

## To Evaluate the Efficacy of Olanzapine Analogues in Schizophrenia Using Various Experimental Model

Harshika Patel<sup>1</sup>, Payal N. Bhalodia<sup>1</sup>, TR. Desai<sup>1</sup>, Hardevsinh Vala<sup>2</sup>, Ashish Radadiya<sup>2</sup>, Abhay Bavishi<sup>2</sup>, Sabera Bijani<sup>2</sup> and Vishwa Dhinoja<sup>2</sup>

<sup>1</sup> Department of Pharmacology, R. K. College of Pharmacy, Rajkot, Gujarat, India.

<sup>2</sup> Department of Chemistry, Saurashtra University, Rajkot, Gujarat, India.

### ABSTRACT

Schizophrenia is a chronic thought disorder in which characteristic psychotic symptoms mainly characterized as positive (hallucinations, agitation, and thought disorder) and negative symptoms (apathy, blunted effect, social isolation, and anhedonia) are observed. Various antipsychotics drug are available in market of which atypical antipsychotics are more preferred. However these drugs also have some limitations in pharmacokinetics and thus, there is need to develop new synthetic analogues with better efficacy and less adverse effects. Study was carried out using various experimental models and animals like Catalepsy in rat, inhibition of Apomorphine induced stereotypy in rat, pole climbing avoidance response in rat and observational assessment (for sedative effect). Effect of test drugs HKV 54, HKV 68, HKV 71, HKV 86, HKV 102 and HKV 115 at 2 mg/kg, i.p. were used to evaluate the efficacy in schizophrenia. All the test drugs showed significant improvement in the score of catalepsy, Apomorphine induced stereotypy and conditional avoidance response and were also effective in reducing the sedative side effect as compared to standard Olanzapine. Test 3 (2 mg/kg, i.p.) showed highly significant therapeutic effect and reduction of side effect as compared to other analogues. Thus, it was observed that synthetic Olanzapine analogues especially [Test 3] have proved to have better efficacy and less adverse effect than standard Olanzapine.

**Keywords:** Schizophrenia, Antipsychotics, Olanzapine, Adverse Effects, Hallucination.

### INTRODUCTION

Schizophrenia = *skhizo* (to split) + *phren* (mind)

The term is given by Swiss psychiatrist and the meaning of Schizophrenia is the split between the emotion and the intellect.

In truth, most members of the public have no real idea about schizophrenia, often believing that sufferers have split personality. In simple term we can say that it is a defect in 'selective attention'. A normal individual quickly accommodates to stimuli of a familiar or inconsequential nature, and responds only to stimuli that are unexpected or significant, but the ability of schizophrenic patients to discriminate between significant and insignificant stimuli seems to be impaired. Since last 19<sup>th</sup> century there have been frequent attempts to define the illness we now call Schizophrenia. Kraepelin, in the late 1890s, coined the term 'dementia praecox' (early madness) to describe an illness where there was deterioration of the personality at a young age. Kraepelin

also coined the terms 'catatonia' (where motor symptoms are prevalent and changes in activity vary), 'hebephrenic' (chilly, childish behavior, affective symptoms and thought disorder prominent), and 'paranoid' (clinical picture by paranoid delusion).

Schizophrenia<sup>1-3</sup> affects about 1% of the population. 30-40% of the homeless are affected. It is one of the most important forms of psychiatric illness because, it affects young people, is often chronic and is usually highly disabling. In addition, deficits in cognitive function (e.g. attention, memory) are often present, together with anxiety and depression, leading to suicide in about 10% of cases<sup>45</sup>. The clinical phenotype varies greatly, particularly with respect to the balance between negative and positive symptoms, and this may have a bearing on the efficacy of antipsychotic drugs in individual cases. Schizophrenia can present dramatically, usually in young people, with predominantly positive features such as hallucinations, delusions and uncontrollable behavior, or more

insidiously in older patients with negative features such as flat mood and social withdrawal. The latter may be more debilitated than those with a florid presentation, and also the prognosis is generally worse.

Two systems for the classification of Schizophrenia are widely used: the *diagnosis and statistical manual of Mental Disorders*, 4<sup>th</sup> edition, (DSM IV; American Psychiatric Association 1994) and the *International Classification of Diseases*, 10<sup>th</sup> edition (ICD 10; WHO 1992)<sup>43</sup>.

