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ATYPICAL ANTIPSYCHOTICS FROM SCRATCH TO THE PRESENT

Ashish Chauhan*, Amit Mittal, Pradeep Kumar Arora

Department of Pharmaceutical Sciences, Lovely School of Pharmaceutical Sciences, Lovely Professional University, Jalandhar-144402, Punjab, India

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Correspondence to Author:

Ashish Chauhan

Research & Development Centre, Jubilant Chemsys Ltd., Noida-201301, Uttar Pradesh, India

E-mail: ashishchauhan.info@gmail.com

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ABSTRACT

Mental illness constitutes the second-largest disease burden in the United States. Psychosis is one of the most common and severe mental illnesses. It is an extremely devastating condition characterised by delusions, hallucinations, distortion of thoughts and deteriorating social functioning experiences. Psychosis in all human societies has approximately same incidence of occurrence as in accordance to "anthropo-parity principle." It has large economic impact on various aspects of cognition, health, and quality of life which has devastated effects on its sufferers and facing them large economic burden. Psychosis (Schizophrenia) is associated with an imbalance of the dopaminergic system, entailing hyper-stimulation of dopamine function in the brain, particularly in the mesolimbic pathway. Consequences of antipsychotic treatment are far reaching and expensive. Detrimental extrapyramidal side effects associated with conventional antipsychotics and non-compliance among patients limits long term treatment with conventional antipsychotics. It gives rise to a new class, atypical antipsychotics owning low propensity to cause EPS, efficacy against refractory cases and better control over negative symptoms, better tolerance and compliance along with lower relapse rate and safer adverse effect profile. Atypical antipsychotics have revolutionized the treatment of psychosis, now being the treatment of choice for patients with psychosis. The positive therapeutic experience with the atypical antipsychotics in the treatment of psychosis and their favourable effects outweighs their unfavourable adverse effects. Though atypical antipsychotics are widely prescribed in the treatment of schizophrenia, however not a single atypical antipsychotic drug having any exceptional efficacy and safety profile. Thus, there is still a lot of research needed to be carried out in the development of novel atypical antipsychotics. This review is comprehensive appraisal about history and development, epidemiology, etiology of psychosis along with treatment with antipsychotics (especially on atypical antipsychotics), their global market, pharmaco-economics, mechanism of action and recent advancements in atypical antipsychotic medications, antipsychotic drugs which are currently under clinical development along with Ayurvedic, Homeopathic, Chinese, Unani treatment for psychosis.

INTRODUCTION: Psychosis comprises several psychiatric illnesses with serious distortion of thought, behaviour, and capacity to recognize reality and of the perception (delusions and hallucinations). Emil Kraepelin classified psychosis as manic depressive illness (bipolar disorder) and dementia praecox (Schizophrenia) [1]. Two main causes of psychosis are "organic" and "functional", organic conditions are primarily medical or pathophysiological, whereas, functional conditions are primarily psychiatric or psychological. Psychosis arising from "organic" (non-psychological) conditions is called secondary psychosis

and is associated with various pathologies such as brain tumour, dementia, multiple sclerosis, sarcoidosis, lyme disease, syphilis, alzheimer's disease and parkinson's disease.

Epidemiology of Psychosis: Mental illness constitutes the second-largest disease burden in US [2]. Psychosis occurs equally in males and females, although typically appears earlier in men, the peak ages of onset are 20-28 years for males and 26-32 years for females [3]. The lifetime prevalence of psychosis is usually given at 1%. However, a 2002 systematic review of many studies found a lifetime prevalence of 0.55% [4]. WHO collaborative study in various parts of World is illustrated in **Table 1** [5].

TABLE 1: WHO COLLABORATIVE STUDY IN VARIOUS PARTS OF THE WORLD

Place	Annual incidence per 100,000 of human population aged 15-54 (both sexes)
Aarhus (Denmark)	0.18
Chandigarh (India) (Rural)	0.42
Chandigarh (India) (Urban)	0.35
Dublin (Ireland)	0.22
Honolulu (Hawaii)	0.16
Moscow (Russia)	0.28
Nagasaki (Japan)	0.21
Nottingham (England)	0.22

Etiology of Psychosis: Multiple factors play important role in the development of psychosis. From which genes and early environmental brain abuses interact to cause neuro-developmental loss and set pre-schizophrenic children on a path of increasing abnormality. However, this neuro-developmental hypothesis is unable to clarify the timing of the onset of psychosis. One view is that an early brain abnormality interacts with normal events of brain during adolescence.

The latter potentially encompass hormonal changes, axonal myelination, and as well as environmental risk factors, drug misuse and social stress. Synaptic pruning has been much invoked and this phenomenon is under "late neuro-developmental model." Another view suggests that the timing of the onset of psychosis is related to the fact that during childhood the hippocampus carries out crucial working memory functions whereas the prefrontal cortex is developing, but then attempts to off-load this cognitive responsibility on to the prefrontal cortex when the latter reaches functional maturity.

Pathology of the prefrontal cortex may prevent this transfer of responsibility occurring from the hippocampus. The prefrontal cortex controls the amygdala and as such reduces the emotional responses to stimuli that are determined to be benign or non-threatening. A disruption of this prefrontal control would lead to a pathological upsurge in emotional responsibility of the subject, which in turn could be mediated via the amygdala's influence over the hypothalamic-pituitary-adrenal (HPA) axis. This in turn may influence the ventral hippocampus most significantly.

Thus, the developmental loss of hippocampus may be compromised by two further factors the inability to pass on the working memory tasks to the prefrontal cortex combined with the effects of stress and high circulating cortisol. Such a model proposes that transition to psychosis is a consequence of primary prefrontal dysfunction leading to secondary enhanced sub cortical stress response and dopamine transmission (due to a loss of prefrontal modulation), composite of stress-induced damage to the hippocampus. Drug use and chronic social adversity may compound dopamine dysregulation and let the susceptible individual to the verge for the expression of frank psychosis [6].

Treatment with Antipsychotics: An antipsychotic (or neuroleptic) is a tranquilizing psychiatric medication used to treat psychosis (including delusions or hallucinations, as well as disordered thought) particularly in schizophrenia and bipolar disorder. Antipsychotics are superior to placebo in the acute and long term treatment of schizophrenia [7].

Patients on placebo treatment have significant relapse rate more often, have to hospitalise more frequently and depicts more psychotic symptoms in comparison to patients continuing antipsychotic treatment after an acute episode. Prophylactic treatment with a standard or slightly reduced dose provides the best protection against relapse [8]. Antipsychotic medications have been demonstrated to reduce relapse rate and re-hospitalisation in psychiatric patients.

Thus anti-psychotics have to be considered an effective treatment of schizophrenia [9].

History and Development: Psychosis in all human societies has approximately same incidence of occurrence as in accordance to "anthropo-parity principle." The absence of evidence for environmental causation suggest the genetic origin of psychosis and in some way characteristic of the human condition [10]. Ernst von Feuchtersleben had introduced the word "Psychosis" in 1845 as an alternative to insanity and mania [11]. The history of antipsychotic drug development is based on chance findings, as in 1891 Paul Ehrlich observed the antimalarial effect of Methylene blue **1**, a phenothiazine derivative [12].

Laborit and Huguenard administered the aliphatic phenothiazine, Chlorpromazine **2**, to patients for its potential anesthetic effects during surgery [13]. Shortly thereafter, Hamon et al. and Delay et al. extended the use of this treatment in psychiatric patients and serendipitously uncovered its antipsychotic activity [14]. The first reported Chlorpromazine-treated case was that of a 57 year old labourer who was admitted in the Central Military Hospital-Val de Grace in Paris because of erratic, uncontrollable behaviour [15].

The identity of the first psychiatrists to administer Chlorpromazine to patients remains a matter of dispute. Laborit, Hamon, Paraire, and Velluz were awarded in 1993 for their role in identifying chlorpromazine's therapeutic effects. In 1952 Rhone-Poulenc launched Chlorpromazine with brand as Largactil, and in 1954 SmithKline and French (Philadelphia, PA) marketed it under the trade name of Thorazine. Chlorpromazine remained the most prescribed antipsychotic agent throughout the 1960s and early 1970s. About 15 antipsychotics drugs were introduced in US during 1954-1975 and 40 throughout the world.

These include Trifluoperazine **3**, Thioridazine **4**, Chlorprothixene **13,** Thiothixene **16**, Haloperidol **17** etc[16].

The last of this series to be approved by the United States Food and Drug Administration (US-FDA) was Loxapine **20**, a dibenzazepine in 1975. Several researchers had argued that Loxapine may behave as an atypical antipsychotic drug [17]. The introduction of Clozapine **21** in 1989 in US market, an antipsychotic with no or minimally associated extrapyramidal symptoms opened the era of atypical antipsychotics.

The first of the new (post-clozapine) atypical antipsychotics medication, Risperidone **22** was approved for use in the United States in December 29, 1993 (Adult) and August 22, 2007 (Pediatric). US-FDA approved another new atypical antipsychotic, Olanzapine **23** in September 30, 1996, Quetiapine **24** in September 26, 1997, Ziprasidone **25** in February 5, 2001, Aripiprazole **26** in November 15, 2002 (Adult) and October 29, 2007 (Pediatric) [18, 19] (**Fig. 1, 2**).

Consequences associated with long term treatment: In long term treatment with antipsychotics, the patients become noncompliant and may refuse treatment due to poor insight ability, and as a result of various psychiatric symptoms such as delusions, hallucinations, incoherent or disorganized speech, odd behavior, serious distortion of thought and behavior, patient is unable to meet the ordinary demand of life [20]. Undesirable side effects such as Akathisia, Acute Muscular Dystonia, Parkinsonism, Tardive Dyskinesia and consequences of increased Prolactin level, all limits long term treatment with antipsychotics.

