BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY
GEORGE OLAH DOKTORAL SCHOOL

Synthesis and biological evaluation of structurally modified new phenothiazine derivatives

PhD Thesis

Author: Daniella Takács

Supervisor: Zsuzsanna Riedl, DSc.
Consultant: György Hajós, DSc.

Hungarian Academy of Sciences
Research Centre for Natural Sciences
Institute of Organic Chemistry

2012

1. Introduction

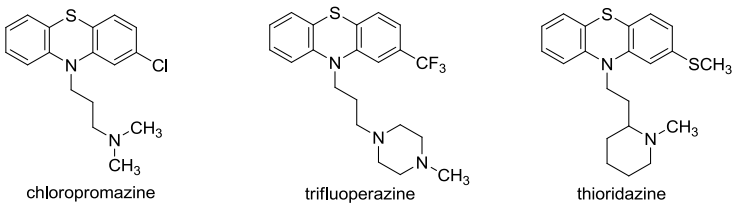
Today worldwide, cancer and malignant tumours play a leader role on the list of terminal diseases. For their control, radiotheraphy, surgical intervention and chemotherapeutical treatments are applied. The appearence of emerging resistance to chemotherapeutical drugs essentially influences the success of these treatments. Moreover this resistance can reduce the chance for healing and survival of patients.

The transport proteins located in the cell membrane are regarded responsible for the accumulation of drugs hindered by multridrug resistance (MDR). Special attention is paid to one of the biggest protein family: the ABC transport proteins, which can be responsible for the mentioned resistance. This protein like an efflux pump, can remove the drug, before it could exert its effect[1,2] using the stored energy obtained from the ATP hydrolysis.

MDR endangers the effectiveness of antibiotics as well, because the efflux pumps of bacteria can block the transport of antibiotics into the citoplasm.[3]

Not only the structure-based functional discovery of proteins, but also the inhibitors of targeted transport proteins are studied very intensively by home institutes and abroad as well.

Several publications about this research field reveals, that phenothiazine ring containing derivatives have widespread biological application and the number of new drugs is continually increasing.[4] Recent biological tests showed that some phenothiazine derivatives used as neuroleptics exhibit also MDR inhibitory property. Some, commercially available phenothiazine derivatives (*Scheme 1.*) behaved as promising inhibitors of efflux pump.

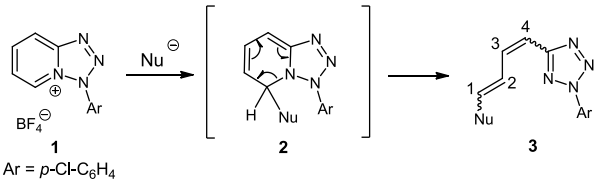


Scheme 1. *Some phenothiazine derivatives as well-known MDR inhibitors*

2. Literature background

In our research group, synthesis of bridge-head nitrogen atom containing fused azolium salts and their reactivity are important areas for a long time. Messmer *et al.* recognized, that tetrazolo[1,5-*a*]pyridinium salts (**1**) can easily react with different nucleophiles. By this transformation, different geometries of novel tetrazolildienes (**3**) can be synthesized. The reaction proceeds by ring opening reaction of the intermediate addition product (**2**) (*Scheme 2.*).[5]

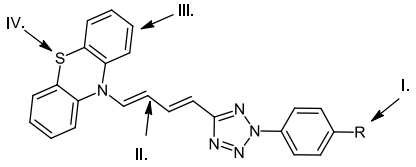
[1] Gatti, L.; Cossa, G.; Beretta, G. L.; Zaffaroni, N.; Perego, P. *Curr. Med. Chem.*, **2011**, *18*, 4237.
[2] Shukla, S.; Ohnuma, S.; Ambudkar, S. V. *Curr. Drug Targets*, **2011**, *12*, 621.
[3] Saier Jr, M. H.; Paulsen, I. T.; Sliwinski, M. K.; Pao, S. S.; Skurray, R. A.; Nikaido, H. *FASEB J.*, **1998**, *12*, 265.
[4] Pluta, K.; Morak-Mlodawska, B.; Jelen, M. *Eur. J. Med. Chem.*, **2011**, *46*, 3179.
[5] Messmer, A.; Gelléri, A. *Tetrahedron Lett.*, **1973**, *44*, 4295.



Scheme 2. *The ring opening reaction of tetrazolo[1,5-a]piridinium salts*

If phenothiazine is the nucleophile partner in the ring opening reaction of tetrazolopyridinum salt (**1**), *N*-dienylphenothiazines can be obtained in good yield.

These synthesized *N*-dienylphenothiazines show structural similarity to the commercially available, well-known MDR inhibitors. Differences can only be found between the alkyl chains attached to the nitrogen atom. It has been suggested, that new phenothiazine derivatives as potential MDR inhibitors could be obtained by substitution and other modifications in certain positions of *N*-dienylphenothiazines (*Scheme 3.*).

