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DOPAMINE IN SCHIZOPHRENIA IT'S TREATMENT WITH NEWER ATYPICAL ANTIPSYCHOTICS: AN OVERVIEW

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ABSTRACTS

Schizophrenia is a chronic and severe mental disorder that affects how a person thinks, feels and behaves. People with schizophrenia may seem like they have lost touch with reality. Although schizophrenia is not as common as other mental disorders, the symptoms can be very disabling. Dopamine is the main catecholamine in the CNS; and is involved in a variety of physiological functions, including sexual behavior, cognition, motor coordination, cardiovascular control, reward and hormonal regulation. Abnormalities in dopaminergic neurotransmission have been implicated in Parkinson's disease, schizophrenia, attention-deficit disorder and depression. Modern treatment for schizophrenia relies primarily on somatic drug therapy Psychotic illness includes various disorders but the term antipsychotic drugs also known as neuroleptics drugs, antischezophrenic drugs. The development of atypical antipsychotics is an important milestone in the history of psychiatry, because it brought effective treatment option with a reduced risk for adverse events. Four dopamine pathways in the brain play a role in the pathophysiology of schizophrenia as well as the therapeutic effects and side effects of antipsychotic agents. Activity in each of them has a unique set of physical, cognitive and psychological effects.

KEYWORDS: Schizophrenia, Dopamine, antipsychotics.

INTRODUCTION

According to WHO report 2016 on mental illness, worldwide 450 million people are affected by mental, neurological or behavioral problems at any time. About 873,000 people die by suicide every year. Mental illness is common to all countries and is a cause of immense

suffering. People with these disorders are often subjected to social isolation, poor quality of life and increased mortality. These disorders are the cause of staggering economic and social costs. One in four patients visiting a health service has at least one mental, neurological or behavioral disorder but most of these disorders are neither diagnosed nor treated. Mental illnesses affect and are affected by chronic conditions such as cancer, heart and cardiovascular diseases, diabetes and HIV/AIDS. Untreated, they bring about unhealthy behavior, non-compliance with prescribed medical regimens, diminished immune functioning, and poor prognosis. Cost-effective treatments exist for most disorders and, if correctly applied, could enable most of those affected to become functioning members of society. Barriers to effective treatment of mental illness include lack of recognition of the seriousness of mental illness and lack of understanding about the benefits of services. Policy makers, insurance companies, health and labour policies, and the public at large – all discriminate between physical and mental problems. Most middle and low-income countries devote less than 1% of their health expenditure to mental health. Consequently mental health policies, legislation, community care facilities, and treatments for people with mental illness are not given the priority they deserve.[1]

Psychosis

Psychosis Greek "psyche", for mind or soul, and "-osis", for abnormal condition, with adjective *psychotic*, literally means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". People suffering from psychosis are said to be *psychotic*. People experiencing psychosis may report hallucinations or delusional beliefs, and may exhibit personality changes and disorganized thinking. This may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out the activities of daily living. A wide variety of central nervous system diseases, from both external poisons, and from internal physiologic illness, can produce symptoms of psychosis.[2,3,4,5,6,7] Psychosis can be divided into two categories, affective disorders and schizophrenia.

AFFECTIVE DISORDERS

1. Acute and chronic organic brain syndrome (cognitive disorder)

Such as delirium and dementia; some toxic as well as pathological basis can often be defined; prominent features are confusion disorientation defective memory and disorganized behavior

2. Functional disorder

No underlying cause can be defined; memory and orientation are mostly retained but emotion, thought and behavior are seriously altered.

3. Depression

Sadness, guilt, physical and mental slowing, self-destructive ideation. It may be bipolar (manic and depressive) with cyclically alternating manic and depressive phases or unipolar (mania or depression) with waxing and waning course.

4. Alzheimer's dementia

Refers to acquired global impairment of intellect, memory and personality in the absence of gross clouding of consciousness or motor involvement. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

Schizophrenia

Schizophrenia is a debilitating mental illness that severely distorts a patient's perception of reality; and significantly impairs various emotional, behavioral, and cognitive functions. This most common form of psychosis boasts a devastating and overwhelming worldwide incidence of 1%. Suicide is the leading cause of premature death among patients with schizophrenia. Overall, patients with schizophrenia have approximately a 50% lifetime risk for suicide attempts and a 9% to 13% lifetime risk for completed suicide. In comparison, the lifetime risk for suicide in the general population of the United States is approximately 1% and in persons with mood disorders, 9% to 15%.[8,9,10,11,12]

History

Although the disease nowadays called schizophrenia has probably been present since early civilization it was not until the beginning of the nineteenth century that the first detailed description of the illness appeared in literature. In 1886, Emil Kraepelin named the disorder dementia praecox of early-onset dementia, distinguished the patients from those with a late-onset dementia and from those suffering from manic-depressive illness. Recognizing that the common characteristics between the patients were a thought disorder or the splitting fabric of thoughts, Eugen Bleuler in 1911 renamed the disease schizophrenia [schizein (Gk) = to split, Phren (Gk) = mind] and split the symptoms into 'positive' and 'negative'.[4,8]

Kurt Schneider divided the symptoms into primary 'first-rank' symptoms, and secondary 'second-rank' symptoms in the year 1959. The patient was diagnosed to be suffering from schizophrenia if any of the primary symptoms were present. If no primary symptoms were present but more of the secondary symptoms were present it was diagnosed as schizophrenia.[4,8]

Etiology of Schizophrenia

It is unclear whether schizophrenia is an old or modern illness. Ancient records (first century) describe a type of insanity in persons labeled either “gifted ” or “cursed ” depending on religious criteria, and early treatment often involved care by the family or church, but some early hypotheses considered the possibility that brain damage or malformation could account for these behaviors. Some authorities argue that no descriptions of true schizophrenia were published until more modern times. The term schizophrenia (splitting of the mind) was introduced in 1911 and is meant to convey a splitting of usually integrated psychic functions.

