5	–	>100	>36	–
	0.064-200	TVYR/NR	Flu A H5N1	-	18	>100	-	>11
Ribavirin	0.1-100	PV	Flu A H5N1	3.2	–	>100	>31	–
	0.1-100	PNR	Flu A H5N1	3.2	–	>100	>31	–
	0.032-100	PV	Flu A H5N1	6.5	–	>100	>15	–
	0.032-100	PNR	Flu A H5N1	5.7	–	>100	>18	–
	0.064-200	SV	Flu A H5N1	0.68	–	>100	>150	–
	0.064-200	SNR	Flu A H5N1	1.7	–	>100	>59	–
	0.064-200	TNR	Flu A H5N1	1.7	–	>100	>59	–
	0.064-200	TVYR/NR	Flu A H5N1	-	2.8	>100	-	>36

Additional tests (SV, SNR and TNR) and VYR-test (decrease in the virus yield assay) for compound **3.2** showed that Ribavirin in this case was more effective anticancer agent. Thus, EC_{90} for Ribavirin was 2.3 μg/ml (SI_{90}>43), while EC_{90} level for most active compound **3.2** was 45 μg/ml (SI>2.2, Tab. 2). In the given tests compound **3.14** (SI_{50}>2.9-3.5) was also less effective comparing to Ribavirin (SI_{50}>18).

Aimed to intensify the antiviral activity among the compounds synthesized we also introduced a phenyl "spacer" between the amide group and adamantine (compounds **3.8-3.11**). Unfortunately, this optimization disappointed us; N-[4-(1-adamantyl) phenyl]-2-[3-methyl-2-oxo-*2H*-[1,2,4]triazino[2,3-*c*] quinazolin-6-yl)thio]acetamides (**3.8-3.11**) showed only a moderate antiviral action (SI_{50} > 1-3.7, Tab. 2). Replacing adamantane (**3.1-3.7**) and 4-(1-adamantyl)phenyl **(3.8-3.11**) moieties with 3-ethylbicyclo [2.2.1]heptane fragment (**3.12-3.19**) allowed to prepare highly effective compounds (Tab. 2). So, compound **3.14** in PV and PNR-tests exhibited a high antiviral action (EC_{50} 4.2 and 3.1 μg/ml, respectively, and SI_{50}>24). The following SV and SNR-test showed that compound **3.14** exceeded by EC_{50} level (EC_{50} = 18-25 μg/ml, SI_{50}=3.5) was inferior to the activity of Ribavirin (EC_{50} = 5.5-7.1 μg/ml, SI_{50}>18).

Compound **3.2** was also assayed for its activity on other strains of Flu A viruses. The preliminary screening conducted (PV) on Flu A H_5N_1 strain showed that compound **3.2** possessed the virus inhibitory concentration (EC_{50} 3.6 μg/ml) at the same level as Ribavirin (EC_{50} 3.2 μg/ml, Tab. 3). The additional VYR-test confirmed a high antiviral activity of compound **3.2** (EC_{90} 18 μg/ml; SI_{90}>11), but according to EC_{90} value, the virus inhibitory activity of the compound mentioned was lower comparing to Ribavirin (EC_{90} 2.8 μg/ml; SI_{90}>36).

The similar results were observed in the process of assay for the virus inhibitory activity of compound **3.2** against Flu A H1N1 strain (Tab. 4). Thus, compound **3.2** in VYR-test demonstrated the virus inhibitory effective concentration (EC_{90}) of 18 μg/ml (SI_{90}>2.6), while the concentration of Ribavirin was 4.9 μg/ml (SI_{90}>36).

The preliminary screening (PV- and PNR-test) conducted for **3.1-3.19** against Flu B showed that the moderate antiviral activity were observed for compound **3.1** (SI_{50}>1.2), **3.11** (SI_{50}>1.3) and **3.13** (SI_{50}>1.3). Chemical modification did not lead to increase of the antiviral action, all other compounds were inactive (SI_{50}>1) against Flu B and substantially inferior to Ribavirin (SI_{50}>34).

So, the conclusion has been made that combination of carcass amine moieties with fragments of insufficiently known [9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]-triazino[2,3-c]quinazolin-6-yl)thio]acetic acid results in the compound with a significant antiviral action. High indicators of the antiviral action of **3.2** and **3.14** against *Influenza Type A H3N2* allow to suppose the expediency of further chemical modification of [1,2,4] triazino[2,3-*c*]quinazoline aimed at the rational search of antiviral agents.

Experimental Part

1. Chemistry

Melting points were determined in open capillary tubes and were uncorrected. Elemental analyses (C, H, N) performed at the ELEMENTAR vario EL

Table 4

Results of the antiviral activity (Flu A H1N1) for the compounds studied

Comp.	Conc. Range (μg/mL)	Assay	Virus	EC_{50}	EC_{90}	CC_{50}	SI_{50}	SI_{90}
3.2	0.1-100	PV	Flu A H1N1	3.2	–	>100	>31	–
	0.1-100	PNR	Flu A H1N1	3	–	>100	>33	–
	0.032-100	PV	Flu A H1N1	25	–	>100	>4	–
	0.032-100	PNR	Flu A H1N1	6.8	–	32	4.7	–
	0.064-200	SV	Flu A H1N1	8.5	–	>100	>24	–
	0.064-200	SNR	Flu A H1N1	5.7	–	>200	>35	–
	0.064-200	TNR	Flu A H1N1	5.7	–	>200	>35	–
	0.064-200	TVYR/NR	Flu A H1N1	–	77	>200	–	>2.6
Ribavirin	0.1-100	PV	Flu A H1N1	3.2	–	>100	>31	–
	0.1-100	PNR	Flu A H1N1	4.9	–	>100	>20	–
	0.032-100	PV	Flu A H1N1	5.7	–	>100	>18	–
	0.032-100	PNR	Flu A H1N1	5.9	–	>100	>17	–
	0.064-200	SV	Flu A H1N1	6.2	–	>100	>16	–
	0.064-200	SNR	Flu A H1N1	6.2	–	>100	>16	–
	0.064-200	TNR	Flu A H1N1	6.2	–	>100	>16	–
	0.064-200	TVYR/NR	Flu A H1N1	–	4.9	>100	–	>20

Cube analyzer (USA) were within ± 0.3% from the theoretical values. IR spectra (4000-600 cm^{-1}) were recorded on a Bruker ALPHA FT-IR spectrometer (Bruker Bioscience, Germany) using a module for measuring attenuated total reflection (ATR). ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz): were recorded on a Varian-Mercury 400 (Varian Inc., Palo Alto, CA, USA) spectrometer with TMS as an internal standard in DMSO-d_6 solution. LC-MS were recorded using the chromatography / mass spectrometric system consisting of an "Agilent 1100 Series" high performance liquid chromatograph (Agilent, Palo Alto, CA, USA) equipped with a diode-matrix and "Agilent LC/MSD SL" mass-selective detector (atmospheric pressure chemical ionization – APCI). Electron impact mass spectra (EI-MS) were recorded on a Varian 1200 L instrument at 70 eV (Varian Inc., Palo Alto, CA, USA).

