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STUDY ON SUBSTITUTED CHROMONES AS CENTRAL NERVOUS SYSTEM (CNS) AGENTS IN GROSS OBSERVATION

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Past century has been full of central nervous system (CNS) problems due to luxurious and fast life. Besides tackling these problems through counseling, treatment through drugs is need of time. Working on this line few substituted chromones were tested in gross observation for behavioral effects like spontaneous motor activity (SMA), respiration, ataxia, reactivity, writhing and effect on body temperature. Few of the tested compounds exhibited stimulating effect in gross visual observations.

KEYWORDS : Chromones, CNS agents, SMA, respiration, ataxia, writhing, reactivity, body temperature, gross observation.

INTRODUCTION

Chromones are benzopyran-4-ones. They constitute essential scaffold of flavones, flavonoids and xanthones [1]. Chromones have been found to be associated with various biological and medicinal activities like CNS [2-5], anti-inflammatory and anticomplementary [6-7], diuretic [8-9], coronary spasmolytic [10] and bronchodilator [11] and antiallergic [12] activities. Styrylchromone, homothamnione, has been found to show potent cytotoxic agent against P388 lymphocytic leukemia and HL-60 human promyelocytic cell line in *in vitro* testing [13]. Ethyl esters of chromone-3-carboxylic acids showed activity against *Pricularia oryzae* [14].

Studies in the field of behavioral science have revealed that CNS plays an important role in psychopathology. Mulhern *et al*. (1991) [15] did comparative study of neuropsychologic performance of children surviving leukemia who received 18-Gy and 24-Gy or no cranial irradiation. Mc Dermott *et al.* (2001) in a population based analysis of behavioral problems analyzed urinary tract infection during pregnancy may lead to mental retardation in children [16]. To cure such behavior based problems CNS active drugs may play a pivotal role. Few behavior based problems are visible in the form of effects on SMA, respiration, ataxia, reactivity, writhing and effect on body temperature. SMA deals with normal movement of the body. Respiration stands for effect on rate of respiration. Ataxia is loss of co-ordination of body muscles. Reactivity is reaction towards sound and touch. Writhing is twisting of

abdominal muscles. Generally muscles produce writhing. Effect on body temperature is either hypothermia *i.e.* fall in body temperature or hyperthermia *i.e*. rise in body temperature.

Table 1. CNS activity of Substituted chromones at 10 mg to 3 g/kg

S. No.	Name of compound	SMA	Resp.	writhing	Ataxia	React.	Body temp.
1.	3-Thiocyanatoacetyl-2,6-dimethylchromone	↓	↓	+	+	↓	↓ (0.7°C)
2.	6-Chloro-3-(2-chlorothiazol-4-yl)-2-methylchromone	↓	↓	---	---	↓	Nil
3.	6-Chloro-3-(2-morpholinyl thiazol-4-yl)-2-methylchromone	↓	↓	+	---	---	↓ (0.2°C)
4.	6-Chloro-3-(2-morpholinyl thiazol-4-yl)-2, 7-dimethylchromone	↑	↑	+	---	↑	↓ (0.4°C)
5.	6-(2-N-methyl aminothiazol-4-yl)-2,3-dimethylchromone	----	↑	---	---	↑	Nil
6.	6-(2-Aminothiazol-4-yl)-2,3-dimethylchromone	↑	---	+	---	---	↓ (0.4°C)
7.	6-(2-N-Ethyl aminothiazol-4-yl)-2,3-dimethylchromone	---	↑	---	---	↑	Nil
8.	3-(2-Aminothiazol-4-yl)-2,6-dimethylchromone	---	↑	---	---	↑	Nil
9.	6-Chloro-3-(2-aminothiazol-4-yl)-2-methylchromone	↓	↓ (5')	---	---	+	Nil
10.	6-Chloro-3-(2-aminothiazol-4-yl)-2,7-dimethylchromone	---	↑	---	---	↑	---
11.	3-(6-p-Chlorophenyl imidazo[2,1-b]thiazol-3-yl)-2-methylchromone	↓	---	---	---	↓	↓ (3°C)
12.	3-(6-p-Bromophenyl imidazo[2,1-b]thiazol-3-yl)-2-methylchromone	↑	---	+	---	↑	↓ (0.2°C)
13.	3-(6-Phenyl imidazo[2,1-b]thiazol-3-yl)-2-methylchromone	↑	---	+	---	↑	↓ (0.2°C)
14.	6-Chloro-3-(6-phenyl imidazo[2,1-b]thiazol-3-yl)-2-methylchromone	↑	---	+	---	↑	↓ (0.2°C)
15.	6-Chloro-3-(6-p-bromophenyl imidazo[2,1-b]thiazol-3-yl)-2-methylchromone	↑	---	---	---	↑	↓ (0.4°C)
16.	6-Chloro-3-(6-phenyl imidazo[2,1-b]thiazol-3-yl)-2,7-dimethylchromone	---	↑	---	---	↑	Nil
17.	6-Chloro-3-(6-p-bromophenyl imidazo[2,1-b]thiazol-3-yl)-2,7-dimethylchromone	---	↑	---	---	↑	Nil

