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New indazole-indolizine-triazine hybrid molecules with farnesyltransferase inhibitory activity

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ABSTRACT

A new series of indazole-indolizine-triazine hybrid molecules was obtained by [3 + 2] cycloaddition reaction between newly synthesized nitrogen ylides with indazole skeleton and previously reported dipolarophile 2-ethynyl-4,6-dimethoxy-1,3,5-triazine and fully characterized. The biological evaluation of hybrids revealed good antitumor growth inhibitory activity against UO-31 renal cancer cell line for the (1*H*-indazole-1-yl)(1-(4,6-dimethoxy-1,3,5-triazin-2-yl)-7-methylindolizin-3-yl)methanone derivative **7a**. Also, for the same compound, a moderate farnesyltransferase inhibitory activity ($IC_{50} = 52.50 \pm 16.07 \mu M$) was observed. However, the best result as farnesyltransferase inhibitor of the series was registered for the 5-bromoindazole substituted analogue **7e** ($IC_{50} = 27.08 \pm 4.93 \mu M$).

Indolizine (compound **I**, Fig. 1) is a heteroaromatic molecule, containing both a π -electron-rich pyrrolic ring and a π -electron-deficient pyridinic ring, the whole system being isoelectronic with indole [1]. This azaheterocycle was discovered in 1980 by the Italian chemist Angeli, and Scholtz synthesized it for the first time in 1912 [2].

The indolizine derivatives are the subject of numerous pharmaceutical research due to their interesting and promising biological properties. With the discovery of camptothecin (a natural alkaloid with an indolizine moiety in the structure and antitumor properties, compound **II**, Fig. 1), the interest on indolizine derivatives registered an enormous growth, but still the biological potential of the indolizine nucleus is largely unexplored [3]. Both, natural and synthetic derivatives, have been identified as possessing antimicrobial [4–6], antitubercular [7–9], anticancer (compounds **III** – **VI**, Fig. 1) [10–14], aromatase inhibitory [15], phosphodiesterase inhibitory [16], herbicidal [17], anti-inflammatory [18–20], phosphatase inhibitory [21], antioxidant [22–24], antihistaminic [25], antileishmanic [26] and antidiabetic [27,28] activity.

The study of substituted indolizin-3-yl(phenyl/heteroaryl) methanones with anticancer properties is also the interest of our research group. As result of our work, we reported for the first time

indolizine derivatives as human protein farnesyltransferase inhibitors, with structures **VII** [29] and **VIII** (Fig. 2) [30]. In the light of molecular hybridization concept [31], we previously successfully combined the indolizine core with another pharmacophoric moieties in new bioactive molecules. Thus, we obtained new farnesyltransferase inhibitors with indolizin-phenothiazine hybrid structure (compounds **IX** [32] and **X** [33]), and a strong cytotoxic effect on two different cancer cell lines, was noticed when a dimethoxy-*s*-triazine residue was linked to the indolizine nucleus, in the structure of compound **XI** (Fig. 2) [34].

s-Triazine is a well-known pharmacophore, found in the structure of some compounds with various biological properties, including anti-tumor activity [35–38]. Moreover, drugs containing the *s*-triazine motif, such as **Tretamine**, **Gedatolisib**, and **Enasidenib** (Fig. 3) are currently used for cancer therapy [39,40].

Besides, our research group highlighted the ability of dimethoxy-*s*-triazine-based compounds **XII** [41], **XIII** and **XIV** [42] (Fig. 2) to inhibit the farnesyltransferase protein.

Additionally, the indazole heterocycle is found in compounds with biological properties such as anti-inflammatory, antibacterial, anti-HIV, antiarrhythmic, antifungal and antitumoral [43]. The pharmacological importance of this heterocycle is also emphasized by the commercially

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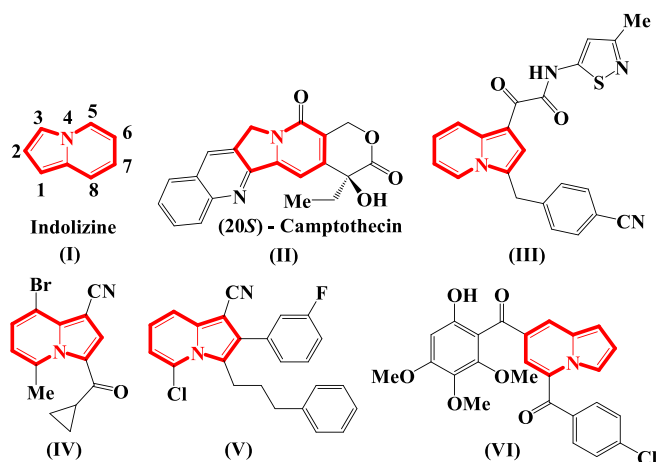


Fig. 1. Structure of indolizine I, camptothecin II and indolizine-based antitumor compounds III-VI.

available drugs with indazole structure. Indazole-based agents such as **Axitinib**, **Lonidamine** and **Pazopanib** (Fig. 2) have already been employed for cancer therapy, demonstrating that indazole compounds are useful templates for the development of novel anticancer agents [44].

