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New indolizine–chalcones as potent inhibitors of human farnesyltransferase: Design, synthesis and biological evaluation

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ABSTRACT

A new family of indolizine–chalcones was designed, synthesized and screened for the inhibitory potential on human farnesyltransferase in vitro to identify potent antitumor agents. The most active compound was phenothiazine **2a**, exhibiting an IC_{50} value in the low nanomolar range, similar to that of known FTI-276, highly potent farnesyltransferase inhibitor. The newly synthesized indolizine–chalcones **2a–d** constitute the most efficient inhibitors of farnesyltransferase bearing a phenothiazine unit known to date.

Cancer is one of the most feared diseases of the century causing more than 8 million deaths in 2012.[1] In order to fight this disease, many chemotherapeutic strategies have been developed to try and stop the fast and abnormal division of tumor cells. One of the targets intensively studied in research is the protein farnesyltransferase (FTase). The isoprenylation, also called prenylation, involves the farnesyltransferase and represents a post-translational modification which represents the addition of the farnesyl group from FPP (farnesyldiphosphate) on a specific cysteine residue of a protein. This transfer results in the formation of a covalent thioether bond type with the cysteine carboxy-terminal position.[2] This process was identified on Ras proteins that play a fundamental role in the signaling pathway that allows cell division and are generally abnormally active in cancer.[3,4] Prevent farnesylation of the process can be an approach in cancer therapy. The transforming influence of the Ras oncogene being dependent on farnesylation, inhibitors of protein farnesyl transferase (FTIs) were designed and prepared to develop specific treatments of tumors with Ras mutations. In recent years, numerous specific competitive inhibitors of farnesyltransferase in vitro were identified either by screening of natural products or by chemical synthesis.[5–8]

FTIs are molecules with high therapeutic potential as evidenced by the many different preclinical and clinical trials published.[9–11] Although their clinical use was inconclusive, the FTIs are very promising in combination with other molecules such as HDAC inhibitors,[12] MEK inhibitors,[13] etc. Over the past last years, our research team has focused its efforts on the design, synthesis and biological screening of new molecules as potential FTase inhibitors[14–18] Our previous investigations have showed that compounds bearing an indolizine or a phenothiazine unit (e.g., compounds **A** and **B**, Fig. 1) displayed good inhibitory activity. We became interested in the association of the indolizine and the phenothiazine core on the same skeleton by a chalcone bridge in order to screen the inhibition potential on human farnesyltransferase of such hybrids (target compounds **1a–l**, **2a–d**, Fig. 1).

Chalcone have long been investigated for their biological activities which include anticancer potential.[19–21] Increasing interest is currently given especially to hybrids of chalcones with different heterocycles.[19] However, very few chalcones were described in the literature as farnesyltransferase inhibitors and exhibited moderate efficacy.[22–24] Indolizines with a chalcone bridge in their position 3 are very sporadic in the literature,[25–28] and, to the best of our knowledge, none was biologically evaluated. Consequently, we became interested in the development of novel indolizine–chalcones for screening of their activity on human farnesyltransferase.

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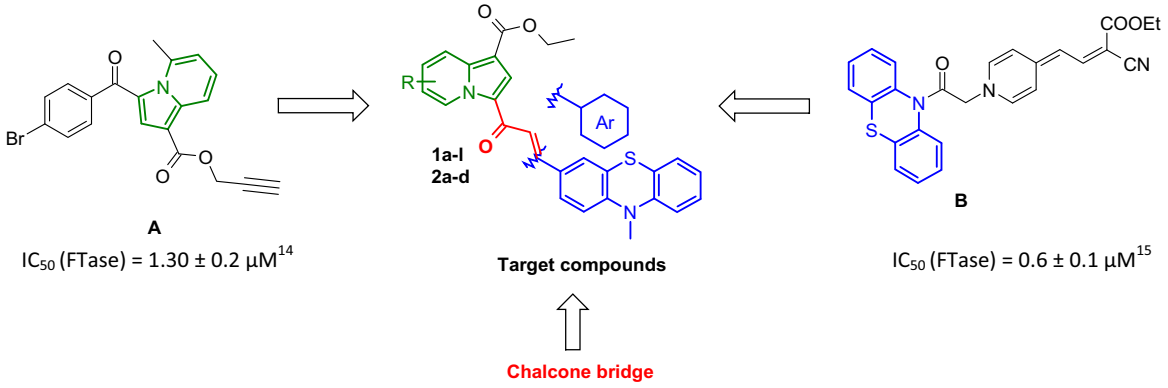