The onset of symptoms differentiable from non affected twins tends to cluster around certain ages (0 –5 and 13 –17 yrs), with a predominance of boys in the younger range and equal number of males and females in the older age group. There is no clear difference in occurrence of schizophrenia among different cultures. Some computed tomography and magnetic resonance imaging studies suggest possible increased cerebral ventricular size, decreased brain mass, or decreased left temporal lobe size in certain subsets of schizophrenics, and some neurodevelopment models implicate possible abnormal brain circuit maturation during the second trimester of gestation. Environmental factors such as viruses, pollution, trauma, dietary deficiencies, toxins, infections, or insecticides have been invoked as causative. Most experts believe that schizophrenia results from a complicated interplay of environmental, biologic, psychological, cultural, and genetic factors.[4,8,12,13]

Subtypes of Schizophrenia

Psychiatrists have traditionally distinguished a number of subtypes of schizophrenia, all the usefulness of these distinctions has been questioned in recent years. Indeed, the various types may overlap of change during the course of illness. And there are cases that do not conform entirely to the conventional subtypes or display characteristics of more than one type (referred to as undifferentiated or mixed types). The traditional categories are briefly reviewed here.[7,8,9]

1. Simple Schizophrenia

In this patient exhibits thought disorders, bland affect, social withdrawal, and reduction in speech and movement, all of which impair work performance; however, hallucinations and delusions are absent. Poverty of psychomotor activity is the dominant feature. At this stage the diagnosis is often uncertain.

2. Catatonic schizophrenia

This, the most readily differentiated type of schizophrenia, is now quite rare. Characterized by an extreme diminution in psychomotor activity. In about 60% of cases, the onset is relatively acute. The facial expression is vacant, the lips are persed; the patient lies supine without motion or sits for hours with hands or knees and head bowed (*catalepsy*). If a limb is lifted by examiner, it will sometimes be held in that position for hour (*flexibilitas cerea*).

3. Disorganized, or Hebephrenic, Schizophrenia

This was believed by Kraepelin to be a particularly malignant form. It tends to occur at an earlier age than the other varieties, hence the prefix *Hebe* ("youth"). The frequent occurrence of hallucinations and delusions leaves little doubt that patient is psychotic. In hebephrenic patients, since early, there is likely to have been a history of tantrums and of being overly pious, shy, fearful, solitary, conscientious, idealistic-traits that may have marked these individuals as odd.

4. Paranoid Schizophrenia

This is one of the most frequent types. The mean age of onset is 42 years, later than that of the preceding types. The central feature is the preoccupation with one or more delusion, accompanied by auditory hallucinations and related to a single thing.

5. Acute Schizophrenia

A special problem arises in the diagnosis of a rapidly evolving psychotic syndrome with florid hallucinations and delusions that clear in weeks or less, with or without treatment. This so-called acute *schizophrenia* most often turns out to be the initial attack of mania *or* intoxication with a psychotropic-hallucinogenic drug, for which reason it is not accorded a separate subtype of schizophrenia.

Symptoms of Schizophrenia

As the understanding of schizophrenia has progressed, researchers have found it useful to distinguish between positive and negative symptoms. The difference between the two

categories may indicate separate disorders within schizophrenia, and thus different treatments. A widely held theory is that positive symptoms are related to biochemical changes in the brain and negative symptoms are indications of structural change.[8,9,10,13]

Table no. 1.1: Positive symptoms of Psychosis.

Delusions
Hallucination
Distortion or exaggeration in language and communication
Disorganized speech
Disorganized behavior
Catatonic behavior
Agitation

Table no. 1.2: Negative symptoms of Psychosis.

Blunted affect
Emotional withdrawal
Poor rapport
Passivity
Apathetic social withdrawal
Difficulty in abstract thinking
Lack of spontaneity
Affective flattening – restrictions in the range of intensity of emotional expression
Alogia- restrictions in the fluency and productivity of thought and speech
Avolition- restrictions in the initiation of goal directed behavior

PHARMACOLOGY

NEUROTRANSMITTERS & RECEPTORS INVOLVED IN SCHIZOPHRENIA

A) Dopamine Receptors

Dopamine is the main catecholamine in the CNS; and is involved in a variety of physiological functions, including sexual behavior, cognition, motor coordination, cardiovascular control, reward and hormonal regulation. Abnormalities in dopaminergic neurotransmission have been implicated in Parkinson's disease, schizophrenia, attention-deficit disorder and depression. Based on similarities; and differences in gene organization, molecular structure, pharmacology and biochemistry these subtypes have been classified into two subfamilies: dopamine 'D_1-like' receptors, comprising the dopamine D_1 and D_5 receptor subtypes. These are G-protein coupled receptors. D_1 receptors are excitatory while D_2 are inhibitory.[9,14,15,16,17]

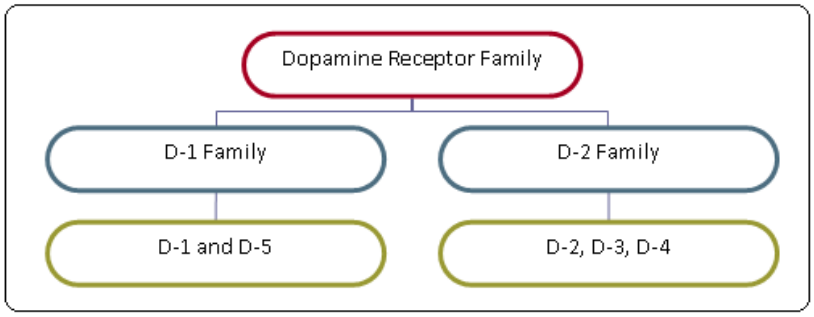


Figure 1.1: Dopamine receptor family.

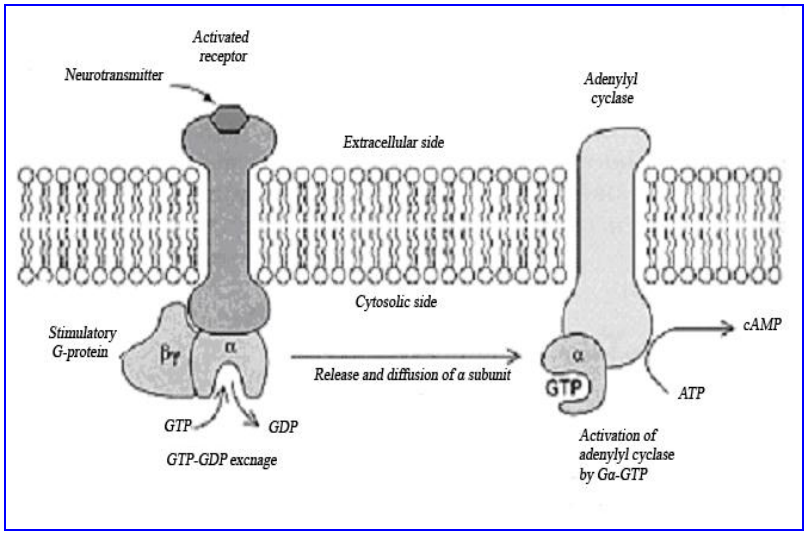


Figure 1.2: Dopamine receptor-a G-protein coupled receptor.