Substances **1.1-1.12** and **2.1-2.7** were synthesized according to the reported procedures [16, 17].

Table 5

Results of the antiviral activity (Flu B) for the compounds studied

Comp.	Conc. Range (μg/mL)	Assay	Virus	EC_{50}	EC_{90}	CC_{50}	SI_{50}
3.1	0.1-100	PV	Flu B	3.2	–	3.2	1
	0.1-100	PNR	Flu B	3	–	3.7	1.2
3.9	0.1-100	PV	Flu B	32	–	32	1
3.11	0.1-100	PV	Flu B	>24	–	24	0
	0.1-100	PNR	Flu B	28	–	35	1.3
3.12	0.1-100	PV	Flu B	>18	–	18	0
	0.1-100	PNR	Flu B	17	–	17	1
	0.1-100	PNR	Flu B	>33	–	33	0
3.13	0.1-100	PV	Flu B	32	–	32	1
	0.1-100	PNR	Flu B	23	–	27	1.3
3.14	0.1-100	PV	Flu B	32	–	32	1
	0.1-100	PNR	Flu B	30	–	34	1.1
Ribavirin	0.32-320	PV	Flu B	10	–	>320	>32
	0.32-320	PNR	Flu B	9.3	–	>320	>34

* The table presents the results of the antiviral activity of compounds against strains for which the selectivity index SI≥1

Other starting materials and solvents were obtained from commercially available sources and used without additional purification.

General procedure for synthesis of N-(1-adamantyl-), N-(4-(1-adamantyl)phenyl-), (3-ethylbicyclo[2.2.1]heptan-2-yl-)-2-[(9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]-triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.1-3.18**)

Method A. N-cycloalkyl-(cycloaralkyl-)-2-chloroacetamides (0.011 mol) were added to the suspension of potassium salt of 9-R^1-10-R^2-3-R-6-thio-6,7-dihydro-2*H*-[1,2,4]triazino[2,3-*c*]quinazolin-2-ones (**1.1-1.11**) (0.01 mol) in 20 ml of propanol-2, water-propanol-2 (1:2) and refluxed for 60-90 min. The mixture was cooled and poured in water. The precipitate was filtered, dried and recrystallized from dioxane-water (1:1).

Method B. Thionyl chloride (1.2 g, 0.011 mol) was added to the solution of proper acid (**2.1-2.5**) (0.01 mol) in 10 mL of anhydrous dioxane with subsequent adding of 2-3 drops of DMF. The mixture was heated on the water bath at 60-80°C till complete elimination of hydrochloric acid. Then proper amine (0.01 mol) was added to the resulting mixture with stirring and refluxing for 2-3 h. The mixture was poured into water, neutralized to pH 6-7 by acetic acid. The precipitate was filtered, dried and recrystallized from dioxane-water (1:1).

Method C. N,N´-carbonyldiimidazole (1.95 g, 0.011 mol) was added to the solution of proper acid (**2.1-2.4**, **2.6**, **2.9**) (0.01 mol) in 10 mL of anhydrous dioxane or DMF and heated on the water bath at 60-80°C for 1 h with a calcium chloride tube. The proper amine (0.01 mol) was added with stirring to the resulting mixture and refluxed for 5-6 h. The mixture was poured in water, neutralized to pH 6-7 by acetic acid. The precipitate was filtered, dried and recrystallized from dioxane-water (1:1).

*N-(Adamantyl-1)-2-[(3-methyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.1**)*. IR (cm^{-1}): 3516, 3358, 3259, 3077, 2907, 2849, 1676, 1663, 1585, 1558, 1505, 1470, 1425, 1388, 1360, 1344, 1306, 1286, 1265, 1210, 1165, 1139, 1103, 1045, 998, 956, 885, 862, 813, 773, 687, 633, 608; ^{1}H-NMR (400 MHz) δ: 1.62 (s, 6H, H-4´, 6´, 10´ Ad), 1.96 (s, 6H, H-2´, 8´, 9´ Ad), 2.01 (s, 3H, H-3´, 5´, 7´ Ad), 2.39 (s, 3H, 3-C$\underline{H}_3$), 3.94 (s, 2H, -S-C$\underline{H}_2$-), 7.67 (t, 1H, *J* = 7.7 Hz, H-10), 7.74 (d, 1H, *J* = 7.9 Hz, H-8), 7.84 (s, 1H, -NH), 7.98 (t, 1H, *J* = 7.7 Hz, H-9), 8.46 (d, 1H, *J* = 7.9 Hz, H-11); ^{13}C-NMR (100 MHz) δ: 18.18 (CH_3), 29.23 (3´, 5´, 7´ Ad), 36.49 (4´, 6´, 10´ Ad), 36.68 (-SCH_2), 41.43 (2´, 8´, 9´ Ad), 51.72 (1´ Ad), 118.55 (11a), 126.05 (8), 126.65 (10), 127.88 (11), 136.03 (9), 144.24 (11b), 151.94 (3), 154.94 (7a), 155.16 (6), 161.02 (2), 166.17 (CONH); LC-MS, *m/z* = 436 [M+1], 438 [M+3]; Anal. calcd. for $C_{23}H_{25}N_5O_2S$: C, 63.43; H, 5.79; N, 16.08; S, 7.36; Found: C, 63.42; H, 5.79; N, 16.08; S, 7.34.

