

N-alkylphenothiazines – synthesis, structure and application as ligands in metal complexes

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Abstract

Phenothiazines are a large group of heterocyclic, aromatic molecules with nitrogen and sulphur between two benzene rings. Their derivatives, *N*-alkylphenothiazines have substituent on heterocyclic nitrogen atom which gives them different properties. Also, a series of these molecules have substitution on carbon atom at place 2 of phenothiazine benzene ring. Alkylphenothiazines contain aminoalkyl substituent and their alkyl, acyl and sulphonil derivatives, as well as monocyclic and bicyclic heterocycles attached at thiazine nitrogen atom or directly linked to benzene ring. The *N*-alkylphenothiazines have been known as antipsychotic drugs, but they also possess antibacterial, antifungal, anticancer activity, and ability to react with macromolecules and to coordinate to the metals. Metal complexes with *N*-alkylphenothiazines are biological active compounds with different antimicrobial activities and cytotoxic effect against tumor cell lines. The large field of application of *N*-alkylphenothiazines is very attractive in terms of synthesis of new related derivatives, metal complexes, studying their properties and applications. This article presents a review of the literature and a contemporary view at *N*-alkylphenothiazines – their synthesis and application, as well as their metal complexes which have promising biological effects.

Keywords: *N*-alkylphenothiazines, antipsychotic drugs, anticancer, antibacterial.

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The *N*-alkylphenothiazines are heterocyclic aromatic compounds with nitrogen and sulphur atoms and substituents on aromatic ring and nitrogen. The central place of these molecules is a molecule of 10*H*-dibenzo-1,4-thiazine, phenothiazine (Fig. 1) known more than a hundred years [1].

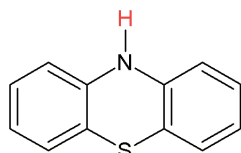


Figure 1. Structure of the 10*H*-dibenzo-1,4-thiazine, phenothiazine.

The first phenothiazines, thionine and methylene blue (Fig. 2) were synthesized in reaction of *p*-phenylenediamine/*p*-aminodimethylaniline with sulphur in hydrochloric acid solution, in the middle of the 19th century [2]. In that time, these compounds with phenothiazine ring had an application in aniline dye industry.

After 20 years, the parent compound, 10*H*-dibenzo-1,4-thiazine was obtained in reaction of diphenylamine

with sulphur by Berntsen (Scheme 1). Until today, more than 5000 phenothiazine derivatives were synthesized with wide range of application [1].

Phenothiazines have many different applications, from industry to medicine. As biological active compounds, these molecules have antipsychotic, antiemetic, anthelmintic, antibacterial, antifungal and insecticidal properties, and they also represent promising anticancer drugs [1–8]. These activities represent the result of the interaction of phenothiazines with biological systems through their pharmacophoric substituent, the multicyclic ring system (π - π interaction, intercalation in DNA) or the lipophilic character allowing the penetration through the biological membranes. The activities were examined by using various biological systems such as cell lines, bacteria, viruses, parasites, laboratory mice, rats and rabbits, and monolayer and bilayer membranes [2]. The *N*-alkylphenothiazines as ligands are used in metal complexes, but biological properties of these complexes are investigated in recent years. This review shows current importance of the *N*-alkylphenothiazines and reveals their metal complexes as potent pharmacological group which can be a rich source of new compounds having desirable biological activities.

Structure of *N*-alkylphenothiazines

Most often, phenothiazines have substituted hydrogen atoms at position 2 (with some small molecule)

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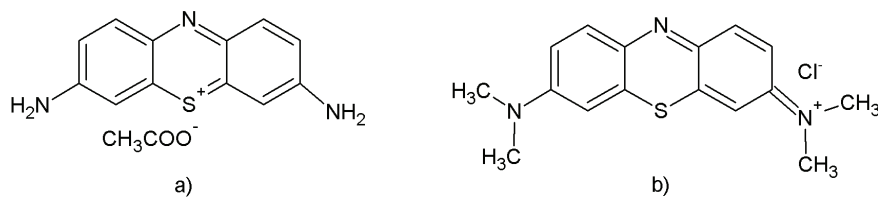
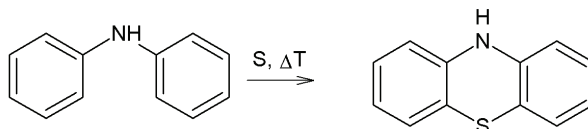


Figure 2. Structure of the 3,7-diamino-5-phenothiazinium acetate (thionine) and 3,7-bis(dimethylamino)phenazathionium chloride (methylene blue).



Scheme 1. Synthesis of 10-H-dibenzo-1,4-thiazine (phenothiazine).

and position 10 (with aminoalkyl groups). At this point, N-alkylphenothiazines (Figure 3) are classified into three groups depending on the type of the substitution on the nitrogen atom of phenothiazine ring [9,10]. First group contains phenothiazines with an aliphatic side chain, then the second group with the piperidine, and the third group contains piperazine derivatives (Table 1).

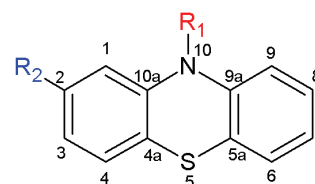


Figure 3. General structure of N-alkylphenothiazine.