Schizophrenia is diagnosed by its positive and negative symptoms. According to severity it is classified as different psychiatric illness. Antischizophrenic agents are also named as major tranquilizers or anti psychotic agents in olden days. Schizophrenia can follow a relapsing and remitting course, or be chronic and progressive, particularly in cases with a later onset. Chronic schizophrenia is used to account for most of the patients in long-stay psychiatric hospitals; following the closure of many of these in the UK; it now accounts for many of society's outcasts. Conventional antipsychotic medications are effective against hallucinations, agitation, and thought disorder (the so-called positive symptoms) in 60% of patients but are often less useful for apathy, blunted effect, social isolation, and anhedonia (negative symptoms). The novel antipsychotic medications Clozapine, risperidone, Olanzapine, Quetiapine, and others has become the mainstay of treatment as they are helpful in patients unresponsive to conventional neuroleptic and may also be useful for negative and cognitive symptoms. Long-acting injectable forms of haloperidol and Fluphenazine are ideal for noncompliant patients. Psychosocial intervention, rehabilitation, and family support are also essential. Some Herbal remedies are also available for the treatment of the Schizophrenia. This treatment does not have any types of adverse reactions but have very less

efficacy and recovery is also very slow. For example *Ginkgo biloba*<sup>35</sup>, St. John wort or whole herb and some orthopartical molecules like vitamins, minerals, etc. All antipsychotic agents are act by influencing the dopamine receptors and some atypical agents also act on NMDA and cholinergic receptors. 5-HT2 receptors are also affected.

Olanzapine is a synthetic atypical antipsychotic drug, which potentially antagonizes 5-HT<sub>2A</sub> receptor and preferentially acts on D<sub>4</sub> receptors rather than D<sub>2</sub> receptors. Synthetic drugs under the given study are synthesized by changing molecular structure of the Olanzapine with an aim to reduce the adverse effects as compared to the parent molecule and to increase the potency.

Objectives of this research are to screen a novel synthetic Olanzapine analogue for the treatment of Schizophrenia and other complications caused by Mental illness in animal model. Further objective of this research is to compare the novel synthetic Olanzapine derivatives for it efficacy with existing antipsychotic agents and have lesser adverse effects.

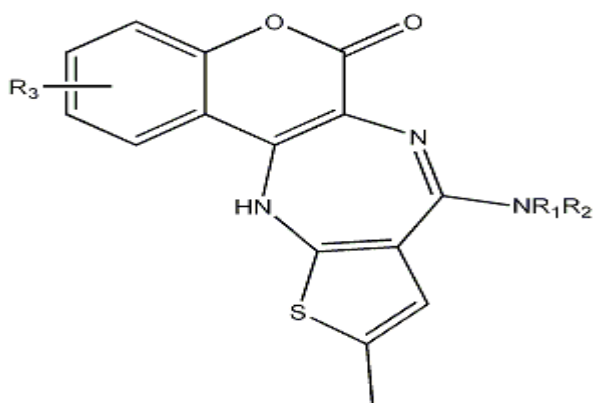
## MATERIALS AND METHODS

### Procurement of synthetic olanzapine analogues

Pure synthetic compound (Olanzapine analogues) powders will be obtained as a gift sample from Saurashtra University, these samples were formulated and approved under "Facility for Preservation of Molecular Diversity", supported by Foundation for MSMF Cluster and under DST Program, for finding the biological activity against schizophrenia.

