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# Electronic Structure Based Classification of Neurotransmitters and Related Drugs

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# ELECTRONIC STRUCTURE BASED CLASSIFICATION OF NEUROTRANSMITTERS AND RELATED DRUGS

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, at Virginia Commonwealth University.

by

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# Abstract

ELECTRONIC STRUCTURE BASED CLASSIFICATION OF NEUROTRANSMITTERS AND RELATED DRUGS

By Amrita Jha, M.S.

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science, at Virginia Commonwealth University.

Virginia Commonwealth University, 2010.

Major Director: Dr. Purusottam Jena, Distinguished Professor, Department of Physics

A fundamental understanding of the relationship between structure and activity of neurotransmitters in the human brain is of vital importance for the design targeted drugs. Using density functional theory and hybrid exchange correlation energy functionals we have studied the structure-activity-relationships of some important neurotransmitters and selected drugs by calculating their absolute hardness ($\eta$) and absolute electronegativity ($\chi$). A plot of the $\eta$- $\chi$ diagram allowed us to assign them into three distinct groups, namely, (i) Acetylcholine analogs (positively charged structure), (ii) GABA analogs (zwitterionic structures) and (iii) monoamines. The results suggest that brain stem is chemically soft because of distribution of monoaminergic nerve pathways. Prefrontal cortex is also chemically soft due to secretion of dopamine from mesocortical dopaminergic nerve A10, whereas neocortex is chemically hard due to presence of zwitterionic neurotransmitters. Target drugs (agonists/antagonists) can also be predicted by comparing the $\eta$- $\chi$ diagram of neurotransmitters with those of the drugs.

# Chapter 1: Introduction

## 1.1 Motivation

Our ability to perceive the world and interact with it is possible with the help of our nervous system. It is responsible for controlling many biological processes: 1) voluntary actions such as movement, muscle coordination, thought and speech; 2) involuntary actions such as digestion, respiration and emotion. Voluntary actions are controlled by Central Nervous System (CNS) whereas involuntary actions are controlled by Peripheral Nervous System (PNS).

Specialized nerve cells called neuron transmit nerve impulses or signal along and between nerve cells. Nerve cells or neurons play key roles in the activity of the nervous system. Communication between neurons occurs through a process called neurotransmission. A mechanism is required to convey the signal across the synaptic gap as the impulse or signal travels along the neuron. Small chemical messengers called "neurotransmitters" which are released at one neuron and travel across the gap to convey the signal to the next neuron. At least 100 substances are known to act as neurotransmitters; about 18 are of major importance. The most important neurotransmitters are serotonin, adrenaline, noradrenalin, dopamine, acetylcholine and γ-amino butyric acid (GABA). The human body possesses billions of neurons and these neurons belong to specific neurotransmitter families. Released neurotransmitters from presynaptic cell interact with receptor at the postsynaptic nerve to transmit nerve impulses. For a single neurotransmitter, multiple types of receptors can exist. Interaction between receptor and

neurotransmitter can be thought of as 'nanolock-nanokey' for regulating neuronal function. Only the correctly sized nanokey (ligand) fits into the key hole (active site) of the nanolock (receptor) to transmit a nerve impulse. Neurotransmitters are the natural ligands for the receptors. Each receptor can be related to a different physiological or pharmacological function. Substances that alter neurotransmission or that change the affinity and number of receptors can manifest different neurological or psychiatric symptoms and result in disease. Examples for disorders associated with the defects in neurotransmission are 1) Alzheimer's disease caused by reduced synthesis of the neurotransmitter acetylcholine; and 2) Parkinson's disease caused by the insufficient formation and action of neurotransmitter dopamine. Several diseases such as Parkinsons and depression can be alleviated by drugs as they modify neurotransmission. Drugs which act on the neurotransmitters system are either agonist to the receptors i.e. stimulating the system or antagonists i.e. inhibiting it.

For millennium, experts have been trying to design drugs to cure diseases. There are two major types of drug design 1) ligand-based drug design 2) structure-based drug design. Ligand-based drug design is based on knowledge of other molecules (ligands) that bind to the biological target of interest whereas structure-based drug design is based on knowledge of the three dimensional structure of the biological target[1]. 3-D structures are obtained through methods such as x-ray crystallography or NMR spectroscopy. Apart from rational drug discovery, recently, computer assisted drug discovery is being pursued with the development of powerful computers. Computational analysis is an essential tool in modern drug design and development. Computer-assisted drug design (CADD) or computer-assisted molecular design (CAMD) studies help to find a ligand that will interact favorably with the receptor that represents the target site[2]. It represents integration of ligand- based drug design and structure-based drug design. CADD uses

application of the quantitative structure activity relationship (QSAR)[3,4,5] technique to identify drugs. QSAR application has been applied at some steps of CADD. CADD steps such as 'computational screening and databases and large virtual libraries', and 'computational design of improved lead compound' use application of QSAR. Computational screening and databases and large virtual libraries try to find out the structure that will most likely to bind with a drug target where as computational design of improved lead compound designs an improved chemical compound which has potential biological or pharmacological activity. CADD uses different methods such as molecular mechanics, molecular dynamics and quantum mechanics. Molecular mechanics or molecular dynamics are mostly used to predict the conformation of large molecule and conformational changes in the biological target that may occur when large molecules bind to it[2,6,7]. Quantum mechanical methods often used to provide optimized parameters for molecular mechanics calculations and also provide an estimate of the electronic properties (electrostatic potential, polarizability, etc.)[2,6,7]. QSAR studies using ab initio quantum mechanics (QM), although rigorous, are slow and expensive. Nevertheless, we need computational parameters derived from first principles. In order to accelerate QM calculations, hybrid QM methods have been developed.

Over centuries, chemists have developed simple rules and classification schemes to provide a general understanding of the stability of atoms and molecules and the way they interact with each other. Among these are Mendeleev's periodic table of elements[8], Lewis acids and bases[9] and the principle of hard and soft acids/bases applied to organic and biological chemistry. Quantum mechanics, developed during the 20$^{th}$ century, provides a basis for these rules and classification schemes. It is expected that the tools developed in physical sciences can enable us

in the 21st century to understand biological processes at the atomic and electronic scale, thus providing an unprecedented opportunity to design and tailor drugs and treat diseases.

In some previous QSAR studies[10,11,12] concepts based on absolute hardness, $\eta$ and absolute electronegativity, $\chi$ have been used. The $\eta - \chi$ activity diagram[10-13], used in QSAR investigations, is a very important technique for predicting ligands (neurotransmitters/drugs) binding at receptor site. Here $\eta - \chi$ activity diagram is used as the coordinate r ($\eta$, $\chi$) of electronic structure of neurotransmitters and drugs. The hard soft acid base (HSAB) principle is used to determine the ligand-receptor interaction[14, 15]. This principle states that hard acids prefer to coordinate with hard bases while soft acids prefer to coordinate with soft bases. Hard chemicals have large $\eta$ values while soft chemicals have small $\eta$ values. The coordinate r ($\eta$, $\chi$) based on electronic structure of neurotransmitters can be graphically classified into certain groups. If we calculate these coordinates ($\eta$, $\chi$) to determine which group target compounds belong to, we can estimate the receptor with which the chemicals can easily interact. This type of classification is helpful to understand the prevalent electronic structure of neurotransmitters and receptors in different regions of brain and identification of agonist/antagonist.

## 1.2 Neurotransmitters and Neurotransmission

The nerve impulses or signals are transmitted along and between specialized nerve cells called neuron. Nerve cells or neurons play the key role in the activity of the nervous system. Communication between neurons occurs through a process called as neurotransmission. Neurotransmission involves through substances termed as "neurotransmitters"[16]. It is a "chemical messenger" which is released from neuron to relay information.

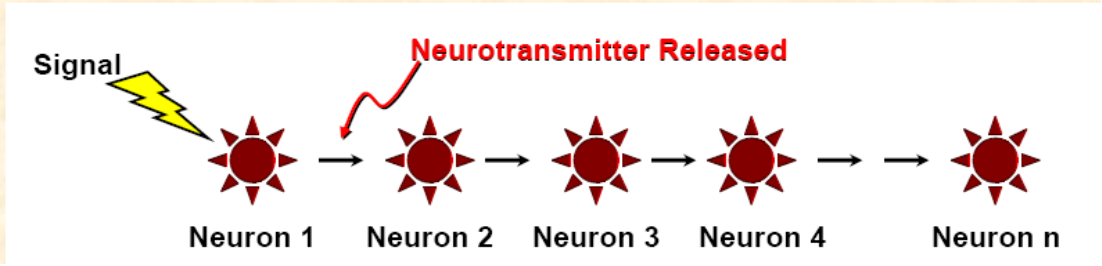



**Figure (1.1): Process of neurotransmission.**

The human body possesses billions of neurons and these neurons belong to specific neurotransmitter families. Neurotransmitters are stored in membranous sacs called **vesicles** that are situated in the axon terminal. These molecules are released into the synaptic space or synaptic cleft. They diffuse across synaptic space to the post synaptic neuron. Neurotransmitter binds to specific receptor (membrane bound protein) on the membrane of postsynaptic neuron. For example, serotonin receptor binds the neurotransmitter serotonin but doesn't bind to other neurotransmitters such as dopamine. The binding of neurotransmitters to receptors that act as ligand-gated ion channels (LGICRs) causes these ion channels to open, leading in some cases to a depolarization of the part of membrane closest to the channel. Depolarization (a decrease in voltage difference) is often caused by influx of cations, e.g. $Na^+$ through $Na^+$ channels, or $Ca^{2+}$ through $Ca^{2+}$ channels. On the other hand, efflux of $K^+$ through $K^+$ channels inhibits depolarization, as does influx of $Cl^-$ (an anion) through $Cl^-$ channels. If depolarization exceeds a certain threshold, an action potential (an impulse) is created which will then travel along the neuron.

There are different types of receptor families[16]. For example

1. G-protein coupled receptors (GPCRs)
2. Ligand-gated ion channel receptors (LGICRs)

The interaction of a receptor and neurotransmitter can be thought of as nanolock and nano key for regulating neuronal function. Neurotransmitter is released off the receptor and diffuses back into the synaptic space, after binding of neurotransmitter to its receptor on the postsynaptic neuron. The neurotransmitter is either degraded by enzymes in the synaptic cleft or taken back into the axon terminal by transporter or reuptake pump.

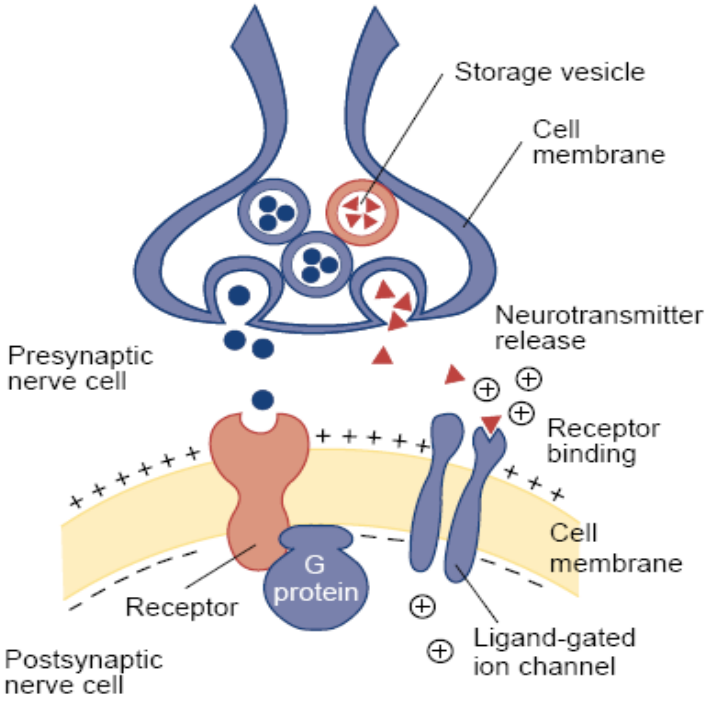



**Figure (1.2): Structure of typical chemical synapse.**[17]

**Propagation of action potential:**

The cell membrane of a resting neuron is more negative on the inside of the cell than on the outside. As the neuron is stimulated, the permeability of the membrane changes allowing $Na^+$ to rush into the cell. This causes the inside of the cell to become more positive. This local change starts a similar change in the adjoining segment of the neuron's membrane. In this manner, the electrical impulse moves along the neuron. Note that an action potential can travel only away

from the site of depolarization because $Na^+$-channel inactivation prevents the depolarization from spreading backward.

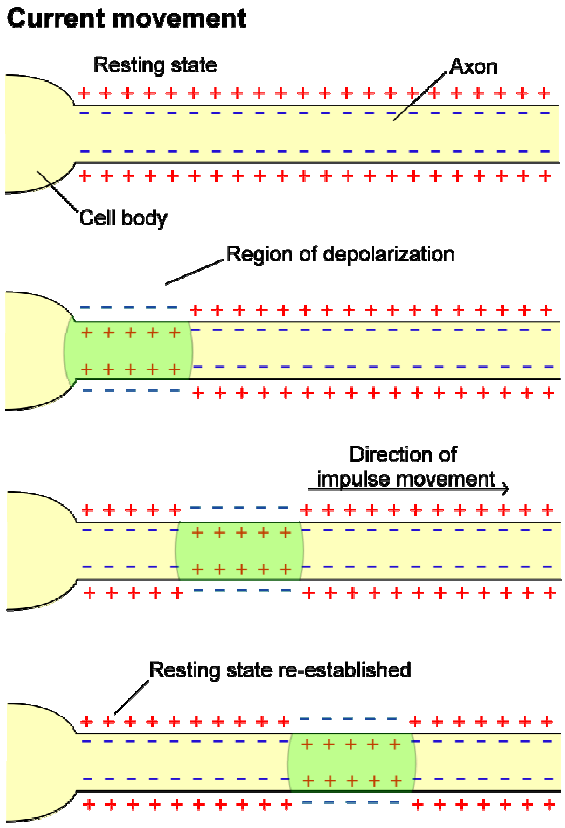



**Figure (1.3): Propagation of action potential along a neuron.**[18]

The three major categories of substances that act as neurotransmitters are 1) **amino acids** (primarily glutamic acid, GABA: γ-Amino Butyric Acid, aspartic acid and glycine), 2) **peptides** (vasopressin, somatostatin, neurotensin, etc.) and 3) **monoamines** (norepinephrine, dopamine and serotonin) plus **acetylcholine**

## 1.3 Agonist *vs*. Antagonist

Agonist is a drug that binds to a receptor of a cell and triggers a response by the cell. An agonist often mimics the action of a naturally occurring substance[16]. It interacts with ion channel receptor to open the pore and allow greater influx of ions.

