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The effect of heterocyclic substituent at C-3 position of 1-(4-methylpiperazin-1-yl)isoquinolines on their anticancer activity

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Aim. A comparative analysis of the anti-cancer activity of 1-(4-methylpiperazin-1-yl)isoquinolines with different heteroaromatic substituents in C-3 position: 2-methylthiazol-4-yl, 2-phenylthiazol-4-yl, 2-(pyridin-4-yl)thiazol-4-yl, imidazo[2,1-*b*]thiazol-6-yl, quinoxalin-2-yl, 6,7-dimethylquinoxalin-2-yl. **Methods.** Biological tests; statistic methods. **Results.** *In vitro* screening of the anticancer activity showed that the derivatives with 2-phenylthiazol-4-yl, quinoxaline-2-yl, 6,7-dimethylquinoxalin-2-yl substituents demonstrated the highest level of anticancer activity; however, they were inferior to 2-(pyridin-4-yl)thiazol-4-yl. The product with the 2-methylthiazol-4-yl residue almost did not demonstrated cytotoxicity. Comparative analysis showed no significant correlation with known drugs; hence these compounds have specific molecular targets. **Conclusions.** The resulting 1-amino-3-hetarylisoquinolines are a promising class of compounds for anticancer drug development. The level and direction of the activity significantly depend on the nature of heterocyclic substituents.

Key words: *in vitro* screening, anticancer activity, 1-amino-3-hetarylisoquinolines.

Introduction

Cancer remains a painful problem even today. A long-known class of bioactive heterocycles, isoquinolines, has received significant attention in the search of new anticancer drugs. The high biological activity of naturally occurring isoquinoline alkaloids prompted the active development of the chemistry of this class of het-

erocycles, and the increasing diversity of isoquinoline modifications led to the discovery of new types of biological activity.

Although numerous examples confirmed the prospects for isoquinoline-based drugs in the cancer treatment, many questions remain about the mechanism of action and the synthe-

sis of new derivatives to establish the SAR more clearly. Review [1] summarized an extensive array of the data on the anticancer activity of widespread natural alkaloids of the isoquinoline group (Berberine, Sanguinarine, Chelerythrine, Noscapine, *etc.*). These compounds are quite effective against many types of cancer. For example, isoquinoline alkaloids display the anticancer effects such as induction of cell cycle arrest, apoptosis, and autophagy. The effects are partly attributed to their bind-

ing to DNA or proteins, inhibition of enzyme activity, or epigenetic modulation. The natural polycondensed structures with an isoquinoline fragment, such as Saframycin A, show high cytotoxicity (Fig. 1) [2], which became the basis for the development of the synthetic anticancer drug Phthalascidin (Pt 650) [3] and several related structures [4, 5]. The anticancer activity of the natural antibiotic (-)-Quinocarcin [6] inspired the authors [7] to create the compounds of general structure **1**, which also

