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CARMEN DUMEA

Synthesis and biological evaluation of novel pentaatomic nitrogen-containing heterocyclic derivatives

DOCTORAL THESIS SUMMARY

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Carmen Dumea

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Doctoral thesis entitled " Synthesis and biological investigation of novel pentaatomic nitrogen-containing heterocyclic derivatives " contains 272 pages, appendices (containing scientific articles published) and are presented in the following structure:

Summary

Part I. Data from the literature

Chapter I. Indolizine - obtaining methods
Chapter II. Contributions of Organic Chemistry team of Iasi in [3 + 2] dipolar cycloaddition reactions of *N*-ylides
Chapter III.1,2,3-Triazoles
Chapter IV. Biologically active pentaatomic nitrogen-containing heterocyclic compounds

Partea a II-a. Cercetări personale

Chapter V. Synthesis of 1,4-disubstituted 1,2,3-triazole derivatives
Chapter VI. Synthesis of indolizines
Chapter VII. Synthesis of triazole-indolizine derivatives
Chapter VIII. Biological activity evaluation
Chapter IX. Optical properties of 1,2,3-triazole derivatives
Chapter X. Experimental part

This doctoral thesis presents 275 references. The presented summary contain a brief presentation of personal research, conclusions and an extract from the bibliography. Was kept the numbering of the chapters, tables, charts and figures presented in the original paper.

Introduction

The nitrogen-containing pentaatomic heterocycles have an important role in the medical chemistry, being found as a building block in the chemical structure of many organic compunds with biological properties. According to the literature, the derivatives of these heterocycles can present anti-cancer, antimicrobial, anti-inflammatory, analgesic activity etc.

Cancer is a threatning disease of the twenty-one century, being one of the main causes of mortality for each region in the world.[1] Every year, fourteen million people are diagnosed with this illness and by 2030 it is estimated that there will yearly be more than 20 million of cancer patients and more than 13 million people will die because of this horrible disease.[2] The drugs used in chemotherapy represent a bright alternative in the fight against cancer but is hasn' t been found a compound that can completely cure this disease. Hoping that the fight against cancer will be won, many researchers in organic chemistry turned their attention to discovery of solutions to cure it.

In recent decades, the chemistry of the 1, 2, 3-triazole derivatives was greatly expanded due to the discovery of many biological activities associated with this heterocyclic skeleton. The 1, 2, 3-triazole derivatives present antimicrobial, antibacterial,[3] antiallergic,[4] anti-HIV,[5] anti-inflammatory and cytostatic activity.[6]

The indolizine derivatives present many biological activities with antihypoglycemic,[7] antitumoral,[8, 9] anti-inflammatory,[10] antibacterial[11] and analgesic[12] activities. The variation of the substituents on the indolizine skeleton have been shown to be useful for the attainment of new therapeutic agents wich present enhanced biological activity and a lower toxicity.[13]

Part II. Personal research

Objectives

The personal researches presented in this doctoral thesis consisted in the substituents' modulation of some nitrogen-containing heterocyclic pentaatomic skeletons (triazole, indolizine, carbazole and indazole compounds), by using pharmacophores building blocks in order to obtain new derivatives with more prominent biological activity. After the synthesis phase, for the final compunds was evaluated the anticancer activity and were realized studies on the relationship between the structure of the newly synthesized compounds and the bioblogical activity.

The main objectives pursued and achieved during the doctoral studies were:

✓Synthesis of derivatives 1,4-disubstituted 1, 2, 3-triazole with the general structures presented in the Figure 1, obtained by the variation of the substituents in positions 1 and 4 of the triazole nucleus with pharmacophores units.

