# SYNTHESIS OF SOME NOVEL BUTYROPHENONE SUBSTITUTED AS ASTEROIDS AND EVALUATION OF ANTIPSYCHOTIC ACTIVITY.

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**Abstract-** The present study is undertaken to investigate the pharmacological activities of azasteroids. Haloperidol has been taken as lead. The major approach implied in present study is to synthesize azasteroidal butyrophenone, in which butyrophenone is attached to the 6 position of azacholesterol, 17a- position of azaandrostenolone ring, and 4- position of azaandrostan. In present study the Compouns7: 6-[3'-(p-Fluorobenzoyl)propyl]-6-aza-5α-cholesterol ,Compound15: 17a-[3'-(p Fluorobenzoyl)propyl]-17a-aza-D-homo-5-androsten-3β-ol, Compound20: 4-[3'-(p-Fluorobenzoyl)propyl]-4-aza-5α-androstan-17β-ol are found to be effective antipsychotics. Compound 7 and Compound 15 show activity comparable to haloperidol. The observed behaviour alterations may be due to dopaminergic supersensitivity in nigrosrtiatal structure. The present study demonstrated that the administration of these compounds did not aggravate extrapyramidal side effects as compared to Haloperidol. This may be due to its possible affinities for 5-HT receptors. Furthermore neurosteroids are specific mediator of $GABA_A$ receptor which regulates the neuronal activity through diverse neurotransmitter mechanism.

**Index terms-** Antipsychotics, Azasteroids, butyrophenones, stereotypic behavoiur

## I. INTRODUCTION

Psychosis is a symptom or feature of mental illness typically described by radical changes in personality, impaired functioning and loss of contact with reality [1]. Psychosis is a heterogeneous syndrome present in 0.85% of individuals worldwide. Antipsychotics or neuroleptic drugs are used to treat psychoses. Neuroleptic, which originates from the Greek word neuron ("nerve") and lepsis ("seizure" or "fit"), was a reference to neurological side effects [2, 3]. Steroids are the most important class of natural as well as synthetic drugs which perform the basic or fundamental biological function [4, 5]. Steroids are generally preferred due to their ability to cross membrane easily.

In 1968, Jensen and Suzuki [6] discovered the concept of steroid hormone and its mechanism. But later on Gorski [7] demonstrated the new concept of hormone receptor which triggers the series of events that permit the expression of specific genes. When a steroid molecule enters the cell it gets modified to produce active molecule that acts on different receptors which shows its function. Medicinal chemist evaluated different changes in steroid molecule when there is introduction of different groups that leads to change in activity [8,9]. With an aim to have more active azasteroidal antipsychotic agents, certain novel analogues of haloperidol have been synthesized, the major approach implied in present study is to synthesize azasteroidal butyrophenone, in which Butyrophenone is attached to the 6 position of azacholesterol and 17a position of azaandrostenolone ring, and 4 position of azaandrostan. The antipsychotic activity was evaluated using inhibition of apomorphine induced stereotypy and biochemical estimations in mice.

## II. EXPERIMENTAL WORK

The melting points reported are uncorrected. IR spectra are recorded on Perkin-Elmer 882 model. Proton NMR spectroscopy was performed using Bruker Avance II 400 NMR Spectrophotometer Reactions were monitored and the homogeneity of the products was checked by TLC. Anhydrous sodium sulphate was used as drying agent.Pharmacological studies were done at UIPS, Panjab University Chandigarh.

SCHEME 1: For the preparation of these compounds, cholesterol was used as starting material. Cholesteryl acetate (2) was obtained by acetylation of cholesterol (1) with acetic anhydride in pyridine. m.p. 112-114°C (lit 112-115°C) Analysis:IR (KBr): C-H stretch 2940, C=O stretch 1720, C=C stretch 1470 $cm^{-1}$ $^1$HNMR ($CDCl_3$): δ 0.9(m, 3H, 21-$CH_3$), 1.09(s, 2H, 18- $CH_3$), 2.3(d, 2H, 4-$CH_2$), 4.5(m, 3H, 3-$CH_3$), 5.3(m, 1H, 6H-vinylic) ppm.