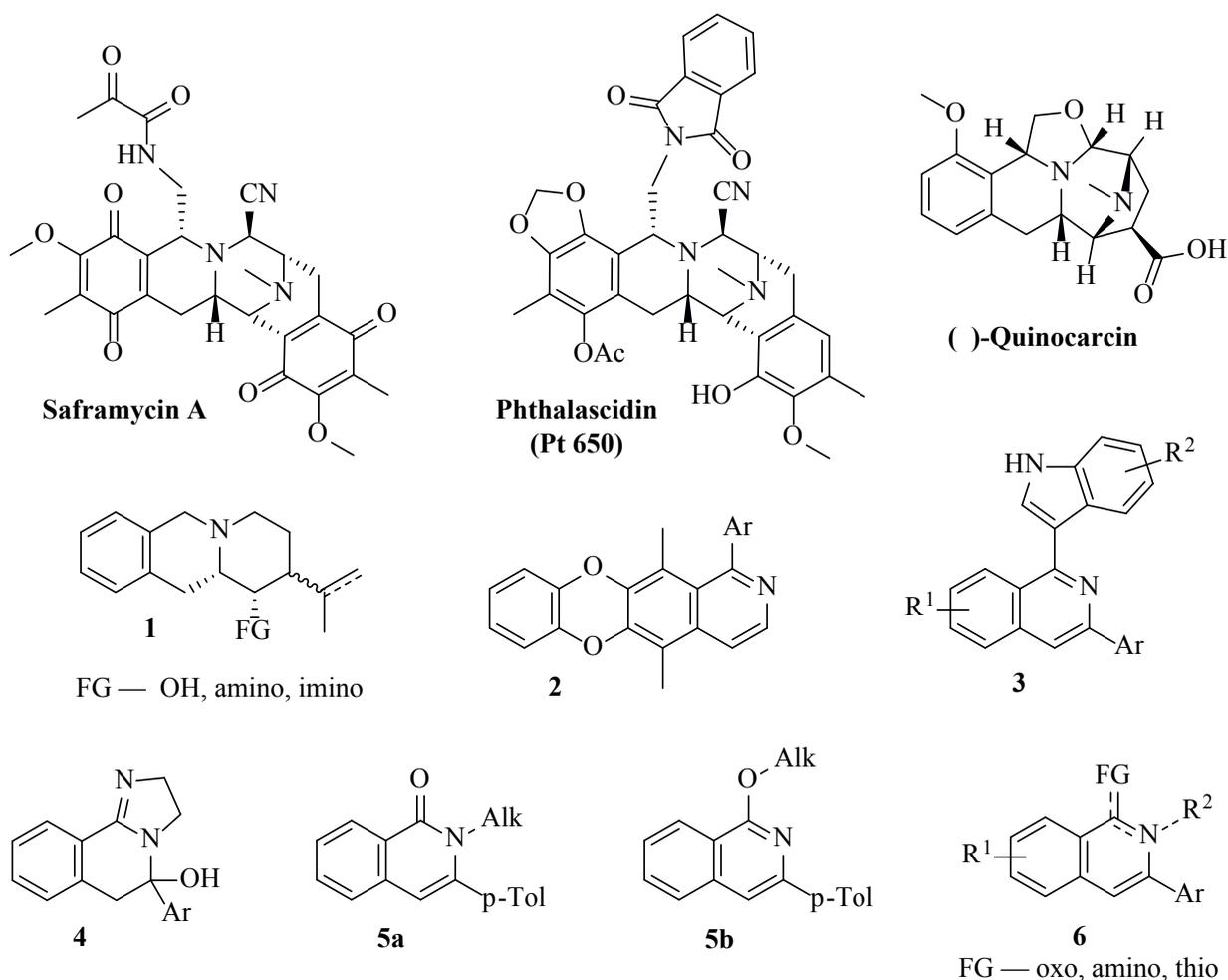


Fig. 1. Natural and synthetic isoquinolines with anticancer activity

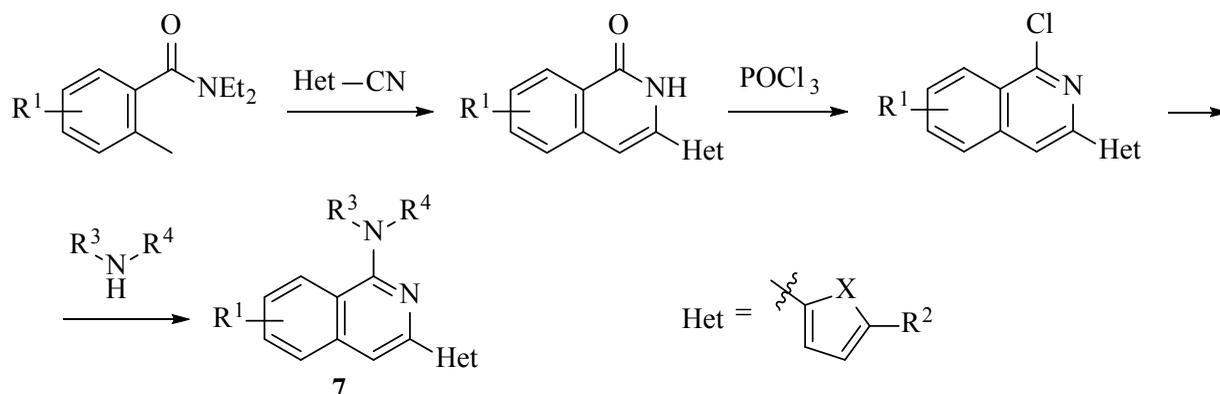
showed some cytotoxicity. Anticancer activity was also confirmed for tetracyclic compounds **2** [8] and indolyisoquinolines **3** [9]. (Fig. 1).

