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Etude qualitative et quantitative des relations structures-activités dans des hétérocycles à intérêt pharmaceutique.

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A mes chers parents, pour m'avoir donné les moyens de réussir.

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Summary :

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List of the principal abbreviations :

WHO	World Health Organization
BPSD	behavioral and psychological symptoms of dementia
AD	Alzheimer's disease
HD	haloperidol
RS	risperidone
PTZ	phenothiazine
OLEDs	organic light-emitting diodes
CNS	central nervous system
GABA	gamma-aminobutyric acid
NMR	Nuclear magnetic resonance
QM	quantum mechanics
HF	Hartree–Fock
$\hat{H}$	Hamiltonian operator
Ψ	wave function
BOA	Born–Oppenheimer approximation
DFT	Density functional theory
MM	molecular mechanic
MD	molecular dynamic
BA	biological activity
MLR	multiple linear regression

PCR	principal component regression
PLS	partial least squares regression
LOO	leave-one-out technique
PRESS	predicted residual sum of squares
TSS	total sum of squares
MDR	multi-drug resistance
3D	three-dimensional
ΔE	energy gap.
HOMO	Highest occupied Molecular Orbital.
LUMO	Lowest unoccupied molecular orbital.
B3LYP	Beck3-Parmetr Lee-Yang-Parr
LCAO	Linear combination of atomic orbital.
μ	dipole moment.
H_f	heat of formation
MC	Monte Carlo.
QSAR	Quantitative Structure-activity Relationships
SAG	Surface Area Grid
Log P	partition coefficient octanol/water.

GENERAL INTRODUCTION

Computational chemistry is supporting research of new chemical compound. It uses sophisticated software to assist in the identification of new chemical compound. The theoretical chemist, must be able to predict and reinterpret the experience using molecular modeling.

Molecular modeling (quantum mechanics , molecular mechanics and molecular dynamics), is the sum of theoretical methods and computational techniques that is used to predict molecular behaviors specifically interactions between molecules [1]. Is the computer simulation of molecular structures , which are used to solve problems related to molecular field.

Quantitative structure – activity relationships (QSARs), as one of the most important areas in chemometrics [2]. QSARs are a suite of tools used to link chemical activities with molecular structure and composition [3]. And is actively used in drug design [4, 5]. The concept of using QSARs to link structure and activity was introduced over 100 years ago and subsequently widely used in medical and biological research [6, 7].

To develop a QSAR model, several statistic methods can be used. Multiple linear regression (MLR) is a mathematical tool that quantifies the relationship between a dependent variable and one or more independent variables (descriptors) [8].

Molecular descriptors define the molecular structure and physicochemical properties of molecules by a single number. A wide variety of descriptors have been reported for using in QSAR analysis [2].

Phenothiazines and related compounds, including tranquilizers [9] and drugs with anti-inflammatory [10], antimalarial [11], antipsychotic [12], antimicrobial [13], antitubercular [14,15], antitumor [16-18], antihistaminic [19] and analgesic [20] properties, have found widespread use in medicinal chemistry, among these, those that act as antihistaminic and antipsychotic agents are the ones most exploited therapeutically [21]. In these compounds, the amino alkyl side chain connected to the nitrogen atom of the heterocyclic unit plays a crucial role in their properties [22,23].

Our research task is placed in context of fundamental and original search on the molecules of phenothiazines. The main objective of this work is the application of various methods of

molecular modeling to predict the chemical reactivities and the expected biological activities, in new bioactive molecules for the studied series of molecules .

This work comprises four chapters. The first chapter is divided into two parts: in the first part, we will present general information on psychotropics and antipsychotics. In the second part, we will be spread out, over general information concerning the pharmacological classification and properties of phenothiazines.

In the second chapter, we will describe the formalism of the methodology chosen in the molecular modeling which comprise the various methods of calculating used and engaged in our work.

The third chapter comprises a structural, electronic and energetic study on phenothiazines, and its derivatives. In this chapter we have the results of a comparative study on three methods used in calculation, PM3 and Density functional theory DFT, and ab initio/HF, thus, the substitution affect on the electronic and energetic parameters of the basic core of phenothiazine . We will also present a qualitative study on the relation structure-properties of a bioactive series of phenothiazines (work published in: Journal of Computational and Theoretical Nanoscience, Volume 11, Number 12, , pp. 2481-2488 (8) ; December 2014).

The fourth chapter comprises a quantitative study, which aimed to describe the structure-property relationships study on a series of eighteen phenothiazines and developed a QSAR model on these compounds with respect to their anti multi-drug resistance MDR activity (work published in: Quantum Matter, Volume 5, Number 1, pp. 124-129(6) February 2016).

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CHAPTER I

GENERAL INFORMATION ON PHENOTHIAZINES AND PSYCHOTROPICS

I.1. INTRODUCTION :

Psychosis is the loss of contact with reality, in which people have trouble distinguishing between what is real and what is not, the psychosis indicates a serious disease caused by a dysfunction of the brain.

Psychotic disorders are mental disorders in which a person's personality is severely confused and that person loses touch with reality. Psychotic disorders are associated with significant impairment in occupational functioning and decline can begin in the prodromal phase of the disorder, individuals with a psychotic disorder are less likely to achieve the same social class as their parents and between 36% and 70% experience a social drift.[1]

The past decade has led to a growing sense of optimism about the prospect of better outcomes for people with schizophrenia and related psychoses, with increasing evidence that better outcomes can be achieved with early intervention [2,3]. Early detection and optimal early treatment are increasingly recognised as best practice [4], with early intervention focused on early detection of new cases [5,6], shortening delays in effective treatment [7,8,5,9] and providing optimal treatment in the early ''critical period'' of the first 3 years of illness [8,10]. The psychosis associates positive and negative symptoms .

The following list provides the different types of psychosis: Schizophrenia, chronic delirious psychosis, delirious acute psychosis, confusional psychosis.

Schizophrenia is a psychic disease appearing by episodes of hallucinations, of be delirious, of disorders of the thought and the language.

Poor insight, or lack of awareness of one's illness, is a common symptom among patients with schizophrenia, the World Health Organization (WHO) International Pilot Study of Schizophrenia in different cultures found that 'lack of insight' was an almost invariable feature of acute and chronic schizophrenia, which found that 50–80% of patients lacked, either partially or totally, insight into their mental disorder. [11]

Within the framework of the treatment, low dose of antipsychotic drugs are used by patients, the treatment should not disturb the daily activities of patient.

I.2. GENERAL INFORMATION ON THE PSYCHOTROPICS :

The chlorpromazine, first psychotropic named nerve sedative, wich revolutionizes the approach with the patient interned psychotics, Heinz Lehmannest the first psychiatrist to use the chlorpromazine in North America.

The sale of these drugs is prohibited for any person except for the pharmacists who can deliver them only on medical ordinances.

Antidepressants, hypnotics and antipsychotics are widely used among patients with neurodegenerative disorders because of concurrent depression, anxiety, sleep complaints, confusion/hallucinations and behavioral disturbances [12]. All psychotropic drugs have been associated with falls and hip fractures. [13]

I.2.1. Definition:

Psychotropic is a drug that affects brain activities associated with mental processes,

One calls psychotropic the whole of the substances of natural or artificial origin, which has a psychological tropism .i.e. which is likely to modify the mental activity, this definition, very broad.

Psychotropic drugs are pharmacological compounds having a psychotropic effect prescribed fort he treatment of the psychiatric diseases.

Psychotropic categories: Anti-psychotics; antidepressants; antianxiety drugs or anxiolytics; hypnotics.

Psychotropic drugs are used in the treatment of behavioral and psychological symptoms of dementia (BPSD) in persons with Alzheimer's disease (AD), treatment with psy- chotropic drugs is recommended only for most severe symptoms and for short-term use if non-pharmacological options are not effective. [13]

I.2.2. Classification of psychotropics :

Psychotropic medications fall into a few large categories, Jean Delay a french psychiatrist worked out with his assistant Pierre Deniker a classification of drugs, this classification distinguish the psychotropic substances according to their activity on the central nervous system :

- Psycholeptic or sedative psychic, slowing the activity of the nervous system.
- Psychoanaleptic or exciting psychic, accelerating the activity of the nervous system.
- Psychodysleptic or disturbing psychic, disturbing the activity of the nervous system.
- Psychoisoleptic are regulators of mood, example of the ion lithium (Teralithe*) was discovered in 1949, which returned the hope to many patients.

In fact, due to their astonishing effects, the psychodysleptic drugs (according to the Delay and Deniker, 1961, nomenclature), also called hallucinogenic drugs, have occupied much of the researchers' time. [14]

The psycholeptic are the substances which we adopt here, which are classified into hypnotic, antipsychotic (neuroleptic, example of phenothiazine), tranquilisers…

I.2.3. The antipsychotic "Neuroleptic" :

Antipsychotic (neuroleptic) medications are an important therapeutic option for many individuals with schizophrenia and other psychoses.**[**15**]**

I.2.3.1. Definition :

The two main forms of treatment for psychotic disorders are medication and psychotherapy. The signature medications to treat psychotic disorders are antipsychotics.

The antipsychotics are a family of drugs intended for the treatment of the mental illness, in particular psychosis, the antipsychotic drugs are used to treat schizophrenia, the mania, and the bipolar disorder, for example the chlorpromazine .

The antipsychotics are the first therapeutic agents which allowed the pharmacological treatment of the psychosis.

Studies regarding the risk of death associated with psychotropic drug use have been inconclusive, numerous studies indicate the association between antipsychotic use and an

increased mortality risk. [13]. Use of antipsychotic agents improves some aspects of clinical symptoms in schizophrenia.[16]

Antipsychotic use has also been associated with an increased risk of death among older persons with and without dementia. [13]

I.2.3.2. Classification of antipsychotics :

It is difficult to establish a pharmacological ranking of antipsychotic because it would be necessary to take account of their beneficial effects on the productive symptoms of the psychosis, biochemical structures, their undesirable effects.

The antipsychotics can be classified according to their biochemical structures, it is the classification which we adopt here;

- phenothiazines

- butyrophenones

- benzamides

- thioxanthenes

- diazepines and oxazepines

- various

If we consider the clinical effects of these substances, antipsychotic medications are generally divided into two categories, first generation (typical), and second generation (atypical) :

Typical antipsychotic agents, such as haloperidol (HD) are effective in reducing positive symptoms but not particularly useful against negative symptoms or cognitive deficits in schizophrenia, in contrast, atypical antipsychotic agents, such as risperidone (RS) have gained popularity over typical antipsychotics due to their efficacy in controlling both the positive and negative symptoms.[16]

The main difference between the two types of antipsychotics is that the first generation drugs block dopamine and the second generation drugs block dopamine and also affect serotonin levels

I.2.3.3. Side-effects of antipsychotics :

For these medications to be maximally beneficial, they must have an acceptable side effect profile and be taken as prescribed. .[15]

One untoward effect of many antipsychotic drugs is weight gain [17] . The extent of weight gain apparently varies by drug, which may be because of the drugs' differing degrees of action on the serotonergic [18], dopaminergic [19] , cholinergic[18], histaminergic[20], and other neurotransmitter systems. [15]

Planansky and Heilizer [21] reported that weight gain was associated with symptom improvement, and weight loss was associated with symptom deterioration.

The subsequent availability of multiple antipsychotic medications has led to the observation that weight gain is a common side effect of antipsychotic treatment. [15]. The degree of weight gain clearly increased with time for the drugs considered. [15]

The two antipsychotic typical and atypical have undesirable effects, their revolves will vary person to person : blurred vision, dry mouth, and constipation, dizziness, agitation and sedation, diabetes, Schizophrenia can cause the diabetes and the antipsychotics can increase this risk.

I.3. PHENOTHIAZINES :

Phenothiazine (PTH) derivatives have a long history, with successive periods of interest in different areas of applied chemistry, such as: dyes, probes, pharmaceuticals, and electrochemistry [22–25].

I.3.1. Definition :

Developement of artificial colorants, initially intended to be used in the clothing industry, led to the synthesis of the phenothiazine molecule, by the german organic chemist Bernthsen as early as 1883, Phenothiazine itself, consists of a tricyclic nucleus of 2 benzene rings (pheno), joined through a central ring containing a sulfur atom (thio, position 5) and a nitrogen atom (azo, position 10) [26] .

The phenothiazine is a chemical compound in the form of yellow crystals turns dark green on exposure to light, its molecular formula is « $C_{12}H_9NS$ », it is a tricyclic compound, a cycle

thiazine and two benzene cycles, there are several groups of phenothiazines, differ by their chemical structure, and their pharmacological effects, all these compounds end in the suffix-azine .

The phenothiazine (PTZ) core scaffold is a class of electron-rich tricyclic nitrogen-sulfur heterocycles, which exhibits relatively intense luminescence, high photoconductivities and undergoes reversible oxidation processes [27] . In general, PTZ derivatives (PTZs) have a low oxidation potential and a high propensity to form stable radical cations [28,29]. PTZs are widely used as organic light-emitting diodes (OLEDs) [30,31], acide-base dyes and pigments [32,33], semiconductors [34,35], chemical sensors [36] or near-IR dyes [37,38]. However, most of these applications use the protected PTZ structure with covalent substitutions on the nitrogen atom at the 10-position (10N-H becomes 10N-R). [27] . The basic structure of phenothiazine is may be described using the ring numbering system shown below:

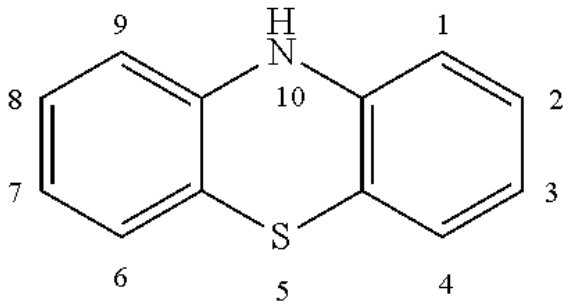


Figure I.1. Scheme of phenothiazine (Chem draw) .

I.3.2. Pharmacology and mode of action of phenothiazines:

The antipsychotics are drugs having primarily effects on the dopaminergique system, this last plays a part in the regulation of the emotional life and the control of the motivation .