1) D_1 receptors

The D_1 receptor is the most widespread DA receptor and is expressed at higher levels than any other DA receptor. D_1 mRNA has been found in the striatum, the nucleus accumbens, and the olfactory tubercle. In addition, D_1 receptors have been detected in the limbic system, hypothalamus, and thalamus. On the other hand, in other areas where the D_1 receptor protein is highly expressed such as the entopeducular nucleus and the substantia nigra pars reticulata, no mRNA has been detected. This suggests that in these areas the D_1 receptor is mainly present in projections.

Atypical neuroleptics, like clozapine, were found to be potent inhibitors of D_1 and D_4 receptor binding, renewing interest in this receptor types.[15,16]

2) D_2 receptor

In 1988 the first DA receptor was cloned, the rat DA D_2 receptor. The DA D_2 receptor turned out to exist in two different splice variants, which were designated the DA D_2S (short) and DA D_2L (long) receptors. The DA D_2Lreceptor has an additional 29 amino acids in the third

cytoplasmic loop. Until today no functional differences have been discovered between the two isoforms, but the DA D_2Lseems to be more abundant than the DA D_2S isoform. Furthermore, the two DA D_2 isoforms have almost the same binding characteristics for several ligands, except for several antagonists of the benzamide type, for which the DA D2S isoform seems to have a slightly higher affinity than the DA D_2L isoform. The neuroleptic compound Haloperidol has been used as binding ligand to study the activity of other neuroleptics.[15,16]

3) D_3 receptor

In 1990 the DA D_3 receptor was cloned. The human DA D_3 receptor comprises 400 amino acids, and shows a 97% sequence identity of the transmembrane regions with the rat DA D_2S receptor. As with the DA D_2 receptor, two aspartate residues (Asp 75 and Asp 110) are thought to bind the protonated amine of dopamine, and three serine residues (Ser 192, Ser 193 and Ser 196) are thought to be involved in hydrogen-bond formation with the dopamine catechol functionality.[15,16]

Interestingly, it was found that DA and many DA agonists bind with much higher affinity to the DA D_3 than to DA D_2 receptors. Further investigations revealed that the DA D_3 receptor exists mainly in a high-affinity state, 26 independent of the degree of G-protein coupling. This contrasts with the DA D_2 receptor, which, depending on the degree of G-protein coupling, can exist in a high- or low-affinity state for agonists. Although the DA D_3 receptor is much less abundant than the

DA D_2 receptor (about 1- 10% of the total DA D_2 receptor protein), its brain distribution raised particular interest. The DA D_3 receptor is found with a relative high density in the nucleus accumbens, islands of Calleja, olfactory tubercle and hypothalamus. These brain areas make part of the limbic system, a group of brain-structures which is associated with cognitive, emotional and endocrine functions. Therefore, this DA receptor subtype was likely to be involved in the etiology of psychiatric disorders such as schizophrenia. To a lesser extent the DA D_3 receptor is also found in striatum and substantia nigra.

4) D_4 receptor

The Dopamine D_4 receptor was cloned in 1991. The human DA D_4 receptor comprises 387 amino acids, and has a 56 % trans-membrane sequence identity with the rat D_2S receptor. Aspartate residues 80 and 115 and serine residues 196, 197 and 200 are thought to be

involved in the binding of DA. In analogy with the DA D_4 receptor displays a high affinity for the atypical antipsychotic clozapine. This suggested that the atypicality of clozapine, a property which until then could not be accounted for, could be explained by its selective blockade of the DA D_4 (over the DA D_2) receptor subtype.[15,16]

1.3.2 Dopamine Pathways and Their Functions

Four dopamine pathways in the brain play a role in the pathophysiology of schizophrenia as well as the therapeutic effects and side effects of antipsychotic agents. Activity in each of them has a unique set of physical, cognitive, and psychological effects. For example, dopamine hyperactivity in the mesolimbic dopamine pathway is thought to induce psychosis, so reducing dopamine activity in that pathway, such as by blocking receptors with an antipsychotic drug, will theoretically alleviate psychotic symptoms. Although D_2 receptor blockade may have a beneficial outcome in one pathway, it may cause problems in another.[18,19,20]

1) Nigrostriatal Dopamine Pathway

The nigrostriatal dopamine pathway, as part of the extrapyramidal nervous system, controls movements. This pathway degenerates in Parkinson's disease, and blockade of D_2 receptors in this pathway causes the drug-induced movement disorders EPS and, eventually, tardive dyskinesia. Dopamine deficiency as well as receptor blockade in this pathway can also cause akathisia and dystonia.

2) Mesolimbic Dopamine Pathway

Hyperactivity in the mesolimbic dopamine pathway is thought to cause psychosis and the positive symptoms of schizophrenia such as hallucinations and delusions. This pathway is also thought to be involved in emotion and sensations of pleasure-stimulants and cocaine increase dopamine activity here. Blocking hyperactivity in this pathway should reduce or eliminate positive symptoms.

3) Mesocortical Dopamine Pathway

The role of the mesocortical dopamine pathway, especially in schizophrenia, is still open to debate. This pathway is thought to control cognitive function, and dopamine deficiency in this pathway may be responsible for the negative and cognitive symptoms of schizophrenia. If this is the case, it presents a therapeutic challenge, since dopamine receptor blockade in this pathway would theoretically lead to a worsening of negative and cognitive symptoms. In

other words, an agent would have to decrease dopamine in the mesolimbic pathway to alleviate positive symptoms but increase it in the mesocortical pathway to treat negative and cognitive symptoms.

4) Tuberoinfundibular Dopamine Pathway

Normal function of the tuberoinfundibular dopamine pathway inhibits prolactin release. In postpartum women, activity in this pathway decreases, allowing lactation. If normal function of this pathway is disrupted, for example, by D_2-blocking drugs, hyperprolactinemia can occur, with side effects such as galactorrhea, amenorrhea, and sexual dysfunction.[18,19,20]

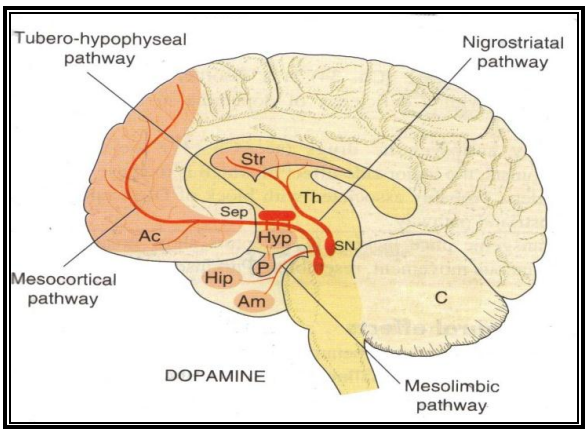


Figure 1.3: Dopamine Pathways in the brain.