Table 1. N-alkylphenothiazines classification depends on the type of substituent on N-10 and C-2 atoms

Compound	R ₁	R ₂
Phenothiazines with an aliphatic side chain		
Promazine (Pr)	(CH ₂) ₃ -N(CH ₃) ₂	H
Chlorpromazine (Cpz)	(CH ₂) ₃ -N(CH ₃) ₂	Cl
Triflupromazine (Tm)	(CH ₂) ₃ -N(CH ₃) ₂	CF ₃
Methotrimeprazine (Mtm)	CH ₂ -CH(CH ₃)-N(CH ₃) ₂	OCH ₃
Phenothiazines with a piperidine side chain		
Thioridazine (Tr)		S(CH ₃)
Mesoridazine (Mr)		SO(CH ₃)
Sulphoridazine (Sr)		OSO(CH ₃)
Phenothiazines with a piperazine side chain		
Prochlorperazine (Pc)		Cl
Trifluoperazine (Tf)		CF ₃
Perphenazine (Pz)		Cl

Table 1. Continued

Compound	R ₁	R ₂
Phenothiazines with a piperazine side chain		
Fluphenazine (Fz)		CF ₃
Thiopropazate (Tp)		Cl

The new derivatives of phenothiazines are synthesized from the parent phenothiazines in several directions: substitution of new groups with the thiazine nitrogen atom [11], an introduction of a new substituent at positions 1–4 and 6–9 aromatic rings, oxidation of the sulfide sulfur atom to a sulfoxide or sulfone group, as well as a substitution one or both benzene ring with homoaromatic or heteroaromatic rings [1].

Synthesis of *N*-alkylphenothiazines

Promazine, *N,N*-dimethyl-3-(10*H*-phenothiazin-10-yl)-propan-1-amine, is synthesized by the alkylation of phenothiazines with 3-dimethylaminopropylchloride in the presence of sodium amide (Scheme 2) [12].

Chlorpromazine, 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N,N*-dimethyl-propan-1-amine is prepared following two steps: in the first step, 3-chlorodiphenylamine with sulphur gives as product 2-chloro-10*H*-phenothiazine, while in the second step, this compound reacts with 3-dimethylaminopropylchloride, similar to the synthesis of promazine (Scheme 3) [12].

Trifluopromazine, *N,N*-dimethyl-3-[2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]propan-1-amine (Fig. 4) is also prepared by alkylation of 2-trifluoromethyl-

-10*H*-phenothiazine in the presence of sodium amide [12].

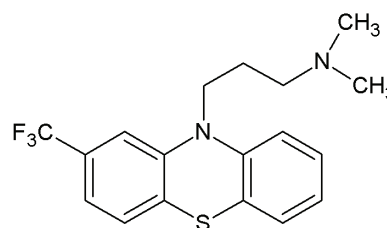
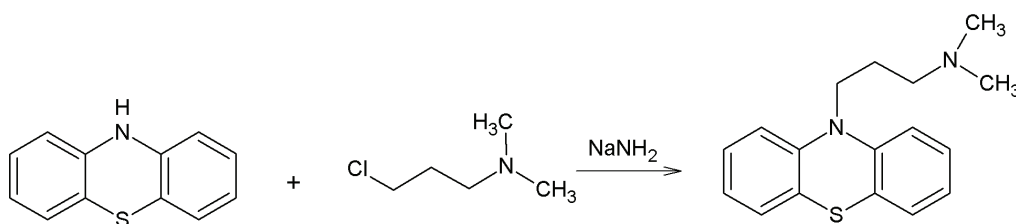


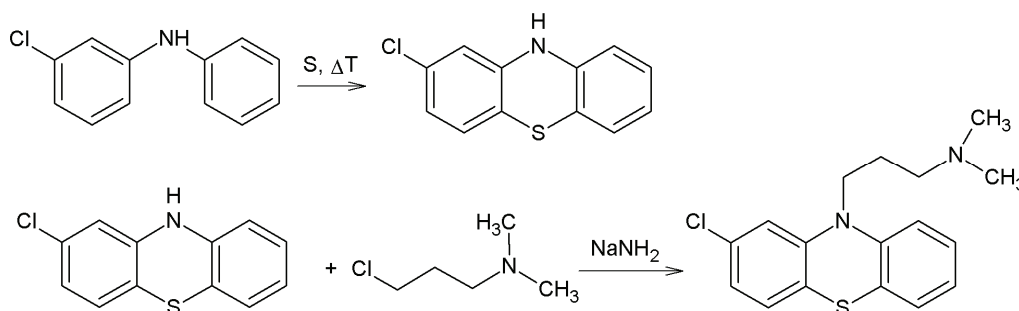
Figure 4. Structure of the *N,N*-dimethyl-3-[2-(trifluoromethyl)-10*H*-phenothiazin-10-yl]propan-1-amine, (trifluopromazine).

A series of molecules has substitution on carbon atom at position 2 of phenothiazine benzene ring of promazine as methopromazine (possess methoxy group) and acetopromazine (with aceto group on C-2 atom) which are synthesized in similar way.

Phenothiazines with a piperidine side chain, thioridazine 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)-10*H*-phenothiazine and mesoridazine 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylsulfinyl)-10*H*-phenothiazine are also synthesized by alkylation of methylsulphonil-10*H*-phenothiazine/2-methylthio-10*H*-pheno-



Scheme 2. Synthesis of *N,N*-dimethyl-3-(10*H*-phenothiazin-10-yl)-propan-1-amine (promazine).