The concept of molecular hybridization is a strategy that has been successfully applied over time for the development of new cytotoxic

compounds with improved efficacy. For example, Hawash et al., reported in 2022 new thiophene-carboxamide hybrid compound with better cytotoxic activity than doxorubicin [45] and in 2023 novel indole-pyrazole hybrids with similar or better cytotoxic activity than sorafenib [46]. The effectiveness of the molecular hybridization tool is also highlighted by a literature review published in 2022, which presents different compounds with hybrid structure and antitumor activity, targeting the tubulin protein [47].

All these results encouraged us to continue our effort to discover new bioactive molecules. The purpose of this study is to combine indolizine with *s*-triazine, two heterocycles found in the structure of compounds with antitumoral and farnesyltransferase inhibitory activity, and also with indazole, a heterocycle present in the structure of antitumoral agents, in a unique compound with improved pharmacological activity. Thereby, we report here the design, synthesis and *in vitro* evaluation for antiproliferative and farnesyltransferase inhibition activity of some new indazole-indolizine-triazine hybrid molecules.

The synthetic route (Scheme 1) started with the preparation of the *N*-acylated indazoles **2a-e**, by treatment of corresponding indazole **1a-e** with chloroacetyl chloride in presence of triethylamine [48]. A key intermediate of our syntheses is represented by the cycloimmonium salts **4a-m**, which were obtained following an alkylation reaction of the pyridinium nitrogen in the structure of compounds **3a-e**, with previously synthesized *N*-chloroacetylindazole derivatives **2a-e**. In the last step, the corresponding ylides **5a-m**, obtained *in situ* by base treatment of the salts **4a-m**, participated to a [3 + 2] cycloaddition reaction with 2-ethynyl-4,6-dimethoxy-1,3,5-triazine **8** [34]. The spontaneous