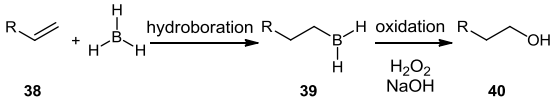


Scheme 3. *Possibilities for modification of N-dienylphenothiazines*

Having joined the team (Hungarian Academy of Sciences, Research Centre for Natural Sciences) structural modifications of *N*-dienylphenothiazines marked with arrows (I-IV., *Scheme 3.*) have been decided as primary aims.

Pertinent literature reveals that catalytic hydrogenation using heterogeneous Pd catalyst is a general methodology for saturation of the double bonds. An interesting method was elaborated for hydrogenation of the unsaturated compound in the presence of catalyst poison[6] (Ph_2S) and Pd/C catalyst to influence the formation of the saturated derivative in a favorable manner.

Alkenes (**38**) can be converted into alcohols (**40**) through the intermediate organoborane compound (**39**) in hydroboration-oxidation with boron-containing reducing agents (*Scheme 4).*[7]



Scheme 4. *Hydroboration-oxidation for synthesis of alcohol starting from alkene*

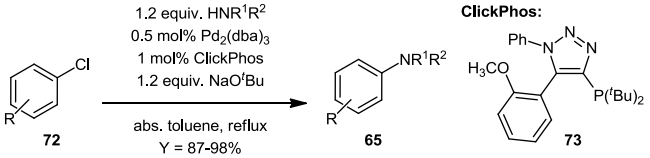
The reaction proceeds in an *anti*-Markovnikov manner by the net addition of water across the double bond. The addition of borane as an electrophile is stereoselective, giving *syn* addition product (BH_2 and H enter on the same face of originally π-bond of the alkene). The oxidation step occurs *via* retention of the stereochemistry. Brown and Zweifel studied this reaction with butadiene derivatives.[8,9] They found that, independently from the applied hydroborating agent, unsaturated monohydroxy and/or diol derivatives are formed as products. They have never observed formation of saturated monohydroxy compound.

If the hydroboration-oxidation leads to a secondary alcohol, the reaction

[6] Mori, A.; Mizusaki, T.; Miyakawa, Y.; Ohashi, E.; Haga, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron*, **2006**, *62*, 11925.
[7] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, **2001**, 1279.
[8] Zweifel , G.; Nagase, K.; Brown, H. C. *J. Am. Chem. Soc.*, **1962**, *84*, 183.
[9] Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.*, **1978**, *43*, 1058.

results in formation of a racemic product having an asymmetric center. Resolution is the process for separating of enantiomers from racemic mixture. When a racemic alcohol is converted into monoesters, then treated with chiral base as resolving agent, one of the two enantiomer is given as the precipitated diastereomer salt, and the amount of the other antipode remains in the mother liquid. The enantiomeric purity can be enhanced with application of the method using half equivalent of the appropriate resolving agent.[10]

Only a few examples for synthesis of phenothiazine derivatives substituted in position 2 and 3 can be found in the literature, multi-step reactions are elaborated for the preparation of 2-aminophenothiazines. In order to functionalize the phenothiazine ring, Buchwald-Hartwig cross-coupling reaction can be applied.[11] In this reaction a carbon-nitrogen bond is created with coupling of aryl halides/pseudohalides (**72**) and amines, so that aniline derivatives (**65**) are synthesized, formally similar to a nucleophilic aromatic substitution (*Scheme 5.*). The catalytic system involves six factors: Ar-X substrate, nucleophile partner, Pd-source (its oxidation state is 0 or +2), ligand (mono- or bidentante) (**73**), base (inorganic or organic), solvent and temperature, which can be altered in order to optimize the reaction conditions.



Scheme 5. *Synthesis of aniline derivatives from the Buchwald-Hartwig cross-coupling reaction of aryl chlorides and amines*

3. Experimental methods

Argon flow was applied in case of hydroboration-oxidation and Buchwald-Hartwig cross-coupling reaction to ensure an inert atmosphere and these reactions were carried out in dry solvent.

The reactions were monitored by thin layer chromatography (TLC). Column- or flash chromatographic methods, recrystallization or trituration were applied for purification of the crude products. Purity of products was controlled by TLC, elemental analysis and determination of melting points, and optical rotation values. Enantiomeric excess of the optically active compounds was determined by high performance liquid chromatography using columns filled with chiral stationary phase. The new compounds were identified by determination of melting points, spectroscopic methods (IR, MS, ^{1}H-, ^{13}C-, ^{19}F- and ^{15}N-NMR) and single crystal diffractometry.

Biological evaluations have been carried out according to previously published protocols.

