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New farnesyltransferase inhibitors in the phenothiazine series

Dalila Belei [a], Carmen Dumea [a], Alexandrina Samson [a], Amaury Farce [b,c], Joëlle Dubois [d], Elena Bîcu [a], Alina Ghinet [a,b,e,*]

[a] Department of Organic Chemistry, 'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I nr. 11, 700506 Iasi, Romania
[b] Univ Lille Nord de France, F-59000 Lille, France
[c] Institut de Chimie Pharmaceutique Albert Lespagnol, EA GRIIOT (4481), IFR114, 3 Rue du Pr Laguesse, B.P. 83, F-59006 Lille, France
[d] Institut de Chimie des Substances Naturelles, UPR2301 CNRS, Centre de Recherche de Gif, Avenue de la Terrasse, F-91198 Gif-sur-Yvette Cedex, France
[e] UCLille, EA 4481 (GRIIOT), Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France

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ABSTRACT

The biological screening of the chemical library of our Organic Chemistry Department, carried out on an automated fluorescence-based FTase assay, allowed us to discover that a phenothiazine derivative (**1d**) was an inhibitor of farnesyltransferase. Three new series of human farnesyltransferase inhibitors, based on a phenothiazine scaffold, were synthesized with protein farnesyltransferase inhibition potencies in the low micromolar range. Ester derivative **9d** was the most active compound in these series. Four synthesized compounds were evaluated for their antiproliferative activity on a NCI-60 cancer cell line panel. The modest results obtained in this preliminary investigation showed that mixing the phenothiazine and the 1,2,3-triazole motif in the structure of a single compound can lead to new scaffolds in the field of farnesyltransferase inhibitors.

The G-protein superfamily is the most important category of human CAAX proteins (A: aliphatic amino acids; X: methionine, glutamine or serine for farnesyltransferase, leucine or isoleucine for type I geranylgeranyltransferase). Many G-proteins, such as Ras, Rho, Rac and CDC42, are located on the plasma membrane or endomembranes. The G-protein superfamily is actively involved in many important cellular signaling pathways, and plays an important role in carcinogenesis. As one of the most important G-proteins, Ras protein has a well-established role in oncogenesis. Ras proteins function as switches that control growth signals from cell surface receptors to nuclear transcription factors. Human cancer studies show that gene mutational activation of the Ras subfamily (K-Ras, N-Ras and H-Ras) occurs in about 20% of human pancreatic and colorectal adenocarcinoma.[1–5] N-Ras mutation has been reported in melanoma, hepatocellular cancer, myelodysplastics syndrome and acute myelogenous leukemia.[6–8] Also, several human cancers such as thyroid follicular and papillary carcinoma, bladder cancer and renal cell cancer harbor H- or N-Ras mutations.[9,10]

Activation of Ras proteins requires their localization on the plasma membrane, which is mainly dependent on the attachment of a farnesyl (15-carbon) or of a geranylgeranyl (20-carbon) group to the cysteine residue located in the C-terminal tetrapeptidic (CAAX) sequence at the carboxyl terminus of these proteins.[11] Inhibition of protein farnesyltransferase (FTase) prevents membrane localization of Ras, and so constitutes a valid target for the conception of new cytostatic anticancer drugs.[12] Farnesyltransferase inhibitors (FTIs) have thus been developed as a new class of promising drugs for cancer treatment.[13] The main FTase inhibitors that have undergone clinical development[14] are non peptidic, heterocyclic compounds such as tipifarnib (R-115777),[15,16] L-778123,[17] BMS-214662,[18] lonafarnib (SCH-66336)[19] and SCH-226374.[20] Such FTase inhibitors have been discovered through systematic screening approaches. X-ray diffraction studies of the complex of BMS-214662 or tipifarnib with protein farnesyltransferase show that they bind to a hydrophobic cleft formed at the interface of the alpha and beta subunits. The inhibitor forms a ternary complex with the FPP substrate and the enzyme, and binds to the catalytic zinc cation to the rim of the active site. Therefore, they act within a peptide-competitive mechanism.[21]

In order to identify new FTIs hits, a screen of the chemical library of our Organic Chemistry Department (Iasi) was carried out on an automated fluorescence-based FTase assay.[22] This led to the discovery of a phenothiazine derivative **1d** (Fig. 1), which exhibits an inhibitory activity on human FTase in the micromolar range (Table 1). Many biological properties have already been described for phenothiazine derivatives;[23] some of them display anthelmintic activities,[24] and others are (reversible) inhibitors of trypanothione reductase,[25] inhibit lipid peroxidation[26] or tubulin polymerization.[27] To the best of our knowledge, phenothiazines and 1,2,3-triazolyl ring have not encountered in the FTIs field. Thus

* Corresponding author. Tel.: +33 328 384 858; fax: +33 328 384 604.
E-mail address: alina.ghinet@hei.fr (A. Ghinet).