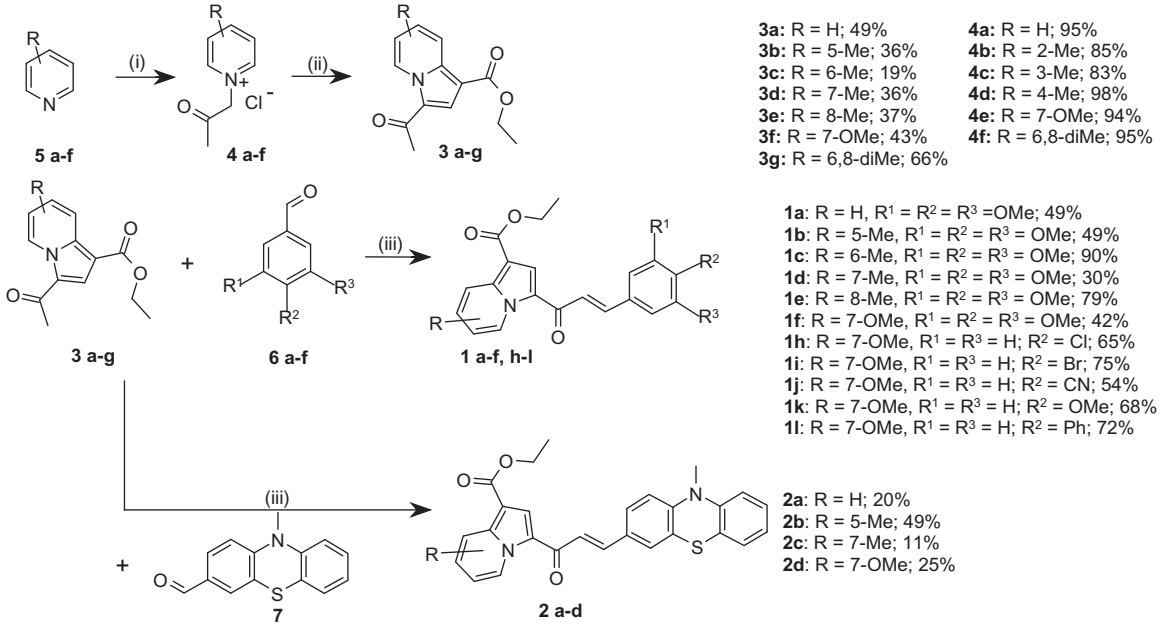
Figure 1. Structure of farnesyltransferase inhibitors with indolizine moiety **A**,[14] with phenothiazine group **B**[15] and of target compounds **1a–l** and **2a–d**.

The strategy used to synthesize the target indolizine–chalcones centered on the preparation of key indolizine precursors **3a–g**. The synthetic pathway started with the formation of pyridinium salts **4a–f**[29–33] by reacting commercially available pyridines **5a–f** with chloroacetone. Indolizines **3a–g** were then obtained by cycloaddition reaction between pyridinium salts **4a–f** and ethyl propiolate under basic conditions. The low yield obtained for indolizine **3c** (19%) is due to the formation of isomer **3e** in the same reaction, which was the main reaction product (37% yield). Final condensation on key intermediates **3a–g** with benzaldehydes **6a–f** or 3-formyl-10-methyl-10*H*-phenothiazine **7**[34–36] yielded chalcones **1a–f**, **1h–l** and **2a–d** in variable yields (Scheme 1). The advantage of this approach is that numerous indolizine–chalcones bearing aromatic or heteroaromatic units can be prepared using a divergent pathway from a single indolizine intermediate. However, this method was unsuccessful to afford the expected chalcone **1m** when using indolizine **3g** as starting reagent (Scheme 2). Nevertheless, additional attempts to generate the desired chalcone were realized. Heating indolizine **3g** and benzaldehyde **6g** in refluxing ethanol in presence of sodium hydroxide yielded the free carboxylic acid analogue **1g** as the unique product while using a large excess of sodium hydroxide delivered the decarboxylated chalcone **1g′** (Scheme 2).