4. New scientific results

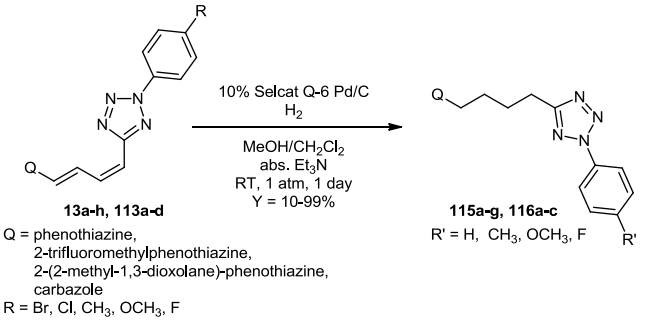
Variously substituted 3-aryl-tetrazolo[1,5-*a*]pyridinium tetrafluoroborate salts when react with *N*-nucleophiles, easily undergo ring opening.[12,13] Such conversions can

[10] Pope, W. J.; Peachy, S. J. *J. Chem. Soc.*, **1899**, *75*, 1066.
[11] Schlummer, B.; Scholz, U. *Adv. Synth. Catal.*, **2004**, *346*, 1599.
[12] Messmer, A.; Gelléri, A. *Angew. Chem., Int. Ed.*, **1965**, *77*, 171.
[13] Messmer, A.; Hajós, Gy.; Gelléri, A. *ESOC III (Canterbury) Abst. of papers*, **1983**, PB 55.

conveniently be carried out by sodium salts of amines (generated by sodium hydride) as the nucleophile agent. Tricyclic compounds: carbazole and 2-substituted phenothiazines - were used as nucleophiles. Tetrazolopyridinium salts variously substituted in position 4 of the phenyl ring can be reacted with nucleophiles under mild reaction conditions (room temperature, atmospheric pressure) according to the earlier known pathway to yield new dienyl derivatives.

Literature data on biological activity of phenothiazine derivatives reveal that the efficient inhibition of MDR by phenothiazines is attributable to the alkyl chain (3 or 4 atoms) attached to the ring-nitrogen atom.[4,14] In knowledge of quantitative structure-activity relationship, reduction of double bond of the new *N*-butadienes (**13a-h**, **113a-d**) seemed to be a new and straightforward pathway to formation of *N*-alkylphenothiazines.

By modification of some literature procedures - basicly patents – heterogeneous Pd/C catalyst was first used for the planned reduction.[15] As the catalyst, 10% Selcat Q-6 type Pd/C was applied. The reaction was carried out in a mixture of dichloromethane and methanol as the solvent at room temperature and under atmospheric pressure to afford new *N*-tetrazolilbutyl-phenothiazines and -carbazoles (**115a-g**, **116a-c**) (*Scheme 6.*). We observed that the starting compounds did not decompose in the presence of triethylamine and, on other hand, the reaction proceeded with 100% conversion. A further advantage is that the sulfur atom did not behave like catalyst poison in every case. Unfortunately, during the reduction of 4-chloro- and 4-bromophenyl derivatives a dehalogenation also occured, and the acid formed in the reaction was neutralized by triethylamine.



Scheme 6. *Catalytic hydrogenation of N-dienylphenothiazines and -carbazoles*

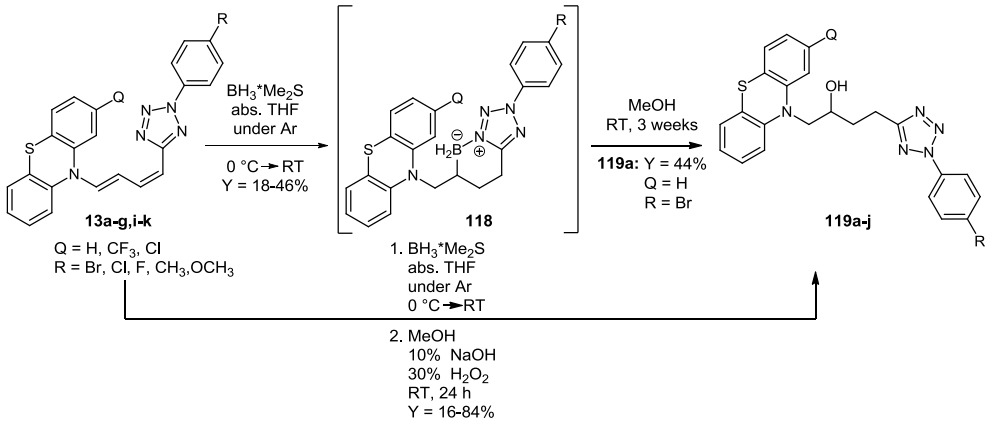
As the halogen atom as an important functional group from synthetic aspects was removed by the dehalogenation reaction, we needed to seek for a new method for reduction. Bélanger *et al.*[16] successfully reduced enamines using the reducing agent BH_3*Me_2S which seemed to be a new possible way for the present reductions. Hydroboration-oxidation[17] of **13a** gave a monohydroxy compound as main product having the hydroxyl group in the position 2 of the alkyl chain (**119a**) (*Scheme 7.*). In order to understand the mechanism, an intermediate, a new zwitterionic azaborinine derivative (**118a**) was isolated and its structure was idetified by X-ray analysis, solution and solide-state ^{1}H-, ^{13}C- and ^{11}B-NMR. In the course of the hydroboration-oxidation of **13k** (Q = Cl, R = OCH_3), besides the main product (**119j**) also two side products appeared: a diol (**121**) and a sulfoxide derivative (**120**), their structures were determined by 2D NMR measurements.