### Synthetic olanzapine analogues

Olanzapine has thienobenzodizepine moiety and these synthetic analogues are altered by changing the peripheral group. Chemical structure of Olanzapine basic moiety and their peripheral groups are mention below:



**Table 1: Test samples which were coded with HKV code**

Serial NO.	Coded NO.	NR1R2	R3
1	HKV 54	6,7 Dimethyl	
2	HKV 63	7-Methyl	
3	HKV 71	-H	
4	HKV 86	7,8-Dimethyl	
5	HKV 102	6-Methyl	
6	HKV115	8-Methyl	

### Selection of animals

All animals will housed at ambient temperature ( $22\pm 10^{\circ}\text{C}$ ), relative humidity ( $55\pm 5\%$ ) and 12h/12h light dark cycle. Animals will have free access to standard pellet diet and water ad libitum. All experimental models were conducted in R. K. College of Pharmacy's Animal house. Experiments were carried out between 08:30 a.m. to 15:00 p.m. The protocol of the experiment will be approved by the Institutional Animal Ethical Committee as per the guidance of the Committee for the Purpose of Control

and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India (RKCP/COL/RP/12/18, dated on 25<sup>th</sup> February, 2012).

### Experimental models and studies (Methods)

The study includes Catalepsy, Inhibition of Apomorphine induced stereotypic reaction, Pole climbing avoidance and sedative effect of newly synthesized Olanzapine analogues.

### 1. Catalepsy in rat PROCEDURE

The 48 animals (rats) divided in to 8 groups containing 6 animals each. [Normal: Distilled water, i.p.; Standard: Olanzapine, 2 mg/kg, i.p.; Test 1: HKV54, 2 mg/kg, i.p.; Test 2: HKV63, 2 mg/kg, i.p.; Test 3: HKV71, 2 mg/kg, i.p.; Test 4: HKV86, 2 mg/kg, i.p.; Test 5: HKV102, 2 mg/kg, i.p.; Test 6: HKV115, 2 mg/kg, i.p.]. The animals were allowed to adapt the box for 2 min. Then, each animal were grasped gently around the shoulders and under the forepaws and placed carefully on the 3 cm and 9 cm high wooden blocks. Scoring was done at different time intervals. Catalepsy score of each rat in a group was taken to compute the mean value of the group <sup>[28, 40, 42]</sup>. From the given data in table 2 the cataleptic score of test samples was compared with the standard and test group produced less stereotypic reactions.

### 2. Inhibition of apomorphine induced stereotypy in rat Procedure

The 54 animals (rats) divided in to 9 groups containing 6 animals each. [Normal: Distilled water, i.p.; Disease control: Apomorphine HCl, 1.5 mg/kg, s.c.; Standard: Olanzapine, 2 mg/kg, i.p.; Test 1: HKV54, 2 mg/kg, i.p.; Test 2: HKV63, 2 mg/kg, i.p.; Test 3: HKV71, 2 mg/kg, i.p.; Test 4: HKV86, 2 mg/kg, i.p.; Test 5: HKV102, 2 mg/kg, i.p.; Test 6: HKV115, 2 mg/kg, i.p.]. The test drug or the standards were administered 60 min prior Apomorphine dosage. Apomorphine HCl was injected s.c. at a dose of 1.5 mg/kg. The animals were placed in individual plastic cages. A 10 s observation period was used to measure the presence of stereotypic activity such as sniffing, licking and chewing 10 min after Apomorphine administration <sup>[24, 25, 28, 40, 42]</sup>. The data of Stereotypic reactions in test groups was compared to standard group. From the Table 3 data, we can say that test drug had potential to inhibit the stereotypy reactions.

### 3. Pole climbs avoidance in rat procedure

The 48 animals (rats) divided in to 8 groups containing 6 animals each. [Normal: Distilled water, i.p.; Standard: Olanzapine, 2 mg/kg, i.p.; Test 1: HKV54, 2 mg/kg, i.p.; Test 2: HKV63, 2 mg/kg, i.p.; Test 3: HKV71, 2 mg/kg, i.p.; Test 4: HKV86, 2 mg/kg, i.p.; Test 5: HKV102, 2 mg/kg, i.p.; Test 6: HKV115, 2 mg/kg, i.p.]. The conditioned stimulus was buzzer tone for 10 seconds and unconditioned stimulus was footshock delivered through the grid of floor applied for 10 seconds. Animals kept in the chamber jumped on the pole on hearing the buzzer tone to avoid electric shock. Failure to do so result in footshock applied for 10 seconds. Escape before the footshock constitute avoidance response. Number of avoidances was noted for each group. Results were expressed in terms of escaping time in second <sup>[28, 40, 42]</sup>. 5 trials were conducted. The avoidance responses of test group animals were compared with standard group animals. From the Table 4 data, we can say that test drugs avoid conditional and unconditional response.