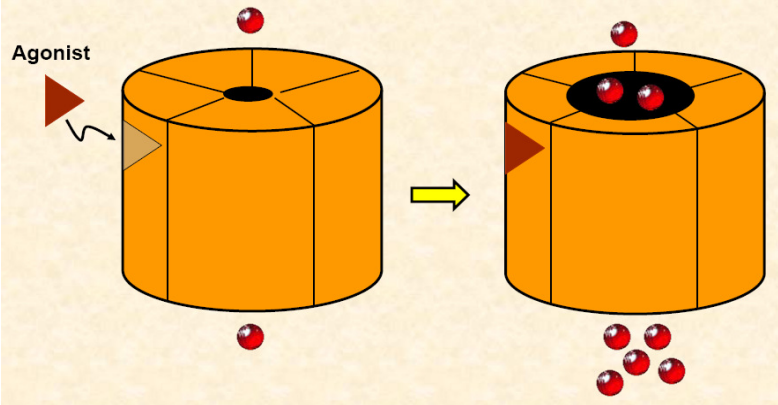



**Figure (1.4): Interaction of agonist with ligand-gated ion channel receptors (LGICRs).**

**ANTAGONIST:** Antagonist ligand blocks or dampens the interaction of agonist/neurotransmitter with the receptor[16]. Thus, it doesn't provoke biological response itself upon binding to a receptor.

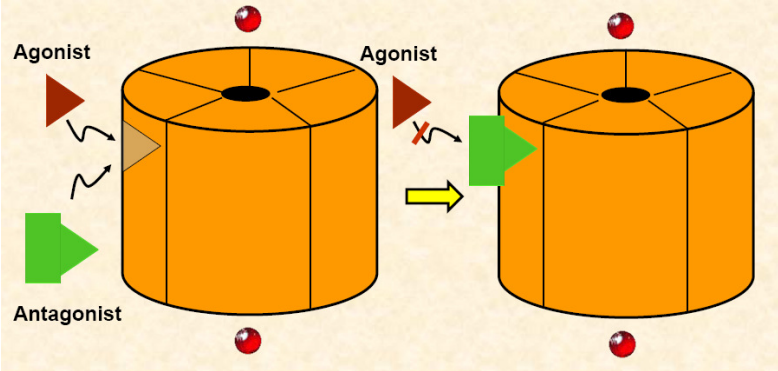



**Figure (1.5): Interaction of antagonist with ligand-gated ion channel receptors (LGICRs).**

## 1.4 Quantitative Structure Activity Relationship (QSAR)

Quantitative structure activity relationship (QSAR) represents an attempt to correlate structural properties of compounds with activities[19]. The structural properties include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods. Activities used in QSAR include

chemical measurements and biological assays. QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment.

## 1.5 Hard Soft Acid Base (HSAB) Principle

This principle states that hard acids prefer to coordinate with hard bases while soft acids prefer to coordinate with soft bases[14,15]. Hard chemicals have large η values while soft chemicals have small η values. Acids and bases are classified as hard and soft as shown below:

**Table (1.1): Characterization of hard/soft acid and base.**

| | Characteristics/Type | Hard | Soft |
|---|---|---|---|
| Acid | Positive Charge | High | Low |
| | Ploarizability | Low | High |
| | Size | Small | Large |
| | | | |
| Base | Electronegativity | High | Low |
| | Ability to Oxidize | Difficult | Easy |
| | Ploarizability | Low | High |

## 1.6 η – χ Activity Diagram

Absolute electronegativity, χ and absolute hardness, η of an atom is defined by following equations:

$$\text{Absolute hardness, } \eta = (I_p - E_a)/2 \qquad (1.1)$$

$$\text{Absolute electronegativity, } \chi = (I_p + E_a)/2, \qquad (1.2)$$

where $I_p$ and $E_a$ are the ionization potential and electron affinity, respectively.

Absolute electronegativity and absolute hardness sum are proposed as coordinate in structure stability diagram[10-13]. This plays important role as a new coordinate of bioactivity in the study of QSARs.

# Chapter 2: Overview of Important Neurotransmitters

This chapter provides a brief summary of the structure, function, and pharmacology of some of the important neurotransmitters.

## 2.1 Acetylcholine (ACh)

**History & overview:** Acetylcholine was the first neurotransmitter discovered and isolated. This is the major neurotransmitter released in the Peripheral Nervous System (PNS). It also works on Central Nervous System (CNS) but its central action is less understood compared to other neurotransmitters. It is the only neurotransmitter used in motor division of the somatic nervous system. ACh is a neurotransmitter at the skeletal neuromuscular junction. It is an **excitatory** neurotransmitter.

**Structure:**

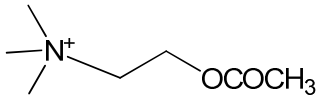



**Figure (2.1): Structure of acetylcholine (ACh).**

**Synthesis**: Reaction of choline with acetyl-CoA using choline acetyltransferase (ChAT) leads to formation of ACh (acetylation of choline)[16].


**Figure (2.2): Synthesis of acetylcholine (ACh).**

**Function:** Acetylcholine activates muscle in PNS. In CNS, it leads to enhancement of sensory perception when we wake up and also helps in sustaining attention. Its function includes arousal and orgasm, voluntary muscle control and proper tone, enhancement of energy and stamina, memory, long term planning and mental focus.

**Pharmacology:** There are two types of receptors for ACh: nicotinic ACh receptor and muscuranic ACh receptor ($M_1$ through $M_5$)[20].

Muscarinic ACh receptor agonists[16]: Muscarine, Oxotremorine, ACh itself

## 2.2 GABA (γ-Amino Butyric Acid)

It is an '**inhibitory**' neurotransmitter.

**Structure:** It occurs mostly in form of zwitterions when $H^+$ ion is separated from the COOH group, leaving it a negatively charged $COO^-$. The $H^+$ ion binding to amine, $NH_2$ produces the positively charged $NH_3^+$.

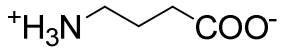



**Figure (2.3): Structure of GABA (γ-Amino Butyric Acid).**

**Synthesis:** GABA is synthesized in the brain from the Krebs citric acid molecule α-keto glutarate. This reaction is known as "GABA shunt". It is produced by the α decarboxylation of L-glutamaic acid[16]. It uses enzyme, glutamic acid decarboxylase (GAD) and pyridoxal phosphate (vitamin B6 derivative) as a cofactor.

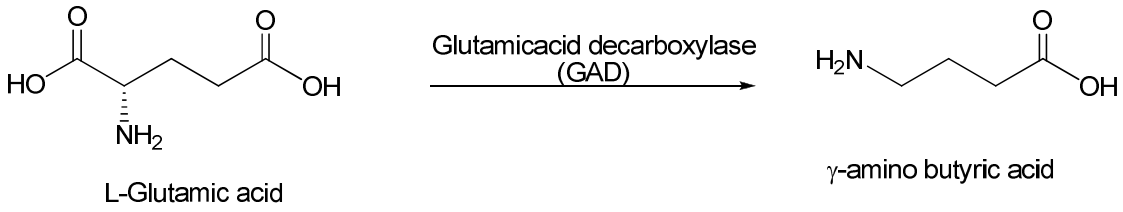



**Figure (2.4): Synthesis of GABA (γ-Amino Butyric Acid).**

**Function:** It binds to receptors on both pre and postsynaptic neurons. Its main action is hyperpolarisation that results in decreased neuronal activity. Hyperpolarization means flow of either negatively charged chloride ions into the cells or positively charged potassium ions out of the cell (charging the interior of neuron negative). Such action has been illustrated by experiments where blocking or impairing the action of GABA results in uncontrolled firing or seizures. Another function of GABA is regulation of muscle tone[21]. In summary its action is: reduction of physical tension, anxiety, insomnia, blood pressure, compulsivity, decreased heart rate and elevation of pain threshold.

**Pharmacology:** GABA receptors: GABA receptors respond to the neurotransmitter GABA or an appropriate agonist which causes a shift in membrane permeability to inorganic ions, mainly $Cl^-$. This results in hyperpolarization of receptive neuron in the case of postsynaptic inhibition or depolarization in the case of pre-synaptic inhibition. There are three major types of GABA receptors[20]: i) $GABA_A$ receptor ii) $GABA_B$ receptor, iii) $GABA_C$ receptor.

**$GABA_A$ receptor drugs:** Benzodiazepines (Diazepam): Benzodiazepam (BDZ) receptor agonist[16]

## 2.3 Dopamine

Dopamine is a monoamine reward neurotransmitter. It is a member of catecholamine family; primarily an '**inhibitory'** neurotransmitter (acts as **excitatory** as well).

**Structure:**

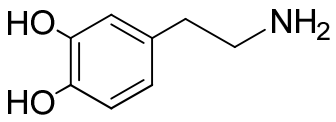



**Figure (2.5): Structure of dopamine.**

**Synthesis:** It originates from amino acid precursor tyrosine. Hydroxylation of the amino acid L-Tyrosine to L-DOPA (dihydroxy phenyl alanine) occurs via an enzyme tyrosine hydroxylase (tyrosine 3-monooxygenase). This reaction occurs using oxygen, iron and tetra hydro biopterin (THB). Decarboxylation of L-DOPA[22] by aromatic L-amino acid decarboxylase (AALD) (which is often referred to as dopa decarboxylase), using pyridoxal phosphate (PLP) as a co-factor, leads to formation of dopamine[16].

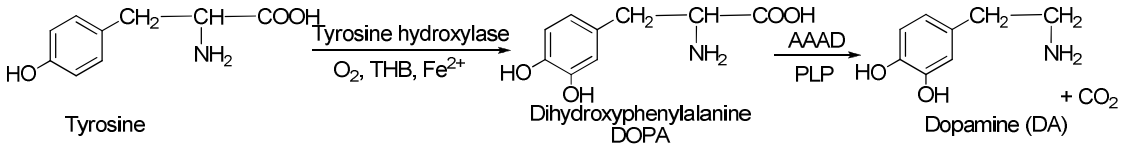



**Figure (2.6): Synthesis of dopamine.**

**Function:** It is involved in motor control and decreased stratial dopamine could cause extrapyramidal symptoms in Parkinson's disease. Dopamine in mesolimbic pathway increases general arousal and goal directed behaviors and decreases latent inhibition; all three effects increase the creative ability, and drive of idea generation[23]. Novelty stimulates dopamine circuits in the brain, circuits that can bring optimism and elation.

In summary its function includes alertness, motivation, motor control, immune function, ego hardening, confidence, optimism, sexual desire, fat gain and loss, lean muscle gain, ability to sleep soundly, inhibits prolactin, thinking, planning and problem solving, aggression, increase psychic and creative ability, reduction of compulsivety.

**Pharmacology:** It has five types of receptors[20]: $D_1$, $D_2$, $D_3$, $D_4$ and $D_5$.

Antagonist: Chlorpromazine, haloperidol (both are $D_2$ antagonist). Haloperidol acts on $D_1$ receptor as well[16].

## 2.4 Serotonin

It is a monoamine neurotransmitter (like the catecholamines, dopamine, noradrenaline). It has an **inhibitory** action on the CNS neurons and in the periphery, it possess **excitatory** action.

**Structure:**

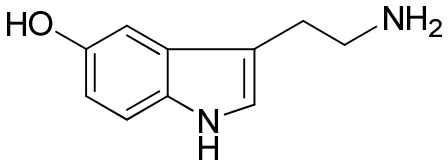



**Figure (2.7): Structure of serotonin.**

**Synthesis:** It is synthesized from amino acid L-tryptophan. The first step involves the enzyme tryptophan hydroxylase with oxygen, iron and tetra hydro biopterin (THB) as co-factor, which leads to formation of 5-hydroxytryptophan (5-HTP). 5-HTP then leads to formation of serotonin with help of aromatic L- amino acid aecarboxylase (AAAD) and pyridoxal phostphate (PLP)[16].

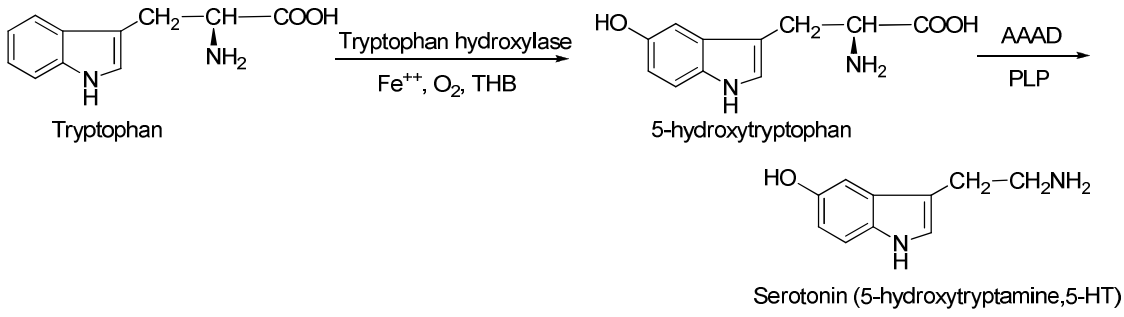



**Figure (2.8): Synthesis of serotonin.**

**Function:** There are seven large families of 5-HT receptors which are named as $5HT_1$ to $5HT_7$ receptors[20] (and many more subfamilies of receptors). Subtype $5HT_{2A}$ receptors mediate platelet

aggression and smooth muscle contraction. Subtype $5HT_2c$ receptors are suspected in control of food intake. The $5HT_3$ receptors are present in gastrointestinal tract and related to vomiting. $5HT_3$ receptors are also present in gastrointestinal tract where they function in secretion and peristalsis. The $5HT_6$ and $5HT_7$ receptors are distributed throughout the limbic system of the brain and the $5HT_6$ receptors have high affinity for antidepressant drugs.