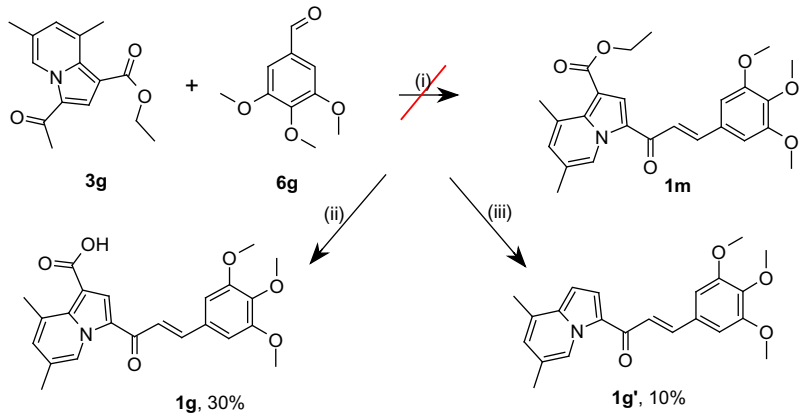
In order to determine the importance of the ester unit on the biological potential and enrich structure–activity relationships in this indolizine–chalcone series, a saponification of the ethyl ester of compound **1h** was realized and afforded the carboxylic acid **1h′** in 52% yield (Scheme 3).

The effect of synthesized chalcones **1a–l** and **2a–d** on human farnesyltransferase was investigated relative to known farnesyltransferase inhibitors (FTI-276 and chaetomellic acid A), along with a DMSO control.[37] Results are indicated in Table 1. The biological screening revealed that both indolizine–chalcones with phenyl (compounds **1a–l**) and phenothiazine unit (compounds **2a–d**) inhibited the protein. However, the phenothiazine derivatives **2a–d** showed better inhibitory potencies compared to phenyl-substituted chalcones **1a–l**. This structure–activity relationship supports once again the importance of the phenothiazine moiety in the structure of farnesyltransferase inhibitors.

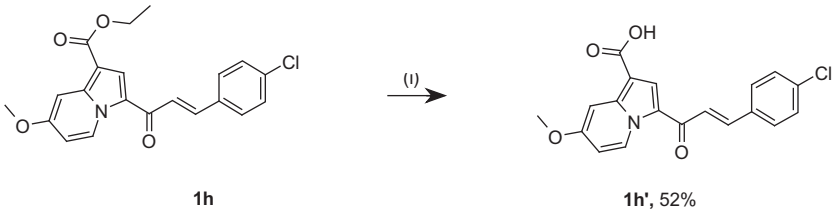
In the first series (compounds **1a–l**), the *p*-chloro or *p*-bromo substitution was the best chemical modulation providing chalcones with IC_{50} values in the submicromolar range (compounds



Scheme 1. Reagents and conditions: (i) 1.2 equiv chloroacetone, THF, rt, 48 h; (ii) 1.2 equiv triethylamine, 1.5 equiv ethyl propiolate, acetonitrile, rt, 24 h; (iii) 1 equiv aqueous NaOH, ethanol, rt, 24 h.



Scheme 2. Synthesis of chalcones **1g** and **1g′**. Reagents and conditions: (i) 1 equiv aqueous NaOH, ethanol, rt, 24 h; (ii) 1 equiv aqueous NaOH, absolute ethanol, reflux, 2 h; (iii) 10 equiv aqueous NaOH, ethanol, rt, 24 h.



Scheme 3. Reagents and conditions: (i) 2 equiv NaOH, ethanol, water, 60 °C, 1 h, then HCl.

Table 1
Inhibitory activities of compounds **1a–l** and **2a–d** on human farnesyltransferase in vitro

Compd no.	% FTI[a,b]	IC_{50} (nM)[b]	R^{2}[c]	Log P[d] ± SD
1a	94	19280	0.9317	4.66 ± 1.10
1b	7	n.d.[f]	—	5.12 ± 1.11
1c	n.t.[e]	n.d.	—	5.12 ± 1.11
1d	n.t.[e]	n.d.	—	5.12 ± 1.11
1e	n.t.[e]	n.d.	—	5.12 ± 1.11
1f	76	11630	0.9506	4.57 ± 1.48
1g	88	15890	0.9852	4.75 ± 1.11
1g′	88	726	0.8604	4.79 ± 0.85
1h	85	931	0.9507	5.58 ± 1.47
1h′	88	2330	0.9340	4.75 ± 1.47
1i	100	602	0.9273	5.76 ± 1.48
1j	95	8740	0.9496	4.42 ± 1.48
1k	68	n.d.	—	4.93 ± 1.47
1l	95	1320	0.9333	6.74 ± 1.48
2a	85	**9**	0.9550	7.34 ± 1.09
2b	91	**23**	0.9248	7.80 ± 1.09
2c	98	155	0.9845	7.80 ± 1.09
2d	84	711	0.9457	7.26 ± 1.47
Chaetomellic acid A	100	180	0.9890	8.00 ± 0.40
FTI-276	100	7	0.8369	2.90 ± 0.71[g]