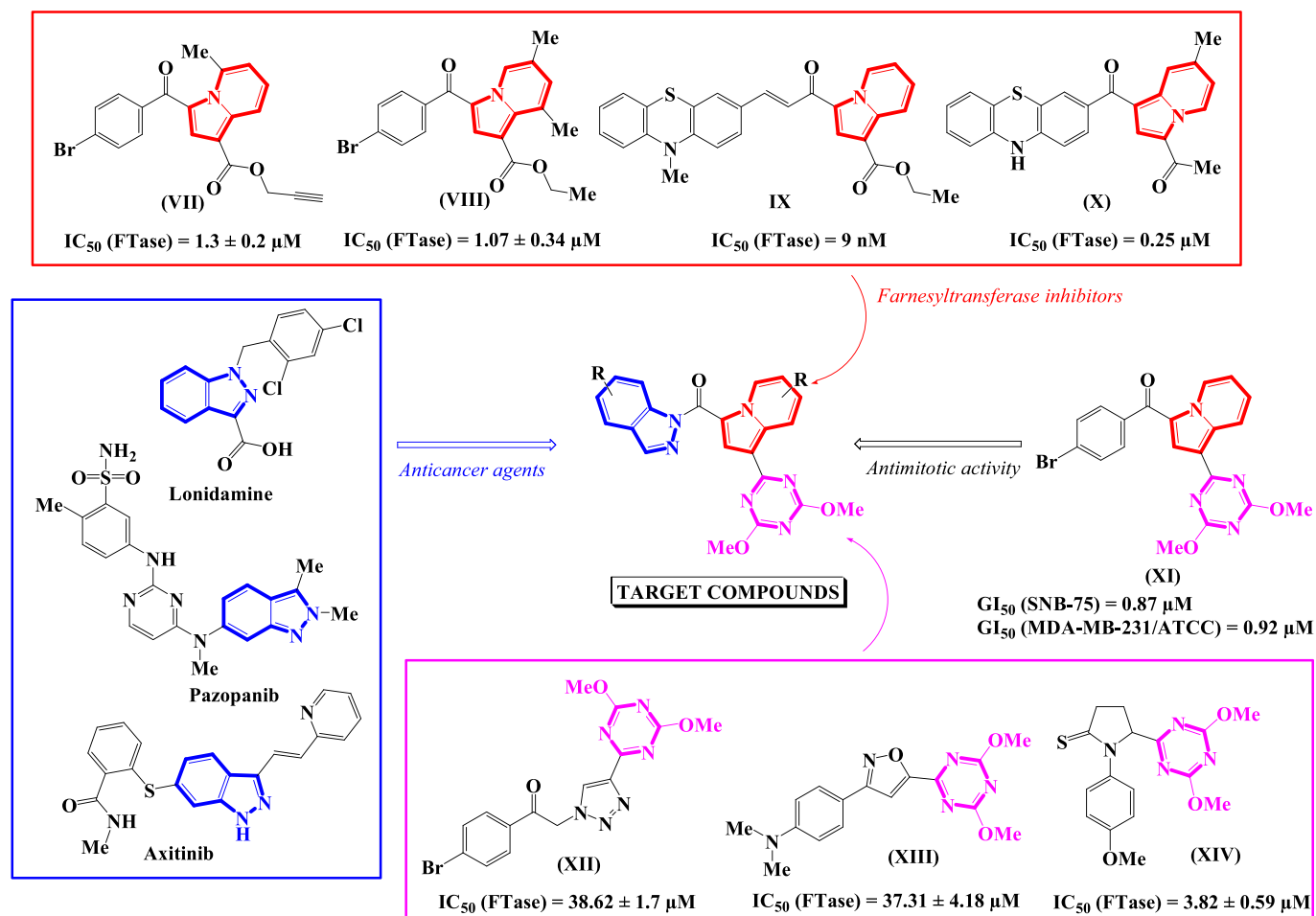


Fig. 2. Structure of some biologically active indolizine derivatives (VII – XI), *s*-triazine derivatives (XII – XIV), indazole derivatives (Lonidamine, Pazopanib, Axitinib) and of target compounds.

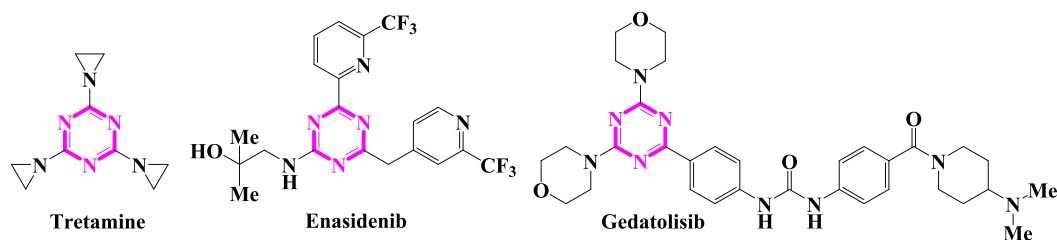
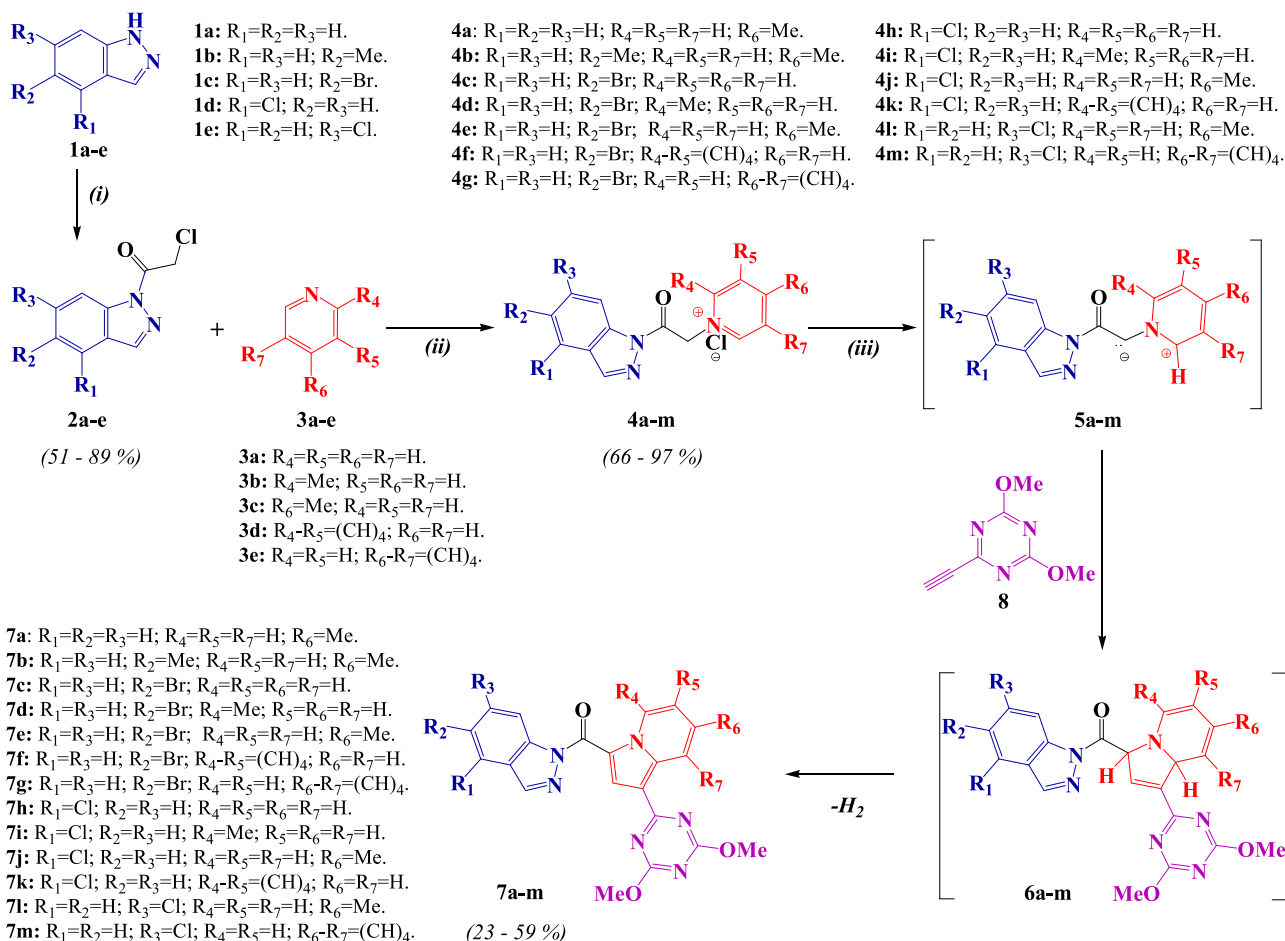