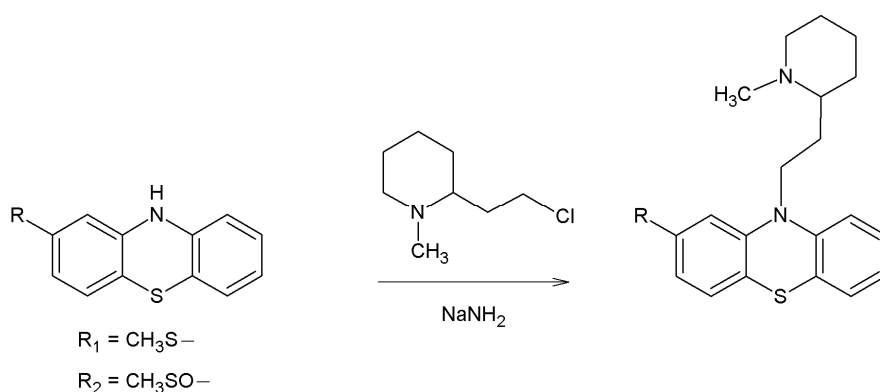


Scheme 3. Synthesis of 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N,N*-dimethyl-propan-1-amine (chlorpromazine).

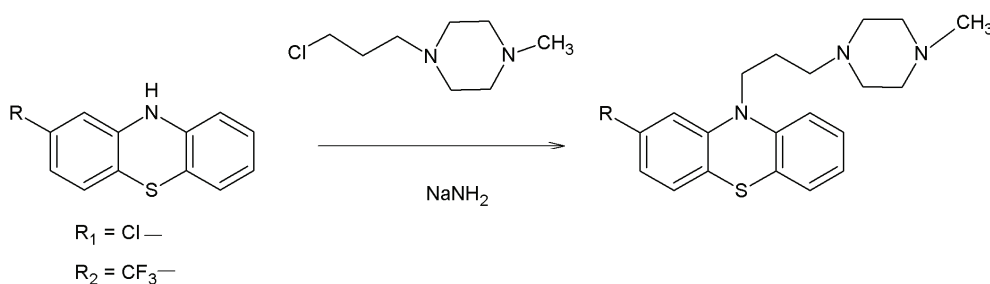
thiazine using 2-(2-chloroethyl)-1-methylpiperidine in the presence of sodium amide (Scheme 4) [12].

At last, phenothiazines with piperazines chain, prochlorperazine, 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10*H*-phenothiazine and trifluoperazine, 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10*H*-phenothiazine are prepared by alkylation of 2-chloro-10*H*-phenothiazine/2-trifluoromethyl-10*H*-phenothiazine using 4-methyl-1-piperazinylpropylchloride in presence of sodium amide (Scheme 5) [12].

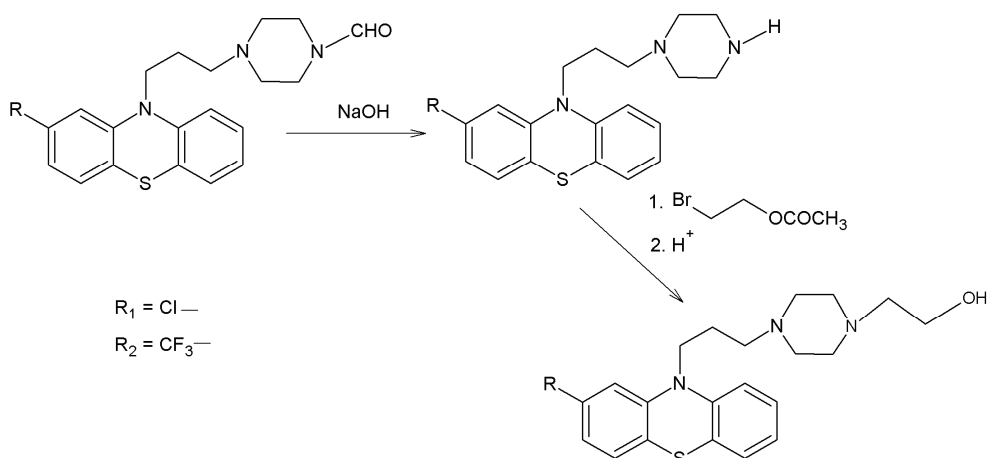
Perphenazine, 2-[4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol, and fluphenazine, 2-[4-[3-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol, are synthesized in a similar way as previously described. In the first step, 2-chloro-10*H*-phenothiazine/2-trifluoromethyl-10*H*-phenothiazine is alkylated using 4-formyl-1-piperazinylpropylchloride in the presence of sodium amide and then *N*-formyl group was removed by alkaline hydrolysis giving the intermediate product (Scheme 6). The final step is alkylation of intermediate compound by 2-bro-



Scheme 4. Synthesis of 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylthio)-10*H*-phenothiazine (thioridazine, R_1) and 10-[2-(1-methyl-2-piperidyl)ethyl]-2-(methylsulfinyl)-10*H*-phenothiazine (mesoridazine, R_2).