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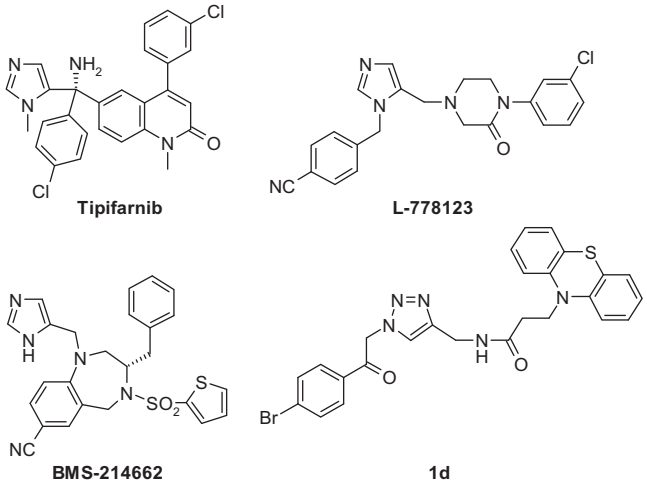


Figure 1. Structure of FTIs.

we decided to perform a preliminary SAR study, and some structural modifications of the scaffold of compound **1d** and we described here the results of this preliminary investigation.

We first modified the nature of the aromatic ring substituent; the general synthesis of 1,2,3-triazole derivatives **1** is outlined in Scheme 1. Starting acid was obtained by condensation of phenothiazine **2** with acrylonitrile in the presence of Triton B[28] then by hydrolysis of nitrile **3** to acid **4** with aqueous sodium hydroxide in methanol.[28] Coupling of carboxylic acid **4** with *N*-hydroxysuccinimide led to activated ester **5**,[29] and then reaction with propargylamine gave acetylenic amide **6**.[30] The expected triazoles **1** were obtained by click chemistry between **6** and α-azidoketones **7** that have already been described[31] but were synthesized by using a new biphasic ($CHCl_3$–H_2O) condition with a phase transfer agent. The same sequence realized with propargyl alcohol yielded ester **8** then triazoles **9**, allowing the evaluation of the importance of the amide group in that position.

The importance of the length between the phenothiazine group and the amido function was considered (Scheme 2). Starting acid was provided from phenothiazine **2** by reacting its sodium salt with ethyl bromoacetate in DMF[32] followed by saponification of ester **10** with aqueous sodium hydroxide.[33] Coupling of carboxylic acid **11** with *N*-hydroxysuccinimide led to activated ester **12**,[34] and then reaction with propargylamine gave acetylenic amide **13**. Then, click chemistry performed between **13** and α-azidoketones **7** afforded triazoles **15**. The same sequence realized with with propargyl alcohol yielded ester **14** then triazoles **16**.

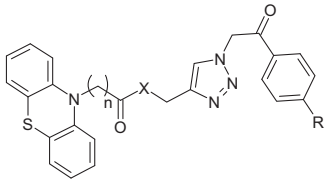
To complete the study of compounds evaluated in this preliminary study, a second phenothiazine group was introduced. Thus, products **22** and **23** were synthesized in a similar way by performing a click chemistry reaction between azidoketones **20**[35a] and **21**[36] and amides **13** and **6** (Scheme 3).

The compound docking onto 1LD7 binding site[37] was realized with GOLD5.1 (CCDC 2011), using the standard parameters, and a sphere of 10 Å around the extracted cocrystallized ligand. The best solution of the docking run was defined as the most frequent conformation among the 30 conformations generated.