Therefore, the methods for synthesizing isoquinoline derivatives of various structures have been developed to create new anticancer drugs. However, complex modifications are not necessary to achieve biological effects. For example, [10, 11] show different biological activities (in particular, cytotoxicity) of alkyl- and benzylisoquinolines and protoberberines of a relatively simple structure. The structure of 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines **4** [12] and 1-oxoisoquinolines **5a, b** [13] (Fig. 1) is also relatively simple, and anticancer activity was established for some of them.

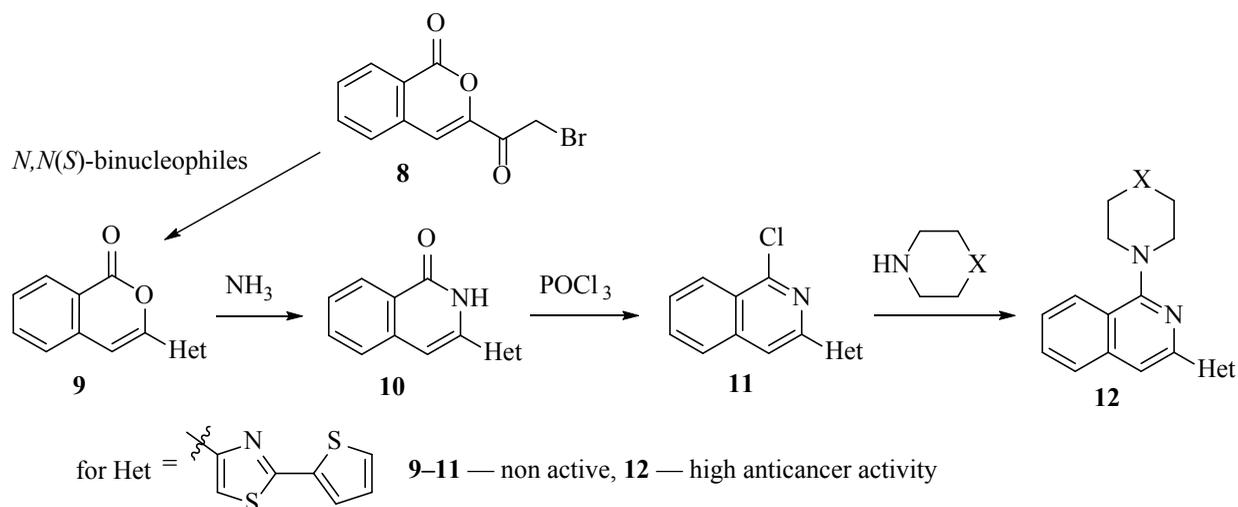
Among various bioactive derivatives of isoquinoline, the isoquinolines with (hetero) aromatic substituents in C-3 position and the aliphatic amine residues in C-1 position drew our attention for studying their anticancer activity.

Several facts confirm the prospects of this type of derivatives. Thus, in [14] kNN QSAR models were developed for 3-arylisoquinoline antitumor agents with general structure **6**

(Fig. 1). The authors of paper [15] studied isoquinolines **7** (Scheme 1) with a nitrogen-containing substituent (preferably an aliphatic amine residue) in C-1 position and a heterocyclic substituent (mainly thiophene and pyrrole) in C-3 position. The experimentally determined anticancer activity of such derivatives was supported by molecular docking, which showed the importance of binding to the Topoisomerase I and II active site by the amino group and heterocyclic substituent in particular (respectively, due to hydrogen bonds and π - π stacking interactions). However, the group of isoquinolines such as compounds **7** is not very numerous, mainly due to their complicated synthesis. For example, the mentioned publication employed isoquinoline-1-one and two consecutive nucleophilic substitution reactions to introduce an amine residue in C-1 of isoquinoline (Scheme 1), and condensation of *ortho*-toluylamides with the corresponding nitriles in the presence of butyllithium to construct the 3-hetarylisoquinolones themselves. This approach provides various synthetic possibilities but is limited by the intolerance of



Scheme 1



Scheme 2

such a strong base to certain functional groups and heterocyclic systems.

