Biological Evaluation of 3-Aminoisoquinolin-1(2*H*)-one Derivatives as Potential Anticancer agents

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Anticancer activity of a series of 3-(hetaryl/aryl)amino substituted isoquinolin-1(2*H*)-ones has been studied within the international scientific program "NCI-60 Human Tumor Cell Lines Screen". Screening was performed *in vitro* on 60 cell lines of lungs, kidneys, CNS, ovaries, prostate, and breast cancer, epithelial cancer, leukemia, and melanoma. The most effective compounds were those with thiazolyl or pyrazolyl substituent at 3-amino group and had no substituents at C(4) of the isoquinoline cycle. We identified a new lead compound, 3-(1,3-thiazol-2-ylamino)isoquinolin-1(2*H*)-one **12**, which effectively prevents tumor cell growth (average lg GI_{50} = -5.18, lg TGI = -4.1, lg LC_{50} > -4.0) with good selectivity.

Introduction

Cancer is one of the main worldwide public health concerns. According to the World Cancer Report published by the World Health Organization in 2020, cancer is one of the leading causes of premature death [1]. The number of people that are diagnoses with cancer every year in Europe will increase from the current 3.5 million to more than 4.3 million by 2035. Therefore, there is an urgent need to pay much attention to update and modify leading drugs in terms of medicinal chemistry and drug design in order to provide more potent and effective therapies. One of the ways to solve this problem is to use the hybrid drugs design strategy which tries to find solutions for undesired properties of the current drug such as drug resistance, drug–drug interactions, and known side effects, just to mention a few. It also provides hybrid structures that are capable of interacting with multiple targets simultaneously with improved efficacy. In essence, the aim of molecular hybridization is to produce a single chemical entity through combination of two or more distinct pharmacophore subunits present in the structures of two or more known bioactive derivatives. For example, pyrazole and thiazole

derivatives can be cited as examples of the successful application of this strategy [2-6].

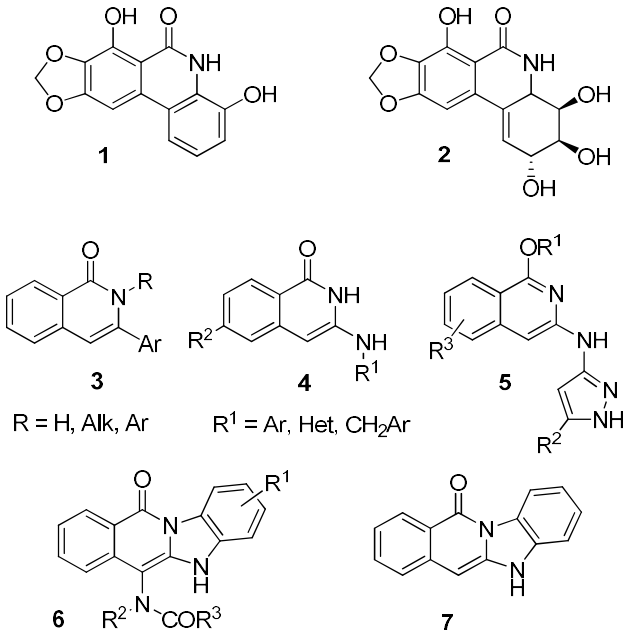


Figure 1. Structures of lead anticancer isoquinoline derivatives.