Scheme 5. Synthesis of 2-chloro-10-[3-(4-methyl-1-piperazinyl)propyl]-10*H*-phenothiazine (prochlorperazine, R_1) and 10-[3-(4-methylpiperazin-1-yl)propyl]-2-(trifluoromethyl)-10*H*-phenothiazine (trifluoperazine, R_2).



Scheme 6. Synthesis of 2-[4-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol (perphenazine, R_1) and 2-[4-[3-(2-(trifluoromethyl)-10*H*-phenothiazin-10-yl)propyl]piperazin-1-yl]ethanol (fluphenazine, R_2).

methanol-1-acetate by acid hydrolysis which removes acetyl group [12]. Also, these molecules contain an alcohol group which provides an opportunity for derivatization in order to obtain new compounds with pharmacological using.

Use and application

The phenothiazine group of compounds has the great spectrum of application from industry to medicine for more than a century due to their diverse syntheses. Substituted phenothiazines have been used for the preparation of the polymers [13], the solar cells [14,15], biological stains [16], as well as medicaments [12]. They possess antimicrobial [6,21–24], anthelmintic [7], antiemetic [8], antihistaminic [8] anticancer properties [2], and they are used in clinical practice more than 50 years as antipsychotics [12,17].

In many researches, it was shown that *N*-alkylphenothiazines possess antimicrobial activity [18–20]. Kristiansen *et al.* [18] demonstrated that chlorpromazine and thioridazine reduce the susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) while Martins *et al.* [19] in their research classified a few *N*-alkylphenothiazines as non-antibiotics (helper compounds) in the treatment of multidrug resistant Gram-negative infections. As anthelmintics, phenothiazines reduced faecal eggs of resistant strains of three nematodes, *Haemonchus contortus*, *Trichostrongylus colubriformis* and *Ostertagia spp.*, but without significant effect on worm number [7].

Phenothiazines have been shown to inhibit *in vitro* growth of multi drug resistance strain (resistant to rifampin and isoniazid) *Mycobacterium tuberculosis*. The killing of intracellular bacteria promoted by phenothiazine can inhibit many transport processes of potassium and calcium pump activation. The increased permeability ensures phenothiazine molecules to reach the DNA, intercalate between the bases, inhibit the entire DNA and hence inhibit transcription and translation processes [21]. The ability of chlorpromazine to cure tuberculosis resulted in a series of *in vitro* studies that showed that chlorpromazine was more effective antimycobacterial compound than other *N*-alkylphenothiazines [21–24]. Because chronic administration of chlorpromazine is known to produce a wide range of mild-to-severe side effects, the use of this compound in tuberculosis therapy was not seriously considered. Thioridazine can more effectively accelerate the recovery of infected mice from *Mycobacterium tuberculosis*, as shown in preliminary study [24], providing strong direct evidence that thioridazine, a neuroleptic that is milder and less toxic than chlorpromazine, kills intracellular *Mycobacterium tuberculosis* isolates that are resistant to two or more antibiotics [22]. These investigations indicate that phenothiazines have been

considered as an adjuvant for the treatment of *Mycobacterium tuberculosis*.

The blockade of histamine receptors in brain gives sedative effect to the most of *N*-alkylphenothiazines. Prochlorperazine, promethazine and perphenazine are known as antipsychotic drugs which block postsynaptic dopaminergic receptors in the brain and have antiemetic effects by their antagonistic actions in the dopamine receptors (D₂) predominantly, but also may possess antagonist actions at histamine 1, cholinergic M₁ and α_1 -adrenergic receptors in the vomiting center to reduce nausea and vomiting [8]. Promethazine hydrochloride is in pharmacological use as Phenergan cream, topical antihistaminic preparation for systemic eczematous dermatitis.

Phenothiazines as lipophilic molecules are interacting with various macromolecules and possess anticancer activity. Chlorpromazine, promethazine, thioridazine and trifluoperazine, in clinically relevant plasma concentrations 2–36 μ M, markedly decreased the viability of leukemic cells without any toxic effects on normal lymphocytes [25]. Phenothiazines show antiproliferative activity against breast, ovarian, lung, CNS, prostate and melanoma cell lines. Trifluoperazine, chlorpromazine and thioridazine in concentration up to 20 μ M expressed a selective cytotoxicity, as well as antiproliferative activity and induced apoptosis [4]. Also, *N*-alkylphenothiazines have the capacity to increase the lethal effect at low doses of the therapeutic drugs [26]. Cytotoxicity of these compounds could be attributed to oxidative stress, *via* glutathione oxidation and lipid peroxidation.

The most common application of phenothiazines is in psychiatry [10,17]. Modern psychopharmacology cannot be imagined without chlorpromazine. Chlorpromazine was synthesized in 1951 by Paul Charpentier, and became available on prescription in France in 1952, under the proprietary name of Largactil as pharmaceutical drug [17]. In medical practice, chlorpromazine is used in the treatment of patients with schizophrenia, neurosis, manic-depressive condition and chronic paranoid, alcoholic psychoses as well as for stress-sampled neuroses, insomnia and fears. Promazine and trifluoperazine have similar application. Trifluoperazine is one of the most active antipsychotic drugs with common synonyms in pharmacy as stelazine, triftazin and others. This drug has strong anticonvulsant activity and it is used in treatment for schizophrenia and other mental diseases. Mesoridazine has application for behavior problems, schizophrenia, chronic alcoholism and other. Phenothiazines with aliphatic side chain and piperidine substituent have more pronounced sedative effect than piperazine derivatives. These molecules are non-selective and competitive D₁ and D₂ antagonists that block dopamine activity at corresponding receptor

site. Also, their activity could be expressed by blocking α -adrenoreceptors, serotonin, cholinergic, nicotine and muscarinic receptors [12].

