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SYNTHESIS AND CHARACTERIZATION OF SOME NEW HETEROCYCLIC AROAMTIC DERIVATIVES, PRECURSORS FOR MATERIALS WITH NONLINEAR OPTICAL PROPERTIES

Ph.D. Thesis Abstract

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CONTENTS

KEYWORDS: phenothiazine, alkylation, Vilsmeier-Haack-, Duff- formylation, phenothiazine-, ferrocene Schiff bases, *aza*-Diels-Alder reactions, phenothiazine dioxane, porphyrins with phenothiazine units, sulphonamides with phenothiazine units, structural analysis by NMR, IR, UV-Vis, fluorescence study, DFT calculations, reaction mechanism.

INTRODUCTION

Since the first synthesis of organic substance, obtaining urea by heating ammonium cyanate by F. Wöhler (1828), have developed many new methods for construct a complex molecular structures, with applications in different fields of science as well as natural compounds with biological activity, with pharmacological applications or in other areas of industry.

The high diversity of macrocycles can be explained by existing virtually endless possibilities to combine simple or complex molecular fragments to form cyclic structures. Thus, construction of macroheterocycles structures is possible through mono- or poly functionalized heterocyclic compounds which in well-controlled reaction conditions leading to saturated or unsaturated macrocycles. One of these heterocyclic compounds is phenothiazine which can be mono- or poly functionalized.

For decades, phenothiazine derivatives have occupied a privileged place in the dyestuffs industry, with special mentions for Lauth's[1] violet, methylene blue, toluidine blue or methylene green. Since the early 20th century, phenothiazine derivatives began to be studied on a large scale because of special biological properties, being used to good effect as anthelmintic[2,3], insecticides[4], antihistamines, antiemetic, anticonvulsants[5], and local anesthetics[6,7], spasmolytic[8], antitumor[9,10], respectively in treat nervous system disorders (Parkinson's[11,12] syndrome, schizophrenia). In the same period have highlighted their antioxidant properties successfully exploited lubricant and rubber industry.

The research work presents the original results in the synthesis of mono- and poly functionalized phenothiazines and their use as intermediates in the synthesis of: mono- and di-Schiff bases, porphyrins, sulphonamides, and dioxane. Cyclization reactions of 3,4-dihydro-2*H*-pyran with the synthesized Schiff bases, resulting quinoline compounds.

The present work proposed the elucidation of the new structure by spectroscopic methods, the interpretation of reactivity and selectivity problems observed by molecular modeling, the results constitute baseline data for future research in the field of application.

1 Literature Review

1.1 Reaction in microwave field

Although no older than 20 years the synthesis of organic compounds under the action of microwaves has grown rapidly both in scope of application, synthesis procedures and equipment dedicated to these processes[13,14]. In the field of organic synthesis reactions under the action of microwave synthesis systems are found in heterocyclic aromatic systems, aliphatic systems, and reactions of these classes of compounds (Figure 1).

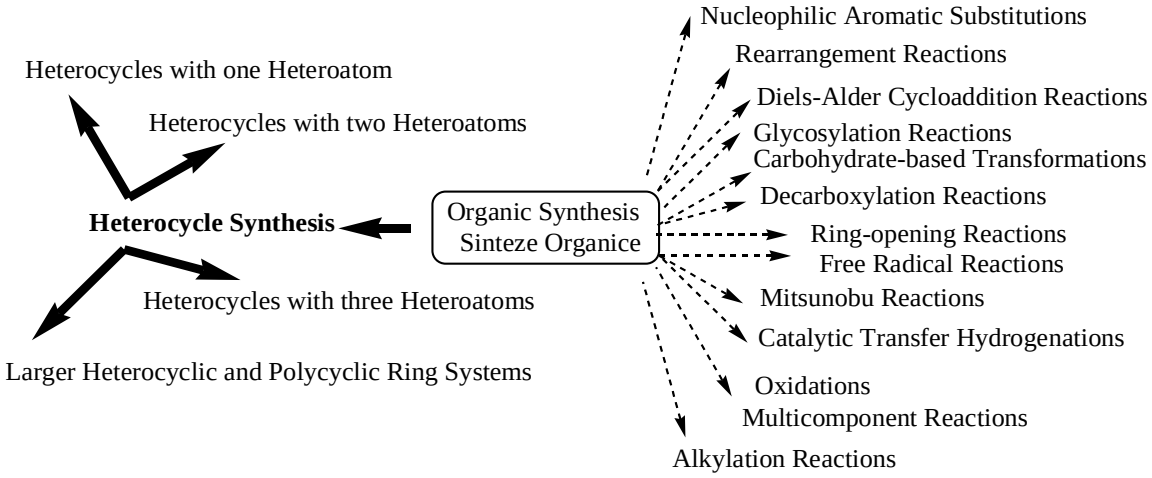


Figure 1.

Syntheses of organic compounds under the action of microwaves is found more frequently in organic chemistry due to the growth and finding new techniques for microwave field work more efficient than classical ones. The reaction without solvent or using water as solvent are becoming more common because they proved to be "clean" and in some cases more effective than traditional methods[18].

1.2 Schiff bases

Schiff bases or *azomethine*, named after Hugo Schiff, is a class of substances that are achieved by condensing a primary amine with an aldehyde or ketone[22,23,24]. The intermediate hemiaminal N-substituted compound is an non-isolated compound which loses a molecule of water forming the corresponding Schiff base[25]. The reaction of aromatic amines to obtain the corresponding imines occurs by acid catalysis. Ng. Ph. Buu-Hoi[22,23] synthesized the first mono-

and di-Schiff bases derived from formyl phenothiazine and 4-keto-5-R-2-thiazolinhidrazone, where R = H, Et, i-Pr, n-Bu, n-$C_{14}H_{29}$, n-$C_{16}H_{33}$ and two units of phenothiazine with 1,2-bis [(10-10H-phenothiazine-ethyl-3-yl) methylene] hydrazine. L. Găină[39] completed the series of di-Schiff bases; change the parameters of the reaction studied by microwave activation on solid support: bentonite, aluminum oxide, silica, irradiation power 650W.

C. Imrie[42] synthesized the ferrocene imine by conventional method using methanol or ethanol as solvent. This type of reaction requires heating and refluxes for several hours, ferrocene imine are thermosensitive and can decompose in the meantime. Another synthetic method is without solvent which requires shorter reaction time, has a better selectivity, easier separation and purification method, compared with conventional solvent[43,44,45,46]. Were investigated the nonlinear optical properties of obtained Schiff bases. Imines are ligands with a high potential for complexation with metal[47].

1.3 Hetero Diels-Alder reactions

The reaction [4π-2π] between a conjugated diene and a substituted alkene, commonly termed the dienophile to form a substituted cyclohexene system is known as Diels-Alder cycloaddition. Such cyclization reactions have been reported in the early 1900s by H. Wieland[54], W. Albrecht[55], Thiele H. Staudinger şi H. V. Euler[56], but products derived structures were not assigned. O. Diels and K. Alder in 1928 established the correct structure of cycloadduct obtained from the reaction between p-quinone and cyclopentadiene[57]. Tetrahydropyridine are obtained by *aza*-Diels-Alder reaction between a diene and imine. The nitrogen atom may be part of the diene or dienophile. Shen Shu-Su[85] and collaborators have studied the iodine catalyzed synthesis of heterocyclic compounds, and developed non-toxic methods of synthesis (green chemistry). The method allow the *aza*-Diels-Alder synthesis at room temperature without solvent in the presence of iodine as catalyst.

1.4 Dioxane

The reaction of aldehydes or ketones with alcohols in acidic or alkaline catalyst, formed hemiacetals, respectively semicetals that can not be isolated, the reaction is reversible. When in the reaction the alcohol is in excess in presence of acid catalyst[92], the obtained compound is an

acetal or cetal those are stable and separable substances. If using 1,2- or 1,3-diol cyclic cetales or acetales are obtained. It was found that probably due to the steric effects, the aldehyde reacts easily with alcohols[93] than ketones and cyclic (a) cetales are easier to obtain than those acyclic[94].

1.5 Porphyrins

The porphyrin core is a tetrapyrolic cycle composed of 20 carbon atoms that form the skeleton of the molecule. The four pyrrol groups are linked by bridges containing one carbon atom. From the first synthesis of protoporphyrin IX by Hans Fischer (1929) [113], the synthesis methods of porphyrins were significantly improved, mainly due to research conducted by: W.A. Johnson[114], G.W. Kenner[115, 116], S.F. MacDonald[117] and R.B. Woodward[118, 119]. In the first half of the twentieth century, the synthesis of porphyrins was oriented towards determining the structure of natural products and development of production methods from known materials and the introduction of substituents or modification of existing functional groups based on known chemical reactions. With the development retro synthetic analysis the synthesis of new porphyrins was shifted to a systematic approach to obtain porphyrins, the chosen synthesis methods are more influenced by the target molecule than the starting material.

The first synthesis of tetra substituted meso-porphyrins was performed by Rothemund (1936) by heating in pyridine pyrrol with an aldehyde in a sealed tube at 150 ° C for 24 h[132, 133].

Studies by Adler and Longo[134, 135] had an important role in elucidating the processes underlying the formation of porphyrins by co-condensation of pyrrol and aldehydes. Rothmund[132] established that the acidic environment and the presence of oxidizing agent, such as oxygen in the air increases the efficiency of the porphyrin synthesis.

1.6 Sulphonamide

The intensive development the chemistry of the organic sulfur compounds, especially those that containing sulfur in various oxidation states: thysulphoxide and thiosulphone combined with naphthoquinone with heterocyclic fragments, including phenothiazine derivatives, due to their scientific and practical importance. Some representatives of these classes of compounds have found applications as intermediates in the synthesis of biologically active compounds with: anti-inflammatory, antiviral, antibacterial, antitumor, anthelmintic properties, and herbicides, fungicides, insecticides, growth regulators. Phenothiazine derivatives have found

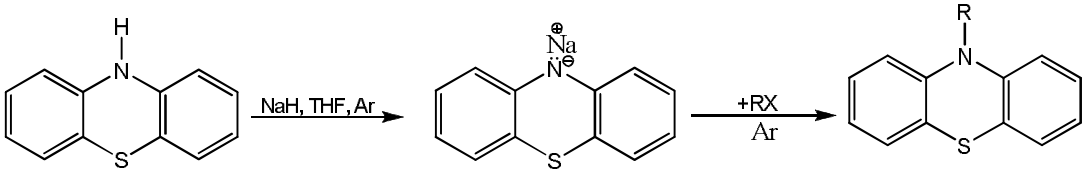
in the last one hundred years applications to treat malaria and other diseases caused by blood parasites. Examples of recently approved drugs whit sulphonamide structure are: hypertensive agents Bosentan ™[144], HIV protease inhibitor Amprenavir ™[145], and phosphodiesterase-5 inhibitor sildenafil, VIAGRA ™[146].

2 ORIGINAL RESULTS

2.1 Synthesis of phenothizine precursors, NMR and mass spectra study

In this chapter are presented the synthesis of N-alkyl phenothiazine derivatives, formylated, acetylated, which is done either directly by introducing functional groups at the N or C atom by nucleophiles or electrophile substitution reactions. To avoid the reactions at the nitrogen atom is necessary to protect the position 10 of the phenothiazine system by alkylation reaction results the N-alchylphenothiazine.

For the N-alkylation of phenothiazine with alkyl halides in general is necessary to ensure a basic medium using KOH, $NaNH_2$ or NaH. When KOH in DMF is used as alchylation agent the yields were low, below 20%, for this reason were used $NaNH_2$ or NaH in THF as solvent[159, 160]. The reaction was carried out in inert atmosphere by treatment of phenothiazine (1) with sodium hydride in THF, results the 10-Na-phenothiazines (red-orange) which further reacted with alkyl iodides or bromides to give the corresponding 10 alchylphenothiazine with good yields. By this procedure (Scheme 2.1) were synthesized: 10-Me-, 10-Et-, 10-iPr, -10-butyl, 10-octyl, 10-dodecyl-phenothiazines (**2.a-f**).



Scheme 2.1

In all cases, the reactions were monitored by TLC (silica gel on aluminum support, eluent toluene or toluene / hexane, 5 / 1, v / v). Purification of N-alkyl-phenothiazines was achieved by recrystallization from ethanol (**2.a, b, c, d**) or by vacuum distillation (**2.e, f**). The characteristic

parameters of reaction: alkylation agent, reaction time, yields for **2.a-f** compounds are presented in Table 2.1.

Table 2.1 The caracteristic parameters of alchylation reactions:

Compound	Alchilation agent	Reaction time (h)	Yield%	Merlting point(C°)
2.a	CH_3I	12	95	99 C°
2.b	CH_3CH_2I	12	94	104 C°
2.c	iPrBr	12	80	62 C°
2.d	$CH_3(CH_2)_3Br$	12	76	65 C°
2.e	$CH_3(CH_2)_7Br$	12	78	< 20 C°
2.f	$CH_3(CH_2)_{11}Br$	12	82	< 20 C°

The structures of obtained compounds were investigated by spectroscopic methods: IR, ^{1}H-NMR, ^{13}C-NMR filled with the data from mass spectrometry.

