UNIVERSITY „ALEXANDRU IOAN CUZA" OF IAŞI

FACULTY OF CHEMISTRY

PHD SCHOOL OF CHEMISTRY AND SCIENCES OF LIFE AND EARTH

DUMITRIU GINA-MIRABELA

Farnesyltransferase inhibitors with azaheterocyclic structure. Synthesis and biological evaluation

ABSTRACT OF PhD THESIS

SCIENTIFIC COORDINATOR
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IAŞI
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Acknowledgment...

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ANNEXES

The summary presented contains a brief of personal research results, conclusions and an extract of the bibliography. It has been kept the numbering of the chapters, tables, schemes and figures included in phD thesis.

INTRODUCTION

Azaheterocyclic compounds were observed because of the crucial roles that are playing in biological processes. As a result of high applicability in medicinal chemistry and materials chemistry, researchers believe that the development of new azaheterocyclic compounds being a very attractive research direction.

Farnesyltransferase (FTase) has a crucial role in post-translational modifications of proteins Ras and is a promising therapeutic target for the treatment of various cancers and other diseases.[2] Therefore, the design and synthesis of anticancer drugs having the biological target the Ras protein have a great therapeutic importance.

The aim of this thesis is the synthesis and biological evaluation of new azaheterocyclic derivatives with phenothiazines, carbazole, triazole and pyrrolidone scaffold. Biological evaluation consisted in testing the inhibitory properties on the human *farnesyltransferase*.

The PhD thesis includes one part of literature describing the current state of knowledge in the field studied and a second part, the original contributions, based on the design, synthesis, spectral characterization and biological evaluation of new azaheterocyclic compounds obtained during the course of research for the development of this theses. The PhD thesis concludes with general conclusions, bibliography and annexes with the papers published in internationals journals.

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II. PERSONAL CONTRIBUTIONS

In this PhD thesis we aimed as a general objective synthesis and biological evaluation of new heterocyclic derivatives with potential biological activity (Figure 1).

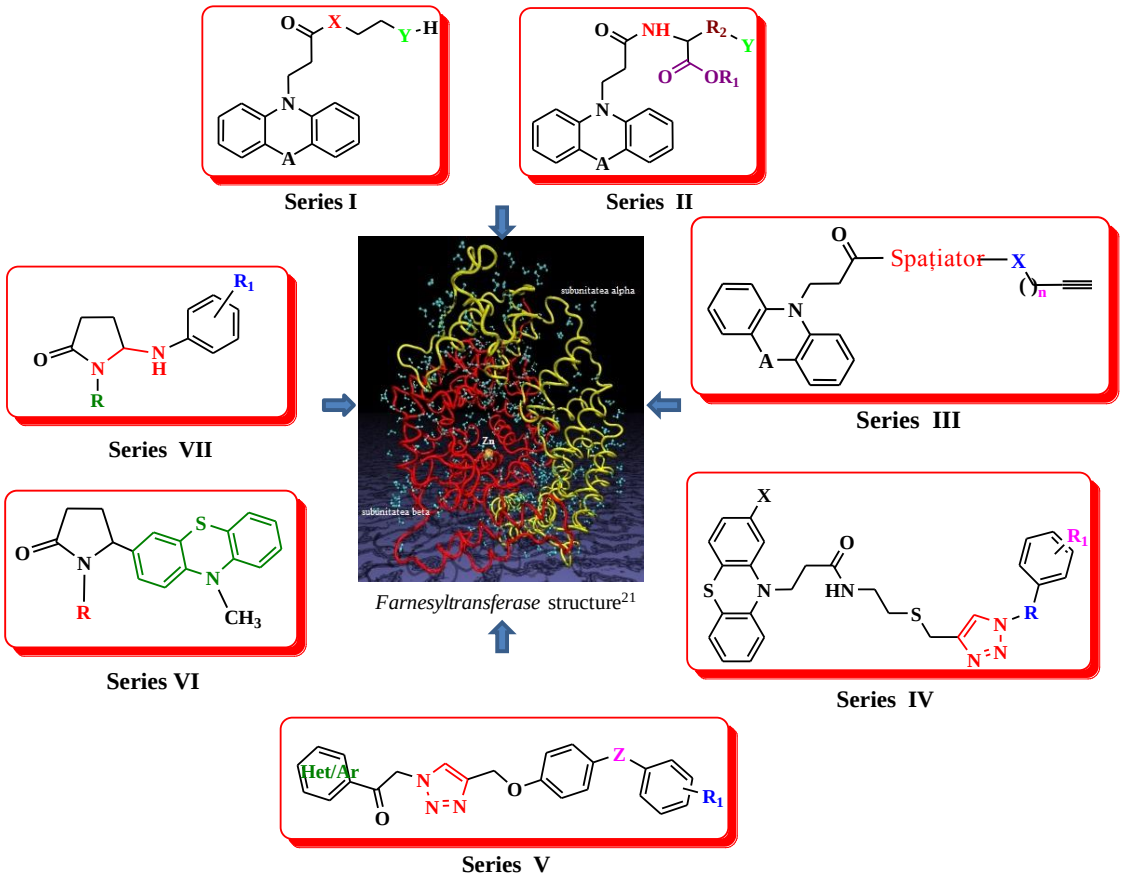
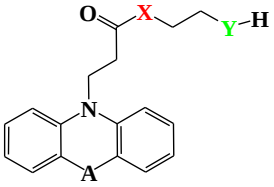


Figure 1. The general objectiv

II.1. The synthesis, characterization and biological evaluation of novel phenothiazine and carbazole derivatives which have grafted to the nitrogen atom residue found in the structure of amino acids

II.1.2. The structural design

We proposed the synthesis of new phenothiazine and carbazole derivatives that have grafted on the nitrogen atom residue found in the structure of the amino acids, according to the general structure of Figure 8.

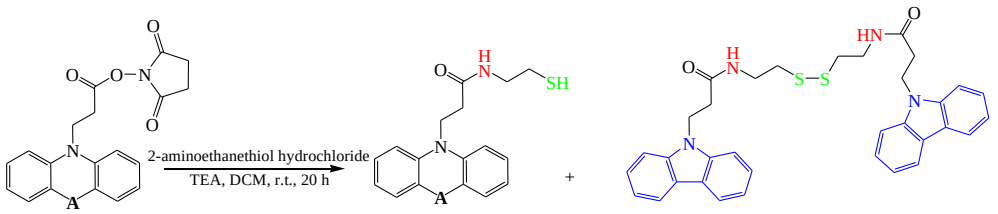


A	X	Y
bond	O	S
S	NH	O

Figure 8. General skeleton of the synthesized compounds

II.1.4. Synthesis of the final compounds

There were synthesized two classes of compounds: phenothiazine derivatives, containing in the chain hydroxy / etilamido or thiol ester, respectively carbazole derivatives (Scheme 4 and 5).