Further oxidation of (2) with chromim trioxide give α, β-unsaturated ketone (3) 7-Keto-3β–cholesteryl acetate m.p. 160-161°C. Analysis: IR (KBr): C-H stretch 2938, 2865.9, C=O stretch 1738, C=C stretch 1457, C-O stretch 1026 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 0.91(s, 3H, 21-$CH_3$), 1.04(s, 3H, 18-$CH_3$), 2.2(d, 2H, 4-$CH_2$), 4.5(t, 3H, 3-CH), 5.2(s, H, 6H-vinylic) ppm. Compound (3)was oxidized with permanganate-peroxide to obtain seco-keto acid 3β-Acetoxy-5-keto,7-seco-6-norcholestan-7-oic-acid (4) m.p. 156-157°C Analysis: IR (KBr): C-H stretch 2938, C=O stretch 1738, C-O stretch 1027 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 0.91 (m, 3H, 21-$CH_3$), 1.04 (d, 3H, 18-$CH_3$) and 1.04 (m, 3H, 19-$CH_3$), 4.5(m, 1H, 3-CH), 7.19 (s, 1H, 7-CO-OH) ppm.

The oxime 3β-Acetoxy-5-oximino-5,7-seco-6-nor-3-cholestan-7-oic-acid (5) [10] was obtained by heating

(4) with hydroxylamine hydrochloride in pyridine. m.p. 164-165.5°C Analysis: IR (KBr):O-H stretch 3400, C-H stretch 2937, C=O stretch 1733 and C=N stretch 1650 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 0.91 (d, 3H, 21-$CH_3$), 1.04(s, 1H, 18-CH), 1.14 (s, 3H, 19-$CH_3$), 1.7(s, 1H, 9-CH) and 2.0 (t, 1H, 5-NOH), 7.19 (s, 1H, 7-CO-OH) ppm.

The oxime (5) on reduction with sodium-pentanol give 6-Aza-5,6-dihydrocholesterol (6) 6-Aza-5,6-dihydrocholesterol [11]. m.p. 115-116°C (lit 116-117°C). Analysis: IR (KBr): N-H stretch 3439.50, O-H stretch 3439, C-N stretch 1373 & C-H stretch 2937 cm-$^{1}$. $^1$HNMR ($CDCl_3$): δ 0.91 (s, 3H, 21-$CH_3$), 1.0 (d, 3H, 18-$CH_3$), 1.7(d, 2H, 4-$CH_2$), 2.2 (s, 1H, 6-NH), 4.4(m, 1H, 3-OH), ppm.

Compound (6) in toluene solution was refluxed with 4-chloro-4'-fluorobutyrophenone in the presence of sodium carbonate and potassium iodide for 96 hr to obtain 6-[3'-(p-fluorobenzoyl)propyl]-6aza-5α-cholesterol (7) m.p. 85-86°C. Analysis: IR (KBr): C-H stretch 2849, C=O stretch 1647.3, C=C aromatic stretch 1462.0, C-N stretch 1411 and C-F stretch 1192.8 cm-$^{1}$. $^1$HNMR ($CDCl_3$): δ 0.95 (s, 3H, 21-$CH_3$), 1.04 (s, 3H, 18-$CH_3$), 3.0(t, 2H, CO-OH), 3.6(m, 1H, 3-OH), 7.4(m, 2H, 3', 5'aromatic ring) and 8.0 (m, 2H, 2', 6' aromatic ring) ppm.Calcd for $C_{36}$ $H_{56}$NOF: C:78.12; H: 10.13; N:2.53 Found: C:78.56; H: 10.86; N:2.40