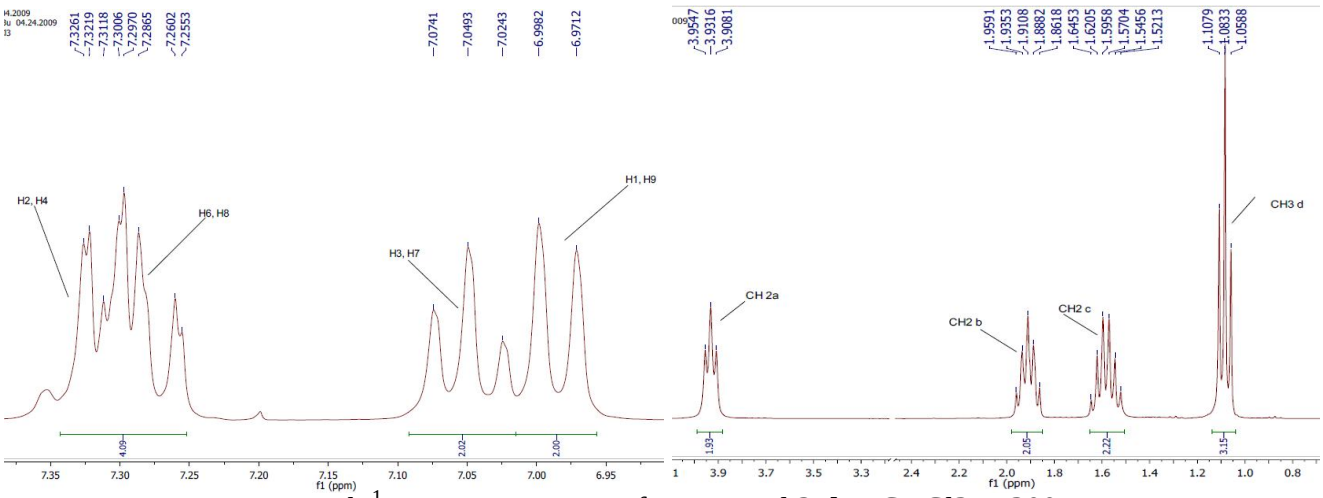
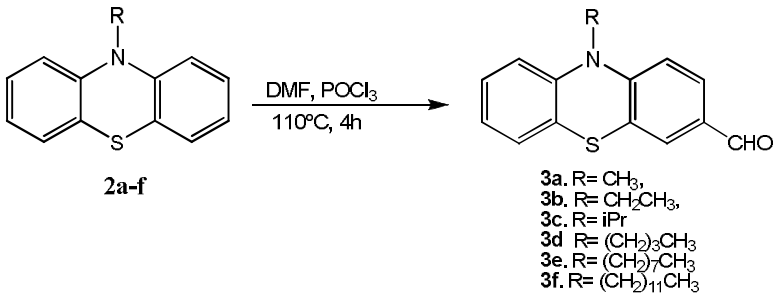


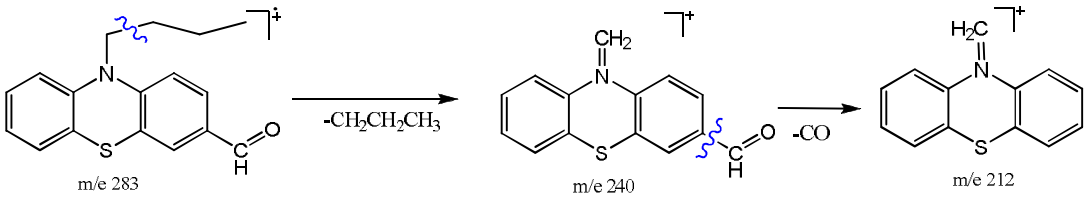
Figure 2.1.b ^{1}H NMR spectrum of compound **2.d** in CDCl3 at 300 MHz.

The alchylphenothiazine were formylated by the method proposed by Bode (1965)[162], with a yield of 71% for 3-formyl-10-methyl phenothiazine and 75% for 3-formyl-10-ethyl phenothiazine, resembling those of literature values (Scheme 2.3). The reaction mechanism explains the formation of mono-and di formyl-derivative and low yields in 10-alkyl-3 ,7-diformyl phenothiazine (ratio of mono-and di formyl-derivative is approximately 10:1), regardless of excess reagent used.



Scheme 2.3 Formylation of 10-alkyl phenothiazines by Vilsmeier-Haack reaction

Purification of synthesized compounds was achieved by column chromatography (Silica gel 60, particle size 0.063 to 0.2 mm, eluent toluene or mixture toluene: ethyl acetate 10 / 1) and recrystallization from ethanol. The NMR spectra recorded in $CDCl_3$ at 300MHz, 500MHz confirmed the structure of 10-alkyl-3- formyl phenothiazines. The aromatic part of proton spectrum contains four distinct signals for the eight hydrogen atoms. Structure of 10-metil-3-formyl phenothiazine was highlighted by ^{1}H-NMR spectra, COSY ^{13}C-NMR, DEPT, HMQC and HMBC. The mass spectrometry studies performed on 10-alkyl-3-formyl phenothiazines confirmed the molecular weight values in all spectra of analyzed compounds and for each compound in different intensity peaks appear at values m / e 240, 226, and 198. Scheme 2.4 presents the fragmentation of 10-butyl-3-formyl phenothiazine 3.d.



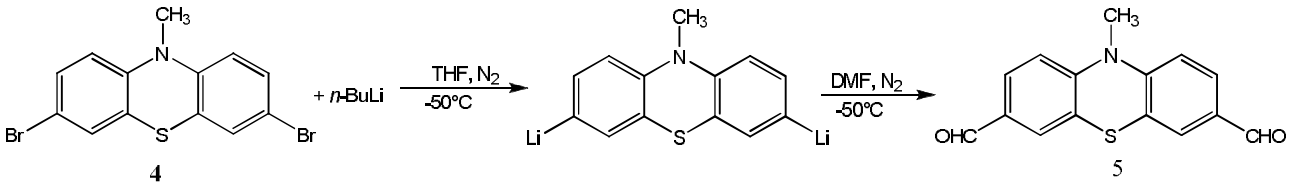
Scheme 2.4 Fragmentation of compound 3.d

The characteristics of Vilsmeier-Haack formylation reaction of N-alkyl-phenothiazines **3.a-f** are presented in Table 2.2 with melting points of synthesized compound.

Tabel 2.2 The caracteristic parameters of Vilsmeyer-Haack formylation

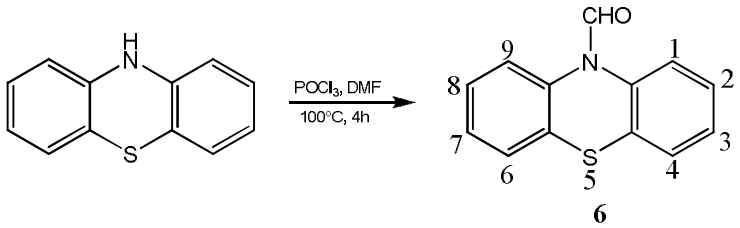
Com.	Formilation agent	Reaction temperature (°C)	Reaction time [h]	Yield [%]	Melting point (°C)
3.a	$POCl_3$, DMF	110	4	81	89°C
3.b	$POCl_3$, DMF	110	4	70	58°C
3.c	$POCl_3$, DMF	110	4	40	51°C
3.d	$POCl_3$, DMF	110	4	47	51°C
3.e	$POCl_3$, DMF	110	4	50	28°C
3.f	$POCl_3$, DMF	110	4	45	30°C

The Vilsmeier-Haack formylation of 10-alkyl-phenothiazines is not the optimal method for obtaining di-formyl-phenothiazines, since by this method only byproducts are formed quantitatively are monoformylated compounds. Synthesis of 3,7-dibromo-10-Me-phenothiazine **4** as precursors the, was achieved by bromination with Br_2, in acetic acid of 10-Me-phenothiazine. The litigation reaction of bromide compound was done with excess of n-BuLi in THF, according to the method of S. Ebdrup[163] resulting the 10-methyl-3,7-dilitium phenothiazine which with DMF and acidic hydrolysis give the 10-methyl-3,7-diformyl-phenothiazine (Scheme 2.4).



Scheme 2.4 Synthesis of 3,7-diformyl-10-methyl-phenothiazine **5**

Formylation Vilsmeier-Haack can be achieved on the free nitrogen atom of the phenothiazine. By pouring the reaction mass on ice, 10- formyl phenothiazines **6** precipitate in form of white crystals, the substance thus obtained is purified by recrystallization from ethanol (Scheme 2.6).



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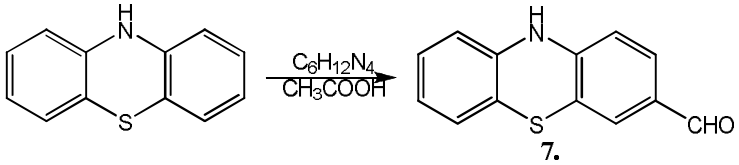
Scheme 2.6 Vilsmeier-Haack formylation of phenothiazine at the N atom

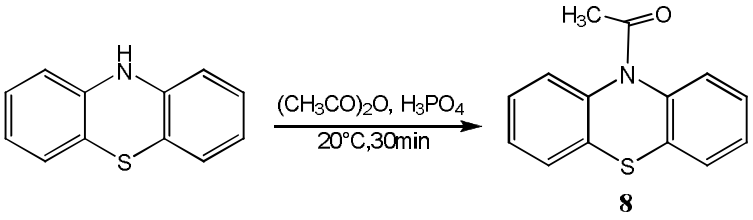
Another method of introduction the formyl group on the phenothiazine molecule is the formylation Düff[164,165,166,167,168,] which involves the C-formylation of unsubstituted phenothiazine at the nitrogen atom. Phenothiazine reacts with urotropine in glacial acetic acid (Scheme 2.7.) resulting the 3-formil phenothiazine, compound with 40% yield**.** The reaction was tested in the microwave field, in this case the reaction time decreased from 18h to 2h and the yield increased significantly.



7.

Scheme 2.7 Düff formylation of phenothiazine

Acylation agent, a weaker electrophile (soft electrophile), consisting of glacial acetic acid and phosphoric acid (H_3PO_4) in catalytic amount was used to acetylating the phenothiazine, and obtained 10-acetyl phenothiazine **8** (Scheme 2.8). The yield is 98%.



8

Scheme 2.8 Acetylation of phenothiazine with glacial acetic acid in the presence of phosphoric acid.

In the ^{1}H NMR spectrum of compound **8** appears a signal to δ = 2.20 ppm for protons of the methyl group (Figure 2.4).

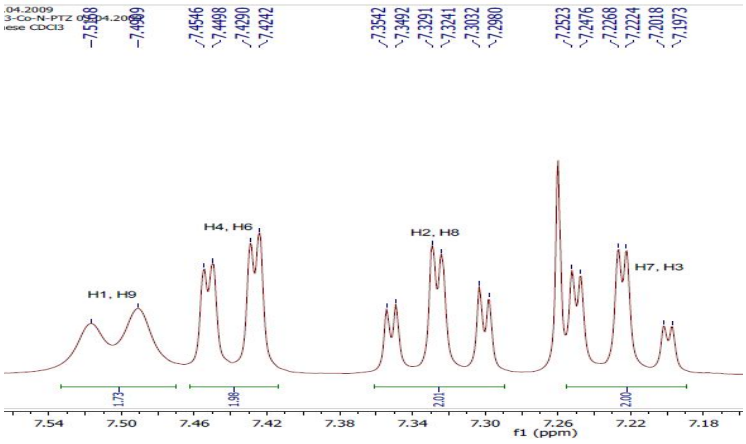


Figure 2.4. ^{1}H NMR spectrum of compound **8** at 300MHz in $CDCl_3$

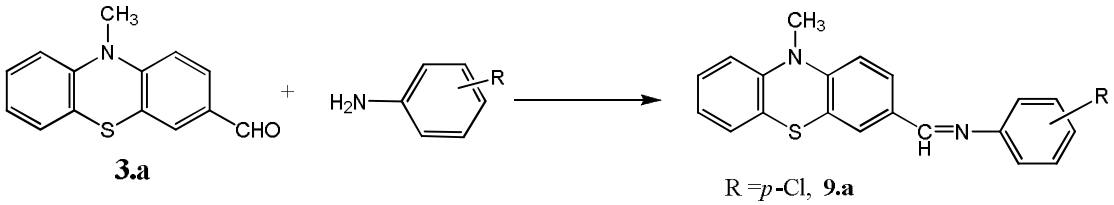
2.2 Schiff bases

2.2.1 Synthesis of phenothiazine mono-Schiff bases

From the reaction of 10-methyl-3- formyl phenothiazine with substituted aniline under reflux was obtained Schiff bases **9.a-h**, for condensation with 3-amino-4-chloro-benzoic acid the solvent was changed to isoamilic alcohol, solvent with a higher boiling point, when **9.g** compound was obtained (Scheme 2.9)[174].

Table 2.3 The characteristics of condensation reactions.

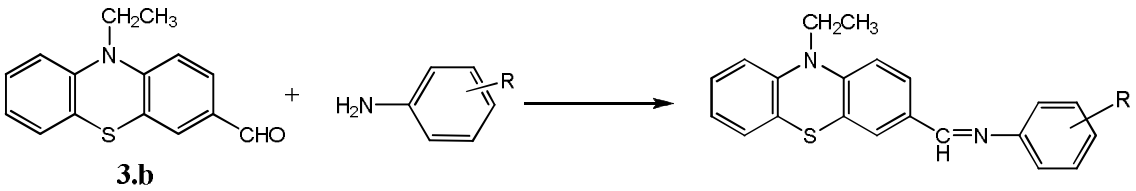
Comp.	Solvent	Reaction time[h] / Temperature[°C]	Yield [%]	Melting point [°C]
9.a	EtOH	24h/78°C	98	125
9.b	EtOH	24h/78°C	80	108
9.c	EtOH	24h/78°C	98	105
9.d	EtOH	5h/78°C	93	190-192°C
9.e	EtOH	24h/78°C	50	101
9.f	EtOH	6h/78°C	76	121
9.g	Alcohol isoamilic	24h/130°C	80	243-244
9.h	EtOH	24h/78°C	70	256



R =*p*-Cl, **9.a**
R = *p*-OCH_3, **9.b**
R = *p*-CH_3, **9.c**
R = *p*-$COOCH_3$, **9.d**
R = *p*-NO_2, **9.e**
R = *m*-NO_2, **9.f**
R = *m*-COOH, *o*-Cl, **9.g**
R = *p*-COOH, **9.h**

Schema 2.9 Synthesis of compounds **9.a-h**

The Schiff bases **10.a** respectively **10.c** was obtained by condensation of 10-ethyl-3-formyl phenothiazine **3.b** with p-amino-benzoic acid and p-methoxy aniline in ethanol under reflux. The Schiff base 10.b was obtained by changing the solvent to isoamilic alcohol from ethanol, solvent with higher boiling point (Scheme 2.10) The reactions were monitorized by TLC (silica gel on aluminum support, eluent toluene / acetone 4 / 1, v / v). The obtained compounds were purified by recrystallization from ethanol.



R = *p*-COOH, **10.a**
R = *m*-COOH, *o*-Cl, **10.b**
R = *p*-OCH_3, **10.c**

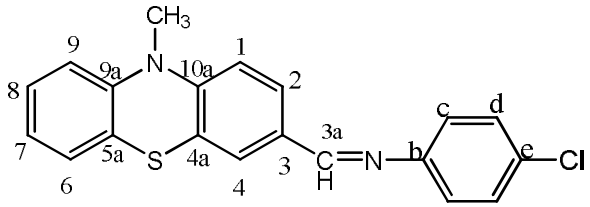
Scheme 2.10 Synthesis of compounds **10.a-c**

Table 2.3 Characteristics of condensation reactions.

Comp.	Solvent	Reaction time[h] / Temperature[°C]	Yield [%]	Melting point [°C]
10.a	EtOH	24h/78°C	80	249
10.b	Isoamilic alcohol	24h/130°C	50	209
10.c	EtOH	6h/78°C	76	108

2.2.2 NMR spectra study

The structure of Schiff bases **9.a-h** was investigated by 1D ^{1}H-NMR spectra, ^{13}C-NMR at 300MHz, 400MHz to 500MHz respectively. In all cases, the proposed structures were confirmed.