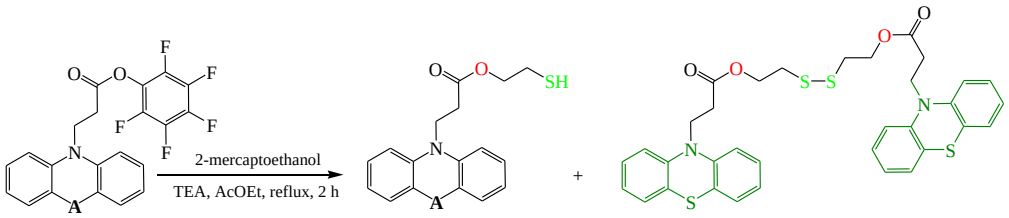


21: A = S
22: A = bond

25a: A = S, 50%
25b: A = bond, 51%

26b, 13%

Scheme 4. The synthesis of amide derivatives of thiols residue



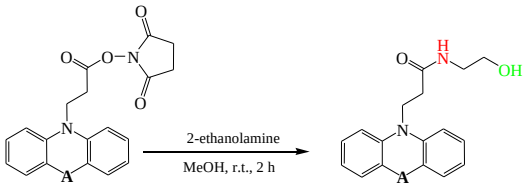
23: A = S
24: A = bond

25c: A = S, 45%
25d: A = bond, 70%

26c, 10%

Scheme 5. The synthesis of esters derivatives of thiols residue

Amide derivatives with free hydroxyl groups are obtained according to Scheme 6.[138]



21: A = S
22: A = bond

25e: A = S, 45%
25f: A = bond, 47%

Scheme 6. The synthesis of amide derivatives with ethanol residue

In the first series of azaheterocyclic compounds were synthesized 11 new phenothiazine and carbazole derivatives. The structure of the new synthesized compounds was confirmed on the basis of spectra recorded: IR, ^{1}H- RMN, ^{13}C- RMN, ^{19}F- RMN, LC-MS

II.1.5. Biological evaluation

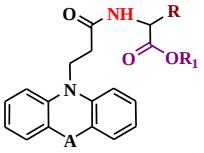
The biological activity of the new derivatives of phenothiazine and carbazole synthesized was evaluated on human farnesyltransferase (FTase). Test results showed compounds **25d** and **26b** carbazole skeleton possessing a FTase inhibitory activity in the micromolar range (IC_{50} = 35,0 μM și 89,8 μM).

These results were reported in the publication *Investigation of new phenothiazine and carbazole derivatives as potential inhibitors of human farnesyltransferase* **Dumitriu**, **Gina-Mirabela**; Ghinet, Alina; Belei, Dalila; Rigo, Benoît; Gautret, Philippe; Dubois, Joëlle; Bîcu, Elena *Letter in Drug Design & Discovery*, **2015**, *12*, 85-92, doi : 10.2174/1570180811666140909010435.[141]

II.2. The synthesis, characterization and biological evaluation of novel phenothiazine and carbazole derivatives with amino acids recognized by FTase found in the structure of CAAX motif

II.2.1. The structural design

To have a complete study on structure-activity relationships in this family of compounds we have continued researches and we aimed to engage amino acids to the azaheterocyclic skeleton. The general structure of this series is shown in Figure 13.



A	R	R_1
bond, S	CH_2OH $CH_2CH_2SCH_3$ $CH(CH_3)_2$ CH_2SH	H CH_3 CH_2CH_3

Figure 13. General skeleton of the synthesized compounds

II.2.2. Synthesis of the final compounds

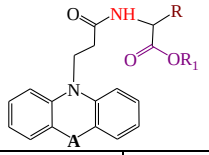
Compounds of interest with phenothiazine skeleton **27a-d** were obtained by the reaction of the activated ester **21** and serine, methionine, valine methyl ester hydrochloride respectively the cysteine ethyl ester hydrochloride. Further, the compounds **27a-d** acted as precursors in the reaction of saponification to obtain the carboxylic acid derivative **29a-d**.

For the synthesis of carbazole derivatives **30a-d** and **31a-d**, we used the same synthetic methodology as presented to phenothiazine derivatives.

II.2.3. Biological evaluation

Heterocyclic derivatives containing marginal amino acids found in the structure of CAAX motif recognized by FTase were tested on human farnesyltransferase (FTase) (Table 2).

Table 2. Inhibitory activities of the compounds synthesized against human FTase



Compound	A	R	R_1	% Inh (FTase)	IC_{50} (μM ± SD)	R^2
27a	S	CH_2OH	CH_3	63	n.d.	-
27b	S	$CH_2CH_2SCH_3$	CH_3	4,5	n.d.	-
27c	S	$CH(CH_3)_2$	CH_3	52	n.d.	-
27d	S	CH_2SH	CH_2CH_3	10	n.d.	-
28d	S	CH_2S-S-27d	CH_2CH_3	0	n.d.	-
29a	S	CH_2OH	H	93,5	12,0 ± 2,6	0,845
29b	S	$CH_2CH_2SCH_3$	H	92,3	11,7 ± 0,9	0,959
29c	S	$CH(CH_3)_2$	H	75,5	44,7 ± 3,5	0,938
29d	S	CH_2SH	H	92,4	4,7 ± 0,5	0,964
30a	bond	CH_2OH	CH_3	22,8	n.d.	-
30b	bond	$CH_2CH_2SCH_3$	CH_3	50,5	n.d.	-
30c	bond	$CH(CH_3)_2$	CH_3	12,2	n.d.	-
30d	bond	CH_2SH	CH_2CH_3	14,6	n.d.	-
31a	bond	CH_2OH	H	32,9	n.d.	-
31b	bond	$CH_2CH_2SCH_3$	H	72,8	40,2 ± 2,2	0,759
31c	bond	$CH(CH_3)_2$	H	22,2	n.d.	-
31d	bond	CH_2SH	H	66,5	65,4 ± 5,1	0,923

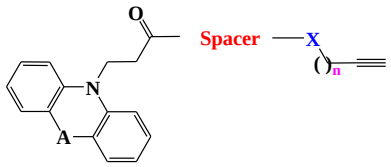
In conclusion, in this series we have presented the synthesis of **25 new phenothiazine and carbazole derivatives**.

These results were reported in the publication *Phenothiazine-based CaaX competitive inhibitors of human farnesyltransferase bearing a cysteine, methionine, serine or valine moiety as a new family of antitumoral compounds* **Dumitriu**, **Gina-Mirabela**; Bîcu, Elena; Belei, Dalila; Rigo, Benoît; Dubois, Joëlle; Farce, Amaury; Ghinet, Alina *Bioorganic & Medicinal Chemistry Letters*, **2015**, 25, 4447-4452, doi: 10.1016/j.bmcl.2015.09.008.[146]

II.3. The synthesis, characterization and biological evaluation of novel heterocyclo-peptide with the acetylenic radical

II.3.1. The structural design

We decided to explore the potential for inhibition of FTase for compounds with tricyclic construction bearing a chain with terminal acetylenic group (Figure 16).