[a] Inhibition of farnesyltranferase at a 100 μM.
[b] Values represent mean of two experiments.
[c] Regression factor.
[d] Predicted value with ACD software.
[e] Not testable, intrinsic fluorescence.
[f] Not determined.
[g] Predicted value with ACD software for free amine derivative.

1h: IC_{50} = 931 nM and **1i**: IC_{50} = 602 nM, Table 1), confirming pre-existing SAR in the farnesyltransferase inhibitors series.[14] The substitution of the para position with a cyano, methoxy or phenyl in compounds **1j**, **1k** or **1l** resulted in diminished inhibitory activity (Table 1). In the same series, the substitution of the indolizine unit has been modified in order to identify the structural requirements for the best biological potency. Therefore, the trimethoxyphenyl unit has been conserved in compounds **1a–g** while modifying the nature and the position of substituents. The 7-methoxy substitution in compound **1f** was the best modulation, the 6,8-dimethyl substitution in compound **1g** or a hydrogen substitution in chalcone **1a** resulted in slightly diminished activity (compare **1f** to **1g** and **1a**, Table 1). The 5-methylsubstitution of the indolizine unit in compound **1b** resulted in a drastic loss of biological activity. In our attempts to produce more potent molecules, the ester group was modified. The suppression of this unit in compound **1g′** resulted in increased inhibitory potential (compare compound **1g** to **1g′**, Table 1) while the saponification of the ethyl ester in compound **1h′** marginally decreased the activity (compare compound **1h** to **1h′**, Table 1).

Additional efforts were made to yield more potent molecules by replacing the phenyl unit by a 10-methyl-10*H*-phenothiazine group. In this light, four derivatives **2a–d** have been designed, synthesized and biologically evaluated. The most potent compound of the series and of the current study was phenothiazine **2a** bearing an indolizine unit with an ethyl ester unit, equivalent to that of FTI-276, a highly effective farnesyltransferase inhibitor, RasCAAX peptidomimetic which antagonizes both H and K-Ras oncogenic signaling. The additional substitution of the indolizine by a methyl in position 5 in compound **2b** slightly reduced the inhibitory activity, while adding a methyl in position 7 in compound **2c** or a methoxy in the same position in compound **2d** decreased the biological potency, suggesting that bulky substituents are less tolerated (Table 1).

In order to better understand the binding mode of the studied series, the behavior of compounds **1f**, **1l** and **2d** in the farnesyltransferase binding site was studied (Fig. 2a–d).[38] For chalcone **1f** (Fig. 2a) just above two thirds of the 30 generated solutions superimposes with the highest score. The trimethoxyphenyl unit lies in the middle of the active site, with a feeble electrostatic interaction between the central oxygen with Trp 602. A very small twisting of this part of **1f** results in contact of one methoxy group with the