Its function can be summarized as modulation of anger and aggression, body temperature, mood and sleep, cardiovascular function, muscle contraction, endocrine regulation, increases introverted personality, sexuality, appetite, while decreases pain reception.

**Pharmacology:**

Antagonist:

Fluoxetine: (antidepressant of the selective serotonin reuptake inhibitor class)

Chlorpromazine (on $5HT_1$ and $5HT_2$ receptors)[16]

## 2.5 Noradrenaline

It is a catecholamine and is an **excitatory** neurotransmitter.

**Structure:**

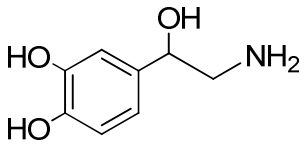



**Figure (2.9): Structure of noradrenaline.**

**Synthesis:** The precursor tyrosine is converted to dopamine which is hydroxylated by dopamine-β-hydroxylase to noradrenaline[16]. [Synthesis of dopamine from tyrosine is discussed in the synthesis of dopamine]

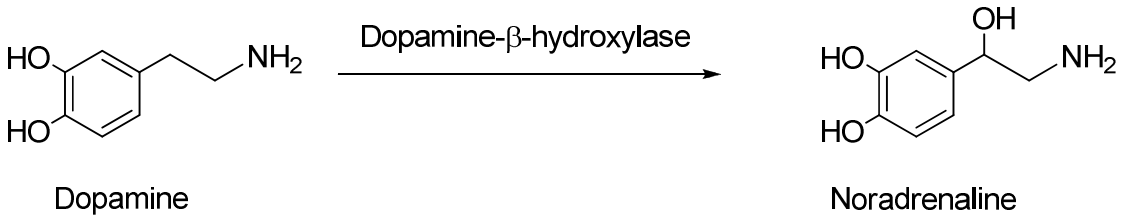



**Figure (2.10): Synthesis of noradrenaline.**

**Function:** It is responsible for stimulatory processes in the body. This neurotransmitter can cause anxiety at elevated excretion levels as well as some "mood dampening effects". It affects large area of brain where attention and responding actions are controlled. It has arousal and reward action. Along with adrenaline, noradrenaline also underlies the fight-or-flight response, increasing blood flow to skeletal muscle, directly increasing heart rate, and triggering the release of glucose from energy stores. It can also suppress neuroinflammation when released diffusely in the brain from the locu ceruleus[24]. Low levels of noradrenaline are associated with low energy, decreased focus and sleep cycle problems.

**Pharmacology:** It has α- and β- types of receptors (adrenoreceptors) and many more subfamilies[20]. Tricyclic antidepressant such as imipramine inhibits the reuptake of noradrenaline[16]

## 2.6 Adrenaline

It is an **excitatory** neurotransmitter.

**Structure:**

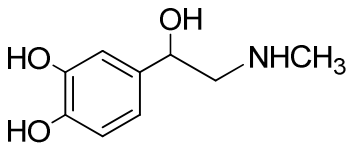



**Figure (2.11): Structure of adrenaline.**

**Synthesis:** Noradrenaline is converted to adrenaline via phenylethanolamine-N-methyl transferase (primary pathway)[16]. Alternative pathway also leads to formation of this neurotransmitter (via dopamine).

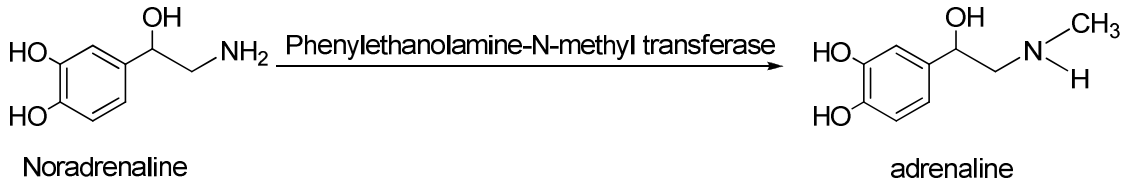



**Figure (2.12): Synthesis of adrenaline.**

**Function:** This excitatory neurotransmitter is reflective of stress. It participates in the fight-or-flight response of the sympathetic nervous system, contracts blood vessels, and dilates air passages, increases heart rate and blood pressure[25]. It also speeds up the conversion of glycogen into glucose, which provides energy to the muscles. This neurotransmitter will often be elevated when attention-deficit hyperactivity disorder (ADHD) like symptoms are present. Long term stress or insomnia can cause adrenaline levels to be depleted (low).

**Pharmacology:** It has α- and β- types of receptors (adrenoreceptors) and many more subfamilies[20]. Tricyclic antidepressant such as imipramine inhibits the reuptake of adrenaline[16].

## 2.7 Glutamic Acid

It is the most abundant swift '**excitatory**' neurotransmitter in the mammalian nervous system. This is an acidic amino acid.

**Structure:** Glutamic acid occurs mostly in the form of zwitterions.

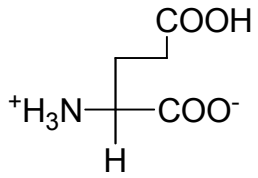



**Figure (2.13): Structure of glutamic acid.**

**Synthesis**: Synthesis occurs via two sources: From glucose via the Krebs cycle; transamination of α-oxoglutatrate.

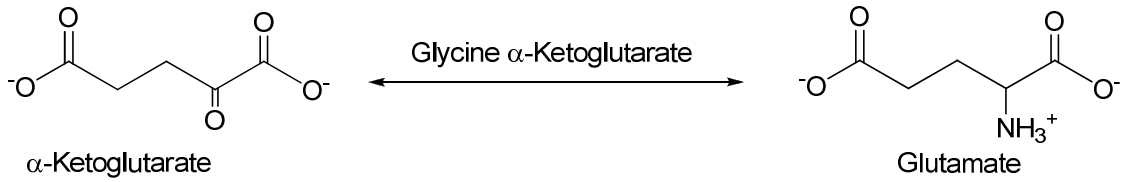



**Figure (2.14): Synthesis of glutamic acid.**

**Function:** Glutamate is involved in intermediary metabolism in the neural tissue. It plays important role in the detoxification of ammonia in the brain (disposal of excess or waste nitrogen). It is a precursor for the inhibitory neurotransmitter GABA. It is an important building block in the synthesis of proteins and peptides. It is involved in cognitive functions such as learning and memory in the brain[26]. Glutamic acid and its amide participate in the respiratory reactions of nervous tissue through their ketoacid.

# Chapter 3: Theoretical Method

QSAR studies using ab initio quantum mechanical methods is time consuming and rigorous. Hybrid density functional method is best in terms of cost and accuracy. In this chapter, I am going to discuss the theoretical methodology of each method and emphasize why B3LYP, a hybrid density functional is best suited for η and χ calculations.

## 3.1 Introduction

The time independent equation as proposed by Erwin Schrödinger (in 1926) can predict the electronic properties of molecules. The time independent Schrödinger equation is written as:

$$H\ \Psi = E\ \Psi \qquad (3.1)$$

where $H$ is *Hamiltonian* operator and $E$ is an eigenvalue.

*Hamiltonian* operator $H$ is a differential operator that acts on the total wavefunction $\Psi$ and can be written as[27]

$$H = -\frac{\hbar^2}{2m_e}\sum_{i=1}^{N}\nabla_i^2 - \frac{\hbar^2}{2M_A}\sum_{A=1}^{M}\nabla_A^2 - e^2\sum_{i=1}^{N}\sum_{A=1}^{M}\frac{Z_A}{r_{iA}} + e^2\sum_{i=1}^{N}\sum_{j>i}^{N}\frac{1}{r_{ij}} + e^2\sum_{A=1}^{M}\sum_{B>A}^{M}\frac{Z_A Z_B}{r_{AB}} \qquad (3.2)$$

where $i$ and $j$ run over N electrons and A, B run over M nuclei. $Z_A$ and $Z_B$ are atomic number, $M_A$, and $m_e$ are mass of nucleus and electron respectively, $\hbar = \frac{h}{2\pi}$ and $h$ is Planck constant.

The first two terms are kinetic energy of electron ($T$) and kinetic energy of nuclei respectively. The third term (potential energy term) is attractive electrostatic interaction between the nuclei and electrons ($V_{Ne}$). The fourth and fifth terms are potential energy due to electron-electron ($V_{ee}$) and nucleus-nucleus interactions, respectively. Both terms are repulsive in nature. Here the Laplacian operator $\nabla_q^2$ is defined as a sum of differential operators

$$\nabla_q^2 = \frac{\partial^2}{\partial x_q^2} + \frac{\partial^2}{\partial y_q^2} + \frac{\partial^2}{\partial z_q^2} \tag{3.3}$$

The first approximation (Born-Oppenheimer approximation)[28] states that since nucleus is so much larger than the electron, it can be assumed stationary. Therefore, their kinetic energy is zero and the repulsive potential energy due to nucleus-nucleus interactions can be assumed to be almost constant. There is no effect on the operator eigenfunctions if we add a constant to an operator, it only adds to the operator eigenvalues. Thus, the complete hamiltonian given in equation (3.2) reduces to so-called electronic hamiltonian; $H_{elec}$

$$H_{elec} = -\frac{\hbar^2}{2m_e}\sum_{i=1}^{N}\nabla_i^2 - e^2\sum_{i=1}^{N}\sum_{A=1}^{M}\frac{Z_A}{r_{iA}} + e^2\sum_{i=1}^{N}\sum_{j>i}^{N}\frac{1}{r_{ij}} = T + V_{Ne} + V_{ee} \tag{3.4}$$

The attractive potential ($V_{Ne}$) is often termed as external potential $V_{ext}$ in the density functional theory.

Since the birth of quantum mechanics, the ultimate goal of the quantum chemist is to find and describe the best approximate solutions to the electronic Schrödinger equation. However, it can be exactly solved only for a single electron system. Approximations are required to solve multi-electron systems because of the complexity of electron-electron interactions in many-particle systems.

## 3.2 The Hartree Approximation

In the Hartree[29] approximation, the one-N electron problem is separated into N-one electron Schrödinger equations. Here, the Hamiltonian has the form

$$H = \sum_{i=1}^{N} h(i) \tag{3.5}$$

where $h(i)$ is the operator describing kinetic energy and potential energy of electron *i*; defined as

$$h(i) = -\frac{1}{2}\nabla_i^2 - \sum_{A=1}^{M}\frac{Z_A}{r_{iA}} + e^2\sum_{j=1}^{N}\frac{1}{r_{ij}} \tag{3.6}$$

The wave function is a simple product of spin orbital wave functions for each electron and is defined as Hartree product wave function.

The Hartree product[30] wave function;

$$\psi^{HP}(\mathbf{x}_1, \mathbf{x}_{2,\ldots,}\mathbf{x}_N) = \chi_i(\mathbf{x}_1)\chi_j(\mathbf{x}_2)\cdots\chi_k(\mathbf{x}_N) \tag{3.7}$$

where $\chi_i$ is spin orbital *i* (solution of one particle Schrodinger equation), $\mathbf{x}_i$ is position and spin of electron *i*. The function uses Hartree equation. The Hartree equation is an eigenvalue equation of the form:

$$h(i)\chi_j(\mathbf{x}_i) = \varepsilon_j\chi_j(\mathbf{x}_i) \tag{3.8}$$

Schrödinger equation for whole system is of the form:

$$H\psi^{HP} = E\psi^{HP} \tag{3.9}$$

Here eigenvalue, *E* is sum of spin orbital energies of each spin orbitals appearing in $\psi^{HP}$

$$E = \varepsilon_i + \varepsilon_j + \cdots + \varepsilon_k \tag{3.10}$$

The Hartree method provides a great foundation for numerically approximating many body systems. However, it has some drawbacks. The important one is that the total wave

function is not anti-symmetric under interchange of electron coordinates and doesn't obey the Pauli Exclusion Principle.

## 3.3 Hartree-Fock Approximation

In Hartree –Fock[30,31] approximation, the total wave function of the N-electron system is approximated by an anti-symmetrized product of N one-electron wave functions $\chi_i(\mathbf{x}_i)$. This product is usually represented by a determinant called *Slater determinant* $\Psi_{SD}$.[32] Here electron-electron repulsion is treated in average way.

$$\Psi_{SD}(\mathbf{x}_1,\mathbf{x}_2,\ldots,\mathbf{x}_N)=\frac{1}{\sqrt{N!}}\begin{pmatrix}\chi_1(\mathbf{x}_1) & \chi_2(\mathbf{x}_1) & .... & \chi_N(\mathbf{x}_1)\\ \chi_1(\mathbf{x}_2) & \chi_2(\mathbf{x}_2) & .... & \chi_N(\mathbf{x}_2)\\ \vdots & \vdots & & \vdots\\ \chi_1(\mathbf{x}_N) & \chi_2(\mathbf{x}_N) & .... & \chi_N(\mathbf{x}_N)\end{pmatrix} \tag{3.11}$$

where $\frac{1}{\sqrt{N!}}$ is the normalization factor. $\chi_i(\mathbf{x}_i)$ is called spin orbital of particle *i.*

In the Hartree-Fock (HF) approximation, the antisymmetry property of electrons is accounted for. $\Psi(\mathbf{x}_1,\mathbf{x}_2)$ is antisymmetric with respect to the interchange coordinates of electron one and two.

$$\Psi(\mathbf{x}_1,\mathbf{x}_2)=-\Psi(\mathbf{x}_2,\mathbf{x}_1) \tag{3.12}$$

The Slater determinant obeys Pauli Exclusion Principle. When two electrons are assigned to the same spin orbital, i.e. $\chi_1$ and $\chi_2$ is same, then the determinant will be zero.