Compounds **1c** and **1d** can take a slightly more common conformation described in Figure 2, where their tricyclic head lies in the hydrophobic part of the pocket, in contact with Trp 602 and the terminal aromatic in front of the zinc atom. In this conformation, their amide analogs are not able to interact with any residue of the binding site. They however also display a second conformation where their tricycle moves away from the hydrophobic cleft, letting the carbonyl of their amide to form a hydrogen bond with Arg 702. Compared with the amides **1c** and **1d**, the esters **9c** and **9d** have a larger cluster of conformations; this may be related to their higher potency (Fig. 2). However, all these compounds bind in a mostly similar way, with the terminal phenyl in front of the zinc ion, while the tricyclic head group is engaged in hydrophobic interactions with Trp 602. Possible hydrogen bonds could further anchor the compounds with the hydroxyls of both Tyr 166 and 861 at the level of the ester carbonyl and the triazole respectively.

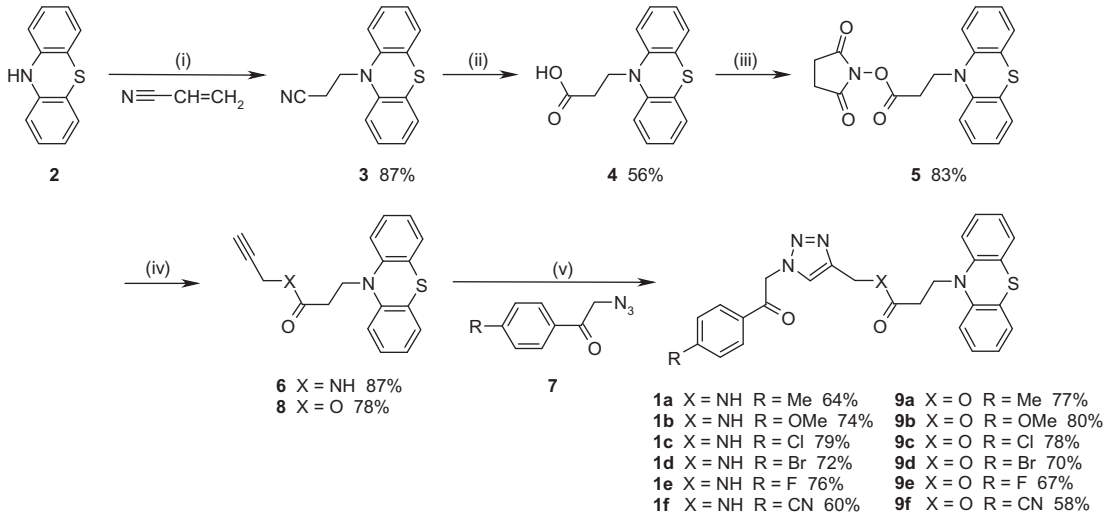
The activity of all the synthesized derivatives was evaluated on human FTase. Results are summarized in Table 1. The *p*-chloro and the *p*-bromo substitutions of the phenyl ring proved to be favorable to bioactivity. We then investigated the influence of different substituents (F, CN, OMe or Me) at the *para*-position of the phenyl ring. These structural modifications caused a significant reduction in biological activity (compound **1a** vs **1c**, Table 1). Next, the replacement of the amide function by an ester enhanced the inhibitory potency on FTase (compound **1c** vs **9c**, Table 1). In addition, when the length of the carbon chain between the phenothiazinic nitrogen and the amide group was shortened from two (**1d**) to one atom (**15d**), FTase inhibition decreased (**1d**:

Table 1
Inhibitory activities of 1,2,3-triazoles **1a–f**, **9a–e**, **15a–f**, **16a–c**, **22a–b** and **23a** on human FTase

