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EVALUATION OF ANXIOLYTIC ACTIVITY OF SUBSTITUTED 1, 2, 4-TRIAZOLE BEARING IMINO, FIVE MEMBERED HETEROCYCLIC MOIETY

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ABSTRACT

A series of 4-[(5-amino-1,3,4-thiadiazol-2-yl)methyl]-5-substituted phenyl-4*H*-1,2,4-triazole-3-thiol **(8a-d)**, 5[(3-mercapto-5-substituted phenyl-4*H*-1,2,4-triazol-4-yl)methyl] 1,3,4–oxadiazole-2-thiol **(9a-d)**, 4-{(5-mercapto-4-(4-substituted phenyl)-4*H*-1,2,4-triazol-3-yl]methyl} -5-substituted phenyl-4*H*-1,2,4-triazole-3-thiols **($10a_1$-a_2-$10d_1$-d_2)**, 2-(3-mercapto-5-substituted phenyl)-4*H*-1,2,4-triazol-4-yl)-N^1-[(1*E*)-substituted phenyl methylene) acetohydrazides (Schiff's bases) **($11a_1$-a_6-$11d_1$-d_6)**, 2-(3-mercapto-5-substituted phenyl-4*H*-1,2,4-triazol-4-yl)-N-(4-oxo-2-substitutedphenyl 1,3-thiazolidin-3-yl) acetamides **($12a_1$-a_3-$12d_1$-$12d_3$)** were synthesized. All these synthesized compounds are characterized by IR, ^{1}H-NMR, ^{13}C-NMR, Mass spectral analysis. In the present work, the test compounds **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12c_3$** are evaluated for Anxiolytic activity by Hole board test, Staircase test. All the test compounds are showed non-significant anxiolytic effect expect **8d, $11a_1$, $11b_2$, $11c_3$** which showed moderate activity when compared to standard.

KEYWORDS: 1,3,4-thiadiazole, 1,3,4-oxadiazole, 1,2,4-triazole, 4-thiazolidinone, Schiff's bases, Anxiolytic.

INTRODUCTION

Anxiety disorders are among the most common mental, emotional and behavioral problems affecting one-eighth of the total population worldwide, and have become a very important area of research interest in psychopharmacology. It is increasingly recognized as a highly

prevalent and chronic disorder with onset during the teenage years, with an incidence of 18.1% and a life time prevalence of 28.8%. The disorder is associated with significant disability (including educational and occupational) which has a negative impact on the quality of life. Anxiety represents a heterogenous group of disorders, probably with no single unifying etiology; various psychodynamic, psychoanalytic, behavioral, cognitive, genetic and biological theories have been proposed to explain the etiology of anxiety disorders.[1,2,3] Because of the side effects associated with current drugs, we are in search of newer drugs with better activity with less side effects.

MATERIALS AND METHODS

Melting Points were determined in an open capillary tube and are uncorrected. IR Spectra (KBr) were recorded on a Perkin Elmer FT-IR Spectrophotometer and ^{1}H-NMR and ^{13}C-NMR Spectra in $CDCl_3$/DMSO-d6 at 300MHz on Bruker Ultrashield NMR spectrophotometer using TMS as an internal standard (Chemical shift in δ ppm). The mass spectra were recorded on a JOEL-Accu TOF JMS –T100LC Mass Spectrometer. The homogeneity of the compounds was determined by TLC. Hole board apparatus (CSI-HB), Mouse stair case model – 80301 were used for the evaluation of anxiolytic activity.

Animals

Albino Wistar rats (200-250g) and Albino Mice (25-30g) of either sex were used for the experiments. They were administered with standard diet. The experiments were carried out according to guidelines of CPCSEA and IAEC.

All the results were statiscally analyzed by ANOVA followed by Newman Keul's multiple range test and expressed as Mean ± SEM.

Hole-board test

Hole-board test is a generally used method for screening the potential anxiolytic character of drugs. The hole-board is made up of wooden ply material and had size of 41×41 cm with 16 holes of 3cm diameter each, distributed evenly on the floor. The board is elevated at the height of 35cm so that the mouse poking its nose into the hole does not see the bottom. Thirty minutes after i.p. administration of test drug (20mg/kg) or standard (Diazepam, 4 mg / kg), the mouse is placed on the hole-board and the number of nose pokings are counted for the period of 5min. The number of counts for nose poking of treated animals are recorded and compared with that of control group[3-5,8] and the results are tabulated.

Table 1: Anxiolytic activity of *s*-triazole derivatives Holeboard Test in mice.