Global Market: The global market for antipsychotic drugs is just about $19.6 billion in 2010 and it will raise up to $20.8 billion in 2011, $14.4 billion in 2013 and $14.8 billion in 2014. It represents a total compound annual growth rate (CAGR) of -4.6%. Due to loss of patent exclusivity through the study period, the compound annual growth rate (CAGR) of -3.7% is estimated [20]. Quetiapine **24** (Seroquel), Aripiprazole **26** (Abilify), Risperidone **22** (Risperdal), Olanzapine **23** (Zyprexa) were among the top 10 most costly drugs with a total turnover of $18 million [21, 22].

Pharmacoeconomics behind Antipsychotic Treatment: Psychosis has large economic impact on various aspects of cognition, health, quality of life which has devastated effects on its sufferers and facing them many costs. Consequences of antipsychotic treatment are far reaching and expensive. The costs associated with treating, caring for psychotic patients are high, with a number of direct and indirect costs contributing to the total economic cost of the disease.

Direct costs related to expenditures on care, treatment that assist the patient to function, include items such as physician visits, hospitalisation, provision of community based mental health services, drug therapy.

Indirect costs are not directly related to care or treatment; often result from loss of what would have otherwise been productive resources, including patients and unpaid caregivers. The indirect cost of psychosis to society is greater than the direct cost, as reflected by the finding that of an estimated total cost of schizophrenia to the US economy of $65 billion in 1991, $46 billion was indirect costs. Indirect costs of schizophrenia were estimated to be at least £1.7 billion in the UK in 1990-1991.

Generally, atypical antipsychotic agents are more expensive (on a per-dose basis) than their conventional antipsychotic counterparts, however the costs of the atypical agents are comparatively minor when the total cost of schizophrenia is considered [23, 24, 25, 26].

New drug therapies that primarily seem expensive in contrast to existing agents can be cost-effective if they improve outcomes and diminish the need for expensive interventions such as hospitalisation.

Pharmaco-economic analysis indicated that the total direct costs of caring for psychotic patients treated with atypical antipsychotic agents are lower, or at least no higher, than treating with conventional antipsychotic agents.

Classification of Antipsychotics: The antipsychotics can be classified as:

First Generation Antipsychotics/Typical Anti-psychotics/Conventional Antipsychotics/ Classical Neuroleptics/ Major Tranquilizers: First-generation antipsychotics or typical antipsychotics are the drugs having a salutary therapeutic effect in psychosis. These drugs tend to block receptors in the brain's dopamine pathways. Typical antipsychotics have also been stated as the major tranquilizers, because of their tendency to tranquilize and sedate. These drugs might also be used to counter psychosis associated with a wide range of other diagnosis, such as psychotic depression. The US-FDA approved typical antipsychotics are:

a. Phenothiazines: Chlorpromazine **2**, Trifluoperazine **3**, Thioridazine **4**, Promethazine **5**, Fluphenazine **6**, Perphenazine **7**, Mesoridazine **8**, Prochlorperazine **9**, Promazine **10**, Periciazine **11**, Triflupromazine **12**.

b. Thioxanthenes: Chlorprothixene **13**, Clopenthixol **14**, Flupenthixol **15**, Thiothixene **16**.

c. Butyrophenones: Haloperidol **17**, Droperidol **18**, Bromperidol **19** (**Fig. 1**).

Second Generation Antipsychotics/Atypical Antipsychotics: Second-generation antipsychotics or atypical antipsychotics possesses superior efficacy in reducing psychotic symptoms while reducing side effects (extrapyramidal side effects in particular) than typical or conventional antipsychotics.

Atypical antipsychotics are distinguished from their typical counterparts in holding more than a single mechanism for achieving atypicality. The US-FDA approved atypical antipsychotics are:

Clozapine **21**, Risperidone **22**, Olanzapine **23**, Quetiapine **24**, Ziprasidone **25**, Aripiprazole **26**, Sertindole **27**, Paliperidone **28**,Amisulpride **29**, Asenapine **30**, Iloperidone **31**, Clotiapine **32**, Zotepine **33**, Sulpiride **34**, Remoxipride **35**, Perospirone **36**, Blonanserin **37**, Mosapramine **38** (**Fig. 2**).

Antipsychotic Drugs under Clinical Trials: Atypical antipsychotics and other drugs (indicated in various treatments for psychosis) under clinical development are illustrated in **Table 2 and 3** [27, 28, 29, 30, 31, 32, 33, 34, 35, 36].

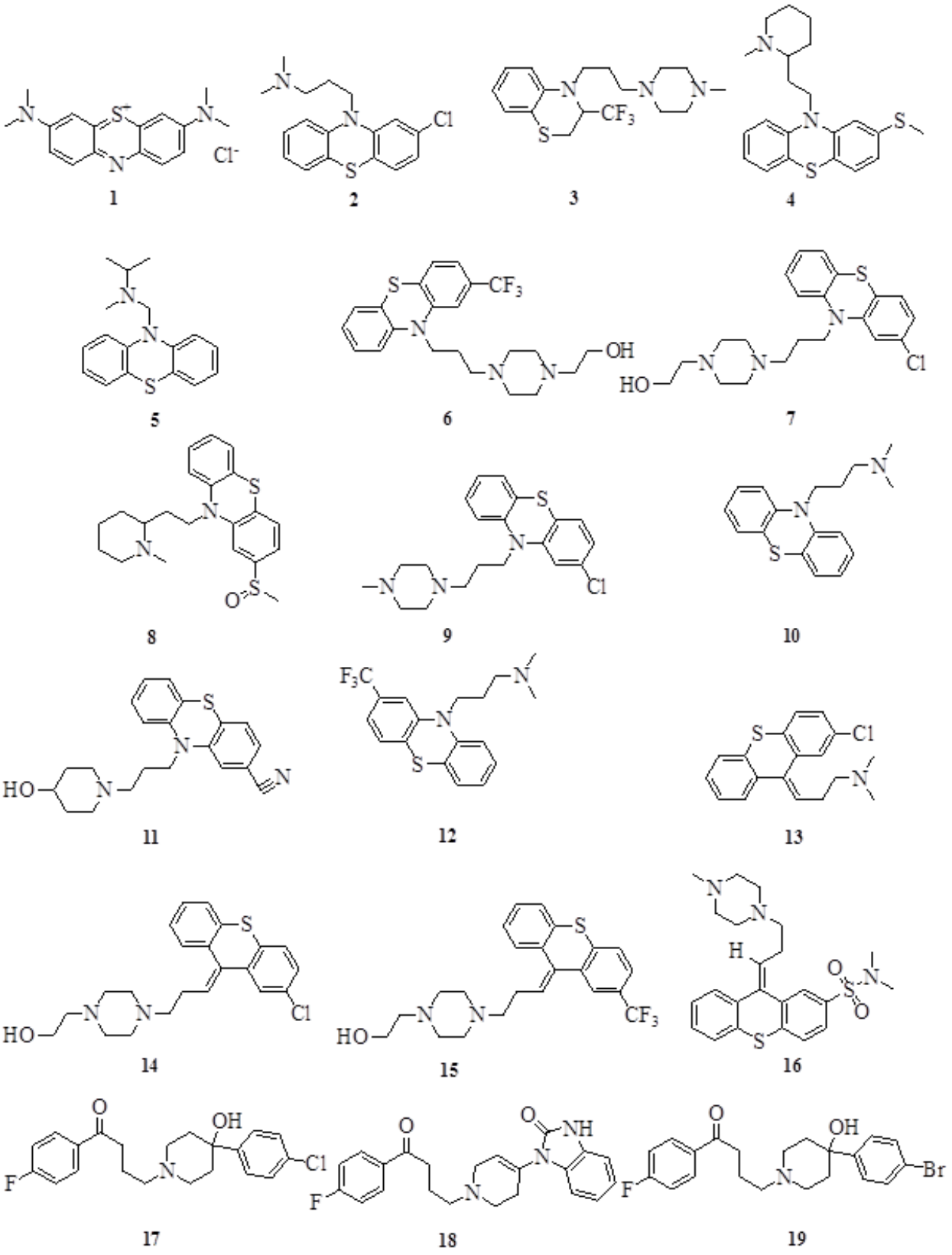


FIGURE 1: METHYLENE BLUE I AND TYPICAL ANTIPSYCHOTIC DRUGS (2-19)