Dopamine receptors are a class of G protein-coupled receptors that are prominent in the vertebrate central nervous system (CNS), the neurotransmitter dopamine is the primary endogenous ligand for dopamine receptors. Dysfunction of dopaminergic neurotransmission in the CNS has been implicated in a variety of neuropsychiatric disorders, including social phobia, [39] Tourette's syndrome,[40] Parkinson's disease,[41] schizophrenia,[40]

Phts are amphiphilic compounds[42]. They are used as antipsychotic drugs, interact with various receptors in the CNS, especially strongly block the dopaminergic receptors [43]. Phts also inhibit other receptors on neurons in the CNS, including *a*-adrenergic, serotonin, histamine, muscarinic or GABA-ergic receptors, however, the affinity for dopaminergic receptors is the strongest [44, 45, 46, 47].

The affinity of Phts to dopaminergic receptors is explained by the fact that the three-dimensional configuration of Phts resembles (to some extent) the dopamine structure [48], as is presented in Figure I.2 [42], where A. is the structure of phenotiazines, B. is the structure of dopamine, C. is the superposition of phenothiazines and dopamine structures [49].

Phts applied as neuroleptic drugs easily cross the blood-brain barrier, since they exhibit a strong affinity to lipid bilayers of the cell membranes in neurons and other lipid-rich tissues since the phenothiazine ring possesses a high degree of lipophilicity [50].

The propyl connector between the phenothiazine ring and the final amine determined the function of Phts as dopaminergic receptor antagonists, and their antipsychotic activity. It was also established that shortening the length of this alkyl linker to two carbon atoms caused a change in the affinity for the receptors [49].

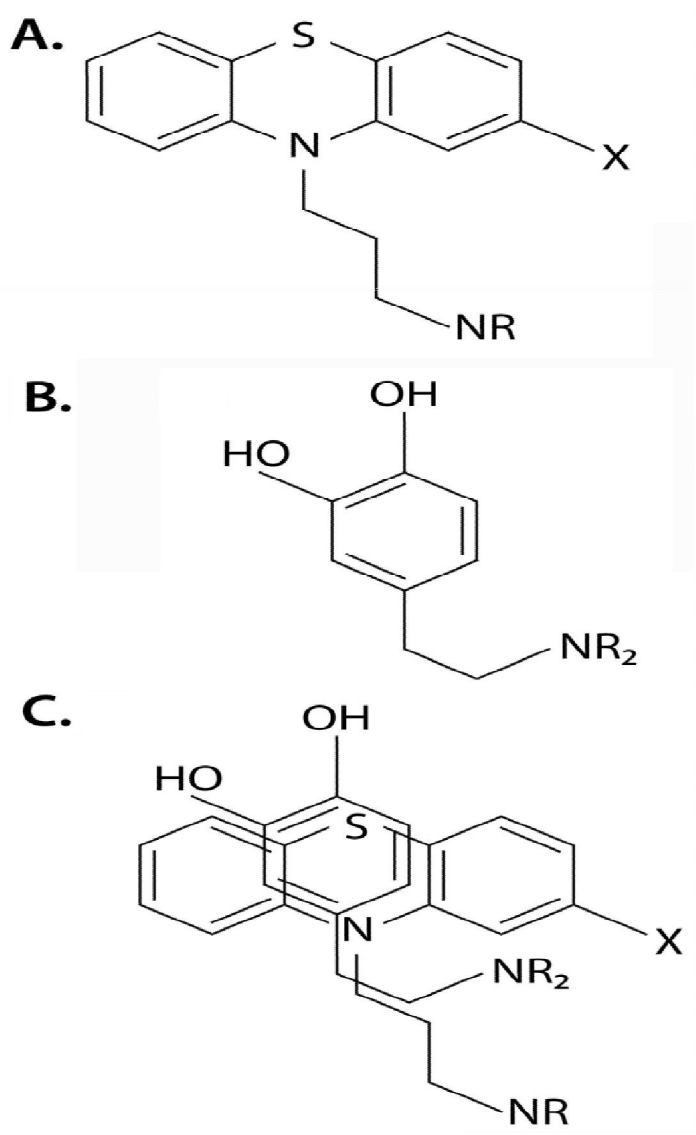


Figure I.2. The structural complementarity between the phenothiazines and dopamine [49].

I.3.3. Classes of phenothiazines :

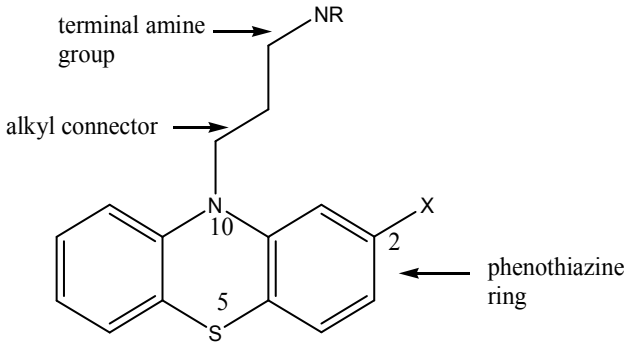
In order to obtain an active neuroleptic derivatives, the hydrogen atoms attached to carbon C-2 and nitrogen N-10 atoms were substituted by different chemical groups, and structures of various Phts given in the literature contained at the N-10 position: piperazine, piperidine, or aliphatic side chain [51] (Fig. I.3).

Phenothiazine antipsychotics are classified into three groups that differ with respect to the substituent on nitrogen:

- The aliphatic compounds (bearing acyclic groups),

- The "piperidines" (bearing piperidine-derived groups),
- The piperazine (bearing piperazine-derived substituents).

Depending on the structure of substituents in the side chain, the intensity of neuroleptic action of Phts could be ranked as follows: piperazine group > piperidine group > aliphatic chain [49]. The piperazine Phts demonstrate the strongest antipsychotic action, but they also induce the central side effects (including dyskinesia and extrapyramidal disorders) [49].These groups are presented in Figure I.3 [42].



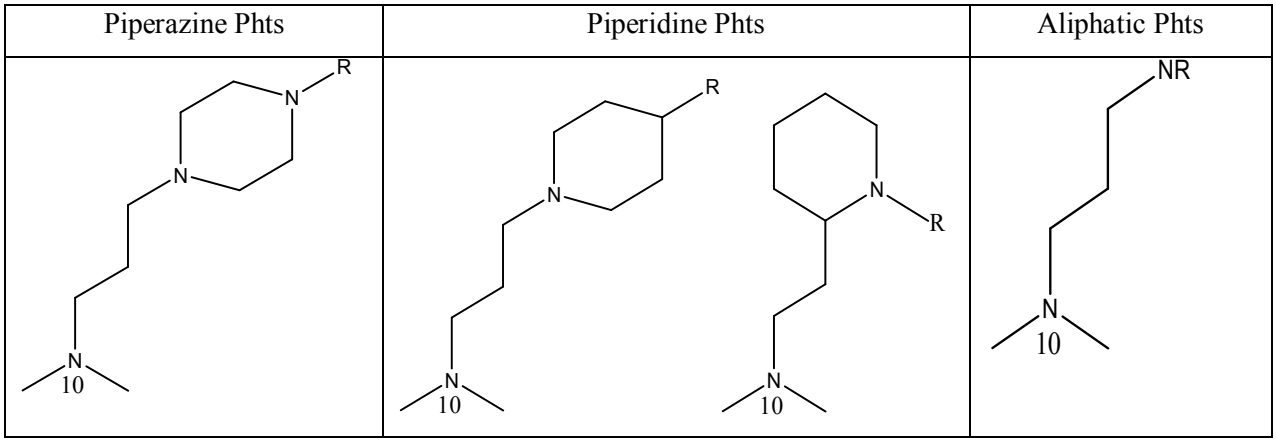
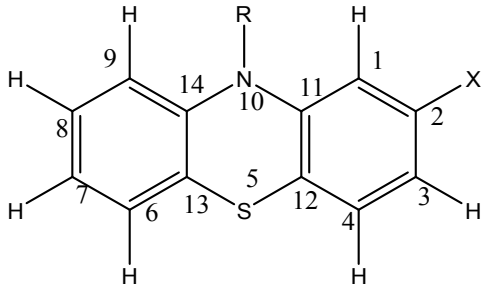


Fig. I.3. General chemical structure of phenothiazines [42]

I.3.3.1. Aliphatic phenothiazines:

Aliphatic phenothiazines are phenothiazines contained at the N-10 position aliphatic side chain (Position R), like Chlorpromazine and Acepromazine, figure I.4, aliphatic phenothiazines are a group of phenothiazine having sedative effects .



Phenothiazines antipsychotiques	X	R
Chlorpromazine (1)	Cl	CH_2-CH_2-CH_2-N$(CH_3)_2$
Acepromazine (2)	CO-CH_3	CH_2-CH_2-CH_2-N$(CH_3)_2$
Acepromethazine, (3)	CO-CH_3	CH_2-$CH(CH_3)$-N$(CH_3)_2$
Alimemazine (4)	H	CH_2-$CH(CH_3)$-CH_2-N$(CH_3)_2$
Levomepromazine (5)	OCH_3	CH_2-$CH(CH_3)$-CH_2-N$(CH_3)_2$
Cyamemazine (6)	CN	CH_2-$CH(CH_3)$-CH_2-N$(CH_3)_2$
Promethazine (7)	H	CH_2-$CH(CH_3)$-N$(CH_3)_2$
Etymemazine (8)	C_2H_5	CH_2-$CH(CH_3)$-CH_2-N$(CH_3)_2$
Methoxypromazine (9)	OCH_3	CH_2-CH_2-CH_2-N$(CH_3)_2$
Triflupromazine (10)	CF_3	CH_2-CH_2-CH_2-N$(CH_3)_2$
Chlorproethazine (11)	Cl	CH_2-CH_2-CH_2-N$(C_2H_5)_2$
Promazine (12)	H	CH_2-CH_2-CH_2-N$(CH_3)_2$

Figure I.4. Aliphatic phenothiazines.

- Some examples of aliphatic phenothiazines :

(1)-Chlorpromazine :

The specialities containing this substance :

- AMINAZINE (The USSR)
- AMPLIACTINE (OTHER COUNTRIES)

- AMPLICTIL (OTHER COUNTRIES)
- CHLORAZIN (SUITZERLAND)
- CLORACIN (SPAIN)
- CLORPROMAZINA BAMA (SPAIN)
- CONTOMIN (JAPAN)
- HIBERNAL (OTHER COUNTRIES)
- LARGACTIL (SUITZERLAND)
- LARGACTIL (BELGIQUE)
- LARGACTIL (ENGLAND)
- LARGACTIL (SPAIN)
- LARGACTIL (ITALY)
- MEGAPHEN (SUITZERLAND)
- MEGAPHEN (GERMANY)
- PROPHAPHENIN (OTHER COUNTRIES)
- THORAZINE (USA)
- THORAZINE (SUITZERLAND)
- WINTERMIN (OTHER COUNTRIES)

(2)- Acepromazine :

The specialities containing this substance :

- ATRAVET (USA)
- NOTENSIL (ENGLEND)
- PLEGICIL (BELGIQUE)
- PLEGICIL (SUITZERLAND)
- PLEGICIL (ITALY)
- PLEGICIL (USA)

(3)- Acepromethzine:

- MEPRONIZINE Sanofi-aventis (FRANCE)

(4)- Alimemazine :

The specialities containing this substance :

- EFRALEN (SPAIN)
- THERALENE SUPOSITOIRES (BELGIQUE)
- VARIARGIL (SPAIN)

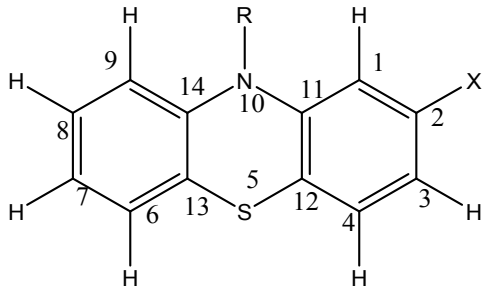
(5) -Levomepromazine :

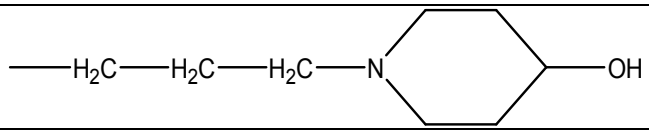
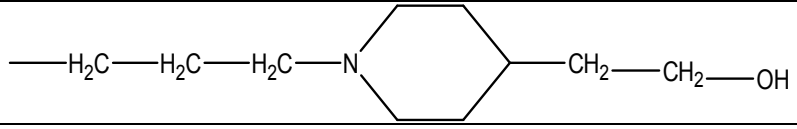
The specialities containing this substance :

- NEUROCIL (GERMANY)
- NOZINAN (BELGIQUE)
- NOZINAN (ITALY)
- NOZINAN (NETHERLANDS)
- NOZINAN (SUITZERLAND)
- VERACTIL (ENGLEND)

I.3.3.2. Piperidine phenothiazines:

Piperidine phenothiazines are used in chronic psychosis, thses phenothiazines having sedative effects, which are contained at the N-10 position piperidine group (Position R), figure I.5, :



DCI:	X:	R:
propericiazine	CN	
Pipotiazine	$SO_2N(CH_3)_2$	

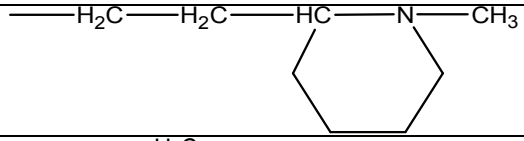
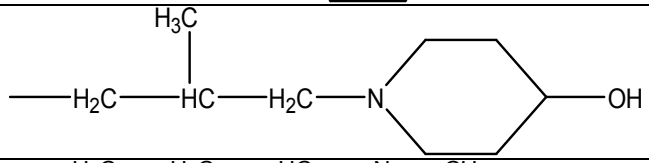
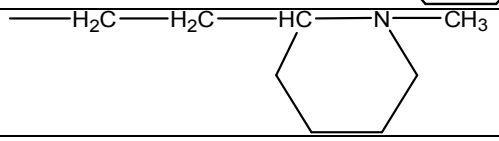
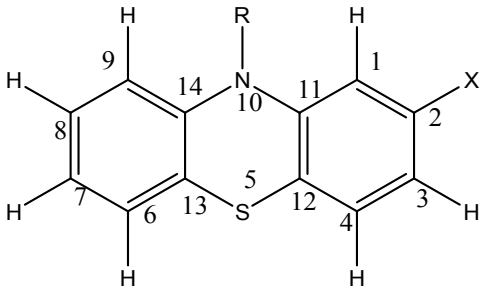
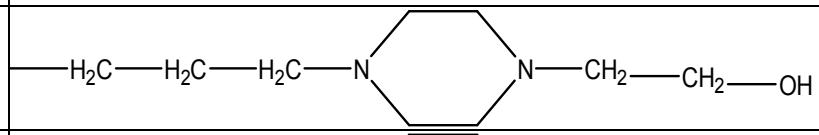
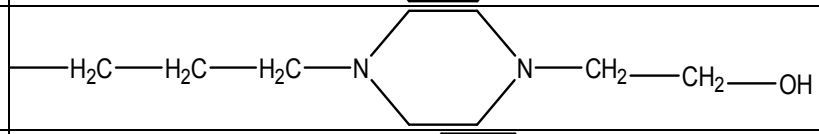
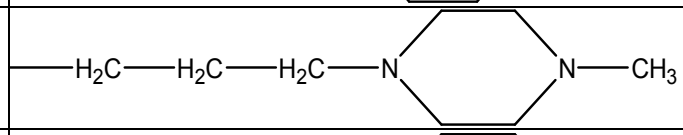
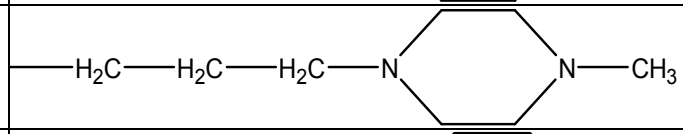
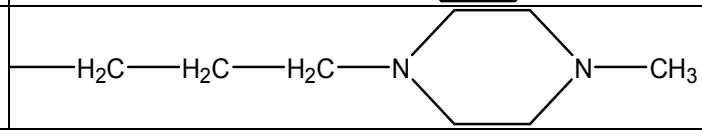
Mesoridazine	$SOCH_3$	
Perimetazine	OCH_3	
Thioridazine	SCH_3	

Figure I.5. Piperidinique phenothiazines.