The aim of the current work was to study the anticancer activity of hybrid structures based on isoquinoline. In recent years, the isoquinoline scaffold has gained recognition as a helpful and promising scaffold for the design and development of effective anticancer drugs. Due to distinct and compelling therapeutic properties, natural and synthetic derivatives of isoquinolin-1(2*H*)-one have been widely investigated in medicinal and organic chemistry. One such example is isoquinolinone alkaloids derived from plants of the Amaryllidaceae family – narciprimine (**1**) and narciclasine (**2**) depicted in **Figure 1** [7]. The latter, in the NCI sixty cell line anticancer drug screen exhibited a mean IC_{50} value of 0.046 μM *in vitro*. 3-Aryl substituted isoquinolinones (**3**, R = H, Alk) displayed diverse anticancer activities against different human cancer cell lines (A549, SK-OV-3, SK-Mel-2, HCT-15, XF-498) comparable to that of doxorubicin [8]. A series of 2,3-diaryl isoquinolinone derivatives **3** (R = Ar) exhibited significant antiproliferative against MCF-7 breast cancer cells and potential anti-angiogenesis effects *in vivo* via ERa and VEGFR-2 dependent mechanisms [9]. Through review of literature, we found that some phosphatase inhibitors (Cdc25B, IC_{50} = 0.77÷13.66 μM) [10, 11] with isoquinolin-l-one scaffold bear 3-(hetaryl/aryl)amino or 3-benzylamino fragments (**4**). The method of synthesis of a number of Aurora kinase inhibitors (**5**) is also based on 3-(pyrazol-3-ylamino)-isoquinolin-1(2*H*)-ones [12]. The strong activity in suppressing proliferation and growth of glioblastoma cells [13], colorectal (SW620, HT29, GI50 = 23.8÷24.13 μM) [14] and CNS (SF-295, GI = 55%) [15] human cancer cell lines was found for condensed derivatives having a 3-aminoisoquinolinone moiety (**6**). The unsaturated 5*H*-benzo[4,5]imidazo[1,2-*b*]isoquinolin-1-one (**7**) exhibited significant Cdc25B inhibition (IC_{50} = 5.3 μM) [11]. In this context, the consolidation of the 3-aminoisoquinolinone template and novel carbo/heteroaromatic rings as novel pharmacophores seems to be promising for obtaining highly effective anticancer drugs.

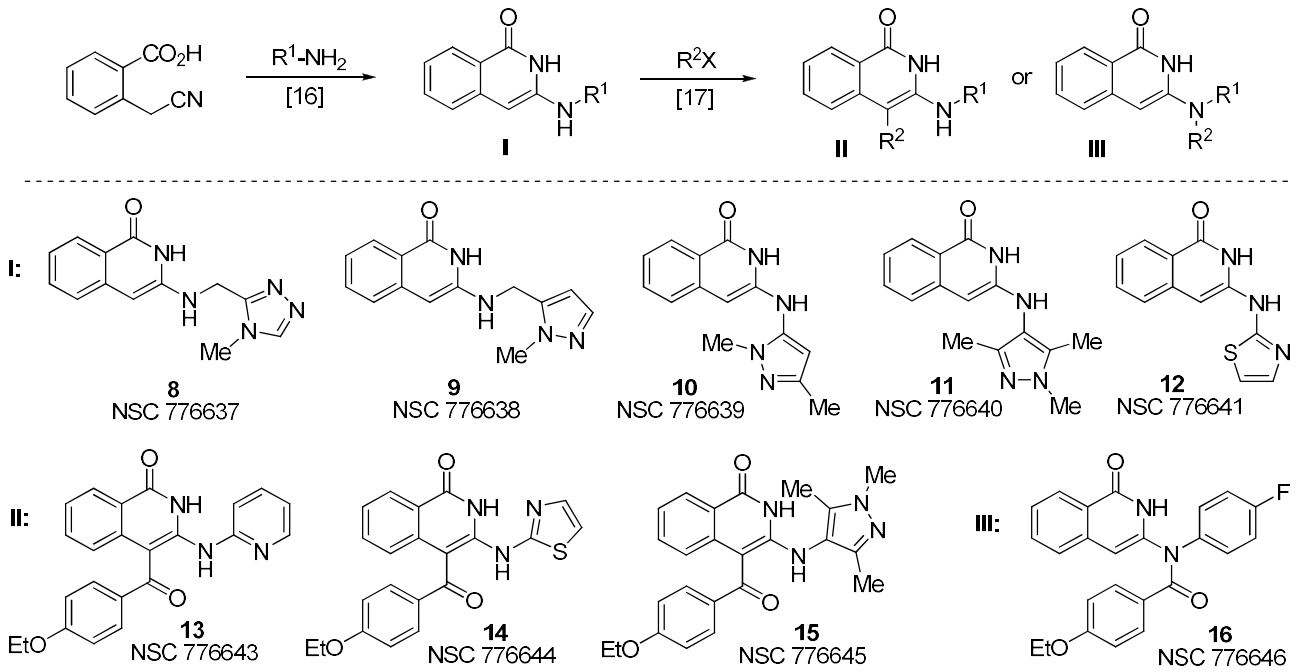


Figure 2. General scheme for the synthesis of isoquinolinone derivatives and compounds selected for *in vitro* testing.