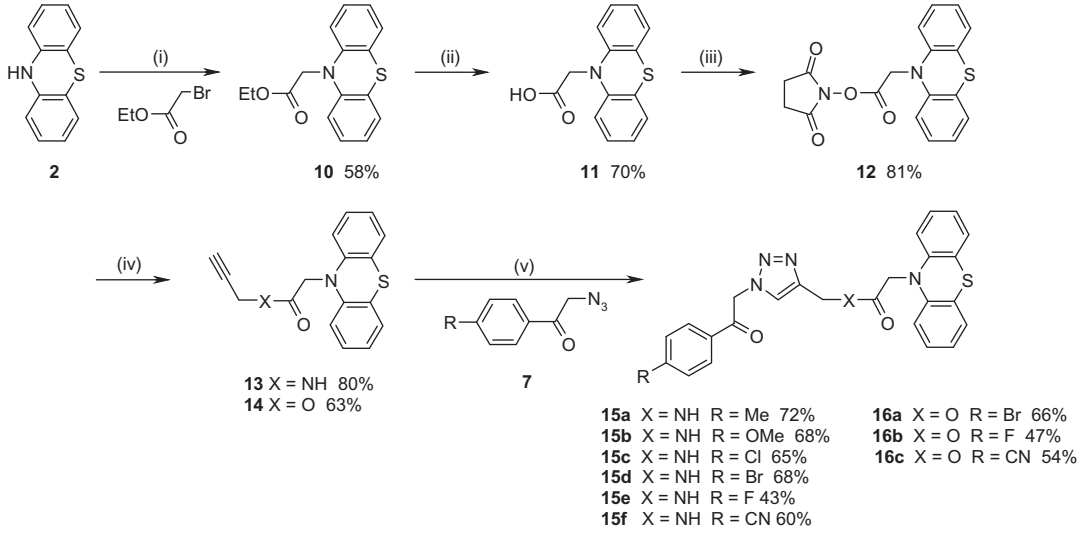


Compound	*n*	X	R	IC_{50}[38] (μM)	Compound	*n*	X	R	Inhibition ratio[a] (%)	Compound	*n*	X	R	Inhibition ratio[a] (%)
1c	2	NH	Cl	7.7 ± 0.8	**1a**	2	NH	Me	44.2	**15c**	1	NH	Cl	40.0
1d	2	NH	Br	8.3 ± 0.9	**1b**	2	NH	OMe	29.3	**15e**	1	NH	F	0
1f	2	NH	CN	5.2 ± 1.3	**1e**	2	NH	F	52.6	**15f**	1	NH	CN	24.9
9c	2	O	Cl	1.5 ± 0.3	**9a**	2	O	Me	10.7	**16a**	1	O	Br	35.5
9d	2	O	Br	1.3 ± 0.3	**9b**	2	O	OMe	22.3	**16b**	1	O	F	31.9
15d	1	NH	Br	24.3 ± 5.0	**9e**	2	O	F	35.2	**16c**	1	O	CN	20.7
					9f	2	O	CN	55.1	**22a**	1	NH	—[b]	0
					15a	1	NH	Me	19.0	**22b**	1	NH	—	0
					15b	1	NH	OMe	24.4	**23a**	2	NH	—	0

[a] Inhibition ratio at a 100 μM concentration.
[b] The terminal phenyl is changed to a phenothiazine unit.



Scheme 1. Reagents and conditions: (i) Triton B, 0 °C → reflux, 2 h, 87% (lit. 92%)[28]; (ii) aqueous NaOH, MeOH, reflux, 15 h, 56% (lit. 60%)[28]; (iii) 1.2 equiv *N*-hydroxysuccinimide, 1.2 equiv EDC, CH_2Cl_2, rt, 24 h, 83%; (iv) 1.7 equiv propargylamine or propargyl alcohol, 2.2 equiv triethylamine, DMF, rt, 24 h; (v) 0.1 equiv $CuSO_4 \cdot 5H_2O$, 0.2 equiv sodium ascorbate, *t*-BuOH:MeOH:MeCN 10:2:1, H_2O, rt, 24 h.