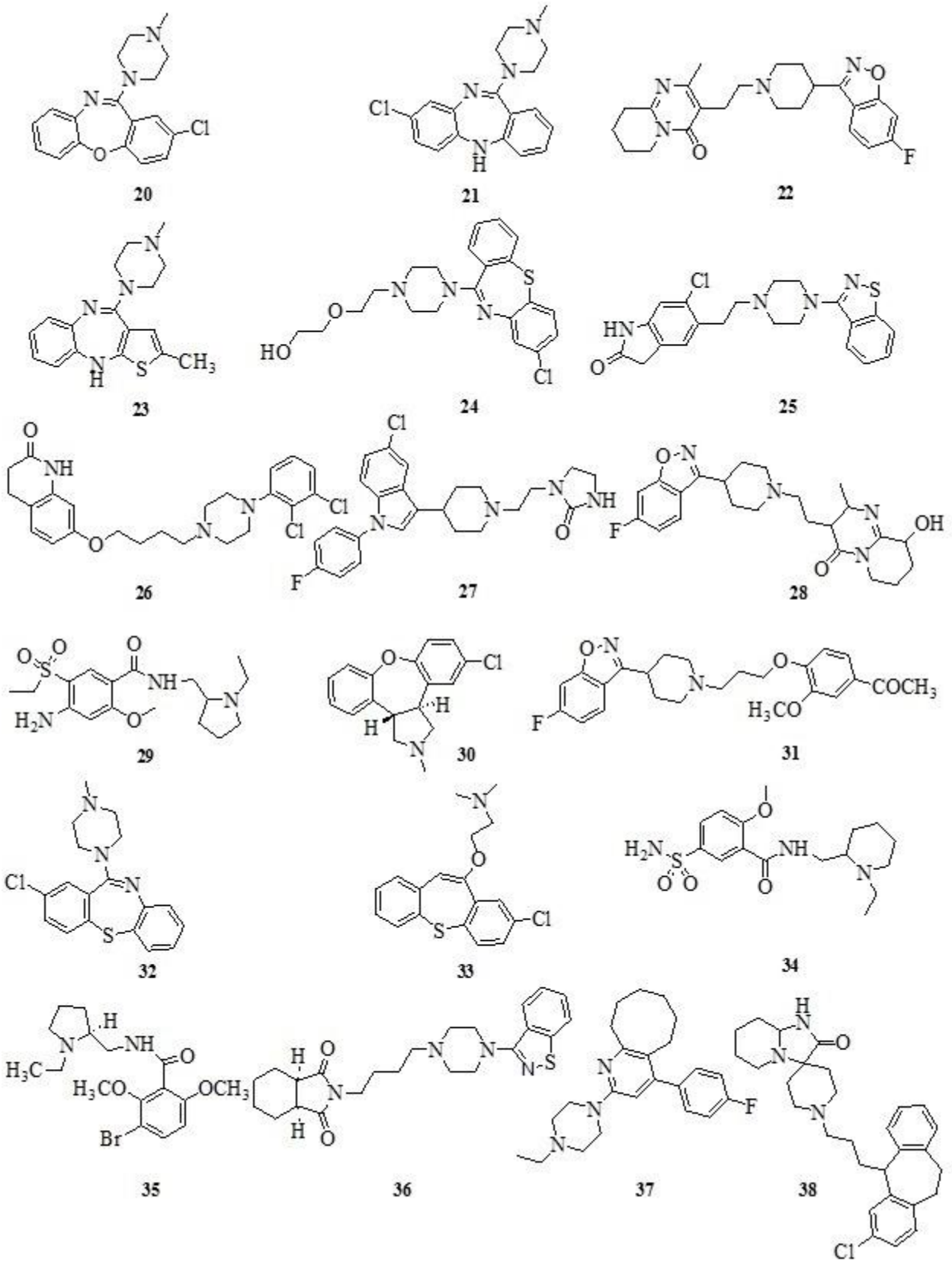


FIGURE 2: LOXAPINE AND ATYPICAL ANTIPSYCHOTIC DRUGS (21-38)

TABLE 2: ATYPICAL ANTIPSYCHOTIC DRUGS UNDER CLINICAL DEVELOPMENT

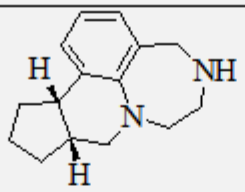
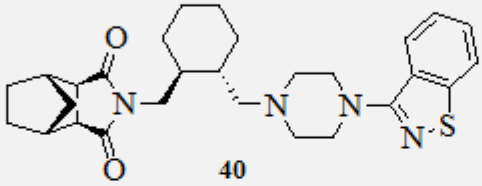
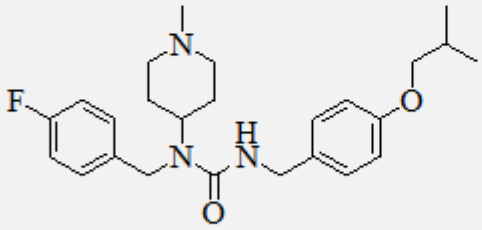
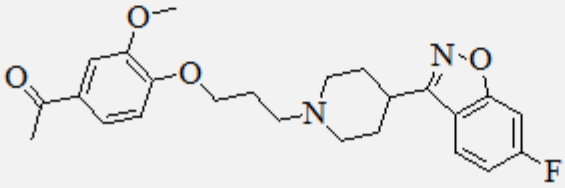
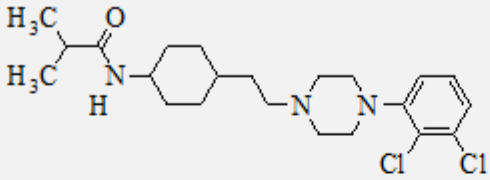
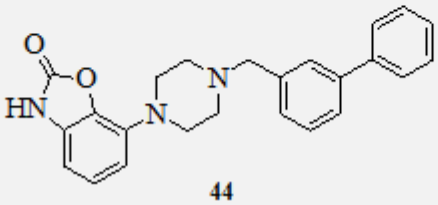
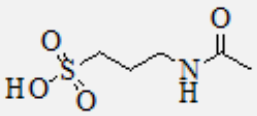
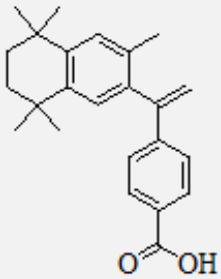
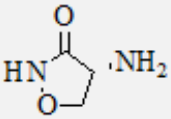
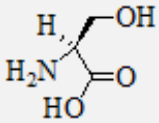
Sr. No	Compound Name	Structure	Company	Stage	Status
1	Vabicaserin	 **39**	Wyeth	Phase II	Terminated May 13, 2010
2	Lurasidone	 **40**	Dainippon Sumitomo Pharma	Phase III	Recruiting July 28, 2010
3	Pimavanserin	 **41**	Acadia Pharmaceuticals	Phase III	Recruiting Sept. 10, 2010
4	Iloperidone	 **42**	Novartis	Phase IV	Recruiting Sept. 21, 2010
5	Cariprazine	 **43**	Gedeon Richter/Forest	Phase III	Recruiting Sept. 22, 2010
6	Bifeprunox	 **44**	Solvay	Phase III	Terminated Sept. 24, 2010

TABLE 3: OTHER DRUGS (INDICATED IN VARIOUS TREATMENTS FOR PSYCHOSIS) UNDER CLINICAL DEVELOPMENT

Sr. No	Compound Name	Structure	Company/ Institute	Stage	Status
1	Acamprosate	 45	National Alliance for Research on Schizophrenia and Depression and National Institute on Alcohol Abuse and Alcoholism	Phase IV	Recruiting June 1, 2010
2	Bexarotene	 46	Beersheva Mental Health Center	Phase III	Recruiting June 28, 2010
3	D-Cycloserine	 47	National Institute of Mental Health (NIMH)	Phase IV	Recruiting Aug 20, 2010
4	D-serine	 48	Sheba Medical Center	Phase II	Recruiting Dec. 24, 2010

Other treatments for Psychosis:

1. Ayurvedic treatment:

Brahmyadiyoga: Brahmyadiyoga is a herbal preparation consists of Brahmi (*Centella asiatica*), Vacha (*Acorus calamus*) Sarpagandha (*Rauwolfia serpentina*), Kusta (*Saussurea lappa),* Tagar (*Nymphoidi macrospermum*) and Jatamansi (*Nardostachys jatamansi*) developed by Central Council for Ayurveda & Siddha, under Ministry of Health & Family Welfare, India for the treatment of schizophrenia (Unmada) [37].

Major Phytoconstituents of brahmyadiyoga are illustrated in **Table 4, Fig. 3**. Herbal combinations of water based extracts of *Bacopa monnieri* and *Nardostachys jatamansi* are as effective as modern anti-psychotic drugs, for treatment of schizophrenia. The treatment is safe even for long term use [38].

TABLE 4: MAJOR PHYTOCONSTITUENTS OF BRAHMYADIYOGA

Sr. No.	Herbal Plant	Major Phytoconstituents
1	*Centella asiatica*	Asiaticoside **49**, Bacoside A **50**.
2	*Acorus calamus*	Asarone **51**.
3	*Rauwolfia serpentina*	Reserpine **52**, Ajmaline **53**,
4	*Saussurea lappa*	Costunolide **54**, Palmitic acid **55**.
5	*Nardostachys jatamansi*	Virolin **56**, Jatamnsone **57**.
6	*Nymphoidi macrospermum*	Betulinic acid **58**.