I.3.3.3. Piperazine phenothiazines:

Piperazine phenothiazines contained at the N-10 position piperazine group (Position R), figure I.6, These compounds having disinhibitory effects :



DCI:	X:	R:
Perphenazine	Cl	
Fluphénazine	CF_3	
Prochlorpérazine	Cl	
TrifLuopérazine	CF_3	
Thiopérazine	$SO_2N(CH_3)_2$	

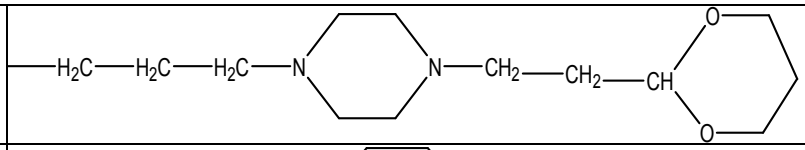
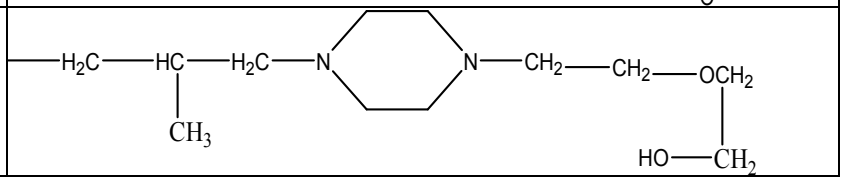
Oxaflumazine	CF_3	
Dixirazine	H	

Figure I.6 Piperazinique phenothiazines:

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CHAPTER II :

MOLECULAR MODELING

II.1. INTRODUCTION :

In recent decades, computer simulation has become an important tool in various fields such as mechanical engineering, chemistry, physics and materials [1-3]. In particular, computer simulations that take account of electronic structures [4].

At the present time, the computer simulation is one of the main tools to identify the regularities of behavior of the molecular systems under various external influences. [5]

Molecular modeling is the computer simulation of molecular structures, which concerns the distances and angles of bonds in chemical molecules, also the results of introduction and substitution of atoms or groups of atoms in the molecule .

Molecular modeling is the sum of theoretical methods and computational techniques that is used to predict molecular behaviours specifically interactions between molecules. [6]

Molecular modeling has been introduced as a valuable methodology for scientific research providing useful tools for the analysis and estimate of the physicochemical parameters and/or biological activity. [7]

Molecular modeling studies are usually correlated with NMR studies since they demonstrate a supplementary method to make experimental information rationalized. [6]

II.2. METHODS OF MOLECULAR MODELING:

The development of molecular modeling techniques has opened a new highway to a more detailed picture on the molecular-level information, molecular modeling is a rapidly evolving discipline which has unquestionably benefited a lot from advances in computing.[8]

Molecular modeling (mechanics and molecular dynamics) is a tool for calculating the energy of molecular structure, it encompasses all theoretical methods and computational techniques, which are used to solve problems of the molecular structure

II.2.1. Quantum mechanics (QM) :

Quantum mechanics explains the energy of a molecule in terms of interactions between electrons and nuclei, which concerns Schrödinger equation.

Electronic structure methods, such as Hartree–Fock (HF) self consistent field method and density functional theory (DFT), are used for modeling molecular properties.[9]

II.2.1.1. Basic principle of the method :

It is needless to repeat that charge transfer processes represent an important and ubiquitous phenomenon in physics, chemistry and biology [10-14].

The starting point of any discussion into quantum mechanics is always the time-independent Schrödinger equation :

$\hat{H}\Psi=E\Psi$ (1)

where $\hat{H}$ is the *Hamiltonian operator*, E is the energy of the molecule and Ψ is the wave function which is a function of the position of the electrons and nuclei within the molecule [15]. The *Hamiltonian* is defined by the sum of (total kinetic energy, and total potential energy) .

According to Löwdin's definition [16,17]: ''A system of electrons and atomic nuclei is said to form a molecule if the Coulombic Hamiltonian H′ with the center of mass motion removed has a discrete ground state energy Eo''[18] where the total Hamiltonian $\hat{H}$ is, respectively, the sum of :

1. The kinetic energy operators for each nucleus in the system;

$$\hat{T}_n - -\sum_i \frac{\hbar^2}{2M_i}\nabla^2_{\mathbf{R}_i} \qquad (2)$$

2.The kinetic energy operators for each electron in the system;

$$\hat{T}_e = -\sum_i \frac{\hbar^2}{2m_e}\nabla^2_{\mathbf{r}_i} \qquad (3)$$

3.The potential energy between the electrons and nuclei is the total electron-nucleus Coulombic attraction in the system;

$$\hat{U}_{en} = -\sum_i \sum_j \frac{Z_i e^2}{4\pi\epsilon_0 |\mathbf{R}_i - \mathbf{r}_j|} \qquad (4)$$

4. The potential energy arising from Coulombic electron-electron repulsions

$$\hat{U}_{ee} = \frac{1}{2}\sum_i \sum_{j\neq i} \frac{e^2}{4\pi\epsilon_0 |\mathbf{r}_i - \mathbf{r}_j|} = \sum_i \sum_{j>i} \frac{e^2}{4\pi\epsilon_0 |\mathbf{r}_i - \mathbf{r}_j|} \qquad (5)$$

5.The potential energy arising from Coulombic nuclei-nuclei repulsions, also known as the nuclear repulsion energy.

$$\hat{U}_{nn} = \frac{1}{2}\sum_i \sum_{j\neq i} \frac{Z_i Z_j e^2}{4\pi\epsilon_0 |\mathbf{R}_i - \mathbf{R}_j|} = \sum_i \sum_{j>i} \frac{Z_i Z_j e^2}{4\pi\epsilon_0 |\mathbf{R}_i - \mathbf{R}_j|}. \qquad (6)$$

Here M_i is the mass of nucleus i, Z_i is the atomic number of nucleus i, and m_e is the mass of the electron, R_i-r_j is the distance between nucleus i and electron j. The Laplace operator of particle i is :

$$\nabla^2_{\mathbf{r}_i} \equiv \nabla_{\mathbf{r}_i} \cdot \nabla_{\mathbf{r}_i} = \frac{\partial^2}{\partial x_i^2} + \frac{\partial^2}{\partial y_i^2} + \frac{\partial^2}{\partial z_i^2}. \qquad (7)$$

The electronic Hamiltonian operator:

$$\hat{H}_{el} = \hat{T}_e + \hat{U}_{en} + \hat{U}_{ee} + \hat{U}_{nn}. \qquad (8)$$

In the Born–Oppenheimer approximation BOA, the electronic part and the nuclear part in the wave function are separated.

A number of solutions exist for Eq. (1), with each one representing a different electronic state of the molecule, importantly the lowest energy solution represents the ground state, it is worth stating that the Schrödinger equation is an eigenvalue equation, in Eq. (1) the wave function (ψ) can be approximated to the electronic state, this being the configuration of the electrons in a series of molecular orbitals, it is then possible to evaluate differing electronic configurations of the wave function in terms of their energies, with the lowest energy configuration being the

ground state, it is the ground state energy that corresponds to the ground state geometry of a given molecule. [15]

II.2.1.2. Electronic wave function :

The wave function in quantum mechanics is the solution of the Schrödinger equation Eq. (1), which describes the quantum state of particles, it is commonly denoted by the variable Ψ.

The wave function is formed from linear combinations of atomic orbitals . The square of the absolute value of the wave function Ψ evaluated at a given point in space is proportional to the probability of finding the particle in the position.

II.2.1.3. Quantum methods: Ab initio :

Having established the importance of the electronic wave function (ψ) in Eq. (1), it is now necessary to discuss the methods that enable the derivation of the electronic states for which Eq. (1) holds true, the following discussion is an outline of the fundamentals of Hartree–Fock theory from which both semi-empirical and density functional methods have been developed [15]. In this theory, the wave function [19], is considered as a series of molecular orbitals, which are occupied by electrons. One of these sets of molecular orbitals will correspond to the ground state and hence have the lowest energy. [15]

Ab initio methods are derived from theoretical principles, with no inclusion of experimental data, it take account both, electron and core in treatment.

Practical *ab initio* calculations are severely limited by the types of atoms and size of molecules. [20]. these calculations are really time consuming and need large CPU memories,

II.2.1.4. The density functional theory (DFT) :

Density functional theory (DFT) is a closely related methodology to Hartree–Fock theory in that it attempts to provide a solution to the electronic state of a molecule directly from the electron density, one can view the methodologies as essentially analogous, for the purpose of this discussion, in terms of using basis functions for orbitals and in the use of the variational principle to locate the lowest energy wave function, however, the major difference is the inclusion of terms to account for both exchange and correlation when evaluating the energy of

the wave function, resulting in a significantly improved description of the electronic structure[15]. Also by using this method, we can calculate the excitation energies.

Differing functionals (for example, B3LYP) use differing mathematical approximations to describe the *Hamiltonian* and thus evaluate the energy of a given wave function [15].

Literature survey reveals that the DFT has a greater accuracy in reproducing the experimental values in geometry, dipole moment, vibrational frequency, etc. [21–24].

It is important only to realize that DFT is a more complete description of the electronic structure than that offered from Hartree–Fock theory and is significantly more complete than semi-empirical methods. However, as would be expected by the inclusion of more complex mathematics, it is also the most time consuming. [15]

In recent years, DFT has been used as a powerful and reliable tool for the prediction of more accurate molecular structure and vibrational frequencies than the conventional ab initio Hartree–Fock calculations.[9]

II.2.1.5. Semi-empirical methods :

Semi-empirical methods generally perform well for calculations upon molecular systems for which the basis functions were optimized (for example, heats of formations are frequently well reproduced). [15]

Both semi-empirical and density functional methods make use of basis functions to represent atomic orbitals (so-called basis sets), it is then possible to calculate the ground state electronic structure by making use of a mathematical procedure known as the variational principle. [15]

CNDO/2 : (Complete Neglect of Differential Overlep) method proposed in 1965 and 1966 by Pople, Santry and Segal [25-29] marked the beginning of the development and the application in molecular physics and theoretical chemistry of semi-empirical methods taking into account all valence electrons, the parametrization of Pople et al. is only extended over the atoms of the three first periods of Mendeleiev's periodic table [30].

INDO: (Intermediate Neglect of Differential Overlap) the INDO method can be used for the molecules containing the first-row atoms [31]. INDO takes account all valence electrons .

NDDO method: (Neglect of Diatomic Differential Overlap): The NDDO method was described by Pople, Santry and Segal [25]. The computer program worked out by Kdhler [32,33] was applied.

MINDO/3: It was described by Bingham, Dewar and Lo in 1975, which estimates heats of formation and equilibrium geometries for hydrocarbons.

MNDO: (Modified Neglect of Diatomic Overlap) The MNDO method was described by Michael Dewar and Walter Thiel, 1977, is the oldest NDDO-based model, the MNDO model uses only s and p orbital basis sets.

AM 1 : (Austrin Model 1) It was described by Dewar and co-workers. The semi-empirical Austin Method 1 (AM1) deals only with the valence electrons [15]

PM 3 : (Parametric Method 3) It was described by James Stewart in 1989, the Hamiltonian used is similar to the AM1 Hamiltonian.

SAM 1 : (Semi-ab-intio Model 1) It was described by Dewar in 1993, SAM 1 builds by adding some new aspects to the AM1 and PM3 methods.

II.2.2. Molecular mechanics (MM) :

Because quantum-mechanical methods cannot currently be used to evaluate the energy hypersurface of molecules with more than about 50 atoms, or more than one or two rotatable bonds, and as it is more difficult to extract qualitative insight from these procedures than from molecular mechanics (MM) methods for phenomena that are predominantly non-covalent, researchers have turned to simpler MM approaches [34].

Molecular mechanics (MM) is one aspect of molecular modelling, which explains the energy of a molecule in terms of a simple function, its goal is to predict the detailed structure, also the properties of molecules.

MM approaches do not' explicitly include electronic effects, the energies can be thought of in the same spirit as the Born-Oppenheimer approximation, one uses empirical data or quantum mechanical calculations on small model systems to derive the parameters of an analytical energy function as a function of nuclear coordinates [34].

The application of MM to molecules requires one to choose a functional form for the energy equation and to derive the parameters . The equation and its parameters are called a force field [34].

MM is taken to refer to the application of such an empirical equation to molecules, using the principles of classical mechanics or semi-classical approaches, in which quantum-mechanics effects that do not correspond to changes in electronic structure can be considered [34].