SCHEME 2: 20-oxo-5,16-pregnadien-3β-yl acetate (8) was treated with hydroxylamine hydrochloride in pyridine to get the oxime, 20-oximino-5,16-pregnadien-3β-yl acetate (9), m.p. 211-213°C Analysis: IR (KBr):O-H stretch 3480, C-H stretch 2850, C=O stretch 1730 and C=N stretch 1260 $cm^{-1}$. $^1$HNMR ($CDCl_3$):δ 0.95 (s, 3H, 18-$CH_3$), 1.05 (s, 3H, 19-$CH_3$), 2.01 (s, 3H, 21-$CH_3$), 2.3 (s, 3H, $OCOCH_3$), 4.6 (m, 1H, 3α-H), 5.5 (m, 1H, 6H-vinylic) and 6.07 (m, 1H, 16H- vinylic)ppm.

Beckmann rearrangement of the oxime (9), thus prepared, using phosphorus oxychloride-pyridine system followed by acid hydrolysis gave intermediate (10) which further converted to final product 17-oxo-5-androsten-3β-yl acetate17-oxo-5-androsten-3β-yl acetate (11) m.p. 162-163°C . Analysis: IR (KBr): C-H stretch 2850, C=O stretch 1735 and C=C stretch 1240 $cm^{-1}$. $^1$HNMR ($CDCl_3$):δ 0.90 (s, 3H, 18-$CH_3$), 1.03 (s, 3H, 19-$CH_3$), 2.3 (s, 3H, $OCOCH_3$), 4.6 (m, 1H, 3α-H) and 5.4 (m, 1H, 6H-vinylic) ppm.

Co Compound (11) [12] was treated with hydroxylamine hydrochloride and sodium acetate trihydrate in ethanol to give its oxime (12) 17-Oximino-5-androsten-3β-yl acetate, m.p. 180-182° C .Analysis: IR (KBr): O-H stretch 3400, C-H stretch 2960, C=C stretch 1740 and C=N Stretch 1245 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 0.92 (s, 3H, 18-$CH_3$), 1.04 (s, 3H, 19-$CH_3$), 2.3 (s, 3H, $OCOCH_3$), 4.6 (m, 1H, 3α-H), 5.4 (m, 1H, 6H-vinylic) and 8.43 (s, 1H, N-OH) ppm. Beckmann rearrangement of the oxime (12) was done using thionyl chloride as the catalyst, to obtain the lactam (13) 17-Oxo-17a-aza-D-homo-5-androsten-3β-yl acetate m.p. 289-292°C (lit.291-294°C). Analysis:IR (KBr): N-H stretch 3220, C-H stretch 2860, C=C stretch 1740 and C=O lactam 1680 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 1.01 (s, 3H, 18-$CH_3$), 1.18 (s, 3H, 19-$CH_3$), 2.3 (s, 3H, $OCOCH_3$), 4.6 (m, 1H, 3α-H), 5.4 (m,1H, 6H-vinylic) and 8.4 (s,1H, NH) ppm.