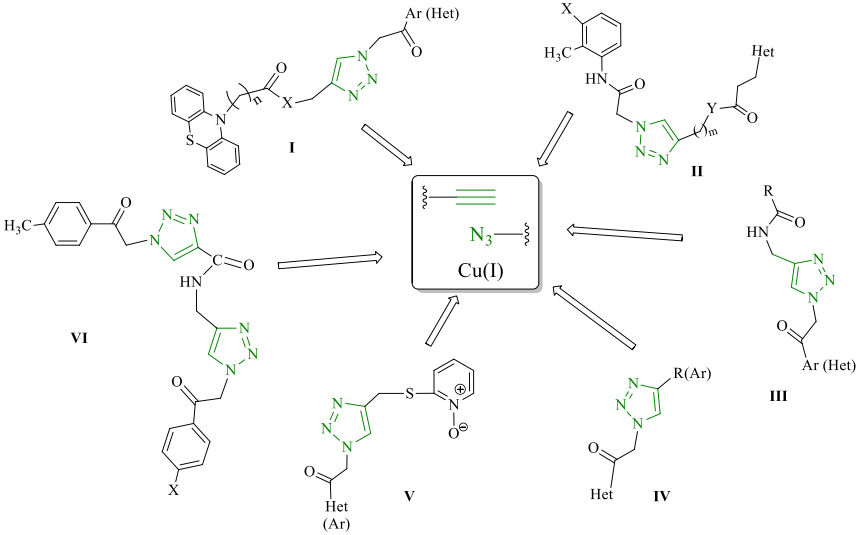


Figure 1. The retrosynthetic scheme to obtain 1, 4-disubstituted 1, 2, 3 triazoles derivatives

✓Synthesis of carboxyl, propargylamine, propargyl ester, butynyl ester substituted indolizine derivatives

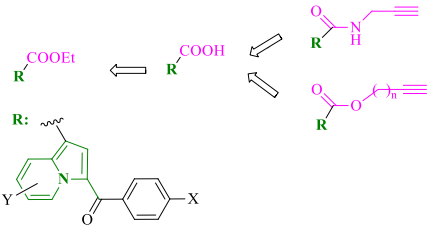


Figure 2. The retrosyntetic scheme to obtain new indolizine derivatives

✓Sinthesis of triazolo-indolizine derivatives with general structure presented in Figure 3.

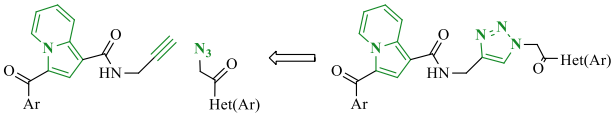


Figure 3. The retrosyntetic scheme to obtain new triazolo-indolizine derivatives

✓-The spectral characterization of the new compounds obtained by spectroscopy IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

✓The biological activity evaluation of the synthesized compounds by the determination of the inhibitory activity on the human farnesyltransferase enzyme or tubulin protein, respectively by the determination of the inhibitory activity on sixty human cancel cell lines found in leukemia, ovarian, kidney, colon, prostate, breast, melanoma cancer and cancer of the central nervous system. The tests on cancer cells were realised by the *National Cancer Institute* of America, for the compunds which were accepted and the tests on farnesyltranspherase and tubulin were realised in collaboration with *The Chemistry Institute of the Natural Substance*s of Paris, France.

✓The achievement of SAR studies (structure-activity relationship).

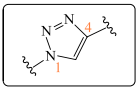
Chapter V.
Synthesis of 1,4-disubstituted 1, 2, 3-triazoles derivatives

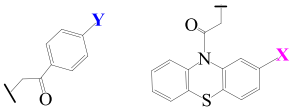
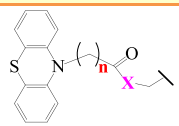
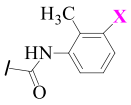
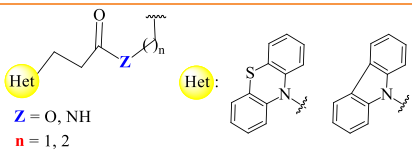
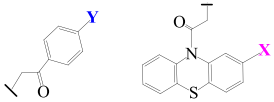
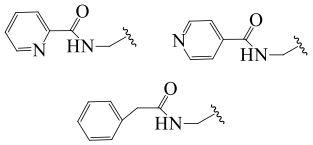
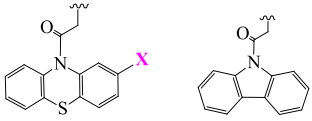
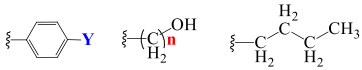
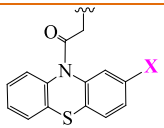
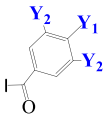
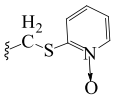
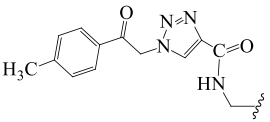
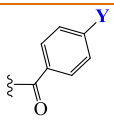
By following different strategies of synthesis, it was obtained six series of 1,4-disubstituted 1,2,3-triazoles compounds unmentioned in literature (Table 1).