Now, we must introduce the variational principle which states that the expectation value of the Hamiltoninan operator *H* from any guessed trial wave function must be greater than or equal to the actual ground state energy. i.e.

$$\left\langle \Psi_{trial} \middle| H \middle| \Psi_{trial} \right\rangle = E_{trial} \geq E_0 = \left\langle \Psi_0 \middle| H \middle| \Psi_0 \right\rangle \tag{3.13}$$

The $E_{trial} = E_0$ equality will hold only if $\Psi_{trial}$ is identical to $\Psi_0$

The Hartree-Fock equation is an eigenvalue equation of the form:

$$f(i)\chi_j(\mathbf{x}_i) = \varepsilon_i \chi_j(\mathbf{x}_i) \qquad \text{(i=1...N)} \tag{3.14}$$

where $\varepsilon_i$ is eigen solutions of N number of equations, $\chi_j$ is spin orbital $j$ and $f(i)$ is an effective one-electron operator, called the *Fock* operator, of the form:

$$f(i) = -\frac{1}{2}\nabla_i^2 - \sum_{A=1}^{M} \frac{Z_A}{r_{iA}} + v^{HF}(i) \tag{3.15}$$

where $v^{HF}(i)$ is *Hartree-Fock potential* (average repulsive potential experienced $i^{th}$ electron due to remaining N-1 electrons). Thus, the complicated two-electron repulsion operator $1/r_{ij}$ in the Hamiltonian is replaced by the simple one-electron operator $v^{HF}(i)$ where the electron-electron repulsion is taken into account only in an average way. $v^{HF}(i)$ has following two components:

$$v^{HF}(i) = \sum_{j}^{N} J_j(\mathbf{x}_i) - K_j(\mathbf{x}_i) \tag{3.16}$$

where $J$ and $K$ are Coulomb and exchange operators, respectively.

The total energy for the HF approximation is given as below:

$$E_{HF} = \left\langle \Psi_{SD} \middle| H \middle| \Psi_{SD} \right\rangle = \sum_{i=1}^{N} \varepsilon_i - \frac{1}{2}\sum_{i=1}^{N}\sum_{j=1}^{N}(J_{ij} - K_{ij}) = \sum_{i=1}^{N} \varepsilon_i - \left\langle \Psi_{SD} \middle| V_{ee} \middle| \Psi_{SD} \right\rangle \tag{3.17}$$

where the Coulomb integral (due to pair-wise Coulomb interaction between the $i^{th}$ electron and the other electrons in all occupied spin orbitals) is given by:

$$J_{ij} = (ii \mid jj) = \int d\mathbf{x}_i d\mathbf{x}_j \frac{|\chi_i(\mathbf{x}_i)|^2 |\chi_j(\mathbf{x}_j)|^2}{r_{ij}} \tag{3.18}$$

and exchange integral, exchange of two variables within spin orbitals, is given by:

$$K_{ij} = (ij \mid ji) = \int d\mathbf{x}_i d\mathbf{x}_j \frac{\chi_i^*(\mathbf{x}_i)\chi_j(\mathbf{x}_i)\chi_j^*(\mathbf{x}_j)\chi_i(\mathbf{x}_j)}{r_{ij}} \tag{3.19}$$

It is to be noticed that HF approximation uses the effects of all the electrons on the one under study in an averaged manner. This is a variational procedure; therefore, the calculated approximate energies, expressed in terms of the system's wave function, are always equal to or greater than the exact energy, and tend to a limiting value called the HF limit as the size of the basis is increased. To improve upon the results obtained from HF, one must include the effect of correlation. Many types of calculations begin with a HF calculation and subsequently correct for electron-electron repulsion, referred to also as electronic correlation.

## 3.4 Density Functional Theory (DFT)

The HF method splits energy term into two parts. One term represents the Coulomb interaction between electrons and is called the Coulomb repulsion integral. The other has its root in quantum mechanics and arises because of the necessity to construct an anti-symmetric wave function. This term is called as exchange integral. It represents the potential experienced by an electron in a particular spin orbital due to the influence of other spin orbitals of the system. HF includes correlation between electrons of parallel spin. In spite of this, however, there is no correlation between electrons of opposite spins. One must go beyond the HF theory in order to account for such correlations. One of these methods is Density Functional Theory (DFT) and others such as Moller-Plesset perturbative theory for correlation energy[44] (for this MP2 is the most common one).

DFT is a quantum mechanical method used in physics and chemistry to investigate the electronic structure of many-body systems. DFT is based on the fact that electron density can be used to describe the fundamental properties of an N-electron system. In 1964, Hohenberg and Kohn[33] proved that the ground state energy of an N-electron system can be represented as functionals of electron density, $\rho$ that depends only on three spatial coordinates. It lays the groundwork for reducing many-body problem of N electrons with 3N spatial coordinates to 3 spatial coordinates, through the use of functionals of electron density.

### 3.4.1 Kohn-Sham Equations

In Kohn-Sham[34] density functional theory, one imagines that a system of independent non-interacting electrons moving in a common, one body potential $V_{eff}$ (one electron potential) yields the same density as the "real" fully-interacting system. A set of independent orbitals $\varphi_i$ (*Kohn-Sham orbitals*) satisfy the following independent single particle Schrödinger equation:

$$(-\frac{1}{2}\nabla^2 + V_{eff}(\vec{r}))\varphi_i(\vec{r}) = \varepsilon_i\varphi_i(\vec{r}) \tag{3.20}$$

where the first term is the kinetic energy of the non-interacting electrons defined as ($T_S[\rho]$). The local one-body potential $V_{eff}$ (one electron potential) is derived from the noninteracting density

$$\rho(\vec{r}) = \sum_{i=1}^{N} |\varphi_i(\vec{r})|^2 \tag{3.21}$$

The above single-particle Schrödinger equations are valid for systems with interacting particles, which satisfy:

$$V_S(\vec{r}) \equiv V_{eff}(\vec{r}) = V_C + V_{xc}(\vec{r}_1) - V_{Ne} = \int \frac{\rho(\vec{r}_2)}{r_{12}} d\vec{r}_2 + V_{xc}(\vec{r}_1) - \sum_{A}^{M} \frac{Z_A}{r_{1A}} \tag{3.22}$$

where $V_C$ is the classical Coulomb potential, $V_{xc}$ is exchange-correlation potential and $V_{Ne}$ or $V_{ext}$ is external energy due to nuclei-electron interaction.

$V_{xc}$ is simply defined as the functional derivative of $E_{xc}$ with respect to $\rho$, i.e.,

$$V_{xc} = \frac{\delta E_{xc}[\rho]}{\delta \rho(\vec{r})} \tag{3.23}$$

Then we express the total electronic energy of the real, fully interacting system as,

$$\begin{aligned} E[\rho(\vec{r})] &= T_S[\rho] + J[\rho] + E_{xc}[\rho] + E_{Ne}[\rho] \\ &= -\frac{1}{2}\sum_i^N \left\langle \varphi_i \mid \nabla^2 \mid \varphi_i \right\rangle + \frac{1}{2}\sum_i^N \sum_j^N \int\int |\varphi_i(\vec{r}_1)|^2 \frac{1}{r_{12}} |\varphi_j(\vec{r}_2)|^2 \, d\vec{r}_1 d\vec{r}_2 + E_{xc}[\rho(\vec{r})] \\ &\quad - \sum_i^N \int \sum_A^M \frac{Z_A}{r_{1A}} |\varphi_i(\vec{r}_1)|^2 \, d\vec{r}_1 \end{aligned} \tag{3.24}$$

where the first term is the kinetic energy of a non-interacting system ($T_S[\rho]$), the second term is the classical electrostatic electron-electron repulsion energy ($J[\rho]$), the third term is exchange-correlation energy of particle $E_{xc}[\rho]$, and the last term is energy due to nuclei-electron interaction ($E_{Ne}[\rho]$). The kinetic energy is represented in terms of corresponding orbital instead of electron density $\rho$.

### 3.4.2 Exchange-Correlation Functionals

The exact form of exchange-correlation energy ($E_{xc}$) is difficult to obtain. Hence, in DFT, one uses an approximate form for $E_{xc}$, which may give accurate results. $V_{xc}$ depends on the electron density at every point. $E_{xc}$ can be treated in two parts:

$$E_{xc}[\rho(\vec{r})] = E_x[\rho] + E_c[\rho] = \int \rho(\vec{r}) \varepsilon_x d\vec{r} + \int \rho(\vec{r}) \varepsilon_c d\vec{r} \tag{3.25}$$

where $E_x$ is the exchange energy of the Slater determinant of Kohn-Sham orbitals in equation (3.20). $E_c$ is the correlation energy, $\varepsilon_x$ is exchange energy per particle and $\varepsilon_c$ is correlation energy per particle. In general, the contribution of exchange energy, $E_x$ is larger than the correlation energy $E_c$.

### 3.4.2.1 Local Density Approximation (LDA)

This is the first approximation made to $E_{xc}$. It is based on the **homogenous** electron gas. In this approximation, the electron density is assumed to be a slowly varying function of $\vec{r}$. The exchange energy, $E_x$ in LDA approximation is defined as:

$$E_x^{LDA} = -\frac{3}{4}(\frac{3}{\pi})^{1/3}\int \rho(\vec{r})^{4/3} d\vec{r} \qquad (3.26);$$

where exchange energy per particle is,

$$\varepsilon_x^{LDA}[\rho] = -\frac{3}{4}(\frac{3}{\pi})^{1/3}\rho(\vec{r})^{1/3} \qquad (3.27)$$

Therefore, the corresponding local exchange potential is given as:

$$V_x^{LDA}(\rho) = \frac{\partial E_x^{LDA}}{\partial \rho} = -(\frac{3}{\pi})^{1/3}\rho(\vec{r})^{1/3} \qquad (3.28)$$

The most widely used LDA functional is the VWN (Vosko, Wilk and Nusair)[35] correlation functional which is given in the form of:

$$\varepsilon_c^{VWN} = \frac{A}{2}[\ln\frac{x^2}{X(x)} + \frac{2b}{Q}\tan^{-1}\frac{Q}{2x-b} - \frac{bx_0}{X(x_0)}(\ln\frac{(x-x_0)^2}{X(x)} + \frac{2(b+2x_0)}{Q}\tan^{-1}\frac{Q}{2x-b})] \qquad (3.29)$$

where $x = r_s^{1/2}$ ($r_s$: effective volume containing one electron), $X(x) = x^2 + bx + c$, and $Q = (4c-b^2)^{1/2}$ and A, $x_0$ and c are constants.

The LDA exchange-correlation energies are insufficiently negative (by about 10%) for almost all atoms. The LDA is a reliable, moderate-accuracy approximation. However, LDA is not accurate enough for most chemical applications, which require the determination of energy differences with considerable accuracy. It overestimates bonding and in turn underestimates equilibrium volume; underestimate bond gap; gives too large bulk modulus.

### 3.4.2.2 Generalized Gradient Approximation (GGA)

Several attempts have been made to improve the LDA, and one of the most important is the inclusion of gradient corrections in the $E_{xc}$ . Here the functionals are dependent on both the density $\rho$ and its gradient, $\nabla \rho$ . Gradient-corrected functionals is of the following form:

$$E_{xc}^{GGA}[\rho] = \int \rho(\vec{r}) \varepsilon_{xc}[\rho(\vec{r}), \nabla(\vec{r})] d\vec{r} \qquad (3.30)$$

**Becke** proposed a correction to the LDA exchange energy that has the correct asymptotic behavior (1/r) (in the LDA exchange the density has an exponential dependence on r in the asymptotic region). The gradient corrected exchange functional due to Becke (B88)[36,37] is given as:

$$E_x^{B88} = E_x^{LDA} + \Delta E_x^{B88} \qquad (3.31)$$

$$\text{where } \Delta E_x^{B88} = -\beta \rho^{1/3} \frac{x^2}{1 + 6\beta x \sinh^{-1} x} \qquad (3.32)$$

where β is a parameter determined from atomic data, and $x = \frac{|\nabla \rho|}{\rho^{4/3}}$

## 3.5 B3LYP Hybrid Density Functional

In 1993, Becke [36,37] gave a gradient corrected exchange functional, which is a combination of both the exact HF exchange and DFT exchange energies, hence termed *hybrid functionals*. In the B3LYP hybrid functional scheme, the non local HF is mixed with the energy functional of Generalized Gradient Approximation (GGA). Here, the Perdew-Wang[38] gradient-corrected correlation energy, which was used in the original work of Becke, is replaced with the Lee-Yang-Parr correlation energy[39]. It is a combination of the Slater[40] [LDA exchange], HF[30,31], and Becke's gradient correction for exchange and with Lee, Yang and Parr gradient corrected correlation functionals. The B3LYP has the form:

$$E_{xc}^{B3LYP} = E_x^{LDA} + a_0(E_x^{HF} - E_x^{LDA}) + a_x \Delta E_x^{B88} + E_c^{VWN} + a_c(E_c^{LYP} - E_c^{VWN}) \qquad (3.33)$$

where $a_0$= 0.20, $a_x$=0.72 and $a_c$=0.81 are semi-empirical coefficients, determined by fitting to experimental data. Here the LDA of Vosko, Wilk, and Nusair[35] is used for $E_x^{LDA}$ and $E_c^{VWN}$. $E_x^{HF}$ is the exact nonlocal HF exchange energy. $E_x^{B88}$ and $E_c^{LYP}$ are the Becke's and Lee-Yang-Parr's gradient corrections for the local exchange and correlation energies, respectively.

## 3.6 Basis sets

The molecular orbitals $\Psi_i$ are represented as linear combination of a finite set of pre-defined N- one electron functionals, known as basis functions, $\chi_\mu$

$$\Psi_i = \sum_{\mu=1}^{N} C_{\mu i}\chi_\mu \qquad (3.34)$$

where $C_{\mu i}$ are molecular orbital expansion coefficients, $\chi_\mu$ is the $\mu$-th orbital and N is number of atomic orbitals. Often basis functions are atomic orbitals in *Linear Combination of Atomic Orbitals*.

There are two types of basis functions commonly used in the electronic structure calculations. They are *Slater Type Orbitals* (STOs)[41] and *Gausssian Type Orbitals* (GTOs)[42]. The *Slater Type Orbitals* are given as:

$$\chi(r,\theta,\phi) = Nr^{n-1}e^{-\zeta r}Y_{l,m}(\theta,\phi) \tag{3.35}$$

where $N$ is normalization constant, $\zeta$ is called "Slater orbital exponent". $r,\theta,\Phi$ are spherical coordinates, and $Y_{l,m}$ are the conventional spherical harmonics. These functions are accurate as they reflect exponential decay of the wave function. However solving the three- and four- centered integrals with STOs are extremely expensive in SCF calculations.