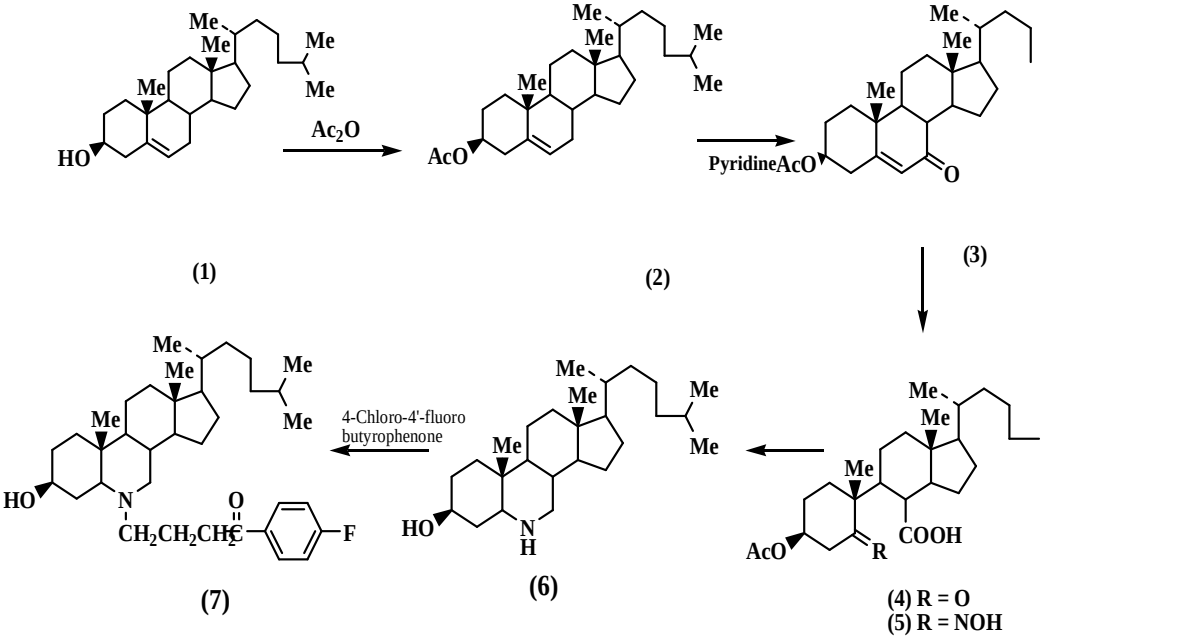
The lactam (13) [13] so obtained was reduced with sodium-pentanol to give secondary amine 17a-aza-D-homo-5-androsten-3β-ol (14). m.p. 230-231° C (lit. 231-233°C). Analysis: IR (KBr): O-H stretch 3481, N-H stretch 3245, C-H stretch 2935 and C=C stretch 1670 $cm^{-1}$. $^1$HNMR ($CDCI_3$): δ 1.0 (s, 3H, 18-$CH_3$), 1.06 (s, 3H, 19-$CH_3$), 3.50 (m, 1H, 3α- CH) and 5.36 (t, 1H, 6H-vinylic) ppm. (14) in toluene solution was refluxed with 4-chloro-4'-fluorobutyrophenone in the presence of sodium carbonate and potassium iodide for 96 hr to obtain product 17a-[3'-(p-fluorobenzoyl)propyl]-17a-aza-D-homo-5-androsten-3β-ol (15). m.p. 249-250°C Analysis: IR (KBr): O-H stretch 3433, C-H aromatic stretch 2918, C=O stretch 1637, C=C stretch 1463 and C-N stretch 1378.25 $cm^{-1}$. $^1$HNMR ($CDCl_3$): δ 1.04 (m, 3H, 18-$CH_3$), 1.29 (s, 3H, 19-$CH_3$), 3.6 (t, 1H, 6H-vinylic), 4.3(m, 1H, 3-OH), 7.0(m, 2H, 3',5' aromatic ring) and 7.9 (m, 2H, 2',6' aromatic ring) ppm. Calcd for $C_{28}$ $H_{40}NO_2F$: C:78.01; H: 9.28; N:3.25 Found: C:78.56; H: 9.83; N:3.40

SCHEME 3: Testosterone acetate,17β-acetoxy-4-androsten-3-one (16) on permanganate-periodate oxidation gave the 17β-hyrodroxy-5-oxo-3,5-seco-4-norandrostan-3-oic acid (17) 70%) m.p. 206-208°C .Analysis: IR (KBr):O-H stretch 3401, C-H stretch 2921, C=O stretch 1738 and C-O 1031 $cm^{1}$ .$^1$HNMR ($CDCI_3$): δ 1.16 (s, 3H, 15-$CH_3$), 1.04(s, 3H, 18-$CH_3$), 2.28(s, 3H, 6-$CH_3$), 4.3(m, 1H, 17-OH), 7.4(d, 1H, 3-CO-OH) ppm.