In the aim of finding new applications of these compounds, they are used as ligands in coordination chemistry. Until today many complexes containing *N*-alkylphenothiazines are synthesized and characterized. Gowda and his group [27,28] prepared Ir(III) and Pd(II) complexes with *N*-alkylphenothiazines and proposed heterocyclic S atom coordination. Keshavan *et al.* synthesized many complexes of lanthanide with *N*-alkylphenothiazines indicating that the tertiary nitrogen, as well as phenothiazine's nitrogen, represents the coordination site of ligand [29,30]. Also, complexes of lanthanide showed moderately antibacterial activity against some Gram-positive and Gram-negative bacteria. The structure of lanthanide complexes with phenothiazine was determined by X-ray single crystal diffraction analysis (Fig. 5) displaying lanthanide-nitrogen bond [31].

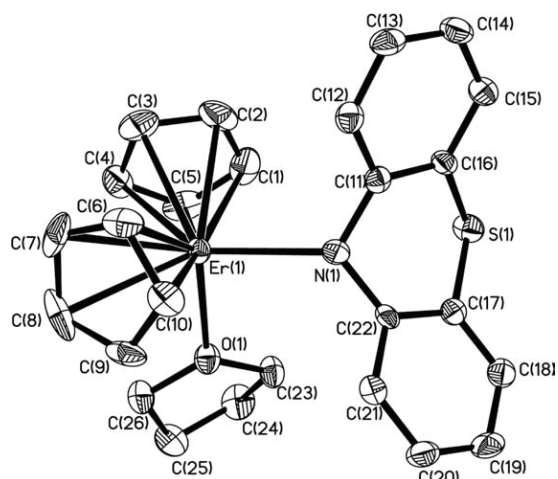


Figure 5. ORTEP diagram of complex $(C_5H_5)_2ErPtz(THF)$ [22].

The complex $HgCl_2(ptz)_2 \cdot HgCl_2$ was synthesized by reaction of $HgCl_2$ and phenothiazine in benzene as dark-blue powder [32]. The final products were characterized by X-ray diffraction which confirmed S-coordination of phenothiazine (Fig. 6).

A series of conjugated polymers with bipyridine groups were synthesized successfully *via* Suzuki coup-

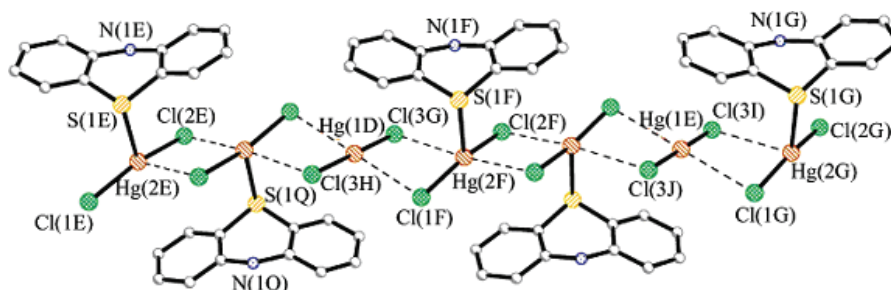


Figure 6. ORTEP diagram of complex $[HgCl_2(ptz)_2]_2 \cdot HgCl_2$ [23].

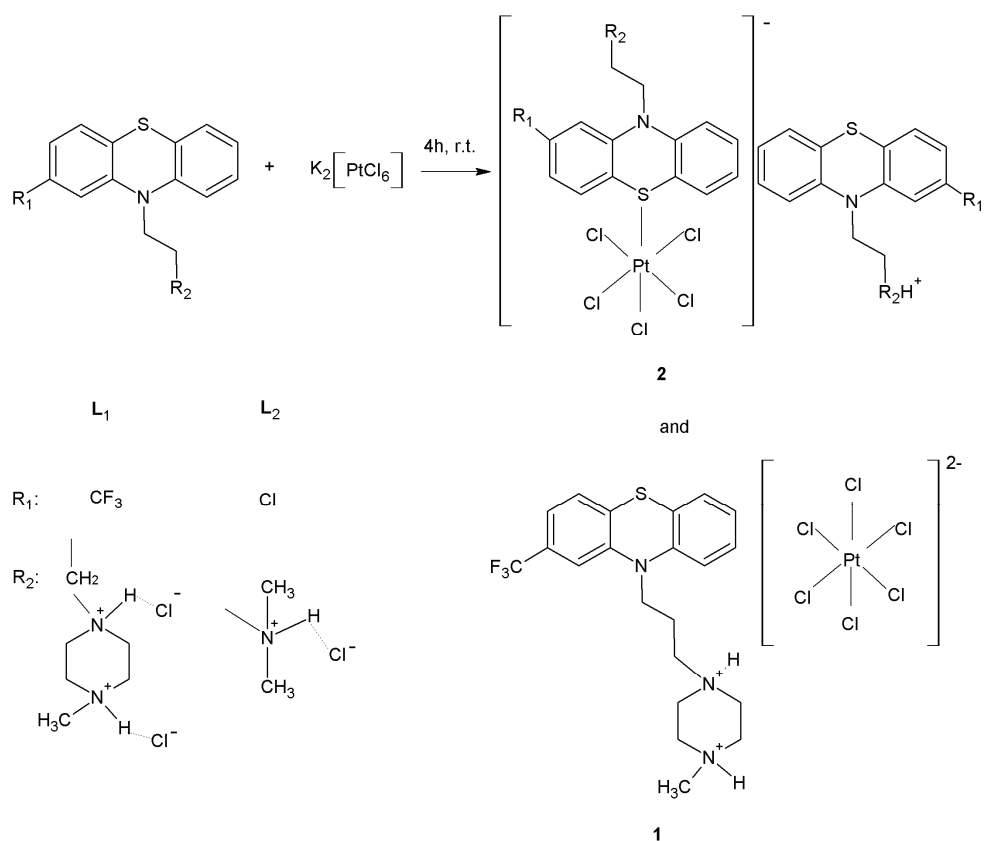
ling polycondensation using carbazole and phenothiazine as the main chain moieties. Through a one-pot post-functionalization reaction, ruthenium complexes were introduced into the polymer through a flexible spacer in high yields, which lead to a new simplified strategy to synthesize this special type of conjugated polymer with metal complex linked to pendant groups through a flexible chain. Furthermore, the obtained Ru-containing polymers PM1PT-x-Ru exhibited broad absorption in the visible region, and possessed a narrow electrochemical band gap (approximately 1.36–1.42 eV) and low HOMO energy level (about 5.47–5.34 eV), indicating that they are suitable candidates as photosensitive materials for solar cells [33].