One of the realised synthesis strategies consisted in the changing of the carbon chain linked at the phenothiazine moiety, respectively in the substitution of the amide functional group with the ester functional group (n=1 or X=O or NH). There were also used different substituents in the *para* position of the fenyl moiety (R=F, Cl, Br, CH_3, OCH_3, CN), also we synthesized compounds which contain the phenothiazine or 2-chloro-phenotiazine nucleus linked to the fenyl ring.

Another synthesis strategy consisted in changing the substituents in the 4 position of the triazole nucleus by reducing the chain of carbon atoms and by substituting the phenothiazinic nucleus with aryl or pyridine ring. Futhermore, it have been linked some alkyl chains containing 2-(methylensulfide)pyridine-*N*-oxide radical in the 4 position of the 1,2,3-triazole nucleus and thus decreasing the length of the carbon chain in the 4 position of the triazole nucleus. We also obtained *bis*-triazoles derivatives, by introducing another triazole skeleton in 4 position of the triazole moiety.

Table 1. The substituents from 1 and 4 position of the 1,2,3-triazole nucleus for the newly synthesized compounds

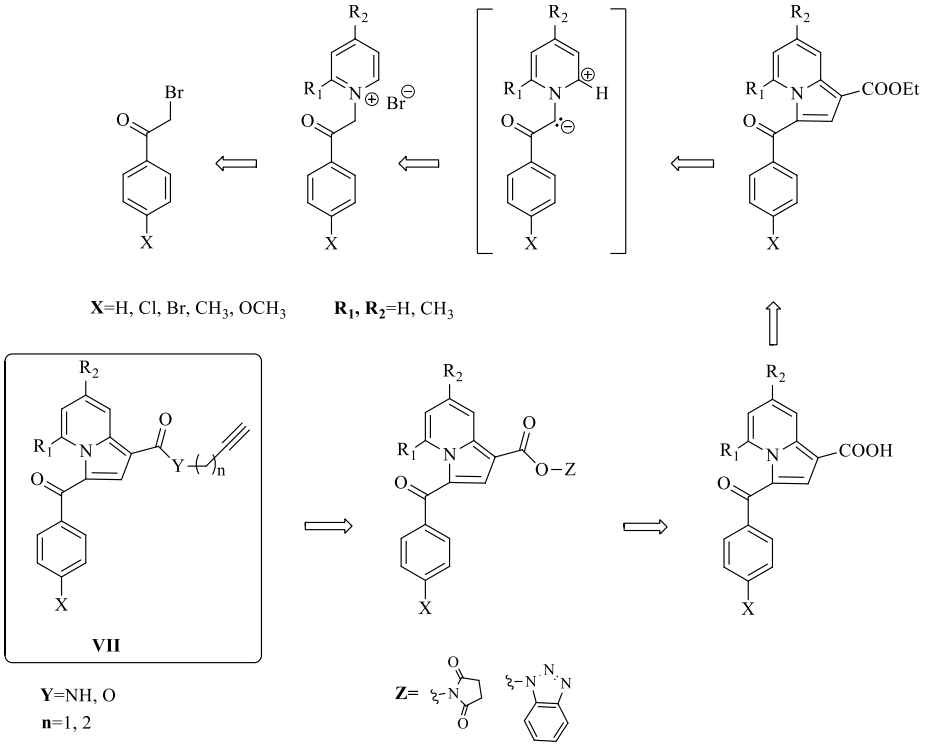


Seria	Substituenți din poziția 1	Substituenți din poziția 4
I	 **Y** = F, Cl, Br, CH_3, OCH_3, CN; **X** = Cl, H	 **n** = 1, 2; **X** = O, NH
II	 **X** = H, Cl	 **Z** = O, NH **n** = 1, 2
III	 **Y** = Cl, Br **X** = H, Cl, CF_3	
IV	 **X** = H, Cl, CF_3	 **Y** = H, CH_3 **n** = 1 sau 2
V	 **X** = H, Cl, CF_3  **a.** Y_1 = H, F, Cl, Br, CH_3, OCH_3; Y_2 = H **b.** Y_1 = OCH_3; Y_2 = OCH_3	
VI		 **Y** = F, Cl, Br, CH_3, CN

Chapter VI.
Synthesis of indolizines

The research objectives presented in this chapter consisted in modulation made in the indolizinic nucleus in order to graft functional groups which can enhance biological activity to the newly obtained compunds. The synthesis strategy has considered the grafting of the carboxyl function in first position of the indolizinic nucleus, respectively of the propargylamide, propargylesteric or butynylester groups.