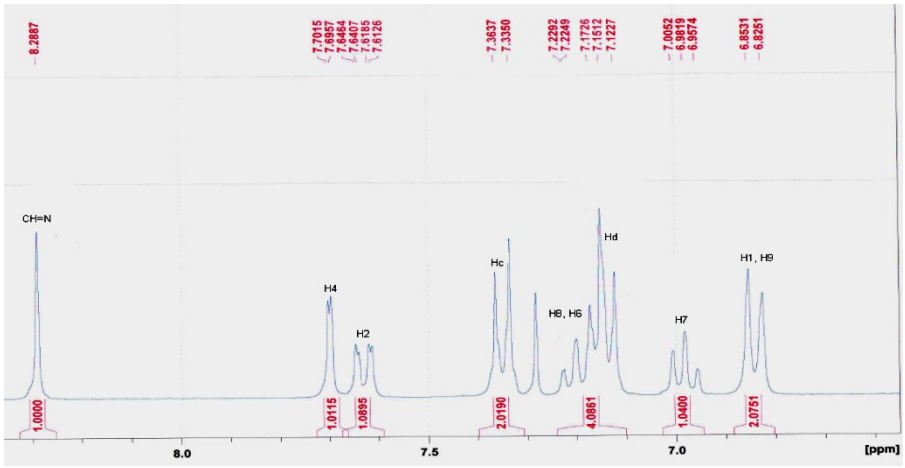
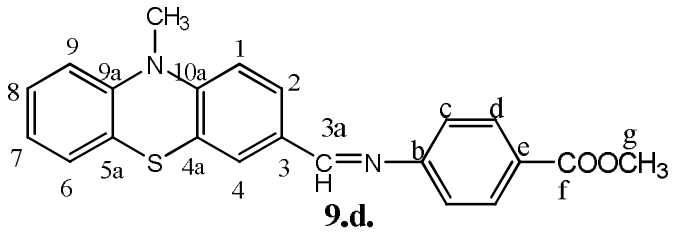


Figure 2.6.a ^{1}H-NMR spectrum for compound **9.a** at 300MHz in $CDCl_3$

In the ^{13}C NMR spectrum in the aliphatic part appear a single signal at δ= 35,64 ppm for CH_3 group. The signal for the carbon 3a appear at the value δ= 159,18 ppm. The signals for the carbon atoms from the phenyl group Ce and Cb are shifted downfield because the presence of the heteroatoms N and Cl, δ= 150,55 ppm for Ce, δ= 148,50 ppm for Cb. Table 2.4 presents the chemical shifts and coupling constants for protons and for the carbon for the **9.d** compound.



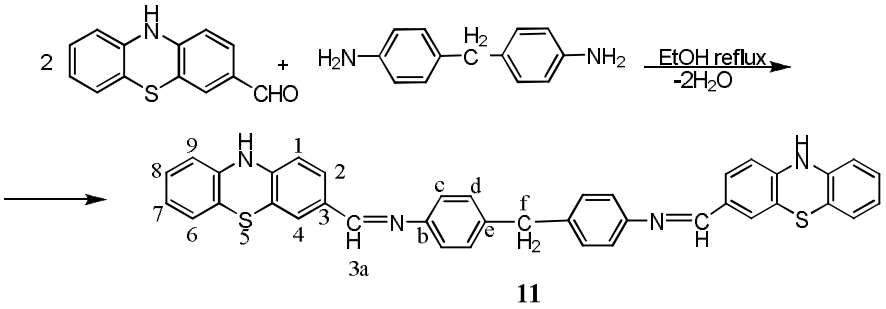
9.d.

Table 2.4 The chemical shifts and coupling constants for compound 9.a.

H 9d	CH=N	H_4	H_2	H_8	H_6	H_7
δ ppm	8,30 s	7,63 s	7,58 d	7,28 dd	7,09 d	6,91 dd
J Hz	-	-	8,4 H_2-H_1	7 H_8-H_7 8 H_8-H_9	8 H_6-H_7	7 H_8-H_7 8 H_6-H_7
H	H_1	H_9	N-CH_3	O-CH_3	H_c	H_b
δ ppm	6,86 d	6,84 d	3,47 s	3,85 s	7,18 d	6,90 d
J Hz	8,4 H_2-H_1	8 H_8-H_9	-	-	8,8 H_c-H_b	8,8 H_c-H_b
C 9d	CH=N	C_4	C_2	C_8	C_6	C_7
δ ppm	153,8	126,9	128,3	127,3	127,3	122,8
C	C_1	C_9	N-CH_3	O-CH_3	C_a	C_b
δ ppm	114,6	115,2	35,9	55,4	144,9	114,3
C	C_c	C_{4a}	C_{5a}	C_{9a}	C_{10a}	C_d
δ ppm	122,1	124,4	123,6	143,8	147,2	158,0

2.2.4 Synthesis of phenothiazine *bis*-Schiff bases

From the condensation of 3-formyphenothiazine with 4,4 '-methylene-dianiline were obtained *bis*-Schiff bases. Reaction were carried out in polar solvent (alcohol), using a molar ratio formyl derivate: diamine 2 / 1 (Scheme 2.14)[163.]

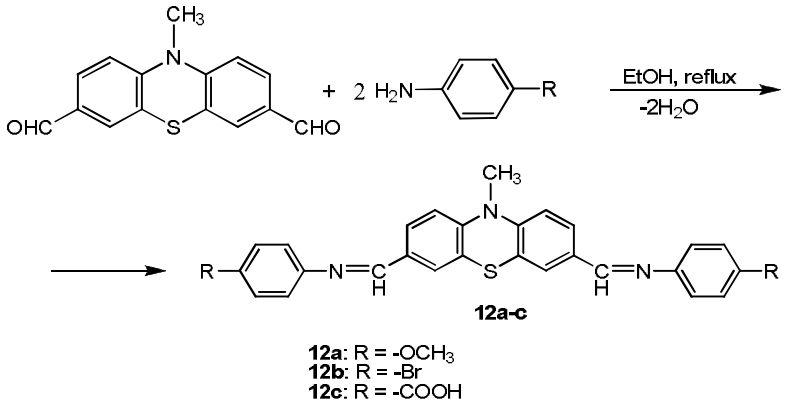


Scheme 2.14 Synthesis of compound **11**

Condensation of 10-methyl-3,7-diformylphenothiazine with different aromatic amines using a molar ratio di formyl phenothiazine: amine 1/2 were obtained the *bis*-Schiff bases **12.a-c** (Scheme 2.15). The reactions were monitorized by TLC (silica gel on aluminum support, eluent toluene / acetone 4 / 1, v / v). Characteristics of the condensation reaction are presented in Table 2.5. The obtained compounds were purified by recrystallization from toluene.

Table 2.5. The characteristics of condensation reactions.

Compound	Solvent	Reaction time [h]	Yield [%]	Melting point [^{o}C]
11	EtOH	6	65	310
12.a	EtOH	16	68	234
12.b	EtOH	10	58	222-224
12.c	iPrOH	24	85	308



Schema 2.15. Synthesis of compounds **12.a-c.**

2.2.5 Studiul spectrelor RMN

The structures of compounds **11, 12.a-c** were investigated by NMR spectra at 400MHz, 300MHz respectively. In ^{1}H-RMN spectrum of compound **11** in DMSO is noted the disappearance of aldehyde proton singlet from δ= 9,80ppm, and the appearance of a singlet for the azomethinic proton at value δ= 8,36ppm. In spectras of **12.b-c** compounds the azomethinic protons appears at δ= 8,30- 8,31 ppm, δ= 8,36 ppm for **12.a** compound respectively.

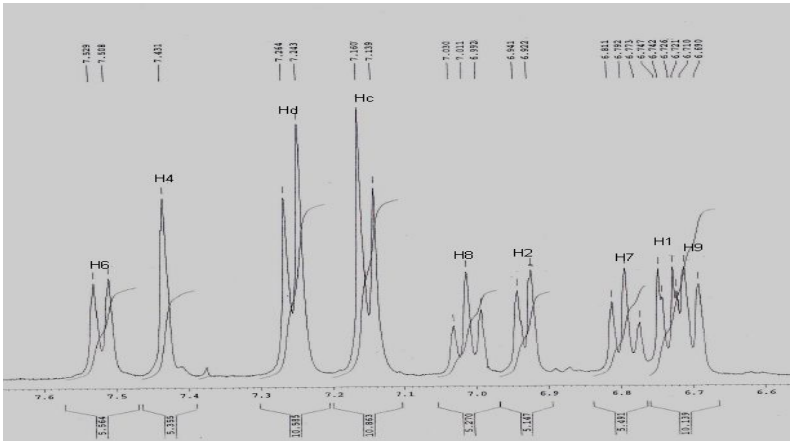


Figure 2.8 ^{1}H NMR spectrum of compound **11** at 400MHz, in DMSO.

The protons Hc from the substituted phenyl group appears as a doublet at value δ= 6,92 ppm with coupling constant J_{Hc-Hd}= 8,8 Hz, and Hd protons at value δ= 7,21 ppm (Figure 2.11.a).

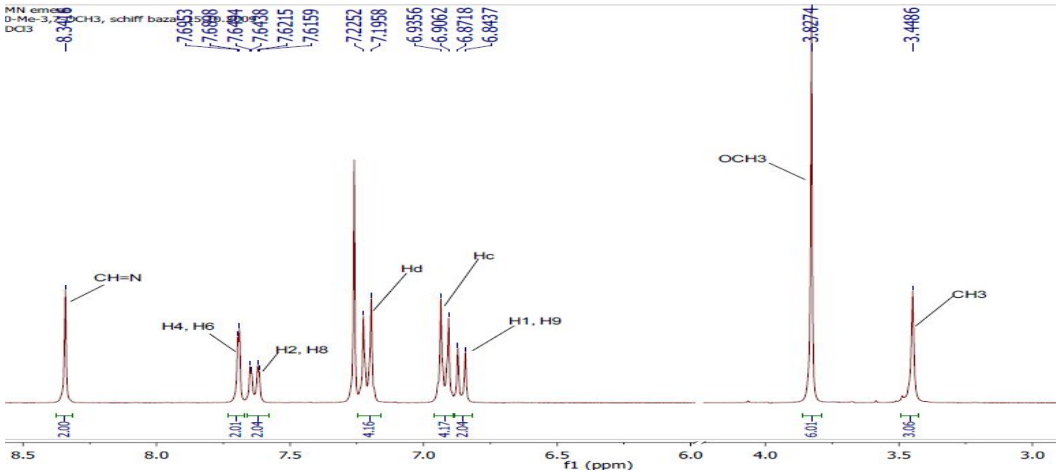


Figure 2.11.a ^{1}H NMR spectra for **12.a** compound at 300MHz, in $CDCl_3$.

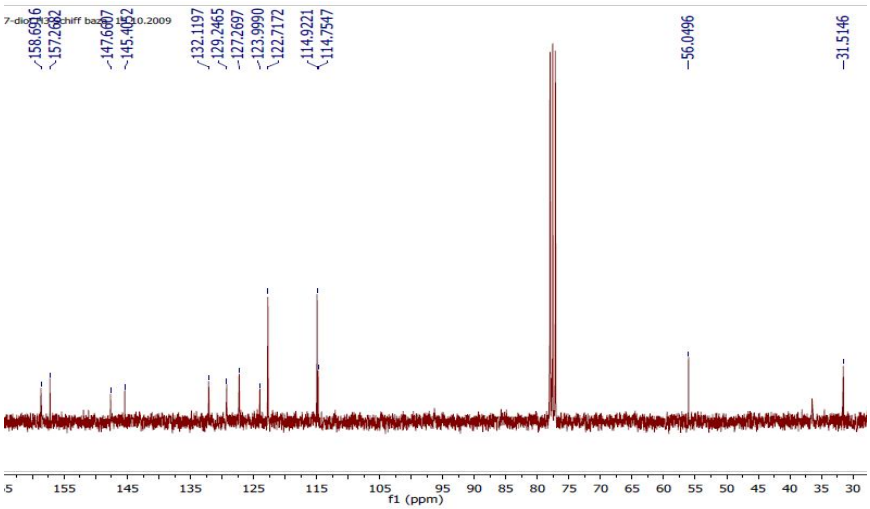
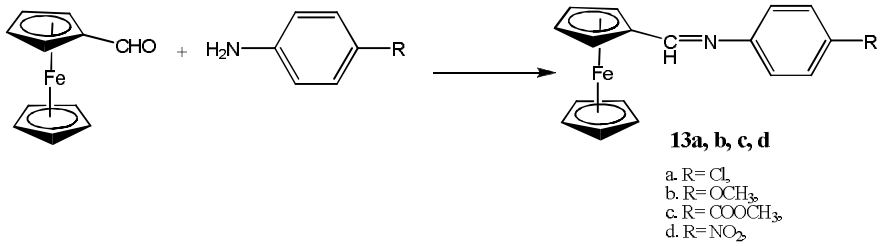


Figure 2.11.b ^{13}C NMR spectra for **12.a** compound at 300MHz, in $CDCl_3$.

In the ^{13}C NMR of compound **12.a** for the azomethinic carbon can be seen a signal downfield at δ= 158,69 ppm. At the aliphatic part of the ^{13}C NMR appear at value δ= 56,04 ppm the methoxy group of substituted phenyl, the carbon from the methyl group at position 10, link at N from phenothiazine appear at value δ= 31,51 ppm.

2.2.7 Synthesis and NMR spectra study of ferrocene Schiff bases

With condensation of ferrocene aldehyde with various aromatic amines under reflux in ethanol were obtained ferrocene Schiff bases **13.a-d** (Schema 2.17.). Characteristics of the condensation reactions are presented in Table 2.6.



Schema 2.17 Synthesis of ferrocene Schiff bases

Table 2.6 Characteristics of ferrocene Schiff bases synthesis

Comp.	Solvent	Reaction time [h]/ Temperature [°C]	Yield [%]	Melting point [°C]
13.a	EtOH	12h / 78°C	89	108-110
13.b	EtOH	12h / 78°C	85	50-52
13.c	EtOH	5h / 78°C	85	146-148
13.d	EtOH	12h/78°C	78	86-88

The obtained ferrocene Schiff bases were purified by recrystallization from heptane.

The structures of compounds **13.a-d** were investigated by NMR spectra at 500MHz. In ^{1}H-NMR spectrum of the compound **13.c** in $CDCl_3$ is noted the disappearance of the aldehyde proton singlet at δ= 9,80 ppm and the appearance of the azomethine proton sign at δ= 8,35 ppm (Figure 2.12.a).