To circumvent this problem GTOs basis functions come into picture. In cartesian coordinates GTOs can be written as:

$$\chi(x,y,z) = Nx^{l_x}y^{l_y}z^{l_z}e^{-\zeta r^2} \tag{3.36}$$

where $l_x$ , $l_y$ and $l_z$ determines the angular part of orbital and $\zeta$ represents the radial part of the function.

The use of *Gaussian-Type orbitals* (GTOs) reduces the computational cost but has some drawbacks. The $e^{-r^2}$ dependence, results in a zero slope at the nucleus.

*Contracted* basis sets were used to reduce computational expense of large number of basis functions describing each of the atomic orbitals. The *Contracted basis functions*, have fixed contraction and coefficients. $\chi_\mu^{CGF}$ can be written as:

$$\chi_{\mu}^{CGF} = \sum_{i=1}^{L} d_{i\mu} \chi_{i}^{GF}(\varsigma_{i\mu}, r) \tag{3.37}$$

where $d_{i\mu}$ is a contraction coefficient, L is the length of the contraction, and $\varsigma_{i\mu}$ is a contraction exponent.

Now, equation (3.34) can be rewritten as:

$$\Psi_{i} = \sum_{\mu=1}^{N} C_{\mu i} \chi_{\mu}^{CGF} \tag{3.38}$$

The widely used minimal basis set can be represented as STO-nG basis. In this basis set, each STO is given by *contraction* of n primitive GTOs. For example, 6-311G acronym implies that the valence basis functions are contractions of three primitive Gaussians (the inner function) and one, one primitive Gaussians (the outer functions), whereas the inner shell functions (core orbital) are contraction of six primitive Gaussians. *Polarization* functions and *diffuse* functions are added to improve the basis set. *Polarization* functions (represented as *) enhance the 'flexibility" of atoms to form chemical bonds whereas *diffuse* functions (represented as +) improve the predicted properties of species with extended electron density such as anion. For example 6-31G** denotes that *d*-type functions is added to heavy atoms (left *), and *p*-type functions is added to hydrogen (right *). Similarly, in 6-31++G; diffuse functions are added to hydrogen (right +) and heavy atoms (left +).

# Chapter 4: Background and Current Work

## 4.1 Previous Work

Kobayashi and Terao[43] calculated the absolute hardness, η and absolute electronegativity, χ parameters and applied this to neurotransmitter in an effort to identify or characterize different categories of neurotransmitters and receptors. They pioneered this research and showed that there is a direct relationship between η and biological activity of neurotransmitters. Using these parameters, they found that the electronic structure of neurotransmitters studied through r (η,χ) plot can be graphically classified into different groups. They also studied the electronic structure of brain and several neurotransmitters of the central nervous system. They based the classification for relationship between electronic structures of neurotransmitters and agonist/antagonist is based on HOMO/LUMO energy values. However, η and χ values calculated using HOMO/LUMO energy gap is an approximate method. In addition, the authors used Hartree-Fock[30,31] theory and 6-31G** basis sets to compute η and χ values for a number of neurotransmitters and drugs using following equation:

$$\text{Absolute hardness, } \eta = 1/2\ (\varepsilon_{lumo} - \varepsilon_{homo}) \qquad (4.1)$$

$$\text{Absolute electronegativity, } \chi = -1/2\ (\varepsilon_{lumo} + \varepsilon_{homo}) \qquad (4.2)$$

where $\varepsilon_{lumo}$=lowest unoccupied molecular orbital energy (eV), and,

$\varepsilon_{humo}$=highest occupied molecular orbital energy (eV)

My work is refining their findings with more accurate method. Although HF method treats exchange interaction exactly, it doesn't take into account of electronic correlation and treats the electron-electron repulsion in an average manner. Thus, calculated energies within the HF method are approximate. They are always the approximate always equal to or greater than the exact energy. By using this theory, the authors ignored the effect of correlation on $\eta$ and $\chi$ values. The authors further used a lower level double zeta split valence basis set with polarization functions added to hydrogen as well as heavy atoms. This basis set doesn't include diffuse functions which are important for calculations of anion energies.

The authors suggested that the electronic structure of neurotransmitters obtained through a $\eta$-$\chi$ plot within the HF scheme can provide a new way of predicting ligands, agonists, and antagonists for drug design. This is because the electronic structure of a drug is characterized by its own $\eta$-$\chi$ plot and is similar to that of the ligand. I am trying to find out whether B3LYP, hybrid functional method is better suited for this type of relationship.

## 4.2 Improvements in Previous Work

The electronic structure classification of the brain has been used by above authors to predict some rules for identifying agonists and antagonists. These rules hold quite well for many drugs. Therefore, Kobayashi and Terao formulated the design of medications such as antidepressants and tranquilizers. This approach is valuable and is the first approach for this type of relationship. Although this is a promising way of drug design, deficiencies in their theoretical methods need to be addressed to improve the accuracy of prediction. This is objective of my work. This is achieved by

1) considering correlation through hybrid functional and higher basis set, and

2) calculating η and χ from total energies of neutral, positive and negatively charged molecules rather than being approximating by HOMO and LUMO energy values.

3) separating drugs and neurotransmitters grouping so that an improved η-χ plot can be obtained. One confusing issue with the work of Kobayashi and Terao was that the whole set of listed compounds were both drugs and neurotransmitters. Our η-χ diagram would have greater clarity. Position of serotonin in the left most corner of graph, separates it from other monoamine neurotransmitters. This can be confirmed from the fact that the serotonin (5-HT) has seven different 5-HT receptor families and more subfamilies. In addition, some compound can bound to both adrenergic, that substantiates its different position compared to other monoamines. 5-HT has an indole ring which also supports its position and lowest value of coordinate r (χ, η).

4) Reconsideration of agonist/antagonist relationship.

## 4.3 Current Work

The new approach taken in the current work is to calculate the η-χ plot by using density functional theory and comparing the results with both HF and perturbative treatment of correlation through second order Moller-Plessett (MP2) method[44]. Our results differ significantly than those, although we agree with the main conclusion that neurotransmitters and drugs can be classified into three minimum groups. In the following chapters, we present computational procedure used in the current approach and compare the results with those of Kobayashi and Terao. In the method used in current approach, η and χ was taken from the work of Parr and Pearson[45]:

$$\text{Absolute hardness, } \eta = 1/2(\partial^2 E/\partial N^2)_{v(r)} = (I_p - E_a)/2 \qquad (4.3)$$

$$\text{Absolute electronegativity, } \chi = -(\partial E/\partial N)_{v(r)} = (I_p + E_a)/2, \qquad (4.4)$$

$$\text{Global softness, } S = (\partial N/\partial \mu)_{v(r)} = 1/\eta \qquad (4.5)$$

Here E is the total electronic energy of a molecule, N is the number of electrons, *v(r)* is the external electrostatic potential, and μ is the chemical potential of the electrons. $I_p$ and $E_a$ are the ionization potential and electron affinity, respectively. The derivatives with respect to N are equated with finite difference expressions.

# Chapter 5: Computational Procedure, Results and Discussion

## 5.1 Validation of Computational Procedure

Structures of neurotransmitters and drugs were optimized using GAUSSIAN 03 code[46]. For the initial structures we used the lowest conformational energy coordinates from the PubChem website. It uses MMFF94 (a quantum mechanical technique) to determine the electronic structure of optimized compounds. Optimization was performed to get a better conformation of molecules. To confirm the conformational structure of neurotransmitters and drugs with the results of Kobayashi and Terao; $\eta$ and $\chi$ were first calculated using HF/6-31G** basis set and the resulting HOMO/LUMO gap.

**Table (5.1): Comparison of results for conformational search using HF/6-31G** basis set.**

| Compounds | $\eta$ (eV) | Kobayashi's & Terao's result $\eta$ (eV) | $\chi$ (eV) | Kobayashi's & Terao's result $\chi$ (eV) |
|---|---|---|---|---|
| Phenethylamine | 6.37 | 6.34 | 2.33 | 2.45 |
| Acetylcholine | 7.90 | 8.71 | 7.33 | 7.41 |

The result for phenethylamine and acetylcholine indicates that the choice of conformation in Pubchem website is same as that of Kobayashi and Terao.

η and χ values were calculated with Becke, three-parameter, Lee-Yang-Parr (B3LYP) using a higher level 6-311++G** basis set[47]. The reason for choosing B3LYP functional is due to the fact that it includes both the exchange and correlation contribution. For comparison with ab-initio methods, HF, MP2 methods were also considered. A variety of basis sets were chosen from split-valence basis sets to correlation-consistent basis sets. HF/6-311++G** and MP2/6-311++G** calculations were also done to compare the results with B3LYP/6-311++G**. η and χ values were calculated from $I_p$ and $E_a$ values. $I_p$ is the energy difference between the ground states of the neutral and cation while $E_a$ is the energy difference between the ground states of the neutral and anion. To confirm the accuracy of B3LYP/ 6-311++G** basis set, η and χ for selected neurotransmitters (table shows only three: Asp, Taurine and GABA) were calculated using HF, MP2 and B3LYP.

**Table (5.2): Comparison of B3LYP with HF and MP2 using 6-311++G** basis set.**

| Neurotransmitters | Method | η (eV) | χ (eV) | CPU time |
|---|---|---|---|---|
| **ASPARTIC ACID** | HF | 4.53 | 3.57 | 49 min |
| | B3LYP | 4.99 | 4.62 | 3 hrs |
| | MP2 | 5.13 | 4.56 | 5 hrs |
| **TAURINE** | HF | 4.33 | 3.96 | 32 min |
| | B3LYP | 4.80 | 4.78 | 56 min |
| | MP2 | 4.84 | 4.78 | 2 hrs |
| **GABA** | HF | 5.25 | 3.43 | 58 min |
| | B3LYP | 5.00 | 4.04 | 2 hrs |
| | MP2 | 5.04 | 3.94 | 5 hrs |

The results show that the B3LYP is as accurate as MP2, but takes comparatively significantly less computational time. For larger molecules, MP2 method, took several days to converge.

Methodology selected: B3LYP/6-311++G**

## 5.2 Correlation between Activity and Chemical Hardness, η for Acetylcholine (ACh) Derivatives

It has already been reported that the molar ratio of equipotency for activity of Acetylcholine (ACh) derivatives for rectus abdominis of frog increases in the following order[48]:

$AcOCH_2CH_2N^+(Et)_3$ (5000) <$AcOCH_2CH_2N^+(Me)(Et)_2$ (300) <$AcOCH_2CH_2N^+(Me)_2(Et)$ (5)< $AcOCH_2CH_2N^+(Me)_3$ (1)

It can be interpreted that the activity of ACh derivatives increases as the bulkiness of substituents of ammonium cation at the nitrogen atom increases. The analysis was made to find out the relationship between the chemical hardness and pharmacological activity of ACh derivate. It was found that the chemical hardness, η is directly proportional to the order of potency for the activity of ACh derivatives. ($R^2$=0.719, where $R^2$ is the correlation coefficient). There was an inverse relationship between molar ratio of equipotency of theses derivatives and the absolute electronegativity. ($R^2$=0.930).

**Table (5.3): Correlation between Activity and η for acetylcholine derivatives.**

| S.No. | Compounds | Relative molar ratio vs. rectus abdominis of frog[1] | Absolute Hardness (η, eV) | Absolute electronegativity (χ, eV) |
|---|---|---|---|---|
| 25 | $CH_3COOCH_2CH_2N^+(C_2H_5)_3$ | 5000 | 5.20 | 7.79 |
| 26 | $CH_3COOCH_2CH_2N^+(Me)(C_2H_5)_2$ | 300 | 5.18 | 7.88 |
| 27 | $CH_3COOCH_2CH_2N^+(Me)_2(C_2H_5)$ | 5 | 5.16 | 7.96 |
| 1 | $CH_3COOCH_2CH_2N^+(Me)_3$ | 1 | 5.05 | 8.07 |

Figure (5.1) shows the 3-D diagram of r (η,χ) of ACh derivatives along the x- and y-axis *vs.* log(activity for rectus abdominis of frog) along z-axis. This figure shows that the log molar ratios of equipotency of ACh derivatives is correlated to the r (η,χ) of the electronic structure and ACh is chemically softer and more acidic than the other ACh derivatives.

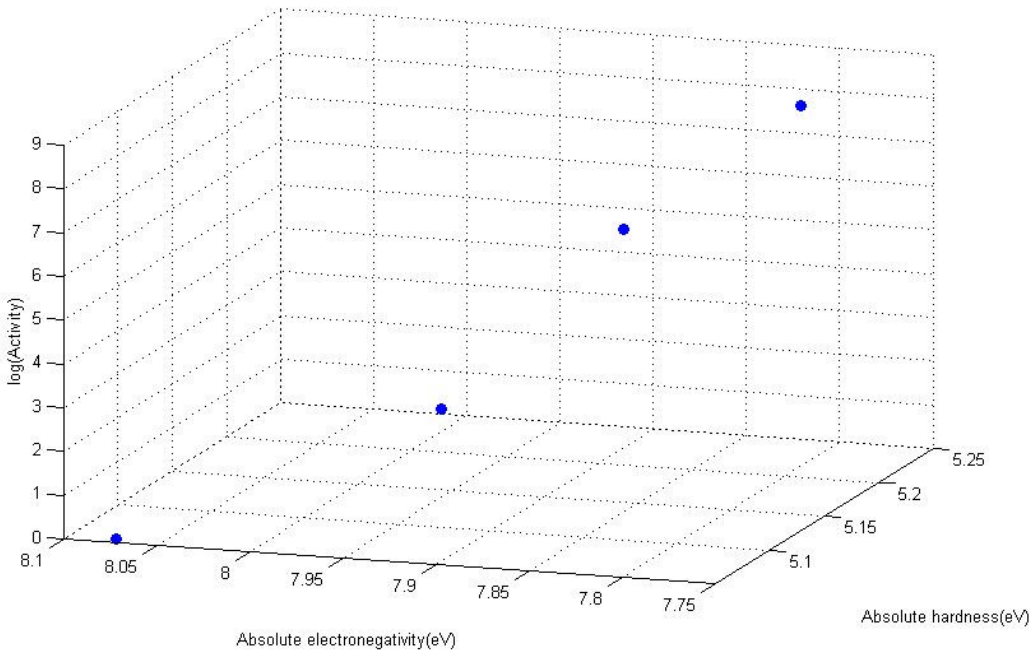



**Figure (5.1): 3-D plot for r (η,χ) vs. log (Activity).**

## 5.3 Results

Absolute hardness (η), absolute electronegativity (χ) and global softness (S) were calculated using equation (4.3), (4.4) and (4.5), respectively for optimized neurotransmitters such as acetylcholine (ACh), serotonin, glutamic acid in the central nervous system.