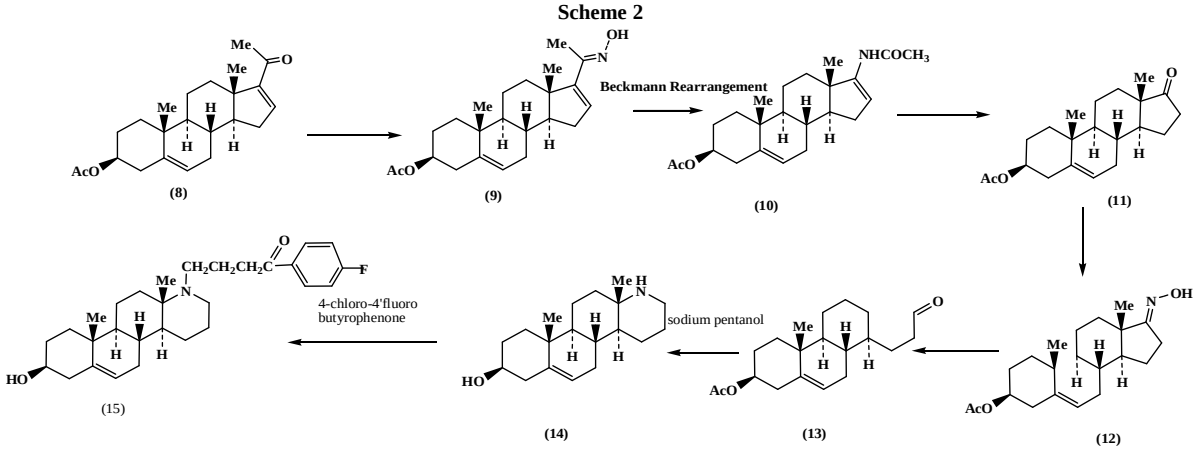
Oxime (18) 17β-Hydroxy-5-oximino-3,5-seco-4-norandrostan-3-oic acid was prepared by was refluxing(17) in ethanol with hydroxylamine hydrochloride and potassium hydroxide %), m.p. 199-201°C (lit 199-202°). Analysis: IR (KBr): O-H stretch 3404, C-H stretch 2934, C=O stretch 1711, and C=N stretch 1267 $cm^{-1}$. $^1$HNMR ($CDCI_3$): δ 1.2 (s, 3H, 18-$CH_3$), 1.29 (s, 3H, 19-$CH_3$), 1.5 (t, 1H, 5-NOH), 7.2 (d, 1H, 3-CO-OH) ppm. The oxime(18) on sodium pentanol reduction gave 4-aza-5α-androstan-17β-ol(19), m.p. 201-203°C (lit$^{94}$ 202-203°C). Analysis: IR (KBr): O-H stretch 3305, C-H stretch 2940, and C=O stretch 1060 $cm^{-1}$. $^1$HNMR ($CDC1_3$): δ 1.04 (s, 3H, 18-$CH_3$), 1.27 (s, 3H, 19-$CH_3$), 1.9 (t, 1H, 5α-H), 2.2(s, 1H, 4-NH), 4.5 (t, 1H, 17-OH) ppm. Compound (19) was refluxed with 4-chloro-4'-fluorobutyrophenone in the presence of sodium carbonate and potassium iodide for 96 hr to obtain final compound 4-[3'-(p-fluorobenzoyl)propyl]-4-aza-5α-androsten-17β-ol (20). Analysis: IR (KBr):O-H stretch 3328, C-H stretch 2919, 1686, C=C stretch 1464, C-N stretch 1375, C=O stretch 1686 $cm^{-1}$. $^1$HNMR ($CDCI_3$): δ 1.07 (s, 3H, 18-$CH_3$), 1.28 (s, 3H, 19-$CH_3$), 3.1(t, 2H, CO-$CH_2$), 3.7 (m, 1H, 17-

OH), 7.1 (m, 2H, 3',5' aromatic ring) and 8.0 (m, 2H, 2',6'aromatic ring) ppm. Calcd for $C_{28}$ $H_{40}NO_2F$: C:78.01; H: 9.28; N:3.25 Found: C:78.67; H: 9.59; N:3.51