Earlier [16], we have developed a simple and convenient method for the synthesis of 3-aminoisoquinolin-1(2*H*)-ones (**I**) from 2-(cyanomethyl)benzoic acid that made possible the variation of the substituent at the 3-amino group (**Figure 2**).

The unique electronic nature of the 3-aminoisoquinolinone moiety allowed regiospecific substitution on the enamine moiety of the molecules, such as acylation at either the C(4) or the 3-N positions [17]. This reaction allowed producing a series of 3-(hetaryl/aryl)amino-isoquinolinones and their acyl derivatives (**II**) and the study of their *in vitro* antiproliferative activities.

Experimental part

Chemistry

3-[(Hetarylmethyl)amino]isoquinolin-1(2*H*)-ones **8,9** [16] and 3-(hetarylamino)-isoquinolin-1(2*H*)-ones **10-12** [16], 4-(4-ethoxybenzoyl)-3-(hetarylamino)isoquinolin-1(2*H*)-ones **13-15** [17] and *N*-(4-fluorophenyl)-*N*-(1-oxo-1,2-dihydro-3-isoquinolinyl)-4-ethoxybenzamide **16** [17] were synthesized following the procedures described in the corresponding cited sources.

In vitro Anticancer Screening

In vitro anticancer screening methodology as well as data interpretation rules are described in details at the NCI Development Therapeutics Program site [18].

Results and discussion

The structures of the 3-aminoisoquinolin-1(2*H*)-ones were submitted to US National Institute of Health, and the nine compounds **8-12** and **13-16** (**Figure 2**) were selected for evaluation of their antiproliferative activity within an international scientific

program. These compounds (**8-16**) were granted NSC codes, viz., NSC 776637 ÷ NSC 776641, and NSC 776643 ÷ NSC 776646, respectively. The elected compounds were submitted to *in vitro* anticancer assay against a full panel of 60 cancer cell lines taken from different tissues (lungs, kidneys, CNS, ovaries, prostate, breast cancer, epithelial cancer, leukemia, and melanoma). The compounds were tested at a single dose concentration of 10^{-5} M. Growth percentage (GP) of cancer cells compared to the control (in the absence of a chemical substance, 100%) was determined [19-22].

Isoquinolinone derivatives **8-16** exhibit different levels of anticancer activity depending on the substituents at the 3-amino group and at C(4) (**Table 1**). It has been shown that 3-hetarylamino derivatives **10-12** are the most active against cancer cells in a wide range of cell lines.

The 1,3-thiazol-2-ylamino derivative **12** was the most potent of all the derivatives tested, with mean GP value of 49.57% for the majority of cell lines. It showed to be selective towards the breast cancer sub-panel, being active against all the corresponding cell lines. The most sensitive were MDA-MB-468 and MCF7 cell lines with GP 10.72% and 26.62%, respectively. Other cell lines that showed more than 70% growth inhibition in the micro molar range were UO-31 (GP 22.78%) and SK-MEL-5 (GP 22.08%) belonging to the renal cancer and melanoma sub-panels respectively. Also, compound **12** showed significant inhibition of most of the leukemia, lung, CNS, renal and breast cancer cell lines with GP less than 50%. It is worthy to note that the thiazol-2-ylamino derivative **12** showed good selectivity towards the colon, melanoma and ovarian cancer sub-panels.