**Table (5.4): Calculated absolute hardness (η) and absolute electronegativity (χ) of optimized neurotransmitters.**

| S.No. | Neurotransmitters | Absolute Hardness (η, eV) | Absolute electronegativity (χ, eV) |
|---|---|---|---|
| 1 | Acetylcholine | 5.05 | 8.07 |
| 2 | Glutamic acid | 4.82 | 4.57 |
| 3 | Aspartic acid | 4.88 | 4.62 |
| 4 | GABA | 5.00 | 4.04 |
| 5 | Taurine | 4.55 | 4.78 |
| 6 | Guanidiyltaurine (Taurocyamine) | 4.98 | 4.59 |
| 7 | Phenethylamine | 4.22 | 3.75 |
| 8 | Thyramine | 3.98 | 3.62 |
| 9 | m-Thyramine | 4.08 | 3.74 |
| 10 | Adrenaline | 3.77 | 3.54 |
| 11 | Noradrenaline | 3.87 | 3.68 |
| 12 | Dopamine | 3.87 | 3.61 |
| 13 | Serotonin | 3.71 | 3.40 |

ACh (+ve charged structure) shows highest value of η whereas serotonin shows the lowest value of η. To understand the relationship between electronic structures of neurotransmitters we plot η and χ in Figure (5.2).

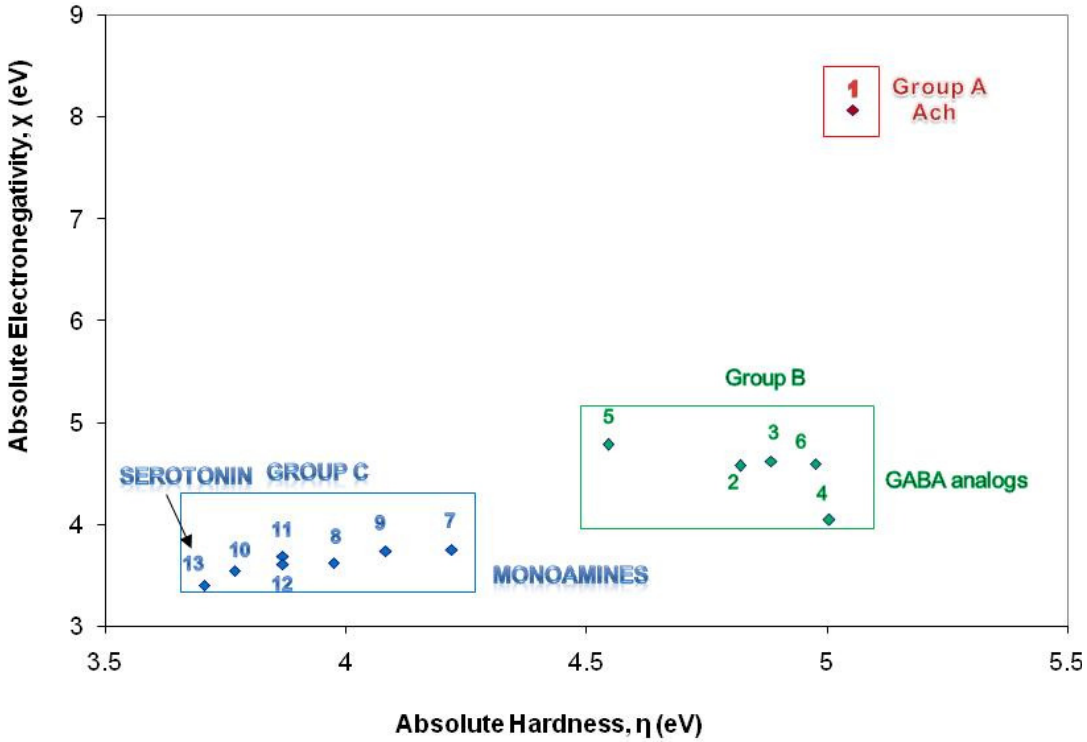



**Figure (5.2): Plot of (η, χ) diagram to describe electronic structure of neurotransmitters.**

Similar plot obtained by Kobayashi and Terao's to describe the electronic structure of neurotransmitters is shown below, for the purpose of comparison.

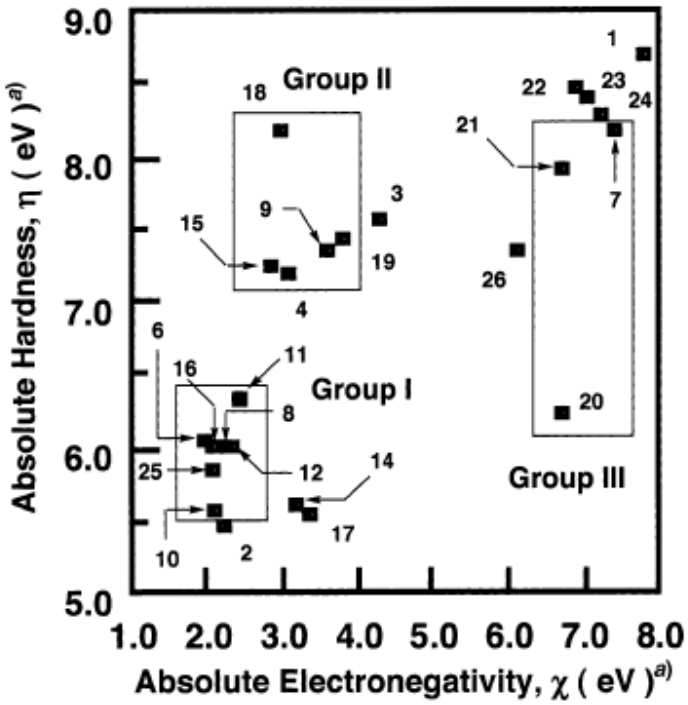



**Figure (5.3): Plot of (η, χ) diagram for the relation between electronic structure and neurotransmitters.**

### 5.3.1 Chemically Hard and Soft Neurotransmitters

Table (5.4 and 5.6) contains the list of neurotransmitters and drugs and their η and χ values. A η-χ activity diagram (using B3LYP/6-311++G** basis set) is plotted in Figure (5.2 and 5.8 respectively) to illustrate the relationship of electronic structures of neurotransmitters and drugs as shown Serotonin has the lowest value of η and χ value {r (3.71, 3.40)}. This shows that the monoamine neurotransmitter serotonin (η=3.71, S=0.27) is the softest among other monoamines , GABA was well as ACh analogs. The χ values for all catecholamine such as dopamine, noradrenaline, adrenaline is small, and their η values are similar. It was also found that monoamine neurotransmitters such as tyramine, m-tyramine, phenetylamine also have similar r (η, χ) as that of catecholamines. Value of η for glutamic acid, aspartic acid, GABA,

taurine, guanidiyltaurine (taurocyamine) is higher than that of monoamine neurotransmitters but values of $\chi$ for theses compounds are similar to that of monoamines. This shows that serotonin ($\eta$=3.71, S=0.27), and dopamine ($\eta$=3.87, S=0.26) are softer than GABA ($\eta$=5.00, S=0.19) and aspartic acid ($\eta$=4.88, S=0.21). From the definition of Hard Soft Acid Base, it can be understood that chemically soft serotonin and dopamine will have higher polarizability as well as are easily oxidizable compared to GABA and aspartic acid. Values of $\eta$ for ACh analogs are better with monoamine neurotransmitters and GABA analogs.

Therefore, based on electronic structure neurotransmitters can be classified into: 1) ACh analog (positive charge structure) as (Group A), 2) GABA analogs (zwitterionic structures) as (Group B), and 3) monoamines such as catecholamine analogs as (Group C). Form this it can be concluded that the electronic structure of neurotransmitters are controlled by 1) hardness and acids (for ACh analogs), 2) hardness and bases (for GABA analogs), and 3) softness and bases (for monoamine neurotransmitters such as catecholamine analogs).

This type of grouping confirms that neurotransmitter with similar structures belong to the same group. Group B has amino acids and amino sulfonic acids.

Amino acids have basic structure as: $NH_3^+$-CHR-$COO^-$

Amino sulfonic acid has basic structure as: $NH_3^+$-CHR-$SO_3^-$

This shows that Group B has similar zwitterionic structures.

Group C contains monoamine neurotransmitters. Under this category, trace amines have the following basic structure

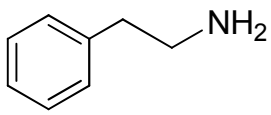



**Figure (5.4): Basic structure of trace amines.**

Some trace amines contain OH group at para, meta depending upon its location with respect to $-CH_2-CH_2-NH_2$ group on the benzene ring.

The important family of monoamine neurotransmitters contains catecholamine which has the following basis structure:

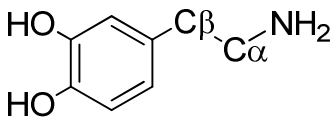



**Figure (5.5): Basic structure of monoamines.**

This confirms that Group C has similar structures.

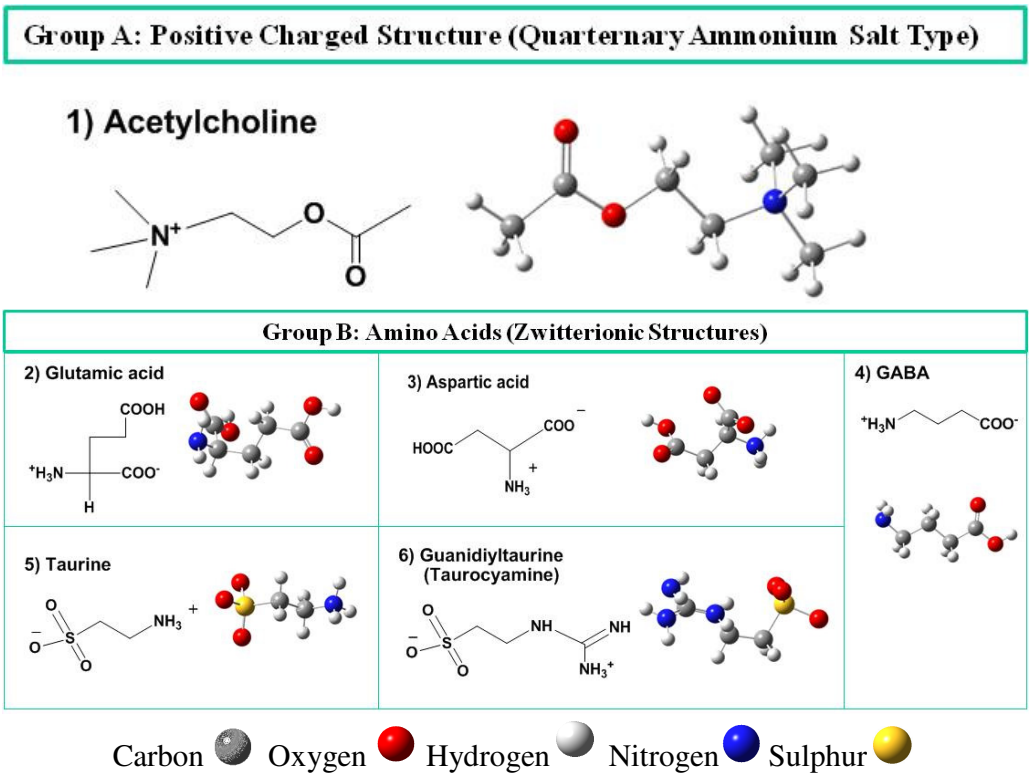



**Figure (5.6a): Structure of several neurotransmitters based on grouping.**

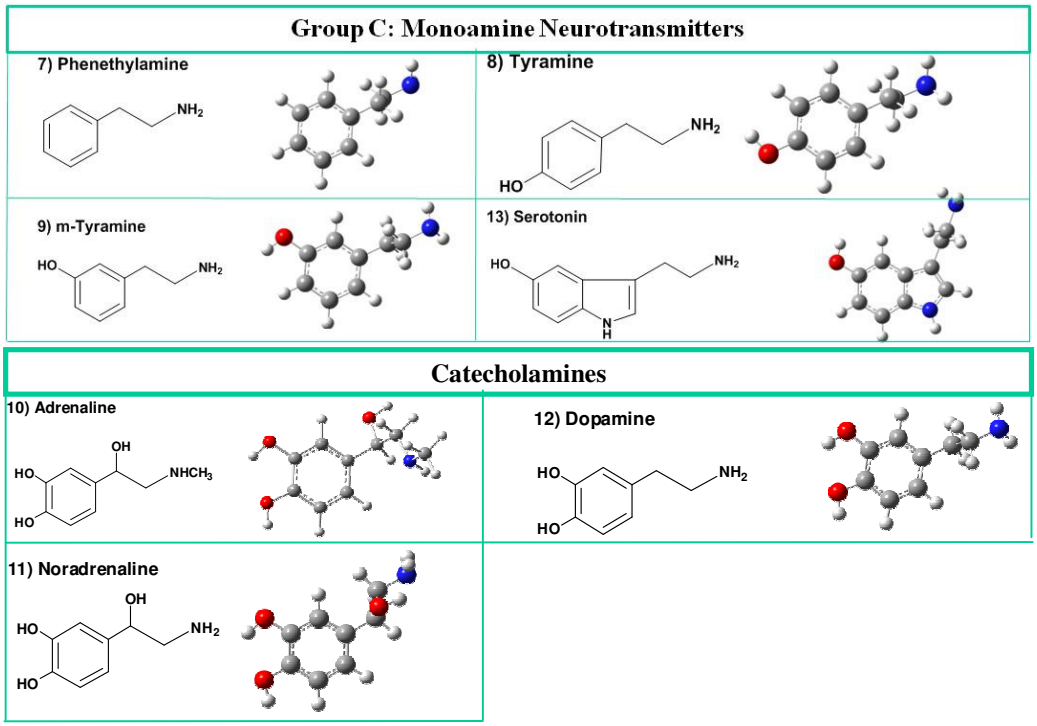



**Figure (5.6b): Structure of several neurotransmitters based on grouping.**

**Table 5.5: Classification of neurotransmitters based on chemical structures.**

| Group | Chemical Group | Examples |
|---|---|---|
| **A** | Choline ester (a type of quarternary ammonium salt) | Acetylcholine |
| **B** | **Amino acids (exist in zwitter ionic structure)** | |
| | Acidic (have second carboxyl group) | Glutamic acid, Aspartic acid |
| | Basic (are polar and positively charged at pH values) | γ-aminobutyric acid (GABA) |
| | **Amino sulfonic acids (exist in zwitter ionic structure)** | taurine, guanidiyltaurine |
| **C** | **Monoamines** | |
| | Trace amines | Tyramine, m-tyramine, phenetylamine |
| | Catechol | Dopamine, Adrenaline, Noradrenaline |
| | Indole | Serotonin (5-HT) |

Figure (5.7a, 5.7b & 5.7c) shows some central nervous system (CNS) drugs for which calculation was done. For example, Chlorpromazine and haloperidol, which are major tranquilizers, act on $D_2$ receptor of CNS.