II.2.2.1. Force field in molecular mechanics :

The total system energy E total is represented by the sum of bonded and non-bonded interactions :

$$E_{total} = E_b + E_\theta + E_\phi + E_{vdw} + E_{electrostatics} \text{ . [8]} \qquad (9)$$

The molecular mechanics model incorporates the intramolecular interactions of covalent bond stretching (2-body) Eb, angle bending (3-body) Eθ, and dihedral angle (4-body) Eϕ, which are based on a fixed list of atoms, the intermolecular interactions which are computed on the basis of a list of non-bonded atoms within a certain radius between atoms separated by more than three bonds or those belong to different molecules.[8], which are Evdw, and Eelectrostatics energies. (figure II.1).

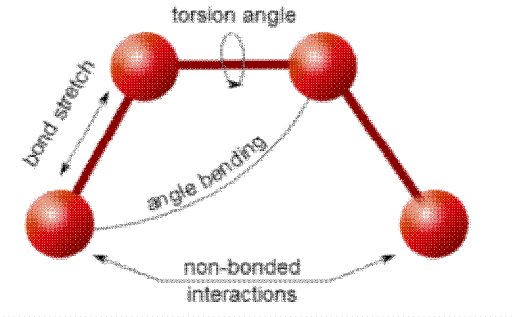

Figure II.1 : Intramolecular interactions between bonded and non-bonded atoms

II.2.2.2. Energy of interaction between bonded atoms :

Bonded interactions are interactions between atoms which are linked by covalent bonds,

II.2.2.2.1. Energy of bond stretching :

Stretching is the change in the length of a covalent bond between two atoms, such as C-H or C-C.

The oscillatory motion of two bonded atoms relative to each other, this motion consist of the two bonded atoms stretching passed their equilibrium position, then returning to their equilibrium position, and finally contracting passed their equilibrium position, the result is bond stretching (figure II.2).

$$E(L) = {}^{1}/_{2}\, K_r(L - L_0)^2 \qquad (10)$$

K_r : is the constant of stretching or constant of Hooke.

L_o : the bond length of reference .

L: the bond length in the model.

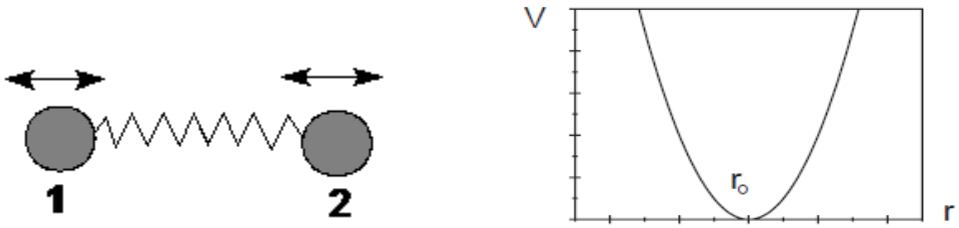

Figure II.2 : Bond stretching between two bonded atoms.

II.2.2.2.2. Energy of angle bending (inflexion) :

Bending is the change in the angle between two covalent bonds, such as the HCH angle in a methylene group, for example, if the two hydrogen atoms in a water molecule move closer together, it will change the angle between the O-H bonds, (figure II.3).

$$E(\theta) = {}^{1}/_{2}\, K_\theta(\theta - \theta_0)^2 \qquad (11)$$

K_θ : constant of bending

θ_o: bond angle of reference.

θ : bond angle.

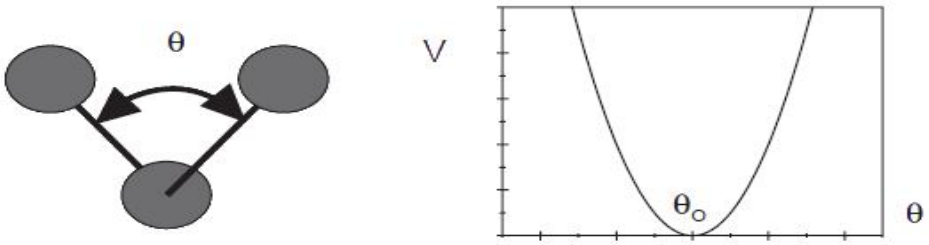

Figure II.3: Angle bending between three dependent atoms .

II.2.2.2.3. Torsion energy :

In geometry, a dihedral or torsion angle is the angle between two planes. where each plane is defined by three bonded atoms, the potential energy is expressed according to the dihedral angle ϕ (figure II.4).

$$E(\phi) = 1/2\ [V_1(1+\cos\phi)+V_2(1 - \cos 2\phi)+V_3(1+\cos 3\phi)] \qquad (12)$$

V_1, V_2, V_3 are the constants of potential energy of torsion.

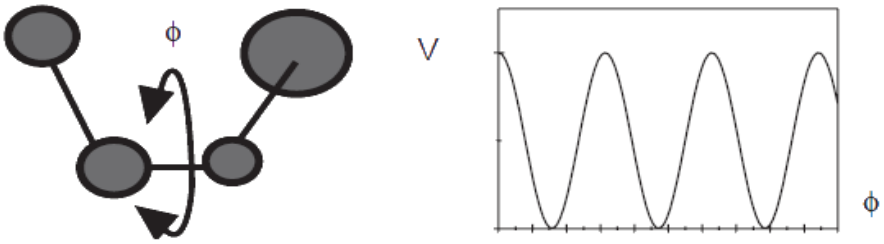

Figure II.4: Torsion between four bonded atoms.

II.2.2.3. Energy of interaction between non-bonded atoms :

non-bonded interactions act between atoms which are not linked by covalent bonds

II.2.2.3.1. Energy of Van der Waals :

The simplest non-bonded interaction is the van der Waals interaction, Van der Waals forces include attractions and repulsions between atoms, molecules, and surfaces, which includes: the force between two permanent dipoles (Keesom force) and force between a permanent dipole and a corresponding induced dipole (Debye force), also force between two instantaneously induced dipoles (London dispersion force).

$$E_{ij} = \sum_i \sum_j -\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} \qquad (13)$$

r_{ij}: distance between the two non-bonded atoms.

A_{ij} and B_{ij} are Van Der Waals constants.

II.2.2.3.2. Electrostatic interactions :

The handling of electrostatics is slightly more complicated. Electrostatic interactions are between and among cations and anions, which can be either attractive or repulsive, depending on the signs of the charges.

$$E_{elect} = \sum \frac{q_i q_j}{D r_{ij}} \qquad (14)$$

q_i, q_j : charges carried by the atoms.

r_{ij} : the distance between the two atoms.

D : dielectric constant of medium.

II.2.2.3.3. Hydrogen binding energy :

Hydrogen bend is an electrostatic bond between an electronegative atom, generally fluorine, oxygen, or nitrogen, and a hydrogen atom bound to another electronegative atom X. Hydrogen bonds are responsible for the properties of water and many other molecules. The solvent abilities of water arise primarily from two properties: its tendency to form hydrogen bonds (very short characteristic lifetime, between 10−13 and 10−12 s) and its dipolar character [35].

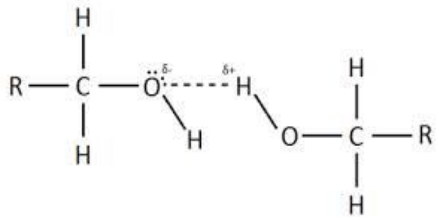

Figure II.5 : Example of hydrogen bonding.

The solid lines represent covalent bonds, and the dotted line represents hydrogen bond between the oxygen atom (O) which is called acceptor of proton, and the hydrogen atom (H). The most functions used to express these interactions are:

$$E_H = A/r_{ij}^{12} - B/r_{ij}^{10} \qquad (15)$$

$$E_H = A'/r_{ij}^{12} - B'/r_{ij}^{6} \qquad (16)$$

Where : A, B, A', B' are specific to hydrogen bonding.

II.3. SCOPE OF APPLICATION OF MOLECULAR MODELING :

Molecular modeling methods are used to investigate the structure, dynamics, surface properties and thermodynamics of inorganic, biological and polymeric systems.

Molecular modeling methods are used in the fields of computational chemistry, drug design, computational biology and materials science for studying molecular systems (small and large chemical systems). Also are used to predict molecular behaviours specifically interactions between molecules.

Molecular mechanics calculates the energy of a molecule, like the steric energy, the energy due to the geometry or conformation of a molecule.

II.4. QSAR METHODS :

II.4.1 Introduction:

It has been nearly 40 years since the quantitative structure-activity relationship (QSAR) paradigm first found its way into the practice of agrochemistry, pharmaceutical chemistry, toxicology, and eventually most facets of chemistry [36]

If we can understand how a molecular structure brings about a particular effect in a biological system, we have a key to unlocking the relationship and using that information to our advantage, formal development of these relationships on this premise has proved to be the foundation for the development of predictive models, if we take a series of chemicals and attempt to form a *quantitative relationship* between the biological effects (i.e. the *activity*) and the chemistry (i.e. the *structure*) of each of the chemicals, then we are able to form a *quantitative structure–activity relationship* or QSAR. [15]

QSAR, a quantum chemical technique [37,38] , is known to relate the biological activity of compounds with their molecular structure [39] and has been extensively used as predicting tool in rational drug design [40-45].

Computational evaluation to give predictive QSAR models is an important tool to avoid unnecessary experimental assays and find an optimum drug target. [46]

II.4.2. Historical Development of QSAR :

More than a century ago, Crum-Brown and Fraser expressed the idea that the physiological action of a substance was a function of its chemical composition and constitution [47].

A few decades later, in 1893, Richet showed that the cytotoxicities of a diverse set of simple organic molecules were inversely related to their corresponding water solubilities [48].

At the turn of the 20th century, Meyer and Overton independently suggested that the narcotic (depressant) action of a group of organic compounds paralleled their olive oil/water partition coefficients [49,50].

In 1939 Ferguson introduced a thermodynamic generalization to the correlation of depressant action with the relative saturation of volatile compounds in the vehicle in which they were administered [51].

In 1962 Hansch and Muir published their brilliant study on the structure-activity relationships of plant growth regulators and their dependency on Hammett constants and hydrophobicity [52].

The Free-Wilson approach addresses structure-activity studies in a congeneric series as described in Equation II.17 [53].

$$BA = \Sigma a_i x_i + u \qquad (17)$$

BA is the biological activity, *u* is the average contribution of the parent molecule, and *ai* is the contribution of each structural feature; *xi* denotes the presence *Xi*= 1 or absence *Xi*= 0 of a particular structural fragment.

Limitations in this approach led to the more sophisticated Fujita-Ban equation that used the logarithm of activity, which brought the activity parameter in line with other free energy-related terms [54].

$$\text{Log BA} = \Sigma G_i x_i + u \qquad (18)$$

In Equation II.18, *u* is defined as the calculated biological activity value of the unsubstituted parent compound of a particular series. *I* represents the biological activity contribution of the substituants, whereas *Xi* is ascribed with a value of one when the substituent is present or zero when it is absent.

II.4.3. Tools and techniques of QSAR:

II.4.3.1 Biological parameters:

In QSAR analysis, it is imperative that the biological data be both accurate and precise to develop a meaningful model, it must be realized that any resulting QSAR model that is developed is only as valid statistically as the data that led to its development.

Biological data are usually expressed on a logarithmic scale because of the linear relationship between response and log dose in the midregion of the log dose-response curve, inverse logarithms for activity (log 1/*C*) are used so that higher values are obtained for more effective analogs.

It is also important to design a set of molecules that will yield a range of values in terms of biological activities. Generally, the larger the range (>2 log units) in activity, the easier it is to generate a predictive QSAR [55].

II.4.3.2. Molecular descriptors :

These are truly structural descriptors because they are based only on the two-dimensional representation of a chemical structure [55]. The most widely known descriptors are those that were originally proposed by Randic [56]. and extensively developed by Kier and Hall [57].

Molecular descriptors are formal mathematical representations of a molecule, obtained by a well-specified algorithm, and applied to a defined molecular representation or a well-specified experimental procedure: *the molecular descriptor is the final result of a logic and mathematical procedure which transforms chemical information encoded within a symbolic representation of a molecule into a useful number or the result of some standardized experiment* [58].

Molecular descriptors play a fundamental role in developing models for chemistry, pharmaceutical sciences, environmental protection policy, toxicology, ecotoxicology, health research, and quality control[15]. Evidence of the interest of the scientific community in molecular descriptors is provided by the huge number of descriptors that have been proposed: more than 5000 descriptors [58]. derived from different theories and approaches are defined and computable by using dedicated software of chemical structure. [15]

Molecular descriptors are numerical indexes encoding some information related to the molecular structure, they can be both experimental physico-chemical properties of molecules and theoretical indexes calculated by mathematical formulas or computational algorithms, they are derived by applying principles from several different theories, such as quantum-chemistry, information theory, organic chemistry, graph theory, they are used to model several different properties of chemicals in scientific fields such as toxicology, analytical chemistry, physical chemistry, medicinal, pharmaceutical, and environmental chemistry.[15]

II.4.3.3. Statistical methods :

Quantitative structure activity relationships (QSAR) in the past 50 years have been considered a versatile tool for the activities prediction of drug and drug-like molecules, the aim of developing a QSAR model is to construct a relation (using statistical methods) between structures and activities. [59]

In most cases, it is more convenient to consider a linear relationship between activity/property and descriptors.[60]

The most commonly used modeling methods are [60]:

- Multiple linear regression (MLR),

- principal component regression (PCR),

- partial least squares (PLS) regression,

- artificial neural networks (ANN) .

The most widely used method is the multiple linear regression (MLR) approach originally proposed by Bartlett and Youd (1995). [61]

II.4.3.4. Multi-linear regression :

Multi-linear regression (MLR) is a statistical method for studying the relationship between a dependent variable and two or more independent variables.

In this method, a dependent variable Y is described in terms of a series of explanatory variables X1, . . ., Xn, as given in Eq II.19 :

$$Y = Y_0 + a_1 X_1 + a_2 X_2 + \cdots + a_n X_n \qquad (19)$$

It is assumed that all the explanatory variables are independent of each other [62]

II.4.3.4.1. Description of the method :

The analysis of multiple linear regression (MLR) is a statistical method that examine cause-effect relationships between dependent and independent variables, in MLR, the relationship between input variable more than one (x1 ,x2, . . .xn) and a dependent variable (y) is examined [63].