### 4. Observational assessment (for sedative effect) Procedure

The 48 animals (mice) divided in to 8 groups containing 6 animals each. [Normal: Distilled water, i.p.; Standard: Olanzapine, 2 mg/kg, i.p.; Test 1: HKV54, 2 mg/kg, i.p.; Test 2: HKV63, 2 mg/kg, i.p.; Test 3: HKV71, 2 mg/kg, i.p.; Test 4: HKV86, 2 mg/kg, i.p.; Test 5: HKV102, 2 mg/kg, i.p.; Test 6: HKV115, 2 mg/kg, i.p.]. Animals were tested for intraperitoneal administrations had water and food ad libitum <sup>[29, 40]</sup>. Immediately after drug administration, the animals are closely observed by a "blind" observer for lose their righting reflex and regain back. From the given data in Table 4 we can say that drug possesses sedative effect.

### Statistical analysis

Results were presented as mean  $\pm$  SEM. Statistical differences between the means of the various groups were evaluated using one-way analysis of variance

(ANOVA) followed by Tukey's test. Data were considered statistically significant at **P value**  $\leq 0.05$  and highly significant at **P**

**value**  $<0.001$ . Statistical analysis was performed using INSTAT statistical software.

## RESULT AND DISCUSSION

### Images of models used in work



**Cook's Pole Climbing Apparatus**



**3cm and 9cm Wooden blocks**

### 1. CATALEPSY IN RAT

Catalepsy is a common problem observed with treatment by atypical antipsychotics due to significant increase the dopamine level, as was also observed in our study in standard Olanzapine group animals. However, administration of in dose of newly synthesized analogues 2mg/kg; intraperitoneally. Significant reduction in cataleptic score was compared to standard Olanzapine group. Among all test, Test 3 sample 2mg/kg, significantly showed more pronounced therapeutic effect among all test analogues.

### 2. Inhibition of apomorphine induced stereotypy reaction in rat

Olanzapine analogues reduced significantly the stereotypy reaction like sniffing, licking, chewing (gnawing) and biting than the standard Olanzapine drug. Apomorphine affects the dopamine and serotonin receptors and produced these types of reactions<sup>24,25,29</sup>. Psychosis is characterized by stereotypy reactions like due to DA excess. Similar results were also observed in our disease control group

by Apomorphine treatment. However, both standard Olanzapine and new Olanzapine analogues significantly prevented the occurrence of stereotypy in treatment group animals.

### 3. Pole climbing avoidance response in rat

Conditional avoidance responses were significantly increased than the Standard group animals. Standard group animals showed significant increase in the CAR values than the control group. Blockade of this response is attributed to blockade of post synaptic DA receptors in nigrostriatal and mesolimbic dopaminergic system as evidenced by the fact that haloperidol a DA antagonist blocks CAR learning<sup>67</sup>.

### 4. Observational assessment (for sedative effect)

Olanzapine act through serotonergic receptor and caused sedation in treated animals<sup>29,30</sup>. Here, also we observed standard Olanzapine treatment caused sedation. However, Olanzapine analogues because of their structural modifications

delayed the onset and shortened the duration of sedation.

## DISCUSSION

Catalepsy is a common problem observed with treatment by atypical antipsychotics due to significant increase the dopamine level, as was also observed in our study in standard Olanzapine group animals. However, administration of in dose of newly synthesized analogues 2mg/kg; intraperitoneally. Significant reduction in cataleptic score was compared as compared to standard Olanzapine group. Among all test, Test 3 sample 2mg/kg, significantly showed more pronounced therapeutic effect among all test analogues.

Olanzapine analogues reduced significantly the stereotypy reaction like sniffing, licking, chewing (gnawing), and biting than the standard Olanzapine drug. Apomorphine affects the dopamine and serotonin receptors and produced these types of reactions<sup>24,25,29</sup>. Psychosis is characterized by stereotypy reactions like due to DA excess. Similar results were also observed in our disease control group by apomorphine treatment. However, both standard Olanzapine and new Olanzapine analogues significantly presented the occurrence of stereotypy in treatment group animals.