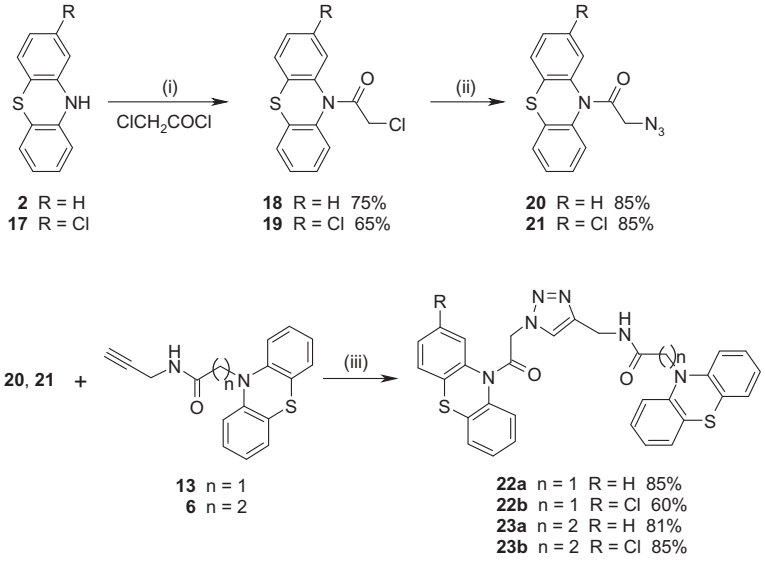


Scheme 2. Reagents and conditions: (i) 1 equiv NaH, DMF, 0 °C → rt, 12 h; 58% (lit. 67%)[32]; (ii) aqueous NaOH, EtOH, MeOH, reflux, 1 h, 70%; (iii) 1.2 equiv *N*-hydroxysuccinimide, 1.2 equiv EDC, CH_2Cl_2, rt, 24 h, 81%; (iv) 1.67 equiv propargylamine, 2.2 equiv triethylamine, DMF, rt, 24 h, 80%; (v) 0.1 equiv $CuSO_4 \cdot 5H_2O$, 0.2 equiv sodium ascorbate, *t*-BuOH:MeOH:MeCN 10:2:1, H_2O, 50 °C, 24 h.

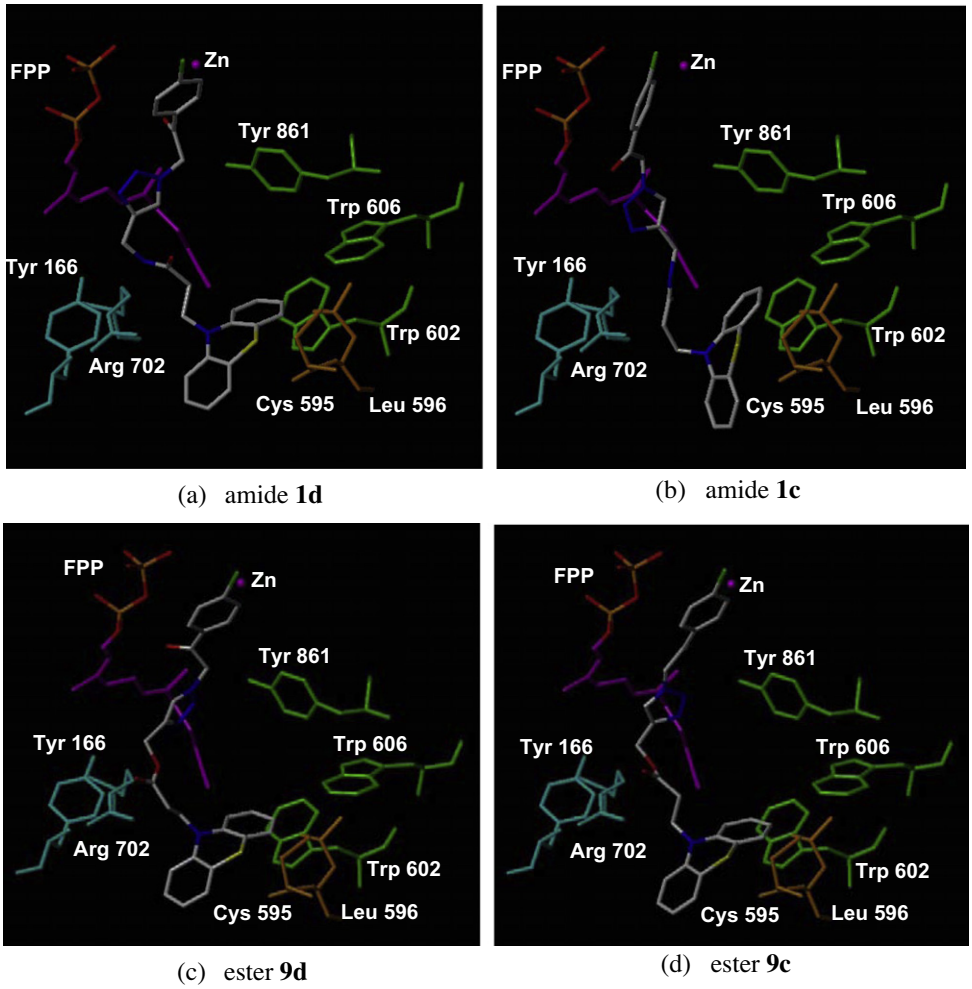
IC_{50} = 8.3 ± 0.9 μM; **15d**: IC_{50} = 24.3 ± 5.0 μM). This tendency is also conserved in the series of esters (e.g., compound **9c** vs **16a**, Table 1; **9c**: IC_{50} = 1.5 ± 0.3 μM; **16a**: 36% inhibition at a 100 μM concentration). Finally, the introduction of a second phenothiazine unit in place of the benzene ring abolished affinity toward FTase (compound **1c** vs **23a**).

