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Antidepressant Activity of Fluoxetine Analogues

Sanjay Kumar Srivastava[1], Pankaj Yadav[2], Vikash Chandra[2], Ankur Srivastava[3], Shweta Singh[4], Navneet Kumar Verma[*5]

[1]Assistant Professor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209 Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[2]Faculty of Pharmacy,Uttar Pradesh University of Medical Sciences, Saifai Etawah, Uttar Pradesh, India

[3]Assistant Professor, Institute of Pharmacy, Dr Ram Manohar Lohia Avadh University Faizabad, UP, India

[4]Associate Professsor, Shambhunath Institute of Pharmacy Jhalwa Prayagraj Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

[5]Associate Professsor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209 Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

ABSTRACT

Fluoxetine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine and choroxamine belong to SSRI group of drugs. Present research work involves synthesis of fluoxetine derivatives by reacting Substituted acetophenone undergoes mannich reaction with substituted secondary amines. In second step mannich bases undergoes reduction with sodium borohydride and in final step etherification was done with the help of p-chlorobenzotrifluride. Structure of final compounds was confirmed by IR, 1 H NMR, and Mass spectral data. Fluoxetine analogues were biologically assessed for antidepressant activity. Since all the five moieties did not show significant decrease in immobility time as compared to the standard drug. This suggests that the fluoxetine and sertraline analogues require further modification to get the desired activity.

Keywords: *Fluoxetine, Antidepressant Activity, Fluoxetine analogues, sertraline analogues*

***Corresponding Author**
Navneet Kumar Verma
Associate Professsor, Buddha Institute of Pharmacy, GIDA, Gorakhpur, UP, India-273209 Affiliated to Dr. APJ Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India

INTRODUCTION

Depression is a mental illness which affects around 16% of the population at some point in their lives and major depressive disorder is a leading cause of disability worldwide[1]. Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. These problems can become chronic or recurrent and lead to substantial impairments in an individual's ability to take care of his or her everyday responsibilities[2]. It is the most common of the affective disorders (defined as disorders of mood rather than disturbances of thought or cognition); it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions. Worldwide, depression is a major cause of disability and premature death[3].

MATERIALS AND METHOD

Chemicals Used

Acetophenone, F-Acetophenone, Benzyl methyl amine, Dibenzyl amine, Paraformaldehyde, Sodium borohydride, Sodium hydride, Dimethyl acetamide, p-Chlorobenztrifluride, α-Napthol, Aluminium chloride, Benzene, Dichlorobenzene, Methyl amine (Alc.), Palladium catalyst, Hydroxyl amine, Sodium metal, Sodium methoxide, Morpholine, N-Phenyl piperazines, Isopropanol, Absolute alcohol,
Methanol, n-Propanol, Ammonia solution etc

Apparatus Used

Reflux condenser, Magnetic stirrer, Electric oil bath, Dimerstat, Rotavapour, Suction pump, Guard tubes, precoated TLC plates

ANTIDEPRESSANT ACTIVITY

Behavioural tests

(a) Tail suspension test in mice

The immobility displayed by rodents when subjected to an unavoidable and inescapable stress has been hypothesized to reflect behavioural despair which in turn may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail[4].

(b) Reserpine induced hypothermia

Depletion of biogenic amines (noradrenaline, 5-hydroxytryptamine, dopamine) in the brain induces not only catalepsy and ptosis but also hypothermia in rodents. The decrease of body temperature induced by reserpine is antagonized by antidepressants, MAO-inhibitors and central stimulants. The subcutaneous administration of 2 mg/kg reserpine leads to a decrease of core temperature in mice to 20–23 °C after 18 h. The fall in temperature can be antagonized by antidepressants, but also by amphetamine-like drugs. However, the time course is different: tricyclic antidepressants have a slow onset of action and a long lasting effect, whereas amphetamine-like drugs have a quick onset of action and a short-lasting effect[4].

(c) Learned helplessness in rats

Animals exposed to inescapable and unavoidable electric shocks in one situation later fail to escape shock in a different situation when escape is possible[4].