B) Serotonin Receptors

Serotonin is formed in cell body (raphe nuclei), transported to the terminals and stored in vesicles. Release of 5HT is a Ca^{++} dependent process. Following its release, the effect of 5HT is terminated principally by reuptake into serotonergic nerve terminals using a Na^{+} / K^{+}-ATPase dependent transporter. Once back inside serotonergic neurons the neurotransmitter is either restored in the vesicles or metabolized by monoamine oxidase.[19,21,22,23,24]

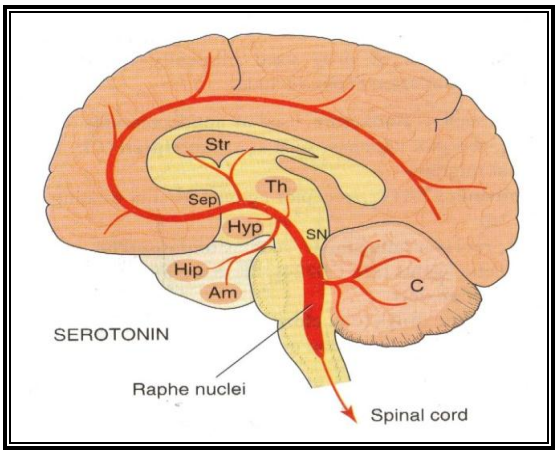


Figure 1.4: Serotonin pathways in the brain.

Serotonin neurons originate in the dorsal and median raphe nuclei of the brain stem and project to virtually every region of the brain with primary targets including the substantia nigra, hypothalamus, thalamus, amyadoloid-hippocampal area, caudate putamen and nucleus accumbens and central areas including the frontal occipital, insular, parietal, temporal and cerebellar cortices.[19]

The serotonin (5-hydroxytryptamine, 5-HT) receptors are a group of G protein-coupled receptors and ligand-gated ion channels found in the central and peripheral nervous system. It cannot cross the blood-brain barrier and must be produced within the brain. They mediate both excitatory and inhibitory neurotransmission. The serotonin receptors are activated by the neurotransmitter serotonin, which acts as their endogenous ligand. The serotonin receptors modulate the release of many neurotransmitters, including glutamate, GABA, dopamine, epinephrine/norepinephrine, and acetylcholine, as well as many hormones, including oxytocin, prolactin, vasopressin, cortisol, corticosterone, corticotropin, and substance P, among others. The serotonin receptors influence various biological and neurological processes such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation. The serotonin receptors are the target of a variety of pharmaceutical and illicit drugs, including many antidepressants, antipsychotics, anorectics, antiemetics, gastroprokinetic agents, antimigraine agents, hallucinogens and entactogens.[24,25]

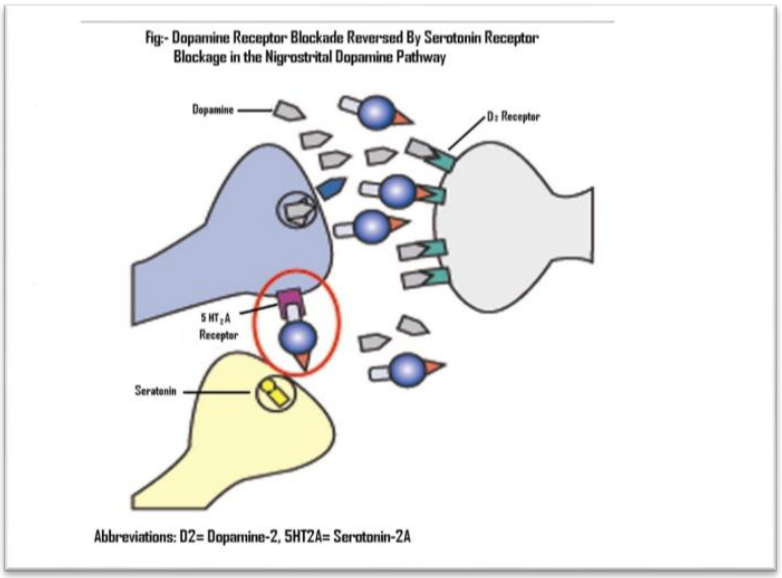
As Serotonin regulates dopamine release the presence of serotonin in some dopamine pathways, such as the nigrostriatal pathway, inhibits the release of dopamine, whereas in the mesolimbic dopamine pathway, serotonin has little or no effect.

In other words, when 5-HT_{2A} receptors are blocked, dopamine is released in the nigrostriatal dopamine pathway but is not released in the mesolimbic dopamine pathway. In the nigrostriatal pathway, this reaction may reverse some of the D2 blockade by atypical antipsychotics through a process called *disinhibition*. When serotonin receptors are blocked in this pathway, dopamine levels increase. The naturally occurring dopamine is then "disinhibited" and fills D_2 receptors, preventing blockade by the antipsychotic agent. With less D_2 blockade in nigrostriatal pathways, motor side effects are reduced.[24,27,28]

However, disinhibition in the nigrostriatal pathway does not affect the blockade of D_2 binding in the mesolimbic dopamine pathway, since few 5-HT_{2A} receptors are in the mesolimbic

dopamine pathway; thus antipsychotic actions are preserved. According to this hypothesis, antipsychotics are atypical when their 5-HT_{2A} antagonism superimposed on their D_2 antagonism reduces their D_2 binding enough to reverse motor side effects but not enough to reverse antipsychotic effects.[19,24,25,26,28]

Figure 1.5: Serotonin receptor family.



Abbreviations: D2= Dopamine-2, 5HT2A= Serotonin-2A.

Figure 1.6: **Dopamine receptor blockade reversed by serotonin receptor blockage in the nigrostriatal dopamine pathway.**

Table 1.3: Function and Localization of Serotonin Receptors.