**Scheme1**




**Scheme 2**

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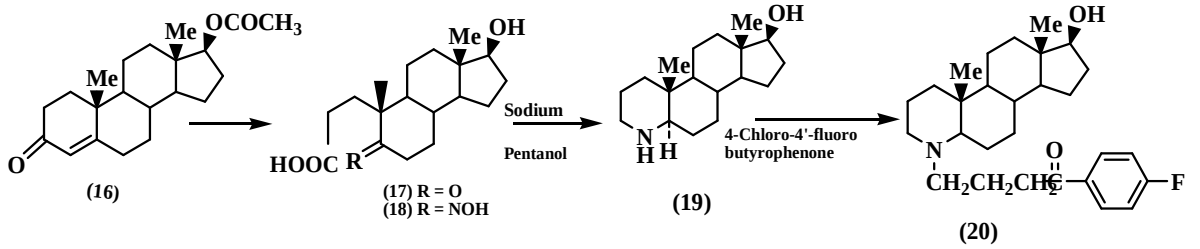


## III. MATERIAL AND METHODS

Animals: Laca mice (female), weighing 20-30 g, were employed in the present study. They were housed in the departmental animal house of UIPS, Punjab University, Chandigarh and were exposed to natural cycles of light and dark. The experimental protocol was approved by the Institutional Animal Ethics Committee (Approval No. PU/IAEC/S/16/13) and care of the animals was carried out as per the guidelines of the CPCSEA, Department of Animal Welfare and Government of India. All groups were under fasting state for 24 hr but they were allowed to drink water only before carrying out the experiment. All mice were orally given particular pretreatment based on their groups and their weight.

Drugs and chemicals Apomorphine (Sigma, India), Haloperidol (Sigma, India) was used. Tween 80 was used as vehicle, Compouns7: 6-[3'-(p-Fluorobenzoyl)propyl]-6-aza-5α-cholesterol ,Compound15: 17a-[3'-(p Fluorobenzoyl)propyl]-17a-aza-D-homo-5-androsten-3β-ol, Compound20: 4-[3'-(p-Fluorobenzoyl)propyl]-4-aza-5α-androstan-

17β-ol were used as the test drugs for antipsychotic activity.

## IV. EXPERIMENTAL PROTOCOL

Table1: The animals were divided into following groups. Group was administered vehicle 30 min before the behavioural study. Animals were scarified immediately after behavioral assessment.

| Group | Name | Treatment |
|---|---|---|
| Group1 | Vehicle | 0.5 % Tween 80(0.5 mg/kg i.p) |
| Group2 | Vehicle+Apomorphine | 0.5 % Tween 80 (1 mg/kg i.p) |
| Group3 | Compound 15 + Apomorphine | 1mg /kg i.p |
| Group4 | Compound 20 + Apomorphine | 1mg /kg i.p |
| Group5 | Compound 7 + Apomorphine | 1mg /kg i.p |
| Group6 | Haloperidol | 0.5mg/kg i.p |

**BEHAVIORAL PARAMETER**

**LOCOMOTOR ACTIVITY**: Locomotor activity (ambulation) was measured by actophotometer. An array of 16 infrared emitter/detector pairs measured the animal activity along single axis of motion. After 45 min of drug treatment mice were individually placed in a transparent plastic cage (30×23×22cm) and mice were allowed to acclimatize to the observation chamber for a period of 2 min. The activity was continuously monitored for a period of 5 min. Percentage increase or decrease in locomotor activity was calculated [11].