*N-(Adamantyl-1)-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.2**)*. IR (cm^{-1}): 3287, 3067, 2904, 2848, 1674, 1644, 1590, 1555, 1509, 1487, 1469, 1455, 1359, 1337, 1310, 1286, 1269, 1242, 1183, 1161, 1136, 1102, 1020, 988, 939, 878, 844, 811, 782, 773, 753, 688, 668, 653, 615; ^{1}H-NMR (400 MHz) δ: 1.63 (s, 6H, H-4´, 6´, 10´ Ad), 1.97 (s, 6H, H-2´, 8´, 9´ Ad), 2.01 (s, 3H, H-3´, 5´, 7´ Ad), 3.99 (s, 2H, -S-C$\underline{H}_2$-), 7.64-7.57 (m, 3H, H-3´, 4´, 5´ 3-Ph), 7.69 (t, 1H, *J* = 7.7 Hz, H-10), 7.76 (d, 1H, *J* = 7.8 Hz, H-8), 7.88 (s, 1H, -NH), 8.01 (t, 1H, *J* = 7.7 Hz, H-9), 8.28 (d, 2H, *J* = 8.1 Hz, H-2´, 6´ 3-Ph), 8.49 (d, 1H, *J* = 7.9 Hz, H-11); LC-MS, *m/z* = 498 [M+1], 500 [M+3]; Anal. calcd. for $C_{28}H_{27}N_5O_2S$: C, 67.58; H, 5.47; N, 14.07; S, 6,44; Found: C, 67.58; H, 5.47; N, 14.09; S, 6.46.

*N-(Adamantyl-1)-2-[(3-(4-methylphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.3**)*. IR (cm^{-1}): 3318, 3065, 3037, 2972, 2905, 2849, 1682, 1658, 1588, 1562, 1538, 1496, 1470, 1453, 1399, 1377, 1359, 1339, 1321, 1304, 1285, 1269, 1240, 1182, 1164, 1154, 1139, 1119, 1089, 1045, 989, 939, 876, 831, 810, 784, 770, 710, 701, 685, 653, 641, 625; ^{1}H-NMR (400 MHz) δ: 1.63 (s, 6H, H-4´, 6´, 10´ Ad), 1.98 (s, 6H, H-2´, 8´, 9´ Ad), 2.01 (s, 3H, H-3´, 5´, 7´ Ad), 2.42 (s, 3H, 3-(4-C$\underline{H}_3$Ph)), 3.99 (s, 2H, -S-C$\underline{H}_2$-), 7.39 (d, 2H, H-3´, 5´ 3-(4-CH_3Ph)), 7.68 (t, 1H, *J* = 7.7 Hz, H-10), 7.82-7.74 (m, 2H, H-8, -NH), 7.98 (t, 1H, *J* = 7.7 Hz, H-9), 8.24 (d, 2H, H-2´, 6´ 3-(4-CH_3Ph)), 8.48 (d, 1H, *J* = 7.9 Hz, H-11); ^{13}C-NMR (100 MHz): δ: 21.66 (CH_3), 29.30 (3´, 5´, 7´ Ad), 36.49 (4´, 6´, 10´ Ad), 36.79 (-SCH_2), 41.43 (2´, 8´, 9´ Ad), 51.74 (1´ Ad), 118.25 (11a), 126.09 (8), 126.73 (10), 127.93 (11), 129.32 (1´ Ph), 129.53 (2´, 6´ Ph), 129.78 (3´, 5´ Ph), 135.99 (9), 142.20 (4´ Ph), 144.20 (3), 149.29 (11b), 150.80 (7a), 155.20 (6), 160.13 (2), 166.17 (CONH); LC-MS, m/z =512 [M +1], 514 [M +3]; Anal. calcd. for $C_{29}H_{29}N_5O_2S$: C, 68.08; H, 5.71; N, 13.69; S, 6.27; Found: C, 69.00; H, 5.71; N, 13.70; S, 6.27.

*N-(Adamantyl-1)-2-{[3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl]thio}acetamides (**3.4**)*. IR (cm^{-1}): 3358, 2905, 2888, 2846, 1745, 1675, 1660, 1587, 1562, 1547, 1511, 1492, 1465, 1408, 1357, 1338, 1317, 1297, 1267, 1230, 1183, 1171, 1157, 1135, 1099, 1072, 1015, 992, 940, 894, 840, 813, 803, 769, 714, 704, 694, 676, 669, 637, 619; ^{1}H NMR δ: 1.67 (br.s., 6H, H-4, 4`, 6, 6`, 10, 10` Ad), 1.99 (br.s., 6H, H-2, 2`, 8, 8`, 9, 9` Ad), 2.06 (br.s., 3H, H-3, 5, 7 Ad), 3.94 (s, 2H, S-CH_2-), 7.32 (t, *J* = 7.7 Hz, 2H, 3-Ph H-3`,5`), 7.67 (m, 2H, -NH, H-10), 7.76 (d, *J* = 7.8 Hz, 1H, H-8), 7.94 (t, *J* = 7.8 Hz, 1H, H-9), 8.53 (d, *J* = 5.5 Hz, 2H, 3-Ph H-2`, 6`), 8.53 (d, *J* = 7.8 Hz, 1H, H-11); LC-MS, m/z =516 [M +1], 518 [M +3]; Anal. calcd. for $C_{28}H_{26}FN_5O_2S$: C, 65.22; H, 5.08; F, 3.68; N, 13.58; S, 6.22; Found: C, 65.20; H, 5.08; F, 3.68; N, 13.55; S, 6.25.

*N-(Adamantyl-1)-2-[(9-fluoro-2-oxo-3-phenyl-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.5**).* IR (cm^{-1}): 3309, 3080, 2905, 2850, 1673, 1649, 1591, 1566, 1556, 1512, 1479, 1443, 1346, 1317, 1283, 1259, 1213, 1193, 1165, 1129, 1102, 988, 971, 927, 881, 860, 841, 811, 753, 704, 686, 653, 625; ^{1}H NMR δ: 1.67 (br.s., 6H, H-4, 4`, 6, 6`, 10, 10`Ad); 1.98 (br.s., 6H, H-2, 2`, 8, 8`, 9, 9` Ad), 2.06 (br.s., 3H, H-3, 5, 7 Ad), 3.93 (s, 2H, S-CH_2-), 7.82-7.21 (m, 6H, H-8, 10, 3-Ph H-3`, 4`, 5`, -NH), 8.33 (d, *J* = 7.1 Hz, 2H, 3-Ph H-2`, 6`), 8.61 (dd, *J* = 7.7, 5.9 Hz, 1H, H-11); LC-MS, m/z =516 [M +1], 518 [M +3]; Anal. calcd. for $C_{28}H_{26}FN_5O_2S$: C, 65.22; H, 5.08; F, 3.68; N, 13.58; S, 6.22; Found: C, 65.23; H, 5.08; F, 3.68; N, 13.59; S, 6.20