[14] Guan, J.; Kyle, D. E.; Gerena, L.; Zhang, Q.; Milhous, W. K.; Liin, A. J. *J. Med. Chem.*, **2002**, *45*, 2741.

[15] *Patent; GEORGETOWN UNIVERSITY; WO2004/7445; (2004); (A2) English*, **2004**.

[16] Bélanger, G.; Doré, M.; Ménard, F.; Darsigny, V. *J. Org. Chem.*, **2006**, *71*, 7481.

[17] Hunter, R.; Bartels, B.; Michael, J. P. *Tetrahedron Lett.*, **1991**, *32*, 1095.



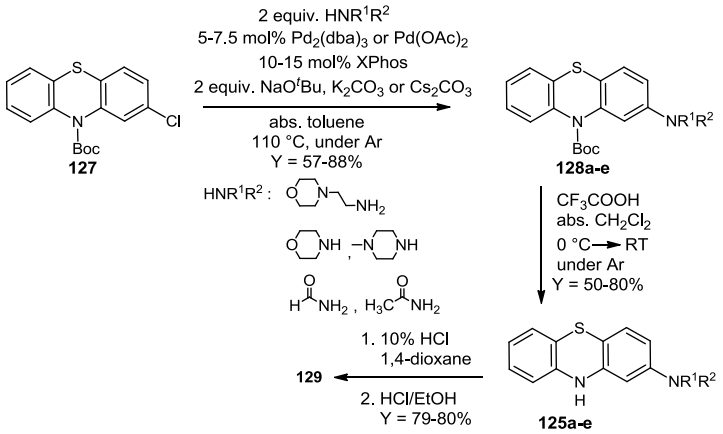
Scheme 7. *Hydroboration-oxidation of N-dienylphenothiazines*

Literature data for 2-aminophenothiazine sparingly exist. Thus, reduction of nitro group can result an amino-moiety in position 2 or 3 of the phenothiazine ring[18,19] and, furthermore, aminophenothiazines can be synthesized by hydrolysis of acid amide derivatives.[20,21]

We were interested in elaboration of a new, easily and economically applicable route to isolate 2-aminophenothiazine derivatives. To this end, a synthetic pathway starting from the commercially available 2-chlorophenothiazine (**12b**) was decided. Under Buchwald-Hartwig cross-coupling reaction conditions we planned the change of chloro atom to an amine moiety. Cross-coupling reactions of unprotected phenothiazine (**12b**) resulted, unfortunately, side products only. In order to avoid the non-desired decomposition of **12b**, protection of the secondary amine in the ring seemed necessary. For this purpose, the ring-nitrogen atom of 2-chlorophenothiazine was protected by benzyl bromide employing earlier described methods[22] and, then, the following Buchwald-Hartwig cross-coupling reaction conditions were optimized to achieve excellent yields. Unfortunately, however, the final step, *i.e.* cleavage of benzyl group could not be accomplished neither by catalytic hydrogenation, nor using $AlCl_3$ reagent. The appropriate 2-aminophenothiazine derivative (**125b**) was treated by cc. HCl/EtOH to yield the product in poor yield. In order to circumvent the problem with deprotection, a new protecting group: *t*-butyloxy-carbonyl protecting group was decided.[23] The subsequent Buchwald-Hartwig-amination [24,25,26] with secondary amines and acid amides took place in acceptable yields and, finally, the critical step, cleavage of protecting goup was carried out with trifluoroacetic acid[27] (*Scheme 8.*). The *N*-Boc protected compounds (**125d-e**) and the deprotected derivative (**128d**) were transformed to 2-aminophenothiazine by acidic hydrolysis to yield the stable hydrochloride salt (**129**).