Alternatively, to diversify the set of 1-amino-3-hetarylisoquinolines, we previously proposed [16] a synthetic sequence based on the use of bromoketone **8** and subsequent cyclization of isochromone to isoquinolone **10** (Scheme 2, Het — substituted thiazoles, quinoxalines, and imidazothiazole, X — O, NMe).

The preliminary evaluation of anticancer activity performed for the derivatives with 2-(thiophen-2-yl)thiazol-4-yl substituent (see structure below in Table 1) confirmed the effectiveness of 1-aminoisoquinoline derivatives, whereas all their precursors almost did not display any cytotoxicity [17]. The morpholine derivative was also inferior in the activity compared to the compound with the *N*-methylpiperazine residue. Thus, the next logical step was to determine the ability of 1-(*N*-methylpiperazin-1-yl)isoquinolines with various heteroaromatic substituents in C-3 position to inhibit the growth of cancer cells.

Materials and Methods

Compounds

The derivatives marked with their NSC codes (Fig. 2) were chosen for the anticancer activity studies; their methods of synthesis and characteristics were given in [16].

In Vitro Anticancer Screening of the synthesized compounds

One Doses Full NCI 60 Cell Panel Assay. Six compounds NSC **831583**, **831584**, **831585**, **831587**, **831588**, **831589** were submitted to National Cancer Institute NCI, Bethesda, Maryland, U.S.A., under the Developmental Therapeutic Program DTP (https://dtp.cancer.gov/discovery_development/nci-60/default.htm). The cell line panel engaged 60 different human tumor cell lines derived from nine cancer types. {Primary *in vitro* one dose anticancer screening was initiated, in which the full NCI 60 panel lines were inoculated onto a series of standard