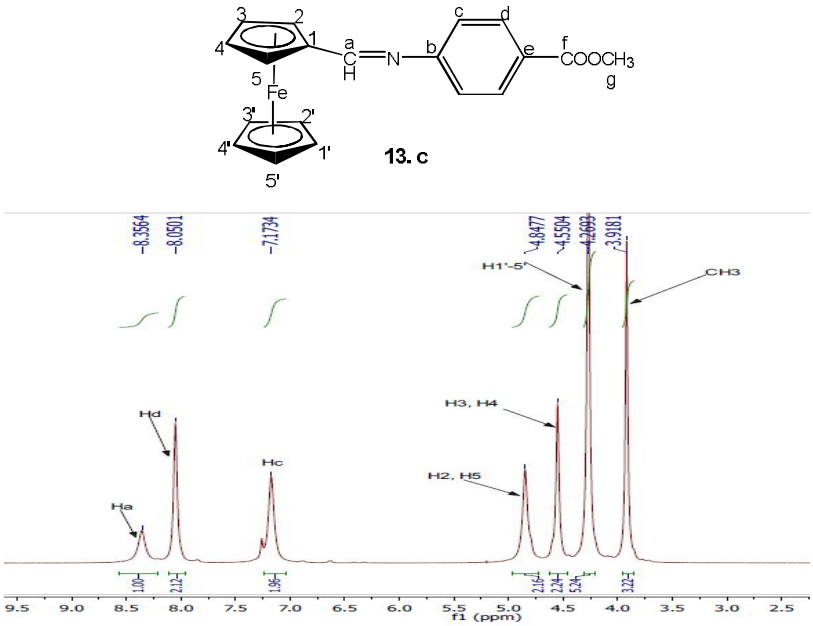


Figure 2.12.a ^{1}H NMR spectra for **13.c** compound at 500MHz, in $CDCl_3$.

The compound **13.c** has three types of carbon atoms in the molecule, found in full in ^{13}C-NMR spectra. The CH_3 carbon signal is downshifted and appears at δ = 52,13 ppm. The signal for carbon in the position a, the azomethinic carbon, is the most downshifted and appears at δ = 166,96 ppm. The signal for carbon from the carboxy group appears at δ = 163,29 ppm.

Quaternary carbon from the phenyl group appears at δ= 156,59 ppm C_b which is more downshifted that the Ce carbon at value δ= 126,90 ppm. The signal value from δ = 79,75 ppm is attributed to quaternary carbon of ferrocene, position 1.

2.2.8 Synthesis of new ferrocene and phenothiazine Schiff bases by microwave activation

Synthesis of organic compounds under the action of microwaves has been reported in literature in 1986 and has the advantage of a significant increase in rate of reaction. Microwaves are electromagnetic waves with a frequency between 300MHz-300GHz, commonly used for industrial-scale syntheses, laboratory tests or medical applications is 2450MHz aparatus and was required by international conventions. The energy brought by this frequency is about 1 J mol^{-1}. Discovery CEM reactor operating in mono mode, uniformly irradiates the reaction mixture. (Figure 2.13) The used reaction vessel is in Pyrex of 10 ml volume, with Teflon cap.

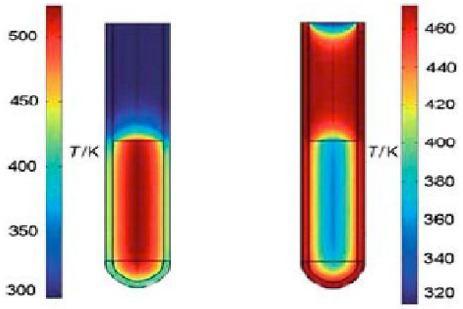


Figure 2.13 The difference between the temperature profiles: after 1 minute of microwave irradiation (left) and heating in oil bath (right)

Purification of obtained Schiff bases was achieved by repeated recrystallization. Identification of products was done by: TLC, using as a standard compound prepared by "classical method" melting point and mass spectrometry. In Table 2.7 are compared the yield and the reaction time for synthesis of Schiff bases by conventional and MAOS (**M**icrowave **A**ctivation **O**rganic **S**ynthesis).

Table 2.7 Characteristics of classical and MAOS reactions

Cmp.	Solvent Classic	Solvent MW	Reaction time		Yield	
			Classic [h]	Microwave [min]	Classic [%]	Microwave [%]
9.a	EtOH	ACN	24	30	98	86
9.b	EtOH	ACN	24	30	80	78
9.c	EtOH	ACN	24	30	98	95
9.d	EtOH	ACN	5	30	93	90
9.e	EtOH	ACN	24	30	50	50
9.f	EtOH	ACN	6	30	76	65
13.a	EtOH	ACN	12	60	89	89
13.b	EtOH	ACN	12	60	85	80
13.c	EtOH	ACN	5	60	85	85
13.e	EtOH	ACN	12	60	78	73

According with Table 2.7 the microwave assisted reactions has the advantage of a shorter reaction time compared to conventional synthetic route. Yields obtained by classical method and by microwave activation field are comparable.

2.2.9 UV-Vis absorption spectras of Schiff bases

The absorption of the *e.m.* radiation in the UV-Vis domain generated electronic spectra with characteristic maxima presented in table 2.8 b. for Schiff bases **9.a, b, c, d, g, h, 11, 12.a, c** quantum yield was calculated. Perilena standard was used, with quantum yield Φ = 0.94% (Figura 2.14)

Table 2.8.b Maximum absorption and emission in the UV-Vis of synthesized Schiff bases (in CH_2Cl_2), and calculated the quantum yield and Stokes shifts

Compound	Absorption $\lambda_{max,abs}$ [nm][a]	Emission $\lambda_{max,em}$ [nm][a]	Quantum yield [%][b]	Stokes shift (cm^{-1})
Perilene	229, 254, **410**, 438	438, **469**	0,94	3100
9.a	242, 283, **392**	**527**	0,036	6500
9.b	239, 275, **380**	**545**	0,069	8000
9.c	235, 276, **392**	**517**	0,027	6200
9.d	234, 278, **386**	**529**	0,017	7000

9.g	220, 264, **390**	**560**	0,011	7800
9.h	243, 275, **388**	**526**	0,017	6800
11	244, 294, **399**	**525**	0,065	6000
12.a	234, 290, **401**	**524**	0,053	5800
12.c	287, **404**	**535**	0,011	6100

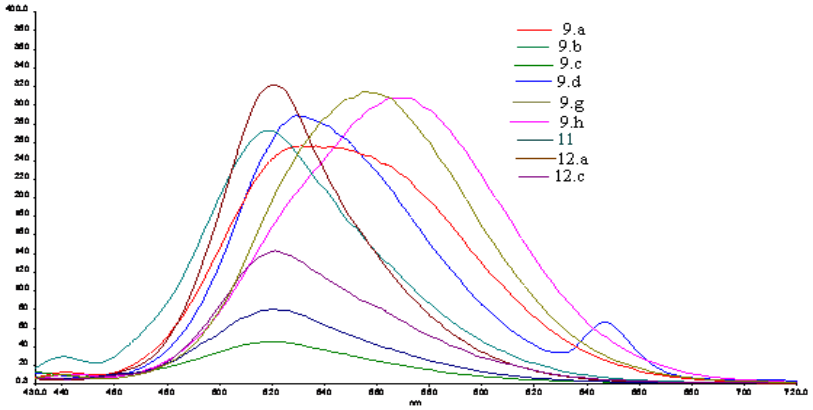


Figure 2.14 Fluorescence spectra recorded for compounds **9.a-h, 11, 12.a-c**

2.3 *Aza*-Diels-Alder reactions

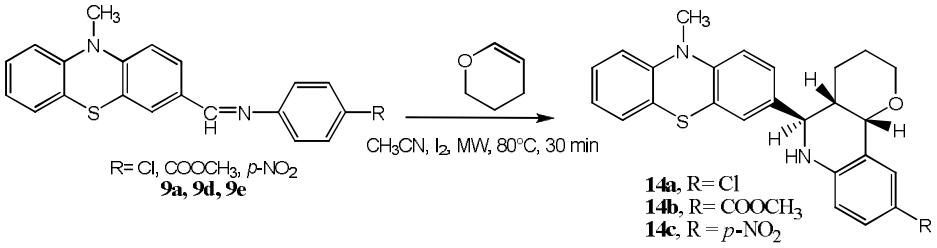
2.3.1 Synthesis of ferrocene and phenothiazine quinolines

Although quinolines are one of the most studied heterocycles in literature phenothiazine and ferrocene quinolines are quite rare. Investigations on new synthetic methods and properties of heterocyclic compounds seem interested, both for fundamental research and industrial applications. Phenothiazine derivatives are used in many types of drugs that are in clinical use (sedatives tranquilizers, antihistamines, antiemetic, etc.), and other biologically active compounds such as antibacterial products, pesticides, compounds with analytical applications (indicators redox and reagents in spectophotometric determination), antioxidants at high temperature for lubricants and[182]. Quinoline and tetrahidroquinolines derivatives occur, natural and synthetic products with biological activity [183,184,185,186].

Otto Paul Hermann Diels and Kurt Alder first documented the novel reaction in 1928 for which they were awarded the Nobel Prize in Chemistry in 1950 for their work on the eponymous reaction. The Diels-Alder reaction is generally considered the "Mona Lisa" of reactions in organic chemistry since it requires very little energy to create a cyclohexene ring, which is useful in many other organic reactions[187,188,189,190]. We note that quinoline derivatives of phenothiazine and ferrocene have been was not synthesized. In this chapter are presented some results regarding the synthesis and stereochemistry of this class of substances.

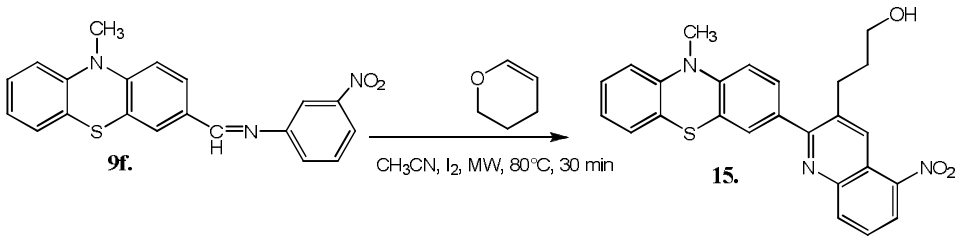
In the synthesis of phenothiazines and ferrocene quinolines in acid catalysis, we started from the ferrocene and phenothiazine Schiff bases **9.a-f, 13.a-c** reacting with 3,4-dihydro-2*H*-pyran. Reaction is an *aza*-Diels-Alder cycloaddition [4+2] between the N-arilimine (azadiene electron poor) and electron-rich dienophile. For synthesis of quinolines was used acetonitrile as solvent, the reactions were realized in microwave reactor for chemical reactions presented in chapter Schiff bases.

From the reactions of 9.a**, d, e** with 3,4-dihydro-2*H*-pyran in the presence of iodine in catalytic amount results the **14.a, b, c,** compounds (Scheme 2.18). Due to relatively high solubility of quinoline compounds in acetonitrile, they do not precipitate the reaction as it forms. Reactions were monitorized by TLC (silica gel on aluminum support, eluent = dichloromethane: methanol 80/10), UV λ=365nm. From the reaction mixture de iodine is removed by filtration on a silica gel layer. Purification of compounds was achieved by column chromatography followed by recrystallization from ethanol.



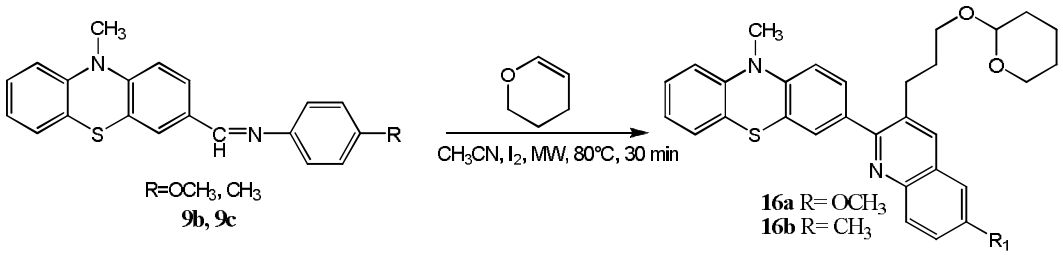
Scheme 2.18 Synthesis of **14.a, b, c**, compounds by microwave-assisted cycloaddition.

From the reaction of Schiff's base 9.f with 2,3-dihydro -2H-pyran in acetonitrile in the presence of catalytic amounts of iodine in the microwave activation was obtained the compound 3-(2-(10-methyl-10-*H*-phenothiazin-3-yl)5-nitroquinoline-3-yl)propane-1-ol, **15** (Scheme 2.19).



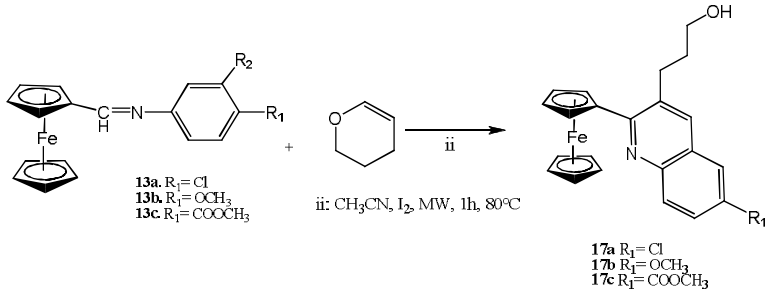
Scheme 2.19 Synthesis of compound 15 by microwave-assisted cycloaddition.

From the reaction of Schiff bases **9.b** and **c**, with 3,4-dihydro-2*H*-pyran were obtained 3 -(6-methoxy/methyl-3-(3-(tetrahydro-2*H*-pyran-2-yl-oxy)propyl)quinolin-2-yl)-10-methyl-10*H*-phenothiazines. The dihydropyranic ring its open and quinoline system become aromatic. Compared with compound **15** the obtained compounds have a 3,4-dihydro-2*H*-pyran system linked by oxygen-pyranic bond.