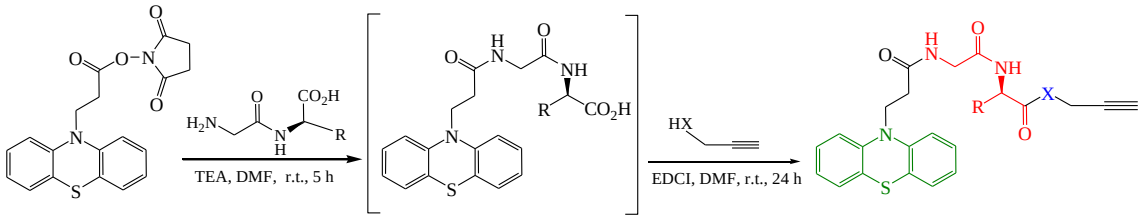


A	Spacer	X	n
bond, S	bond (Gly)x(Tyr)y (x = 0,1,2; y = 0,1)	O NH	1 2

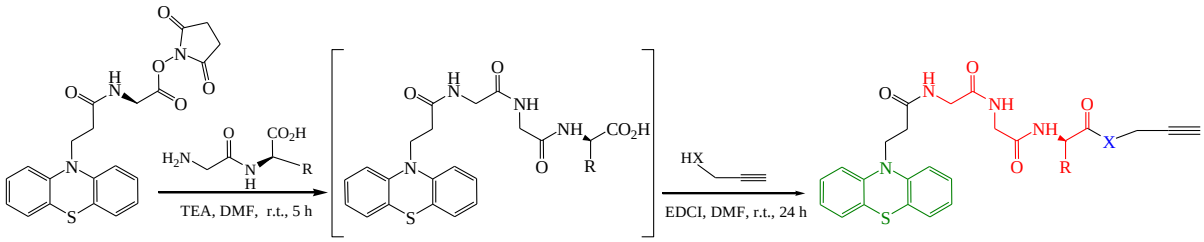
Figure 16. General skeleton of the compounds heterocyclo-peptide with the acetylenic radical

II.3.2. Synthesis of the final compounds

The synthesis of the peptido-propargyl derivatives **46-48** was carried out without isolation of intermediates, using the one-pot reaction (Scheme 19).



21 **45**: R = $CH_2C_6H_4OH(p)$ **46a**: R = $CH_2C_6H_4OH(p)$, X = NH, 65%
46b: R = $CH_2C_6H_4OH(p)$, X = O, 45%



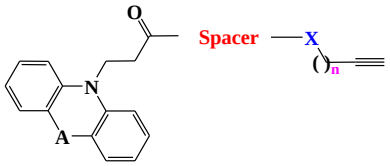
41 **47**: R = $CH_2C_6H_4OH(p)$ **48a**: R = $CH_2C_6H_4OH(p)$, X = NH, 62%
48b: R = $CH_2C_6H_4OH(p)$, X = O, 40%

Scheme 19. Synthesis of derivatives of glycyl-tyrosine or glycyl-glycyl-tyrosine propargyl amide and propargyl ester

II.3.3. Biological evaluation

Also in this case the biological activity of all the compounds synthesized were evaluated in the human farnesyltransferase (Table 4).

Table 4. The inhibitory activities of the compounds of the propargyl amino acid residue **40a-d**, **44a,b**, **46a,b** and **48a,b** on the human farnesyltransferase

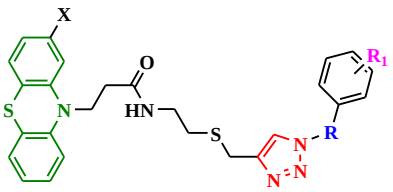


Compound	Spacer	X	% Inh (FTase)	IC_{50} (μM ± SD)	R^2
40a	Gly	NH	42	n.d.	-
40b	Gly	O	25	n.d.	-
40c	Tyr	NH	43	n.d.	-
40d	Tyr	O	90	18,0 ± 2,4	0,935
44a	Gly-Gly	NH	42	n.d.	-
44b	Gly-Gly	O	59	78,7 ± 5,5	0,939
46a	Gly-Tyr	NH	68	24,4 ± 3,3	0,898
46b	Gly-Tyr	O	69	36,3 ± 0,9	0,994
48a	Gly-Gly-Tyr	NH	82	39,7 ± 1,0	0,994
48b	Gly-Gly-Tyr	O	70	30,1 ± 2,7	0,909

In conclusion, in this study, we synthesized and evaluated biologically 21 new azaheterocyclic derivatives. Aceste These results were reported in the publication: *Peptide chemistry applied to a new family of phenothiazine-containing inhibitors of human farnesyltransferase* **Dumitriu**, **Gina-Mirabela**; Ghinet, Alina; Bîcu, Elena; Rigo, Benoît; Dubois, Joëlle; Farce, Amaury; Belei, Dalila *Bioorganic & Medicinal Chemistry Letters*, **2014**, *24*, 3180-3185, doi: 10.1016/j.bmcl.2014.04.102.[147]

II.4. The synthesis, characterization and biological evaluation of novel triazolo-phenothiazine derivatives

II.4.2. The structural design

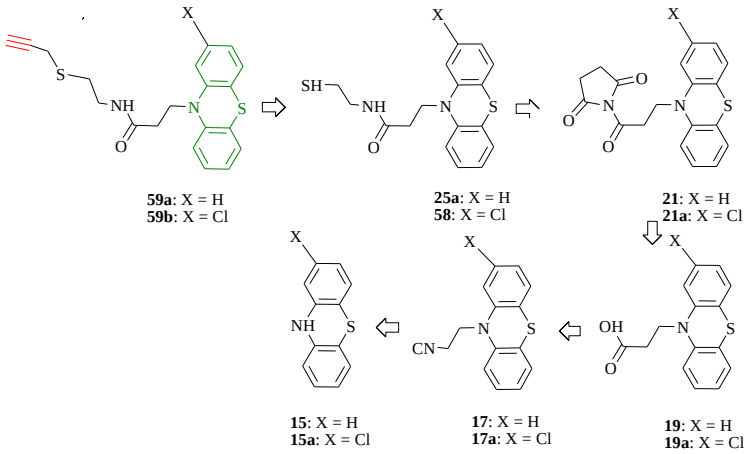


X	R	R_1
H, Cl	bond, CH_2CO	m(p)-COOMe, m(p)-COOH Cl, Br, CN, OMe, Ph

Figure 26. General skeleton of the compounds triazolo-phenothiazine

II.4.3. Synthesis of the precursors

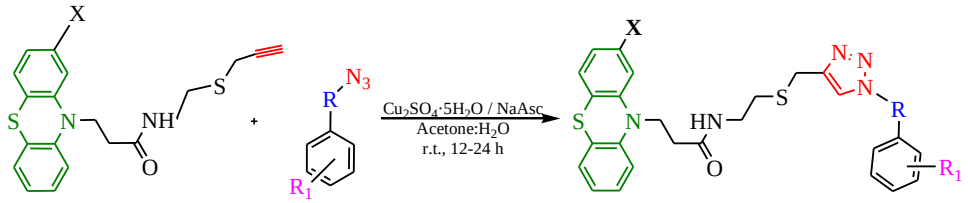
1,4-Disubstituted triazoles followed were synthesized by propargyl derivatives and the corresponding azides according to Scheme 20 of retro-synthesis.