The four phenothiazine derivatives **1c–e** and **15d** were selected by NCI for screening against 60 human tumor cell lines. The representative results are summarized in Table 2. Compound **1c** exhibited the most interesting cell growth inhibitory activity among the tested compounds (68% inhibition on HL-60(TB), 40% inhibition on MOLT-4 and 38% inhibition on PC-3 cell lines at 10 μM concentration). As observed in the FTase assay (Table 1), nearly identical activities were observed on most cell lines for compound **1d** (41% inhibition on HL-60(TB), 34% inhibition on MOLT-4 and 42% on PC-3 cell lines). Replacement of the *p*-chloro group of **1c** with a *p*-fluoro moiety (**1e**) caused a reduction in antiproliferative activity (only 20% inhibition on HL-60(TB), 38% inhibition on MOLT-4 and 26% inhibition on PC-3). Compound **15d** showed very modest cell growth inhibition, conserving antiproliferative potential only on MOLT-4 cell lines (42% inhibition), compared to compound **1c**.

The biological screening of the chemical library of our Organic Chemistry Department, carried out on an automated fluorescence-based FTase assay, allowed us to discover that a compound with a phenothiazine scaffold (**1d**) was an inhibitor of farnesyltransferase. Structural modifications of this compound were envisaged in order to enhance inhibitory activity. Three families of new phenothiazine derivatives were synthesized and evaluated for their ability to inhibit human farnesyltransferase in vitro. The length of the chain between the phenothiazine group and the amido function proved to be very important in determining inhibitory activity, as shown for compounds **1d** and **15d** (Table 1). Replacement of the amidic function by an ester group enhanced biological activity (e.g., compound **9d** vs **1d**, Table 1). The introduction of a second phenothiazine motif in place of the *p*-substituted



Scheme 3. Reagents and conditions: (i) toluene, reflux, 5 h, 75% for compound **18** (lit. 76%)[35b] and 65% for compound **19** (lit. 65%)[36]; (ii) 1.1 equiv NaN_3, 0.012 equiv TBAB, $CHCl_3$, H_2O, rt, 48 h, 85% for compounds **20** and **21**[35]; (iii) 0.1 equiv $CuSO_4 \cdot 5H_2O$, 0.2 equiv sodium ascorbate, *t*-BuOH:MeOH:MeCN 10:2:1, H_2O, 50 °C, 24 h.



(a) amide **1d** (b) amide **1c**

(c) ester **9d** (d) ester **9c**

Figure 2. Docking of compounds **1c–d** and **9c–d** in the active site of FTase.

Table 2
Results of the in vitro human cancer cell growth inhibition[39]

Cell type	Cell line	Inhibition ratio (%) at 10 μM[a]			
		1c	**1d**	**1e**	**15d**
Leukemia	CCRF-CEM	19	18	20	17
	HL-60 (TB)	68	41	20	13
	MOLT-4	40	34	38	42
	RPMI-8226	19	15	3	22
CNS cancer	SNB-75	20	18	19	18
Colon cancer	HCT-15	8	7	na[b]	16
Non-small cell lung cancer	EKVX	30	24	22	na
melanoma	LOX IMVI	9	17	12	na
	SK-MEL-5	13	24	14	5
	UACC-62	26	29	14	25
Ovarian cancer	OVCAR-8	17	na	na	6
Renal cancer	UO-31	36	42	18	13
	CAKI-1	32	37	17	13
Prostate cancer	PC-3	38	42	26	nd[c]
Breast cancer	MDA-MB-231/ATCC	4	14	3	9
	T-47D	22	29	7	12

[a] Data obtained from NCI's in vitro 60 cell single dose screen (10 μM).
[b] Not active.
[c] Not determined.

phenyl group was detrimental to biological potency (e.g., compound **23a** vs **1d**, Table 1). The modest results obtained in this preliminary investigation showed that mixing the phenothiazine and the 1,2,3-triazole motif in a single compound structure can lead to new scaffolds in the field of farnesyltransferase inhibitors.

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Supplementary data

Supplementary data (synthesis details and physico-chemical characterization for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.06.007.

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