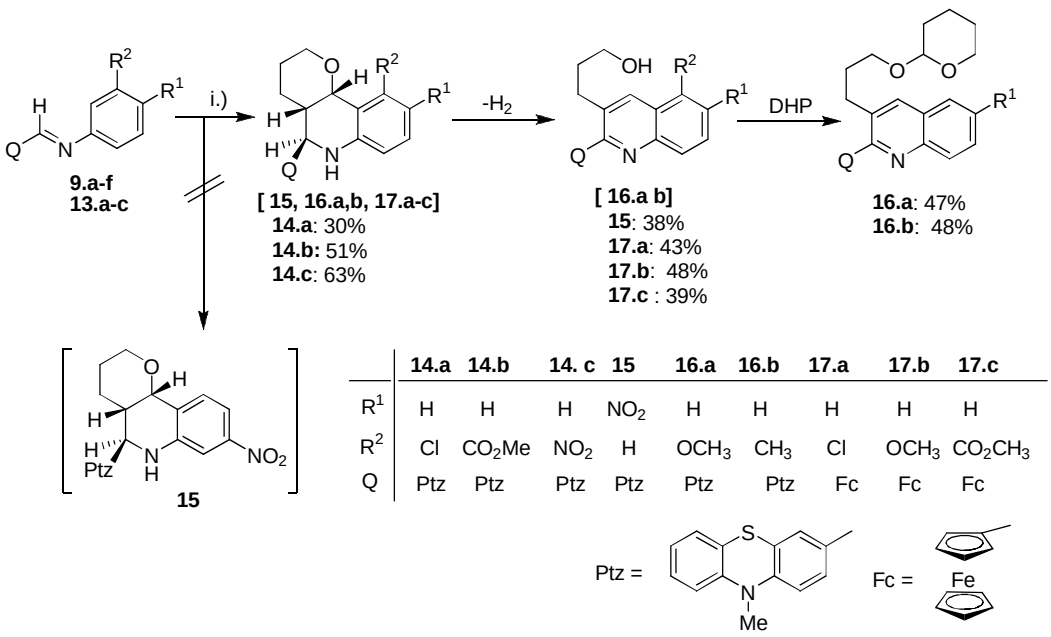
Scheme 2.20 Synthesis of compounds 16.a,b by microwave-assisted cycloaddition.

Ferrocene **13.a-b** Schiff bases condensation with 3,4-dihydro-2*H*-pyran by microwave activation led to compounds **17.a-c.** The quinolinic system become aromatic, the dihydropyran ring opened resulting the 1-propanol quinolinic derivatives.



Scheme 2.21 Synthesis of compounds **17.a-c** by microwave assisted cycloaddition.

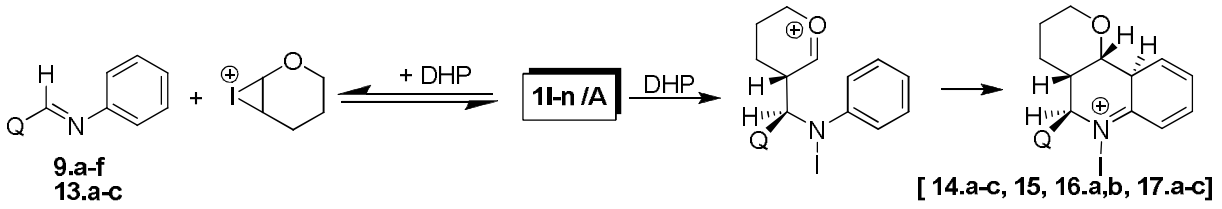
In order to disclose the characteristic substituent-dependence experimentally observed for cycloadditions and subsequent aromatisation of the quinoline moiety comparative DFT calculations were carried out on appropriately selected models at B3LYP level of theory using DGZVP basis set (Scheme 2.22).



	14.a	14.b	14. c	15	16.a	16.b	17.a	17.b	17.c
R^1	H	H	H	NO_2	H	H	H	H	H
R^2	Cl	CO_2Me	NO_2	H	OCH_3	CH_3	Cl	OCH_3	CO_2CH_3
Q	Ptz	Ptz	Ptz	Ptz	Ptz	Ptz	Fc	Fc	Fc

i.) DHP, MeCN, I_2 (1 mol%), MW, 80°C, 0.5 h pentru **14-16** si 1 h pentru **17.a-c**.

Scheme 2.22 Microwave-assisted [4+2] cycloadditions of phenothiazinyl- and ferrocenyl Schiff bases with DHP catalyzed by iodine.



pentru **9.a-f, 13.a-c, fenil** + DHP → **14.a-c, 15, 16.a,b 17.a-c** ΔE(**fenil**) = + 5.58 kcal/mol; ΔE(**PTZ**) = + 13.30 kcal/mol; ΔE(**Fc**) = + 25.53 kcal/mol

Scheme 2.23 Proposed mechanism of iodine-catalyzed cycloaddition reactions of activated model imines **1l-n/A** and the energetics of the first step calculated by B3LYP/DGZVP method.

Table 2.9 Global and local reactivity indices for the optimized structures[a] of activated model imines **1g/A**, **1d/B**, **1l-n/A** and **1l-n/B** (Figure 1) obtained by B3LYP/DGZVP calculations.

	ε_{HOMO} (eV)	ε_{LUMO} (eV)	μ (eV)	η (eV)	ε_{LUMO+1} (eV)	Σc^2_{LUMO} on C=N	Σc^2_{LUMO+1} on C=N	ρ(NBO) on C=N
1g/A	–8.52	–6.53	–7.53	0.95	–5.93	0.0202	0.3320	0.215
1d/B	–4.87	–3.81	–4.34	0.53	–2.04	0.2810	0.0125	0.157
1l/A	–10.67	–7.18	–8.93	1.75	–6.69	0.0206	0.3820	0.259
1l/B	–10.50	–6.94	–8.72	1.78	–4.49	0.3779	0.0066	0.246
1m/A	–8.46	–6.45	–7.46	1.00	–5.93	0.0241	0.3308	0.217
1m/B	–8.52	–6.15	–7.34	1.19	–4.19	0.3302	0.0174	0.204
1n/A	–9.33	–6.78	–8.50	1.28	–5.90	0.0220	0.4920	0.228
1n/B	–9.41	–6.18	–7.80	1.62	–4.19	0.4750	0.0142	0.222

[a] Interplanar angle (Θ [°]) between the imine- and N-phenyl moieties: 88.2 (**1g/A**); 8.6 (**1d/B**); 80.8 (**1l/A**); 22.5 (**1l/B**); 89.2 (**1m/A**); 23.6 (**1m/B**); 71.9 (**1n/A**); 20.9 (**1n/B**).

In each case the geometry optimization was followed by the calculation of the energy and population of frontier orbitals HOMO, LUMO and LUMO+1. Besides global molecular reactivity indices such as electronic chemical potential [$\mu=(E_{HOMO}+ E_{LUMO})/2$] and chemical hardness [$\mu=(E_{LUMO} - E_{HOMO})/2$] local reactivity indices on the imino carbon atom such as fractional electron deficiency of the available acceptor orbitals (Σc^2_{LUMO} and Σc^2_{LUMO+1}) as well as natural charge [ρ(NBO)] are also listed in table 2.9. Contrary to the experimental findings comparison of reactivity indices μ and Σc^2_{LUMO+1} and atomic charges calculated for **1m/A** and **1n/A** (Table 2.9) would lead to a conclusion that the ferrocene-containing iodoiminium ion is more reactive than the phenothiazinyl-substituted ion. The experimentally observed decreased reactivity of ferrocenylimines (reaction time: 1h) relative to that of phenothiazinyl analogues (reaction time: 0.5h) can be attributed to the unfavourable energetics of the addition step with DHP as demonstrated on model reactions **1l̃n/A** → **6l̃n** by means of B3LYP/DGZVP method (Scheme 2.23). The order of calculated energetics seems to correlate with the electron-donating ability of the Q-substituents and the experimental observations pointing to the significantly decreased reactivity of **1n/A** stabilized by the highly electron-donating ferrocenyl group (ΔE=25.53 kcal/mol). This stabilization is probably associated with the bonding overlap between the iron centre and the imino carbon atom as clearly discernible on the contour plot of the HOMO shown on Figure 2.15

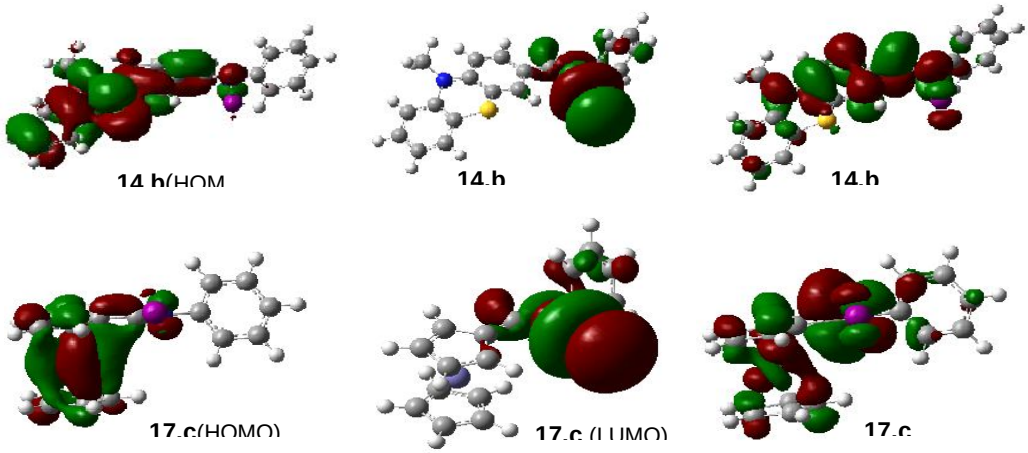
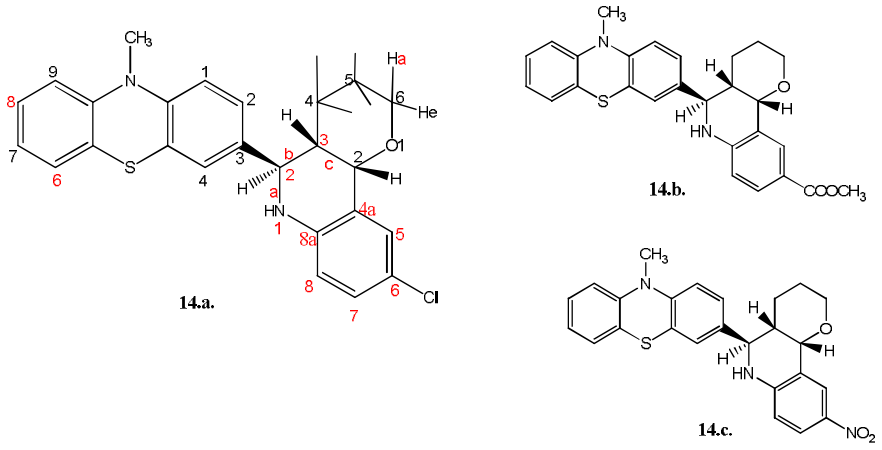


Figure 2.15 Contour plot of frontier MO's of iodoiminium ions for compounds **14.b, 17.c**

2.3.2 NMR spectra study

Quinoline-phenothiazine derivatives **14.a, b, c** has a rigid structure with the phenothiazinyl group in equatorial position. This assertion is supported by NMR spectra analysis. In ^{1}H-NMR spectra separate signals are observed for axial and equatorial protons for positions 1, 5, 7, 8, 9, 10 of quinoline system. If the structure could be mobile quinoline system (with two conformers in equilibrium and in equivalent proportions), ^{1}H-NMR spectrum should show single signals (singlet) for axial and equatorial protons for positions 1, 5, 7, 8, 9, 10. It is also apparent that the Schiff base azomethine signal, raw material, from 8,30 ppm in ^{1}H-NMR spectrum disappears, and the NH proton signal appears at approximately δ= 3,95 ppm.

Given the analysis of NMR spectras, we propose the following structures for 14.a-c compounds (Scheme 2.25).



Scheme 2.25 Structure of compounds **14.a-c.**

In ^{1}H-NMR spectrum for compounds **14.a, b, c** are two different areas in which appears the signals for the aliphatic quinoline protons and methyl protons of phenothiazine in the aliphatic part 5,39 to 1,00 ppm while for aromatic protons of phenothiazine and quinoline from 8,20 to 7,25 ppm. After the NMR spectra analysis we can say the following:

a. The axial and equatorial protons of the same carbon atom in the spectrum have distinct signals
b. axial protons in positions 6, 5, 4 shows in the spectrum multiplets (d, t, q), as well as equatorial protons in positions 6, 5, 4.
c. Axial protons in positions 2, 2 pyrane being situated near two heteroatoms (N, O) in spectrum appear as doublets and are most upshifted protons of the quinoline system.

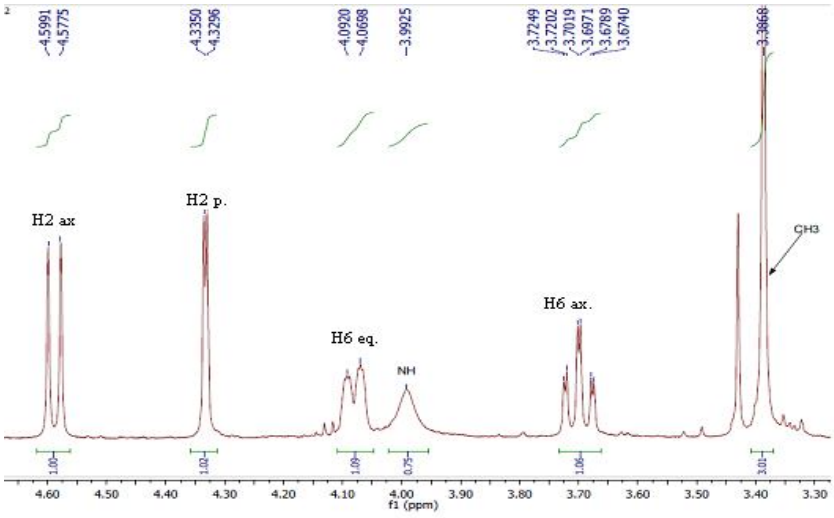


Figure 2.17.a ^{1}H NMR spectra, details for the aliphatic part for compound **14.a** in $CDCl_3$, at 500MHz.

Assign signals of carbon atoms in compounds 14.a-c was conducted based on ^{13}C-NMR spectra (Figure 2.22.a), DEPT 135and 2D (^{1}H-^{13}C) HMQC and HMBC.