1,3-Dimethyl-1*H*-pyrazol-5-yl (**10**) and 1,3,5-trimethyl-1*H*-pyrazol-4-yl (**11**) isoquinolinones, unlike the thiazolyl derivative **12**, showed higher selectivity level towards cancer cells of all sub-panels, but with higher mean GP value of 59.51% and 61.68%, respectively. Replacement of the thiazole with pyrazole in compounds **10** and **11** maintained the antitumor activity against most of the cell lines of leukemia and breast cancer sub-panels. The most sensitive are RPMI-8226 (leukemia, GP 34.33% (**10**) and 28.68% (**11**)) and MDA-MB-468 (breast cancer, GP 19.94% (**10**) and 15.70% (**11**)). Pyrazolyl derivatives **10** and **11** showed high effectiveness against ovarian OVCAR-4 cell line with GP values of 30.45% and 18.20%, respectively. The dimethylpyrazolyl derivative **10** had a lethal effect on renal A498 cell line (GP -3.00%) and inhibited the growth of melanoma SK-MEL-5 cells by more than 70% (GP 25.26%). At the same time, the trimethylpyrazolyl derivative **11** showed the opposite result: lethal effect on melanoma SK-MEL-5 cell line (GP -12.06%) and GP of 25.60% against renal A498 cells. In addition, compounds **10** and **11** proved to have a comparable effect on the SF-295 cell line of CNS cancer with GP values of 40.97% and 40.21%, respectively.

Table 1. Mitotic activity (GP) of the 3-aminoisoquinolin-1(2*H*)-one derivatives **8-16** towards NCI 60 cell lines at the 10^{-5} M concentration

Cell line name	8	9	10	11	12	13	14	15	16
Leukemia									
CCRF-CEM	–	–	47.31	56.48	43.13	–	–	66.59	–
HL-60(TB)	–	–	76.26	–	48.51	–	–	–	51.48
K-562	–	–	47.23	41.21	49.27	–	–	52.95	–
MOLT-4	–	–	50.93	57.97	30.19	70.00	–	41.92	70.87
RPMI-8226	–	–	34.33	28.68	30.30	–	78.96	40.58	–
SR	–	–	59.37	38.72	47.84	–	–	66.44	–
Non-Small Cell Lung Cancer									
A549/ATCC	–	–	59.38	58.23	54.69	–	–	68.00	–
HOP-62	–	–	64.13	65.22	49.89	–	–	–	–
NCI-H226	–	–	59.51	54.54	44.97	–	–	–	–
NCI-H23	–	–	46.32	42.19	50.20	–	–	–	–
NCI-H322M	–	–	79.19	78.97	57.37	–	–	–	–
NCI-H460	–	–	70.47	75.59	66.98	–	–	75.50	–
NCI-H522	–	–	nt	36.21	42.28	68.59	61.18	55.16	39.68
Colon Cancer									
COLO 205	–	–	76.77	–	61.01	–	–	75.68	–
HCC-2998	–	–	–	–	61.42	–	–	–	–
HCT-116	–	–	58.56	52.17	52.60	–	–	69.24	–
HCT-15	–	–	63.27	70.68	44.44	–	–	74.72	–
HT29	–	–	nt	78.58	55.21	–	–	71.19	–
KM12	–	–	67.91	78.19	50.48	–	–	71.49	–
SW-620	–	–	–	–	78.85	–	–	–	–
CNS Cancer									
SF-268	–	–	78.96	72.71	58.62	–	–	73.04	–
SF-295	–	–	40.97	40.21	47.57	–	–	69.72	–
SF-539	–	–	52.13	75.91	45.07	–	–	–	–
SNB-19	–	–	–	69.33	45.45	–	–	71.05	–
SNB-75	–	–	64.51	64.44	45.61	77.98	–	70.15	–
U251	–	–	67.79	69.53	36.12	–	–	71.03	–
Melanoma									
LOX IMVI	–	–	47.20	69.35	50.88	–	–	–	–
M14	–	–	70.38	64.78	56.36	–	–	73.03	76.33
MDA-MB-435	–	–	68.89	61.42	48.07	–	–	77.36	–
SK-MEL-2	–	–	nt	–	72.60	–	–	–	–
SK-MEL-28	–	–	–	–	–	–	–	–	–
SK-MEL-5	–	77.47	25.26	-12.06	22.08	–	–	42.60	79.71
UACC-257	–	–	53.52	48.81	55.00	–	–	–	–
UACC-62	–	–	53.99	67.76	51.34	72.56	–	65.87	64.92

Table 1. (Contd.)