Scheme 20. Retro-synthesis of the phenothiazine derivatives with propargyl thioether residue

II.4.4. Synthesis of the final compounds

The last step of our synthesis consisted of closing the catalytic cycle 1,2,3-triazole by click chemistry-type reactions. The synthesis of these derivatives is shown in Scheme 24.



59a,b (H, Cl) **61a-e; 64a-d** **65a-j; 66a-h**

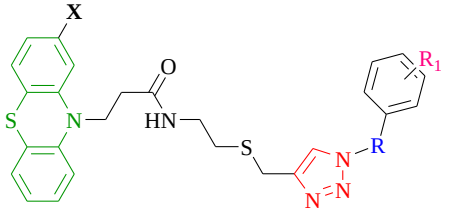
Scheme 24. The synthesis of 1-(phenacyl)- and 1-phenyl- triazole-4-substituted derivatives

The structure of the new synthesized compounds was confirmed on the basis of spectra recorded: IR, ^{1}H-RMN, ^{13}C- RMN and LC-MS.

II.4.5. Biological evaluation

The biological activity of the new derivatives of triazolo-phenothiazine synthesized was evaluated on human farnesyltransferase (Table 6).

Table 6. The inhibitory activities of the compounds **65a-j** and **66a-h** on the human farnesyltransferase



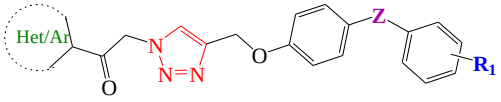
Compound	X	R	R_1	% Inh (FTase)	IC_{50} (µM ± SD)	R^2
65a	H	CH_2-CO-	*p*-Cl	68,8	17,0 ±3,9	0,899
65b	H	CH_2-CO-	*p*-Br	58	12,6 ±3,5	0,64
65c	H	CH_2-CO-	*p*-CN	82,8	8,44±1,3	0,935
65d	H	CH_2-CO-	*p*-OMe	34	n.d.	-
65e	**H**	**CH_2-CO-**	***p*-Ph**	**88,9**	**4,2 ± 0,83**	**0,81**
65f	Cl	CH_2-CO-	*p*-Cl	70,9	13,1 ± 1,1	0,816
65g	Cl	CH_2-CO-	*p*-Br	69	11,5 ± 1,1	0,821
65h	Cl	CH_2-CO-	*p*-CN	92	16,4 ± 2,8	0,994
65i	Cl	CH_2-CO-	*p*-OMe	4,4	n.d.	-
65j	Cl	CH_2-CO-	*p*-Ph	69	12,2 ± 1,0	0,891
66a	H	-	*m*-COOH	90,7	28,6 ± 5,9	0,928
66b	H	-	*p*-COOH	86,9	38,6 ± 6,1	0,948

66c	H	-	*m*-COOMe	49,3	n.d.	-
66d	H	-	*p*-COOMe	45,3	n.d.	-
66e	Cl	-	*m*-COOH	96,2	14,3 ± 1,28	0,984
66f	Cl	-	*p*-COOH	92,8	16,5 ± 1,8	0,973
66g	Cl	-	*m*-COOMe	5,8	n.d.	-
66h	Cl	-	*p*-COOMe	24	n.d.	-

In conclusion, in this section we have reported the synthesis, characterization and biological evaluation of novel triazolo-phenothiazine were synthesized **21 compounds** not described in the literature.

II.5. The synthesis, characterization and biological evaluation of novel chalcono-triazole derivatives

II.5.1. The structural design

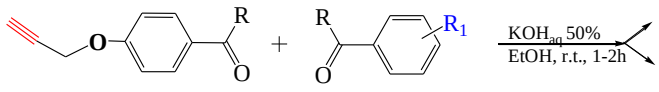


Het/Ar	Z	R_1
Phenothiazine, Carbazole, Biphenyl	-CH=CH-CO- -CO-CH=CH-	*p*-Br, *p*-N$(CH_3)_2$, *p*-phenyl, 3,4,5-OMe

Figure 30. General skeleton of the chalcono-, respectively retrochalcono-triazole derivatives

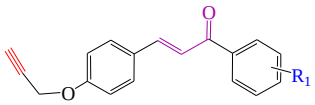
II.5.2. Synthesis of the precursors

Propargylether chalcono-targeted compounds (Scheme 29).

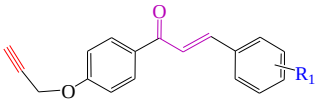


74a: R = H
74b: R = CH_3

75a-h



80a: R_1= *p*-Br, 94%
80b: R_1= *p*-N$(CH_3)_2$, 65%
80c: R_1= *p*-Ph, 92%
80d: R_1= 3,4,5-OMe, 94%

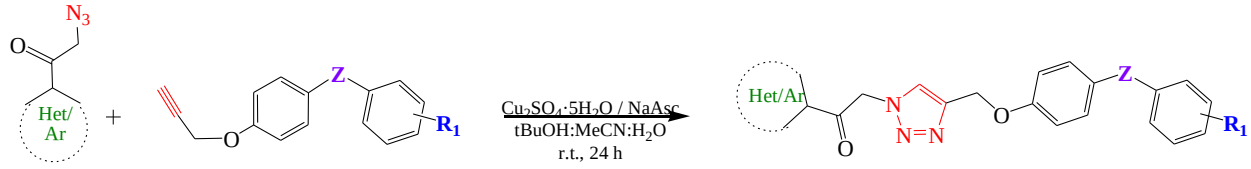


80e: R_1= *p*-Br, 90%
80f: R_1= *p*-N$(CH_3)_2$, 81%
80g: R_1= *p*-Ph, 96%
80h: R_1= 3,4,5-OMe, 88%

Scheme 29. The synthesis of propargylether chalcono/retrochalcono derivatives

II.5.3. Synthesis of the final compounds

Chalcono-triazole compounds of interest were obtained by the reaction of azide **70a,b**, **72** and chalcono-acetylenic derivatives **80a-h** (Scheme 30).



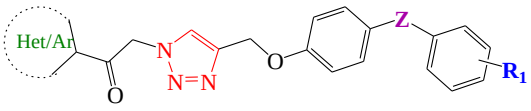
70a,b (Het); 72 (Ar) **80a-h** **81a-l; 82a-l**

Scheme 30. The synthesis of chalcono/retrochalcono-triazole derivatives

II.5.4. Biological evaluation

The biological activity was evaluated on a screening test on human farnesyltransferase (Table 8).