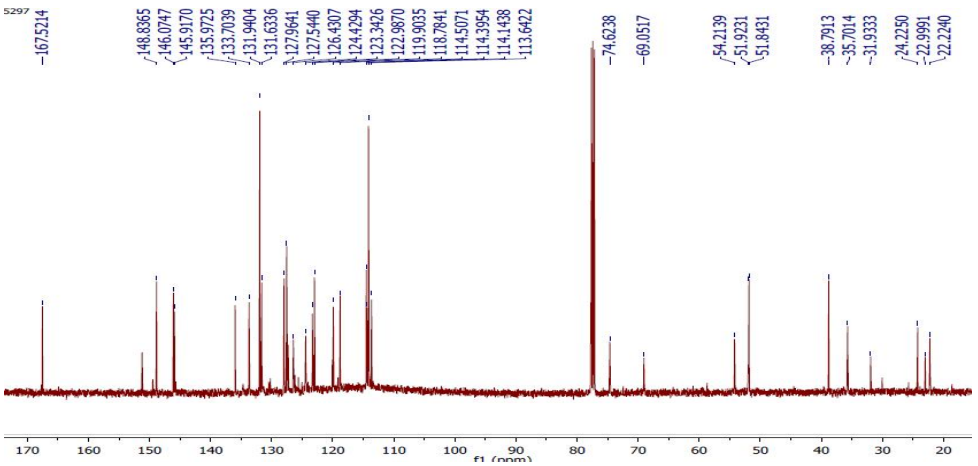
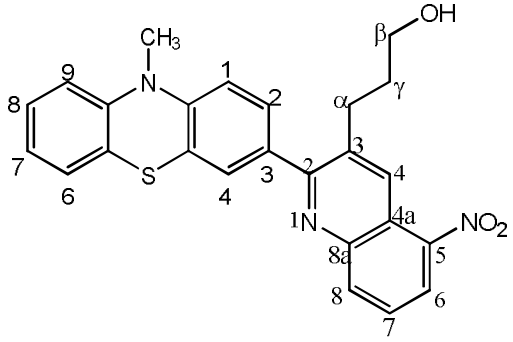


Figure 2.22.a ^{13}C RMN spectra for the compound **14.c** at 500 MHz, in $CDCl_3$

In the spectrum of compound 15 no signal can be seen for axial and equatorial protons. In ^{1}H-NMR spectrum for methylene protons of alkyl chain is observed distinct signals. The methylene group γ–CH_2, linked directly to hydroxyl group is the most downshifted appears as triplet at value δ= 3,46 ppm, with coupling constant $J_{CH2\text{-}\gamma CH2}$= 6,10 Hz, the α-$CH_2$ methylene group is linked to the aromatic quinolinic system and appear as a triplet at value δ= 2,85 ppm, with coupling constant $J_{\alpha CH2\text{-}\beta CH2}$= 7,70 Hz. Given the analysis of NMR spectra, we propose the following structure for compound **15** (Scheme 2.26).



Scheme 2.26 Proposed structures for the compound **15**

In the NMR spectra of compound **15** can be distinguished two areas: aromatic parts for quinoline and phenothiazine protons 8,20 to 7,25 ppm and the aliphatic part for the methylene group from phenothiazine and the alkyl chain protons from 3,70 to 1,60 ppm (Figure 2.23.b).

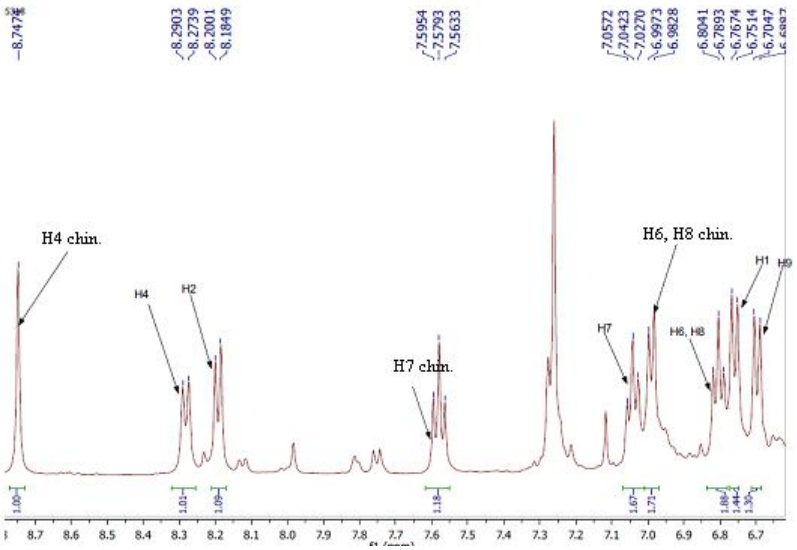
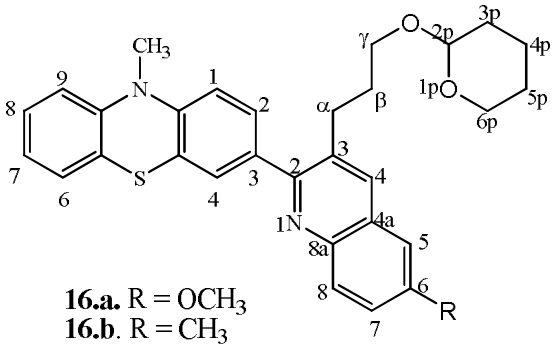


Figure 2.23.b ^{1}H RMN spectra details for the aliphatic part for compound **15** at 500MHz, in $CDCl_3$.

The γ–CH_2 group, linked directly to the oxygen atom is upshifted, appears as a triplet at δ= 3,67 ppm whit coupling constant $J_{\beta CH2\text{-}\gamma CH2}$= 8,8 Hz, the β–$CH_2$ group appear at δ= 3,33 ppm the protons from α-CH_2 appears as a multiplet at δ= 2,90 ppm whit coupling constant $J_{\alpha CH2\text{-}\beta CH2}$= 14,8 Hz. It may be note that azomethine signal from phenothiazine Schiff base from 8,30 ppm in ^{1}H NMR spectrum disappears, in comparison with the spectra of compounds **14.a-c** were NH proton signal appears in the spectrum of compounds **16.a, b** is not present. It is noteworthy that the singlet at δ= 7.94 ppm value has been at attributed to H4 proton of the quinoline system (Figure 2.26.a.b).

Given the analysis of NMR spectra, we propose the following structure for compounds 16.a -b.



16.a. R = OCH_3
16.b. R = CH_3

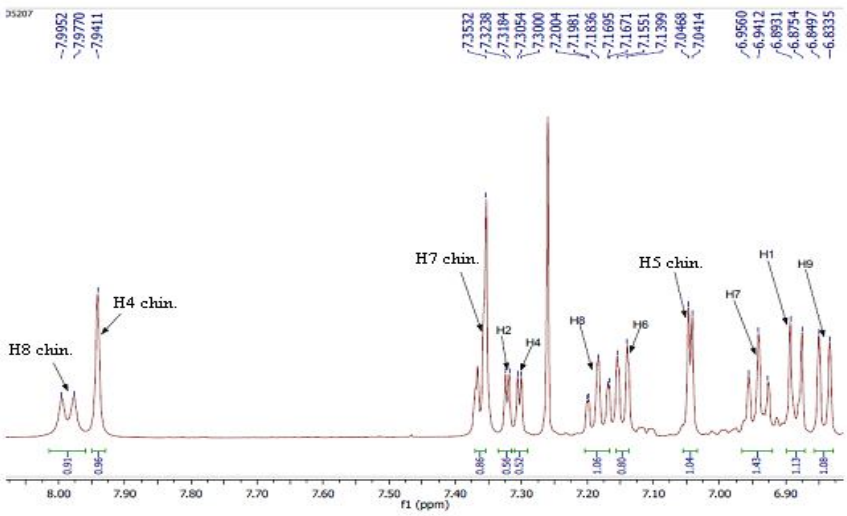


Figure 2.26.a ^{1}H NMR spectra details for the aromatic part for compound **16.a**, detaliu partea at 500MHz, in $CDCl_3$

The chemical shifts for carbon of compounds **16.a, b** are presented in table 2.12.

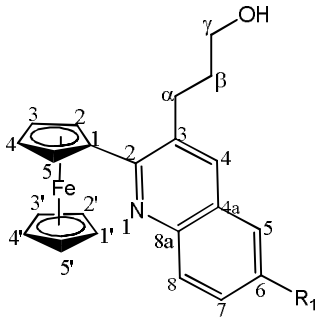
Table 2.12 The chemical shifts for carbons at 500MHz in $CDCl_3$.

C 16.a	**C_9**	**C_1**	**C_7**	**C_2**	**C_4**	**C_6**	**C_8**
δ	113,4	113,8	122,3	126,9	125,0	127,4	127,2
C	**C_{5a}**	**C_{4a}**	**C_3**	**C_{9a}**	**C_{10a}**	**N-CH_3**	**$CH_2\alpha$**
δ	123,3	123,4	133,3	145,6	146,2	35,2	29,4
C	**$CH_2\beta$**	**$CH_2\gamma$**	**C_{2chin}**	**C_{8achin}**	**C_{5chin}**	**C_{4chin}**	**C_{3chin}**
δ	30,4	66,3	157,5	145,4	126,9	133,4	128,3
C	**C_{6chin}**	**C_{7chin}**	**C_{8chin}**	**O-CH_3**	**C_2p**	**C_6p**	
δ	140,8	126,9	129,2	55,3	104,2	62,1	
C	**C_5p**	**C_4p**	**C_3p**				
δ	25,2	19,3	30,3				
C 16.b	**C_9**	**C_1**	**C_7**	**C_2**	**C_4**	**C_6**	**C_8**
δ	113,5	113,9	122,4	125,6	122,4	127,4	127,0
C	**C_{5a}**	**C_{4a}**	**C_3**	**C_{9a}**	**C_{10a}**	**N-CH_3**	**$CH_2\alpha$**

δ	123,3	123,4	133,2	145,4	144,7	35,3	29,5
C	**$CH_2\beta$**	**$CH_2\gamma$**	**C_{2chin}**	**C_{8achin}**	**C_{4achin}**	**C_{4chin}**	**C_{3chin}**
δ	30,4	66,3	158,4	145,6	127,0	133,2	128,1
C	**C_{5chin}**	**C_{6chin}**	**C_{7chin}**	**C_{8chin}**	**CH_3**	**C_2p**	**C_6p**
δ	126,9	142,8	127,2	129,4	19,4	98,6	62,1
C	**C_5p**	**C_4p**	**C_3p**				
δ	25,3	19,4	30,5				

The reaction of Schiff bases **13.a-c** with 3,4-dihidro-2*H*-pyran as describe above leading to compounds **17.a-c.** In the spectrum of compounds **17.a, b, c** the signals for axial and equatorial protons are not present neither the signals for protons of dihydropyranic cycle. In ^{1}H-NMR spectra may be observed the signals from alkyl chain, 6 protons from 3 methylene groups. The γ–CH_2 group, linked directly to the oxygen atom is upshifted, appears as a triplet at δ= 3,78 ppm, with coupling constant $J_{\beta CH2\text{-}\gamma CH2}$= 11 Hz, the protons from α-CH_2 appears as a triplet at value δ= 3,20 ppm, with coupling constant $J_{\alpha CH2\text{-}\beta CH2}$= 14 Hz. The β-$CH_2$ protons are the most upshifted and appears as a quintet at value δ= 1,96 ppm, with coupling constant between α and β methyl is *J*= 14 Hz.

Given the analysis of NMR spectra, we propose the following structures for compounds **17.a, b, c.**



17a R_1= Cl
17b R_1= OCH_3
17c R_1= $COOCH_3$

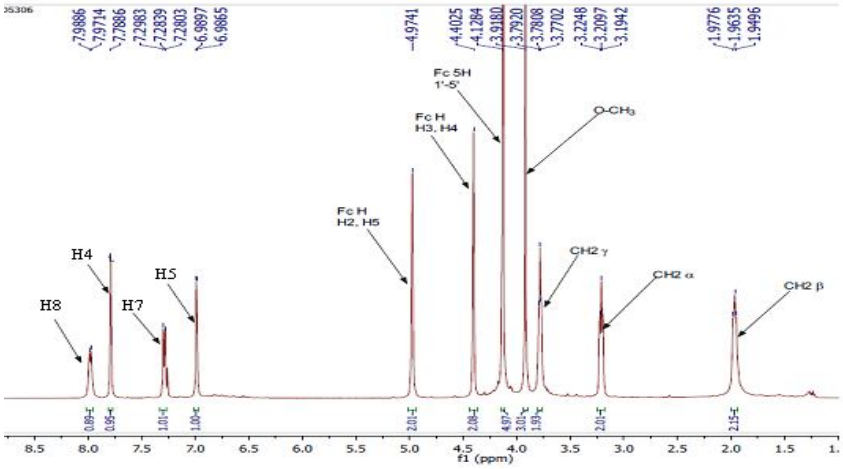


Figure 2.29 ^{1}H NMR spectra for compound **17.c,** in $CDCl_3$, at 500MHz.

Assignments of carbon atoms for compounds **17.a- c** are based on ^{13}C-RMN, DEPT and 2D (^{1}H-^{13}C) HMQC and HMBC (Figure 2.30.a, b).

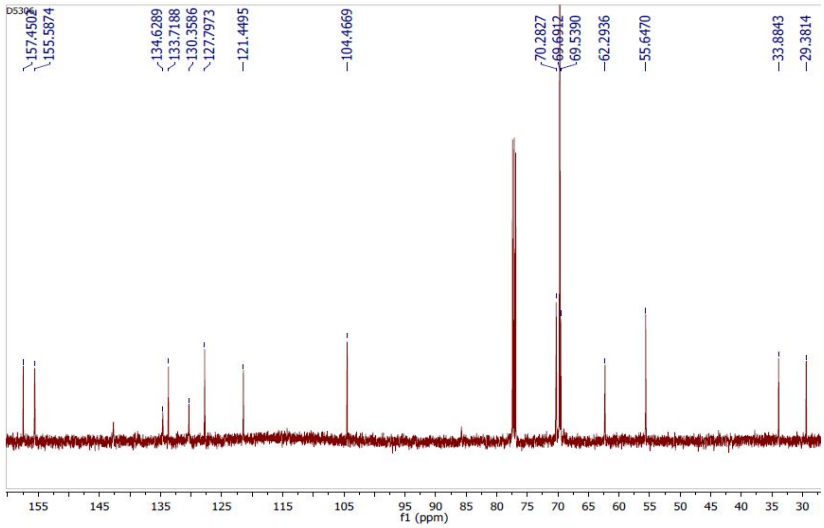


Figure 2.30.a ^{13}C NMR spectra for compound **17.c,** in $CDCl_3$, at 500MHz.

2.3.4 Study of UV-Vis absorption spectras of cycloadition compounds

To highlight the optical properties due to the extended conjugation between the phenothiazine and quinoline system, have been studied the UV-Vis spectras for synthesized compounds 9.d**, 13.c**, **14.a-c, 15, 16.a-b** and **17.a-c**.

Small bathochromic shift can be notice for absorption maxima for corresponding π-π* electronic transition explained by the effect of heteroatom +E electromer, which presume the

extension of conjugated system. Small shifts can be correlated with the nature of auxochrome groups attached in position *meta* or *para* of the quinoline system.

Tabel 2.13 Absorption maxima and extinction coefficients calculated for the compounds synthesized.