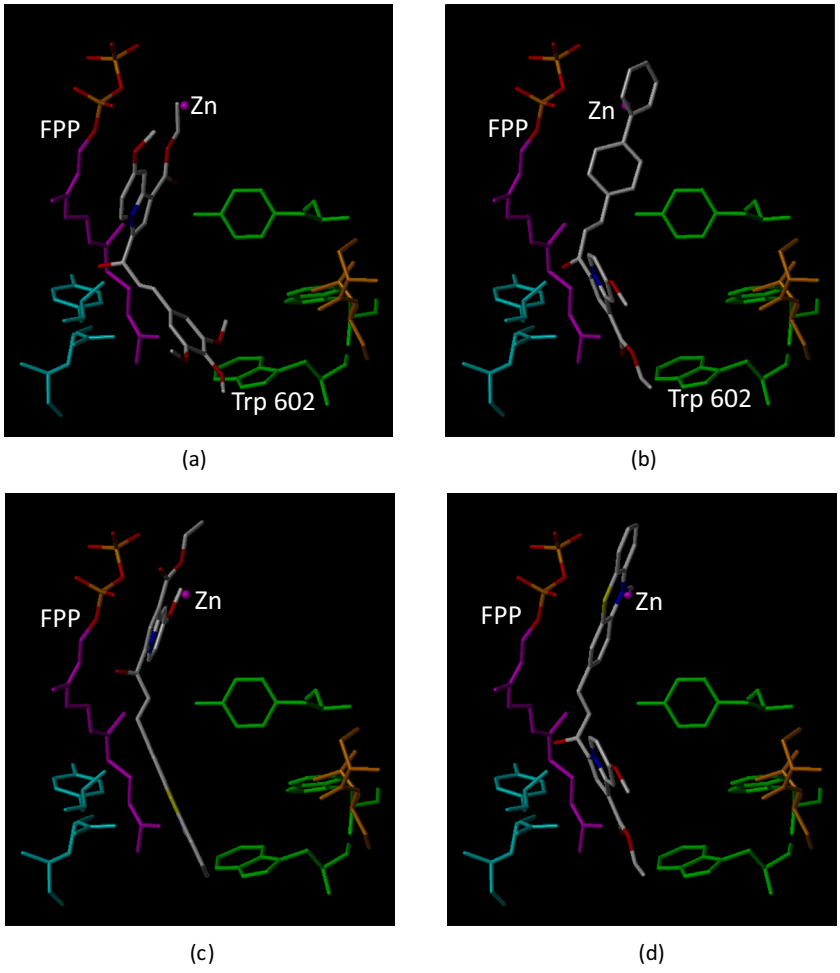


Figure 2. Docking of chalcones **1f** (a), **1l** (b), and **2d** (c), (d) in the farnesyltransferase binding site.

aromatic residue of Trp 602. The other end of **1f** does not move at all, with the ester consistently in interaction with the zinc of the enzyme. Compound **1l** (Fig. 2b) also displays a near unique solution, with only two poses different from the main solution. However, the longer and more rigid diphenyl extremity of the molecule is not able to fit in the too short cavity in front of Trp 602 and ends up instead in front of the zinc atom. The other half of the molecule occupies the active site so that it is in lateral stacking with Tyr 166 with a distance of only 2 Å between the two. Chalcone **2d** displays two conformations. The highest score conformation has a cluster of about half the poses. The methoxy moiety is placed in front of the zinc atom of farnesyltransferase while the molecule lies quite closely along FPP (Fig. 2c). The other cluster is formed by the other half of the poses, and if it lies exactly in the same part of the active site, it is inverted, with its tricycle in front of the zinc atom. This may hint to a less than perfect interaction of this compound with the metal of the protein, due to the single interaction formed by the methyl borne on the nitrogen of the phenothiazine and the zinc atom (Fig. 2d).

To identify new potent inhibitors of human farnesyltransferase, a new family of indolizine–chalcones was designed, synthesized and screened for the inhibitory potential on the protein. Indolizines bearing a chalcone bridge in their position 3 are very rare and not investigated for their biological activity. The current work has the advantage of describing a simple synthesis of indolizine–chalcones using a divergent pathway from indolizine intermediates, readily accessible.

The newly indolizine–chalcones were divided in two series: compounds with phenyl unit (**1a**–**l**) and phenothiazine derivatives (**2a**–**d**). The biological screening exhibited that phenothiazine derivatives were generally more active than indolizines with phenyl ring, showing inhibition efficiencies in the nanomolar range. Phenothiazine **2a** showed optimum biological potential in the current work with an IC_{50} value on farnesyltransferase of 9 nM. The current studies confirm preexisting or establish new SAR: (1) the phenothiazine unit is important in the structure of farnesyltransferase inhibitors; (2) the *para*-chloro or bromo substitution on the phenyl unit is well tolerated; (3) the association of two fragments retrieved in the structure of known farnesyltransferase inhibitors (indolizine and phenothiazine) by a chalcone bridge represented the best pharmacomodulation providing lead compounds; (4) finally, the presence of bulky substituents on the indolizine unit generally decreases the biological efficacy.

The newly synthesized phenothiazine derivatives are very potent in vitro and deserve further chemical and biological investigation to provide inhibitors that can be used in cancer treatment.

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compounds (the URL for the website of the center is: http://cernesim.uaic.ro/index.php/en/).

Supplementary data

Supplementary data (^{1}H, ^{19}F and ^{13}C NMR spectra, IR data, elemental analysis and physic-chemical characteristics of newly synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.05.074.

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