**APOMORPHINE INDUCED STEREOTYPY**: Apomorphine 1mg/kg, i.p was injected to induce stereotypy. Stereotypy was measured by placing the mice individually in 500 ml glass beaker. Intensity of rearing, sniffing and licking behavior was noted for 30 min at time intervals of 10 min. The severity of response was scored as 0 = presence, 1 = mild, 2= moderately severe, 3 = intense and continuous action. The cumulative stereotypy score was calculated by adding all the scores for the purpose of comparison. The test was employed 15 min after performing locomotor activity [12]

**BIOCHEMICAL ESTIMATIONS:** Preparation of homogenate: animals were sacrificed by decapitation immediately after behavioral assessment. Brain was removed and 10% (w/v) tissue homogenate was prepared and centrifuged at 10,000 rpm for 15 min .Clear supernatant was used for different biochemical estimations [13] of lipid peroxidation (MDA content), reduced glutathione (GSH) and catalase (CAT).

**STATISTICAL ANALYSIS:** The results were expressed as Mean ± S.E.M.. The results were analyzed using one-way and two-way ANOVA followed by analysis using Tukey's Multiple Comparison Test. For comparison between different groups Graph Pad prism (6 versions) was used. The p value***<0.001, **<0.01, *<0.05 was considered to be statistically significant.

**RESULTS: LOCOMOTOR ACTIVITY IN MICE:** Compound 20, 7 (1mg/kg, i.p.) treated mice, shows significant (**p<0.001) decrease the hyperlocomotor activity count measured for 5min against the standard drug. The decrease in locomotor activity by the compound 15, was observed with the dose of the 1mg/kg,i.p but not to the significant value(fig 1).

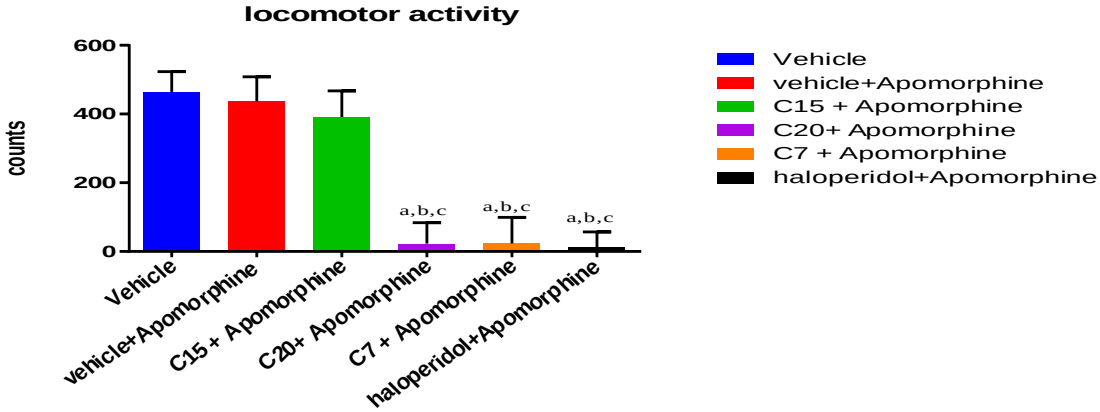


**Fig1: Bars represent mean±SEM (**p<0.001). The data was analyzed by one way ANOVA followed by tukey's test. Values are mean ± SEM of 5 animals a group. [a] denotes significant**p<0.001 as compared to vehicle treated group. [b] denotes significant at **p<0.001 as compared to vehicle+ apomorphine treated group. [c] denotes significant at **p<0.001 as compared to compound (15)+ apomorphine.**