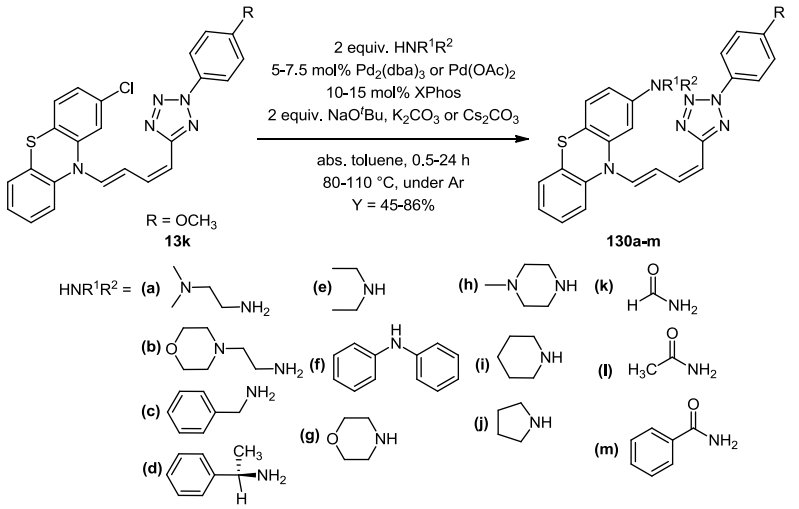
---

[18] Gritsenko, A. N.; Zhuraviev, S. V.; Panova, E. D.; Skorodumov, V. A. *Khim. Geterotsikl. Soedin.*, **1967**, *3*, 668.
[19] Lin, A. J.; Kasina, S. *J. Heterocycl. Chem.*, **1981**, *18*, 759.
[20] Shagako, N. K.; Gritsenko, A. N.; Skorodumov, V. A. ; Zhuravlev, S. V. *Khim. Geterotsikl.*, **1967**, *3*, 281.
[21] Richards, L. E. ; Pieniaszek, H. J.; Schatzmiller, S.; Page, G. O.; Blom, K. F.; Read, J. M.; Davidson, A. F.; Confalone, P. N. *Xenobiotica*, **1997**, *27*, 217.
[22] Self, J. L.; Khanapure, S. P.; Biehl, E. R. *Heterocycles*, **1991**, *32*, 311.
[23] Okamoto, T.; Karutsu, M.; Kozaki, M.; Hirotsu, K.; Ichimira, A.; Matsushita, T.; Okada, K. *Org. Lett.*, **2004**, *6*, 3493.
[24] Guram, A.; Rennels, R.; Buchwald, S. L. *AIEE*, **1995**, *34*, 1348.
[25] Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.*, **2006**, *71*, 3928.
[26] Koteczki, B. J.; Fernando, D. P.; Haight, A. R.; Lukin, K. A. *Org. Lett.*, **2009**, *11*, 947.
[27] Hardouin, C.; Kelso, M. J.; Romero, F. A.; Rayl, T. J.; Leung, D.; Hwang, I.; Cravatt, B. F.; Boger, D. L. *J. Med. Chem.*, **2007**, *50*, 3359.



Scheme 8. *Synthesis of 2-aminophenothiazine and 2-phenothiazine-amide derivatives starting from N-Boc protected 2-chlorophenothiazine*

We applied the aforementioned cross-coupling reaction conditions for 2-aminophenothiazine/2-phenothiazine-amide derivatives too in order to synthesize new *N*-dienylphenothiazines. Primary, secondary amines and acid amides, respectively, were subjected to cross-coupling reaction to result thirteen new phenothiazine derivatives (**130a-m**) (*Scheme 9.*). Buchwald-Hartwig amination was also carried out in case of *N*-dienylphenothiazines containing two halogen atoms (**13i**, Q = Cl, R = Br) to form mono- or dimorpholino derivatives (**131**, **132**).



Scheme 9. *Synthesis of new N-dienlyphenothiazines by Buchwald-Hartwig amination*

During the synthetic work, the new synthesized phenothiazine derivatives were submitted to biological evaluations. The results revealed that further functionalization of the monohydroxy compound (**119j**, Q = Cl, R = OCH_3) by building in amine moiety may increase the MDR-inhibitory property of these derivatives. To the end, three possible routes were elaborated for preparation of molecules **133a-n**:

„Route I": Hydroboration-oxidation of 2-aminophenothiazine/2-phenothiazine-amide moieties containing dienes (**130a-i**,**k-m**);

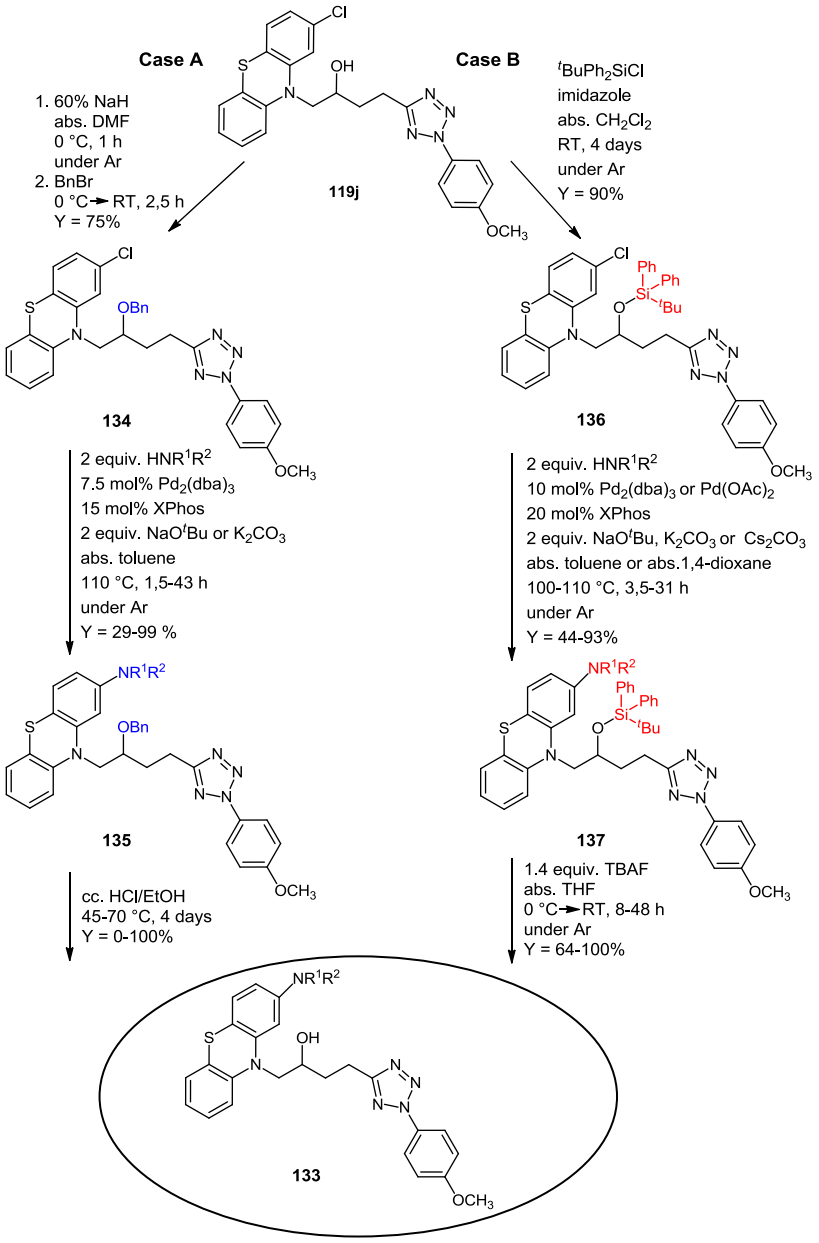
„Route II": Hydroboration-oxidation of **13k** forming the appropriate monohydroxy compound (**119j**) followed by Buchwald-Hartwig amination with amines;