Conditional avoidance responses were significantly increased than the Standard group animals. Animals were trained and administered with the 2 mg/kg standard Olanzapine and test samples (Olanzapine analogues) intraperitoneally. Animal was habituate with hearing buzzer tone before passing the foot shock for 10 second. Control group animals were significantly avoid the condition avoidance response and jump before passing the shock. Standard group animals showed significant increase in the CAR values than the control group. Blockade of this response is attributed to blockade of post synaptic DA receptors in nigrostriatal and mesolimbic dopaminergic system as evidenced by the fact that haloperidol a DA antagonist blocks CAR learning.<sup>67</sup>

Olanzapine act through serotonergic receptor and caused sedation in treated animals<sup>29,30</sup>. Here, also we observed

standard Olanzapine treatment caused sedation. However, Olanzapine analogues because of their structural modifications delayed the onset and shortened the duration of sedation.

## CONCLUSION

Dopamine level and glutamate level were altered in schizophrenia which causes severe types of behavior symptoms. Typical antipsychotics and various atypical antipsychotics caused so many adverse effects. Olanzapine is an atypical anti psychotic drug which act through the dopaminergic and Serotonergic receptors. Olanzapine caused various adverse effects like sedation, catalepsy, behavioral activity, extrapyramidal side effects, obesity and diabetes mellitus, etc.

Olanzapine analogues produced beneficial effects on various schizophrenic models which influenced the catalepsy, stereotypy reaction, CAR and sedation.

Our study also shows good differentiation between antipsychotic and sedative agents from the model of Pole climbing avoidance response in rat. CARS were increased by Olanzapine analogues. Our study shows effect of analogues against the catalepsy production by standard Olanzapine. And it also reduced the apomorphine induced stereotypy reaction and sedation. Our study indicates the newer Olanzapine analogues in schizophrenia and play essential role in preventing adverse effects and much efficacious.

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**Table 2: Effect of Synthesized Olanzapine Analogues on rats by measuring their cataleptic score**

Groups (Dose: mg/kg, i.p.)	Mean Cataleptic Score (min)			
	30	60	90	120
control	0	0	0	0
Standard(2)	3.0±0.36 <sup>#</sup>	4.33±0.76 <sup>#</sup>	4.5±0.71 <sup>#</sup>	5.66±0.33 <sup>#</sup>
Test 1(2)	2.0±0.57	1.83±0.54*	2.33±0.42*	2.33±0.55***
Test 2(2)	2.16±0.54	1.33±0.84*	2.66±0.71	1.66±0.66***
Test 3(2)	0.66±0.66**	0.66±0.66**	1.0±1.0**	2.33±0.76***
Test 4(2)	1.66±1.08	1.16±0.47**	2.5±0.95	3.5±0.88*
Test 5(2)	1.83±0.9	1.13±0.98*	1.5±0.95*	2.83±0.74**
Test 6(2)	1.33±0.84	2.33±1.2	1.66±1.08*	3.33±0.71**

Where, Values are expressed as Mean ± S.E.M

\*, \*\*, \*\*\*- significantly different from standard

(p < 0.05, p < 0.01, p < 0.001 respectively)