Table 8. The inhibitory activities of the chalcono-triazole derivatives **81j-l** and retrochalcono-triazole derivatives **82a-f** and **82j-l** on the human farnesyltransferase



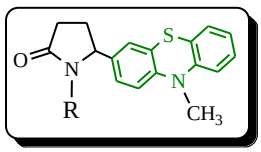
Compound	Het/Ar	Z	R_1	% Inh (FTase)	IC_{50} (μM ± SD)	R^2
81j	Pt	-CH=CH-CO-	3,4,5-OMe	67,1	n.d.	-
81k	Cb	-CH=CH-CO-	3,4,5-OMe	71,4	n.d.	-
81l	BiPh	-CH=CH-CO-	3,4,5-OMe	101,5	3,2 ± 0,3	0,972
82a	Pt	-CO-CH=CH-	*p*-Br	83,6	10,5 ± 0,4	0,984
82b	Cb	-CO-CH=CH-	*p*-Br	87,4	6,2 ± 0,9	0,895
82c	BiPh	-CO-CH=CH-	*p*-Br	35,1	n.d.	-
82d	**Pt**	**-CO-CH=CH-**	***p*-N(CH$_3$)$_2$**	**87**	**2,3 ± 0,4**	**0,843**
82e	**Cb**	**-CO-CH=CH-**	***p*-N(CH$_3$)$_2$**	**88,9**	**3,4 ± 0,4**	**0,957**
82f	**BiPh**	**-CO-CH=CH-**	***p*-N(CH$_3$)$_2$**	**91,7**	**2,6 ± 0,2**	**0,981**
82j	Pt	-CO-CH=CH-	3,4,5-OMe	65,3	n.d.	-
82k	Cb	-CO-CH=CH-	3,4,5-OMe	0	n.d.	-
82l	BiPh	-CO-CH=CH-	3,4,5-OMe	101	22,4 ± 3,0	0,948

In conclusion, in this chapter we reported the synthesis, characterization and biological evaluation of new chalcono-triazole compounds. Thus, we synthesized **31 compounds not described in the literature**.

II.6. The synthesis, characterization and biological evaluation of novel phenothiazin-pyrrolidones derivatives

II.6.2. The structural design

The design of these compounds involved merging two units pharmacophores to potentiate synergistic properties of biological activity (Figure 34).

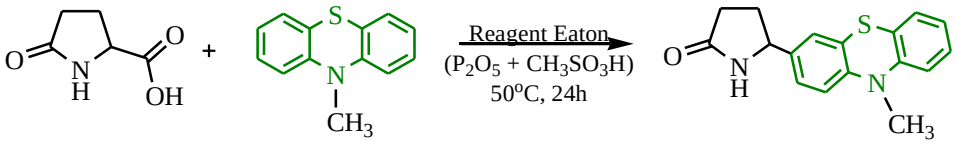


R: H, phenylsubstituted

Figure 34. General skeleton of the new phenothiazin-pyrrolidones derivatives

II.6.3. The synthesis of phenothiazin-pyrrolidones derivatives

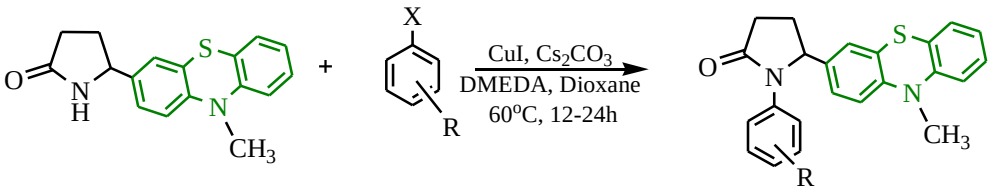
Phenothiazine-pyrrolidonees derivatives, were obtained by a two-step synthesis strategy according to Scheme 32.[187]



92 **93** **94**, 50%

Scheme 32. The synthesis of 5-(10-methyl-phenothiazine-3-yl)pyrrolidin-2-one

In the second stage this derivative acted as an intermediary in substitution reactions with various halogenated aromatic radicals, isolating proposed derivatives (Scheme 33).



94 **95a**-c

96a: R = 2,4-Cl, 45%
96b: R = 3,5-Cl, 57%
96c: R = 4-CN, 40%

Scheme 33. Synthesis of derivatives of 1-aryl-5-phenothiazine-3-yl-pyrrolidone

II.6.4. Biological evaluation

The biological activity of novel phenothiazin-pyrrolidone derivatives was assessed *in vitro* against farnesyltransferase.

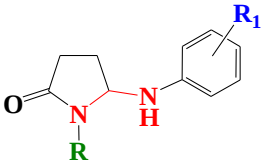
Only derivative **94**, phenothiazine-pyrrolidone compound unsubstituted at the nitrogen atom pyrrolidone, having a percent inhibition of farnesyltransferase 54%.

In conclusion, we have synthesized, characterized and evaluated biological 4 new phenothiazin-pyrrolidone derivatives.

II.7. The synthesis, characterization and biological evaluation of novel N,N-aminal derivatives with pyrrolidones moiety

II.7.1. The structural design

In order to have a full study structure-activity we proposed synthesis of novel compounds and i replaced phenothiazine from the position five of pyrrolidone with aromatic amines (Figure 36).



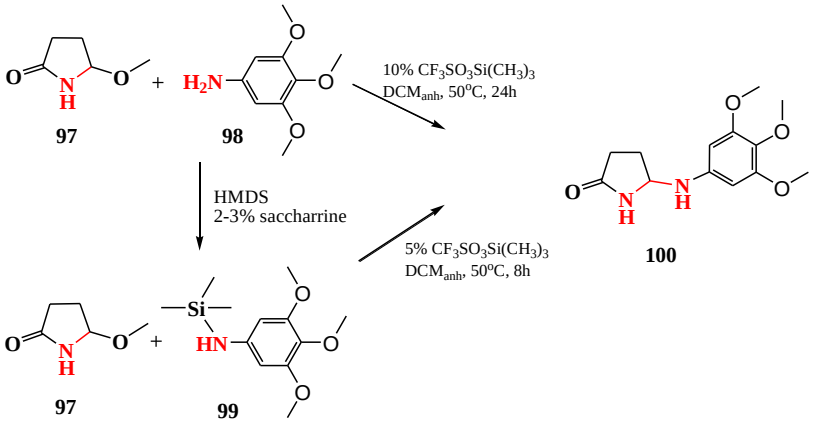
R: H, CH_3, benzyl, phenyl
R_1: *o*-(*m*-,p-)OCH_3, 3,4,5-OCH_3

Figure 36. General skeleton of the *N,N*-aminal derivatives

II.7.2. The synthesis of *N,N*-aminal derivatives

The aim was to obtain the target compounds using as reagents derivatives 5-methoxy-pyrrolidine-2-one, silylated aromatic amines or non silylated. All reactions were conducted under acid catalysis.