Sr. No.	Receptors	Regional localization	Subcellular localization	Function
1	$5HT_{1A}$	High in brain limbic areas, cortex, dorsal and median raphae nuclei in the mesencephalon.	Postsynapitcally on 5HT neurons.	In the midbrain raphae nuclei act as autoreceptor that controls negatively 5HT firing and synthesis or release of 5HT.
2	$5HT_{2A}$	In the cortex of forebrain regions.	Postsynaptic membranes.	Control of NA release, hallucinogenic induced behaviour, sleep.
3	$5HT_{2c}$	In the choroid plexus, area of cortex, caudate nucleus, substantia nigra.	Postsynaptic	Anticunvulsive effect, hypoactivity,
4	$5HT_3$	Within the dorsal veal complex in the brainstem.	Postsynaptic membranes	Sensory function, emesis, control of neurotransmission.
5	$5HT_6$	Cortex, caudate, accumben	Unknown	Unknown motor function? Affective behaviour?
6	$5HT_7$	Hypothalamus, raphe nuclei.	Unknown	Unknown motor function?, Affective behaviour?

C) Other Receptors

Line of evidence has been accumulating that implicates the involvement of cholecystokinin, neurotensin, glutamate, symptoms. The major limitations of conventional antipsychotic drugs are their marked tendency to cause extrapyramidal symptoms, poor efficacy against negative schizophrenic symptoms, inability to reverse or prevent the development of the cognitive impairment of schizophrenia and inability to permit a normal level of psychosexual and work function. These factors lead to a poor quality of life even for patients whose positive and disorganized symptoms respond to neuroleptic treatment. In the past 20 years, several basic research findings have provided hypotheses about physiopathology of schizophrenia. This research, which spans many different disciplines, includes studies of the receptor pharmacology of neuroleptics at dopamine, serotonin, glutamate, purinergic and muscarinic receptors, electrophysiological studies with rats treated chronically with drugs, and molecular biological studies measuring the expression of immediate early genes. Conversely, the adenosine competitive antagonist caffeine potentiates behavioral effects similar to a dopamine agonist. A modulation of dopamine D_2 receptors by adenosine A_2 receptors in the ventral striatum has been proposed and supported by few clinical trials.[16,17,18]

1.3.5 Antipsychotic induced adverse effects

Adverse drug effects such as EPS and metabolic disturbances constitute an important drawback for patient safety and compliance to the therapy. Treatment failure, relapse of psychosis, increased metabolic and cardiovascular morbidity and mortality are potential consequences of these adverse effects. EPS may occur in up to 90% of patients within days or years of antipsychotic treatment. The most common EPS are ***dystonia*** (involuntary muscular spasms, abnormal postures including oculogyric crisis, tongue protrusion, trismus, torticollis, laryngeal-pharyngeal constriction, bizarre positions of limbs and trunk), ***parkinsonism*** (tremor, rigidity, bradykinesia), ***akathisia*** (a subjective feeling of restlessness, agitation, repetitive purposeless actions), and ***tardive dyskinesia*** (persistent involuntary movements, especially around the mouth).

Metabolic adverse effects show a large interindividual variation in severity, from weight gain, glucose intolerance, lipid abnormalities and hypertension to type 2 diabetes mellitus, diabetic coma and death. Both classical and atypical antipsychotics may cause metabolic disturbances; however, olanzapine and clozapine have been most frequently associated with these adverse effects.[13,29,30]

1.3.6 Treatment of Schizophrenia

Modern treatment for schizophrenia relies primarily on somatic drug therapy. Pharmacological treatment for schizophrenia did not begin until approximately a century ago. Before this, beliefs surrounding all mental illness were grounded in religious dogma and it was not until the 19th century that any substantial advances were made. Drugs from the phenothiazine class were originally used as anthelmintics in veterinary medicine, but in 1950 in Paris, Paul Carpenter synthesized chlorpromazine, a mild antihistamine that appeared notable as a sedative agent and revolutionized psychiatric treatment.[31,32,33]

RISK FACTORS

There are several factors that contribute to the risk of developing schizophrenia.

Genes and environment: Scientists have long known that schizophrenia sometimes runs in families. However, there are many people who have schizophrenia who don't have a family member with the disorder and conversely, many people with one or more family members with the disorder who do not develop it themselves.

Scientists believe that many different genes may increase the risk of schizophrenia, but that no single gene causes the disorder by itself. It is not yet possible to use genetic information to predict who will develop schizophrenia.

Scientists also think that interactions between genes and aspects of the individual's environment are necessary for schizophrenia to develop. Environmental factors may involve:

- Exposure to viruses
- Malnutrition before birth
- Problems during birth
- Psychosocial factors.

Different brain chemistry and structure: Scientists think that an imbalance in the complex, interrelated chemical reactions of the brain involving the neurotransmitters (substances that brain cells use to communicate with each other) dopamine and glutamate, and possibly others, plays a role in schizophrenia.

Some experts also think problems during brain development before birth may lead to faulty connections. The brain also undergoes major changes during puberty, and these changes

could trigger psychotic symptoms in people who are vulnerable due to genetics or brain differences.

TREATMENT

1. ANTIPSYCHOTIC AGENTS

Psychotic illness includes various disorders but the term antipsychotic drugs also known as neuroleptics drugs, antischezophrenic drugs. Pharmacologically they are characterized as dopamine receptor antagonist, though many of them also act on other targets, particularly 5-HT receptors, which may contribute to their clinical efficacy. Existing drug have many drawbacks in the terms of their efficacy and side effects. Gradual improvements are being achieved as new drugs are developed, but radical new approaches will probably have to wait until we have a better understanding of the biological nature of the disease, which is till poorly understood.

A distinction is drawn between the drugs that were originally developed (e.g. Chlorpromazine, haloperidol) often referred to as classical or typical antipsychotic drugs, and more recently developed agents (e.g. clozapine, quetiapine), which are termed atypical antipsychotic drugs. The term widely used but not clearly defined.[22,31,33]

Typical Antipsychotics

- Effective against positive symptoms
- Block dopamine D_2 receptor
- Associated with extrapyramidal toxicity

E.g.: Chlorpromazine, Haloperidol

Atypical Antipsychotics

- Effective against both positive and negative symptoms
- Block serotonin $5HT_{2A}$ receptor
- These agents lack or have very low extrapyramidal toxicity

E.g.: Quetiapine, Olanzepine

1.1 The Atypical Antipsychotics

The development of Atypical Antipsychotics is an important milestone in the history of psychiatry, because it brought effective treatment option with a reduced risk for adverse events. In particular the atypical antipsychotics appear to be much less likely to cause EPS (a

group of movement disorders associated with physical disability and subjective discomfort and distress, including Parkinsonism, akathisia dystonia and tardive dyskinesia).[33,34]

Why Atypical Antipsychotics?