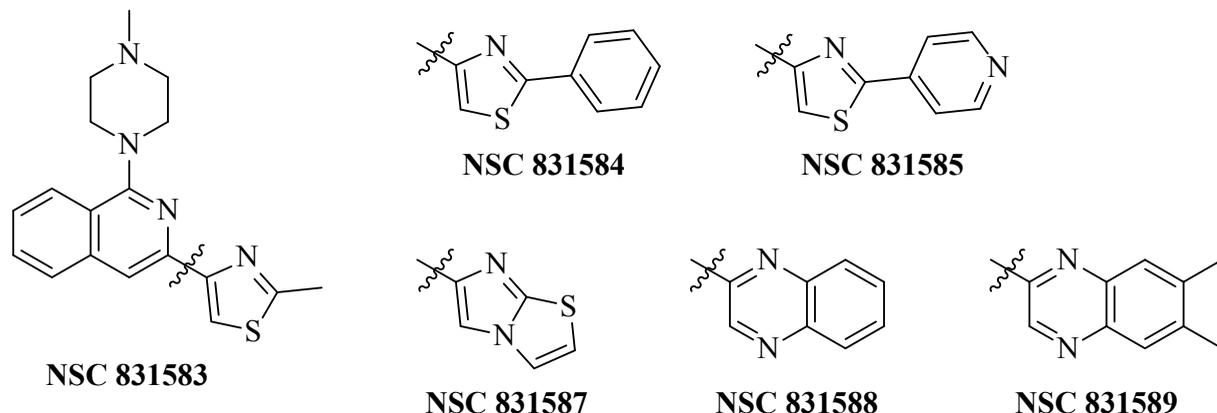


Fig. 2. Investigated compounds

96-well microtiter plates on day 0 at 5000–40,000 cells/well in RPMI 1640 medium containing 5 % fetal bovine serum and 2 mM L-glutamine, and then preincubated in the absence of drug at 37 °C, and 5 % CO₂ for 24 h. The test compounds in the concentration of 10⁻⁵ M were added to all 60 cell lines (the preparation of drug solution see in [18]) and incubated for 48 h under the same incubation conditions. The media were removed, and the cells were fixed *in situ*, washed, and dried. The sulforhodamine B assay was used for the cell density determination based on the measurement of cellular protein content. After the incubation period, cell monolayers were fixed with 10 % (wt/vol) trichloroacetic acid and stained for 30 min. The excess dye was removed by repeated washing with 1 % (vol/vol) acetic acid. The bound stain was resolubilized in 10 mM Tris base solution and measured spectrophotometrically on automated microplate readers for OD determination at 510 nm.

Five Doses Full NCI 60 Cell Panel Assay. All 60 cell lines, representing nine cancer

subpanels (*Fig. 1*), were incubated in five different concentrations (0.01, 0.1, 1, 10, and 100 μM; drug solution preparation see in [18]) of the tested compounds. The outcomes were used to create log₁₀ concentration *versus* percentage growth inhibition curves, and three response parameters (**GI**₅₀, total growth inhibition (**TGI**), and **LC**₅₀) were calculated for each cell line. The GI₅₀ value (growth inhibitory activity) corresponds to the concentration of the compound, causing a 50 % decrease in the net cell growth. The TGI value (cytostatic activity) is the concentration of the compound resulting in total growth inhibition. The LC₅₀ value (cytotoxic activity) is the concentration of the compound causing a net 50 % loss of initial cells at the end of the incubation period of 48 h. Data calculations were made according to the method described by the NCI Development Therapeutics Program (https://dtp.cancer.gov/discovery_development/nci-60/default.htm).

COMPARE correlations were performed as described in [19]. Vectors of Log GI₅₀ concentrations were correlated with the set of corre-

sponding average GI_{50} vectors from the standard agents' database (https://dtp.cancer.gov/discovery_development/nci-60/default.htm) or all public NCI-60 vectors that contained at least 40 overlapping cell lines.

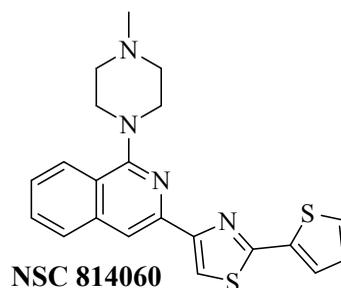
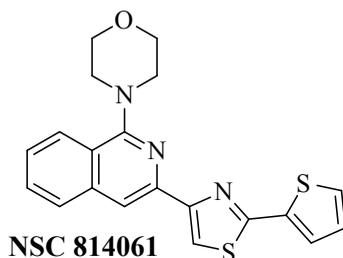
Results and Discussion

In Vitro Screening

One Doses Assay. Table 1 presents the primary data on the test compounds' inhibition

Table 1. The effect of investigated compounds on the growth of cancer cells, determined by single-dose assay ($C = 10^{-5}$ M); GP — Growth Percent, Mean — average value GP, Range — range of values GP, %; N_{50} — number of lines with $GP \leq 50$ %; N_0 — number of lines with $GP \leq 0$ %