18.	6-Chloro-3-(6-p-nitrophenyl imidazo[2,1-b]thiazol-3-yl)-2,7-dimethylchromone	---	↑	---	---	↑	Nil
19.	Ethyl(E)-3-[[4-(6-chloro-2-methyl-4-oxo-4H-1-benzopyran-3-yl)-2-thiazolyl]amino]crotonate	↑	---	+	---	↑	↓ (0.6°C)
20.	3-(7-Methyl-5H-thiazolo[3,2-a]pyrimidin-5-one-3-yl)-2-methylchromone	↑	---	---	---	↑	↓ (0.4°C)
21.	6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2-methylchromone	---	↑	---	---	↑	Nil
22.	6-Chloro-3-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2-methylchromone	↓	---	+	---	↑	↓ (0.3°C)
23.	6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2,7-dimethylchromone	↓	---	+	---	↓	↓ (0.2°C)
24.	6-Chloro-3-[2-(3,4,5-trimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2,7-dimethylchromone	↓	---	+	---	↓	↓ (0.6°C)
25.	3-[2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2,6-dimethylchromone	↑	---	---	---	↑	↓ (0.1°C)
26.	3-(2-Benzothiazolyl)-6-methylchromone	↑	---	+	---	↑	↓ (0.8°C)
27.	3-(2-Benzimidazolyl)chromone	---	↑	---	---	↑	Nil
28.	6-Chloro-3-(2H-1,4-benzothiazin-3-yl)-2-methylchromone	---	↑	---	---	↑	Nil

SMA = Spontaneous Motor Activity

↑ = Increase

↓ = Decrease

--- = Not done

\+ = Positive

In quest to find effective and safe drug to cope up above mentioned effects few of which are controlled by CNS, effect of some heterocycally substituted chromones was observed on mice in gross observation results of which are being presented in this publication.

MATERIAL AND METHODS

Compounds were synthesized by one of the authors (VPS) and are already published [8-9, 17-23]. Few of the synthesized compounds were tested for behavioral changes in gross observation on mice for different body reactions which have been mentioned above. Observations were made in following manner:

1. SMA: Normal movement of mice was observed by naked eyes.
2. Respiration: Effect on rate of respiration was recorded through visual observation.
3. Ataxia: Loss of co-ordination of body muscles was also recorded through visual observation.
4. Reactivity: Normal activity of mice towards sound and touch too was observed visually.
5. Writhing: Twisting of abdominal muscles was also observed visually.
6. Effect on body temperature: Immediately after drug administration, the anal temperature was recorded through thermometer for rise or fall with respect to control group.

Results of above observations are being reported in Table-1. Approximate lethal dose for 50% mortality (ALD_{50}) were determined also in mice according to Horn technique [24]. ALD_{50} of most of the compounds was in safe range. In addition to mentioned observations compounds were also screened for analgesic and anoroxgenic activities.

Results and discussion

Compounds (1), (2), (3), (9), (11), (22), (23), (24) showed decrease in SMA. But, compounds (4), (6), (12), (13), (14), (15), (19), (20), (25), (26) increased SMA. It is clear that compounds containing Cl substitution in most of the cases decreased SMA which is contrary to the fact that Cl substituent increases activity [25]. On the other hand, SMA has been increased by the compounds with greater number of methyl substituents, Br containing compounds and imidazothiazolyl system attached to C3-position of chromones. Thiazolo [3, 2-a] pyrimidone system at C3-position of chromone[compound (20)] also increased SMA. It is clear greater number of substituted chromones increased SMA Stimulation of CNS may be responsible for increase in SMA. Thus substituted chromones act on CNS.

Compounds (1), (2), (3), (9) showed decrease in rate of respiration; whereas compounds (4), (5), (7), (8), (10), (16), (17), (18), (21), (27) and (28) increased rate of respiration. Increase in rate of respiration may have been due to stimulating effect of chromone ring present in them.

By compounds (1), (3), (4), (6), (12), (13), (14), (19), (22), (23), (24) and (26) writhing has found positive. This twisting of abdominal muscles might have been due to stimulus caused by CNS which may have been activated by these compounds.

Compound (1) was only compound to cause ataxia *i.e.* loss of co-ordination of body muscles which indicates that it caused loss of balancing in rats. From this it is concluded that this compound is extremely toxic as also revealed by the fact that this compound has ALD_{50} equal to 383 [26]. Highly toxic thiocyanato group may have been responsible for this toxicity.

General body reaction *i.e.* reactivity decreased by the compounds (1), (2), (11), (23) and (24). Rest of the tested compounds increased reactivity, Hence, 3-heterocycally substituted chromones have stimulating effect on CNS in gross observation as body reaction can increase only due to stimulus.

Effect on body temperature has been hypothermic by the tested compounds as decrease in body temperature ranged from 0.2 to 3.0°C. This shows compounds are very mild antipyretic. Only compound (1), (3), (4), (6), (11), (12), (13), (14), (15), (19), (20), (22), (23), (24), (25) and (26) brought down the temperature. Out of all these compounds only compound (11) *i.e.*

3-(6-(p)-chlorophenyl imidazo [2, 1-b]thiazol-3-yl)-2-methylchromone is important that lowered the temperature by 3.0°C. Hypothermia indicates endothermic nature of compounds.

All the tested compounds were for analgesic and anoroxigenic activities. But none relieved pain and no one effected appetite.

CONCLUSION

From the results and discussion it may be concluded that 3-heterocycally substituted chromones are generally CNS stimulating in gross observation and they are hypothermic, non-analgesic and non-anoroxigenic too.

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