Treated group	Dose mg/kg	No. of nose poking in 5 min (Mean±SEM)	% decrease in nose pose
Control	10ml/kg	30.13 ± 3.132^{ns}	-
Diazepam	3	15.95 ± 2.011**	47.06
8a	20	27.36 ± 0.726^{ns}	10.12
8b	20	28.12 ± 1.263^{ns}	06.67
8c	20	27.01 ± 0.926^{ns}	10.35
8d	20	22.16 ± 0.327*	26.45
9a	20	28.15 ± 0.003^{ns}	06.57
9b	20	29.00 ± 0.721^{ns}	03.75
9c	20	27.97 ± 0.132^{ns}	07.16
$10a_1$	20	26.92 ± 0.175^{ns}	10.65
$10b_1$	20	28.56 ± 0.731^{ns}	05.21
$10c_2$	20	26.98 ± 0.631^{ns}	10.45
$11a_1$	20	21.07 ± 0.221*	30.07
$11b_2$	20	23.06 ± 1.729*	23.46
$11c_3$	20	23.79 ± 0.771*	21.04
$12a_1$	20	25.98 ± 0.231^{ns}	13.77
$12b_2$	20	26.52 ± 0.718^{ns}	11.98
$12c_3$	20	28.14 ± 0.237^{ns}	06.60

*Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns = Non significant compared with the respective control*

Staircase method

Stair case is made up of wooden ply material and composed of five identical steps of 2.5cm high, 10cm wide and 7.5cm depth. The internal height of the walls is constant along whole length of the staircase. The mice are placed on the floor of the box with its back to the staircase. The number of steps climbed and the number of rears are counted over a period of 5min. After each test, the box is cleaned in order to eliminate any olfactory cues which might modify the behavior of the next animal, the average number of steps and rearing of the control group are recorded. A step is considered to be climbed only if the mouse had placed all four paws on the step. The values for treated animals (Std-Diazepam, 4mg/kg and test drug, 20mg/kg) are compared to those of the control group[3-5,6,7] and the results were tabulated.

Table 2: Anxiolytic activity of *s*-triazole derivatives by Staircase method in mice.

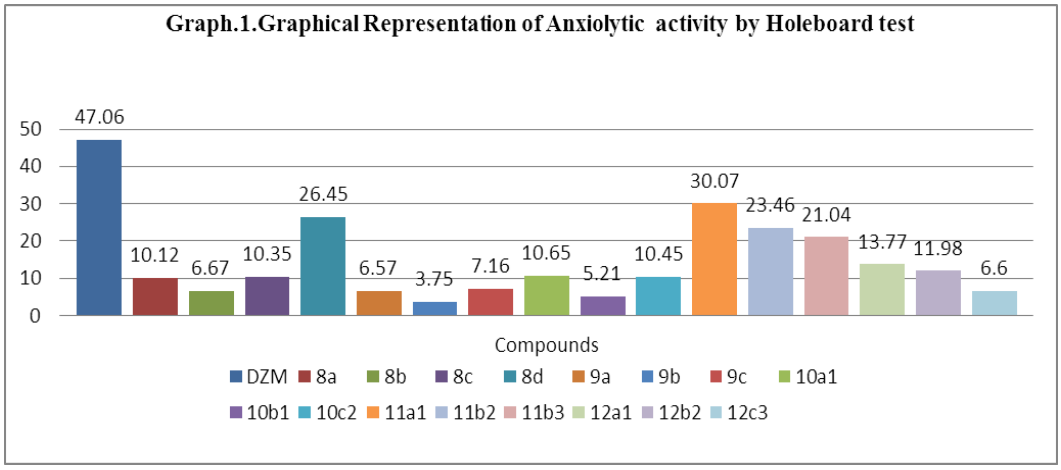
Treated group	Dose mg/kg	No. of steps climbed in 5min (Mean±SEM)	No. of rearing in 5min (Mean±SEM)	% Decrease in rearing
Control	10ml/kg	25.76 ± 1.320	23.62 ± 1.091^{ns}	-
Diazepam	2	36.26 ± 0.920	14.12 ± 1.152**	40.22
8a	20	26.45 ± 0.728	21.26 ± 0.327^{ns}	09.99
8b	20	27.32 ± 0.125	22.81 ± 0.325^{ns}	03.42
8c	20	24.12 ± 0.326	20.97 ± 0.472^{ns}	11.21
8d	20	27.12 ± 0.727	18.08 ± 0.321*	23.43
9a	20	23.32 ± 0.126	20.78 ± 0.126^{ns}	12.02
9b	20	20.45 ± 0.267	20.18 ± 0.276^{ns}	14.56
9c	20	24.26 ± 0.712	21.71 ± 0.912^{ns}	08.08
$10a_1$	20	21.82 ± 0.615	20.99 ± 0.213^{ns}	11.13
$10b_1$	20	20.14 ± 0.222	19.91 ± 0.137^{ns}	15.70
$10c_2$	20	22.46 ± 0.121	20.12 ± 0.243^{ns}	17.39
$11a_1$	20	28.54 ± 0.279	17.01 ± 0.721*	27.98
$11b_2$	20	27.47 ± 0.172	18.52 ± 0.173*	21.63
$11c_3$	20	29.13 ± 0.542	17.85 ± 0. 712*	24.42
$12a_1$	20	26.14 ± 0.312	21.01 ± 0.781^{ns}	11.05
$12b_2$	20	27.14 ± 0.124	20.75 ± 0.561^{ns}	12.15
$12c_3$	20	24.15 ± 0.745	21.56 ± 0.124^{ns}	08.72