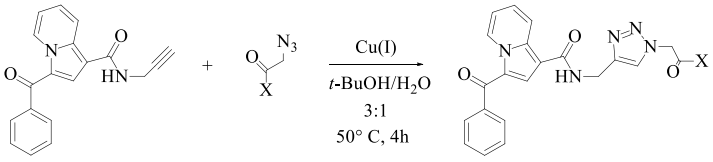
Thus, it was realised the synthesis of the indolizinic derivatives with the general structure VII in Scheme 23, their obtaining being realised in 6 phases: the synthesis of pyridinium salts, the generation of pyridiniumylides, closing of the indolizinic cycle, hydrolysis of the esteric function, obtaining of activated esters, the synthesis of amides and esters with marginal triple bond.



Scheme 23. The retrosynthesis of the indolizine derivatives with general structure VII

Chapter VII.
Synthesis of triazole-indolizine derivatives

The indolizine derivatives substituted in first position with propargylamide function with the structure **47a**, in the presence of various azides, which presents the structure **4a-c, f, g, l**, leads to the triazole-indolizine and triazole-indolizine- phenothiazine hybrids **59a-f**. The synthesis were catalytically conducted in the presence of Cu generated *in situ* by reducing the copper sulphate crystallized by 5 water molecules with sodium ascorbate (Scheme 35).



47a

4f X=*p*ClC_6H_5
4g X=*p*BrC_6H_5
4l X=3,4,5$(OCH_3)_3C_6H_2$
4a X=phenothiazin-10-yl
4b X=2Cl-phenothiazin-10-yl
4c X=2CF_3-phenothiazin-10-yl

59a X=*p*ClC_6H_5 (51%)
59b X=*p*BrC_6H_5 (49%)
59c X=3,4,5$(OCH_3)_3C_6H_2$ (50%)
59d X=phenothiazin-10-yl (80%)
59e X=2Cl-phenothiazin-10-yl (79%)
59f X=2CF_3-phenothiazin-10-yl (81%)

Scheme 35. The synthesis of the triazole-indolizine hybrids

Chapter VIII.
Biological activity evaluation

VIII. 2. Evaluation of the anticancer activity for the 1,4-disubstituted 1,2.3-triazole derivatives

The 1,4-disubstituted 1,2,3-triazole derivatives with the general structure presented in Table 5 have inhibitory activity on the human farnesyltransferase according to the nature of the substituents. Thus, the presence of the various substituents in *para* position of the fenyl ring modifies the biological activity. If the fenyl ring is *p*-chloro or *p*-bromo substituted, then the biological activity will increase. From these results, it was changed the nature of the substituents in *para* position of the fenyl radical with F, CN, OMeor Me, but the biological activity hasn' t been enhanced.

The substitution of the amide group with the esteric function leads to the increase of the inhibitory activity on the human farnesyltransferase.

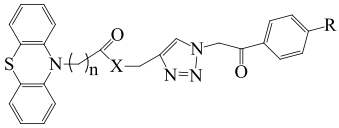
When the length of the carbon chain between the phenothiazinic nitrogen and the amide group was shortened from two to one atom, farnesyltransferase inhibition decreased.

The changing of the fenyl radical with another phenothazine nucleus abolished affinity toward human farnesyltransferase.

The compound with structure **29b** presents selective inhibitory activity on cancer cell lines, inhibiting by 46 % the lung cancer NCI-H522 cell line and by 62% the SNC cancer SNB-

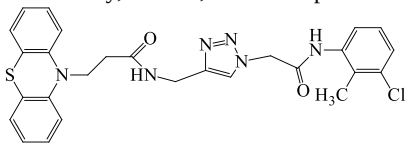
75 cell line. The most enhanced inhibitory activity is presented on the ovarian cancer OVCAR-4 cell line, causing 80% inhibition of the cancer cells.