(d) Forced swim test

The forced swim test is one commonly used stressor, where rats (or mice) are forced to swim in an environment from which escape is not possible. In this paradigm, rats go through a period of behavioural activation characterized by vigorous swimming and diving to search for alternate routes of escape. This period of behavioural activation may persist for as much as 3–5 min, after which the rats cease attempts to escape and adopt a characteristic posture of immobility. This second, more passive phase of behaviour is thought to reflect a state of depressed mood, and has been referred to as behavioural despair[5].

Active rats usually show two apparently different behaviours:

Rodents forced to swim in a narrow space from which there is no escape adopt, after an initial period of vigorous activity, a characteristic immobile posture, moving only when necessary to keep their heads above the water. The animals immobility was hypothesized to show they had learned that escape was impossible and had given up hope. Immobility was therefore given the name "behavioural despair." It was subsequently found that immobility could be reduced by a wide range of clinically active antidepressant drugs. This simple behavioural procedure has since become a useful test for screening novel antidepressants[6].

MATERIALS AND METHOD

Animals: Swiss Albino Mice of both the sexes were used in this experiment and all the experiments were carried out in the pharmacology division of Central Drug Research Institute (C.D.R.I.), Lucknow and were raised in the breeding centre. Animals were approximately 30 days old upon their arrival in the laboratory. The mice were housed in a controlled environment (light on 0730 to 1900 hours, temperature 22^0 C) for at least 10 days before starting the experiments. Food and water were always provided ad libitum**.**

Drugs: Fluoxetine(20mg/kg), N-benzyl-N-methyl-3-phenyl-3-(4-(trifluoromethyl) phenoxy)propan-1- amine **1(c)** , N,N-dibenzyl-3-phenyl-3-(4-(trifluoro methyl) phenoxy)propan-1-amine **2(c)**, 1-Morpholin-4-yl-1,2,3,4-tetrahydro-naphtha len-2-ol **3(c)**.

General Procedure: On the first day screening was done and the mice were placed in a group of 5 mice in each cage after FST. In the FST (Porsolt Test) mice was introduced (in the morning) into the transparent cylindrical glass tank (height = 40cm, internal diameter = 15cm) containing water to a level 22cm (25^0 C). The time spent making the following behaviour was measured with a stop-watch:
"Immobility" which occurred when the animals remained floating with all limbs motionless. On the second day test compounds were dissolved with 2%DMSO in distilled water and standard drug (Fluoxetine) were given by oral route in each group. The FST was conducted after 1hr of dose administrated. The behaviour of mice was observed for duration of 5 min after placing in water tank. The total time speed spent making the immobile behaviour was measured by stop-watch. The water of tank was replaced with fresh water after testing each group.

Evaluation: Duration of immobility is measured in control and animals treated with standardized dose of test and standard drug[7].

Table.1: *In vivo* antidepressant activity in Swiss Albino Mice Forced Swim test Model.

S.No.	Body Weight(gm)	Dose	Drug	Immobility Time(sec)	Mean(I.T.) (sec)	Standard Error of Mean(±)
1	28		Control	207	185.4	10.117
2	26		(Distilled	184		
3	29		Water)	190		
4	31			198		
5	30			148		
1	33	20mg/kg	Fluoxetine	220	70	40.014
2	33			25		
3	31			85		
4	30			16		
5	27			4		
1	27	30mg/kg	1(c)	171	75.6	25.117
2	30			55		
3	26			47		
4	35			74		
5	29			30		
1	29	30mg/kg	2(c)	167	76.4	23.286
2	33			65		
3	30			54		
4	31			62		
5	28			34		
1	28	30mg/kg	3(c)	170	98.6	22.87
2	37			85		
3	32			71		
4	26			128		
5	30			39		