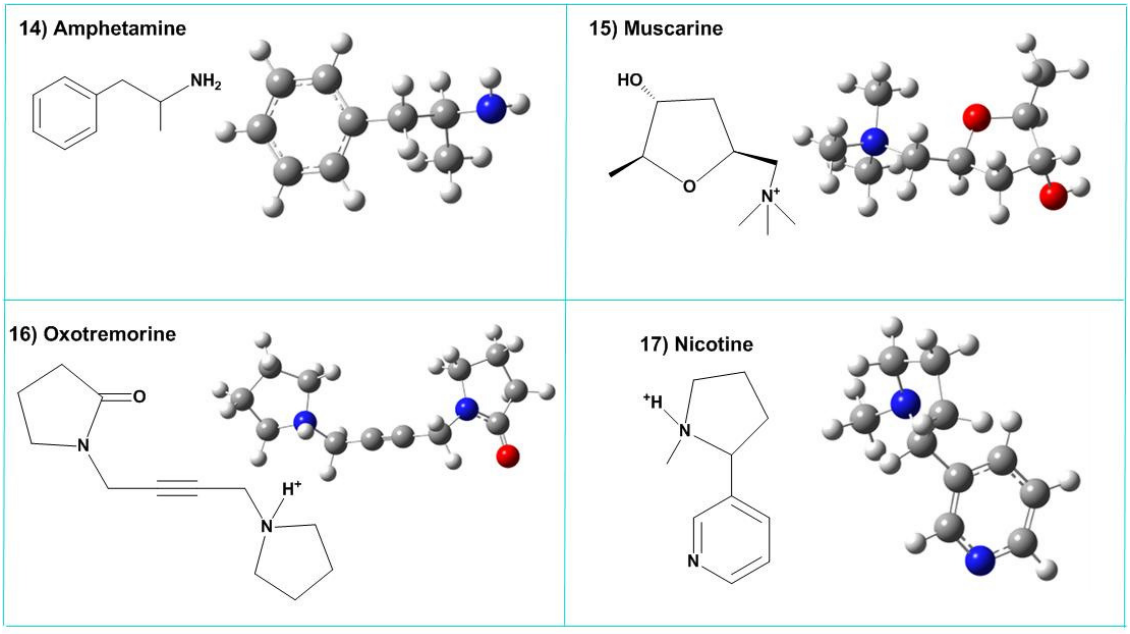



**Figure (5.7a): Structure of several drugs acting on CNS.**

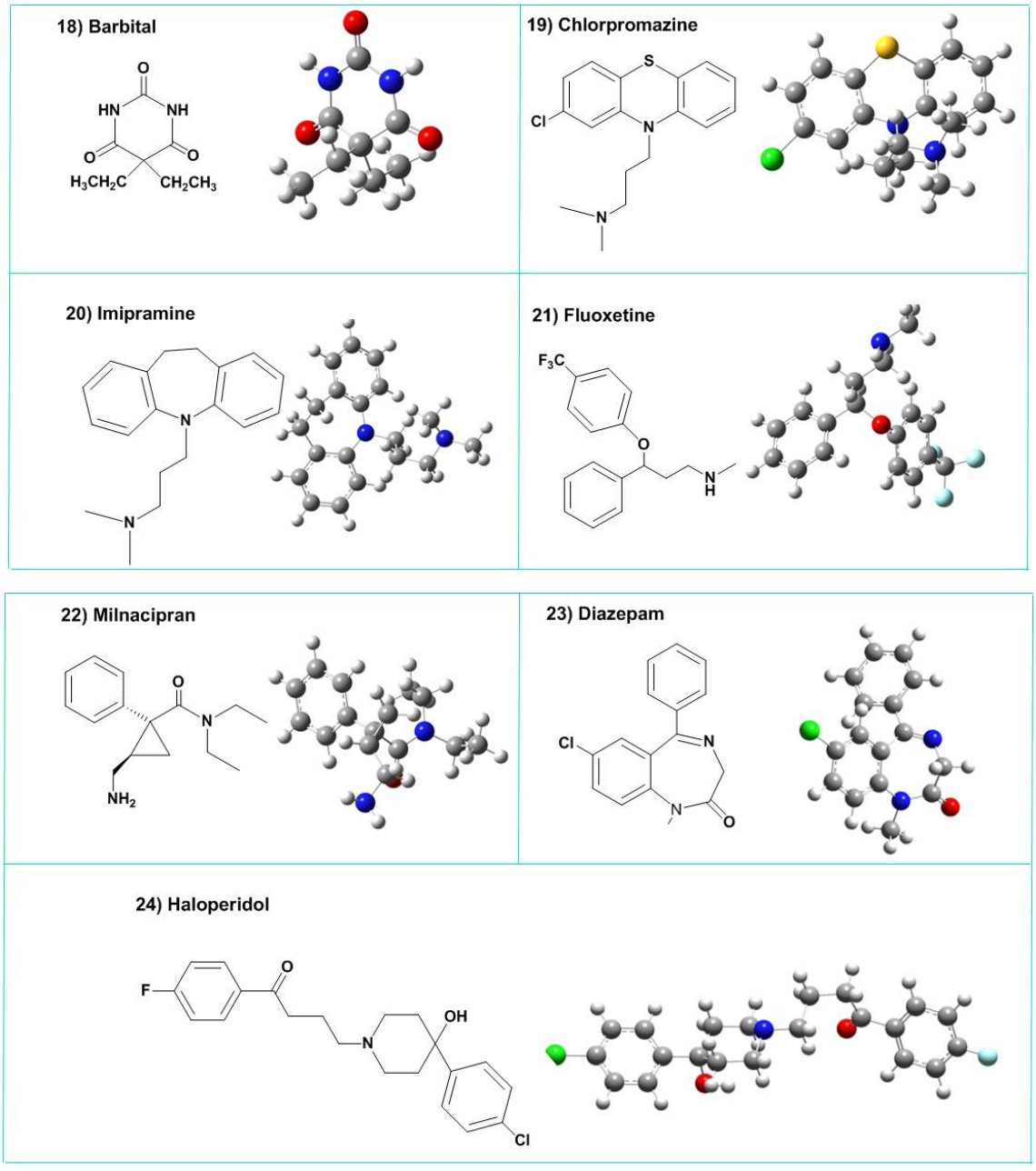



**Figure (5.7b): Structure of several drugs acting on CNS.**

**Table 5.6: Calculated absolute hardness (η) and absolute electronegativity (χ) of optimized drugs.**

| S. No. | Drugs | Absolute hardness (η, eV) | Absolute electronegativity (χ, eV) |
|---|---|---|---|
| 14 | Amphetamine | 4.17 | 3.73 |
| 15 | Muscarine | 4.74 | 7.47 |
| 16 | Oxotremorine | 4.38 | 7.26 |
| 17 | Nicotine | 3.58 | 8.67 |
| 18 | Barbital | 4.66 | 4.88 |
| 19 | Chlorpromazine | 3.45 | 3.22 |
| 20 | Imipramine | 3.52 | 3.17 |
| 21 | Fluoxetine | 3.93 | 3.77 |
| 22 | Milnacipran | 4.08 | 3.50 |
| 23 | Diazepam | 3.58 | 4.40 |
| 24 | Haloperidol | 3.18 | 3.87 |

Muscarine (+ve charged structure) has highest value of η.

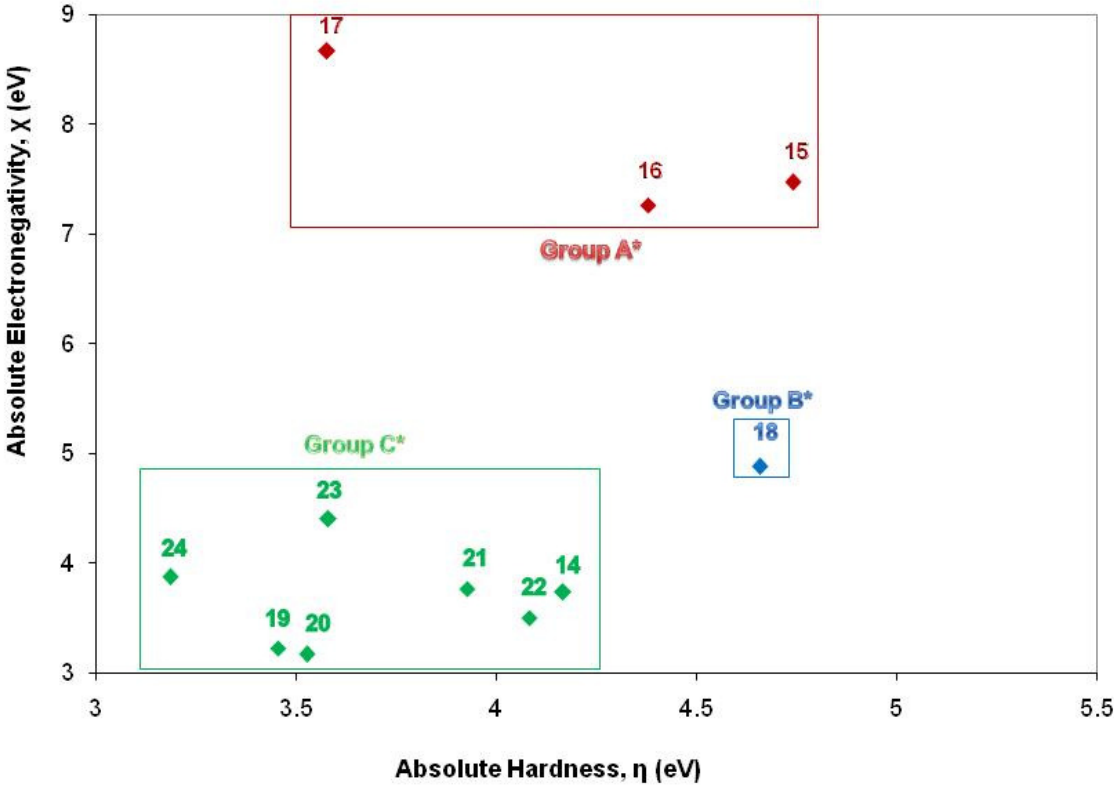



**Figure (5.8): Plot of (η, χ) diagram reflecting the relationship between electronic structure and (η, χ) drugs of drugs.**

Plot of η-χ diagram showing the relationship between electronic structure and properties of drugs shows three distinct grouping 1) positive charge structure (such as Muscarine) as Group A* (corresponding to A) 2) partial +ve and –ve charge structure (by delocalization of electrons) such as barbital as group B* (corresponding to B), and 3) remaining compounds are in group C*. Structure of amphetamine (14) can be considered quite similar to monoamine neurotransmitter.

### 5.3.2 Electronic Structure of Human Brain in Central Nervous System (CNS)

The nervous system is divided into two parts: Central Nervous System (CNS) and Peripheral Nervous System (PNS). CNS includes brain and spinal cord where as PNS consists of nerve and ganglia outside the brain and spinal cord.