*N-(Adamantyl-1)-2-{[9-fluoro-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl]thio} acetamides (**3.6**).* IR (cm^{-1}): 3271, 3069, 2903, 2850, 1673, 1657, 1620, 1598., 1585, 1570, 1555, 1510, 1501, 1483, 1471, 1445, 1413, 1368, 1344, 1324, 1298, 1279, 1262, 1242, 1227, 1175, 1159, 1128, 1100, 1093, 1070, 10456, 1015, 994, 973, 960, 930, 909, 869, 859, 822, 799, 761, 730, 714, 696, 678, 655, 637, 620; ^{1}H NMR δ: 1.67 (br.s., 6H, H-4, 4`, 6, 6`, 10, 10` Ad), 1.98 (br.s., 6H, H-2, 2`, 8, 8`, 9, 9` Ad), 2.06 (br.s., 3H, H-3, 5, 7 Ad), 3.94 (s, 2H, S-CH_2-), 7.34 (t, *J* = 8.0 Hz, 2H, 3-Ph H-3`,5`), 7.56-7.41 (m, 2H, H-8, H-10), 7.69 (br.s, 1H, -NH), 8.51-8.32 (m, 2H, 3-Ph H-2`, 6`), 8.65-8.52 (m, 1H, H-11); LC-MS, m/z =534 [M +1], 536 [M +3]; Anal. calcd. for $C_{28}H_{25}F_2N_5O_2S$: C, 63.03; H, 4.72; F, 7.12; N, 13.12; S, 6.01; Found: C, 63.06; H, 4.72; F, 7.12; N, 13.11; S, 6.00.

*N-(Adamantyl-1)-2-{[10-chloro-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl]thio} acetamides (**3.7**).* IR (cm^{-1}): 3271, 3052, 2902, 2849, 16734, 1657, 1585, 1550, 1539, 1509, 1497, 1467, 1411, 1368, 1360, 1336, 1324, 1310, 1281, 1256, 1232, 1213, 1164, 1136, 1120, 1104, 1089, 1046, 1013, 990, 954, 908, 894, 857, 830, 821, 800, 769, 744, 731, 708, 691, 671, 638, 623; ^{1}H NMR δ: 1.67 (br.s., 6H, H-4, 4`, 6, 6`, 10, 10` Ad), 1.98 (br.s., 6H, H-2, 2`, 8, 8`, 9, 9` Ad), 2.03 (br.s., 3H, H-3, 5, 7 Ad), 3.93 (s, 2H, S-CH_2-), 7.33 (t, *J* = 8.4 Hz, 2H, 3-Ph H-3`,5`), 7.68 (s, 1H, -NH), 7.77 (d, *J* = 8.6 Hz, 1H, H-9), 7.92 (d, *J* = 8.3 Hz, 1H, H-8), 8.45 (m, 3H, H-11, 3-Ph H-2`, 6`); LC-MS, m/z =551 [M +1], 553 [M +3]; Anal. calcd. for $C_{28}H_{25}ClFN_5O_2S$: C, 61.14; H, 4.58; Cl, 6.45; F, 3.45; N, 12.73; S, 5.83; Found: C, 61.17; H, 4.58; Cl, 6.45; F, 3.45; N, 12.72; S, 5.81.

*N-[4-(1-Adamantyl)phenyl]-2-[(3-methyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.8**).* IR (cm^{-1}): 3251, 3184, 2897, 2845, 1655, 1583, 1558, 1503, 1466, 1449, 1433, 1405, 1393, 1361, 1332, 1315, 1286, 1259, 1220, 1206, 1190, 1163, 1131, 1101, 1046, 1016, 969, 955, 832, 807, 772, 715, 699, 685, 630, 607; ^{1}H-NMR (400 MHz) δ: 1.73 (s, 6H, H-4′, 6′, 10′ Ad), 1.84 (s, 6H, H-2′, 8′, 9′ Ad), 2.05 (s, 3H, H-3′, 5′, 7′ Ad), 2.39 (s, 3H, 3-C$\underline{H}_3$-), 4.21 (s, 2H, -S-C$\underline{H}_2$-), 7.30 (d, 2H, *J* = 8.5 Hz, H-3′, 5′ -NHC$_6\underline{H}_4$-Ad), 7.55 (d, 2H, *J* = 8.5 Hz, H-2′, 6′ -NHC$_6\underline{H}_4$-Ad), 7.66 (t, 1H, *J* = 7.7 Hz, H-10), 7.70 (d, 1H, *J* = 7.9 Hz, H-8), 7.95 (t, 1H, *J* = 7.7 Hz, H-9), 8.45 (d, 1H, *J* = 7.9 Hz, H-11), 10.36 (s, 1H, -NH); LC-MS, *m/z* = 512 [M+1], 514 [M+3]; Anal. calcd. for $C_{29}H_{29}N_5O_2S$: C, 68.08; H, 5.71; N, 13.69; S, 6.27; Found: C, 68.10; H, 5.71; N, 13.70; S, 6.29.