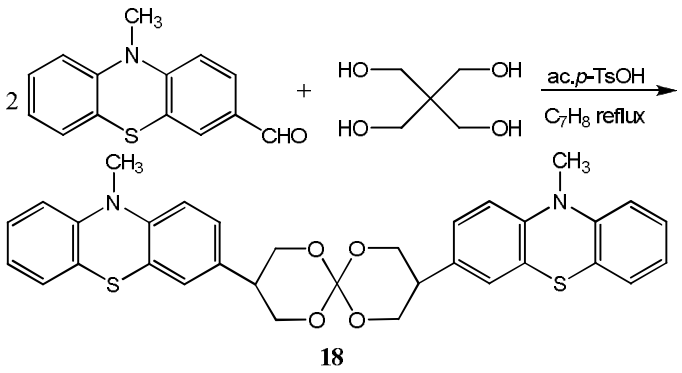
Comp.	**UV-Vis (nm), ε ($L \cdot mol^{-1} \cdot cm^{-1}$)$^{\pm}$**
9.d	273 (55881); 386 (897)
13.c	271 (227300); 468 (1421)
14.a	229 (28940); 259 (39754)
14.b	275 (175105)
14.c	258 (58982); 379 (8145)
15	269 (174466)
16.a	229 (36656); 261 (46009); 333 (9064)
16.b	270 (229712)
17.a	273 (473989); 380 (3864)
17.b	273 (489344)
17.c	274 (42360)

2.4 Phenothiazine dioxanes

2.4.1 Synthesis of phenothiazine dioxanes by microvawe irradiation

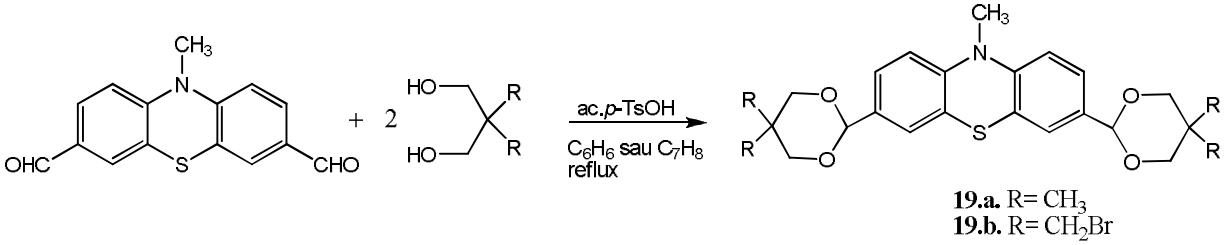
Synthesis of 1,3-dioxanes based on acetalization reaction, is a vast filed in literature. Acetalization reactions of 3,7-di substituted phenothiazine were done by activating in microwave under green chemistry conditions by changing the solvent tolen to a less toxic one. Table 2.15 presents the classical and microwave conditions. By microwave activation the reaction time was reduced substancially with classical method of acetalization.

From the reaction of 3-formyl-10-methyl phenothiazine with 2,2-bis(hydroximethyl)propan-1,3-diol using a molar ratio 2/1 were obtained spiran 18 (Scheme 2.30) **.** The reaction was studied with microwave activation (Table 2.34).



Scheme 2.30 Synthesis of spiran **18**

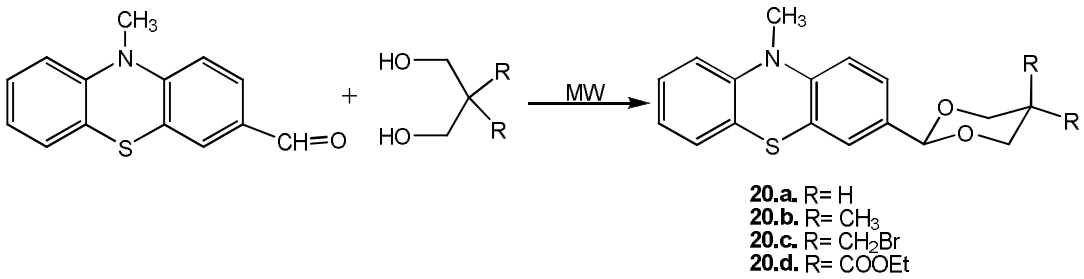
From the reaction of 3,7-diformyl-10-methyl-phenothiazine with 2,2-dibromo-propane-1 ,3-diol respectively with 2,2-bis (bromomethyl) propane-1 ,3-diol in the presence of acid p-toluene-sulfonic by azeotropic distillation using Dean-Stark separator, was obtained dioxane 19.a-b compounds, using a molar ratio diformyl-phenothiazine: diol 1/2. The reactions were monitorized by thin layer chromatography (eluent toluene: ethyl acetate 10/1) (Scheme 2.31).



Scheme 2.31 Synthesis of dioxane phenothiazine **19.a-b**.

Successive recrystallizations from toluene of compounds 19.a-b were isolated in pure crystalline form. The structures of obtained compounds were investigated using the 500MHz, NMR spectras ^{1}H RMN, COSY–45, ^{13}C-NMR and 2D-RMN, HMQC and HMBC.

Were studied and compared the acetalization reactions of 3-formyl-10-methyl-phenothiazine with 1,3-propanediol and 1,3-propanediol disubstituted by microwave irradiation in different solvents (Schema 2.32).



Scheme 2.32 Synthesis of compounds **20.a-d** by microwave irradiation

Reactions were carried out in quartz vessels using a microwave reactor type Synth 3000, the temperature inside the reaction vessel and internal pressure were continuously monitored.

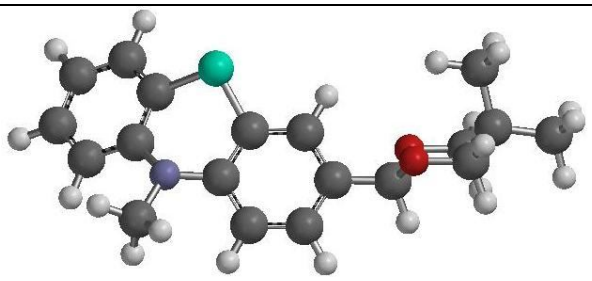
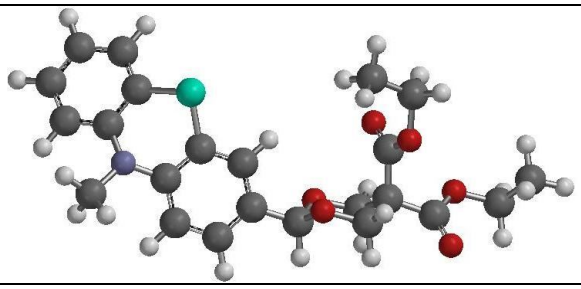
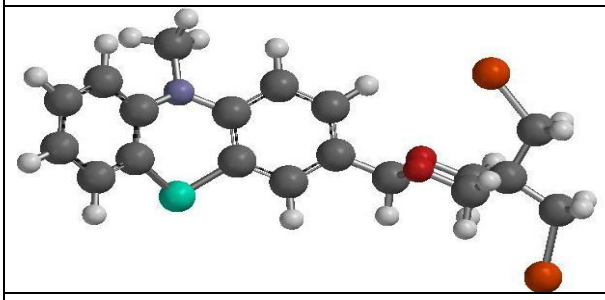
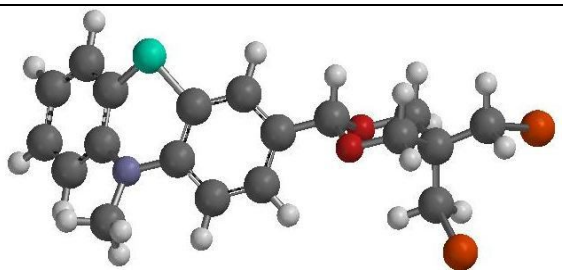
In table 2.15 is presented the results obtained at different reaction conditions (classic and activation by microwave irradiation) that have been applied. Synthesis by microwave irradiation requires a shorter reaction time; yields are considerably lower especially in the presence of toluene, which is a solvent with low absorption of microwave irradiation (dielectric loss value 0,096). The ethylene glycol is a solvent able to effectively absorb the microwave energy and thus ensure rapid heating of the reaction mixture (dielectric loss value 49.95). Better results were obtained in microwave with water as solvent by heating to 130-200°C for compounds **19.a-b**. In case of compound 18 with microwave irradiation in solvents PEG and water were achieved very good results.

Table 2.15 The obtained results at different reaction conditions (classic and MAOS)

Comp.	**Reaction time**		**Reaction temperature** °C		**Yield%**			
	Clasic [h]	MW [min]	Clasic	MW	Clasic Toluen	MW Toluen	MW PEG 400	MW Apă
18.	8	20	112	150	95	10	77	65
19.a	15	30	112	130	80	20	28	43
19.b	15	30	112	130	80	27	30	44
20.a	15	40	112	130	75	15	17	25
20.b	11	50	112	200	85	40	37	50
20.c	12	40	112	150	85	25	25	36
20.d	12	50	112	130	60	15	37	30

Conformational analysis of stereoisomers for compounds **20.b-d** and molecular modeling based on semi-empirical and DFT calculations (Figure 2.37). Minimum of energy for compounds was obtained by conformer optimization generated with Spartan '06[193] *Confanal* module and semi-empirical calculations (PM3) şi 6-31G(d) B3LYP DFT[194,195,196].

Figure 2.37 Conformers and heat of formation of dioxanes.

	
20.b H_f [kcal/mol] -840895.78	**20.d** H_f [kcal/mol] -4070412.49
	
20.c H_f [kcal/mol] -1126881.80	**20.c** H_f [kcal/mol] -1126881.80

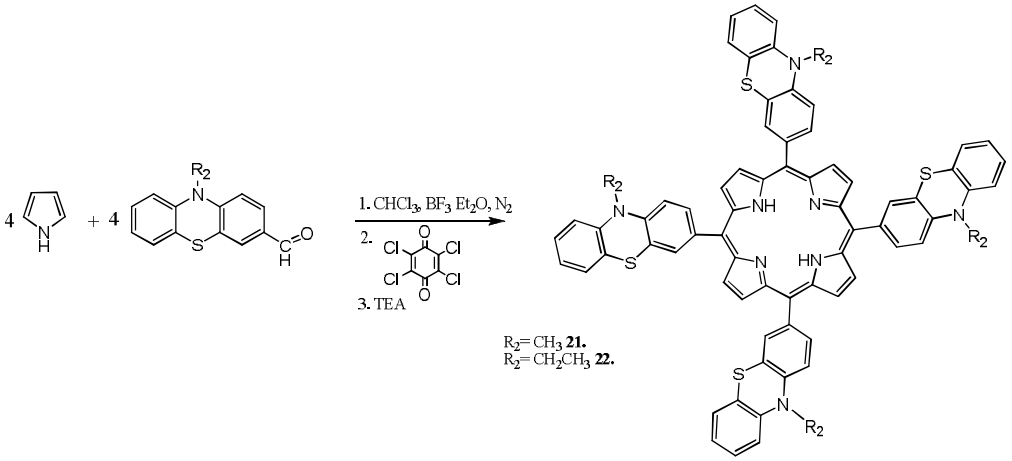
2.5 Porphyrins

2.5.1 Synthesis of porphyrins with phenothiazine units

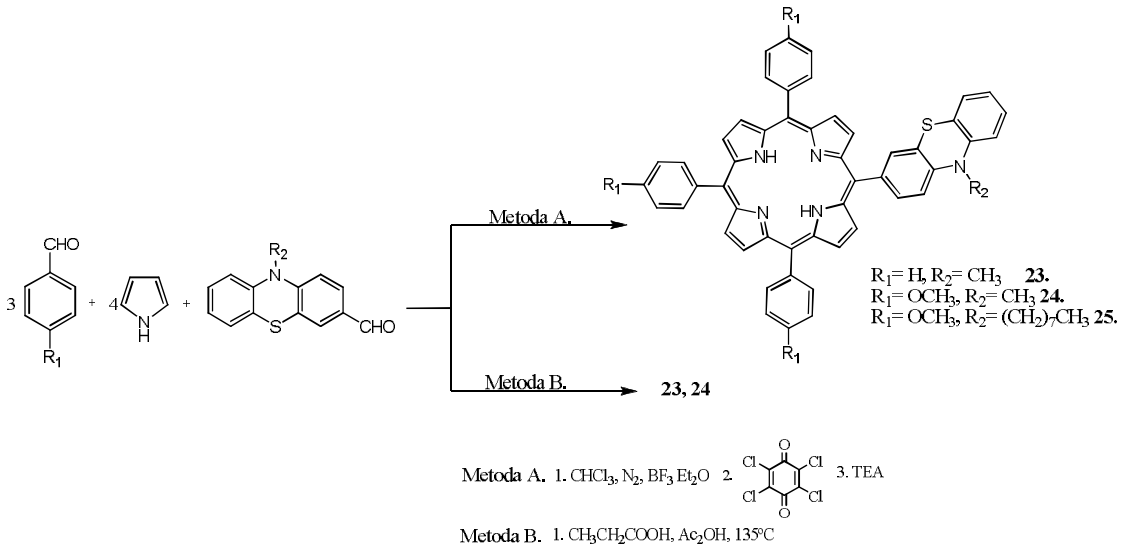
Porphyrins are macrocyclic molecules with rigid structure having aromatic character and many reaction centers. These compounds and structurally related substances (chlorine, bacteriochlorine and corine) have an important role in nature especially in the form of metal complexes: Fe, Cr and Mn. Synthetic chemistry of porphyrins is remarkable, research is currently focused on porphyrins which are steric impediments on one side of the molecule, with applications in stereoselective oxidation processes.

The first synthesis of tetra substituted meso-porphyrins was performed by Rothemund (1936) by heating in pyridine pyrrol with an aldehyde in a sealed tube at 150 ˚ C for 24 h. Studies by Adler and Longo[134, 135] had an important role in elucidating the processes underlying

the formation of porphyrins by co-condensation of pyrrol and aldehydes. From the reaction of 10-methyl-, 10-buthyl-phenothiazine whit pyrrol in chloroform in presence of $BF_3 \cdot (EtO)_2$, by oxidation with *p*-chloranil **26** and **27** compounds were obtained (Scheme 2.38).