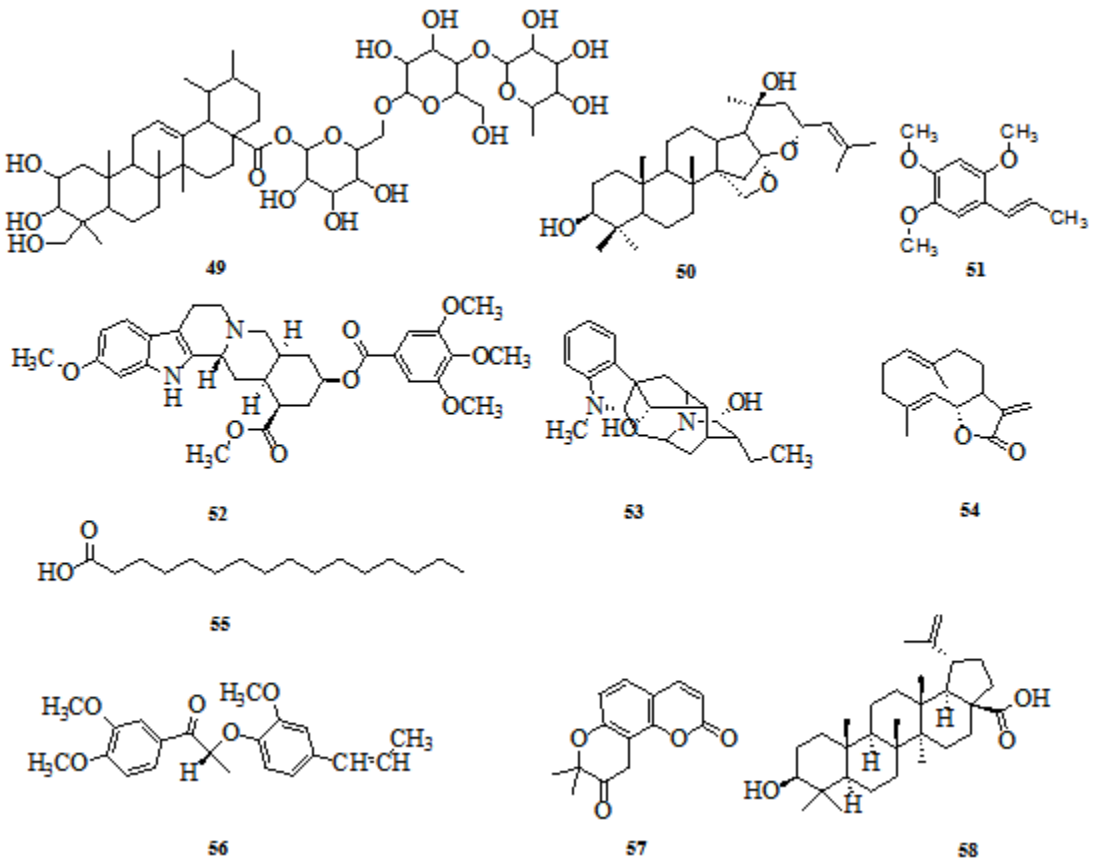


FIGURE 3: MAJOR PHYTOCONSITUENTS OF BRAHMADIYOGA

2. **Homeopathic treatment** [39]: Homeopathy treats the person as a whole, i.e. homeopathic treatment emphasis on the patient as a person, as well as his pathological condition. Following homeopathic medicines overcome symptoms of various types and stages of schizophrenia: Lachesis, Lycopodium, Sulphur, Ignatia, Merc-sol, Rhus-tox, Causticum, Kali-brom, etc.

i. Hyoscyamus, Stramonium, Aconite, Belladona, Helleborous, *Cannabis indica* has proven specifically useful in sudden onset of schizophrenia and acute crisis of schizophrenia.

ii. Ars-alb, Aurum-met, Psorinum, Calc-carb, Cimicifuga, Natrum-sulph, Aurum-mur has proven specifically useful in depression and suicidal tendencies.

iii. Lycopodium, Pulsatilla, Anacardium, Brom, Opium, Sepia, *Cannabis indica* has proven specifically useful in 'flat-effect' manifested in psychosis.

3. **Chinese treatment:**

a. **Ci Zhu Wan** (Magnetite-Cinnabar Pill) [40]

Actions: Calms the mind, heavy-duty sedative, improves hearing and vision.

Indications: Ascendant Heart Yang with a loss of the mutual balance between water and fire.

b. **Healthy Brain, Bu Nao Wan** [41]

Ingredients: Sweet flag, Sour date seed, Sage root, Schisandra, Sichuan lovage, Fleece flower branch, Polygala, Reishi.

Indications: Psychosis, compulsive disorders.

4. **Unani treatment:**

a. **Usool Ilaj** [42]

i. Musakkinat and Manumat advia.

ii. Munazziz and Mushil sauda advia.

iii. Martab and Martab advia.

Treatment:

i. Sirka 50 ml, Arq gulab 100 ml, Shandal 3 gm, Kafoor 3 gm mix and apply locally on scalp region and centre of head.

ii. Clean intestines through giving enema.

iii. Decoction of Barg gauzaban 3 gm, Ustookhudoos 3 gm, Basfaiz 3 gm and Afteemoon 3 gm.

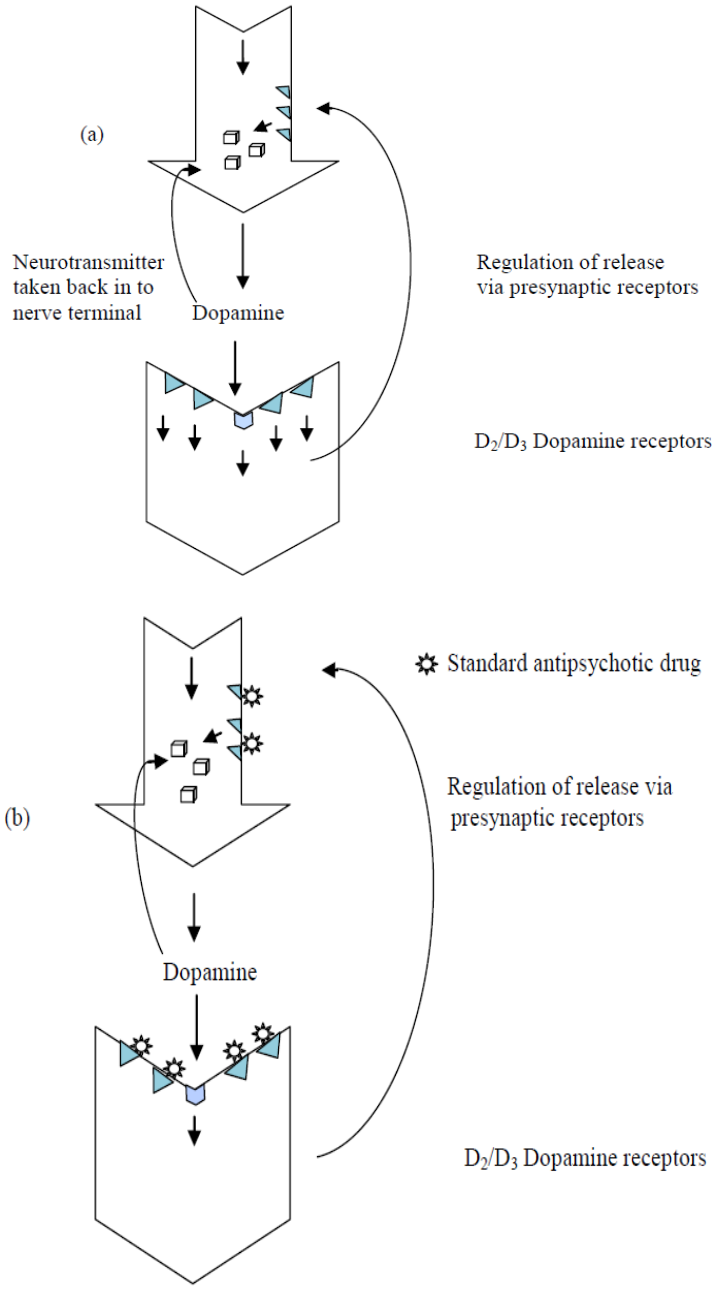
iv. Khameera gauzaban ambari or Dawaul musk mutadil or Mufarah yaqooti.

Antipsychotic Drug Action: "Dopamine hypothesis of psychosis" states that psychosis results from an over activity of dopamine function in brain, particularly in the mesolimbic pathway. Dopaminergic pathway is the primary common target for all antipsychotics drugs. There are two types of dopamine receptors; excitatory includes D_1 and D_5 and inhibitory includes D_2, D_3, D_4. All antipsychotics, typical as well as atypical, have relevant affinities for the dopamine D_2 receptor. Blockade of dopamine receptors in the mesolimbic area is responsible for antipsychotic activity and in striatum cause extrapyramidal dysfunctions. The general mechanism of antipsychotic drug action is depicted in **Fig. 4**.

(a) Dopamine releases at presynaptic site, entrenches upon D_2/D_3 dopaminergic receptors at postsynaptic site and carry out changes in activity in postsynaptic cell. The release of dopamine is modulated by its interaction with presynaptic D_2/D_3 receptors which inhibit dopamine release and terminates its signal by presynaptic re-uptake via dopamine transporter.

(b) Standard antipsychotic drug blocks D_2/D_3 receptors. The receptor occupancy is about 50 - 70%. It will attenuates dopamine signal to postsynaptic cell, reduces feedback inhibition on release, overall reduction in postsynaptic dopamine activity.

(c) Partial agonist antipsychotic drug has low efficacy at D_2/D_3 receptors. The receptor occupancy is 90% e.g. Aripiprazole **26**, so the ultimate effect is to occupy the receptors, stimulate them at level dependent on intrinsic efficacy of drug, amplification in system. Agonist has high efficacy at presynaptic than postsynaptic receptors so the release of dopamine is attenuated however the ultimate effect is to stimulate postsynaptic receptors at a low level dependent on intrinsic efficacy of the drug [43, 44].



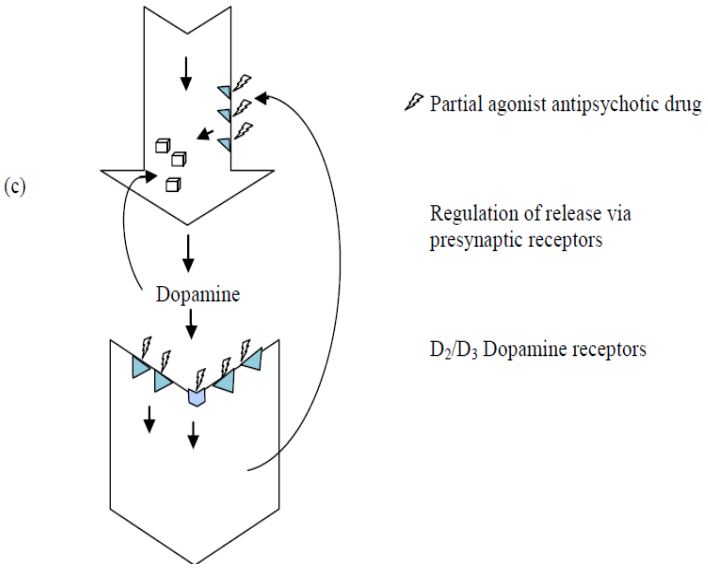


FIG. 4: GENERAL MECHANISM OF ANTIPSYCHOTIC ACTION

Atypical about Atypical Antipsychotics: Classically, "atypical" is defined as a chemical that has clinical antipsychotic effect while producing minimal catalepsy in animal models. The atypical antipsychotics also have minimal extrapyramidal side effects or EPS (parkinsonism, acute muscular dystonia, akathisia, malignant neuroleptic syndrome, tardive dyskinesia) or movement disorders at antipsychotic doses, do not or minimally elevate prolactin level, significantly reduce chances of positive symptoms (hallucinations, delusions, thought disorders, some psychomotor abnormalities) and negative symptoms (emotional withdrawal, poverty of speech and thought, lack of motivation, disinterest, social withdrawal) of schizophrenia [45].