„Route III, case A": O-benzylation[28] of **119j** followed by amination, then cleavage of

[28] Agnelli, F.; Sucheck, S. J.; Marby, K. A.; Rabuka, D.; Yao, S.-L.; Sears, P. S.; Liang, F.-S.; Wong, C.-H. *Angew. Chem., Int. Ed.*, **2004**, *43*, 1562.

benzyl protecting group[29] (*Scheme 10.*),

„Route III, case B": O-silylation[30] of **119j** with *t*-butylchlorodiphenylsilane, then amination of the protected compound (**136**) and, finally, desilylation[31] (*Scheme 10.*).



Scheme 10. *„Route III, cases A and B'': synthesis via employing benzyl and t-butyldiphenylsilyl protecting groups*

Among the planed routes, „*Route III, case B*" – *via* silylation of the monohydroxy compound (**119j)** – resulted formation of derivatives containing amine/amide moieties (**133**) in the highest yield. Application of this route also allowed to extend the synthesis for isolation of also sulfoxide and sulfone derivatives. Monohydroxy compounds containing diethylamine, morpholine and *N*-methylpiperazine groups in position 2 of

[29] Petersen, R. V.; Gisvold, O. *J. Am. Pharm. Assoc.*, **1956**, *45*, 572.
[30] Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.*, **2001**, *123*, 10903.
[31] Hu, Q.-Y.; Rege, P. D.; Corey, E. J. *J. Am. Chem. Soc.*, **2004**, *126*, 5984.

the phenothiazine ring (**133e**,**g**,**h**) were oxidized selectively by *m*-CPBA[32] in order to obtain sulfoxides and sulfones as promising MDR-inhibitors.
The Buchwald-Hartwig cross-coupling reaction of the sulfoxide compound (**120**) and secondary amines gave the coupled products (**138**) in very poor yield. In the case of sulfone derivatives, the synthesis started from the silyl protected hydroxy molecule (**136j**), it was oxidized by *m*-CPBA to the sulfone (**144**) and, then, following the *„route III, case B" N*-(2-hydroxybutyl)-2-aminophenothiazines (**146a-c**) were prepared in good yield.

Hydroboration-oxidation led to racemic mixture of the monohydroxy derivative (**119j)**, because hydroxyl group formed a chirality center, therefore the obtained biological results referred to those of the racemic alcohols. To decide, there is any difference between inhibition properties of antipodes of racemic **133e**,**g**,**h** on biological tests, enantiomers of the racemic derivative **119j** were separated by resolution with half equivalent of resolving agent[33], *S*-(-)-1-phenylethylamine resulting in formation of the two antipodes with high enanatiomeric excess. Accomplishment of the elaborated *„route III, case B*", **(+)-** and **(-)-133e**,**g**,**h** phenothiazine derivatives were prepared starting from the appropriate antipodes. Enantiomeric purity was determined by high performance liquid chromatography using chiral stationary phase containing columns and measurement of optical rotation values.

Pharmacological assays aiming at MDR inhibition in rat hepatocyte cell culture[34,35] and four different bacteria[36,37,38] demostrated that, sulfone derivatives (**146a-c**) showed the highest inhibition-activity. Comparison of effects of enantiomeric pairs revealed that their activities were comparable to that of the racemic derivatives.