Platinum complexes with chlorpromazine and trifluoperazine were prepared from $K_2[PtCl_6]$ in water (Scheme 7). Complexes were characterized by spectral (IR, 1H , ^{13}C , 2D 1H - ^{13}C heteronuclear correlation spectra, ^{195}Pt NMR and MS) analysis. Outer-coordination sphere was proposed for $((TFH \cdot HCl)[PtCl_5H_2O])$, while in $((CP \cdot H)[Pt(CP \cdot HCl)Cl_5] \cdot H_2O)$, the ligand was coordinated to the metal *via* heterocyclic sulphur. The complexes exhibit antibacterial effect on strains of *Bacillus subtilis*, *Bacillus cereus*, *Bacillus pumilus* and methicillin-resistant *Staphylococci* as Gram-positive bacteria, and an *Escherichia coli* as Gram-negative bacteria, as well as the reference strains [34].

Ru(II) complexes with *N*-alkylphenothiazines

Three new complexes of the general formula $L[RuCl_3(DMSO)_3]$ (**1–3**), where L is chlorpromazine hydrochloride, trifluoperazine dihydrochloride or thioridazine hydrochloride, were prepared by the reaction of the starting complex $[RuCl_2(DMSO)_4]$ and the corresponding ligands in a mole ratio of 1:1.6 in absolute ethanol [35]. The complexes were characterized by elemental analysis and spectroscopic methods. The crystal structure of the complex $(TF \cdot H_2)[RuCl_3(DMSO)_3]Cl \cdot C_2H_5OH$ contains trifluoperazine dihydrochloride in outsphere position, but its chloride atom had substituted one of DMSO molecules in starting complex and coordinated to the Ru(II) atom (Fig. 7).

The investigation of antitumor properties of complexes **1–3** in four human cell lines (MCF-7, MDA-MB-453, SW-480 and IM9) showed dose-dependence and



Scheme 7. Reaction scheme for synthesis Pt(II) complexes with chlorpromazine hydrochloride and trifluoperazine dihydrochloride.

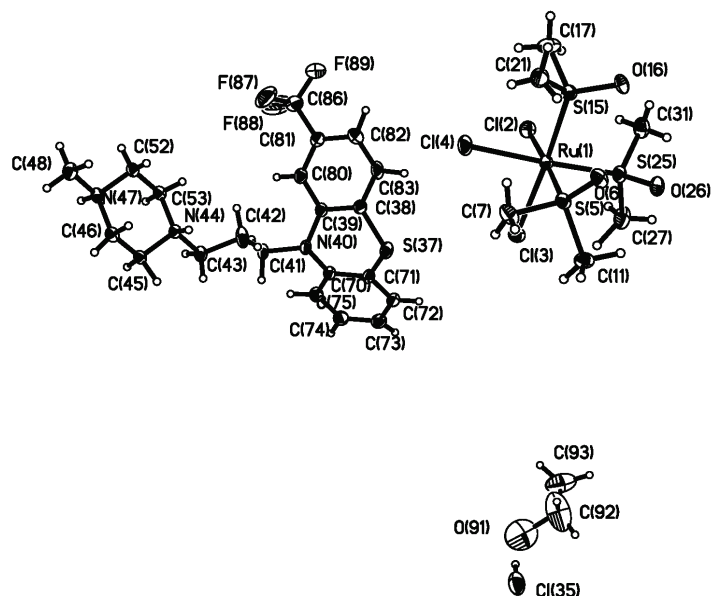


Figure 7. Asymmetric unit of $(TF.H_2)[RuCl_3(DMSO)_3]Cl \cdot C_2H_5OH$.