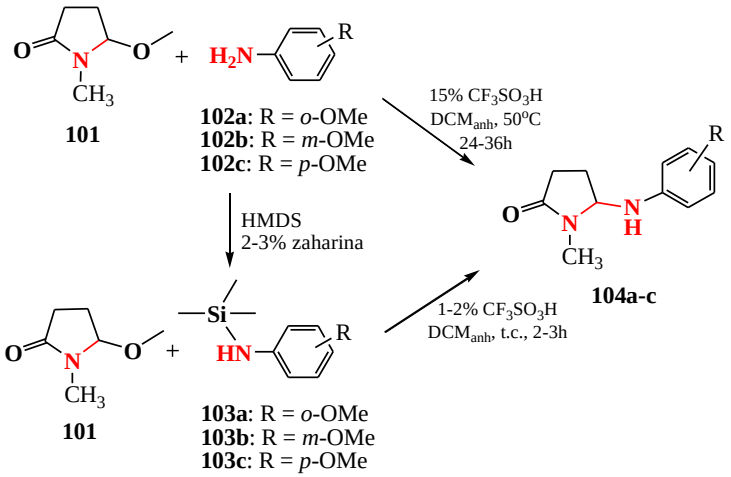
Our study has started with the pyrrolidone derivative unsubstituted on the nitrogen atom (Scheme 34).



Scheme 34. The synthesis of 5-(3,4,5-trimethoxy-phenylamino)pyrrolidin-2-one

As expected the use of the silylated amine has led to the increased yield of 55% further the reaction time was much shorter.

To generalize the method, we substituted the nitrogen atom with methyl, benzyl or aryl different substituted, we also used various amines (Scheme 35).

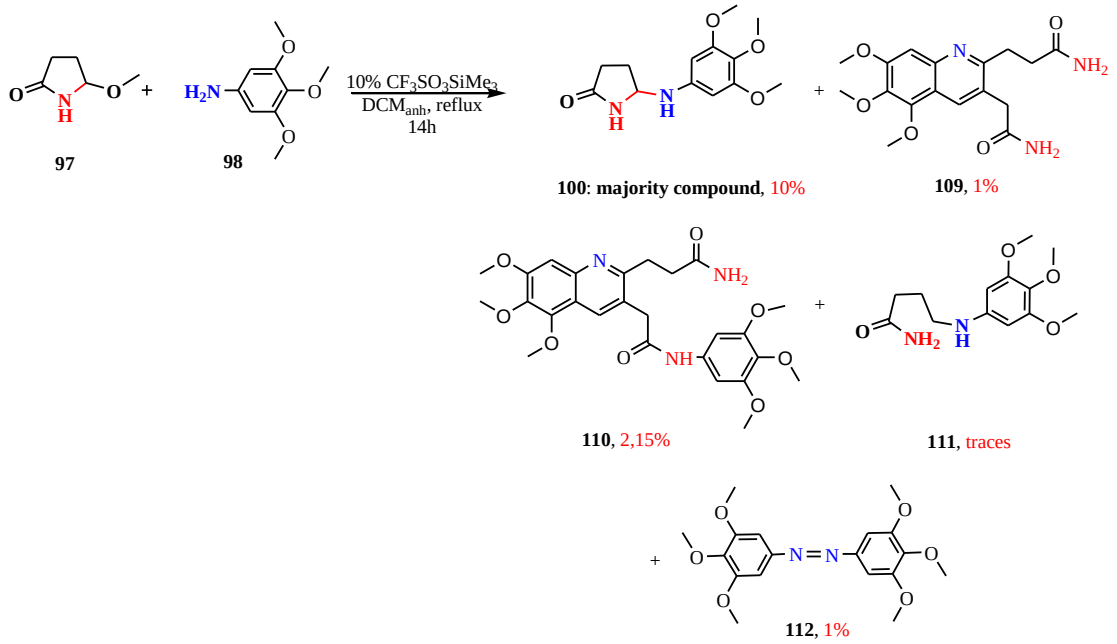


Compound	Amine type	R	Yield
104a	nonsilylated	*o*-OMe	28%
	silylated	*o*-OMe	50%
104b	nonsilylated	*m*-OMe	40%
	silylated	*m*-OMe	45%
104c	nonsilylated	*p*-OMe	40%
	silylated	*p*-OMe	52%

Scheme 35. The synthesis of 1-methyl-5-(methoxy-phenylamino)pyrrolidin-2-one

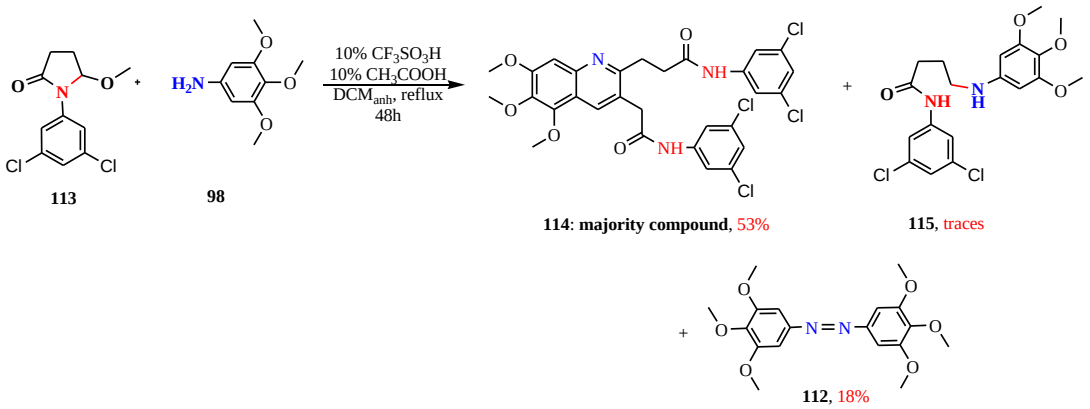
II.7.3. The synthesis of the quinoline derivatives

Desiring to elucidate the course of reactions 1-phenyl-pyrrolidone derivatives with amines, under acid catalysis, we have continued the study by changing the concentration of catalyst added to the reaction. Thus, we were surprised to see that reaction with nonsilylated amines afforded us the quinoline derivatives (Scheme 38).