Table 6. The IC_{50} values for compounds with significant activity



Compounds	n	X	R	IC_{50} (FT) (µM)
25c	2	NH	Cl	7,73 ± 0,81
25d	2	NH	Br	8,31 ± 0,87
25f	2	NH	CN	5,21 ± 1,34
26c	2	O	Cl	1,49 ± 0,31
26d	2	O	Br	1,30 ± 0,28
23d	1	NH	Br	24,31 ±4,97

Table 12. The anticancer activity, in vitro, of the compound **29b**

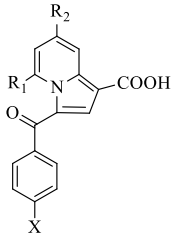


Cell type	Cell line	Inhibition ratio (%) at 10 µM
Ovarian cancer	**OVCAR4**	80
CNS cancer	**SNB-75**	62

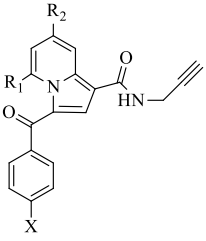
VIII.3. Evaluation of the anticancer activity for the indolizine derivatives

By analizing the relationship between the compounds' structure and the inhibitory activity on farnesyltransferase, we can conclude that the substitution of the fenyl nucleus, in *para* position, with bromine or chlorine, led to an important increase of the biological activity, while the lack of the substituent with electron-withdrawing effect from *para* position has determined a significant increase of the activity. The introduction of the propargylamide group in position one of the indolizine nucleus has determined a slight decrease of the biological activity, compared to the indolizine derivatives which contain in first position the propargylester and butynylester groups. Another investigated aspect was how the biological activity is influenced by the length of the carbon chain between the esteric function and the marginal triple bond. By comparing the results obtained for propargylesters with those of the butynylesters, we can note that these compounds presents similar activities.

Table 14. Inhibitory activities of indolizines **44a-k** and **47a-k** on human farnesyltransferase



44a-k



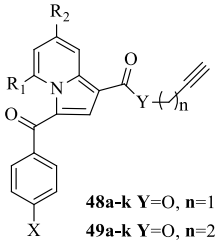
47a-k

a R_1=H, R_2=H, **X**=H
b R_1=H, R_2=H, **X**=Cl
c R_1=H, R_2=H, **X**=Br
d R_1=H, R_2=H, **X**=CH_3
e R_1=H, R_2=H, **X**=OCH_3
f R_1=CH_3, R_2=H, **X**=H
g R_1=CH_3, R_2=H, **X**=Cl
h R_1=CH_3, R_2=H, **X**=Br
i R_1=H, R_2=CH_3, **X**=H
j R_1=H, R_2=CH_3, **X**=Cl
k R_1=H, R_2=CH_3, **X**=Br

Compound	%IFT[a]	IC_{50} (µM ± SD)	Compound	%IFT[a]	IC_{50} (µM ± SD)
44a	100	19,7 ± 0,4	**47a**	100	22,1 ± 7,3
44b	100	20,7 ± 9,1	**47b**	93,9	5,9 ± 1,6
44c	100	19,4 ± 12,8	**47c**	100	4,4 ± 1,2
44d	42,48	nd[b]	**47d**	0	nd
44e	0	nd	**47e**	0	nd
44f	47,8	nd	**47f**	74,2	nd
44g	78,9	32,2 ± 3,6	**47g**	96,7	14,9 ± 2,5
44h	90,6	14,8 ± 1,6	**47h**	90,4	11,4 ± 1,3
44i	100	72,3 ± 33,6	**47i**	100	15,3 ± 9,1
44j	0	nd	**47j**	fluorescent[c]	-
44k	0	nd	**47k**	fluorescent	-

[a] Inhibition of human farnesyltransferase at a 100 µM concentration [b] Undetermined
[c] Not quantifiable; competition with the fluorophore fluorescence

Table 15. Inhibitory activities of indolizines **48a-k** and **49a-k** on human farnesyltransferase



48a-k **Y**=O, **n**=1
49a-k **Y**=O, **n**=2

a R_1=H, R_2=H, **X**=H
b R_1=H, R_2=H, **X**=Cl
c R_1=H, R_2=H, **X**=Br
f R_1=CH_3, R_2=H, **X**=H
g R_1=CH_3, R_2=H, **X**=Cl
h R_1=CH_3, R_2=H, **X**=Br
i R_1=H, R_2=CH_3, **X**=H
j R_1=H, R_2=CH_3, **X**=Cl
k R_1=H, R_2=CH_3, **X**=Br