*N-[4-(1-Adamantyl)phenyl]-2-[(3-phenyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.9**).* IR (cm^{-1}): 3349, 3047, 2982, 2899, 2849, 1678, 1657, 1596, 1587, 1564, 1546, 1519, 1498, 1486, 1470, 1444, 1407, 1380, 1341, 1331, 1311, 1287, 1263, 1246, 1237, 1187, 1171, 1138, 1100, 1076, 1033, 1017, 1002, 988, 963, 941, 895, 877, 848, 836, 810, 779, 768, 751, 706, 687, 665, 654, 636; ^{1}H-NMR (400 MHz) δ: 1.73 (s, 6H, H-4′, 6′, 10′ Ad), 1.84 (s, 6H, H-2′, 8′, 9′ Ad), 2.05 (s, 3H, H-3′, 5′, 7′ Ad), 4.25 (s, 2H, -S-C$\underline{H}_2$-), 7.31 (d, 2H, *J* = 8.5 Hz, H-3′, 5′ -NHC$_6\underline{H}_4$-Ad), 7.56 (d, 2H, *J* = 8.5 Hz, H-2′, 6′ -NHC$_6\underline{H}_4$-Ad), 7.77-7.59 (m, 5H, H-3′, 4′, 5′ 3-Ph, H-8, 10), 7.98 (t, 1H, *J* = 7.7 Hz, H-9), 8.30 (d, 2H, *J* = 7.3, H-2′, 6′ 3-Ph), 8.49 (d, 1H, *J* = 7.9 Hz, H-11), 10.40 (s, 1H, -NH); EI-MS, *m/z* (I_{rel}, %) = 396 (6.3), 395 (5.7), 348 (16.9), 347 (73.5), 346 (49.1), 345 (16.1), 339 (7.2), 316 (5.4), 307 (8.7), 302 (15.9), 301 (64.8), 269 (16.0), 268 (5.2), 258 (5.1), 254 (13.8), 253 (57.9), 252 (10.8), 246 (7.0), 245 (16.1), 244 (99.9), 243 (26.4), 240 (5.4), 228 (5.8), 227 (49.5), 226 (8.0), 218 (25.8), 217 (29.8), 216 (58.8), 213 (8.9), 212 (7.1), 211 (7.0), 210 (16.6), 197 (9.5), 196 (55.8), 195 (5.6), 189 (5.4), 188 (9.0), 186 (7.2), 185 (20.9), 184 (11.2), 183 (7.0), 182 (8.6), 180 (6.1), 179 (8.3), 178 (43.2), 170 (42.5), 161 (5.0), 160 (5.6), 159 (17.8), 158 (9.6), 157 (9.0), 156 (20.0), 155 (8.7), 154 (9.4), 153 (12.0), 152 (9.6), 148 (21.9), 145 (8.0), 144 (7.8), 143 (16.9), 142 (7.5), 141 (6.0), 135 (22.4), 134 (8.4), 133 (24.1), 132 (32.9), 131 (12.6), 130 (16.0), 129 (22.9), 128 (18.2), 127 (12.5), 119 (10.4), 118 (21.9), 117 (22.4), 116 (18.3), 115 (12.5), 106 (5.3), 105 (7.2), 104 (14.4), 103 (80.9), 101 (12.8), 95 (7.0), 94 (27.6), 93 (34.4), 92 (12.9), 90 (12.7), 89 (10.5), 86 (13.8), 79 (26.3), 77 (10.2), 75 (5.4), 67 (16.5), 66 (7.4), 65 (21.6), 64 (14.3), 63 (15.4), 56 (14.9), 55 (19.1), 53 (6.1), 47 (9.2), 43 (15.2), 41 (21.1)LC-MS, *m/z* = 574 [M+1], 575 [M+2], 576 [M+3]; Anal. calcd. for $C_{34}H_{31}N_5O_2S$: C, 71.18; H, 5.45; N, 12.21; S, 5.59; Found: C, 71.19; H, 5.45; N, 12.23; S, 5.61.

*N-[4-(1-Adamantyl)phenyl]-2-[(3-(4-methylphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl) thio]acetamides (**3.10**).* IR (cm^{-1}): 3344, 2982, 2915, 2898, 2882, 2849, 1675, 1655, 1584, 1562, 1542, 1517, 1490, 1469, 1451, 1406, 1368, 1340, 1329, 1308, 1285, 1264, 1237, 1189, 1139, 1125, 1106, 1071, 1036, 1017, 989, 961, 942, 893, 875, 834, 807, 779, 768, 708, 686, 665, 643, 624; ^{1}H-NMR (400 MHz) δ: 1.73 (s, 6H, H-4′, 6′, 10′ Ad), 1.84 (s, 6H, H-2′, 8′,

9′ Ad), 2.05 (s, 3H, H-3′, 5′, 7′ Ad), 2.42 (s, 3H, 3-(4-C$\underline{H}_3$Ph)), 4.25 (s, 2H, -S-C$\underline{H}_2$-), 7.31 (d, 2H, *J* = 8.5, H-3′, 5′ -NHC$_6\underline{H}_4$-Ad), 7.41 (d, 2H, *J*= 7.9 Hz, H-3′, 5′ 3-(4-CH_3Ph)), 7.56 (d, 2H, *J* = 8.5 Hz, H-2′, 6′ -NHC$_6\underline{H}_4$-Ad), 7.68 (t, 1H, *J* = 7.7 Hz, H-10), 7.74 (d, 1H, *J* = 7.8 Hz, H-8), 7.99 (t, 1H, *J* = 7.7 Hz, H-9), 8.25 (d, 2H, *J* = 7.9 Hz, H-2′, 6′ 3-(4-CH_3Ph)), 8.49 (d, 1H, *J* = 7.9 Hz, H-11), 10.39 (s, 1H, -NH); LC-MS, *m/z* = 588 [M+1], 590 [M+3]; Anal. calcd. for $C_{35}H_{33}N_5O_2S$: C, 71.53; H, 5.66; N, 11.92; S, 5.46; Found: C, 71.53; H, 5.66; N, 11.92; S, 5.44.

*N-[4-(1-Adamantyl)phenyl]-2-[(3-(4-methoxyphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl) thio]acetamides (**3.11**).* IR (cm^{-1}): 3346, 2982, 2898, 2849, 1678, 1654, 1597, 1563, 1538, 1518, 1504, 1490, 1469, 1452, 1406, 1370, 1341, 1315, 1304, 1255, 1244, 1177, 1140, 1117, 1050, 1036, 1016, 989, 942, 879, 843, 808, 780, 769, 722, 701, 687, 665, 643, 621; ^{1}H-NMR (400 MHz) δ: 1.73 (s, 6H, H-4′, 6′, 10′ Ad), 1.84 (s, 6H, H-2′, 8′, 9′ Ad), 2.05 (s, 3H, H-3′, 5′, 7′ Ad), 3.88 (s, 3H, 3-(4-C$\underline{H}_3$OPh)), 4.25 (s, 2H, -S-C$\underline{H}_2$-), 7.17 (d, 2H, J = 8.3, H-3′, 5′ 3-(4-CH_3OPh)), 7.31 (d, 2H, J = 8.5 Hz, H-3′, 5′ -NHC$_6\underline{H}_4$-Ad), 7.56 (d, 2H, J = 8.5 Hz, H-2′, 6′ -NHC$_6\underline{H}_4$-Ad), 7.68 (t, 1H, J = 7.7 Hz, H-10), 7.74 (d, 1H, J = 7.8 Hz, H-8), 7.97 (t, 1H, J = 7.7 Hz, H-9), 8.39 (d, 2H, J = 8.3, H-2′, 6′ 3-(4-CH_3OPh)), 8.49 (d, 1H, J = 7.9 Hz, H-11), 10.40 (s, 1H, -NH); LC-MS, m/z = 604 [M+1], 607 [M+3]; Anal. calcd. for $C_{35}H_{33}N_5O_3S$: C, 69.63; H, 5.51; N, 11.60; S, 5,31; Found: C, 69.64; H, 5.51; N, 11.61; S, 5.32.