Cell line name	8	9	10	11	12	13	14	15	16
Ovarian Cancer									
IGROV1	–	–	78.16	78.49	42.80	–	–	–	–
OVCAR-3	–	–	58.43	50.36	33.18	–	–	74.84	–
OVCAR-4	–	–	30.45	18.20	40.97	–	–	66.05	–
OVCAR-5	–	–	–	–	–	–	–	–	–
OVCAR-8	–	–	57.87	55.31	46.51	–	–	61.00	70.11
NCI/ADR-RES	–	–	70.79	69.97	57.30	–	–	64.62	–
SK-OV-3	–	–	–	–	52.41	–	–	–	–
Renal Cancer									
786-0	–	–	65.52	65.03	75.74	–	–	–	–
A498	–	–	-3.00	25.60	35.19	77.76	63.45	65.98	–
ACHN	–	–	72.93	69.95	65.46	–	–	–	–
CAKI-1	–	–	66.59	67.37	48.41	–	–	–	–
RXF 393	–	–	64.65	59.43	45.86	–	–	65.60	–
SN12C	–	–	57.25	68.09	42.49	–	–	67.22	–
TK-10	–	–	nt	62.59	48.06	–	–	–	–
UO-31	77.45	–	32.51	50.28	22.78	43.33	–	46.51	78.76
Prostate Cancer									
PC-3	–	–	58.96	79.43	52.77	64.41	–	58.19	–
DU-145	–	–	71.58	66.69	68.66	–	–	79.83	–
Breast Cancer									
MCF7	–	68.83	33.10	52.14	26.62	72.31	78.93	68.12	–
MDA-MB-231/ATCC	–	–	41.93	54.19	31.45	–	–	66.08	77.50
HS 578T	–	–	71.50	75.26	61.98	–	–	79.63	–
BT-549	–	–	46.35	41.70	36.39	–	–	67.39	–
T-47D	–	–	42.27	45.05	36.00	–	–	66.67	–
MDA-MB-468	–	78.74	19.94	15.70	10.72	77.42	67.73	51.97	–
Mean GP	**99.72**	**102.14**	**59.51**	**61.68**	**49.57**	**89.49**	**95.13**	**73.55**	**90.31**

–: GP more than 80%, nt: not tested

Replacement of the azolyl fragment with azolylmethyl as in compounds **8** and **9** leads either to a sharp decrease (growth inhibition < 20%) or to a complete loss of the antitumor activity (**Table 1**), which may be attributed to restricted conformation of compounds **8** and **9** on the receptor binding site due to an increase in the spatial volume of the substituent at the 3-amino group.

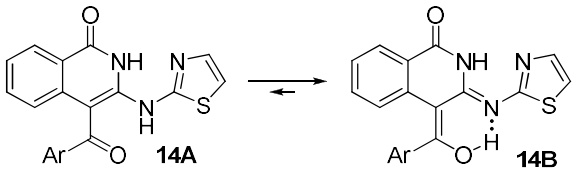
A similar effect was noted in an earlier study [11] evaluating the requirements of 3-anilinoisoquinolinone scaffold for the inhibition of the *in vitro* phosphatase activity of recombinant human Cdc25B. Thus, the retention of a relatively low inhibitory activity of isoquinolinone derivative **9** towards some breast cancer cell lines (MCF7, MDA-MB-468) and melanoma (SK-MEL-5) is probably due to the

presence of another strong pharmacophore (pyrazolyl fragment) in the molecule.