Mechanism by which drug may be Atypical: Following specific strategies have to be considered for understanding atypical action of any drug, although within each one, variations are possible.

1. *Magic bullet* drugs with significant selectivity for a dopamine receptor isoform.

2. *Magic bullet* drugs with significant selectivity for a nondopamine receptor (i.e. a glutamate receptor).

3. *Magic shotgun* drugs that produce atypical actions owing to a mixture of concomitant actions at two or more receptors in different families.

4. *Functionally selective* drugs that can cause significantly different functional effects even when binding [46].

To distinguish the atypical antipsychotics from their typical counterparts one has to go through various competing theories reviewed below and there might have more than a single mechanism for achieving atypicality.

1. **High affinity for 5-HT_2 Receptors:** Addition of 5-HT_2 receptor antagonism along with D_2 receptor antagonism in ongoing treatment leads to an atypical profile of antipsychotic effects[47]. Most of the current atypical antipsychotics do have a higher affinity for 5-HT_2 receptors than for D_2 receptors and is characterized by meltzer ratio i.e. pK_i 5-HT_{2A}/D_2 ratio. Role of the 5-HT_{2C} receptor in atypical antipsychotics has been identified and the evidence suggested that 5-HT_{2C} receptor antagonism could have important benefits in atypical antipsychotics profile and does not directly contribute to weight gain.

2. **High affinity for Dopamine D_4 Receptors**: Prototypical atypical antipsychotic, Clozapine **21** has very high affinity for D_4 receptor relative to D_2 receptor. The high D_4 receptor antagonism suggests the role of D_4 receptor in atypicality.

3. **Fast dissociation from Dopamine D_2 Receptor:** Antipsychotic drugs with low affinity for the D_2 receptor dissociate much more quickly from the receptor, and this low affinity/fast dissociation at the D_2 receptor is the single best predictor of atypicality. Atypical antipsychotics antagonizes D_2 receptor involving "Fast Off" theory of atypical antipsychotics which predicts their low doses in treatment of patients with psychosis in Parkinson's disease as they are rapidly released from D_2 receptors and less extrapyramidal side effects occur due to loose binding. Activity at D_2 receptors is the basic property which unites atypical antipsychotics in their atypical behaviour irrespective of their different efficacy at different receptors [48] (**Table 5**).

Pharmacological and clinical features of Atypical Antipsychotics:

1. Lower affinity for D_2 receptors (except Amisulpride **29**).
2. Higher affinity for 5-HT_2 receptors (except Amisulpride **29**).
3. Effective against positive symptoms.
4. Questionably effective against negative symptoms.
5. Lower propensity to cause extrapyramidal side effects.
6. Lower propensity to cause tardive dyskinesia.
7. Lower prolactin increase (except Risperidone **22** and Amisulpride **29**) [49].

Side effects of Atypical Antipsychotics: Dopaminergic transmission blockade results in an increase of prolactin secretion which leads to dysfunction of the menstrual cycle, loss of libido, swelling of the mammillary glands as well as galactorrhoea and possibly osteoporosis. Hyperglycemia and Type 2 diabetes mellitus as there is development of glucose intolerance while treatment with atypicals [50], diabetic ketoacidosis [51], weight gain [52], QTc-prolongation, sexual side effects such as dysfunctions of the female cycle, libido, disorders of erection and ejaculation.

TABLE 5: PHARMACOLOGICAL AND SELECTED SIDE-EFFECT PROFILE OF ATYPICAL ANTIPSYCHOTICS

Compound	Amisulpride	Zotepine	Clozapine	Risperi-done	Olanzapine	Quetiapine	Sertindole	Ziprasidone
Receptor binding profile								
D_1	-	++	++	-	+++	+	++	+
D_2	++++	++	++	+++	+++	++	+++	+++
5-HT_2	-	+++	++++	++++	++++	+++	+++	+++
A_1	-	+++	+++	+++	+++	++++	+++	++
A_2	-	+	+++	+++	-	+	-	-
H_1	-	+++	++++	+	++++	++++	+	+
M_1	-	+	++++	-	++++	+++	+	-
Side effects								
EPS	++	++	+/-	++	+	+/-	++	++
Prolactin	+++	++	-	++++	+		+	+
Weight gain	++	++	++++	++	++++	++	++	-

D_1 = D_2 = dopamine; 5-HT_2 = serotonin; A_1 = A_2 = adrenergic; H_1 = histamine; M_1 = acetylcholine (muscarinic); + = Increase effect; - = No effect

Metabolic problems associated with Atypical Antipsychotics: Conventional (First-generation antipsychotics) are often associated with extrapyramidal symptoms while newer one (Second-generation atypical antipsychotics) has improved efficacy, fewer extrapyramidal side effects and having broad spectrum in the treatment of both schizophrenia and bipolar disorders. However, the area of concern is about their metabolic effects particularly with respect to weight gain, hyperglycaemia, dyslipidaemia, and development of diabetes which limits their use in psychosis treatment [53].

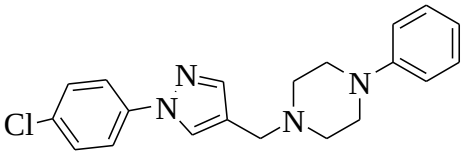
Neuroprotection with Atypical Antipsychotics: Atypical antipsychotics decrease both cognitive and non-cognitive behavioural losses in different animal models of neurotoxicity. This effect is not only related to their dopamine and serotonin receptor blockade, but also to their effects on neuroprotection, neurotrophins and neuro-genesis. The neuroprotective potential of atypical antipsychotics may contribute to their therapeutic effects in treating cognitive and non-cognitive impairments in schizophrenia and other neurodegenerative disorders [54].

Need for Antipsychotic Research: Atypical antipsychotics are widely prescribed in the treatment of schizophrenia. But, there is still no single atypical antipsychotic drug having any exceptional efficacy and safety profile for all type of patients [55]. The most important considerable issue with atypical antipsychotics are extrapyramidal side-effects, weight gain, drug's prolactin profile, hyperglycaemia, dyslipidaemia.

These concomitant limitations with atypical antipsychotics can never be neglected. Today, patient's quality of life is considered as much as imperative to eradicate the disease. Thus, it becomes apparent that we still have many unmet medical rudiments in atypical antipsychotics medication. We need some more antipsychotic medications that are more effective against both positive and negative symptoms of psychosis, that work more quickly and are better tolerated, that improve cognitive function and, ideally, work well against comorbid anxiety and depression. Thus, still a lot of research is needed to be carried out in the development of novel atypical antipsychotics.

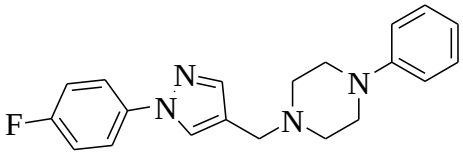
Recent Advancements:

***N*-Phenylpiperazine heterocyclic compounds:**



1-((1-(4-chlorophenyl)-1*H*-pyrazol-4-yl)methyl)-4-phenylpiperazine

59



1-((1-(4-fluorophenyl)-1*H*-pyrazol-4-yl)methyl)-4-phenylpiperazine

60

Fig. (5). *N*-Phenylpiperazine heterocyclic compounds **(59-60)**.

Neves *et al*., designed, synthesized and evaluated the *N*-phenylpiperazine heterocyclic derivatives, the isosteric replacement of the heterocyclic ring at the biaryl motif generating pyrazole, 1,2,3-triazole, and 2-methylimidazole[1,2-a]pyridine derivatives with different substitutions at the para-biaryl and para-phenylpiperazine position. Among the synthesized compounds, **59** and **60** exhibit the highest affinity for binding to D_2-like, 5-HT_{1A}, 5-HT_{2A} receptors and have a potential in treating positive symptoms of schizophrenia (Fig. (5)). The apparent affinities for D_2-like, 5-HT_{1A} and 5-HT_{2A} receptors of both ligands are given in **Table 6** [56].

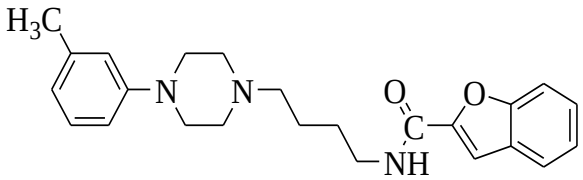
TABLE 6: APPARENT AFFINITIES OF LIGANDS FOR VARIOUS RECEPTORS

Compound	K_i (μM)			Ratio		
	D_2	5-HT_{1A}	5-HT_{2A}	D_2/5-HT_{1A}	D_2/5-HT_{2A}	5-HT_{1A}/5-HT_{2A}
59	0.001	0.0004	0.007	2.50	0.14	0.057
60	0.07	0.06	0.92	1.07	0.07	0.07

Arylalkylpiperazine analogues: Butini *et al*. combined D_3 antagonism with serotonin 5-HT_{1A} and 5-HT_{2A} receptor occupancy which may represent a novel concept for developing innovative antipsychotics. They synthesized novel arylpiperazine atypical antipsychotic agents characterized by specific occupancy of D_3, 5-HT_{1A}, and 5-HT_{2A} receptors.

Among the compounds synthesized, **61** was identified as potential atypical drug candidate having high affinity for D_3, 5-HT_{1A}, 5-HT_{2A} receptors, together with a low affinity for D_2 receptors (to minimize extrapyramidal side effects), 5-HT_{2C} receptors (to reduce the risk of obesity under chronic treatment), and for hERG channels (to reduce incidence of torsade des pointes (ventricular tachycardia)). These findings illustrate the high and selective activity of **61** toward the mesolimbic and mesocortical dopaminergic system.