*N-(3-Ethylbicyclo[2.2.1]hept-2-yl)-2-[(3-methyl-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl)thio]acetamides (**3.12**).* IR (cm^{-1}): 3287, 2944, 2866, 1667, 1636, 1584, 1558, 1538, 1509, 1469, 1454, 1418, 1386, 1360, 1337, 1287, 1261, 1208, 1173, 1133, 1102, 1045, 955, 880, 856, 768, 698, 685, 630, 607; ^{1}H-NMR (400 MHz) δ: 1.48-0.94 (m, 11H, 3-C$\underline{H}_3$CH$_2$-, 3-CH$_3$C$\underline{H}_2$-, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl), 2.16-2.09 (m, 2H, H-3, 4 bicyclo[2.2.1]heptyl), 2.38 (s, 3H, 3-C$\underline{H}_3$), 2.66 (m, 1H, H-1 bicyclo[2.2.1]heptyl), 3.50-3.39 (m, 1H, H-2 bicyclo[2.2.1]heptyl), 3.96 (s., 2H, -S-C$\underline{H}_2$-), 7.66 (t, 1H, J = 7.7 Hz, H-10), 7.73 (d, 1H, *J* = 7.9 Hz, H-8), 7.97 (t, 1H, *J* = 7.7 Hz, H-9), 8.05 (d, 1H, *J* = 8.5 Hz, -NHC(O)-), 8.46 (d, 1H, *J* = 7.9 Hz, H-11); ^{13}C-NMR (100 MHz): δ: 18.17 (CH_3), 18.79 (C$\underline{H}_3$CH$_2$), 20.70 (6′), 28.87 (CH$_3$C$\underline{H}_2$), 30.33 (5′), 35.78 (-SCH$_2$), 36.33 (7′), 36.85 (1′), 38.95 (4′), 48.51 (3′), 49.37 (2′), 118.50 (11a), 125.99 (8), 126.70 (10), 127.90 (11), 135.91 (9), 144.21 (3), 151.92 (11b), 154.74 (7a), 155.16 (6), 160.98 (2), 166.39 (CONH); EI-MS, *m/z* (I_{rel}, %) = 303 (7.2), 302 (45.1), 285 (31.8), 246 (7.9), 245 (24.1), 244 (100.0), 143 (16.3), 218 (5.6), 217 (17.7), 216 (51.5), 188 (4.9), 179 (6.3), 170 (7.9), 148 (12.6), 143 (7.7), 129 (7.0), 123 (5.9), 122 (9.0), 95 (24.4), 93 (14.0), 91 (5.3), 90 (8.6), 81 (11.8), 67 (20.2), 57 (8.7), 56 (9.4), 55 (12.9); LC-MS, *m/z* = 424 [M+1], 426 [M+3]; Anal. calcd. for $C_{22}H_{25}N_5O_2S$: C, 62.39; H, 5.95; N, 16.54; S, 7.57; Found: C, 62.40; H, 5.95; N, 16.54; S, 7.58.

*N-(3-Ethylbicyclo[2.2.1]hept-2-yl)-2-[(3-(4-methylphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl) thio]acetamides (**3.13**).* IR (cm^{-1}): 3285, 3078, 2950, 2868, 1668, 1633, 1589, 1562, 1549, 1501, 1468, 1454, 1391, 1372, 1335, 1308, 1270, 1239, 1183, 1135, 1104, 1019, 991, 939, 830, 782, 770, 712, 699, 684, 641, 626; ^{1}H-NMR (400 MHz) δ: 1.51-0.94 (m, 11H, 3-C$\underline{H}_3$CH$_2$-, 3-CH$_3$C$\underline{H}_2$-, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl, 2.16-2.09 (m, 2H, H-3, 4 bicyclo [2.2.1]heptyl), 2.42 (s, 3H, 3-(4-C$\underline{H}_3$Ph), 2.67 (m, 1H, H-1 bicyclo[2.2.1]heptyl), 3.60-3.41 (m, 1H, H-2 bicyclo[2.2.1]heptyl), 4.00 (s., 2H, -S-C$\underline{H}_2$-), 7.41 (d, 2H, J = 7.5 Hz, H-3, H-5 4-CH_3Ph), 7.68 (t, 1H, *J* = 7.7 Hz, H-10), 7.76 (d, 1H, *J* = 7.9 Hz, H-8), 7.98 (t, 1H, *J* = 7.7 Hz, H-9), 8.07 (d, 1H, *J* = 8.5 Hz, -NHC(O)-), 8.24 (d, 2H, *J* = 7.5 Hz, H-2, H-6 4-CH_3Ph), 8.48 (d, 1H, *J* = 7.9 Hz, H-11); LC-MS, *m/z* = 500 [M+1], 502 [M+3]; Anal. calcd. for $C_{28}H_{29}N_5O_2S$: C, 67.31; H, 5.85; N, 14.02; S, 6.42; Found: C, 67.31; H, 5.85; N, 14.02; S, 6.42.

*N-(3-Ethylbicyclo[2.2.1]hept-2-yl)-2-{[3-(4-methoxyphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl) thio]acetamides (**3.14**).* IR (cm^{-1}): 3274, 3067, 2945, 2866, 1668, 1643, 1590, 1563, 1545, 1500, 1469, 1454, 1421, 1372, 1340, 1317, 1306, 1288, 1272, 1259, 1238, 1174, 1137, 1105, 1049, 1016, 989, 965, 940, 878, 840, 810, 766, 723, 700, 684, 641, 622; ^{1}H-NMR (400 MHz) δ: 1.47-0.92 (m, 11H, 3-C$\underline{H}_3$CH$_2$-, 3-CH$_3$C$\underline{H}_2$-, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl), 2.16-2.11 (m, 2H, H-3, 4 bicyclo[2.2.1]heptyl), 2.60 (m, 1H, H-1 bicyclo[2.2.1]heptyl), 3.55-3.43 (m, 1H, H-2′ bicyclo[2.2.1]heptyl), 3.87 (s, 3H, 3-(4-C$\underline{H}_3$OPh), 4.00 (s, 2H, -S-C$\underline{H}_2$-), 7.16 (d, 2H, *J* = 7.9 Hz, H-3, H-5 4-CH_3OPh), 7.68 (t, 1H, *J* = 7.7 Hz, H-10), 7.76 (d, 1H, *J* = 7.9 Hz, H-8), 7.98 (t, 1H, *J* = 7.7 Hz, H-9), 8.08 (d, 1H, *J* = 8.5 Hz, -NHC(O)-), 8.37 (d, 2H, *J* = 7.9 Hz, H-2, H-6 4-CH_3OPh), 8.48 (d, 1H, *J* = 7.9 Hz, H-11); LC-MS, *m/z* = 516 [M+1], 518 [M+3]; Anal. calcd. for $C_{28}H_{29}N_5O_3S$: C, 65.22; H, 5.67; N, 13.58; S, 6.22; Found: C, 65.24; H, 5.67; N, 13.56; S, 6.20.