The unique 'enamine-like' structure of the isoquinolinone core provides an additional area for diversification. Therefore, several compounds (**13-16**) among the readily available 4-acyl and 3-*N*-acyl substituted derivatives of 3-aminoisoquinolinones [17] with an additional pharmacophore – *p*-ethoxybenzoyl fragment – were selected for evaluation of their antiproliferative activity. However, the introduction of a 4-(*p*-ethoxybenzoyl) substituent proved to be detrimental to the inhibitory activity for all tested compounds, similar to that observed for 3-[(4-methylphenyl)amino]isoquinolinone with an unsubstituted 4-benzoyl group [11]. Preliminary *in vitro* antitumor screening revealed that unsubstituted 3-[(4-fluorophenyl)amino] and 3-[(4-pyridyl)amino] derivatives of isoquinolinone showed good inhibition [11], while their benzoyl derivatives **13** and **16** turned out to be inactive for most of the cancer cell lines excepted a few of them. The most sensitive were leukemia HL-60(TB) and lung cancer NCI-H522 cell lines for compound **16** with GP 51.48% and 39.68%, respectively. Renal UO-31 cell line was sensi-tive to compound **13** with GP value of 43.33%.

Benzoylated thiazolyl derivative **14** is also almost completely inactive against most of the cancer cell lines. The value of its growth inhibition exceeded 30% in only three cases: lung cancer NCI-H522, renal A498 and breast cancer MDA-MB-468 cell lines. Pyrazolyl derivative **15** displayed the most potent overall antiproliferative activity among the 4-benzoyl derivatives tested, with mean GP value of 73.55%. It exhibited a more than 50% inhibition for some of the cell lines belonging to different tumor sub-panels: leukemia cells MOLT-4 and RPMI-8226 giving GP values of 41.92%, and 40.58%, respectively, melanoma cells SK-MEL-5 with GP a value of 42.60%, and renal cancer cells UO-31 with a GP value of 46.51%.

Among all the 4-benzoyl derivatives tested, the sharpest decrease of the antitumor activity was observed for the thiazolyl derivative **14** as compared to its unsubstituted analogue **12**, and may be attributed to the presence of two acceptor substituents in the molecule. In the case of compound **14**, this leads to deeper changes in the distribution of electron density in the isoquinolinone moiety due to the formation of an *ortho*-quinone structure favored by an intramolecular hydrogen bond between the 3-imino and 4-enol fragments [17], as shown in **Scheme 1**.



Scheme 1. Tautomeric forms of thiazolyl derivative **14**.

Thus, **Table 1** revealed that compound **12** is the most active towards numerous cancer cell lines belonging to different tumor sub-panels. Therefore, it was selected in advanced assay against a panel of approximately 60 tumor cell lines at 10-fold dilution of five concentrations (10^{-4}-10^{-8} M), the set of which was identical to that for the pre-screening stage (**Table 2**). The results were compared with 5-fluorouracil (5-FU) as reference drug (**Table 2**), which has been used as a standard for more than 40 years [23, 24].

Table 2. Parameter values (lg) of the anticancer activity of compound **12** and 5-fluorouracil as reference compound against the NCI 60 human cancer cell lines (five-dose assay).