All antipsychotics have actions at dopamine-2 receptors, but the atypical agents behave differently than the conventional antipsychotics at those receptors. In addition, the atypical antipsychotics block serotonin-2 receptors. These differences in receptor-binding profiles provide the basis for 2 theories that explain why the 2 classes of antipsychotics are similar in efficacy but different in side effect profile, especially in their propensity to cause motor side effects such as extrapyramidal symptoms and tardive dyskinesia.

The atypical antipsychotics—clozapine, risperidone, olanzapine, quetiapine, and ziprasidone have improved treatment for schizophrenia but have confused the terminology. These antipsychotics have been grouped into a new therapeutic class often referred to as ***atypical***. Grouping these new agents together, despite some dissimilarity, helps to distinguish them as a class from most of the older conventional antipsychotics, which are clearly less tolerable and possibly less effective for negative symptoms.

Underlying the different clinical profiles are differences in receptor binding, especially at D_2 and serotonin-$_{2A}$ (5-HT_{2A}) receptors. While these drugs are bound to a receptor, that receptor is blocked from the naturally occurring substance, in this case, dopamine or serotonin. The improved tolerability of atypical antipsychotics is Linked to reduced D_2 receptor blockade in parts of the brain where side effects are mediated. This reduced blockade, in turn, may be linked to antagonism of 5-HT_{2A} receptors, a drug's ability to quickly dissociate from D_2 receptors, or both.[12,34,35]

Hypotheses of Atypicality

All antipsychotics have actions at D_2 receptors in the brain. One way to distinguish the atypical antipsychotics from the conventional agents is that they block 5-HT_{2A} receptors as well as D_2 receptors and have fewer motor side effects such as EPS than the conventional antipsychotics have at standard doses. One atypical antipsychotic (quetiapine) has no more EPS than placebo. Additionally, at least 2 antipsychotics (olanzapine and risperidone) have shown greater efficacy than a conventional antipsychotic for negative symptoms, and 3 (olanzapine, ziprasidone, and quetiapine) do not raise prolactin levels like the conventional

drugs do. Ziprasidone is associated with less weight gain compared with conventional and other atypical antipsychotics.[34,35]

History

Phenothiazine compounds were synthesized in Europe in the late 19th century as apart of development of amine dyes such as Methylene blue. In the late 1930s a phenothiazine derivatives, promethazine was found to have antihistaminic and sedative effects. Attempt to treat agitation in psychiatric patient with promethazine and other antihistamines followed in 1940s but with little success.

In the early 1950s some antipsychotic effects were obtained with the extracts of Rauwolfia plant and then with large doses of Reserpine which was latter chemically synthesized by Woodland. Although Reserpine and related compounds that shows its ability to deplete monoamines from their vescicle storage sites in neurons, exerts antipsychotic effects. These are relatively weak and are typically associated with severe side effects like sedation, hypotension, diarrhea, depressed mood.

Meanwhile the ability of Promethazine to prolong barbiturate sleeping time in rodents was discovered in 1949-50. The development of effective pharmacotherapy began with the development of chlorpromazine in 1952, which revolutionized the treatment of schizophrenia. Between 1954 and 1975, about 15 antipsychotic drugs were introduced in the United States and about 40 throughout the world. Thereafter, there was a hiatus in the development of antipsychotics until the introduction of clozapine treatment in the United States in 1990 opened the era of "atypical" antipsychotic drugs, which show a reduced potential to induce extrapyramidal symptoms (EPS), an increased efficacy for the negative symptoms of schizophrenia

Table 1.4: Difference between typical & atypical Antipsychotics.[33,34]

Typical Antipsychotics	**Atypical Antipsychotics**
Effective against positive symptoms	Effective against positive and negative symptoms
Block Dopamine D_2 receptor	Block serotonin $5HT_{2A}$ receptor
Associated with Extrapyramidal toxicity	These agents lack or have very less EPS
e.g. Triflupromazine, haloperidol, Loxapine	e.g. Clozapine, Quetiapine, Olanzepine

Table 1.5 Structural Classification

1) Phenothiazine(Typical)

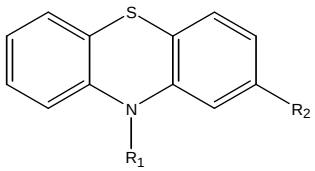
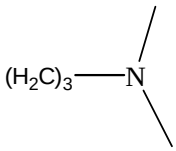
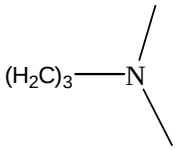
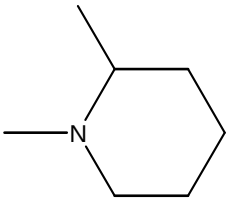
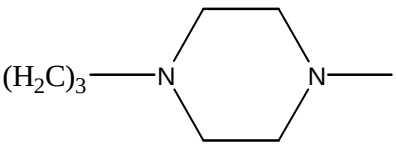
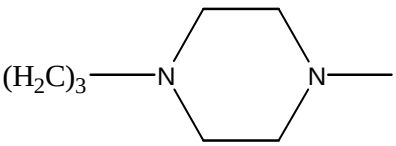
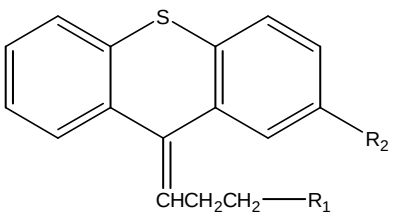
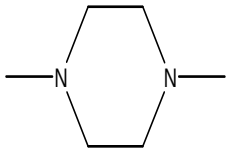
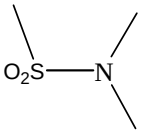


Table No.1.5 Classification of Antipsychotics.