variation by cell types. The most active compound is complex $(CP.H)[RuCl_3(DMSO)_3] \cdot C_2H_5OH$, which demonstrates a higher activity against MCF-7 and IM9, but it is less effective against other cell lines and did not cause complete cell death. Complex:

$(TF.H_2)[RuCl_3(DMSO)_3]Cl \cdot C_2H_5OH$

is the most sensitive against human breast cancer cell line (MDA-MB-453) and human colon adenocarcinoma cell line (SW-480), while other two complexes were active even in low concentrations, and induced almost total cell death at 25 μM during 48 h of treatment. Moreover, complex $(TF.H_2)[RuCl_3(DMSO)_3]Cl \cdot C_2H_5OH$ is

the only compound in our investigations displaying cytotoxic activities against all tumour cell lines. The selective cytotoxicity of these complexes, especially complex (TF.H2)[RuCl₃(DMSO)₃]Cl·C₂H₅OH, against the cancer cells suggests their great potential for development as anticancer drugs. It is also investigated the effect of this complex on antioxidative enzymes in rat blood. Biological assays provide the clear evidence that complex (TF.H2)[RuCl₃(DMSO)₃]Cl·C₂H₅OH under physiological conditions can act as a scavenger of NO[•] radicals in lower doses of 0.4 and 4.5 μM/kg bw, and as a scavenger of free radicals, such as superoxide anion and hydroxyl radicals (Fig. 8). This compound also influences the SOD and CAT activities, even in dose of 90.4 μM/kg bw. As non-toxic compound under physiological conditions, this complex could provide potential therapeutic benefits in lower doses (0.4 and 4.5 μM/kg bw) for disorders where these reactive species are involved.

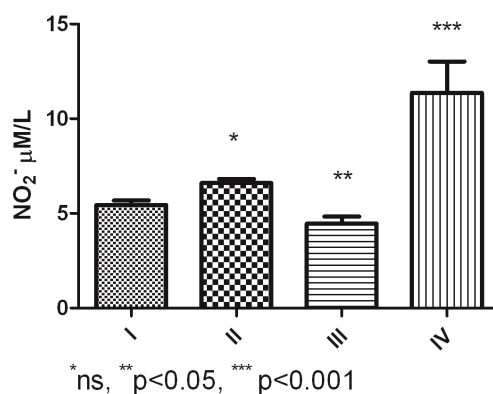


Figure 8. Content of NO₂⁻: I – control group; II – rats treated *i.p.* with complex (TF.H2)[RuCl₃(DMSO)₃]Cl·C₂H₅OH at dose of 0.4 μM/kg bw; III – rats treated *i.p.* with complex (TF.H2)[RuCl₃(DMSO)₃]Cl·C₂H₅OH at dose of 4.5 μM/kg bw; IV – rats treated *i.p.* with complex (TF.H2)[RuCl₃(DMSO)₃]Cl·C₂H₅OH at dose of 90.4 μM/kg bw.

The thermal decomposition pattern of the starting complex [RuCl₂(DMSO)₄] and complexes L[RuCl₃(DMSO)₃],

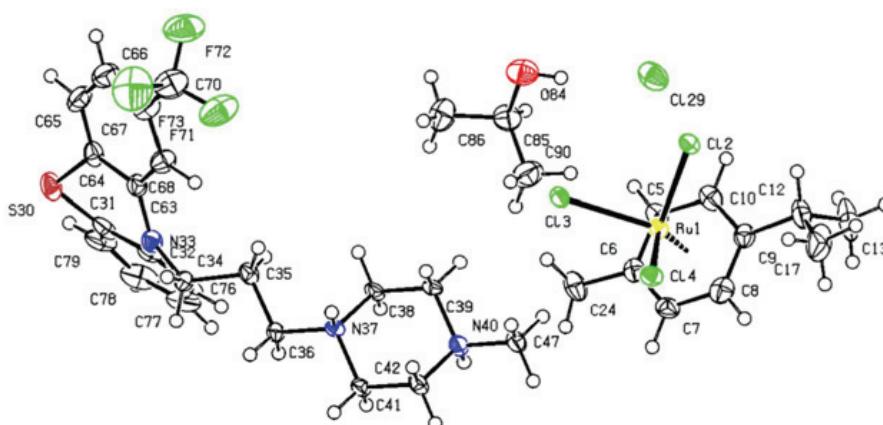


Figure 9. Asymmetric unit of (TF.H2)[RuCl₃(η⁶-*p*-cymene)]Cl·C₃H₇OH.

where L is protonated chlorpromazine hydrochloride, trifluoperazine dihydrochloride or thioridazine hydrochloride, does not depend on the atmosphere: the thermal curves are almost identical in nitrogen and air atmospheres [36]. Also, decomposition of these complexes is not completed at 700, but near 1000 °C as residue is elemental ruthenium. This property of complexes is in agreement to biological potential and provides an opportunity for these compounds to adapt to different ambient conditions.