5. Theses

1. Novel dienylphenothiazine and -carbazole derivatives have been prepared by ring opening reaction of tetrazolopyridinium salts [3].

2. Catalytic hydrogenation with Pd/C was applied for reduction of dienes. Hydroboration-oxidation applying the reagent BH_3*Me_2S resulted in formation of monohydroxy compound [3].

3. We proved that the monohydroxy compound was formed *via* a new zwitterionic azaborinine containing intermediate [3]. Its structure was identified by X-ray analysis as well as by ^{1}H- ^{13}C- and ^{11}B-NMR measurements carried out in both solution and in solid-state [1].

4. 2-Aminophenothiazine/2-phenothiazine-amide derivatives and novel *N*-

[32] Tosa, M.; Paizs, Cs.; Majdik, C.; Poppe, L.; Kolonits, P.; Silberg, I. A.; Novák, L.; Irimie, F.-D. *Heterocycl. Commun.*, **2001**, *7*, 277.
[33] Kiss, V.; Egri, G.; Bálint, J.; Ling, I.; Barkóczi, J.; Fogassy, E. *Tetrahedron: Asymmetry*, **2006**, *17*, 2220.
[34] Seglen, P. O. *Meth. Cell. Biol.*, **1976**, *13*, 29.
[35] Hirsch-Ernst, K. I.; Ziemann, C.; Rustenbeck, I.; Kahl, G. F. *Toxicology*, **2001**, *167*, 47.
[36] Spengler, G.; Martins, A.; Schelz, Z.; Rodrigues, L.; Aagaard, L.; Martins, M.; Costa, S. S.; Couto, I.; Viveiros, M.; Fanning, S.; Kristiansen, J. E.; Molnár, J.; Amaral, L. *In vivo*, **2009**, *23*, 81.
[37] Viveiros, M.; Martins, A.; Paixáo, L.; Rodrigues, L.; Martins, M.; Couto, I.; Faehnrich, E.; Kern, W. V.; Amaral, L. *Int. J. Antimicrob. Agents*, **2008**, *31*, 458.
[38] Spengler, G.; Viveiros, M.; Martins, M.; Rodrigues, L.; Martins, A.; Molnár, J.; Couto, I.; Amaral, L. *Anticancer Res.*, **2009**, *29*, 2173.

dienylphenothiazines substituted with 2-aminophenothiazine/2-phenothiazine-amide derivatives have been prepared by application of Buchwald-Hartwig cross-coupling reaction [4].

5. A synthetic route has been elaborated for preparation of monohydroxy compound containing amine and amide groups in position 2 of the phenothiazine ring. Selective oxidation to sulfoxides and sulfones has also been carried out [5].

6. The resolution of the racemic monohydroxy compound was accomplished and aminohydroxy derivatives were isolated in high enantiomer-purities starting from both antipodes [5].

7. The efflux pump inhibition of our synthesized phenothiazine derivatives was tested in bacteria [2] and in rat hepatocyte cells. Some derivatives showed promising MDR inhibitory effect [3] [5].

6. Application possibility

The structural modification of *N*-dienylphenothiazines allowed the synthesis of a „molecule-library" containing 40-50 potential MDR inhibitors. It could play a role as starting point in research and drug development against MDR by functinalization of the phenothiazine ring.
Structure-activity relationship can be concluded from the pharmacological assay of Rh123 accumulation, in rat hepatocyte cell, in the presence of the well-known reference, Verapamil. The MDR inhibition of our compounds was investigated in bacteria, at different pH conducted the accumulation of ethidium bromide. These results were found to be in agreement with those obtained from biological evaluation of experiments carried out in rat hepatocyte.

7. Publications

7.1. Papers in periodicals

[1] Daniella Takács, Péter Király, Ildikó Nagy, Petra Bombicz, Orsolya Egyed, Zsuzsanna Riedl, György Hajós: **Formation of a new ring system: Tetrazolo[5,1-*f*][1,2]azaborinine** *Journal of Organometallic Chemistry*, **2010**, *695*, 2673-2678. [IF (2011): 2.384]

[2] Daniella Takács, Pedro Cerca, Ana Martins, Zsuzsanna Riedl, György Hajós, József Molnár, Miguel Viveiros, Isabel Couto, Leonard Amaral: **Evaluation of forty new phenothiazine derivatives for activity against intrinsic efflux pump systems of reference *Escherichia coli, Salmonella* Enteritidis, *Enterococcus faecalis* and *Staphylococcus aureus* strains** *In Vivo*, **2011**, *25*, 719-724. [IF (2011): 1.264]

[3] Daniella Takács, Ildikó Nagy, Petra Bombicz, Orsolya Egyed, Katalin Jemnitz, Zsuzsanna Riedl, József Molnár, Leonard Amaral, György Hajós: **Selective hydroboration of dieneamines. Formation of hydroxyalkylphenothiazines as MDR modulators** *Bioorganic & Medicinal Chemistry*, **2012**, *20*, 4258–4270. [IF (2011): 2.921]