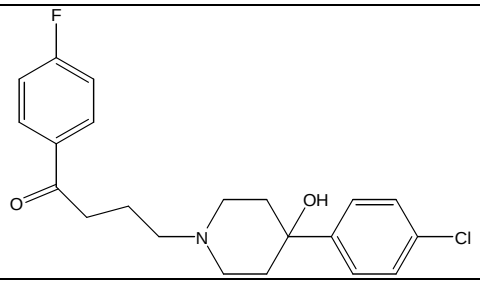
SIDE CHAIN	R_1	R_2
a) **Aliphatic side chain**		
i) Chlorpromazine		-Cl
ii) Triflupromazine		$-CF_3$
b) Piperidine side chain		
i) Thioridazine		$-SCH_3$
c) Piperazine side chain		
i) Trifluperazine		-Cl
ii) Fluphenazine		$-SCH_3$

2) Thioxanthene (Typical)

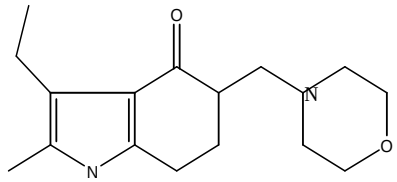


Examples	R_1	R_2
i) Chlorprothixene ii) Thiothixene	-N $(CH_3)_2$ 	-Cl 

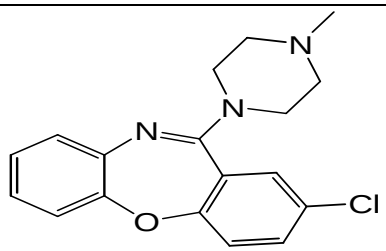
3) Butyrophenone (Typical)

Haloperidol	

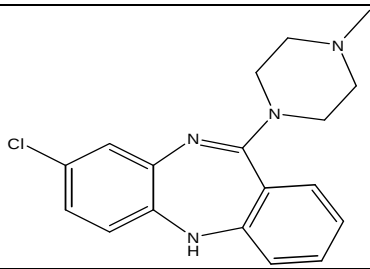
4) Dihydroindolone (Typical)

i) Malindone	

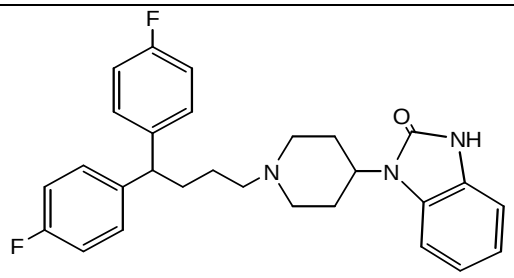
5) Dibezoxazepine(Atypical)

i) Loxapine	

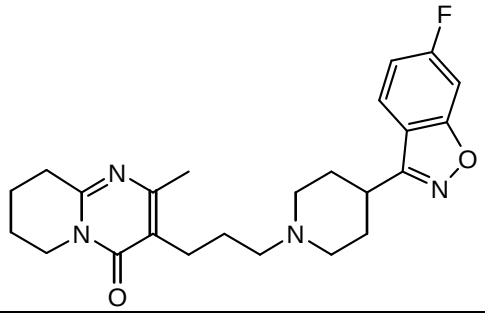
6) Dibenzodizepine(Atypical)

i) Clozapine	

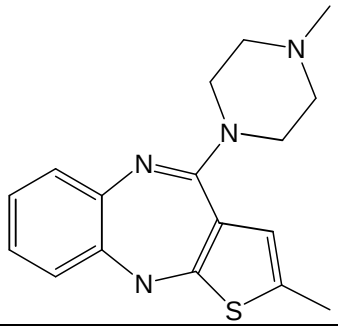
7) Biphenyl butyl piperidine (Typical)

i) Pimozoid	

8) Benzisoxazole (Atypical)

i) Resperidone	

9) Thienbenzodiazepine (Atypical)

i) Olanzepine	

REFERENCES

1. The World Health Report: 2016: Mental health: new understanding, new hope. World Health Organisation: Geneva, 2016.
2. Gennaro A R, The Science and Practice of Pharmacy, 20th edition (Lippincott Williams and Wilkins), Baltimore USA, 2001; 1421-1438.
3. Donald J Abrahm, Burger's Medicinal Chemistry and Drug Discovery, 6th edition, A John Wiley and Sons publication, New York, 2003; 599-671.
4. German E B, Rogelio L, and José M V, International Journal of Psychology and Psychological Therapy, 2003; 3: 111-140.
5. Tripathi K D, Essential of Medical Pharmacology, 4th edition ,(Jaypee Brothers Medical publications Pvt Ltd), New Delhi, 1998; 403-430.
6. Wetterling T, Mussigbrodt H, J. Cli. Psycho. Pharmacol, 1999; 19: 316-321.

7. Andreasen, N.C.; Olsen, S. Negative v positive schizophrenia: Definition and Validation. *Arch. Gen. Psychiatry*, 1982; 39: 789-794.
8. Danyang Liu, Design, Synthesis and Pharmacological Evaluation of enone Prodrugs, Groningen University, 2006; 1-8.
9. Van Tol M, Bunzow J R, Guan H C, Sunahara R K, Seeman P, Civelli O, Nature, 1991; 350: 610-614.
10. Shahin Akhondzadeh, Current Drug Therapy, 2006; 1: 1-7 1.
11. American Psychiatric Association, Diagnostic and statistical manual of mental disorders, 4th edition, Washington, 1994; 1-25.
12. Stanton J M, Schizophrenia Bulletin, 1995; 21: 463-472.
13. Richelson E, J. Clin. Psychiatry, 1999; 60: 5-14.
14. Leonard Alexander, synthesis and Pharmacological Evaluation of compounds with (partial)selectivity for the Dopamine D_1, D_2, D_3, D_4 receptor, Groningen University, 1998; 1-11.
15. Snyder S, Am. J. Psychiat, 1976; 133: 197-202.
16. Davis K L, Kahn R S, Davidson M, Am. J. Psychiat, 1991; 148: 1474-86.
17. Robert A O Brien, Clinical Pharmacology – Receptor binding in Drug Research, Marcel Dekker Inc, 1986; 123-143.
18. Rang H P, Dale M M, Ritter J M & Moore P K, Pharmacology, Sixth Ed, (Churchil Livingstone), USA, 2003; 494-500.
19. Darlsson A, Neuropsychopharmacology, 1988; 1: 179-86.
20. Kasper S, Tauscher J, Kufferle B, Barnas C, Pezawas L & Quiner S, Eur. Arch. Psychiat. Clin. Neurosci, 1999; 249: 83-90.
21. Ruth Rudisaar, Neuropharmacology of Atypical Antipsychotics and an Animal Model of Psychoses, University of Tartu, 2006; 11-12.
22. Abi Dargham A, Laruelle M, Aghajanian G K, Charney D & Krystal J, J. Neuropsychiatry Clin. Neurosci, 1997; 9: 1-17.
23. Busatto G F, Kerwin R W, J. Psychopharmacology, 1997; 11: 3-12.
24. Darlsson A, Waters N, Darlsson M L, Biol. Psychiat, 1999; 15: 1388-95.
25. Lieberman J A, Mailman R B, Biol. Psychiat, 1998; 44: 1099-1117.
26. Meltzer H Y, Neuropsychopharmacology, 1999; 21: 106-115.
27. Meltzer H Y, J. Clin. Psychopharmacology, 1995; 15: 2S-3S.
28. Breier A, Wolkowitz O M, Doran A R, Am. J. Psychiat, 1987; 144: 1549-1555.
29. Anderson N C, Olsen S A, Arch.Gen.Psychiat, 1989; 39: 789-794.