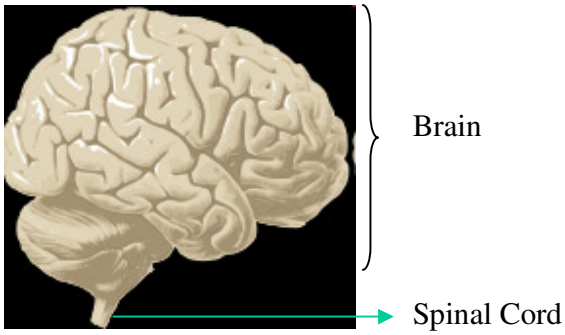
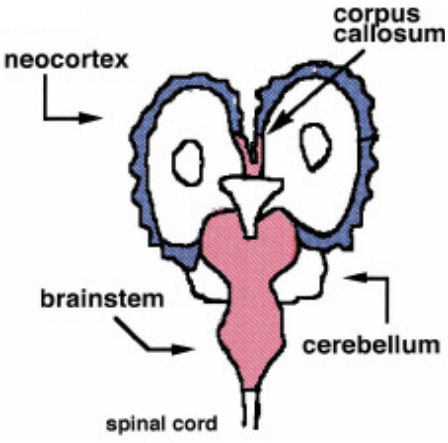



**Figure (5.9): Structure of central nervous system (CNS) of human brain.**



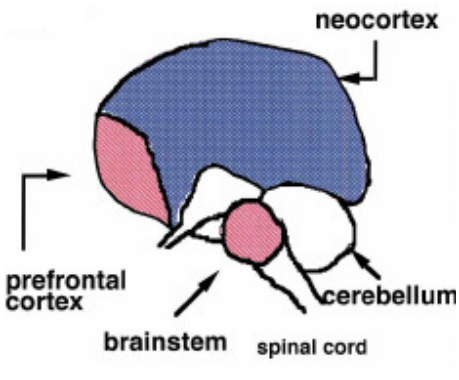




**Figure (5.10a): Front view of human brain.** **Figure (5.10b): Flank view of human brain.**

**Figure (5.10): Electronic structures (synaptic connections) of neurotransmitters and receptors in different regions of brain obtained from chemical hardness (pink and blue color shows the areas of the brain which are classified as chemically soft and hard, respectively).**

The monoamines (catecholamines: dopamine, adrenaline and noradrenaline) and serotonin are neurotransmitters of monoaminergic neuron. It is a well known fact that the monoaminergic nerve pathways are systemically distributed in the nucleus of nerves of the brainstem[16]. Monoaminergic such as serotonergic nerve system is composed of the pathways B1-B9[49] whereas monoaminergic such as noradrenergic, dopaminergic and adrenergic nerve systems are classified into pathways A1-A7[50], A8-A16[51] and C1-C3[49],respectively (also called A and C nerves). They are placed around the brain stem and unmyelinated nerve fibres. My result shows that the monoamine neurotransmitters are chemically softer than ACh and GABA. (Chemically soft base easily donate electron). Mesocortical dopaminergic nerve A10 secretes dopamine into prefrontal cortex[51], which confirms that prefrontal cortex is also chemically soft. However, GABA, glutamic acid, taurine are widely distributed in the neocortex of brain. Since they are chemically hard, neocortex is naturally chemically hard. These neurotransmitters act on myleinated nerves. Thus, the computed r ($\eta$, $\chi$) values of serotonin, noradrenaline, dopamine and

adrenaline support that the A, B and C nerves and brainstem are chemically soft. This is summarized in the fillowing.

**Table 5.7: Distribution of brain parts according to hardness and softness.**

| Brain art | Chemically soft/chemically hard | Reason for chemical softness or hardness |
|---|---|---|
| Brainstem | Chemically soft | Serotonin (from serotonergic nerve B1-B9), noradrenaline (from noradrenergic nerve A1-A7), dopamine (from dopaminergic nerve A8-A16) and adrenaline (from adrenergic nerve C1-C3) are all unmyelinated nerves and chemically soft. |
| Prefrontal cortex | Chemically soft | Dopamine is excreted from the mesocortical dopaminergic nerve A10 into the prefrontal cortex and is chemically soft. |
| Neocortex | Chemically hard | GABA, Glu and Taurine (act on myleinated nerves and are chemically hard.) |

### 5.3.3 Characterization of Agonist and Antagonist

The following rules are applied for designing agonist and antagonist for neurotransmitter receptors (from Figure (5.11):

(i) An agonist has electronic structure similar to a ligand i.e. the value of $\eta$ and $\chi$ is approximately equal to zero.

$$\Delta\chi = |\chi_l - \chi_a| = \sim 0 \qquad \Delta\eta = |\eta_l - \eta_a| = \sim 0$$

where a=agonist and l=ligand

(ii) A pure antagonist has similar value of $\chi$ where as the difference in $\eta$ is large.

$$\Delta\chi = |\chi_l - \chi_{an}| = \sim 0 \qquad \Delta\eta = |\eta_l - \eta_{an}| > 0$$

where an=antagonist and l=ligand

### 5.3.3.1 Few Examples of Agonist/Antagonist Relationship

1) Nicotine as antagonist for nicotinic ACh receptor and muscarine as agonist for muscarinic ACh receptor:

Conformational analysis of ACh shows that it has two types of conformers, cisoid and transoid in contact with nicotinic and muscarinic ACh receptors, respectively and the cisoid conformation is 2 kcal/mol more stable than the transoid conformation.[52] The coordinates r ($\eta$, $\chi$) of nicotine and muscarine are ($\eta$=3.58, $\chi$ =8.67) and ($\eta$=4.74, $\chi$ =7.47) respectively. Chemical softness (S) for nicotine and muscarine is 0.28 and 0.21 respectively which suggests that the nicotine is softer than muscarine. $\Delta\eta$ for nicotine and ACh is 1.48 eV and $\Delta\chi$ for nicotine and ACh is |0.59 | eV. $\Delta\eta$ for muscarine and ACh is 0.31 eV and $\Delta\chi$ for muscarine and ACh is 0.60 eV. There is large difference of $\Delta\eta$ for nicotine and ACh compared to that of muscarine and ACh (where as $\Delta\chi$ is similar). This suggests an agonist/antagonist relationship of acetylcholine receptors. From this, we can conclude that the activity of acetylcholine receptor is related to the r ($\eta$, $\chi$) of ammonium salt.

2) Haloperidol which is a major tranquilizer acts as an antagonist for dopamine at its $D_2$ receptor. This drug is chemically softer than dopamine. The gap in electronic structure coordinate r ($\eta$, $\chi$) for haloperidol r ($\eta_{\text{haloperidol}}$, $\chi_{\text{haloperidol}}$) and dopamine r ($\eta_{\text{dopamine}}$, $\chi_{\text{dopamine}}$) are equal to $\Delta\eta = |\eta_{\text{dopamine}} - \eta_{\text{haloperidol}}| = 0.69$ eV and $\Delta\chi = |\chi_{\text{dopamine}} - \chi_{\text{haloperidol}}| = |0.26|$ eV respectively. This confirms that the $\Delta\eta$ value for antagonist is large whereas $\Delta\chi$ value for antagonist is small (~0 eV). This also confirms the antagonist relationship of chlorpromazine and haloperidol.

3) Imipramine is an antidepressant drug. It inhibits the reuptake of dopamine, noradrenaline and adrenaline. It strongly interacts with the binding sites of catecholamines. The

gap in electronic structure coordinate r ($\eta$, $\chi$) for imipramine r ($\eta_{imipramine}$, $\chi_{imipramine}$) and dopamine r ($\eta_{dopamine}$, $\chi_{dopamine}$) are equal to $\Delta\eta = |\eta_{dopamine} - \eta_{imipramine}| = 0.35$ eV and $\Delta\chi = |\chi_{dopamine} - \chi_{imipramine}| = 0.44$ eV, respectively. Since $\Delta\eta$ and $\Delta\chi$ values are quite similar, one can conclude that imipramine is a dopamine receptor agonist.

4) Oxotremorine is a muscarinic acetylcholine receptor agonist: The gap in electronic structure coordinate r ($\eta$, $\chi$) for oxotremorine r ($\eta_{oxotremorine}$, $\chi_{oxotremorine}$) and acetylcholine r ($\eta_{acetylcholine}$, $\chi_{acetylcholine}$) are equal to $\Delta\eta = |\eta_{acetylcholine} - \eta_{oxotremorine}| = 0.68$ eV and $\Delta\chi = |\chi_{acetylcholine} - \chi_{oxotremorine}| = 0.81$ eV, respectively. Since $\Delta\eta$ and $\Delta\chi$ values are quite similar, we conclude that oxotremorine is a muscarinic acetylcholine receptor agonist. Similarly, the gaps of r ($\eta$, $\chi$) for oxotremorine r ($\eta_{oxotremorine}$, $\chi_{oxotremorine}$) and acetylcholine r ($\eta_{muscarine}$, $\chi_{muscarine}$) are equal to $\Delta\eta = |\eta_{oxotremorine} - \eta_{muscarine}| = |0.36|$ eV and $\Delta\chi = |\chi_{oxotremorine} - \chi_{muscarine}| = 0.21$ eV, respectively. Since the electronic structure coordinates are similar for oxotremorine and muscarine, both of them act on muscarine receptor of Acetylcholine.

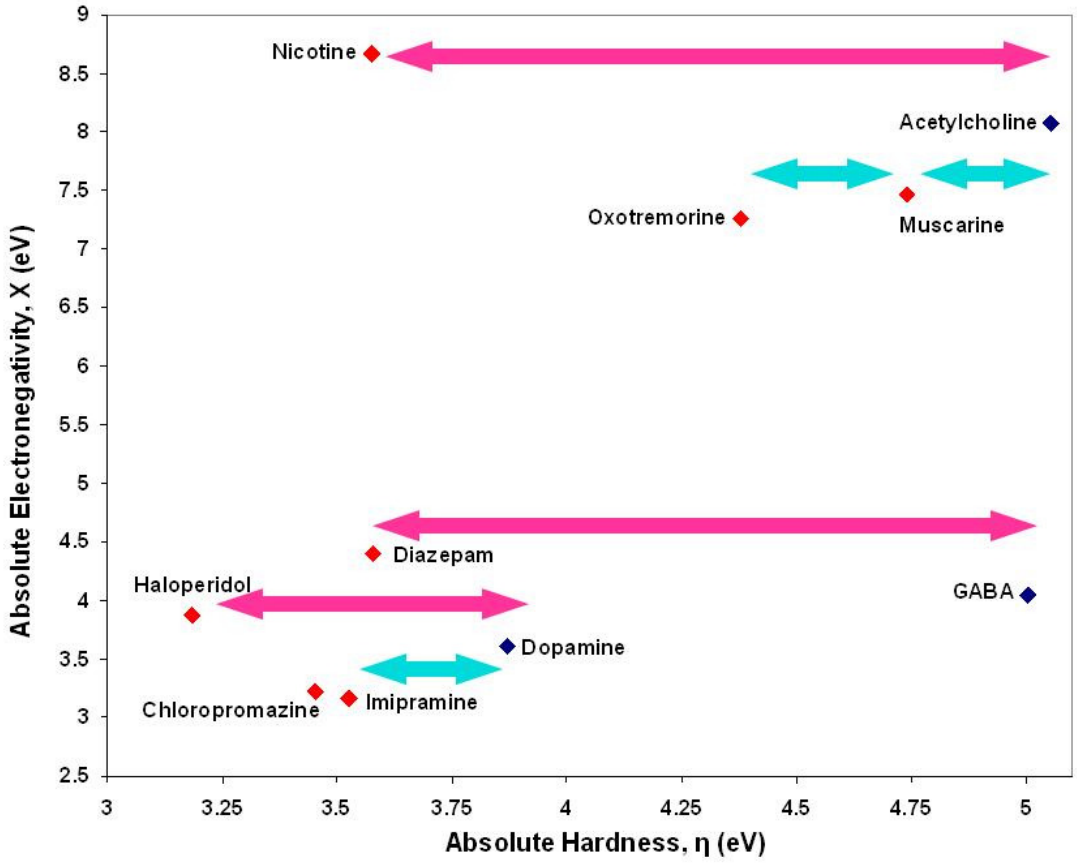



**Figure (5.11): Relationship of electronic structures between agonists and antagonists for neurotransmitter receptors. (♦: neurotransmitters; ♦ : drugs)**

Such relationship is valid only if agonist or antagonist acts on same site of receptor.

### 5.3.3.2 Critical Analysis

While the above rules explain quite well for some agonist/antagonist relationships for neurotransmitter and receptor but doesn't hold for all.

Diazepam is a BDZ agonist (acts on Benzodiazepam (BDZ) receptor). The large difference in η between diazepam and GABA predicts an antagonist relationship with the

receptor on different site. BDZ receptor and $GABA_A$ receptors are related to each other. GABA is an agonist for $GABA_A$ receptor.

## 5.4 Discussion

The interactions between Neurotransmitter (NT) and Neurotransmitter Receptor (NR) can be depicted with the following chemical process:

$$NT + NR \rightleftharpoons (NT.NR) \qquad (5.1)$$

According to the Hard Soft Acid Base principle, the quantity of electron transfer ($\Delta Q$) is determined by equation[53]

$$\Delta Q = (\chi_{NT} - \chi_{NR}) / 2 (\eta_{NT} + \eta_{NR}) \qquad (5.2)$$

where $\Delta Q$ is the charge transferred from electron donor to electron acceptor. The stabilization energy ($\Delta E$) for the interaction between neurotransmitter and neurotransmitter receptor is given by equation

$$\Delta E = (\chi_{NT} - \chi_{NR})^2 / 4 (\eta_{NT} + \eta_{NR}) \qquad (5.3)$$

Note that, $\Delta E$ increases when the absolute hardness, $\eta$ in the denominator decreases.

I illustrate the above relationship with the example in figure (5.11). It is clear that although $\chi$ is similar for dopamine and haloperidol, $\eta$ is larger for dopamine compared to haloperidol, i.e. softer haloperidol will bind more tightly to the dopamine receptor than dopamine itself.

# Chapter 6: Conclusions

## 6.1 Summary

Results indicate that the electronic structure of neurotransmitters analyzed through r (η, χ) plot can be can be graphically classified into 1) ACh analogs (positive charge structure) as in Group A, 2) GABA analogs (zwitterionic structures) as in group B, and 3) monoamine neurotransmitters such as catecholamines as in Group C. Thus, electronic structure of a neurotransmitter in the central nervous system plays an important role in its activity.

Electronic structure of the brain can be similarly qualitatively described by using the η-χ plot. It can be concluded that the brainstem and prefrontal cortex of brain are chemically soft and neocortex is chemically hard. This is because the unmyelinated nerve is chemically soft and the myleinated nerve is chemically hard. A, B, C nerve classification of monoaminergic neurotransmitters can also be confirmed from our results because these neurotransmitters are situated in the brain stem and prefrontal cortex which are chemically soft.

In addition, η-χ plot can provide a new way of predicting agonists, and antagonists for drug design depending upon its location in the Group A, B or C.

## 6.2 Future Direction of Project

It will be interesting to extend the present work to study other neurotransmitters not covered in this work. This will provide a comprehensive understanding of the classifications of neurotransmitters in the human brain and design of drugs targeted for several diseases.

One can make direct connections between binding pocket of receptor protein (enzyme) based on harder/softer binding of drugs. Binding pocket may prefer hard or soft drugs based on HSAB principle.

It is very important tool for drug design using CADD. The use of newer computer-based technique in combination with techniques that have been successful in the past provides means to greatly reduce the number of new compounds that must be synthesized and tested and thus speeds up the process of drug discovery.

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# Vita

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