Compound	%IFT[a]	IC_{50} (µM ± SD)	Compound	%IFT[a]	IC_{50} (µM ± SD)
48a	100	14,4 ± 5,9	**49a**	60,7	nd
48b	53,9	nd[b]	**49b**	0	nd
48c	fluorescent[c]	-	**49c**	0	nd
48f	93,0	20,8 ± 3,3	**49f**	94,1	7,3 ± 0,9
48g	100	2,6 ± 0,4	**49g**	97,3	20,7 ± 3,4
48h	100	1,3 ± 0,2	**49h**	100	2,2 ± 0,4
48i	71,6	nd	**49i**	0	nd
48j	0	nd	**49j**	0	nd
48k	fluorescent	-	**49k**	68,1	nd

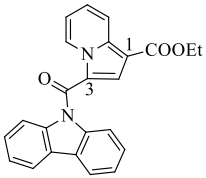
[a] Inhibition of human farnesyltransferase at a 100 µM concentration [b] Undetermined
[c] Not quantifiable; competition with the fluorophore fluorescence

VIII.4. Evaluation of the anticancer activity for the indolizines which contain carbazole and indazole moiety

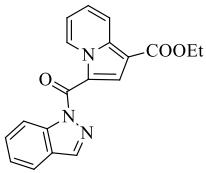
The compounds **57a** and **57b** were evaluated in terms of the anticancer activity. For this purpose, it was determined the inhibitory activity on the human farnesyltransferase, respectively on 60 cancer cell lines (the compounds have been accepted by NCI to be tested).

The obtained results reveals that the indolizine-carbazole derivative **57a** and the indolizine-indazole derivative **57b** are inactive on human farnesyltransferase, but the *in vitro* activity of the carbazole derivative **57a**, on all 60 cancer cell lines, is very good, with values for GI_{50} situated in the nanomolar range. The results are presented in Table 19.

Table 19. The results of *in vitro* anticancer activity for derivatives **57a** and **57b**



57a



57b

Cell type	Cell line	Inhibition ratio (%) at 10 μM		GI_{50} (nm)
		57b	**57a**	**57a**
Lung cancer	**A549/ATCC**	6	77	0,414
	HOP-92	n.d.	65	0,136
	NCI-H522	7	94	0,356
Colon cancer	**COLO 205**	0	-78	0,263
	HCC-2998	0	91	0,394
	SW-620	7	80	0,471
Melanoma	**LOX IMVI**	nd	66	0,644
	M14	8	78	0,333
	MDA-MB-435	10	-48	0,132

[a] Undetermined

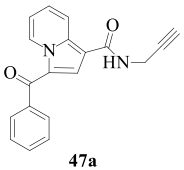
VIII.5. Evaluation of the anticancer activity for the triazole-indolizine derivatives

In Table 20 are presented the results obtained from testing the inhibitory activity on 60 cancer cell lines for the triazolo-indolizine **59a**, **59c-e** derivatives, compared to the propargylamide **47a** derivative.

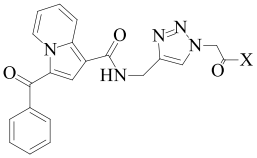
The indolizine substituted with the propargylamide radical in first position (the compound **47a**), doesn't have an signifiant inhibitory activity on the cancer cell lines, the highest inhibition percentage being by 25% on the SR leukemia cell line. The substitution of the alkyl marginal group with the 1, 4-disubstituted 1,2,3-triazole nucleus leads to a selective significant increase of the inhibitory percentage on the cancer cell lines. For instance, the compound **59a** inhibits the MOLT4 leukemia cell line percentage with 50%, in contradiction to

the compound **47a**, which is inactive. Furthermore, the triazole-indolizine-phenothiazine derivative **59d** inhibits SW-620 colon cancer cell line with 51%.

Tabel 20. The *in vitro* anticancer activity for the triazole-indolizine **59a**, **59c-e** derivatives compared to the propargyl derivative **47a**



47a



59a X=*p*ClC_6H_5
59c X=3,4,5$(OCH_3)_3C_6H_2$
59d X=phenothiazin-10-yl
59e X=2-chlorophenothiazin-10-yl

Cell type	Cell line	Inhibition ratio (%) at 10 μM				
		47a	**59a**	**59c**	**59d**	**59e**
Leukemia	**CCRF-CEM**	0	30	27	5	12
	MOLT-4	2	**50**	32	39	16
	SR	25	**53**	**50**	32	21
Lung cancer	**NCI-H522**	0	25	3	36	24
Colon cancer	**HCT-116**	7	32	12	17	24
	SW-620	4	2	0	**51**	30
Melanoma	**M14**	0	7	0	38	33
	MDA-MB-435	0	20	0	39	14
	SK-MEL-2	0	4	0	nd[a]	**49**
	SK-MEL-28	2	0	2	35	14
	SK-MEL-5	3	20	23	nd	**48**

[a] undetermined

Conclusions

✓In this PhD thesis, it was made the synthesis and the evaluation of biological activity for the new triazoles, indolizines and triazolo-indolizine derivatives. The biological activity was evaluated by the determination of the new derivatives' ability to inhibit the farnesyltranferase enzyme, the protein tubulin polimerization, respectively the antiproliferative capacity on 60 cancer cell lines found in different types of cancer.