*N-(3-Ethylbicyclo[2.2.1]heptan-2-yl)-2-[(9-fluoro-3-(4-methoxyphenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c] quinazolin-6-yl)thio]acetamides (**3.15**).* IR (cm^{-1}): 3289, 3072, 2954, 2869, 1667, 1634, 1591, 1564, 1546, 1502, 1477, 1455, 1443, 1422, 1392, 1350, 1323, 1285, 1259, 1217, 1176, 1164, 1131, 1104, 1071, 1023, 992, 974, 926, 872, 841, 808, 779, 766, 723, 694, 681, 641, 619; ^{1}H NMR δ: 1.74-0.64 (m, 11H, 3-C$\underline{H}_3$CH$_2$-, 3-CH$_3$C$\underline{H}_2$-, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1] heptyl), 2.12 (m, 1H, H-3 bicyclo[2.2.1]heptyl), 2.18 (m, 1H, H-4 bicyclo[2.2.1]heptyl), 2.69 (m, 1H, H-1 bicyclo [2.2.1] heptyl), 3.46 (s, 1H, H-2 bicyclo[2.2.1] heptyl), 3.91 (s, 3H, O-CH_3), 3.94 (s, 2H, S-C$\underline{H}_2$-), 7.08 (d, *J* = 8.4 Hz , 2H, 3-Ph H-3`, 5`), 7.51-7.42 (m, 1H, H-10), 8.17 (s, 1H, H-8), 8.41 (d, *J* = 8.2 Hz, 2H, 3-Ph H-2`, 6`), 8.66-8.52 (m, 1H, H-11); LC-MS, m/z =534

[M +1], 536 [M +3]; Anal. calcd. for $C_{28}H_{28}FN_5O_3S$: C, 63.02; H, 5.29; F, 3.56; N, 13.12; S, 6.01; Found: C, 63.05; H, 5.29; F, 3.56; N, 13.10; S, 6.03.

*N-(3-Ethylbicyclo[2.2.1]hept-2-yl)-2-{[9-fluoro-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c] quinazolin-6-yl]thio}acetamides (**3.16**).* IR (cm^{-1}): 3270, 3073, 2954, 2871, 1672, 1644, 1586, 1555, 1510, 1498, 1483, 1445, 1412, 1375, 1347, 1321, 1297, 1279, 1262, 1229, 1159, 1132, 1101, 1070, 1015, 995, 973, 929, 869, 858, 847, 823, 761, 715, 696, 679, 657, 637, 621; ^{1}H NMR δ: 1.66-0.64 (m, 14H, 3-C<u>H</u>$_3$CH$_2$-, 3-CH$_3$C<u>H</u>$_2$-, H-1, 3, 4, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl), 3.67-3.40 (m, 1H, H-2 bicyclo [2.2.1]heptyl), 3.95 (s, 2H, S-CH$_2$-), 7.33 (t, *J* = 8.9 Hz, 2H, 3-Ph H-3`,5`), 7.57-7.42 (m, 2H, H-8,10), 8.18 (s, 1H, NH), 8.52-8.39 (m, 2H, 3-Ph H-2`, 6`), 8.61 (dd, *J* = 10.6, 5.4 Hz, 1H, H-11); LC-MS, m/z =522 [M +1], 524 [M +3]; Anal. calcd. for $C_{27}H_{25}F_2N_5O_2S$: C, 62.17; H, 4.83; F, 7.28; N, 13.43; S, 6.15; Found: C, 62.19; H, 4.83; F, 7.28; N, 13.45; S, 6.14.

*N-(3-Ethylbicyclo[2.2.1]heptan-2-yl)-2-[(9-bromo-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c] quinazolin-6-yl)thio]acetamides (**3.17**).* IR (cm^{-1}): 3275, 3072, 2949, 2868, 1670, 1639, 1583, 1556, 1498, 1458, 1424, 1411, 1392, 1373, 1339, 1312, 1296, 1270, 1237, 1179, 1161, 1149, 1103, 1075, 1060, 991, 968, 939, 895, 845, 820, 765, 715, 681, 647, 615; ^{1}H NMR δ: 1.66-0.78 (m, 12H, 3-C<u>H</u>$_3$CH$_2$-, 3-CH$_3$C<u>H</u>$_2$-, H-3, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl), 2.25-2.03 (m, 2H, H-1, 4 bicyclo[2.2.1]heptyl), 3.61-3.42 (m, 1H, H-2 bicyclo [2.2.1]heptyl), 4.04-3.81 (m, 2H, S-CH$_2$-), 7.32 (t, *J* 7.6 Hz, 2H, 3-Ph H-3`,5`), 7.77 (d, *J* = 7.6 Hz, 1H, H-10), 8.07-7.82 (m, 2H, H-8, NH), 8.53-8.34 (m, 3H, H-11, 3-Ph H-2`, 6`); LC-MS, m/z =582 [M +0], 586 [M +4]; Anal. calcd. for $C_{27}H_{25}BrFN_5O_2S$: C, 55.67; H, 4.33; Br, 13.72; F, 3.26; N, 12.02; S, 5.50; Found: C, 55.69; H, 4.33; Br, 13.72; F, 3.26; N, 12.00; S, 5.53.

*N-(3-Ethylbicyclo[2.2.1]heptan-2-yl)-2-(10-bromo-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c] quinazolin-6-yl)thio]acetamides (**3.18**).* IR (cm^{-1}): 3278, 2952, 2868, 1668, 1644, 1588, 1556, 1496, 1466, 1412, 1377, 1336, 1283, 1261, 1236, 1218, 1175, 1161, 1139, 1121, 1103, 1077, 1064, 1015, 991, 952, 896, 845, 773, 730, 717, 691, 669, 656, 635, 624; ^{1}H NMR δ: 1.67-0.59 (m, 12H, 3-C<u>H</u>$_3$CH$_2$-, 3-CH$_3$C<u>H</u>$_2$-, H-3, 5, 5′, 6, 6′, 7, 7′ bicyclo[2.2.1]heptyl), 2.29-1.98 (m, 2H, H-1, 4 bicyclo[2.2.1]heptyl), 3.61-3.32 (m, 1H, H-2 bicyclo[2.2.1]heptyl), 3.96 (s, 2H, S-CH$_2$-), 7.34 (t, *J* = 8.5 Hz, 2H, 3-Ph H-3`,5`), 7.70 (d, *J* = 6.4 Hz, 1H, H-9), 8.11-7.96 (m, 2H, H-8, NH), 8.43 (d, *J* = 6.5 Hz, 2H, 3-Ph H-2`, 6`), 8.58 (s, 1H, H-11); LC-MS, m/z =582 [M +0], 586 [M +4]; Anal. calcd. for $C_{27}H_{25}BrFN_5O_2S$: C, 55.67; H, 4.33; Br, 13.72; F, 3.26; N, 12.02; S, 5.50; Found: C, 55.69; H, 4.33; Br, 13.72; F, 3.26; N, 12.00; S, 5.51.