If it is assumed that the relationship is well represented by a model that is linear in the regressed variables, a suitable model may be [60]:

$$y = b_0 + b_1 x_1 + b_2 x_2 \ldots . + e \qquad (20)$$

In Eq II.20, the b's are unknown constants called regression coefficients and the objective of regression analysis is to estimate these constants, the algebraic MLR model is defined in Eq II.20, and in matrix notation. [60]:

$$y = X \beta + \varepsilon \qquad (21)$$

The matrix X is referred to as the *design matrix :*

$$y = \begin{bmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_n \end{bmatrix} \quad X = \begin{bmatrix} 1 & x_{11} & x_{12} & . & . & . & x_{1n} \\ 1 & x_{21} & x_{22} & . & . & . & x_{2n} \\ . & . & . & & & & . \\ . & . & . & & & & . \\ . & . & . & & & & . \\ 1 & x_{n1} & x_{n2} & . & . & . & x_{nn} \end{bmatrix} \quad \beta = \begin{bmatrix} \beta_0 \\ \beta_1 \\ . \\ . \\ . \\ \beta_n \end{bmatrix} \quad \text{and } \epsilon = \begin{bmatrix} \epsilon_1 \\ \epsilon_2 \\ . \\ . \\ . \\ \epsilon_n \end{bmatrix}$$

Multiple linear regression (MLR) techniques based on least-squares procedures are very often used for estimating the coefficients involved in the model equation [64,65].

II.4.3.4.2. Test of the total significance of the regression :

a. Determination coefficient (R^2) :

The *coefficient of determination (R^2)* is a measure of how well the regression line represents the data on the scatter plot. R^2 is a measure of the fit of the regression model [66]. The R^2 can be used to determine the linear relationship between the measured and estimated values. [63]. R^2 ranges from 0 to 1

The coefficient of determination R^2 is the ratio of the explained sum of squares to the total sum of squares.

$$R^2 = \frac{ESS}{TSS} = \frac{TSS-RSS}{TSS} = 1 - \frac{RSS}{TSS} \qquad (22)$$

where:

TSS is the total sum of squares: $TSS = \sum(Y_{obs} - \bar{Y})^2$ (23)

ESS ist he explained sum of squares: $ESS = \sum(Y_{cal} - \bar{Y})^2$ (24)

RSS is the residual sum of squares: $RSS = \sum(Y_{obs} - Y_{cal})^2$ (25)

b. Correlation coefficient (R)

The quantity *R*, called the *correlation coefficient*, it is a correlation coefficient between observed and predicted values of dependant variable Y, where $0 < R < 1$

$$R = (ESS/TSS)^{0.5} = (1-RSS/TSS)^{0.5} \qquad (26)$$

c. Test Fisher-Snedecor (F)

F the Fisher test, reflects the ration of the variance explained by the model and variance due to error in the model, high values of F-test indicate the significance of the equation. [66]

$$F = [ESS/(k)] / [RSS/(n-k-1)] \qquad (27)$$

Where n, and (k-1) are degrees of freedom associated to ESS and RSS respectively.

d. Standard deviation (s)

S is called the standard deviation

$$s = \sqrt{\frac{RSS}{n-k-1}} \qquad (28)$$

Where *k* is the number of independent variables

e- Prediction coefficient (Q^2)

it measures the predictive capacity of a model

$$Q^2 = 1 - \frac{PRESS}{SSY} \qquad (29)$$

II.4.4. Models Validations :

The best multiple linear regression model is one that has high R and F-values, low standard error, the least number of variables and high prediction ability [67].

To test the validity of the predictive power of model we use some techniques:

Cross-validation *LOO* (leave-one-out) is a model validation technique, for assessing how the results of a statistical analysis will generalize to an independent data set, in which we use these statistical parameters:

PRESS (predicted residual sum of squares) $\text{PRESS} = \sum(Y_{obs} - Y_{cal})^2$ (30)

TSS (total sum of squares) $\text{TSS} = \sum(Y_{obs} - \overline{Y})^2$ (31)

R^2_{adj} (adjusted R-squared) $R^2_{adj} = (1 - r^2)\left(\frac{n-1}{n-p-1}\right)$ (32)

R^2_{CV} (cross-validated correlation coefficient) $R^2_{CV} = 1 - \frac{PRESS}{TSS}$ (33)

S_{PRESS} (standard validation of the prediction errors) $S_{PRESS} = \sqrt{\frac{PRESS}{n}}$ (34)

PE (Prediction error) $PE = 0.6745\,(1 - r^2)/\sqrt{n}$ (35)

The PRESS (predicted residual sum of squares) statistic appears to be the most important parameter accounting for a good estimate of the real predictive error of the models. Its small

value indicates that the model predicts better than chance and can be considered statistically significant. [60]

II.5. PROGRAMS AND MATERIALS USED :

This work was carried out within team of Computational and pharmaceutical chemistry of the laboratory of molecular chemistry and environment (LMCE) at the university of Biskra.

The first calculations were optimized by using a software HyperChem 8.03[68]

The geometry of phenothiazine and its derivatives initially were entirely optimized by molecular mechanics, with the force field MM + (rms = 0.001 Kcal / A). Further geometries were fully re-optimized by using PM3 method.

Then a parallel study was made by using the Gaussian software 09 [69]. One based on *ab* initio of Hartree-Fock (HF) type HF/6-311++G (d,p), and the density functional theory DFT with functional calculus B3LYP, by using the following base : 6-311++G (d,p).

DFT with B3LYP/6-31G, this theory was used to calculate a number of electronic descriptors: dipole moment (DM), energy of frontier orbital's, E_{HOMO} and E_{LUMO}.

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows.[70].

All calculations are carried out in a Station (HP Intel micro-processor ® Xeon® CPU X3430, 4 Go of RAM). And in a PC (Acer Intel Micro-processor ® Core™ 2 Quad CPU Q8300 4Go of RAM).

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CHAPTER III

ELECTRONIC STRUCTURE AND PHYSICAL-CHEMISTRY PROPERTIES RELATIONSHIP FOR PHENOTHIAZINE DERIVATIVES BY QUANTUM CHEMICAL CALCULATIONS

III.1 INTRODUCTION :

The evolution of the chemistry of phenothiazine several periods can be discerned, first this heterocycle was of interest owing to its quinonoid derivatives, an important chapter of the sulfur dye chemistry,[1,2] phenothiazine derivatives might be obtained by addition of different substitutions to phenothiazine molecule.[3]

The brightest period started with the introduction of phenothiazine derivatives in medicine.[4] The present period brought the focusing on the synthesis and the investigation of the properties of new phenothiazines,[5,6] which are used for the treatment of psychotic disorders.[7]

Drugs from phenothiazine family exhibit a wide range of biological activities: neuroleptic action,[8, 9] antidepressant,[10] and anticancer, antibacterial, antiviral and multidrug resistance reversal activities,[11,12] anti-CaM activity, inhibition of the PKC activity, decrease of cell proliferation, and inhibition of the Pgp transport function.[13]

The biological activities of phenothiazine derivatives depend on their real structure,[14] which is given in the literature contained at the N-10 position : piperazine, piperidine or aliphatic side chain,[15] the intensity of neuroleptic action of these compounds could be ranked as follows: piperazine group > piperidine > aliphatic chain,[16] present work concerning aliphatic phenothiazines.

QSAR has done much to enhance our understanding of fundamental processes and phenomena in medicinal chemistry and drug design.[17–21]

Quantum chemistry methods play an important role in obtaining molecular geometries and predicting various properties.[22]

To obtain highly accurate geometries and physical properties for molecules that are built from electronegative elements, expensive *ab initio*/HF electron correlation methods are required.[23–25] Density functional theory methods offer an alternative use of inexpensive computational methods which could handle relatively large molecules.[26–32]

Quantitative Structure-Activity Relationships (QSAR) are attempts to correlate molecular structure, or properties derived from molecular structure [33–35] with a particular kind of chemical or biochemical activity.

The first QSAR and 3D-QSAR models of phenothiazines and related compounds are described in the studies of Pajeva and al.[36, 37]

A representative set of phenothiazine derivatives was chosen from the large set tested by Ramu and coworkers.[38]

The present paper reports molecular properties of phenothiazine, by using PM3, *ab initio* and density functional theory methods, next some of phenothiazine derivatives are reported by using *ab initio* method; lastly, we terminate with QSAR proprieties of aliphatic phenothiazines.

The paper deals with a specific organization form of molecular matter. Other forms are given for example in the References. [39–45].

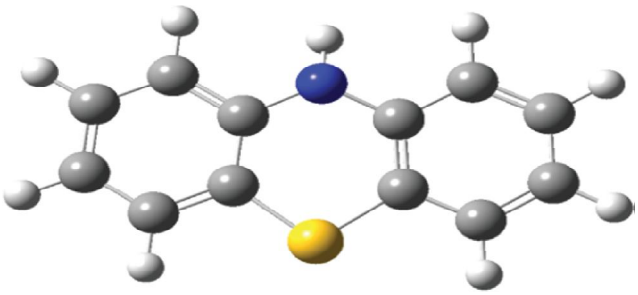


Figure III.1. 3D Conformation of phenothiazine (Gauss View 3.09).

III.2. MATRIALS AND METHODS :

All calculations were performed by using HyperChem 8.03 software.[46] The geometries of phenothiazine and its derivatives, were first fully optimized by molecular mechanics, with MM+ force-field (rms = 0.001 Kcal/Å).

Further geometries were fully re-optimized by using PM3 method.[47] After that, a parallel study has been made by using Gaussian 09 program package,[48] with HF/6-311++G(*d, p*) and B3LYP/6-311++G(*d, p*).

The calculation of properties QSAR is performed by the module (QSAR Properties, version 8.0). QSAR Properties is a module that, together with HyperChem, allows several properties commonly used in QSAR studies to be calculated. The calculations are empirical, and so, generally fast. The calculated results have been reported in the present work.

III.3. RESULTS AND DISCUSSION :

III.3.1. Geometric and Electronic Structure of Phenothiazine and Phenothiazine Systems:

The efficiency of DFT method may be scrutinized by comparison with the results obtained by more elaborate calculation such as *ab initio*/HF. Present results concerning bond length values for phenothiazine (Table III.1) and charge densities (Table III.2), and dihedral angles (Table III.3).

Table III.1. Bond lengths (angstrom) of phenothiazine.

Bond length	PM3	ab initio/HF (6-311G**)	DFT/B3LYP (6-311G**)
C1-C2	1.388	1.383	1.392
C2-C3	1.391	1.384	1.392
C3-C4	1.388	1.385	1.394
C4-C12	1.395	1.384	1.393
C12-C11	1.404	1.390	1.403
C11-N	1.436	1.401	1.404
C11-C1	1.402	1.388	1.398
S-C12	1.759	1.776	1.785

Table III.2. Net charge distribution for phenothiazine.

Atoms	PM3	ab initio/HF (6-311G**)	DFT/B3LYP (6-311G**)
C1	-0.138	-0.514	-0.416
C2	-0.069	-0.193	-0.218
C3	-0.122	-0.107	-0.110
C4	-0.047	-0.027	0.193
S	0.198	-0.246	-0.292
N	0.142	0.019	0.113
C11	-0.060	-1.259	-1.238
C12	-0.204	1.553	1.276

Table III.3. Dihedral angles in degree.

Dihedral angle	PM3	ab initio/HF (6-311G**)	DFT/B3LYP (6-311G**)
C11-C1-C2-C3	000.61	001.49	001.68
C1-C2-C3-C4	000.25	000.43	000.50
C2-C3-C4-C12	000.82	001.33	001.47
C3-C4-C12-C11	000.52	002.03	002.28
C3-C4-C12-S	179.15	174.88	173.84
C4-C12-C11-C1	000.34	000.96	001.01
C4-C12-C11-N	175.13	179.73	179.57
C4-C12-S-C13	163.27	148.69	151.50
S-C12-C11-C1	179.99	175.99	175.04
S-C12-C11-N	004.51	003.32	004.28
C11-C12-S-C13	017.07	034.38	032.36
C12-C11-C1-C2	000.90	000.79	000.87
N-C11-C1-C2	174.69	178.52	178.45
C12-C11-N-C14	031.51	038.89	034.58
C1-C11-N-C14	152.96	141.81	146.11
C1-C11-N-C12	175.52	179.30	179.31
C11-C12-C4-S	179.67	176.91	176.12
C12-C11-C14-C13	000.00	000.00	000.00

From these results a good correlation can be seen between the *ab initio*, PM3, and DFT for bond lengths, also the charge densities calculated by these methods are approximately similar.

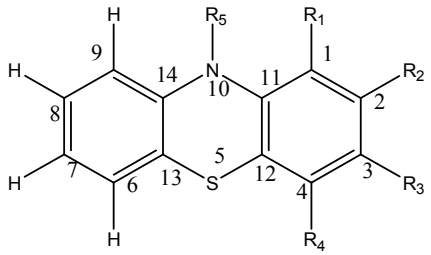
The Dihedral angles vary between 000.00 and 179.99 degree, also we note that these angles calculated by *ab initio*/HF are more similar to those calculated by DFT method, (Table III.3). The geometry of phenothiazine is symmetric and pseudo-planar.

After that, in Tables III.4 and III.5 we studied the energies of phenothiazine, and (methyl, chloride) substituted phenothiazines (Fig.III. 2), which are: heat of formation (H_f) , dipole moment (μ), HOMO (highest occupied molecular orbital), LUMO (lowest unoccupied molecular orbital), and their difference (ΔE). In Tables III.6 and III.7 charge densities of these compounds are reported.

We note that the heat of formation approximately 7 kcal/mol is diminished at each addition of methyl group, in the base compound phenothiazine.

Compound 6 (substitution N-10) has the greatest value of the heat of formation. This compound (6) is more stable compared to other derivatives. This is in good agreement with

experiment, because the majority of bioactive phenothiazine derivatives have a significant substituent at this position.[16]



Series 1

1. R1=R2=R3=R4=R5=H
2. R1=CH_3, R2=R3=R4=R5=H
3. R1=R3=R4=R5=H, R2=CH_3
4. R1=R2=R4=R5=H, R3=CH_3
5. R1=R2=R3=R5=H, R4=CH_3
6. R1=R2=R3=R4=H, R5=CH_3

Series 2

1. R1=R2=R3=R4=R5=H
2. R1=Cl, R2=R3=R4=R5=H
3. R1=R3=R4=R5=H, R2=Cl
4. R1=R2= R4=R5=H, R3=Cl
5. R1=R2=R3= R5=H, R4=Cl
6. R1=R2=R3=R4=H, R5=Cl

Figure III.2. Scheme of phenothiazine systems.

Table III.4. Energies of phenothiazine and methyl-substituted phenothiazines.