Compound NSC code	GP, Mean	GP, Range	N_{50}	N_0	The most significant inhibition, GP
831583	93.8	47.7	–	–	61.1 HOP-92 (Non-Small Cell Lung Cancer)
831584	22.1	182.5	35	15	-84.7 HCC-2998 (Colon Cancer) -84.4 COLO 205 (Colon Cancer) -80.7 LOX IMVI (Melanoma)
831585	51.6	124.6	22	4	-26.45 RXF 393 (Renal Cancer) -18.55 M14 (Melanoma) -18.2 SR (Leukemia)
831587	83.1	97.1	4	–	17.4 MCF7 (Breast Cancer) 17.7 HOP-92 (Non-Small Cell Lung Cancer)
831588	53.1	180.5	18	6	-80.0 M14 (Melanoma) -65.2 COLO 205 (Colon Cancer) -52.15 K-562 (Leukemia)
831589	3.7	186.9	39	25	-87.8 MDA-MB-435 (Melanoma) -85.7 M14 (Melanoma) -85.7 HCT-116 (Colon Cancer) -84.3 HCC-2998 (Colon Cancer) -83.8 LOX IMVI (Melanoma)
814061	86.2	123.5	8	–	0.6 (MALME-3M / Melanoma) 5.8 (MDA-MB-468 / Breast Cancer)
814060	39.8	145.7	35	6	-51.1 COLO 205 (Colon Cancer) -44.9 M14 (Melanoma) -38.2 HCC-2998 (Colon Cancer)



of 60 cancer cell lines. The corresponding data obtained previously for isoquinolines NSC 814061 and NSC 814060 with 2-(thiophen-2-yl)thiazole-4-substitute are given after the list of the studied objects for comparison.

The data obtained unequivocally indicate a significant influence of the nature of heterocyclic substituent in C-3 position of the studied isoquinolines on the level of anticancer activity. Particularly striking is the sharp increase in the activity of 2-methylthiazol-4-yl compared to 2-phenylthiazol-4-yl derivative (compounds NSC 831583 and NSC 831584, respectively): while the first substance shows virtually no cytotoxicity, slightly inhibiting the development of only several separate lines, the second compound demonstrates significant anticancer activity and is even lethal for 15 lines; showing the most significant effectiveness against Colon Cancer and Melanoma. In contrast, isoquinoline NSC 831585 with 2-(pyridin-2-yl)thiazol-4-yl substituent in C-3 position, despite the structural parameters close to phenylthiazole, was significantly less active. However, it was lethal to some Leukemia, Melanoma, and Renal Cancer lines. These facts are consistent with the estimates

[15] for binding the heterocyclic substituent at C-3 position of isoquinoline to the enzyme active site by π - π stacking interactions.

The inhibitory ability of the imidazothiazole derivative NSC 831587 is, on average, low. Furthermore, the cytotoxicity of compounds NSC 831588 and 831589 with quinoxaline substituents is high, and dimethylquinoxaline NSC 831589 was the most active for the studied series (Table 1). Compound NSC 831589, like phenylthiazole derivative NSC 831584, is particularly effective at inhibiting Colon Cancer and Melanoma (Table 2).

Five Doses Assay. Out of 6 tested isoquinolines, 3 that showed the best results in single-dose tests were selected for a five doses assay. Table 3 shows the cell lines, the GI₅₀ concentration for which was the lowest.

Unfortunately, the tested compounds weakly inhibit the growth of cancer cells at a concentration below micromolar. On the other hand, these compounds remain lethal to many cancer cell lines at the same order of concentration. In general, given the strong dependence of anticancer activity on the nature of the heterocycle, the search for more effective drugs should continue, focusing on quinoxala-

Table 2. The effect of compounds NSC 831584 and NSC 831589 on the growth of Colon Cancer and Melanoma cells

Colon Cancer	Growth Percent, %		Melanoma	Growth Percent, %	
	NSC 831584	NSC 831589		NSC 831584	NSC 831589
COLO 205	-84.4	-57.9	LOX IMVI	-80.7	-83.8
HCC-2998	-84.7	-84.3	MALME-3M	49.0	-69.1
HCT-116	2.3	-85.7	M14	-70.8	-85.7
HCT-15	-48.6	-69.7	MDA-MB-435	7.3	-87.8
HT29	-52.0	-60.4	SK-MEL-28	-25.3	-69.9
KM12	18.7	-3.5	SK-MEL-5	58.7	16.2
SW-620	-19.1	1.5	UACC-257	46.6	99.1
			UACC-62	-38.4	-46.6

Table 3. The effect of compounds NSC 831584, NSC 831588, NSC 831589 on the growth of cancer cells, determined by a five-dose assay (the concentrations GI₅₀, TGI, and LC₅₀*, mol/l, given as log)