[4] Daniella Takács, Orsolya Egyed, László Drahos, Zsuzsanna Riedl, György Hajós: **A new synthetic approach to phenthiazine-2-amines** *Tetrahedron Letters*, **2012**, *53*, 5585-5588. [IF (2011): 2.683]

[5] Daniella Takács, Petra Bombicz, Orsolya Egyed, László Drahos, Pál Szabó, Katalin Jemnitz, Mónika Szabó, Zsuzsa Veres, Júlia Visy, József Molnár, Zsuzsanna Riedl, György Hajós: **Synthesis and pharmacological investigation of new 2-amino-*N*-hydroxyalkylphenothiazines exhibiting marked MDR inhibitory effect** *Journal of Medicinal Chemistry*, **2012,** *submitted.* [IF (2011): 5.248]

7.2. Review

György Hajós, Katalin Jemnitz, Zsuzsanna Riedl, Daniella Takács, Zsuzsa Veres: **Heterocyclic compounds as MDR modulators** *Letters in Drug Design & Discovery*, **2011**, *8*, 102-113. [IF (2011): 0.872]

7.3. Lectures

1. Daniella Takács, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Diénlánc redukciója boránnal és katalitikus hidrogénezéssel** MTA KK, Szerves Kémiai Szeminárium, 2008.

2. Daniella Takács, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Dienil-fenotiazinok redukciója-Egy új borazin gyűrű képződése** MTA KK, XI. Doktori Kémiai Iskola, Mátrafüred, 2008.

3. Daniella Takács, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Dienil-fenotiazinok redukciója-Egy új borazin gyűrű képződése** MTA KK, Tudományos Intézeti Napok, 2008.

4. Daniella Takács, Zsuzsanna Riedl, György Hajós: **Új fenotiazin-származékok szintézise Pd-katalízis alkalmazásával** Heterociklusos Kémiai Munkabizottsági Ülés, Balatonszemes, 2009.

5. Daniella Takács, Zsuzsanna Riedl, György Hajós: **Új fenotiazin-származékok szintézise Pd-katalízis alkalmazásával** MTA KK, XII. Doktori Kémiai Iskola, Mátraháza, 2009.

6. Daniella Takács, Zsuzsanna Riedl, György Hajós: **Recent advances in phenothiazine chemistry** ATENS WG4 Krakkó (Lengyelország) 2009.

7. Daniella Takács, Jemnitz Katalin, Zsuzsanna Riedl, György Hajós: **Új MDR-gátló fenotiazinok szintézise** XIII. Doktori Kémiai Iskola, Balatonkenese, 2010.

8. Daniella Takács, Zsuzsanna Riedl, György Hajós: **New heterocyclic molecules in the service of research on MDR inhibition** Progress in studies on ABC transport inhibition MTA KK, 2010.

9. Orsolya Egyed, Péter Király, Daniella Takács, Petra Bombicz, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Új tetrazolo-azaborinin származékok multinukleáris oldat és szilárd fázisú NMR-vizsgálata** MTA KK, Tudományos Intézeti Napok, 2010.

10. Orsolya Egyed, Péter Király, Daniella Takács, Petra Bombicz, Zsuzsanna Riedl, György Hajós: **Oldat és szilárd fázisú NMR módszerek kombinált alkalmazása bórtartalmú heterociklusos vegyület vizsgálatában** NMR Munkabizottsági Ülés, Richter Gedeon Nyrt., 2010.

11. Daniella Takács, Zsuzsanna Riedl, György Hajós, Leonard Amaral: **Fenotiazin-származékok szintézise és vizsgálata baktériumokon** Kálmán Erika Doktori Konferencia, MTA KK, 2011.

12. Daniella Takács, Zsuzsanna Riedl, György Hajós, Leonard Amaral: **Potenciális multidrog rezisztenciát gátló fenotiazin-származékok vizsgálata baktériumokon** MTA, KK, Szerves Kémiai és Biomolekuláris Szeminárium, 2011.

7.4. Posters

1. Daniella Takács, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Diénlánc redukciója boránnal és katalitikus hidrogénezéssel** Vegyészkonferencia, Hajdúszoboszló 2008.

2. Daniella Takács, Ildikó Nagy, Zsuzsanna Riedl, György Hajós: **Synthesis of a new group of MDR inhibitory phenothiazines** 13th Blue Danube Symposium of Heterocyclic Chemistry, Bled (Szlovénia) 2009.

3. Orsolya Egyed, Péter Király, Daniella Takács, Petra Bombicz, Zsuzsanna Riedl, György Hajós: **Multinuclear solution and solid-state NMR investigation of heterocycles incorporating a B-N bond** Joint EUROMAR 2010 and 17th ISMAR Conference, Florence (Olaszország) 2010.

4. Daniella Takács, Zsuzsanna Riedl, György Hajós, Leonard Amaral: **Investigation of a new group of phenothiazines on multidrug resistant bacteria** 14th Blue Danube Symposium of Heterocyclic Chemistry, Podbanské (Szlovákia) 2011.