Compound	System	Heat of formation (kcal/mol)	-HOMO (a.u)	LUMO (a.u)	ΔE (a.u)	μ(D)
1	Phenothiazine	59.66	0.277	0.056	0.333	2.397
2	1-methyl phenothiazine	51.51	0.275	0.056	0.331	2.757
3	2- methylphenothiazine	50.27	0.274	0.056	0.330	2.682
4	3-methyl phenothiazine	50.33	0.255	0.053	0.308	2.537
5	4- methylphenothiazine	52.43	0.275	0.057	0.332	2.005
6	10-methyl phenothiazine	56.30	0.279	0.058	0.337	2.342

Note: Heat of formation by PM3, Δ*E* and μ by *ab initio*.

Table III.5. Energies of phenothiazine and chloride-substituted phenothiazines.

Compound	System	Heat of formation (kcal/mol)	-HOMO (a.u)	LUMO (a.u)	ΔE (a.u)	μ(D)
1	Phenothiazine	59.66	0.277	0.056	0.333	2.397
2	1- chloro phenothiazine	53.57	0.285	0.059	0.344	1.208
3	2- chloro phenothiazine	53.08	0.285	0.053	0.338	2.198

4	3- chloro phenothiazine	53.24	0.284	0.051	0.335	3.632
5	4- chloro phenothiazine	55.44	0.284	0.052	0.336	3.920
6	10- chloro phenothiazine	63.10	0.296	0.061	0.357	1.840

Heat of formation by PM3, ΔE and μ by ab initio

Table III.6: Net atomic charges for methyl-substituted phenothiazines.

Compound	**1**	**2**	**3**	**4**	**5**	**6**
C-1	-0.5139	0.1667	-0.4655	-0.0229	-0.4457	0.2254
C-2	-0.1928	-0.5028	0.8577	-0.6478	-0.2595	-0.3475
C-3	-0.1070	-0.3262	-1.1900	0.7964	-0.9612	-0.2059
C-4	-0.0273	0.4436	0.3125	-0.4538	0.8976	0.1020
Sulfur	-0.2458	-0.3503	-0.3937	-0.4741	-0.4390	-0.3544
C-6	-0.0273	0.0190	-0.2701	-0.4239	0.0463	0.1020
C-7	-0.1070	-0.1121	-0.1616	-0.1184	-0.2737	-0.2059
C-8	-0.1928	-0.2973	-0.2217	-0.3336	-0.1285	-0.3475
C-9	-0.5139	-0.5655	-0.5130	-0.4072	-0.5860	0.2254
Nitrogen	0.0198	0.0346	0.0154	-0.1084	0.0227	0.3340
C-11	-1.2593	-0.7723	-0.9059	-0.5570	-0.6258	-0.7410
C-12	-1.5532	-0.7860	1.2281	0.7567	1.2683	0.3497
C-13	-1.5532	1.9387	1.6019	1.4493	1.1249	0.3497
C-14	-1.2593	-1.5609	-1.0194	-0.6725	-0.8063	-0.7410
C-methyl 1	–	-0.5362	–	–	–	–
C-methyl 2	–	–	-0.4541	–	–	–
C-methyl 3	–	–	–	-0.3500	–	–
C-methyl 4	–	–	–	–	-0.4457	–
C-methyl 10	–	–	–	–	–	-0.2686

Note: Net charge calculated by *ab initio*.

Table III.7. Net atomic charges for chloride -substituted phenothiazines.

Compound	**1**	**2**	**3**	**4**	**5**	**6**
C-1	-0.5139	1.0984	-0.8026	-0.5690	-0.5330	0.7941
C-2	-0.1928	-0.4849	0.9382	-0.8798	-0.3085	-0.3180
C-3	-0.1070	-0.4140	-0.9612	1.0016	-0.8130	0.0385
C-4	-0.0273	0.4302	0.1312	0.0250	0.5916	-0.4003
Sulfur	-0.2458	-0.3085	-0.3437	-0.2691	-0.3856	-0.2060
C-6	-0.0273	-0.0255	-0.1164	-0.0089	0.0464	-0.3996
C-7	-0.1070	-0.1150	-0.2016	-0.1382	-0.2714	0.0386
C-8	-0.1928	-0.2766	-0.2003	-0.1911	-0.1538	-0.3177
C-9	-0.5139	-0.4799	-0.5668	-0.6232	-0.5894	0.7949
Nitrogen	0.0198	0.1693	0.0189	0.0217	0.0311	0.6480
C-11	-1.2593	-2.1172	-1.1126	-1.3024	-0.7485	-1.5330
C-12	-1.5532	0.7187	1.1179	1.0427	1.1757	0.6657
C-13	-1.5532	1.6156	1.5781	1.5186	1.3356	0.6669
C-14	-1.2593	-1.1855	-1.0022	-1.1408	-0.9495	-1.5317
C- Chloro 1	–	0.1334	–	–	_	–
C- Chloro 2	–	–	0.2759	–	–	–

C- Chloro 3	–	–	–	0.2623	–	–
C- Chloro 4	–	–	–	–	0.3626	–
C- Chloro 10	–	–	–	–	–	-0.1085

Net charge calculated by ab initio

For these compounds the negative atomic charge on sulfur is increased considerably, also, on nitrogen the atomic charge is increased, except for compounds 3 and 4 (Table III.6).

In methyl-substituted phenothiazines the 3-methyl phenothiazine (compound 4) shows greatest positive charge on 3rd position carbon (0.7964) which leads to nucleophilic substitution (Table III.6).

The substitution in positions C11, C12, C13, and C14 was neglected because of the presence of the effect of the hyperconjugaison in these positions.

This is further supported by the least HOMO–LUMO energy gap (0.308) (Table III.4) which depicts the chemical reactivity of the compound, the higher is the HOMO–LUMO energy gap, the lesser is the flow of electrons to the higher energy state, making the molecular hard and less reactive.

On the other hand in lesser HOMO–LUMO gap there is easy flow of electrons to the higher energy state making it reactive and softer (HSAB principle: hard and soft acids and bases). Hard bases have highest occupied molecular orbitals (HOMO) of low energy; and hard acids have lowest unoccupied molecular orbitals (LUMO) of high energy.[49]

From the results of Table III.4, the 3-methyl phenothiazine (compound 4) shows an important dipole moment value (2.537 D).

We also note that the methyl substituent (donor effect) has the effect of increasing the energy of the HOMO except (compound 6), with little change in the LUMO (Table III.4).

In Table III.5 we have studied chloride-substituted phenothiazines, along the same line of methyl-substituted phenothiazines for a comparative study. We note that the heat of formation is decreased approximately 5 kcal/mol at each addition of chloride group, except for (compound 6).

It is attractive to note that the positive atomic charge on nitrogen is increased for these chloride derivatives, except for (compound 3), also on sulfur the negative atomic charge is increased considerably, except for compound 6 (Table III.7).

In chloride-substituted phenothiazines, the 3-chloro phenothiazine (compound 4) is predicted to be the most reactive with least HOMO–LUMO energy gap (0.335) (Table III.5), the 3rd position shows maximum positive charge (1.0016) which refers to nucleophilic attack.

Also this compound 3-chloro phenothiazine shows an important dipole moment value (3.632 D).

III.3.2. Study of Structure Physical-Chemical Properties :

We have studied six physical-chemical proprieties of aliphatic phenothiazines (twelve compounds) by HyperChem software.

For example, Figure III.3 shows the favored conformation in 3D of the compound 1. We will continue this work in the future by a quantitative calculation.

QSAR proprieties are, molar polarizability (Pol), partition coefficient octanol/water (log *P*), hydration energy (HE), molar volume (MV), Surface area grid (SAG) and molar weight (MW).

Calculation of log *P* is carried out using atomic parameters derived by Viswanadhan and coworkers.[50] Computation of molar refractivity was made via the same method as log *P*.

Ghose and Crippen presented atomic contributions to the refractivity.[51]

The solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bodor et al.[52] using the atomic radii of Gavezzotti.[53]

The polarizability was estimated from an additivity scheme given by Miller [54] with a precision on the calculation of 3%, where different increments are associated with different atom types. The hydration energy is a key factor determining the stability of different molecular conformation.[55]

The calculation is based on exposed surface area, and employs the surface area as computed by the approximate method (above), weighted by atom type.

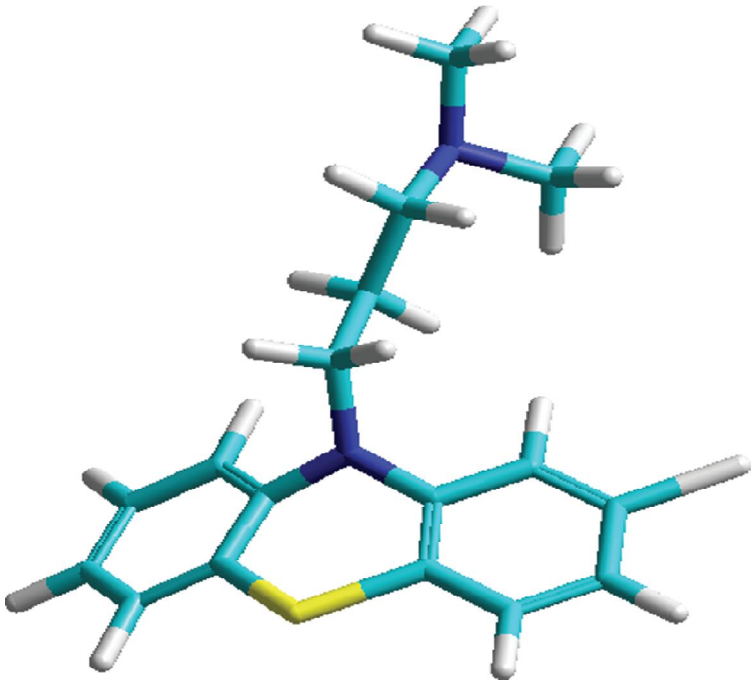


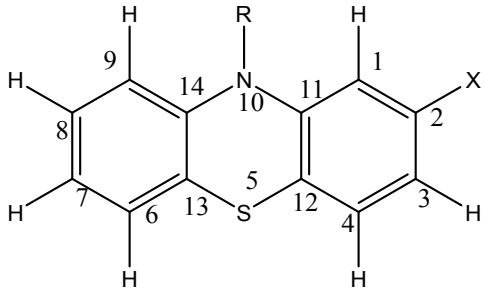
Figure III.3. 3D Conformation of compound 1 (HyperChem 8.03).

III.3.2.1. Structural Comparison of the Aliphatic Phenothiazines :

Based on our conclusions on the effect of substitution on the phenothiazine molecule, we chose a series of aliphatic phenothiazines, which are a class of heterocyclic synthetic compounds, many of which, such as chlorpromazine and ethopropazine have been primarily used for treatment of neurological disorders, .[56] including schizophrenia and tremor.[57, 58]

Initially, we performed a structural comparison of this series (Figure III. 4). In these molecules, the type of the side-chain group and eventually the group substituting the phenothiazine ring system at position 2 is essential for the different effects exerted by these compounds.[59,60]

We used molecular mechanics, with MM+ force-field to calculate the stable conformations of this series. In a window of 2 kcal/mol, only one favored conformation is found, for each structure. These molecules have a weak conformational flexibility, with regard to the other macrocycles of macrolide type .[61–66]



Compounds	X	R
1 Chlorpromazine	Cl	CH_2-CH_2-CH_2-N(CH_3)$_2$
2 Acepromazine	CO-CH_3	CH_2-CH_2-CH_2-N(CH_3)$_2$
3 Aceprometazine	CO-CH_3	CH_2-CH_2-CH_2-N(CH_3)$_2$
4 Alimemazine	H	CH_2-CH(CH_3)-CH_2-N(CH_3)$_2$
5 Levomepromazine	OCH_3	CH_2-CH(CH_3)-CH_2-N(CH_3)$_2$
6 Cyamemazine	CN	CH_2-CH(CH_3)-CH_2-N(CH_3)$_2$
7 Prometazine	H	CH_2-CH(CH_3)-N(CH_3)$_2$
8 Etymemazine	C_2H_5	CH_2-CH(CH_3)-CH_2-N(CH_3)$_2$
9 Methoxypromazine	OCH_3	CH_2-CH(CH_3)-N(CH_3)$_2$
10 Triflupromazine	CF_3	CH_2-CH(CH_3)-N(CH_3)$_2$
11 Chlorproethazine	Cl	CH_2-CH_2-CH_2-N(C_2H_5)$_2$
12 Promazine	H	CH_2-CH_2-CH_2-N(CH_3)$_2$

Figure III.4. Structural comparison of aliphatic phenothiazines.

III.3.2.2. Structure Physical-Chemistry Property Relationship :

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity.

Lipophilicity has been studied and applied as an important drug property for decades. It can be quickly measured or calculated.

Lipophilicity has been correlated to many other properties, such as bioavailability, storage in tissues, permeability, volume of distribution, toxicity, plasma protein binding and enzyme receptor binding.[67,68]

Log *P* value has been used to estimate the facility with which a compound will crows the blood-brain barrier by diffusion, experimentally, this is done by partitioning the molecule

between water and the hydrophobic solvent *n*-octanol, and determining the *P* value as the ratio of the concentration of the compound in *n*-octanol and that in water.[69]

The values of polarizability are generally proportional to the values of surfaces and of volumes, the decreasing order of polarizability for these studied phenothiazines is: 11, 8, 5, 2 and 3, 6, 9, 1, 4, 10, 7 and 12 (Table III.8).

The order of polarizability is approximately the same one for volume and surface. This is explained by the relation between polarizability and volume, for the relatively non polar molecules.

The polarizability of a molecule depends only on its volume, the thermal agitation of the non-polar molecules does not have any influence on the appearance of dipole moments in these molecules.

On the other hand for the polar molecules, the polarizability of the molecule does not depend solely on volume but also depends on other factors such as the temperature, because of the presence of the permanent dipole.[70]

One way to represent the molecular volume is to select a surface of fixed electron density (0.001 e/bohr^3, in this case) and to compute the volume within that isodensity surface.[71]

The surface and the volume of distribution of these molecules are definitely higher than that of more polar molecules like the lipopeptides or beta-lactams. For example, Deleu et al. used TAMMO software [72] on the surfactins C13, C14 and C15 having cores similar to the macrolides. They found that their surfaces vary from 129 to 157 Å^2,[73] contrarily for these phenothiazines surfaces vary from 479.93 to 586.68 Å^2. These phenothiazines have a great variation of distribution volume, in particular compound 8 and compound 11, which have respective volumes: 1002.63 and 1000.18 Å^3 (Table III.8).