Compound NSC code	Cell line	Value of cancer cell lines growth inhibition		
		log GI ₅₀	log TGI	log LC ₅₀
831584	<i>Mean value</i>	-5.57	-5.17	-4.74
	COLO 205 (Colon Cancer)	-5.78	-5.50	-5.22
	HCC-2998 (Colon Cancer)	-5.78	-5.51	-5.24
	HCT-116 (Colon Cancer)	-5.79	-5.53	-5.26
	SW-620 (Colon Cancer)	-5.79	-5.51	-5.22
	LOX IMVI (Melanoma)	-5.78	-5.51	-5.24
831588	<i>Mean value</i>	-5.08	-4.49	-4.25
	HL-60(TB) (Leukemia)	-5.77	-5.44	-5.10
	COLO 205 and HCT-116 (Colon Cancer)	-5.75	-5.49	-5.22
	LOX IMVI (Melanoma)	-5.77	-5.49	-5.21
	SK-MEL-28 (Melanoma)	-5.75	-5.49	-5.23
831589	<i>Mean value</i>	-5.36	-4.87	-4.47
	HL-60(TB) (Leukemia)	-5.81	-5.45	-5.09
	HCC-2998 (Colon Cancer)	-5.77	-5.50	-5.22
	HCT-116 (Colon Cancer)	-5.78	-5.51	-5.24
	M14 and SK-MEL-28 (Melanoma)	-5.76	-5.49	-5.23
	CAKI-1 (Renal Cancer)	-5.79	-5.51	-5.22

* GI₅₀ (growth inhibitory activity) – concentration of the compound causing 50 % decrease in net cell growth; TGI (cytostatic activity) – concentration of the compound resulting in total growth inhibition; LC₅₀ (cytotoxic activity) – concentration of the compound causing net 50 % loss of initial cells at the end of the incubation period of 48 h

line derivatives and structurally related heterocycles.

NCI 60 Cell Panel COMPARE Correlations. COMPARE analysis, the results of which are summarized in *Table 4*.

Compound **NSC 831583** showed a moderate correlation with Flavoneacetic acid (FAA) for all parameters tested. The antitumor effects of FAA are due to its immunomodulatory activity, leading to an indirect antiproliferative effect on human tumor cells by induction of physiological factors involved in the immune response, as well as the effects on the vasculature, which include impaired blood flow up to the closure of blood vessels, followed by the impaired blood supply to the tumor. FAA-induced im-

munomodulation consists of activating natural killer cells and releasing several cytokines, among which TNF- α plays a significant role [20, 21]. The latter promotes the release of nitric oxide due to iNOS activation [22]. At that, pharmacological inhibition of nitric oxide synthesis reduces the antitumor activity of FAA [20]. Moreover, the growth inhibition matrix of this compound moderately correlated with Dihydrolenperone, being a haloperidol analog, appears to act mainly through the blockade of the dopamine D2 receptor leading to inhibition of cancer cell proliferation [23]. At the same time, its cytostatic activity is also moderately correlated with O6-methylguanine, leading to the formation of Guanine — Adenosine transi-

Table 4. Standard agents showing the highest COMPARE correlation with tested compounds

Compound NSC code	log GI ₅₀	log TGI	log LC ₅₀
831583	Dihydroelenperone (0.60) Flavoneacetic acid (0.58)	O6-methylguanine (0.61) Flavoneacetic acid (0.60)	Flavoneacetic acid (0.50)
831584	5-HP (0.56)	Tamoxifen (0.50)	Tamoxifen (0.47)
831585	Tamoxifen (0.66)	Tamoxifen (0.61)	Thalicarpine (0.51)
831587	Tamoxifen (0.56)	Flavoneacetic acid (0.56)	PALA (0.44)
831588	Tamoxifen (0.66)	Tamoxifen (0.65)	Tamoxifen (0.55)
831589	L-cysteine analogue (0.61) Tamoxifen (0.59)	Tamoxifen (0.65)	Tamoxifen (0.55)

tion mutations, a known mechanism of human oncogene activation and tumor suppressor gene inactivation [24, 25].