Compound **61** may pave the way for the development of a novel class of drugs for the treatment of neuropsychiatric disorders (**Fig. 6**). Binding affinities for D_1, D_2, D_3, 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors and hERG Channels in comparison to standard drug Risperidone **22** are given in **Table 7** [57].



61

N-(4-(4-*m*-Tolylpiperazin-1-yl)butyl)benzofuran-2-carboxamide

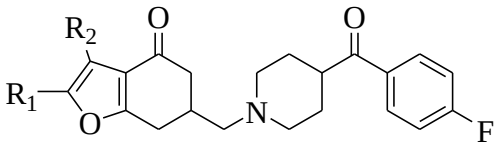
Fig. (6). Arylalkylpiperazine analogue **(61)**.

TABLE 7: BINDING AFFINITIES OF COMPOUND IN COMPARISON TO STANDARD FOR VARIOUS RECEPTORS.

Compound	K_i (μM) + SD						
	D_1	D_2	D_3	$5HT_{1A}$	$5HT_{2A}$	$5HT_{2C}$	hERG
61	3290 ± 418	263 ± 31	4.5 ± 0.8	11.9 ± 1.7	15.3 ± 3.2	206 ± 14	0.93
22	50 ± 2	3.8 ± 0.3	6.7 ± 0.7	190 ± 15	0.15 ± 0.02	32 ± 2.2	0.92

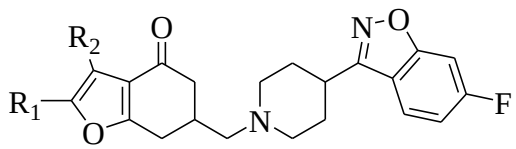
6-Aminomethylbenzofuranone analogues: Butyrophenone analogues with benzofuranone cores were synthesized and examined for their affinities and selectivities as 5-HT_{2A}/D_2 dual ligands. Substitutions at the piperidine ring and the benzofuranone core were made in the series of new 6-aminomethylbenzofuranones. Apart from the worth of these new compounds, biological and computational studies of 5-HT_{2A} and D_2 receptors recognized the receptor serine residues S3.36 and S5.46 as the molecular keys to elucidating the differences in affinity and selectivity between these new compounds for this group of receptors. These differences appear to be related to the presence of either the 4-benzoylpiperidine series **62** or 4-benzisoxazolylpiperidine series **63**.

4-Fluorobenzoyl compounds cannot establish strong H-bonds with the residues at positions S3.36 and S5.46 of the D_2 receptor, and they can establish only one H-bond with the same residues of the 5-HT_{2A} receptor. In contrast, the 4-Benzisoxzolyl compounds can establish one H-bond and two H-bonds with the same receptors, respectively. Among the 4-benzisoxazolylpiperidine series, compound **64** has higher affinities for D_2, 5-HT_{2A} receptors and meltzer ratio in comparison to standard drug Clozapine **21** (**Fig. 7, Table 8** [58]).



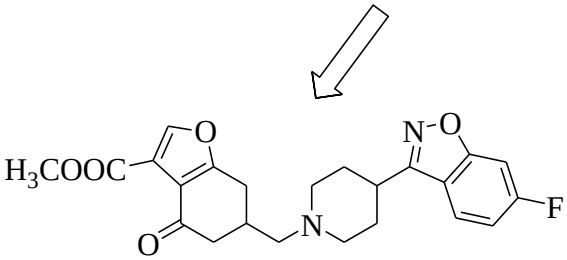
62

4-Benzoylpiperidine series



63

4-Benzisoxazolylpiperidine series



64

Methyl-6-((4-(6-fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)methyl)-4,5,6,7-tetrahydro-4-oxobenzofuran-3-carboxylate

Fig. (7). 6-Aminomethylbenzofuranone analogues **(62-64)**.

TABLE 8: BINDING AFFINITITES OF COMPOUND IN COMPARISON TO STANDARD FOR VARIOUS RECEPTORS.

Compound	pK_i D_2	pK_i $5HT_{2A}$	pK_i $5HT_{2C}$	Meltzer Ratio
64	7.07 ± 0.08	8.81 ± 0.22	<5	1.25
21	6.65 ± 0.17	8.04 ± 0.31	7.98 ± 0.11	1.21

Aminobutyrophenone analogues: The development of strategies for the preparation of new D_2/5-HT_{2A} receptor antagonists as atypical antipsychotics, there is a possibility of synthesizing conformationally constrained analogues of aminobutyrophenones **65** in which the phenyl ring is replaced by a pyrimidine to form a tetrahydroquinazolinone system **66** (**Fig. 8**). Carro *et al*. synthesized a series of new tetrahydroquinazolinone derivatives which were evaluated for their binding affinities to D_2 and 5-HT_{2A} human receptors. Among the synthesized derivatives **67** was the most promising candidate based on its good binding affinity for various receptors [59].

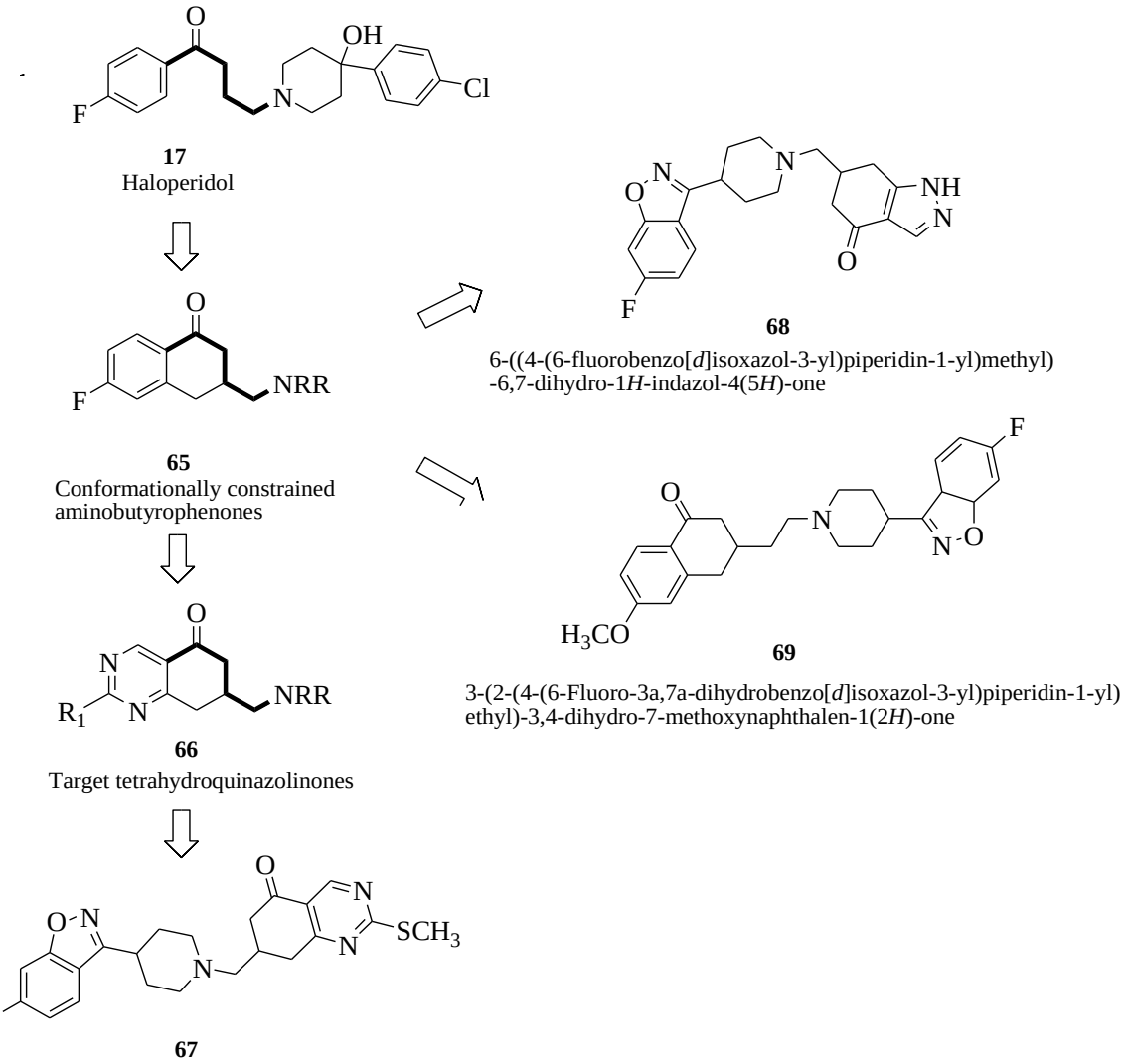


Fig. (8). Haloperidol **(17)** and aminobutyrophenone analogues **(65-69)**.

Barcelo *et al.* synthesized and evaluated the binding affinities of 6-aminomethyl-6,7-dihydro-1*H*-indazol-4(5*H*)-ones and 6-aminomethyl-6,7-dihydro-3-methyl-benzo[*d*]isoxazol-4(5*H*)-ones as conformationally constrained butyrophenone analogues on D_2, 5-HT_{2A} and 5-HT_{2C} receptors. Among the synthesized compounds, **68** have the higher affinities for D_2, 5-HT_{2A} and 5-HT_{2C} receptors [60].

The binding affinities (pK_i) of the compound **67** and **68** at various receptors in comparison to standard drug Risperidone **22** are given in **Table 9**. Alvarado *et al.,* had synthesized and evaluated the binding affinity of series of CNS agents (aminovalerophenones), which are higher homologues of the 3-aminomethyl-1-tetralones (conformationally constrained butyrophenones).