Cell Line	12		5-FU[a]	Cell Line	12		5-FU[a]
	GI_{50}	TGI	GI_{50}		GI_{50}	TGI	GI_{50}
Leukemia							
CCRF-CEM	-5.07	>-4.00	-5.01	MOLT-4	-5.27	>-4.00	-6.45
HL-60(TB)	-4.82	>-4.00	-5.60	SR	-4.98	>-4.00	-5.01
K-562	-5.28	>-4.00	-5.45				
Non-small cell lung cancer							
A549/ATCC	-4.89	>-4.00	-6.80	NCI-H23	-5.30	>-4.00	-6.75
HOP-62	-5.48	-4.19	-7.28	NCI-H322M	-5.11	>-4.00	-6.67
HOP-92	-5.57	-5.06	-6.64	NCI-H460	-4.64	>-4.00	-6.03
NCI-H226	-5.18	>-4.00	-6.96	NCI-H522	-4.98	>-4.00	-6.80
Colon cancer							
COLO 205	-5.09	>-4.00	-6.80	HT29	-4.48	>-4.00	-6.75
HCC-2998	-4.63	>-4.00	-7.28	KM12	-5.04	>-4.00	-6.67
HCT-116	-5.16	>-4.00	-6.64	SW-620	-4.42	>-4.00	-6.03
HCT-15	-5.39	>-4.00	-6.96				
CNS cancer							
SF-268	-5.26	>-4.00	-5.80	SNB-19	-5.29	>-4.00	-5.42
SF-295	-5.15	>-4.00	-6.64	SNB-75	-5.69	-4.97	-4.10
SF-539	-5.42	>-4.00	-7.20	U251	-5.41	-4.12	-6.04
Melanoma							
LOX IMVI	-5.16	>-4.00	-6.61	SK-MEL-28	-4.80	>-4.00	-5.99
MALME-3M	>-4.00	>-4.00	-7.29	SK-MEL-5	-5.41	-4.54	-6.33
M14	-5.21	>-4.00	-6.01	UACC-257	-4.94	>-4.00	-5.45
MDA-MB-435	-5.16	>-4.00	-	UACC-62	-5.32	>-4.00	-6.28
SK-MEL-2	-4.83	-4.07	-4.25				
Ovarian cancer							
IGROV1	-5.28	>-4.00	-5.91	OVCAR-8	-5.32	>-4.00	-
OVCAR-3	-5.26	>-4.00	-7.80	NCI/ADR-RES	-5.15	>-4.00	-4.66
OVCAR-5	-4.01	>-4.00	-5.76	SK-OV-3	-5.29	>-4.00	-5.91
Renal cancer							
786-0	-4.95	>-4.00	-6.14	RXF 393	-5.57	-5.00	-5.58
A498	-5.85	-4.63	-6.40	SN12C	-5.11	>-4.00	-6.30
ACHN	-5.21	>-4.00	-6.53	TK-10	-5.07	-4.05	-5.95
CAKI-1	-5.14	>-4.00	-7.14	UO-31	-5.86	>-4.00	-5.85
Prostate cancer							
PC-3	-5.41	>-4.00	-5.63	DU-145	-4.61	>-4.00	-6.44
Breast cancer							
MCF7	-5.86	>-4.00	-7.10	BT-549	-5.69	-4.78	-4.97
MDA-MB-231/ATCC	-5.79	-4.17	-5.18	T-47D	-5.72	>-4.00	-5.09
HS 578T	-5.41	>-4.00	-5.01	MDA-MB-468	-5.94	-	-

[a] Data for 5-fluorouracil are given according to [25]

The high antitumor potential of compound **12** has been confirmed by a significant level of inhibition (average lg GI_{50} = -5.18) and cytostatic (average lg TGI = -4.1) effects for some cell lines. However, the level of cytotoxic effect lg LC_{50} of all cell lines was not high and exceeded average value of -4.00. The cell lines that were the most sensitive to the tested compound **12** were: HOP-92 non-small cell lung (lg GI_{50} = -5.57, lg TGI = -5.06), SNB-75 CNS (lg GI_{50} = -5.69, lg TGI = -4.97), A498 renal (lg GI_{50} = -5.85, lg TGI = -4.63), RXF 393 renal (lg GI_{50} = -5.57, lg TGI = -5.00), MDA-MB-231/ATCC breast (lg GI_{50} = -5.79, lg TGI = -4.17) and BT-549 breast (lg GI_{50} = -5.69, lg TGI = -4.78). 3-(Thiazolylamino)isoquinolinone **12** showed the greatest activity against most of the cell lines of the lung, colon, CNS, ovarian, renal and breast cancer sub-panels.

Overall, the activity of 5-fluorouracil (average lg GI_{50} = -6.10 [25]) is higher than isoquinolinone **12**. Nevertheless, compound **12** demonstrates a higher activity than standard 5-fluorouracil does against: SNB-75 (CNS); SK-MEL-2 (melanoma); NCI/ADR-RES (ovarian); MDA-MB-231/ATCC, HS 578T, BT-549 and T-47D (breast). Moreover, compounds **12** and 5-fluorouracil proved to have similar efficiency against the renal RXF 393 and UO-31 cell lines. Additionally, compound **12** demonstrated a remarkable activity towards breast MDA-MB-468 with lg GI_{50} value of -5.97.