The GI₅₀ vector of compound NSC **831584** moderately correlated with the inhibitor DNA polymerase, 5-HP, and weakly correlated with Tamoxifen in cytostatic and cytotoxic activities. The antiproliferative activity of compounds NSC **831585**, NSC **831588**, and NSC **831589** moderately correlated with an antineoplastic nonsteroidal selective estrogen receptor modulator Tamoxifen. Additionally, tamoxifen up-regulates the production of transforming growth factor B (TGFb), a factor that inhibits tumor cell growth, and down-regulates insulin-like growth factor 1 (IGF-1), a factor that stimulates the breast cancer cell growth. Tamoxifen also down-regulates the protein kinase C (PKC) expression in a dose-dependent manner, inhibiting signal transduction and producing an antiproliferative effect in tumors that overexpress PKC. This agent is also most closely correlated with compounds 831588 and 831589 in cytotoxicity.

In contrast, compound NSC **831585** was closer in this parameter to Thallicarpine, which inhibits p-glycoprotein, the multidrug resistance efflux pump. Thallicarpine also induces single-strand breaks in DNA and arrests cancer

cells at the G2/M and G1 phase of the cell cycle [26]. Compound NSC **831587** showed a uniform correlation with Tamoxifen and Flavoneacetic acid for the GI₅₀ and TGI vectors, respectively, and only a weak correlation with PALA for cytotoxicity.

In general noteworthy, the lack of a high correlation with standard agents suggests that these compounds have specific molecular targets underlying their antitumor activity. The latter, of course, does not exclude the possible involvement of the mechanisms inherent in the above drugs.

Conclusions

The studied isoquinolines with heteroaromatic residues at C-3 position and 4-methylpiperazin-1-yl residue at C-1 position demonstrate a significant impact of the heterocyclic substituent on their anticancer activity levels. Derivatives with thiazole substituent differed the most: the activity of 2-phenylthiazol-4-yl derivative was relatively high, 2-(pyridin-4-yl)thiazol-4-yl's was above average, whereas 2-methylthiazol-4-yl does not exhibited almost any activity. The product with 6,7-dimethylquinoxalin-2-yl substituent has the highest activity (this compound was lethal for 25 out of 60 cancer cell lines at the concentration of

10^{-5} M). This interrelation can serve as the reason for finding new, more effective anticancer agents among 1-amino-3-hetarylisoquinolines through the variation of their substituents.

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Disclaimer

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- Вплив природи гетероциклічного замісника у положенні 3 1-(4-метилпіперазин-1-іл)ізохінолінів на протипухлинну активність**
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- Мета.** Проведено порівняльний аналіз протиракової активності 1-(4-метилпіперазин-1-іл)ізохінолінів з різними гетероароматичними замісниками в 3-му положенні: 2-метилтіазол-4-іл, 2-фенілтіазол-4-іл, 2-(піридин-4-іл)тіазол-4-іл, імідазо[2,1-*b*]тіазол-6-іл, хіноксалін-2-іл, 6,7-диметилхіноксалін-2-іл. **Методи.** Біологічні дослідження; статистичні методи. **Результати.** *In vitro* скринінг протиракової активності показав, що найвищий рівень демонструють похідні із 2-фенілтіазол-4-ільним, хіноксалін-2-ільним, 6,7-диметилхіноксалін-2-ільним замісниками, їм дещо поступається ізохінолін із 2-(піридин-4-іл)тіазол-4-ільним замісником, а сполука із 2-метилтіазол-4-ільним фрагментом цитотоксичності майже не виявила. СОМРАЕ аналіз не виявив значних кореляцій з відомими препаратами, отже, ці сполуки мають специфічні молекулярні мішені. **Висновки.** 1-Аміно-3-гетарилізохіноліни – перспективний клас сполук для пошуку протиракових засобів, рівень і напрям активності яких суттєво залежить від характеру гетероциклічного замісника.
- Ключові слова:** *in vitro* скринінг, протиракова активність, 1-аміно-3-гетарилізохіноліни.

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