ANTI-CATATONIC ACTIVITY OF SOME NOVEL SERIES OF N-SUBSTITUTED-6-METHYL-N-5-SUBSTITUTED, 1, 5-DIHYDRO-4H-PYRAZALO (3, 4-d)-PYRIMIDINE-4(5H)-ONE

Vamshi Krishna V [1]., Pavan Kumar K [2]., Mukkanti K., [3]

[1] Department of Quality Assurance, B.Block, Jeedimetla, Hetero Drugs Limited-Unit-III, Hyderabad-500055, Andhra Pradesh, India.

[2]Department of Pharmaceutical chemistry, Department of Pharmacology, Sultan-ul-uloom College of Pharmacy, Banjarahills, Hyderabad-500034, Andhra Pradesh, India.

[3] Centre for Environment Institute of Science and Technology, JNT University, Hyderabad-5000072, Andhra Pradesh, India.

Summary

Neurodegenerative disorders include Parkinsonism, Alzheimer's disease, dementia and brain trauma. In this disease has an overall prevalence of about 1/1000 of the general population but it more common in the elderly, the prevalence rising to 1% of those over 60 years. The cause of the disease is unknown but genetic factors are not important in typical cases, and there is no good evidence for a viral mechanism. The discovery that methyl-phenyl-tetra hydro pyridine(MPTP) caused severe Parkinsonism in drug addicts has provoked the theory that the idiopathic disease may be due to an environmental toxin .There some evidence to suggest that Parkinsonism is more common in country areas sprayed with herbicides: paraquat which have chemical similarity to MPTP. The pathology of Parkinsonism includes of pigmented neurons in substantia nigra, hyaline material in nigral cells, atrophic changes in substantia nigra. Oxidative stress is also one of the reason for neurodegeneration. According to literature survey some of the pyrazolopyrimidine derivatives showed significant activity as A_{2A} antagonists. A novel series of pyrazolopyrimidine derivatives are screened for anti-catatonic activity. Since both pyrazole and pyrimidines have analgesic, anti-inflammatory, CNS depressant and anti catatonic activity. The title compounds may be therapeutically more potent agents.

Key words: Neurodegenerative, Parkinsonism, anti-catatonic, pyrazolopyrimidine.

Introduction

Pyrazoles represent one of the most active classes of compounds possessing a wide spectrum of biological activities (1). Many of the therapeutically useful compounds such as phenylbutazone, oxyphenbutazone, antipyrine, and aminopyrine are having analgesic and muscles relaxant action (2).Pyrazalopyrimidines possess a wide variety of pharmacological activities like CNS depressant activity, Anti-inflammatory activity(3),Ca^{++} blocking activity(4),anti-arrhytmic activity(5), Antiallergic ,antileishmanial activity(6),selective inhibitors of Cyclic guanosine (3,5-monophosphate diesterase(GMP, PDE) in treatment of various CVS disorders such as angina,hypertension,heartfailure,atherosclerosis (7),orally active corticotrophin releasing factor antagonists(8),A_{2A} Adenosine antagonists(9), A_{2A} Adenosine receptor antagonists(10), Anti-tumour activity(11), treatment of herpes viral infection(12).A_{2A} Adenosine receptor inactivation in a model of Parkinson's disease(13).The present study is to evaluate anticatatonic activity of novel series of some substituted pyrazolopyrimidines.

Materials and Methods

Anti-Catatonic Activity

Requirements

Wistor Albino rats of either sex were obtained from sainath agencies, authorized agency Hyderabad. The animals were housed in polypropylene cages at 24±2^{o}C and fed with commercial pellet diet and water ad litium.All animal experiments were carried out in accordance with guidelines of CPCSEA and the study was approved by the Institutional Animal Ethical committee.

Drugs:

Chlorpromazine: - (Dose: 3 mg / kg ip: prepare a stock solution containing 1mg /ml of the drug and inject according to body weight of the animal).

Atropine :-(Dose 2mg/kg ip: Prepare a stock solution containing 0.4mg/ml of the drug and inject according to body weight of the animal).

Test solution: - All the test compounds were administered orally by suspending in 2% w/v acacia suspension separately. The dose selected was 200 mg/kg body weight.

Equipment: -Two wooden blocks, One being 3 cm high and the other 9 cm high.

Experimental Procedure

Albino Rats of either sex weighing between 120-200 gm were procured from the central animal house of the institution. The experimental protocols were duly approved by the Institutional Animal Ethics Committee. Rats of either sex were randomly distributed into ten groups of six animals each. Group I was injected with chlorpromazine (3mg/kg i.p) which served as control. Group II received atropine (2mg/kg i.p) which served as standard. Rests of the VIII groups were administered with the compounds under study at dose of 200 mg / kg, orally.

After 30 mins of administration of standard drug and test compounds all the animals were administered with chlorpromazine (3 mg /kg i.p) and the catatonic activity was observed as follows.

Stage I: Rat moves normally when placed on the table, score = 0.

Stage II: Rat moves only when touched or pushed, score= 0.5.

Stage III: Rat placed on the table with front paws set alternatively on a 3cm high block fails to correct the posture in 10 seconds, score= 0.5 for each paw with a total of 1 for this stage.

Stage IV: Rat fails to remove when the front paws are placed alternatively on a 9cm block, score = 1 for each paw with a total score of 2 for this stage.