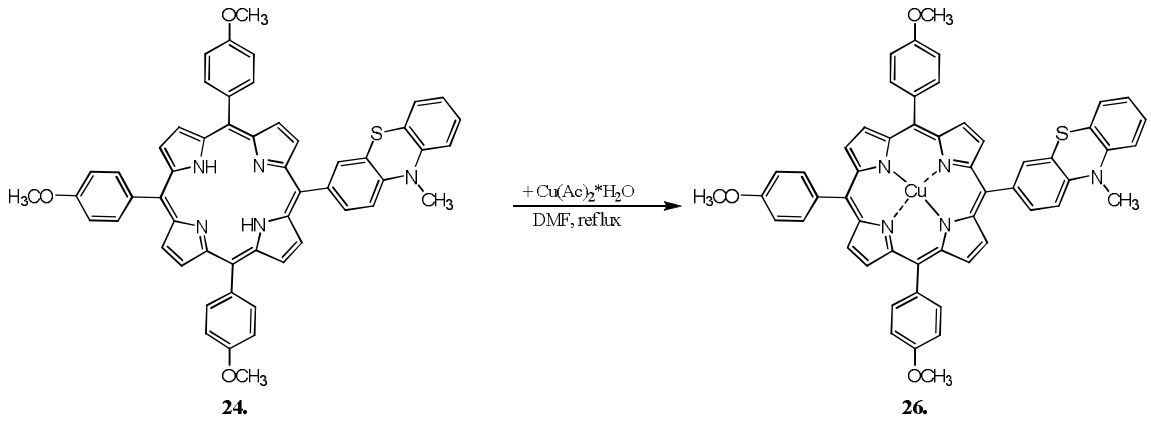


Scheme 2.38 Synthesis of **21, 22** compounds



Scheme 2.39 Synthesis of **23, 24, 25** compounds

In the synthesis of porphyrin complexes it started from compound **24**, using DMF (dimethylformamide) as solvent and $Cu(Ac)_2 \cdot H_2O$ (Scheme 2.40). The reaction was monitored by thin layer chromatography (eluent chloroform: petroleum ether 1: 0,5).



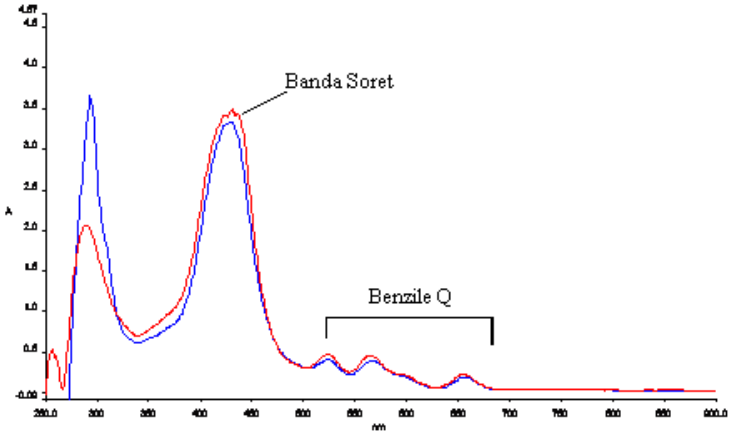
Scheme 2.40 Synthesis of porphyrin complexed with Cu **26**

2.5.2 Study of NMR IR, UV-vis, Fluorescence and mass spectras

Porphyrins are well known for their intense colors, which is a consequence of extended conjugation of the macrocycle, and their applications key.

In the UV-Vis spectra of porphyrins are two distinct areas: the purple region, a very intense absorption band known as the Soret band extinction coefficient of about $1x10^5$ M^{-1} cm^{-1}.

For compounds **21-26** have been registered UV-Vis spectras fluorescence respectively (Table 2.17). Diprotonate forms, free metal and metaloporphyrins have a maximum absorption around 417 nm, the Soret band which is characteristic for the macrocyclic system. Outside of the Soret band in UV-Vis are 4 bands Q(IV-I), la 515 (IV), 545 (III), 590 (II) and 646 (I). By changing the *meso* substituents the Soret band remains constants the exchange may be notice in Q bands. (Figure 2.44, 2.45).



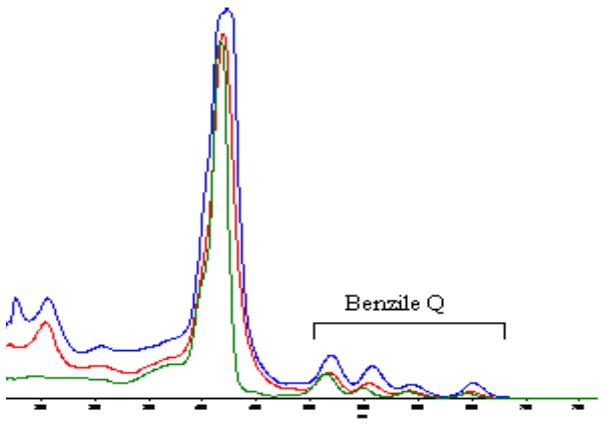


Fig. 2 44 UV-Vis spectras of compounds **21, 22**

Fig. 2.45 UV-Vis spectras of **23, 24, 25**

Table 2.17 Absorptions maximum of synthesized porphyrins

Compus	Banda Soret [nm][a]	Banda Q_4 [nm][a]	Banda Q_3 [nm][a]	Banda Q_2 [nm][a]	Banda Q_1 [nm][a]	λ_{abs} [nm][a]
TPP	419	514	540	590	650	-
21	428	523	565	-	655	285
22	432	524	567	-	656	290
23	419	517	554	591	648	-
24	422	518	555	593	649	-
25	422	519	557	593	651	-
26	422	-	540	-	-	-

The UV-Vis spectras were recorded in CH_2Cl_2

In the case of compounds **21-26** the excitation wavelength was 520nm according to literature (Figure 2.47)[200, 201].

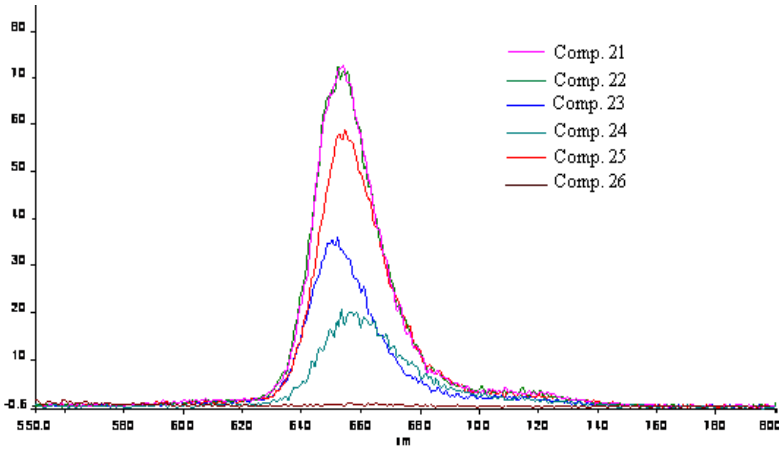


Figure 2.47 Fluorescence spectras of **21, 22, 23, 24, 25 and 26** compounds

In table 2.18 are presented the absorption and emission maximum, the quantum yield and the Stokes shifts for the tetrapyrolic compounds **21-25**.

Table 2.18 Emission and absorptions maximum, quantum yield and Stokes shifts of synthesized porphyrins.

Comp.	Absorption $\lambda_{max,abs}$ [nm][a]	Emission $\lambda_{max,em}$ [nm][a]	Quantum yield [%][b]	Stokes shifts (cm^{-1})
TPP	514	**649**, 717	0,11	4047
21	518	660	0,230	3564
22	518	653	0,241	3830
23	517	646	0,112	4005
24	518	654	0,174	4015
25	520	647	0,095	3445

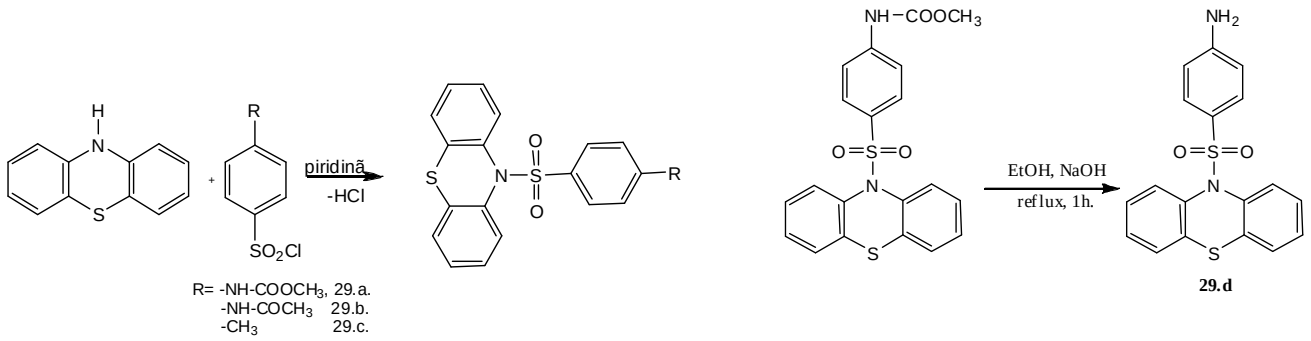
[a] spectras were recorded in CH_2Cl_2 [b] Determinated with TPP as standard with 0,11% quantum yield.

2.6 Phenothiazine sulphonamide

2.6.1 Synthesis of phenothiazine sulphonamide

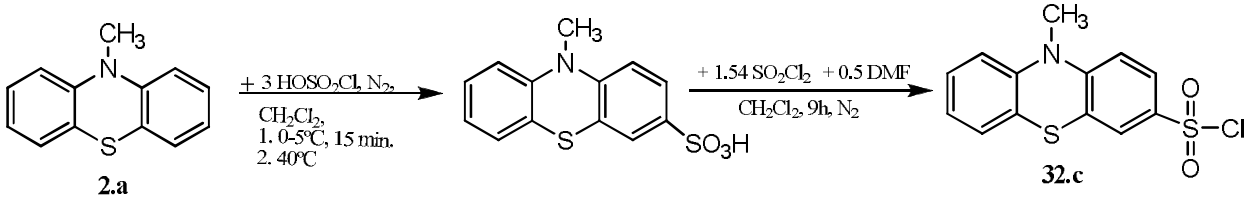
Sulfonamide synthesis based on a condensation reaction, is a vast filed in literature. In literature chapter (chapter 1.6) were presented the current state of research on the synthesis of phenothiazine sulfonamide, respectively the performed structural studies

Among the possible variants of synthesis of phenothiazine sulfonamides, after preliminary testing of several methods was chosen condensation of amine (phenothiazine) with chlorosulfonated aromatic compounds in a polar solvent (acetone, THF, anhydrous alcohol, pyridine), at reflux. In this way, the yield is high, but the reaction times are large and require repeated recrystallization.



Scheme 2.42 Synthesis of **29.a-d** compounds

By chlorosulphonation of 10-methyl-*10H*- phenothiazine with chlorosulphonic acid and thionyl chloride as describe above resulting the 10-methyl-10*H*-phenothiazine-3-sulphonic acid **32.c** (Figure 2.43).



Scheme 2.43 Synthesis of compound **32.c**

The synthesis of compounds **29.a- c** was studied with microwave activation on different media and solvents. Identification of reaction products was done by thin layer chromatography, using as standards the compounds prepared by classical method, melting point and mass spectrometry. For the synthesis of sulfonamide **29.a- c, 30** were used a special microwave reactor CEM Discovery LabMate.

In table 2.19 are compared the yields and reaction times for sulphonamide by classical and microwave activation.

Table 2.19 Conditions used and results obtained at different reaction conditions (classic and activated by microwave irradiation)

Comp.	Solvent/ Solid support MW	Reaction time		Yield	
		Classic [h]	Microwave [min]	Classic [%]	Microwave [%]
29.a	Pyridine	24	60	67	45
29.b	Pyridine	24	60	72	47
29.c	Pyridine	24	60	87	75
29.a	Al_2O_3 basic	-	30	-	48
29.b	Al_2O_3 basic	-	30	-	50
29.c	Al_2O_3 basic	-	30	-	55
29.a	EtOH	24	60	15	10 >
29.b	EtOH	24	60	20	10 >
29.c	EtOH	24	60	17	10 >
30	DMSO	24	30	68	25
30	Pyridine	24	30	-	15

To predict pharmacological properties of the synthesized compounds were used the *PASS* program. Interpretation of results is based on the values of Pa (predicted activity).

The results show that substances **29.c** and **d** have increased biological activity as: fungicides and neuroprotective, compound **32.c** have also biological activity as antidepressant.

4 Conclusions

The thesis presents the synthesis and structural investigation of 72 compounds, of which 39 are new substances, of the following classes of compounds:

- 6 compounds (**2.a-f**) from alkylated phenothiazine, in which 1 new, and 8 compounds (**3.a-f, 4, 5, 6, 7**) mono-, and di- formyl derivatives in which 1 new, and 1 N-acyl phenothiazine (**8**).
- 15 compounds (**9.a-h, 10.a-c, 11, 12.a-c)** from phenothiazine Schiff base class of which 13 new, 4 compounds (**13.a-d)** from Schiff base class with ferrocene units of which 1 new.
- 9 compounds from quinolines class of which 6 substances (**14.a-c, 15, 16.a-b**) with phenothiazine units and 3 substances (**17.a-17.c)** with ferrocene. A new synthetic method has been developed, by MAOS (Microwave Activation Organic Synthesis).
- 6 compounds (**19.a-19.b, 20.a-d)** from dioxane class with phenothiazine units, and 1 new compound (**18**) spiran with phenothiazine units.
- There have been aimed to optimizing the reaction conditions in spirit of green chemistry by introducing solvents (eg. PEG 400) water use at high temperatures.
- 6 new compounds (**21, 22, 23, 24, 25)** from class of porphyrins with phenothiazine units and one new complex with Cu (**26**).
- 14 compounds from class of sulphonamide (**29.a-d, 30, 31.a-b, 32.a-c, 33, 34.a-b**) of which 7 new substances.
- The synthesized compounds are testing ‘’in vivo’’ to determine the pharmacological properties. The predictions were made in the PASS program, which has shown 50% more likely biological activities
- In case of thermal activated reactions as an alternative convective heating technique was used MAOS (Microwave Activation Organic Synthesis), applying the technique of irradiation in solvent (ACN, etc) or ‘’dry media’’ technique in the presence or absence of solid support.

Full structural characterization of synthesized compounds was achieved by:

- High resolution NMR (300, 400, 500 MHz) spectras 1D (^{1}H-RMN, ^{13}C-RMN, DEPT) and 2D ((^{1}H-^{1}H) COSY, (^{1}H-^{13}C) HMQC and (^{1}H-^{13}C) HMBC).

- Mass spectrometry (EI, CI and APCI)
- IR spectrometry
- Elemental analysis
- The optical properties were studied based on UV-Vis and fluorescence spectras and by calculating the quantum yield and Stokes shifts.
- For compounds from strucural classes of quinoline, dioxane and porphyrins were modeled and calculated the quantum parameters using *Spartan* program, with DFT (PM3), 6-31G(d) B3LYP method, respectively *Gaussian* method B3LYP/DGZVP method.
- The results presented in this Ph.D. thesis were published in two article published and one articles submitted for publication [174], and one poster presentation at international conference.

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