✓The conducted researches were completed by the synthesis and the characterization of 163 new compounds, unmentioned in the literature. Their spectral characteristics are not found in scientific articles. Of these, it were evaluated for anticancer activity a number of **79** 1,4-disubstituted 1,2,3-triazoles derivatives, 40 indolizines and 6 triazole-indolizine derivatives.

✓The triazoles derivatives were cathalitically obtained, by dipolar cycloadditionreactions between azides dipoles and monosubstituted acetylene dipolarophiles, in the presence of Cu(I) generated in the reaction medium.

✓The indolizine derivatives were also obtained by dipolar [3+2] cycloaddition reactions, the synthesis being realised between pyridinium-*N*-ylides and the ethyl propiolate. The carboxylate group from indolizine first position was subsequently turned in

propargylamide, propargyl ester and butynylester groups. The optimization of the reaction conditions has permitted the getting of indolizines in a short time and in good yields.

✓The triazole-indolizine derivatives were obtained by [3+2] dipolar cycloaddition reactions between 3-benzoyl-*N*-propargyl-indolizine-1-carboxamide dipolarophile with marginale triple bond and azido dipoles.

✓All the synthesized compounds were characterised by IR, ^{1}H NMR, ^{13}C NMR spectroscopy.

✓By analysing the relationship between the structure of the newly synthesized compounds and the inhibitory activity on farnesyltransferase, we can conclude that the fenyl nucleus substitution, in *para* position, with bromine or chlorine led to an important increase of the inhibitory activity, while the lack of the electron-withdrawing substituent effect in *para* position has determined a significant increase of it. The introduction of the amide group, as a building block, has determined a slight decrease of the biological activity, compared to the derivatives which contains propargylester or butynylester group in the same position. The length of the carbon chain between ester group and the marginal triple bond determines similar activities.

✓The indolizine derivatives which contain in first position the carboxyl, propargylamide, propargylester or butynylester groups present good inhibitory activity on the farnesyltransferase, but it also presents moderate inhibitory activity on the tubulin polimerization.

✓In terms of the inhibitory activity on the cancer cells, the triazole, indolizine and triazole-indolizine derivatives presents selective inhibitory activity at a 10 μM concentration. Good results were recorded for the triazole derivative **29b**, which inhibits by 80% ovarian cancer OVCAR4 cell line and for the indolizine **48a** which inhibits by 94% lung cancer HOP92 cell line. The tested triazolo-indolizine derivatives present superior inhibitory activity on the cancer cells, compared to the propargylamide intermediate **47a**.

✓The most active compound is the carbazole-indolizine derivative **57a**. It has values of GI_{50} in the nanomolar range on most of the human cancer cell lines.

✓For the 1,2,3-triazole compounds substituted in 4 position with radical 2-(methylensulfide)-pyridin-*N*-oxide were evaluated the optical properties and the results show that these compounds present aggregation-induced emission due to the limited intramolecular rotations.

The results of research carried out for the development of doctoral thesis have been the subject of two scientific papers published and one paper in press in ISI journals respectively of 10 participation in scientific conferences:

- Belei, D., Dumea, C., Samson, A., Farce, A., Dubois, J., Bicu, E., Ghinet, A., „New Farnesyltransferase Inhibitors in the Phenothiazine Series", *Bioorg. Med. Chem. Lett.*, **2012**, 22, 4517-4522.
- Dumea, C., Belei, D., Ghinet, A., Dubois, J., Bicu, E., „Novel indolizine derivatives with unprecedented inhibitory activity on human farnesyltransferase", *Bioorg. Med. Chem. Lett.*, **2014**, 24, 5777-5781.

Belei, D., Dumea, C., Bicu, E., Marin, L., „Phenothiazine and pyridine-*N*-oxide based AIE-active triazoles: synthesis, morphology and photophysical properties", *RSC Advances*, accepted article.

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