30. Arzu Gunes, Pharmacogenetics and Antipsychotic Treatment in Schizophrenia with special Focus on adverse drug reaction, Uppsala University, 2008; 14.
31. Wirshing D A, Boyd J A, Meng L R et al, J Clin Psychiatry, 2002; 63: 856-65.
32. Block J H, Bele Jr J M, 'Wilson and Gisvold's Textbook of Organic Chemistry', 11th edition, (Lippincott Williams And Wilkins, Baltimore), USA, 2004; 496-502.
33. Yia Liao, Peter DeBoer, Eddie Meier & Hakan Wikstrom, J. Med. Chem, 1997; 40: 4146-4153.
34. Leiberman J A, Mendelowitz A J, Psychiatric Drugs, 2000; 1-43.
35. Capuano, B.; Crosby, I. T.; Lloyd, E.J.; Taylor, D.A. Synthesis and preliminary pharmacological evaluation of 4'-arylalkyl analogue of clozapine. I. The effect of aromatic substituents. *Aust. J. Chem,* 2002; *55*: 565-576.
36. Johnstone E, Crow T, Frith C, Lancet, 1978; 1: 848-51.
37. Awouters F H L, Niemeggers C J E, Megens A H P, J. Pharm. Exp. Therapeutics, 1990; 254: 945-951.
38. Barar F S K, Essentials of Pharmacotherapeutics, 3rd edition, (S. Chand and company Ltd), New Delhi, 2000; 138-143.
39. Sokoloff P, Giros B, Martres M P, Bouthenet M L, Schwartz J C, Nature, 1990; 347; 146-151.
40. Hoffsommer R D, Taub D, Wendler N L, J. Org. Chem, 1962; 27: 4134-4137.
41. Rockwell W J K, Ellinwood E H, Trader D W, South Med. J, 1983; 76: 1407-1412.
42. Trevor I, Prior M D, Glan B, J.Psychiatry. Neurosci, 2003; 28: 99-111.
43. Herbert Y, Meltzer M D, International Suicide Prevention Trial, 1995; 1: 98-99.
44. Wetterling T, Mussigbrodt H, J. Cli. Psycho. Pharmacol, 1999; 19: 316-321.
45. Cole J.D, Arch. Gen. Psychiatr, 1965; 10: 246-261.
46. Littrel R A, Schneiderhan M, the Neurobiology of Schizophrenia Pharmacotherapy, 1996; 23: 143S-147S.
47. Dennis S C, Eric J N, Benjamin S B, Neurobiology of Mental Illness, Oxford University Press, 2001; 8-10: 56-62.
48. Claridge G, Human Psychopharmacol, 1994; 9: 343-351.
49. Daniel Lednicer, Lester A., Mitscher with Gunda I. George, The Organic Chemistry of Drug Synthesis, (A Wiley Interscience Publication, John Wiley and sons, Inc), New York, 2001; 212: 397.
50. Schumutz J, Eichenberger E, Chronicles of Drug Discovery, 1982; 1: 39-59.
51. Hunziker F, Fischer E, & Schumutz J, Helv. Chim. Acta, 1967; 50: 1588-1599.

52. Upjohn Co, Neth App, Chem. Abstr, 1966; 64: 8218-8219.
53. Jiban K Chakraborty, Linda Horsman, Terrence M Hotten, Ian A Pullar, David E Tupper & Francesca C Wright, J. Med. Chem, 1980; 23: 876-884.
54. Jiban K chakraborty, John Fairhust, Norman J A Gutteridge, Linda Horsman, Ian A Pullar, Colin W Smith, David J Steggles, David E Tupper, & Francesca C Wright J, Med. Chem, 1980; 23: 884-889.
55. Lars K Ottesen, Fredrik E K, & Roger Olsson, Organic Letters, 2006; 8: 1771-1773.
56. Hussenether, T.; Hubner, H.; Gmeiner, P.; Troschutz, T. Clozapine derived 2,3-dihydro-1*H*-1, 4-benzodiazepines with D_4 receptor selectivity: Synthesis and biological testing. *Bioorg. Med. Chem,* 2004; 12: 2625-2637.
57. Yi Liao, Bastiaan J Venhuis, Nienke Rodenhuis, Wia Timmerman & Hakan Wickstrom, J. Med. Chem, 1999; 42: 2235-2244.
58. Capuano, B.; Crosby, I. T.; Lloyd, E.J.; Podloucka, A.; Taylor, D.A. Synthesis and preliminary pharmacological evaluation of 4'-arylalkyl analogue of clozapine. II.* Effect of the nature and length of the linker. *Aust. J. Chem,* 2003; *56*: 875-886.
59. Chandra Sekhar, K.V.G.; Rao, V. S.; Vyas, D. R. K.; Kumar, M.M.K. Synthesis and preliminary pharmacological evaluation of N-2-(4-(2-substitutedthiazol-4-yl) piperazine-1-yl)-2-oxoethyl) acetamides as novel atypical antipsychotic agents. *Bioorg. Med. Chem. Let.*
60. Liégeois, J. F.; Eyrolles, L.; Bruhwyler, J.; Delarge, J. Dopamine D_4 receptors: a new opportunity for research on schizophrenia. *Curr. Med. Chem,* 1998; *5*: 77–100.
61. Capuano, B.; Crosby, I. T.; Lloyd, E.J.; Neve, J. E.; Taylor, D.A. Aminimides as potential CNS acting agents. II.* Design, synthesis and receptor binding of 4'-arylalkyl analogue of clozapine as prospective novel antipsychotics. *Aust. J. Chem,* 2008; *61*: 5-10.
62. Capuano, B.; Crosby, I. T.; Lloyd, E.J.; Podloucka, A; Taylor, D.A. Synthesis and preliminary pharmacological evaluation of 4'-arylalkyl analogue of clozapine. III. Replacement of tricyclic nucleus with a bicyclic template. *Aust. J. Chem,* 2007; *60*: 928-933.