Fig. 3. Structure of anticancer drugs containing the *s*-triazine motif.



Scheme 1. Reagents and conditions: (i) 1.2 equiv triethylamine, 1.5 equiv chloroacetyl chloride, toluene, r.t., 4 h; (ii) 2 equiv pyridinium derivative, EtOAc, reflux, 24 h; (iii) 1.2 equiv TEA, acetonitrile, 1.3 equiv 2-ethynyl-4,6-dimethoxy-1,3,5-triazine, r.t., 24 h.

aromatization of the resulting intermediates **6a-m**, led to target compounds **7a-m**. The synthesis of 2-ethynyl-4,6-dimethoxy-1,3,5-triazine **8** was previously reported [41]. Every step of the synthetic pathway was monitored using thin layer chromatography (TLC). After the purification by recrystallisation from ethanol, all target compounds were characterized through different spectroscopic techniques such as IR, 1H NMR and ^{13}C NMR.

The thirteen synthesized hybrid molecules were then tested *in vitro* for their inhibitory potential against human farnesyltransferase. The obtained results are summarized in Table 1. It can be observed that the presence of the bromine on the indazole nucleus and of the methyl residue on indolizine core is favorable for the inhibitory activity. The most active compound of the series was **7e**, a derivative with a 5-bromoindazole and a 7-methylindolizine in the structure. The biological activity decreased when the methyl residue occupied the position 5 on the indolizine cycle, in the structure of analogue **7d**. Other modulations

on the structure of the most active 5-bromoindazole derivative **7e**, such as the removal of the methyl group from indolizine core **7c**, or the condensation of indolizine with the benzene nucleus **7f** and **7g**, led to inactive compounds. When the bromine of compound **7e** was replaced with a methyl group in compound **7b**, the biological activity was considerably reduced. Also, the presence of a chlorine atom on the indazole ring resulted in the loss of inhibitory activity, regardless of the substituents present on the indolizine nucleus. For the analogue with unsubstituted indazole nucleus **7a**, a promising inhibitory activity was registered as well, but lower than for compound **7e**. It can be observed that the presence of the methyl on the indolizine core is favorable for the inhibitory activity only for the unsubstituted or 5-bromo-substituted indazole derivatives.

Five of the newly synthesized compounds passed the selection program of National Cancer Institute (NCI) to be evaluated for their cytotoxic activity against a panel of 60 tumor cell lines [49–51]. The most

Table 1Results of *in vitro* testing of inhibitory potential against human farnesyltransferase.