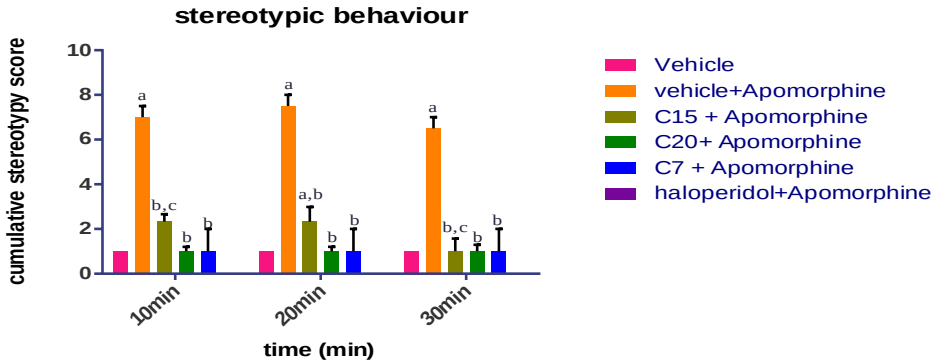


**Fig2: Effect of (compound15, 20& 7), on stereotypy behaviour use in mice.**

Values are mean±SEM of 5 animals a group****p<0.0001. (Two way ANOVA followed by tukey's test as compared to control group fig 2. Values are mean ± SEM of 5 animals a group. [a] denotes significant ****p<0.0001 as compared to vehicle treated group. [b] denotes significant at **p<0.001 as compared to apomorphine treated group. [c] denotes significant at *p<0.01 as compared to haloperidol.

**Table2: Effect of antipsychotic activity on biochemical estimation use of mice.**

| Experimental group (mg/kg i.p) | TBARS (nmol/mg protein) | GSH (µmol/mg protein) | Catalase (µmol/mg protein) |
|---|---|---|---|
| Vehicle (0.5 mg/kg i.p) | 0.3873± 0.1691 | 0.0136±0.1136 | 1.9522±0.1 |
| Vehicle +Apomorphine (1 mg/kg i.p) | 0.2141 ±0.0164 | 0.1641±0.10227 | 2.0112±1.23 |
| Compound 15 + Apomorphine (1 mg/kg i.p) | 52.908± 52.691 | 0.0036±0.00134 | 0.9415±0.6415 |
| Compound 20 + Apomorphine(1 mg/kg i.p) | 57.709 ±57.490 | 0.0022±3.0665 | 0.612±0.229 |
| Compound 7 + Apomorphine (1 mg/kg i.p) | 6.3800±6.1618 | 0.0088±0.0066 | 1.481±1.043 |
| Haloperidol + Apomorphine (0.5mg/kg i.p) | 61.12± 0.09818 | 0.0022±1.1760 | 0.3845±0.3475 |

Effect of antipsychotic on changes in lipid peroxidase (TBARS) level: Antipsychotics resulted in an increase in brain TBARS levels as compared to control group. Pretreatment apomorphine decreased the brain TBARS levels. Treatment with compound (15, 20, 7) (1mg/kg i.p) and standard drug haloperidol (0.5mg/kg i.p) shows significant increase in the brain TBARS levels (table2).

Effect of antipsychotic on changes in reduced glutathione (GSH) level: Antipsychotics resulted in a decrease in brain reduced GSH levels as compared to control group. Pretreatment apomorphine decreased the brain TBARS levels. Treatment with compound (15, 20, 7) 1mg/kg i.p & haloperidol (0.5mg/kg i.p) decrease the brain GSH levels (table2).

Effect of antipsychotic on changes in catalase (CAT) level: Antipsychotics resulted in a decrease in brain CAT levels as compared to control group. Pretreatment with apomorphine increase the brain catalase levels. Treatment with compound (15, 20, 7) (1mg/kg i.p) and standard drug haloperidol (0.5mg/kg i.p) decrease show CAT level in a significant manner (table 2).

## DISCUSSION AND CONCLUSION

The compound (15, 20, 7), drugs are found to be effective antipsychotics. Compound 15 &20 show activity comparable to haloperidol. The observed behaviour alterations may be due to dopaminergic supersensitivity in nigrostriatal structure. The present study demonstrated that the administration of compound (15, 20, 7), did not aggravate extrapyramidal side effects as compared to haloperidol. This may be due to its possible affinities for 5HT receptors. Stereotypes are abnormal repetitive behavioural pattern that are highly prevalent and are thought to reflect impaired behaviour. Neurosteroids are specific mediator of $GABA_A$ receptor which regulates the neuronal activity through diverse neurotransmitter mechanism. These neuroactive steroids alter neuronal excitability by modulating the activity of several neurotransmitter receptors & thus can influence behaviour.

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