Among the synthesized compounds benzisoxazolyl piperidine compound **69** emerged as potential antipsychotic compound, as a result of its good affinity for dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} and Meltzer's ratio. Although butyrophenone moiety has been acknowledged as an optimized side chain for the D_2 receptor, significant increases in affinity at this receptor have been described with the elongation of the chain length of the butyrophenone to the valerophenone moiety.

Also, extension of butyrophenones to valerophenones has been reported to enhance σ-receptor affinity and these receptors have been pointed out as potential sites of action of atypical antipsychotics. The pK_i values and Meltzer ratio of compound **69** in comparison to standard drug Clozapine **21** are given in **Table 10** [61].

TABLE 9: BINDING AFFINITIES OF COMPOUND IN COMPARISON TO STANDARD FOR VARIOUS RECEPTORS.

Compound	pK_i			(Meltzer ratio)
	$5HT_{2A}$	$5HT_{2C}$	D_2	pK_i ratio $5HT_{2A}/D_2$
67	8.34 ±0.15	-	7.49 ± 0.09	1.11
68	8.67 ± 0.19	6.91 ± 0.16	6.97 ± 0.06	1.25
22	9.30 ± 0.25	8.13 ± 0.16	8.21	1.13

TABLE 10: BINDING AFFINITIES OF COMPOUND IN COMPARISON TO STANDARD FOR VARIOUS RECEPTORS

Compound	pK_i			(Meltzer ratio)
	$5HT_{2A}$	$5HT_{2C}$	D_2	pK_i ratio $5HT_{2A}/D_2$
69	8.23 ± 0.14	6.89 ± 0.19	7.04 ± 0.31	1.17
21	8.04 ± 0.31	7.98 ± 0.11	6.65 ± 0.17	1.21

3-(Cyclopenten-1-yl) benzyl/ 3-(Cyclopenten-1-yl) heteroarylmethylamine analogues

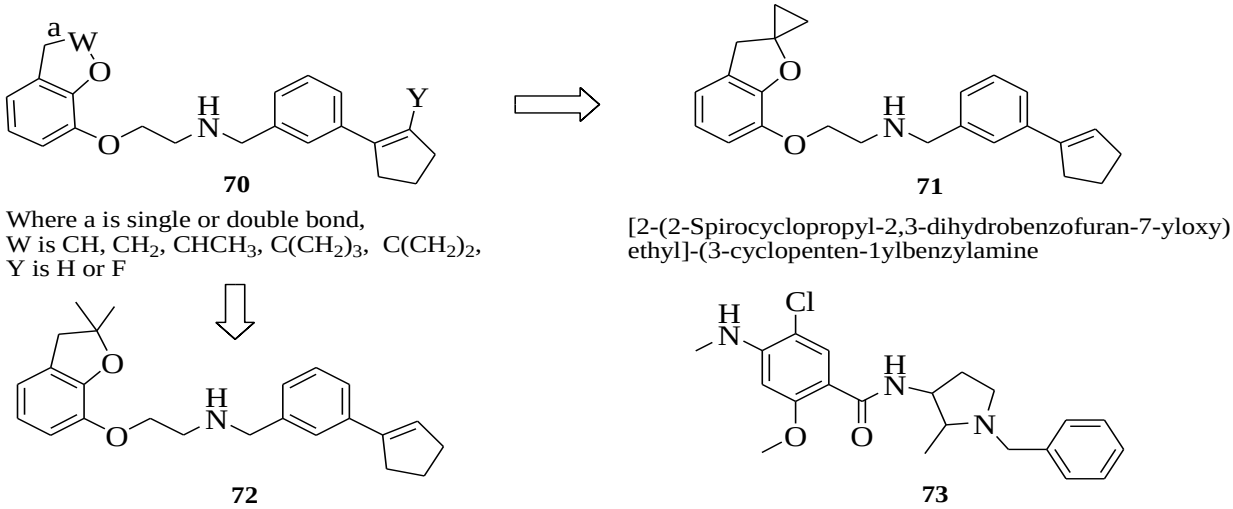


Fig. (9). 3-(Cyclopenten-1-yl) benzyl/ 3-(Cyclopenten-1-yl) heteroarylmethylamine analogues **(70-72)** & Nemonapride **73**.

Vacher *et al.* considered compound of formula **70** as lead and synthesized 3-(Cyclopenten-1-yl)-benzyl/ 3-(Cyclopenten-1-yl)-heteroarylmethylamine derivatives as potential candidates for treatment of schizophrenia. Among the synthesized compounds, **71** and **72** exhibits high affinity for D_2 receptors and 5-HT_{1A} receptors (**Fig. 9**). The pK_i values on the D_2 and 5-HT_{1A} receptors and effective doses (ED_{50}) in comparison to standard atypical drug Risperidone **22** and typical drug Nemonapride **73** is given in **Table 11** [62].

1-(Aryloxypropyl)-4-(chloroaryl)piperazines analogues:

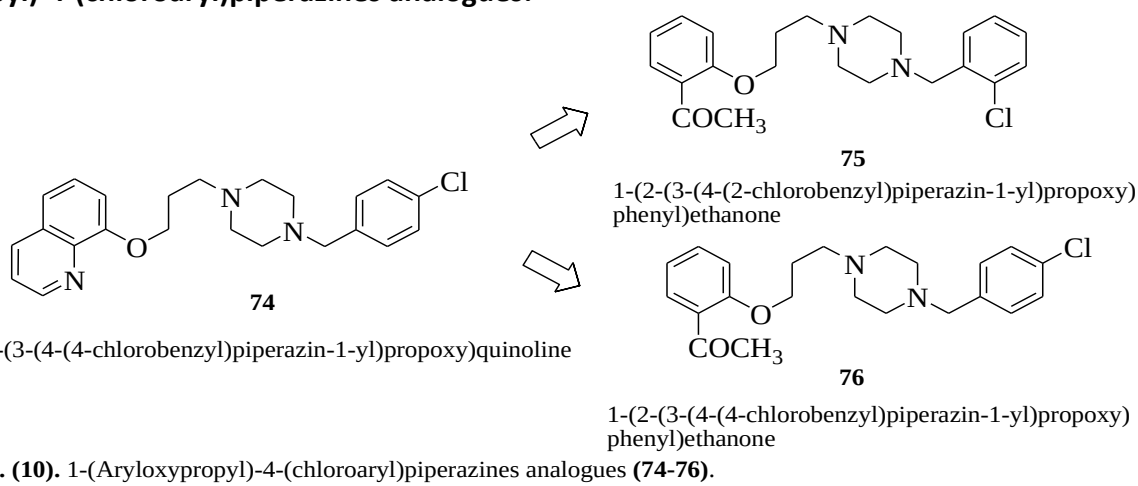


Fig. (10). 1-(Aryloxypropyl)-4-(chloroaryl)piperazines analogues **(74-76)**.

TABLE 11: BINDING AFFINITITES AND ED_{50} OF COMPOUNDS IN COMPARISON TO STANDARDS FOR VARIOUS RECEPTORS

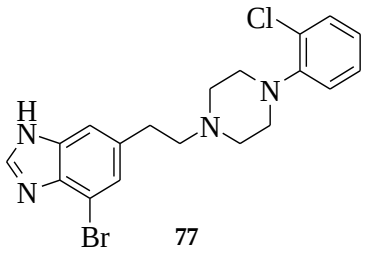
Compound	pK_i		
	$5HT_{2A}$	D_2	ED_{50}
71	8.2	9.2	>40
72	8.2	9.5	>40
73	8.4	9.9	5.0
22	6.0	8.7	3.5

A series of quinoliloxypropyl piperazines where the quinolin-8-yl derivative **74** had emerged as an important lead compound as a potential atypical antipsychotic. As quinoline is considered "likely to be carcinogenic in humans" the synthesis, pharmacological evaluation and 2D similarity studies on another series of 1-(aryloxypropyl)-4-(chloroaryl) piperazine derivatives which incorporate an acetophenone system as a replacement for the quinoline system is carried out and their preliminary pharmacological evaluation has shown potential atypical antipsychotic effect in compound **75 (**ED_{50} = 10.0) and **76 (**ED_{50} = 10.5) (**Fig. 10**). Both compounds have shown good similarity with respect to the standard drugs, particularly, Risperidone **22**. The log BB values and molecular parameters values are important for blood brain barrier penetration and are calculated as log BB values are 0.26, 0.24 respectively. Topological polar surface area (TPSA) and log P computed for both the compounds are same, TPSA is 32.78 and log P is 3.371 indicated that both of these compounds have a good potential to penetrate the blood brain barrier and show CNS activity [63].

Computational studies on Atypical Antipsychotics:

4-Halo-6-[2-(4-arylpiperazin-1-yl)ethyl]-1*H*-benzimidazoles: Halogenated 6-[2-(4-arylpiperazin-1-yl)ethyl]-1*H*-benzimidazoles showed higher affinity compared to their non-halogenated congeners. *In-silico* docking analysis were modelled and done by simulated annealing. Docking analysis suggests the stabilizing interactions (i.e. H-bond and charge transfer interactions) between the halogen atom at the benzimidazole ring and the Ser122 of the D_2-like and Trp358 of the 5-HT_{1A} receptor.

The affinities of the newly synthesized 6-[2-(4-(2-chlorophenyl)piperazin-1-yl)ethyl]-1*H*-benzimidazole **77** towards D_1-like, D_2-like and 5-HT_{1A} receptors were evaluated using *in vitro* by radio ligand binding assays (**Fig. 11, Table 12**) [64].