Scheme 38. The synthesis of quinoline using 5-methoxy-pyrrolidin-2-one

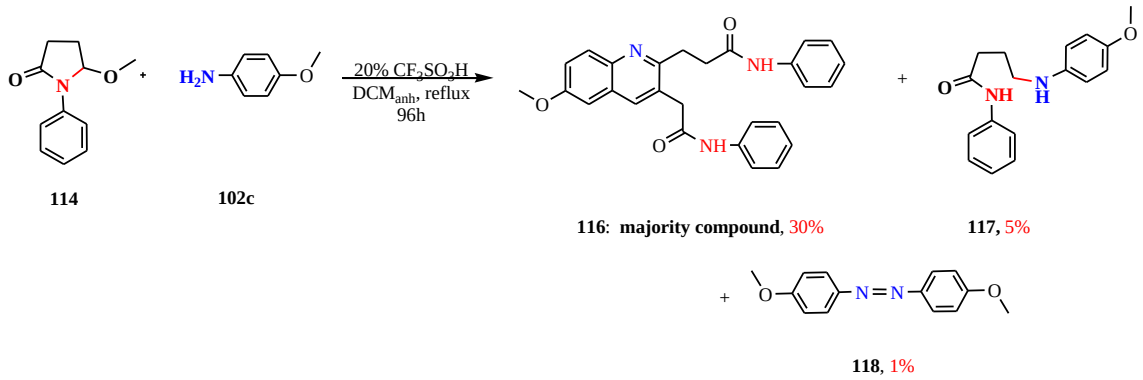
Another reaction that we have obtained the quinoline derivatives has been one of the pyrrolidone derivative substituted on the nitrogen atom with a 3,5-dichlorophenyl residue, and 3,4,5-trimethoxyaniline **98** (Scheme 39).



113 **98** **114**: **majority compound**, 53% **115**, traces **112**, 18%

Scheme 39. Acid-catalyzed synthesis of quinoline derivative using 1-(2,4-dichlorophenyl)-5-methoxy-pyrrolidin-2-one

We carried out the reaction of the derivative of 1-phenyl-pyrrolidone and p-methoxyaniline. However, in this case we have identified the same reaction products (Scheme 40).



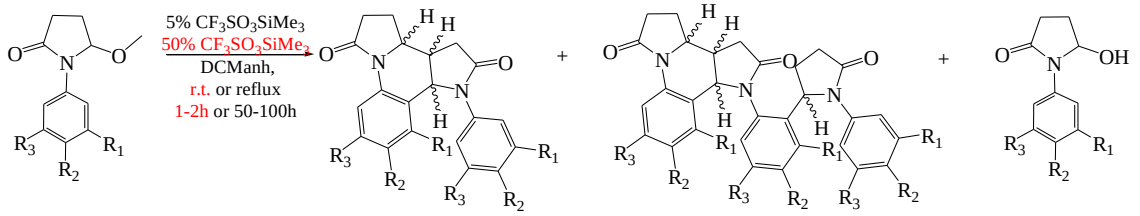
114 **102c** **116**: **majority compound**, 30% **117**, 5% **118**, 1%

Scheme 40. Acid-catalyzed synthesis of quinoline derivative using 1-phenyl-5-methoxy-pyrrolidin-2-one

II.7.3. Study the reactivity of the core pterolactamic (pyrrolidin-2-one)

In order to confirm the mechanism of obtaining the quinoline derivatives, we plan to study the reactivity of the pterolactamic core substituted on nitrogen with aryl.

Further, these derivatives were solubilized in dichloromethane anhydrous added 5% $CF_3SO_3SiMe_3$ or 50% $CF_3SO_3SiMe_3$ (Scheme 43).



119a: R_1, R_3 = Cl, R_2 = H
119b: R_1, R_2 = OMe, R_3 = H
119c: R_1, R_2, R_3 = OMe

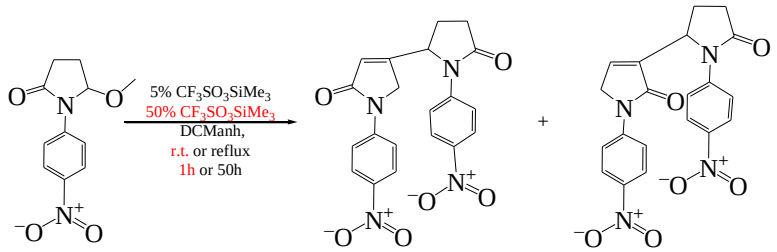
120a: R_1, R_3 = Cl, R_2 = H, 30%; 5%
120b: R_1, R_2 = OMe, R_3 = H, 42%; 59%
120c: R_1, R_2, R_3 = OMe, 30%; 60%

120a: R_1, R_3 = Cl, R_2 = H, 90%
121c: R_1, R_2, R_3 = OMe, 24%; traces

122b: R_1, R_2 = OMe, R_3 = H, 40%; traces
122c: R_1, R_2, R_3 = OMe, 40%; 10%

Scheme 43. The reaction of the pterolactam derivatives with electrondonor groups **119a-c** under acid catalysis

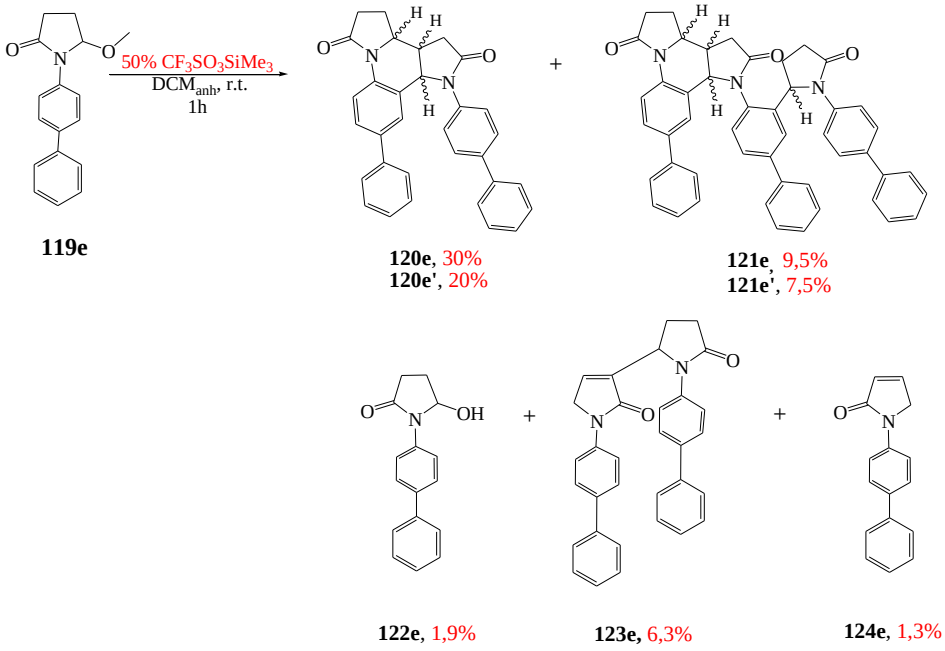
In the case of compound **119d** with electronacceptor group (NO_2) in its structure, the use of 5% $CF_3SO_3SiMe_3$ required a long reaction time (Scheme 44).



119d **123d,** 10%; 50% **123d',** 5%

Scheme 44. The reaction of the pterolactam derivative with electronacceptor group **119d** under acid catalysis

The reaction in which it was used the 5-methoxy-1-biphenyl-pyrrolidin-2-one **119e** led to the isolation of seven compounds (Scheme 45).