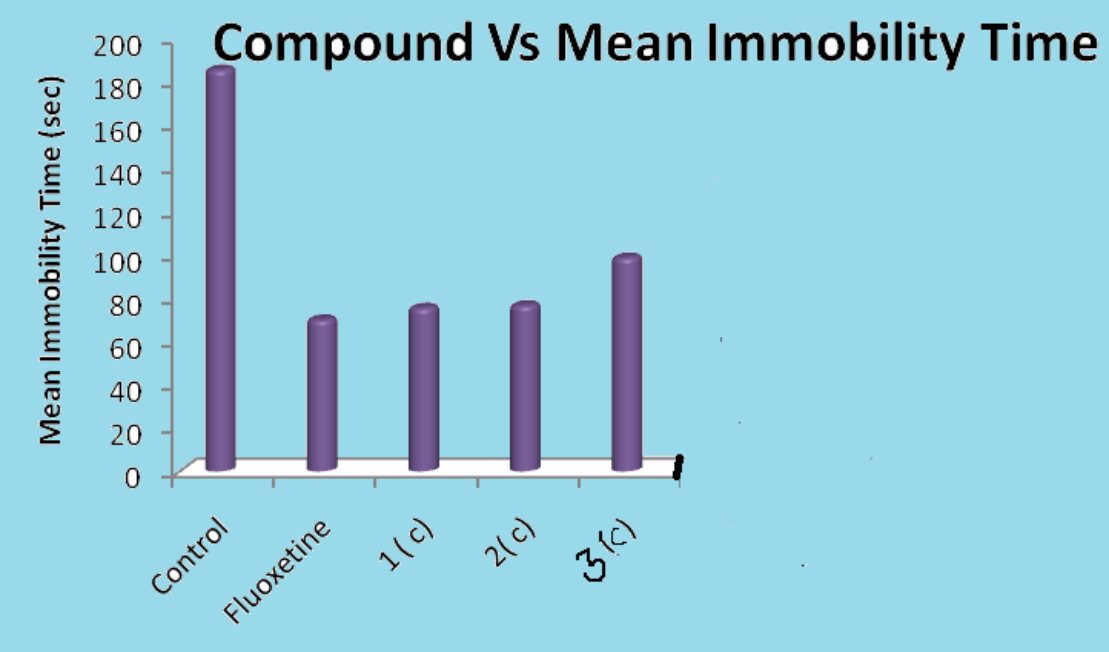

Fig.1: Comparision of Mean Immobility Time of the tested compounds with Fluoxetine

The compounds N-benzyl-N-methyl-3-phenyl-3-(4-(trifluoromethyl) phenoxy)pre opan-1-amine **1(c)** , N,N-dibenzyl-3-phenyl-3-(4-(trifluoromethyl)phenoxy) propan-1-amine **2(c)**, N-benzyl-3-(4-fluorophenyl)-N-methyl-3-(2-nitro-4-(trifluorome thyl)-phenoxy)propan-1-amine 3(c), were tested for antidepressant activity by standard method and compared with the standard drug fluoxetine. The result of the biological activity has been depicted in table 2. The significant difference of the immobility time of treated and standard group was determined by unpaired student's Test

(two tailed). None of the tested compound showed significant decrease in immobility time from the standard drug. The statistical significance of results was evaluated with one way analysis of variance (ANOVA). The one way ANOVA revealed a significant effect of fluoxetine, 1(c), 2(c), 3(c) on the immobility time in comparison to control group.

CONCLUSION

The SSRIs are chemically distinct from traditional antidepressants like tricyclic, tetracyclic and monoamine oxidase inhibitors, but share the common route of selective and potent inhibition of neuronal reuptake of serotonin, and have none or very little effect on neuronal reuptake of norepinephrine, acetylcholine and histamine. Thus, these drugs have less sedative, anticholinergic and cardiovascular effects than other antidepressants of tricyclic and tetracyclic class. Fluoxetine, fluroxamine, sertraline, indalpine, paroxetine, alproclate, femorxetine and choroxamine belong to SSRI group of drugs. On the basis of literature survey, various analogues of fluoxetine were synthesized and screened for antidepressant activity. In brief, we prepared the fluoxetine and sertraline analogues and biologically assessed these compounds for antidepressant activity. Since all the five moieties did not show significant decrease in immobility time as compared to the standard drug. This suggests that the fluoxetine and sertraline analogues require further modification to get the desired activity.

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