N-(3-Ethylbicyclo[2.2.1]hept-2-yl)-2-{[10-iodo-3-(4-fluorophenyl)-2-oxo-2H-[1,2,4]triazino[2,3-c]quinazolin-6-yl]thio}acetamides (***3.19***). IR (cm^{-1}): 3274, 3080, 2946, 2866, 1667, 1641, 1585, 1555, 1495, 1462, 1410, 1374, 1331, 1280, 1261, 1234, 1216, 1158, 1138, 1101, 1074, 1013, 988, 946, 843, 771, 717, 688, 646, 633, 622; ^{1}H NMR δ: 1.58-0.82 (m, 12H, 3-C<u>H</u>$_3$CH$_2$-, 3-CH$_3$C<u>H</u>$_2$-, H-3, 5, 5′, 6, 6′, 7, 7` bicyclo [2.2.1]heptyl), 2.28-2.00 (m, 2H,H-1, 4 bicyclo[2.2.1] heptyl), 3.63-3.33 (m, 1H, H-2 bicyclo [2.2.1]heptyl), 3.95 (s, 2H, S-CH$_2$-), 7.33 (t, *J* = 8.1 Hz, 2H, 3-Ph H-3`,5`), 7.55 (dd, *J* = 8.3, 1.8 Hz, 1H, H-8), 8.08 (m, 1H, NH), 8.18 (d, *J* = 8.2 Hz, 1H, H-9), 8.46 (t, *J* = 5.6 Hz, 2H, 3-Ph H-2`, 6`), 8.79 (s, 1H, H-11); LC-MS, m/z =630 [M +1], 632 [M +3]; Anal. calcd. for $C_{27}H_{25}FIN_5O_2S$: C, 51.52; H, 4.00; F, 3.02; I, 20.16; N, 11.13; S, 5.09; Found: C, 51.55; H, 4.00; F, 3.02; I, 20.16; N, 11.10; S, 5.08.

2. Methods for assay of the antiviral activity

A. Rapid Screening Assay

The primary antiviral assay was performed at a respiratory viruses panel (Flu A H1N1/California/07/2009/MDCK, Flu A H3N2/Perth/16/2009/MDCK, Flu A H5N1/Vietnam/1203/2004H/MDCK, Flu B/Florida/4/2006/MDCK) with the protocol of the NIAID's Antimicrobial Acquisition and Coordination [27-29]. This drug was ribavirin for Flu A H1N1, Flu A H3N2, Flu A H5N1, Flu B.

Results for each compound tested were reported as the virus–inhibitory concentration, 50% endpoint (EC_{50} μg/ml), or 90% effective concentration (EC_{90} μg/ml) and the cell-inhibitory concentration, 50% endpoint (CC_{50} μg/ml) were determined. The total selectivity index (SI_{50}) was calculated as a ratio of (EC_{50})/(CC_{50}). The SI_{50} of 3 or greater indicates that confirmatory testing is needed.

2.1. Inhibition of the Viral Cytopathic Effect (CPE)

This test, run in 96 well flat-bottomed microplates, was used for the initial antiviral evaluation of compounds. In this CPE inhibition test, four $\log_{10}$ dilutions of each test compound (e.g. 1000, 100, 10, 1 Eg/ml) were added to 3 cups containing the cell monolayer; within 5 min. At the next step the virus was added and the plate was sealed and incubated at 37 °C. The CPE read microscopically when untreated infected controls developed a 3 to 4+ CPE (approximately 72 to 120 h). The known positive control drug was evaluated in parallel with test drugs in each test.

2.2. Increase in Neutral Red (NR) Dye Uptake

This test was run to validate the CPE inhibition seen in the initial test, and utilized the same 96-well microplates after the CPE had been read. When neutral red was added to the medium, cells that were not damaged by virus took up a greater amount of dye displayed on a computerized microplate autoreader. The EC_{50} was determined from this dye uptake.

2.3. Decrease in the Virus Yield Assay (VYR-test)

Compounds considered active by CPE inhibition and by NR dye uptake were re-tested on reduction

of the virus yield by assaying frozen and thawed eluates from each cup for a virus titer by serial dilution onto monolayers of susceptible cells. Development of CPE in these cells is indication of the presence of an infectious virus. Similarly as in the initial tests, a known active drug were run in parallel as a positive control. The 90% effective concentration (EC_{90}), being the drug concentration inhibiting the virus yield by 1 $\log_{10}$, was determined from these data.

2.4. Methods for assay of cytotoxicity

In the CPE inhibition tests, two wells of uninfected cells treated with each concentration of the test compounds was run in parallel with the infected, treated wells. At the time CPE was determined microscopically. The toxicity control cells were also examined microscopically for any changes in cell appearance compared to normal control cells run in the same plate. These changes may be enlargement, granularity, cells with ragged edges, filmy appearance, rounding, detachment from the surface of the well, or other changes. These changes were given a designation of T (100% toxic), PVH (partially toxic-very heavy-80%), PH (partially toxic-heavy-60%), P (partially toxic-40%), Ps (partially toxic-slight-20%), or 0 (no toxicity-0%), conforming to the degree of cytotoxicity seen. The 50% cell inhibitory (cytotoxic) concentration (IC_{50}) was determined by regression analysis of these data.

Conclusions

A new class of potent antiviral agents, namely of [9-R^1-10-R^2-3-R-2-oxo-2H-[1,2,4]-triazino[2,3-c]quinazolin-6-yl)thio]acetamides derivatives with the fragments of carcass amines has been developed. High indicators of the antiviral action of **3.2** and **3.14** against Influenza Type A H3N2 allow to suppose the expediency of further chemical modification of [1,2,4]triazino [2,3-c]quinazoline aimed at the rational search of antiviral agents.

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