In reaction of *N*-alkylphenothiazines with [RuCl₂(η⁶-*p*-cymene)]₂ in 2-propanol, after about 3 h, orange precipitate was formed. As in previously research, complex with trifluoperazine gave single crystal for X-ray analysis (Fig. 9). The crystal structure of complex 2 contains the Ru center in a pseudo-octahedral “piano-stool” geometry, with *p*-cymene and three chloride ions in the coordination sphere, and *N*-alkylphenothiazine in the outer-sphere. *In vitro* cytotoxic activities of complexes were assayed in four human carcinoma cell lines MCF-7, MDA-MB-453, SW-480 and IM9. The highest cytotoxicity (12.1 ≤ IC₅₀ ≤ 17.3 μM) and induced a total (SW-480) or almost total cell death (MCF-7, MDA-MB-453) at 25 μM in 48 h of treatment were observed for complex (TF.H2)[RuCl₃(η⁶-*p*-cymene)]Cl·C₃H₇OH [37].

Biological assays provide clear evidence that this compound demonstrates a positive effect on the heart muscle, as suggested by unchanged LDH1 levels and a lower level of LDH2. Complex (TF.H2)[RuCl₃(η⁶-*p*-cymene)]Cl·C₃H₇OH inhibited SOD activity in all doses, although influence on CAT activity was not observed. Results of this study suggest the cardio protective potential of complex (TF.H2)[RuCl₃(η⁶-*p*-cymene)]Cl·C₃H₇OH, since the decreased activity of LDH2 was revealed after its oral administration. This investigation illustrates the potential of Ru(II)-cymene complexes with pharmacologically active substances as novel and promising bioinorganic drugs.

Thermal analysis of these complexes were shown a great thermal stability of starting complex $[\text{RuCl}_2(\eta^6\text{-}p\text{-cymene})]_2$, while thermal decomposition of chlorpromazine's and trifluoperazine's Ru-complex began at low temperature [38].

CONCLUSIONS

The phenothiazine belongs to the group of heterocyclic aromatic compounds with nitrogen and sulphur atoms. The *N*-alkylphenothiazines are formed in the reaction of substitution on the nitrogen atom of phenothiazines ring with aliphatic side chain, piperidine, piperazine or with some new group of molecule. The other substituent is at carbon atoms in position 2 of benzene ring, but new generation of *N*-alkylphenothiazines introduces substituent at position 1-4 and 6-9 at the benzene ring. These molecules possess many applications, but the most important implementation is in medicine. They are medicinal drugs with the major effect on central nervous system almost irreplaceable in treatment of mental diseases. Many of them have shown cytotoxic effect against different cancer cell lines or in small doses supported the therapeutic drugs to lead apoptosis of cancer cells.

N-alkylphenothiazines are also used in synthesis of metal complexes which showed antibacterial activity. Complexes of Ru(II) with *N*-alkylphenothiazines showed significant anticancer activity against four cancer lines. These complexes possess positive effect in small doses on antioxidant enzymes, as well as the complex $(\text{TF.H}_2)[\text{RuCl}_3(\eta^6\text{-}p\text{-cymene})]\text{Cl}\cdot\text{C}_3\text{H}_7\text{OH}$ demonstrated cardio protective potential by decreased activity of LDH2 isoenzymes. Having into consideration all of the above, *N*-alkylphenothiazines have promising potential in both bioinorganic chemistry and medicine in the future.

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IZVOD

***N*-ALKILFENOTIAZINI – SINTEZA, STRUKTURA I PRIMENA KAO LIGANADA U KOMPLEKSIMA METALA**Milena Krstić¹, Sofija Sovilj², Sunčica Borozan¹, Milica Rančić³, Jelena Poljarević², Sanja R. Grgurić-Šipka²¹*Fakultet veterinarske medicine, Univerzitet u Beogradu, Beograd, Srbija*²*Hemijski fakultet, Univerzitet u Beogradu, Beograd, Srbija*³*Šumarski fakultet, Univerzitet u Beogradu, Beograd, Srbija*

(Pregledni rad)

Fenotiazini pripadaju velikoj grupi heterocikličnih, aromatičnih molekula koji između dva benzenova prstena sadrže azot i sumpor. Njihovi derivati, *N*-alkilfenotiazini poseduju supstituent na heterocikličnom azotovom atomu koji molekulima daje različita svojstva. Takođe, serija ovih jedinjenja ima supstituent i na ugljenikovom atomu u položaju 2 benzenovog prstena fenotiazina. Alkilfenotiazini sadrže aminoalkil grupu kao supstituent i njegovi alkil, acil i sulfonil derivati, kao i mono- i biciklični heterocikli vezani su za tiazinski azotov atom ili direktno za benzenov prsten. *N*-alkilfenotiazini su poznati kao antipsihotici, ali poseduju i antibakterijsku, antifungalnu, antitumorsku aktivnost, kao i sposobnost da reaguju sa makromolekulima i da se koordinuju za jone metala. Kompleksi metala sa *N*-alkilfenotiazinima pokazala su se kao biološki aktivna jedinjenja sa različitom antimikrobnom aktivnošću i citotoksičnim efektom na različite tumorske ćelijske linije. Upravo zbog njihovog širokog polja primene *N*-alkilfenotiazini su veoma atraktivni u smislu sinteza novih srodnih derivata, kompleksa metala, proučavanja njihovih svojstava i istraživanjima na polju njihove dalje primene. Ovaj rad predstavlja pregled literature i savremeni pogled na *N*-alkilfenotiazine – njihovu sintezu i primenu, kao i njihovih metalnih kompleksa koji poseduju značajna biološka svojstva.

Ključne reči: *N*-Alkilfenotiazini • Antipsihotici • Antitumorski efekat • Antibakterijski efekat