# - significantly different from control (p < 0.001)

**Table 3: Effect of Synthesized olanzapine analogues on rats by measuring their stereotypic score**

Groups (Dose: mg/kg, i.p.)	Stereotypic Scores (mins)				
	10	30	60	90	120
Control (2)	0.83±0.16	0.83±0.30	0.83±0.30	1.0±0.25	0.66±0.21
Disease control (s.c.,1,5)	1.83±0.30	6.0±0.68	7.33±0.33	5.83±0.30	4.33±0.42
Standard(2)	0.66±0.21 <sup>#</sup>	3.83±0.47 <sup>#</sup>	4.16±0.94 <sup>#</sup>	3.83±0.47 <sup>###</sup>	2.66±0.21 <sup>#</sup>
Test 1(2)	0.5±0.22 <sup>#</sup>	2.16±0.30	2.83±0.473	3.16±0.40 <sup>#</sup>	2.0±0.25 <sup>#</sup>
Test 2(2)	0.83±0.30 <sup>#</sup>	3.0±0.36 <sup>#</sup>	3.83±0.30 <sup>#</sup>	2.83±0.30 <sup>#</sup>	1.66±0.33 <sup>#</sup>
Test 3(2)	0.33±0.21 <sup>#</sup>	1.5±0.56 <sup>#</sup>	1.0±0.36 <sup>###</sup>	1.66±0.21 <sup>###</sup>	1.0±0.36 <sup>###</sup>
Test 4(2)	0.83±0.16 <sup>#</sup>	2.16±0.30 <sup>#</sup>	2.83±0.47 <sup>#</sup>	2.0±0.36 <sup>###</sup>	1.5±0.22 <sup>#</sup>
Test 5(2)	0.5±0.22 <sup>#</sup>	2.66±0.33 <sup>#</sup>	3.33±0.21 <sup>#</sup>	2.83±0.30 <sup>#</sup>	1.66±0.33 <sup>#</sup>
Test 6(2)	0.66±0.21 <sup>#</sup>	2.5±0.42 <sup>#</sup>	3.5±0.42 <sup>#</sup>	2.66±0.21 <sup>#</sup>	1.33±0.21 <sup>#*</sup>

Where, Values are expressed as Mean ± S.E.M

#, ## - Significantly different from disease group. (p < 0.05, p < 0.01 respectively)

\*, \*\*, \*\*\* - Significantly different from standard group. (p < 0.05, p < 0.01, p < 0.001 respectively)

**Table 4: Effects on car by the treatment With olanzapine analogues and standard olanzapine in rats**

Groups (Dose: mg/kg, i.p.)	Conditional Avoidance Response (Sec)					
	Trial 0	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5
Control (2)	1.5±0.34	2.5±0.42	3.5±0.42	2.0±0.36	2.5±0.22	1.5±0.22
Standard (2)	1.66±0.33 <sup>#</sup>	4.5±0.22 <sup>#</sup>	5.33±0.21 <sup>#</sup>	5.5±0.34 <sup>#</sup>	5.16±0.3 <sup>#</sup>	5.5±0.34 <sup>#</sup>
Test 1(2)	2.16±0.30	3.66±0.42	5.0±0.44	5.0±0.44	3.66±0.42	5.0±0.25
Test 2(2)	2.0±0.36	5.0±0.51	5.0±0.25	4.5±0.42	4.5±0.42	4.83±0.30
Test 3(2)	1.66±0.33	6.16±0.30 <sup>#</sup>	6.33±0.21	7.16±0.30 <sup>#</sup>	5.16±0.30	6.66±0.3
Test 4(2)	2.33±0.33	5.33±0.42	5.66±0.33	5.33±0.33	5.0±0.36	6.33±0.42
Test 5(2)	1.83±0.30	6.0±0.36	5.33±0.21	5.66±0.33	4.16±0.47	4.66±0.21
Test 6(2)	1.33±0.21	4.83±0.30	6.0±0.36	6.5±0.22	4.0±0.36	4.83±0.30

Where, Values are expressed as Mean ± S.E.M

\*, \*\* - Significantly different from standard group. (p < 0.05, p < 0.01 respectively)

#, ##, ### - Significantly different from control group. (p < 0.05, p < 0.01, p < 0.001 respectively).

**Table 5: Effect of sedation which was produced by standard olanzapine and synthesized olanzapine analogues**

Groups (Dose: mg/kg, i.p.)	Onset of Action (mins)	Duration of action (mins)
Control	0	0
Standard(2)	23.33±0.553#	73.5±0.99#
Test 1(2)	28.5±0.42***	60.16±1.66***
Test 2(2)	25.16±0.40*	69.33±0.95**
Test 3(2)	29.5±1.08***	52.83±0.70***
Test 4(2)	27.16±0.94**	66.66±0.95***
Test 5(2)	25.5±0.56*	69.5±0.62**
Test 6(2)	29.16±1.19***	64.33±1.96***

Where, Values are expressed as Mean ± S.E.M

\*, \*\*, \*\*\* - Significantly different from standard group. (p <0.05, p <0.01, p <0.001 respectively)  
#, ##, ### - Significantly different from control group. (p <0.05, p <0.01, p <0.001 respectively)

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