77

6-[2-(4-(2-chlorophenyl)piperazin-1-yl)ethyl]-1*H*-benzimidazole

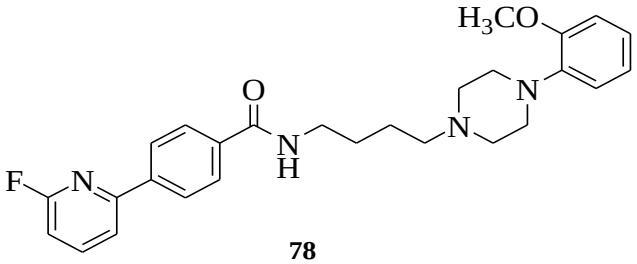
Fig. (11). 4-Halo-6-[2-(4-arylpiperazin-1-yl)ethyl]-1*H*-benzimidazole **(77)**.

TABLE 12: BINDING AFFINITITES OF COMPOUND IN COMPARISON TO STANDARD FOR VARIOUS RECEPTORS

Compound	K_i (nM)		
	D_1	D_2	$5HT_{1A}$
77	>1000	5.77±1.2	0.14±0.16

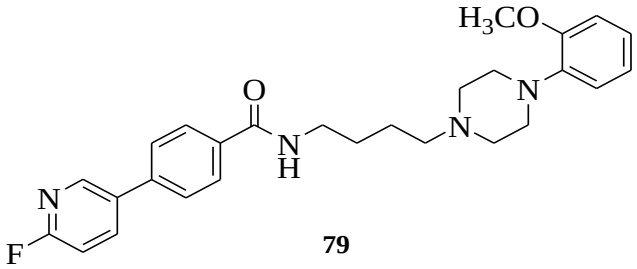
D_3 Selective PET radioligands: Revelation of the physiological role of the D_3 receptor and its allocation in the brain using positron emission tomography (PET) is laden by the lack of bio available subtype selective tracer ligands. To develop appropriate D_3 radio-ligands, Salama *et al*., designed an integrative process involving the elucidation of structural features determining D_3 selectivity over both congeners D_2 and D_4 by comparative molecular analysis.

Thus, successfully generated CoMFA and CoMSIA models based on the affinity differences of a series of ligands representing a broad range of selectivities. These models yielded highly significant cross validations [q^2_{cv} (D_3/D_2) = 0.86; q^2_{cv} (D_3/D_4) = 0.92] and excellent predictions of a 16-ligand test set (r^2_{pred} = 0.79-0.93). Making use of this information and receptor binding studies, this had directed to the development of fluorinated lead compounds **78** and **79**, having subnanomolar D_3 affinities and significant selectivities over D_2 and D_4 (**Fig. 12, Table 13**) [65].



78

4-(6-Fluoropyridin-2-yl)-*N*-(4-(4-(2-methoxyphenyl) piperazin-1-yl)butyl)benzamide



79

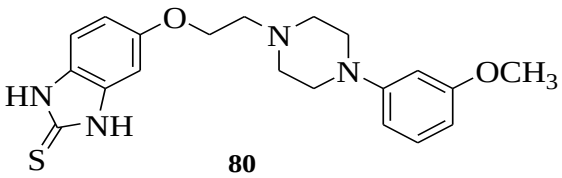
4-(6-Fluoropyridin-3-yl)-*N*-(4-(4-(2-methoxyphenyl) piperazin-1-yl)butyl)benzamide

Fig. (12). D_3 Selective PET radioligands **(78-79)**.

TABLE 13: BINDING AFFINITITES OF LIGANDS FOR VARIOUS RECEPTORS

Compound	K_i ± SD (nM)			
	D_{2long}	D_{2short}	D_3	D_4
78	27 ± 7.1	16 ± 1.4	0.37 ± 0.064	28 ± 3.5
79	15 ± 7.1	12 ± 0.71	0.45 ± 0.007	34 ± 1.4

5-[2-(4-Arylpiperazin-1-yl)ethoxy]-1*H*-benzimidazole analogues



80

5-{2-[4-(2-Methoxyphenyl)-piperazin-1-yl]ethoxy}-1,3-dihydro-2*H*-benzimidazole-2-thione

Fig. (13). 5-[2-(4-Arylpiperazin-1-yl)ethoxy]-1*H*-benzimidazole analogue **(80)**.

Sukalovic *et al.* synthesized and evaluated the binding affinity of 5-[3-(4-Arylpiperazin-1-yl)propyl]-1*H*-benzimidazoles and 5-[2-(4-arylpiperazin-1-yl)ethoxy]-1*H*-benzimidazoles on D_1, D_2 and 5-HT_{1A} receptors Among the synthesized compounds, **80** possess maximum number of attractive ligand-D_2 interactions (Fig (13)). The main features of interactions revealed by docking analysis: salt bridge between piperazine ring protonated N_1, Asp86, hydrogen bonds of ligand benzimidazole part with Ser141, Ser122 and His 189, edge-to-face interactions of arylpiperazine aromatic ring with Phe178, Tyr216 and Trp182 and hydrogen bond between ethereal oxygen in ethylenoxy ligands and hydrogen of Phe185 or Trp115 and has highest affinity for D_2 dopamine receptor. The K_i value of **80** for D_1, D_2 and $5HT_{1A}$ receptors is given in **Table 14** [66].

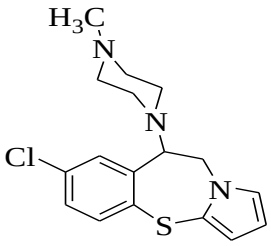
TABLE 14: BINDING AFFINITITES OF COMPOUND FOR VARIOUS RECEPTORS

Compound	K_i ± S.E.M (nM)		
	D_1	D_2	$5HT_{1A}$
80	>1000	0.19±0.06	308±29

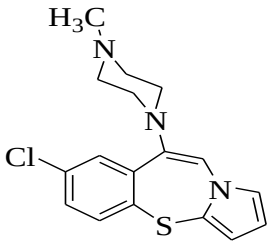
Pyrrolo[1,3]benzothiazepine based serotonin and dopamine receptor antagonists: Campiani *et al.* studied the SAR studies of the class of pyrrolo[1,3]benzothiazepine dopamine and serotonin receptor antagonists represented by an atypical antipsychotic agent **81** possesing an optimum pK_i 5-HT_{2A}/D_2 ratio of 1.21 (pK_i 5-HT_{2A} = 8.83; pK_i D_2 = 7.79). The analogues of core structure **81** with specific substituents were investigated and the structure-activity relationship (SAR) was studied along with the designing of other analogues characterized by a pyrrolo [2,1- *b*] [1,3] benzothiazepine skeleton, substituted on the benzo fused ring or on the pyrrole system.

Substituents introduced on the pyrrole ring on the 9,10-dihydro analogues determines the affinity for dopamine and for 5-HT_{2A} receptors, but the incorporation of a double bond at C-9/10 on the structure **81** led to a potent D_2/5-HT_{2A} receptor ligand **82** with a typical binding profile (p*K*i 5-HT_{2A}/D_2 ratio of 1.01, log *Y* = 8.43). Another series of potential atypical antipsychotic agents, with optimized $5HT_{2A}$/D_2 receptor affinity ratios were generated with the help of a molecular modelling approach.

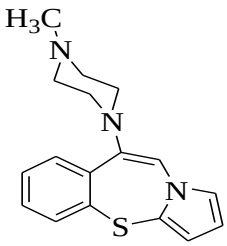
Among the various series generated compound **83** and **84** have the most interesting multi receptor affinity profile having atypical log *Y* scores respectively 4.98 and 3.18 (p*K*i 5-HT_{2A}/D_2 ratios of 1.20 and 1.30, respectively) and are promising atypical agents. Compound **83** has binding profile of atypical (log *Y* score similar to that of Olanzapine **23**, 3.89), was confirmed to have an atypical antipsychotic profile *in-vivo* by further biological investigation. In conclusion, the pharmacological profile of **83** proved better than standard compounds Clozapine **21** and Olanzapine **23**, making this compound a potential atypical antipsychotic (**Fig. 14**) [67].



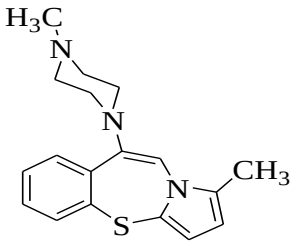
81
7-Chloro-9-(4-methylpiperazin-1-yl)9,10-dihydropyrrolo[2,1-*b*][1,3]benzothiazepine



82
7-Chloro-9-(4-methylpiperazin-1-yl) pyrrolo[2,1-*b*][1,3]benzothiazepine



83
9-(4-Methylpiperazin-1-yl)pyrrolo[2,1-*b*][1,3] benzothiazepine



84
1-Methyl-9-(4-methylpiperazin-1-yl)pyrrolo [2,1-*b*][1,3]benzothiazepine

Fig. (14). Pyrrolo[1,3]benzothiazepine based serotonin & dopamine receptor antagonists **(81-84)**.

Black Box Label Warning: "Black box" label warning is a type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that the drug possesses a significant risk of serious or even life-threatening adverse effects indicated by the medical studies. Elderly patients with dementia-related psychosis treated with atypical antipsychotics are at higher risk of death than those who take a placebo and these drugs are not approved for the treatment of dementia related psychosis.

The U.S. FDA has recommended a "black box" label warning of this risk for all conventional and atypical antipsychotic drugs and antipsychotics are not indicated for the treatment of dementia-related psychosis [68].

Black box label warning issued by the U.S. FDA to some medications other than antipsychotics are:

i. Antidepressant medications those may result in increased risk of suicidal tendencies in children and adolescents.

ii. Non-steroidal anti-inflammatory drug named Celecoxib.

iii. Depo-Provera contraceptive injection, due to the risk of significant loss of bone density with long-term use.

iv. Anticoagulant warfarin due to the risk of bleeding to death.

v. Antidiabetic medication Avandia, citing the risk of heart failure or heart attack to patients with underlying heart disease, or are at a high heart attack risk.

vi. Antibiotic medications, fluoroquinolone, which has been linked to tendon ruptures and tendinitis.

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