Compound	%Inhibition ratio (FTase) ^{a,b}	IC ₅₀ ± SD (μM)	Compound	%Inhibition ratio (FTase)	IC ₅₀ (μM)
7a	68.3	52.50 ± 16.07	7j	39.9	–
7b	12.1	–	7 k	86.5 ^c	–
7c	58.5	–	7 l	60.2	–
7d	70.4	58.60 ± 16.79	7 m	51.4	–
7e	82.4	27.08 ± 4.93	7f	24.8	–
7f	5.5	–	7 g	37.7	–
7 h	67.0	–	7 h	11.1	–
7i	55.8	–	7 k	55.8	–

^a Inhibition ratio of protein farnesyltransferase obtained at a concentration of 100 μM.^b Mean values of two determinations.^c Not quantifiable; competition with the enzyme fluorescence.**Table 2**Selected results of the *in vitro* evaluation of cell growth inhibition (GI%) for compounds 7a, 7 h, 7i, 7 k, and 7 l against the NCI panel of tumor cell lines.

Panel	Compound	7a	7 h	7i	7 k	7 l
	Cell line	Cell growth inhibition, GI% (10 ⁻⁵ M) ^a				
Leukemia	CCRF-CEM	– ^b	–	15	–	–
	RPML-8226	13	–	–	–	–
Non-Small Cell Lung Cancer	A549/ATCC	–	–	9	–	12
	HOP-62	10	7	10	–	22
	HOP-92	–	13	13	27	8
	NCI-H226	12	16	8	11	20
	NCI-H460	17	7	–	–	7
Colon Cancer	HCT-116	8	–	–	6	14
	SW-620	–	8	–	6	–
CNS Cancer	SF-295	–	–	5	–	11
	SNB-75	12	19	22	13	24
Melanoma	LOX IMVI	–	–	10	7	10
	M14	–	–	6	14	11
Ovarian Cancer	IGROV1	38	–	–	–	19
	SK-OV-3	–	–	9	–	19
Renal Cancer	786-0	–	–	–	–	18
	ACHN	18	–	8	–	15
	CAKI-1	9	16	8	14	18
	UO-31	50	27	26	30	31
Prostate Cancer	PC-3	9	8	18	20	21
	HS 578 T	–	8	9	5	21

^aData provided by NCI for the *in vitro* screening of compounds at 10 μM concentration^bGI% (10⁻⁵ M) < 5.

significant results are presented in Table 2. The best antiproliferative potential was observed for compound 7a on the UO-31 renal cancer cell line, with 50 % cell growth inhibition, and on IGROV1 ovarian cancer cell line, with 38 % cell growth inhibition, at a 10 μM dose. It can be observed that for all the tested compounds, the best results were obtained against the UO-31 renal cancer cell line.

To conclude, for the purpose of developing new molecules with antitumor properties, three heterocyclic units, namely indolizines, s-triazine and indazole, were combined following the molecular hybridization strategy. This resulted in 13 new compounds with hybrid structure, which were fully characterized and evaluated for their farnesyltransferase inhibitory activity and for cytotoxicity on the NCI-60 human cancer cell lines panel. Regarding the farnesyltransferase assay, the best result of the series was obtained for compound 7e, a 5-bromindazole derivative. Lower inhibitory activity was observed for the 5-methylindolizine analogue 7d, and for the unsubstituted indazole

analogue 7a. Any other investigated substituents on the structure of compound 7e led to the loss of the biological activity. Furthermore, the unsubstituted indazole analogue 7a showed a selective antiproliferative activity against UO-31 renal cancer cell line. Overall, correlating the results of the two biological evaluations, compound 7a was the best of the series, showing moderate antitumor activity, with farnesyltransferase enzyme as a possible cellular target. Thus, compound 7a represents a promising candidate for future modulations, such as the replacement of s-triazine with another heterocycle or other functional group. The chemical structure of the newly obtained hybrids includes three heterocycles important for organic and medicinal chemistry: indazole, indolizine and s-triazine. To the best of our knowledge, this is the first association of the indazole and the indolizine units in the structure of compounds with potential antitumor activity.

CRedit authorship contribution statement

Liliana Ciurlă-Lucescu: Investigation, Writing – original draft, Writing – review & editing. **Elena Bîcu:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing. **Dalila Belei:** Supervision, Writing – review & editing. **Alina Ghinet:** Conceptualization, Funding acquisition, Investigation, Supervision, Visualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rechem.2024.101451>.

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