The most important hydration energy in the absolute value, is that of the compound 6 (5.28 kcal/mol) and the weakest is that of compound 8 (0.31 kcal/mol) (Table III.8). Indeed in the biological environments the polar molecules are surrounded by water molecules.

Hydrogen bonds can be established between a water molecule and these molecules.

The donor sites of proton interact with the oxygen atom of water and the acceptor sites of proton interact with the hydrogen atom.

The first correspond to the complex with the strongest hydrogen bond. These hydrated molecules are dehydrated at least partially before and at the time of their interaction.

These interactions of weak energy, which we observe in particular between messengers and receivers, are generally reversible.[74]

Compound 6 does not possess any donor site of proton, but it has four acceptor sites of proton (2 N on the alkyl groups *R* and *X*, and 1N, 1S on the core base).

On the other hand, compound 8 does not possess any donor site, but it possesses three acceptor sites of proton (1N, on the alkyl group *R*, 1N and 1S on the core base). The first having higher value, it has one more donor site of protons. This property supports the first compound, not only by fixing on the receiver, but in more activates it. It is thus about an agonist. It has as a consequence a better distribution in fabrics. All (log*P*) of studied molecules have optimal values.

For good oral bioavailability, the log*P* must be greater than zero and less than 3 ($0 < \log P < 3$). For log*P* too high, the drug has low solubility and a log *P* too low; the drug has difficulty penetrating the lipid membranes.[57]

Compound 9 presents the low coefficient of division (−1.55), comes after the compound 5 (−1.05). When the coefficient of division is rather low, it has as a consequence a better gastric tolerance. Compounds 8 and 10 which have respectively higher values 0.49 and 0.01, have capacities to be dependent on plasmatic proteins.

Table III.8. QSAR proprieties for aliphatic phenothiazines.

phenothiazine derivative	Molecular Volume ($Å^3$)	Molecular Surface ($Å^2$)	Molecular Mass (uma)	Partition coefficient (Log P)	Hydratation energy (Kcal/mol)	Polarizability ($Å^3$)
1	908.92	541.12	318.86	-0.78	-1.39	36.12
2	965.96	571.10	326.46	-0.63	-0.93	37.95
3	920.73	525.17	326.46	-0.27	-0.66	37.95
4	897.38	527.34	298.45	-0.06	-1.17	36.03
5	977.74	566.17	328.47	-1.05	-2.72	38.50
6	951.41	558.90	323.46	-0.33	-5.28	37.88
7	823.52	479.93	284.42	-0.20	-1.12	34.20
8	1002.63	583.03	326.50	0.49	0.31	39.70
9	942.32	561.30	314.45	-1.55	-3.06	36.67
10	945.35	561.84	352.42	0.01	-1.19	35.76
11	1000.18	586.68	346.92	-0.10	-0.64	39.80
12	836.92	488.39	284.42	-0.56	-1.10	34.20

III.4. CONCLUSION :

The present work studied the molecular proprieties of aliphatic phenothiazines. The PM3, DFT and *ab initio* method can be used quite satisfactorily in predicting the chemical reactivity of the molecules and the effect of substitution of either donor or acceptor electron.

In the substituted methyl group, 3-methyl phenothiazine is predicted to be the most reactive with least HOMO- LUMO energy gap of all aliphatic phenothiazines.

4-chloro phenothiazine presents the higher value of dipole moment, but the presence of a donor group in this position diminishes this value.

Compound 9 presents the lower coefficient of division (log*P*), as a consequence, it has the best gastric tolerance. Compound 6 has important hydration energy; it has a better distribution in fabrics.

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CHAPTER IV :

STRUCTURE ACTIVITY RELATIONSHIP AND QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIPS MODELING OF CYTO-TOXICITY OF PHENOTHIAZINE DERIVATIVES

IV.1. INTRODUCTION :

Quantitative Structure-Activity Relationships (QSAR) are attempts to correlate molecular structure,[1–6] or properties derived from molecular structure[7–9] with a category of biological activity,[10–14] and has been extensively used as predicting tool in rational drug design.[15–20]

Multiple linear regression (MLR) is a mathematical tool that quantifies the relationship between a dependent variable and one or more independent variables,[21] it was used to develop QSAR models,[22] and all the variables that have been included in the model are significant.[21]

Drugs from phenothiazine family exhibit a wide range of biological activities which depend on their real structure:[23] neuroleptic action,[24, 25] antidepressant,[26] and anticancer, antibacterial, antiviral activities,[27, 28] anti-CaM activity, inhibition of the PKC activity, decrease of cell proliferation, and inhibition of the Pgp transport function.[29]

Apart of their well known activity in nerve cells some phenothiazine derivatives were discovered to be effective chemo sensitizers in multidrug resistant (MDR) tumor cells.[30]

Their MDR reversing activity has been assessed in different resistant tumor cell lines and several structure-activity relation-ships have been derived, studies of Ford et al.[31,32]

The first QSAR models of phenothiazines and related compounds are described in the studies of Pajeva and Weise,[33,34] using these compounds with MDR reversing activity.

In the work of Tsakovska, he confirmed the important role of hydrophobicity, and also hydrogen bond acceptor interaction on anti MDR activity.[35]

Following our interest in this field, our present research aimed to describe the structure-property relationships study on phenothiazines and developed a QSAR model on these compounds with respect to their anti multi-drug resistance activity.

A representative set of 18 phenothiazines was chosen from the large set tested by Ramu and Cowerkers,[36] and Tsakovska which selected the compounds to have a common parental structure and to range in biological activity by more than two log units so that to reduce the risk of chance correlation.[35]

IV.2. EXPERIMENTAL DETAILS :

IV.2.1. Biological data

The activity parameter as evaluated in P388 sensitive cell line

was used: A = ED50 compound P388, μ M [35]

A represent cyto-toxicity of the compounds in the sensitive cell line,[35, 36] which is the concentration of drug effective in inhibiting the cell-growth rate by 50% (ED_{50}), dose-response curves were thus produced and used to determine this concentration.[36]

Tsakovska transformed the values of biological parameter to logarithmic scale, the inverse values of ED_{50} were used to obtain higher values for the more active compounds.[35]

IV.2.2. Descriptors generation

Firstly, the eighteen investigated molecules were pre-optimized by means of the Molecular Mechanics Force Field (MM+) included in HyperChem version 8.03 package.[37] After that, the resulted minimized structures were further refined using the semiempirical PM3 Hamiltonian implemented also in Hyper-Chem. We chose a gradient norm limit of 0.01 kcal/Å for the geometry optimization. Then, these structures were re-optimized by using Gaussian 09 program package,[38] with DFT B3LYP/6-31G, this theory was used to calculate a number of electronic descriptors: dipole moment (DM), energy of frontier orbital's, E_{HOMO} and E_{LUMO}.

The QSAR properties module from HyperChem 8.03 was used to calculate: molar polarizability (Pol), the molar refractivity (MR), partition coefficient octanol/water (log *P*),

hydration energy (HE), molar volume (MV), Surface area grid (SAG) and molar weight (MW).

Calculation of log *P* is carried out using atomic parameters derived by Viswanadhan and coworkers.[39] Computation of molar refractivity was made via the same method as log *P*. Ghose and Crippen presented atomic contributions to the refractivity.[40]

Solvent-accessible surface bounded molecular volume and van der Waals-surface-bounded molecular volume calculations are based on a grid method derived by Bodor et al.,[41] using the atomic radii of Gavezotti.[42] Polarizability was estimated from additivity scheme given by Miller with a 3% in precision for the calculation,[43] where different increments are associated with different atom types.

The hydration energy is a key factor determining the stability of different molecular conformations.[44]

IV.2.3. Regression analysis

Multiple linear regression analysis of molecular descriptors was carried out using the stepwise strategy in SPSS version 19 for Windows.[45]

IV.3. RESULTS AND DISCUSSION :

IV.3.1. Structure activity relationship (SAR)

We have studied seven physical chemical proprieties of series of eighteen phenothiazine derivatives using HyperChem software.

QSAR proprieties such as van der Waals surface molecular volume, octanol-water partition coefficient (log *P*), molar refractivity (MR), polarizability (Pol), solvent-accessible, surface bounded molecular volume and molecular weight (M) were investigated.

Molecular polarizability of a molecule characterizes the capability of its electronic system to be distorted by the external field, and it plays an important role in modeling many molecular properties and biological activities.[46]

The attractive part of the Van der Waals interaction is a good measure of the polarizability. Highly polarizable molecules can be expected to have strong attractions with other molecules.

The polarizability of a molecule can also enhance aqueous solubility.[47]

The molar refractivity (MR) is important criterion to measure the steric factor. It is usually designated as a simple measure of the volume occupied either by an individual atom or a cluster (group) of atoms.[48]

Polarizability and molar refractivity relatively increase with the size and the molecular weight of the studied phenothiazines (Table IV.2). This result is in agreement with the formula of

Lorentz-Lorenz which gives a relationship between polarizability, the molar refractivity and volume.[49]

This relationship shows that the polarizability and the molar refractivity increase with the volume and the molecular weight. For example, the compound AHR 06601 (Compound 8) has great values of polarizability (54.17) and molar refractivity (154.31).

In contrast, the Promethazine (compound 5) and Promazine (compound 1) are small molecules in the series of studied phenothiazines, which have a small values of polarizability (34.20), and of molar refractivity (97.95) (98.39) respectively.

The presence of the hydrophobic groups in the structure of the phenothazines induces a decrease of the hydratation energy; however, the presence of hydrophilic groups increases the hydratation energy (Table IV.2). The most important hydratation energy in the absolute value, (8.86 kcal/mol) is that of the compound 14 (Thioproperazine), but the lower one (0.28 kcal/mol) was performed for the compound 13 (Butaperazine) (Table IV.2).

Indeed in the biological environment the polar molecules are surrounded by water molecules where the Hydrogen bonds can be established between the water molecule and the molecules under study.

The donor sites of proton interact with the oxygen atom of water and the acceptor sites of proton interact with the hydrogen atom. The first corresponds to the complex having strongest hydrogen bond. At least, these hydrated molecules are partially dehydrated before their interaction.

These interactions of weak energy are generally reversible in particular between messengers and receivers.[50]

Compound 14 does not possess any donor site of proton, but it has eight acceptor sites of proton (2N on the alkyl group R and 1S, 2O, 1N, on the group *R*1, and 1N, 1S on the core base).

On the other hand, the compound 13 has no donor site of proton, but it has five acceptor sites of proton (2N on the alkyl group R and 1O on the group *R*1, and 1N, 1S on the core base). The first having higher value, it has three more donor site of protons.

This property supports the compound 14 not only by fixing the receptors, but also activates it by playing the role of agonist. It has as a consequence a better distribution in fabrics.

Lipophilicity is a property that has a major effect on solubility, absorption, distribution, metabolism, and excretion properties as well as pharmacological activity. Hansch and Leo reasoned that highly lipophilic molecules will partition into the lipid interior of membranes and will be retained there.[51]

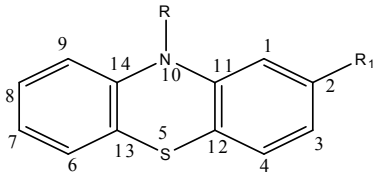
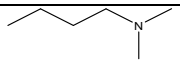
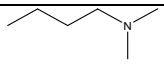
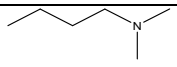
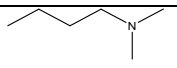
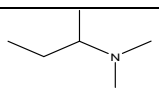
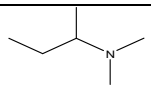
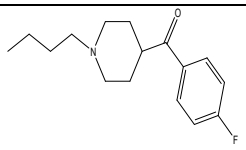
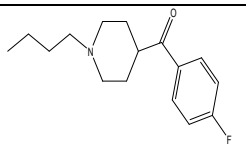
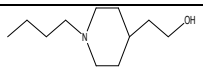
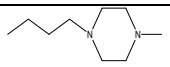
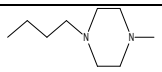
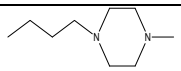
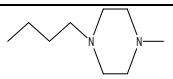
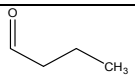
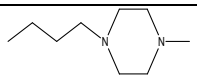
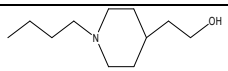
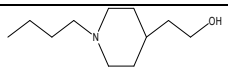
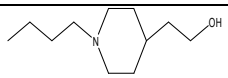
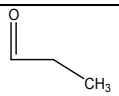
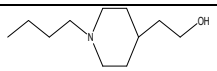


Table IV.1. Chemical structures and experimental activity of the phenothiazine derivatives

Compound		R	R^1	log(1/A) exp	log(1/A) pred
1	Promazine		H	-1.602	-1.571
2	Chlorpromazine		Cl	-1.079	-1.169
3	Triflupromazine		CF_3	-1.079	-1.138
4	Acepromazine			-1.477	-1.426
5	Promethazine		H	-1.778	-1.801

6	Acepromethazine			-1.602	-1.533
7	Duoperone		CF_3	-1.000	-0.981
8	AHR 06601			-1.000	-0.995
9	Piperacetazine			-1.301	-1.382
10	Perazine		H	-1.079	-1.051
11	Prochlorperazine		Cl	-0.653	-0.714
12	Trifluoperazine		CF_3	-0.653	-0.627
13	Butaperazine			-0.653	-0.696
14	Thioproperazine		$SO_2N(CH_3)_2$	-0.903	-1.084
15	Perphenazine		Cl	-0.903	-0.915
16	Acetophenazine			-1.176	-1.000
17	Carphenazine			-1.079	-0.996
18	Fluphenazine		CF_3	-0.903	-0.839

For good oral bioavailability, the log *P* must be greater than zero and less than 3 ($0<\log P<3$). For log *P* too high, the drug has low solubility and a log *P* too low, the drug has difficulty to penetrate the lipid membranes.[52]

In opposition to hydratation energy, the presence of the hydrophobic groups in the structure of the phenothiazines induces an increase of the lipophilicity.

Compound 15 (Perphenazine) presents the low coefficient of division (−1.42), then compounds 16 and 14 with log *P* (−1.27) and (−1.20), respectively. When the coefficient of division is rather low, it has as a consequence a better gastric tolerance.

Compound 7 (Duoperone) which have higher value (1.16) have capacities to be dependent on plasmatic proteins.