We have performed COMPARE [26] analyses for the active compound **12** in order to investigate the similarity of its cytotoxicity pattern with those of known anticancer standard agents, NCI active synthetic and natural compounds, which are present in public available databases [27]. According to the Chaddock scale [28], compound **12** has a low positive COMPARE correlation of GI_{50} vector with triciribine phosphate (r = 0.35). Moreover, matrix COMPARE using TGI vector showed moderate positive correlations with triciribine phosphate and spirohydantoin mustard (r = 0.6 for both) (**Figure 3**).

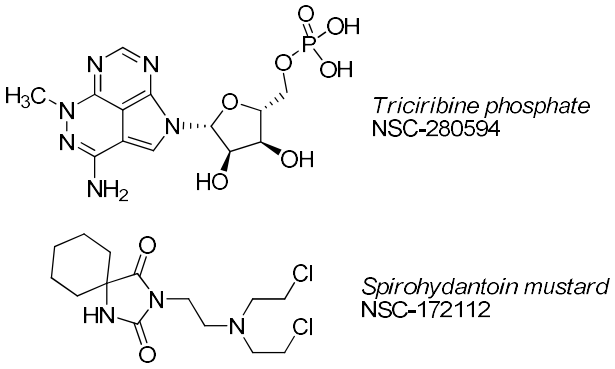


Figure 3. Structures of NCI anticancer standard agents.

The mechanism of action for triciribine (NCS 280594) includes its prevention Protein kinase B (AKT) membrane translocation [29], and specifically its binding to the PH domain of AKT, thereby blocking its recruitment to the membrane, leading to subsequent inhibition of AKT phosphorylation in tumours [30, 31]. The mechanism of antineoplastic activity of spirohydantoin mustard (NCS 172112), like for all other alkylating agents, lies in its ability to alkylate DNA guanine nucleobases and, thus, to

prevent uncoupling of DNA strands, which is a required step for any cell to divide [32]. Obviously, the antiproliferative activity of 3-(thiazolylamino)isoquinolinone **12** is not associated with the ability to alkylate DNA guanine nucleobases. Taken together, this suggests that the most likely molecular target for 3-(thiazolylamino)isoquinolinone **12** is Protein kinase B. However, the absence of a very high positive correlation with the above compounds requires further experimental studies for the correct interpretation of the results obtained.

Conclusions

Herein we demonstrated the *in vitro* anticancer activity of some 3-(hetaryl/aryl)aminoisoquinolin-1(2*H*)-ones against the NCI 60 human cancer cell lines. Therein, the nature of the substituent at the C(4) and 3-N positions of isoquinoline cycle critically affects the level of activity. More favorable is the presence of a thiazolyl or a pyrazolyl substituent at the 3-amino group. In the same time, the presences of acceptor substituents at C(4) position or at 3-amino group and an increase in the spatial volume of the substituent at the 3-amino group are detrimental to the inhibitory activity. Although the critical biochemical targets of 3-hetarylaminoisoquinolin-1(2*H*)-ones have not been identified, they show an interesting antiproliferative profile against different human tumor-derived cell lines, especially: 3-[(1,3-dimethyl-1*H*-pyrazol-5-yl)amino] and 3-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)amino]isoquinolin-1(2*H*)-ones **10** and **11** against RPMI-8226 (leukemia), MDA-MB-468 (breast cancer), OVCAR-4 (ovarian), A498 (renal) and SK-MEL-5 (melanoma) cell lines. We identified a new lead compound, 3-(1,3-thiazol-2-ylamino)isoquinolin-1(2*H*)-one **12**, which efficiently prevents tumor cell growth of MDA-MB-468 and MDA-MB-231/ATCC (breast cancer), UO-31 and A498 (renal), SNB-75 (CNS) and HOP-92 (non-small cell lung) cell lines. Thus, the 3-aminoisoquinoline series provides an attractive new core structure for additional analysis and optimization.

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