*Results are expressed in Mean ± SEM (n=6); Significance levels **P<0.01, *P<0.05, ns= Non significant compared with the respective control.*

RESULTS AND DISCUSSION

Hole Board Test

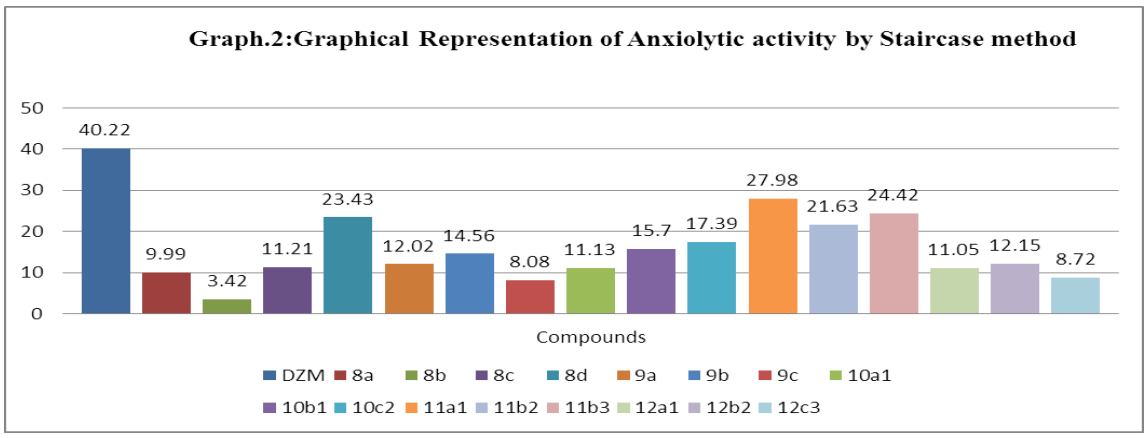
In vehicle treated control, the mean number of nose poking by mice was 30.13. Diazepam (3mg/kg) as a reference standard showed decrease in number of nose poking by 47.06%. Injection of test compounds **8a-d, 9a-c, $10a_1$, $10b_1$, $10c_2$, $11a_1$, $11b_2$, $11c_3$, $12a_1$, $12b_2$, $12c_3$** at 20mg/kg showed not significantly decrease in nose poking except the compounds **8d, $11a_1$, $11b_2$, $11c_3$** whereas other test compounds at a dose of 20mg/kg did not affect the counts of nose poking indicating absence of anxiolytic activity. The graphical representation is given below.



X axis = Compounds, Y axis =% Activity

Staircase model

In the vehicle treated control group, number of steps climbed and rearing was 25.76 and 23.62 respectively. Diazepam (2mg/kg) as a reference standard showed significant increase in number of steps climbed by 60.54% and decrease in rearing by 40%. Test compounds **8a-d, 9a-c, 10a$_1$, 10b$_1$, 10c$_2$, 11a$_1$, 11b$_2$, 11c$_3$, 12a$_1$, 12b$_2$, 12c$_3$** screened for anxiolytic activity at the dose of 20mg/kg did not show any significant effect on anxiolytic activity expect the **8d, 11a$_1$, 11b$_2$, 11c$_3$** showed slight decrease in number of rearing indicates the presence of mild anxiolytic activity when compared to diazepam. The graphical representation is given below.



X axis = Compounds, Y axis =% Activity

CONCLUSION

All the *s*-triazole derivatives bearing imino and five membered heterocyclic moieties were evaluated for anxiolytic activity. These compounds were proved to have poor anxiolytic activity. From this study we conclude that further optimization and structural modification

might lead to the discovery of more potent anxiolytic agents. Hence a detailed study on these derivatives may be quite desirable.

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