IV.3.2. Quantitative Structure-Activity Relationships Studies

Firstly, different substituted phenothiazines (Table IV.1) were evaluated for their anti MDR activity. The biological parameter (A) was introduced in this search and the results are illustrated in Table IV.1. In order to determine the role of structural features.

A series of 18 phenothiazines was investigated by QSAR method. These compounds were used for multilinear regression model generation.

Different physicochemical descriptors such as steric, electronic and molecular structure were used as independent variables and were correlated with biological activity.

Developing a QSAR model requires a diverse set of data, and, thereby a large number of descriptors have to be considered.

Table IV.2 Values of molecular descriptors used in the regression analysis.

Comp	E_{HOMO}	E_{LUMO}	DM	Log P	HE	Pol	MR	MV	SAG	MW
1	-0.181	-0.012	2.973	-0.56	-1.93	34.20	98.39	862.62	508.00	284.42
2	-0.191	-0.023	2.546	-0.78	-1.62	36.13	103.11	914.10	538.81	318.86
3	-0.196	-0.041	3.337	0.01	-1.50	35.76	103.61	942.15	547.12	352.42
4	-0.191	-0.062	4.904	-0.63	-1.44	37.95	107.94	953.37	548.34	326.46
5	-0.185	-0.009	2.081	-0.20	-1.80	34.20	97.95	839.80	488.76	284.42

6	-0.191	-0.061	1.833	-0.27	-0.97	37.95	107.50	944.62	548.48	326.46
7	-0.197	-0.071	2.736	1.16	-3.07	51.98	149.98	1296.18	724.11	514.58
8	-0.194	-0.071	3.760	0.52	-2.86	54.17	154.31	1324.45	742.57	488.62
9	-0.196	-0.062	4.330	-0.33	-6.40	46.99	131.16	1166.11	653.63	410.57
10	-0.167	-0.008	2.320	-0.76	-1.52	40.28	114.44	990.15	559.65	339.50
11	-0.171	-0.019	2.834	-0.98	-1.24	42.21	119.16	1032.36	584.13	373.94
12	-0.172	-0.039	3.874	-0.19	-1.08	41.84	119.66	1070.15	606.26	407.50
13	-0.171	-0.060	4.709	0.20	-0.28	47.71	133.22	1205.64	682.31	409.59
14	-0.165	-0.084	4.953	-1.20	-8.86	49.57	138.70	1248.56	693.76	446.63
15	-0.172	-0.019	2.168	-1.42	-7.32	44.68	125.45	1104.76	626.52	403.97
16	-0.173	-0.061	3.842	-1.27	-6.93	46.51	130.28	1168.79	658.92	411.56
17	-0.173	-0.060	3.708	-0.64	-6.67	48.34	134.91	1222.93	690.81	425.59
18	-0.174	-0.040	3.493	-0.63	-7.16	44.31	125.95	1141.74	647.19	437.52

Descriptors are numerical values that encode different structural features of the molecules. Selection of a set of appropriate descriptors from a large number of them requires a method, which is able to discriminate between the parameters.

Pearson's correlation matrix has been performed on all descriptors by using SPSS Software. The analysis of the matrix revealed sixteen descriptors for the development of MLR model. The values of descriptors selected for MLR model are presented in Table IV.2.

The correlation between the biological activity (A) and descriptors expressed by the following relation:

$$\log(1/A) = -3.823 + 6.739E_{LUMO} - 0.383\log P + 0.121HE - 0.059MR + 0.007MV + 0.008MW.$$

n =18; r= 0.971; s= 0.1; F= 29.900; Q= 9.71

The values of fraction variance may varied between 0 and 1.

QSAR model having $r^2 > 0.6$ will only be considered for validation. For example, the value $r = 0.971$ and $r^2 = 0.942$ allowed us to indicate firmly the correlation between different parameters (independent variables) with cyto-toxicity of the compounds in the sensitive cell line.

The F -value has found to be statistically significant at 95% level, since the calculated F value is higher as compared to tabulated value. The positive value of quality factor (Q) for this QSAR's model suggests its high predictive power and lack of over fitting.

In equation of log(1/A), the negative coefficient of log P explains that any increase in Lipophilicity of the molecules causes a decrease in the biological activity. This result is in agreement with the work of Tsakovska, which confirmed the important role of hydrophobicity in anti MDR activity.[26]

In order to test the validity of the predictive power of selected MLR model (eq log(1/A)), the leave-one-out technique (LOO technique) was used.

The developed model was validated by calculation of the following statistical parameters: predicted residual sum of squares (PRESS), total sum of squares deviation (SSY) and adjusted correlation coefficient (r^2 adj) (Table IV.3).

PRESS is an important cross-validation parameter as it is a good approximation of the real predictive error of the model. Its value being less than SSY points out that model predicts better than chance and can be considered statically significant.

The smaller PRESS value means the better of the model predictability. From the results depicted in Table IV.3, the model is statistically significant.

Also, for reasonable QSAR model, the PRESS/SSY ratio should be lower than 0.4 [53]. The data presented in Table IV.3 indicate that for the developed model this ratio is 0.058. Our result of r^2cv for this QSAR model has been to be 0.942. The high value of r^2cv and r^2adj are essential criteria for the best qualification of the QSAR model.

However, the only way to estimate the true predictive power of developed model is to predict the by calculation of log(1/A) values of the investigated phenothiazines using this model (Table IV.1).

Table IV.3. Cross-validation parameter

Model	PRESS	SSY	PRESS/SSY	S_{PRESS}	r^2_{cv}	r^2_{adj}
1	0.109	1.889	0.058	0.078	0.942	0.911

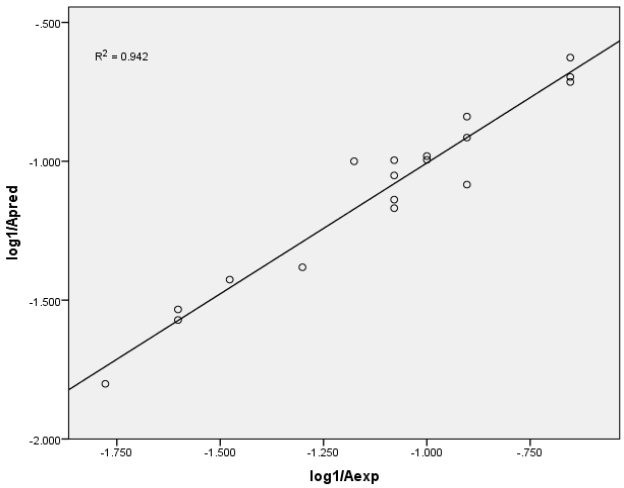


Figure IV.1. Predicted plot versus experimental observed cyto-toxicity of phenothiazines in the sensitive cell line.

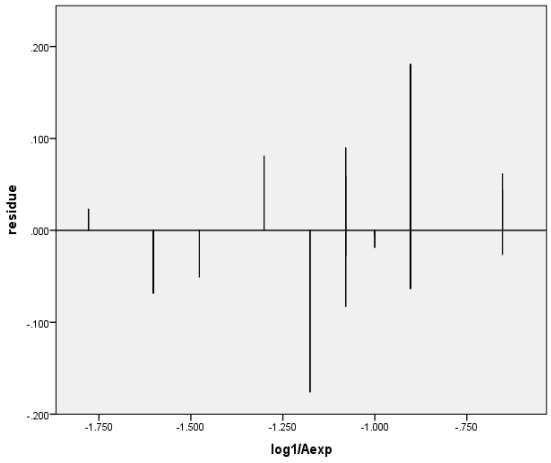


Figure IV.2. Plot of the residual values against the experimentally observed (log(1/A)).

Figure IV.1 shows the plots of linear regression predicted versus experimental value of the biological activity of phenothiazines outlined above. The plots for this model show to be more convenient with $r^2 = 0.942$. It indicates that the model can be successfully applied to predict the cyto-toxicity of these compounds in the sensitive cell line.

To investigate the presence of a systematic error in developing the QSAR model, the residual of predicted values of the biological activity log(1/A) was plotted against the experimental values, as shown in Figure IV.2.

The propagation of the residuals on both sides of zero indicates that no systematic error exists, as suggested by Jalali-Heravi and Kyani.[54]

It indicates that this model can be successfully applied to predict the cyto-toxicity of these compounds in the sensitive cell line.

IV.4. CONCLUSION :

QSAR study of phenothiazine derivatives has been made with the help of chemical descriptors. QSAR model, "$\log(1/A) = -3.823 + 6.739E_{LUMO} - 0.383\log P + 0.121HE - 0.059MR + 0.007MV + 0.008MW$" can be useful for predicting the activity of new phenothiazine derivatives prior to their synthesis.

E_{LUMO}, Log *P*, HE, MR, MV, and MW, are reliable descriptor for predicting activity. QSAR model indicates that these descriptors have significant relationships with observed bioactivity. We have observed a high relationship between experimental and predicted activity values, indicating the validation and the excellent quality of the derived QSAR model.

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GENERAL CONCLUSION

In this work, we applied the methods of computational chemistry on the molecules of phenothiazines. Our study contains:

- a conformational analysis for the basic core of phenothiazines.
- a qualitative study on the relations structure-properties of a bioactive series of phenothiazines.
- a quantitative study, of the structure-property relationships on a series of eighteen phenothiazines and developed a QSAR model.

Various methods of molecular modeling have been used in our work. Molecular mechanics has been used in the study of the most stable conformations for the phenothiazine and its derivatives .

Quantum mechanics methods were used in the study of chemical reactivity of phenothiazine and its derivatives, with methods: PM3, ab initio (HF/ 6-311** G (d,p)) and DFT (B3LYP/6-311** G(d,p)) whose purpose is to determine the structural , electronic and energetic parameters associated with the molecules studied.

The effectiveness of these methods has been confirmed by the comparison structural parameters between the results obtained by the three methods ab initio and DFT and also PM3 between themselves with the experimental data. The nature of such substituent (donor , acceptor) affects electronic and energetic parameters of the basic core of phenothiazines. This study allows us to predict chemical reactivity of phenothiazine derivatives .

The qualitative study of the relation structure-properties was conducted on the series of phenothiazine derivatives. The molecules used in this study have pharmacological activities. The substitution on the basic core of phenothiazines affect on the physico-chemical properties of the phenothiazine derivatives and consequently on their pharmacological properties.

The quantitative study of the relation structure-properties (QSAR) was performed on a series of phenothiazine derivatives.

A QSAR model was established using multi-linear regression method (MLR). QSAR model "$\log(1/A) = -3.823 + 6.739E_{LUMO} - 0.383\log P + 0.121HE - 0.059MR + 0.007MV + 0.008MW$" can be useful for predicting the anti-multi-drug resistance MDR activity of new phenothiazine derivatives .

QSAR model indicates that these descriptors have significant relationships with observed bioactivity.

E_{LUMO}, Log *P*, HE, MR, MV, and MW, are reliable descriptors for predicting activity. We have observed a high relationship between experimental and predicted values of anti-multi-drug resistance MDR activity, indicating the validation and the excellent quality of the derived QSAR model.

QSAR model indicates that, in equation of log(1/A), the negative coefficient of log *P* explains that any increase in Lipophilicity of the molecules causes a decrease in the biological activity. This result is in agreement with the work of Tsakovska, which confirmed the important role of hydrophobicity in anti MDR activity.

The predictive power of the QSAR model obtained was confirmed by the cross validation *LOO* method (leave-one-out) technique.

Abstract

This work involves a fundamental and original research on phenothiazines, the aim is to predict the chemical reactivity and biological activity and to establish a pharmacophore model for new bioactive molecules.
The molecular modeling methods used in our work are: quantum methods, empirical methods. These methods were used to determine the structural parameters, electronics and energy associated with molecules studied. This study shows similar results between these various methods of calculation. The nature of such substituent (donor, acceptor) affects the electronic and energy parameters of basic structure of phenothiazines. A study of the structure-properties/activity has been carried out for a series of bioactive derivatives of phenothiazine. The nature of the groups on heterocyclic ring of the studied molecules affects on their physico-chemical properties and by consequence on their pharmacological properties. We established a pharmacophore model of anti-MDR activity.

ملخص

العمل الحالي يحتوي على بحث أساسي وأصلي على الفينوتيازينات بهدف التنبؤ بالفاعلية الكيميائية والفاعلية البيولوجية و وضع نموذج فارماكوفوري لجزيئات جديدة نشطة بيولوجيا.

أساليب النمذجة الجزيئية المستخدمة في عملنا: : الطرق الكمية، طرق النمذجة الجزيئية
و قد استخدمت هذه الأساليب لتحديد العوامل الهيكلية والإلكترونية و العوامل الطاقية المرتبطة بالجزيئات المدروسة.
هذه الدراسة بينت نتائج مماثلة بين هذه الأساليب المختلفة للحساب، وطبيعة نوع مستبدل (المانح،المستقبل) الذي يؤثر على العوامل الإلكترونية والطاقية للنواة الأساسية للفينوتيازينات.
الدراسة نوعية للعلاقة هيكل ــ خاصيات/فعالية قدمت أيضا لسلسلة من مشتقات الفينوتيازينات النشطة بيولوجيا. طبيعة المجموعات على الهيكل الحلقي للجزيئات المدروسة تؤثر على خصائصها الفيزيائية، وبالتالي على خصائصها الصيدلانية. انشانا نموذج فارماكوفوري للنشاط المضاد للمقاومة المتعددة للأدوية .

Résumé

Le présent travail comporte une recherche fondamentale et originale sur les phénothiazines, dans le but est de prédire la réactivité chimique et l'activité biologique et d'établir un modèle pharmacophore pour des nouvelles molécules bioactives,
Les méthodes de modélisation moléculaire utilisées dans notre travail sont : les méthodes quantiques, les méthodes empiriques. Ces méthodes ont été utilisées pour déterminer les paramètres structuraux, électroniques et énergétiques associés aux molécules étudiées.

Cette étude présente des résultats similaires entre ces différentes méthodes de calcul. La nature de type de substituant (donneur, accepteur) influe sur les paramètres électroniques et énergétiques du noyau de base des phénothiazines. Une étude qualitative de la relation structure –propriétés/activité a été effectuée également pour une série bioactive de dérivés de la phénothiazine. La nature des groupements sur le noyau hétérocyclique des molécules étudiées affecte leurs propriétés physicochimiques et par conséquence sur leurs propriétés pharmacologiques. Nous avons établi un model pharmacophore de l'activité anti MDR.