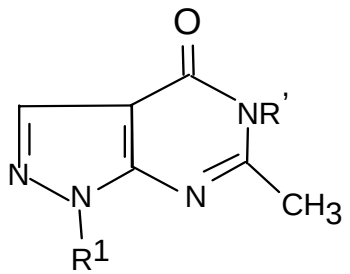
Thus for a single rat, the maximum possible score should be 3.5 revealing total catatonia. The severity of catatonia was observed at 5, 15, 30, 45, 60, 90 and 120 min after chlorpromazine treatment. The anti-catatonic activity exhibited by the test compounds were compared with the control and standard group in order to know the potency of the test compounds(14,15,16,17,18,19).The Structures of synthesized compounds were represented in Table-1.All readings are expressed as mean ± standard deviation and standard error of means Table 2.

Statistical Analysis

For the comparison of various treatment groups in each group of animals, the data was analyzed using one way analysis of variance (ANOVA), followed by Dunant's multiple comparison. P-value of <0.05 was considered statistically significant.

TABLE-1

STRUCTURES OF SYNTHESIZED COMPOUNDS



N' - Substituted 6 - Methyl -N 5 Substituted
- 1, 5 - dihydro - 4H- pyrazolo (3,4-d) pyrimidin - 4 - One -

S.No	Code	R	R'	Molecular Formula
1	IV-a	Phenyl	Phenyl	$C_{18}H_{14}N_4O_1$
2	IV-b	Phenyl	Ethoxy	$C_{14}H_{14}N_4O_2$
3	IV-c	Phenyl	Chloro phenyl	$C_{18}H_{13}N_4OCl$
4	IV-d	Phenyl	Chloro phenyl	$C_{18}H_{13}N_4OCl$
5	IV-e	H	Phenyl	$C_{12}H_{10}N_4O$
6	IV-f	H	Ethoxy	$C_8H_{10}N_4O_2$
7	IV-g	H	Chloro phenyl	$C_{12}H_9N_4OCl$
8	IV-h	H	Chloro phenyl	$C_{12}H_9N_4OCl$

Results and Conclusions

A novel series of pyrazolopryimidines synthesized as per the procedure described (20). The anti-catatonic activity of test compounds were studied and found that 200m/kg dose has protected the animals form catatonia. In control group 4 of the 6 animals observed severe catatonia at 30 mins intervals and after 45 mins in all the 6 animals severe catatonia is observed. Where as in test group only 1 or 2 animals observed severe catatonia at 120 mins interval and others shown anti -catatonic activity. All the test compounds (IV a-h) showed significant anti-catatonic activity. Among them compounds IVc, IVd, IVg and IVh are more active than remaining ones. In general it is clear from the results that an electronegative atom at position 4 as in the case of compound IV c & IV g and at position 2 & 4. In the case of IV d & IV h has favorable effect on anti-catatonic potency when compared with IV b and IV f which has no substituent at 2, 4 positions.

TABLE-2: ANTI-CATATONIC ACTIVITY OF SUBSTITUTED PYRAZOLOPYRIMIDINES

S.No	Treatment (mg/kg.b.wt) Route:i.p	Degree of catatonic response after min						
		5	15	30	45	60	90	120
1. Mean±SEM	Control(Chlorpromazine 3mg)	1.08 ±0.52	1.83 ±0.42	3.0 ±0.34	3.5 ±0.00	3.5 ±0.00	3.5 ±0.00	3.5 ±0.00
2. Mean±SEM	Standard (Atropine 2mg + Chlorpromazine 3mg)	0±0	0.33 ±0.10	0.33 ±0.10	0.33 ±0.10	0.42 ±0.08	0.67 ±0.28	1.0 ±0.41
3. Mean±SEM	Test (IV-a 200mg+ Chlorpromazine 3mg)	0± 0	0.08 ±0.08	0.17 ±0.10	0.25 ±0.11	0.5 ±0.22	0.75 ±0.25	1.08 ±0.37
4. Mean±SEM	Test (IV-b 200mg+ Chlorpromazine 3mg)	0±0	0.25 ±0.26	0.25 ±0.26	0.33 ±0.10	1.0 ±0.22	1.17 ±0.21	2.17 ±0.42
5. Mean±SEM	Test (IV-c 200mg+ Chlorpromazine 3mg)	0±0	0±0	0±0	0.17 ±0.10	0.33 ±0.10	0.05 ±0.22	0.83 ±0.40
6. Mean±SEM	Test (IV-d 200mg+ Chlorpromazine 3mg)	0±0	0.08 ±0.08	0.17 ±0.10	0.17 ±0.10	0.25 ±0.11	0.58 ±0.30	0.67 ±0.28
7. Mean±SEM	Test (IV-e 200mg+ Chlorpromazine 3mg)	0±0	0.17 ±0.10	0.25 ±0.11	0.5 ±0.22	1.0 ±0.34	1.67 ±0.17	2.17 ±0.42
8. Mean±SEM	Test (IV-f 200mg+ Chlorpromazine 3mg)	0±0	0.17 ±0.10	0.33 ±0.10	0.33 ±0.10	0.5 ±0.22	1.0 ±0.22	1.5 ±0.26
9. Mean±SEM	Test (IV-g 200mg+ Chlorpromazine 3mg)	0±0	0.08 ±0.08	0.17 ±0.10	0.5 ±0.00	0.67 ±0.17	1.17 ±0.21	1.33 ±0.17
10. Mean±SEM	Test (IV-h 200mg+ Chlorpromazine 3mg)	0±0	0.17 ±0.10	0.25 ± 0.11	0.5 ±0.13	0.42 ±0.15	0.92 ±0. 2	0.92 ±0.02

Note: p is less than 0.01 compared to control.Degrees of freedom (9, 60).

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