119e

120e, 30%
120e', 20%

121e, 9,5%
121e', 7,5%

122e, 1,9% **123e,** 6,3% **124e**, 1,3%

Scheme 45. The reaction of the pterolactam derivative with π-π conjugation **119e** under acid catalysis

II.7.4. Biological evaluation

The biological activity of novel pyrrolidone derivatives was assessed *in vitro* against farnesyltransferase.

Only compound **106** substituted at the amino nitrogen atom with 2,4-dichlorobenzyl presented a satisfactory inhibitory activity, allowing calculation of the mean inhibitory concentration of 78.4 μM.

In conclusion, in this chapter we investigated the synthesis, characterization and biological evaluation of new compounds *N,N*-aminal type with pyrrolidone skeleton. Thus, we synthesized 39 compounds not described in the literature.

CONCLUSION

PhD thesis **Farnesyltransferase inhibitors with heterocyclic structure. Synthesis and biological evaluation** of new compounds present seven series with potential anticancer activity. Within these series of compounds were synthesized 188 compounds and **152 not described in the literature**.

In conclusion, the **100 final compounds** were biological evaluated on the ability to inhibit the of human farnesyltransferase and **40** compounds possess inhibitory average concentration in the range of 1-90 μM. Another 29 compounds are currently being tested.

Scientific papers published in ISI journals:

1. *Peptide chemistry applied to a new family of phenothiazine-containing inhibitors of human farnesyltransferase* **Dumitriu**, **Gina-Mirabela**; Ghinet, Alina; Bîcu, Elena; Rigo, Benoît; Dubois, Joëlle; Farce, Amaury; Belei, Dalila *Bioorganic & Medicinal Chemistry Letters*, **2014**, *24*, 3180-3185, doi: 10.1016/j.bmcl.2014.04.102.
2. *Investigation of new phenothiazine and carbazole derivatives as potential inhibitors of human farnesyltransferase* **Dumitriu**, **Gina-Mirabela**; Ghinet, Alina; Belei, Dalila; Rigo, Benoît; Gautret, Philippe; Dubois, Joëlle; Bîcu, Elena *Letter in Drug Design & Discovery*, **2015**, *12*, 85-92, doi :10.2174/1570180811666140909010435.
3. *Phenothiazine-based CaaX competitive inhibitors of human farnesyltransferase bearing a cysteine, methionine, serine or valine moiety as a new family of antitumoral compounds* **Dumitriu**, **Gina-Mirabela**; Bîcu, Elena; Belei, Dalila; Rigo, Benoît; Dubois, Joëlle; Farce, Amaury; Ghinet, Alina *Bioorganic & Medicinal Chemistry Letters*, **2015**, 25, 4447-4452, doi: 10.1016/j.bmcl.2015.09.008.
4. *Studies on pyrrolidinones. A Practical and Efficient Method for the Synthesis of 5-arylaminopyrrolidinones* **Dumitriu**, **Gina-Mirabela**; Bîcu, Elena; Belei, Dalila; Rigo, Benoît; Daïch,Adam; Ghinet, Alina *Manuscript under publication.*

Scientific papers presented at national and international conferences:

1. *Synthesis and biological evaluation of new phenothiazine and carbazole derivatives as potential inhibitors of human farnesyltransferase* **Gina-Mirabela Dumitriu**, Dalila Belei, Philippe Gautret, Benoît Rigo, Elena Bîcu, Alina Ghineț, *2ème Colloque Franco-Roumain de Chimie Médicinale*, 03-05 Octobre **2012**, Iași (poster).
2. *New phenothiazine and carbazole derivatives as inhibitors of human farnesyltransferase. Design, synthesis and biological evaluation* **Gina-Mirabela Dumitriu**, Dalila Belei, Philippe Gautret, Benoît Rigo, Elena Bîcu, Alina Ghineț, *Faculty of Chemistry Conference*, 25-26 October **2012**, Iași (poster).
3. *New propargyl derivatives containing phenothiazine moiety. Synthesis and biological evaluation* **Gina-Mirabela Dumitriu**, Dalila Belei, Elena Bîcu, Joëlle Dubois, Alina Ghineț, *27èmes Journées franco-belges de Pharmacochimie et 21èmes Conférences européennes du GP2A,* 5-7 june **2013**, Lille, France (poster).
4. *New phenotiazine derivatives N-substituted. Synthesis and biological evaluation* **Gina-Mirabela Dumitriu**, Alexandra Moraru, Alina Condrea, Dalila Belei, Alina Ghineț, Joëlle Dubois, Elena Bîcu, *Scientific Session of undergraduate, postgraduate and doctoral students "Chemistry - open border to knowledge", Fourth Edition,* 28 June **2013**, Iași (poster).
5. *Novel heterocyclic amino acids recognized by FTase* **Gina-Mirabela Dumitriu**, Dalila Belei, Elena Bîcu, Joëlle Dubois, Alina Ghineț *Scientifical communications session organized within the Days of the University, Faculty of Chemistry*, October 31-November 2 **2013**, Iași (oral communication).
6. *Nouveaux dérivés triazoliques avec un squelette phénotiazinique. Synthèse et évaluation biologique* **Gina-Mirabela Dumitriu**, Alina Ghineț, Dalila Belei, Joëlle Dubois, Elena Bîcu, *Journée jeunes chercheurs et PO interne HEI*, 17 April **2014,** Lille, France (poster).

7. *Sylilated assisted synthesis of aminals with potential microtubule-interacting properties* **Gina-Mirabela Dumitriu**, Elena Bîcu, Dalila Belei, Benoît Rigo, Philippe Gautret, Alina Ghinet, *3ème Colloque Franco-Roumain de Chimie Médicinale*, 30-31 October **2014**, Iași (oral communication).

8. *Design, synthesis, and biological evaluation of novel pyrrolidinone-bridged analogues of Combretastatin–A4* **Gina-Mirabela Dumitriu**, Elena Bîcu, Dalila Belei, Benoît Rigo, Philippe Gautret, Alina Ghinet, *3ème Colloque Franco-Roumain de Chimie Médicinale*, 30-31 October **2014**, Iași (poster).

9. *Identification of triazole-chalcone hybrids as potential protein farnesyltransferase inhibitors* **Gina-Mirabela Dumitriu**, Alina Ghinet, Dalila Belei, Joëlle Dubois, Elena Bîcu, *22èmes Journées Jeunes Chercheurs*, 4-6 February **2015**, Biocitech, Romainville, Paris, France (poster).

10. *Design and Biological Evaluation of Unprecedented FTase Inhibitors Based on Triazole-chalcone Hybrids* **Gina-Mirabela Dumitriu**, Alina Ghinet, Dalila Belei, Joëlle Dubois, Elena Bîcu, *Journées Jeunes Chercheurs*, 26 Martie **2015**, HEI, Catholic University of Lille, Lille, France (poster).

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148. **Dumitriu, G. M.**; Ghinet, A.; Bîcu, E.; Rigo, B.; Dubois, J.; Farce, A.; Belei, D. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3180–3185.