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Effect of novel phenothiazine derivatives on brain dopamine in Wistar rats

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Abstract

Background: Neurotransmitters are involved in several functions in the brain and the body of living things. Changes in the level of neurotransmitters in the brain are associated with several illnesses. Some of the drugs are controlling the neurotransmitter by adjusting the level in the brain and are exclusively used in the treatment of psychological disorders. The purpose of the study was to find out the effect of novel synthesised phenothiazine derivatives (GC1, GC2 and GC8) either alone (7.5 mg/kg or 15 mg/kg, oral) or in combination with amphetamine on the experimental animals.

Results: Dopamine level in rat brain was estimated by a spectroscopic method using the UV-visible double beam spectrophotometer at 735 nm. The results revealed that these derivatives blocked the brain dopamine level significantly. The compound GC8 (15 mg/kg) significantly reduced the level of dopamine (0.151 ± 0.04, 0.284 ± 0.03) as similar to that of a standard drug. Furthermore, compounds GC2 (15 mg/kg) and GC1 (15 mg/kg) exhibited a varying level of dopamine inhibition level and have been found at 0.203 ± 0.06 μg/ml, 0.302 ± 0.04 μg/ml, 0.234 ± 0.02 μg/ml and 0.318 ± 0.07 μg/ml, respectively, after the administration of these derivatives either alone or in combination with amphetamine.

Conclusions: The study revealed that the compound 2-amino-6-(3-hydroxy-4-methyl phenyl) pyrimidine-4-yl) (7-chloro-10-(3- (N, N-dimethylamino) propyl)-10H-phenothiazine-3-yl) methanone (GC8, 15 mg/kg) extensively reduced the dopamine level. The order of dopamine-inhibiting effect of the selected compound was found to be GC8 > GC2 > GC1. The increased body weight and relative brain-body weight were also observed in the tested animals due to more intake of food and fluid retention.

Keywords: Phenothiazine derivatives, Brain tissue, Homogenisation, UV spectrophotometer

1 Background

Neurotransmitters are endogenous chemicals that enable neurotransmission. These chemical substances are released from the neuron that carries the nerve impulse to other nerve cells in the nervous system. They allow the individual nerve fibres to communicate with each other [4] and involve a major role in shaping the everyday life of living things [34]. Changes in the level of neurotransmitters in the brain are linked to certain psychological illness, such as schizophrenia, psychomotor diseases, neurodegeneration, hallucinations and Parkinson's disease [36]. They are characterised by delusional thought processes, illogical thought patterns, muscle rigidity, tremors, lack of fine motor skill, etc., [27]. People with schizophrenia are at high risk of changes in the level of dopamine, serotonin, and other neurotransmitters [24]. It is a severe mental disorder that affects men with an age group of 16 to 30 years old than women [7]. Although many of the drugs are used to control dopamine, all of them are differing considerably in qualitative and quantitative with phenothiazine derivatives. Even though the parent molecule of phenothiazine has no uses, the derivatives of phenothiazine are employed in different pharmaceutical aids [14]. The research on phenothiazine found countless numbers of phenothiazine derivatives and increased their potency and specificity against different health hazards. A recent study stated that phenothiazine derivatives also exhibited

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promising activity such as antibacterial, antifungal [28], anticancer [26], antiviral [21], anti-inflammatory [29], anti-tubercular [33], anti-malarial [17], anti-diabetic [16], trypanocidal [30], anticonvulsant [2], analgesic [6], immunosuppressive [8], and multidrug resistance reversal properties [18]. In the present study, aforesaid benefits of phenothiazine heterocyclic nucleus promoted us to prepare some derivatives bearing with phenothiazine nucleus and evaluate the dopamine-inhibiting effect. These compounds were prepared by modifications of the existing phenothiazine by performing (1) a new substitute at nitrogen element in phenothiazine ring and (2) an introduction of a hetero-aromatic ring. A slight variation in the substitution pattern on the phenothiazine ring often causes distinguishable changes in the biological activities [25]. These derivatives controlled the brain dopamine and exclusively used in the treatment of the psychotic disorder [31]. The amount of dopamine present in the brain of the tested rat after repeated ingestion of these derivatives either alone or in combined with amphetamine was evaluated by using the UV-visible spectrophotometer. The report stated that the synthesised compounds were exhibiting significant blockage of dopamine in the tested animals. Furthermore, the study stated that there was a significant difference in body weight and relative brain-body weight was observed in the experimental animals during the study period.

2 Materials

2.1 Phenothiazine derivatives

Phenothiazine derivatives were synthesised according to the reported procedure [9], and selected synthesised compounds (GC1, GC2 and GC8) were employed for the determination of body weight, relative brain-body weight, behavioural assessment and brain dopamine level after repeated administration of synthesised compounds either alone or in combination with amphetamine (Table 1).

3 Methods

3.1 Experimental procedure

3.1.1 Animals

Wistar rats were procured from Sainath Agencies, Hyderabad, Andhra Pradesh, India. These animals were placed in the cages 5 days prior to the experiment and ascertained the health status. Animals were selected with an average weight of 180–225 g, grouped (nine), placed into different cages and kept under standard conditions with free access to food and water. Six experimental groups were allotted to find out the effect of the synthesised compounds and also used three more groups for amphetamine, chlorpromazine and control, respectively. Each group maintained with six animals. These animals were used for the determination of body weight, relative brain-body weight, behavioural assessment and brain dopamine level after repeated administration of synthesised compounds either alone or in combination with amphetamine [3, 22] (Table 2).

3.1.2 Body weight test

Experimental animals were accurately weighed on the first day of the experiment. Thereafter, each animal was administered with either standard or synthesised compounds. On the last day of the experiment, animals were weighed again and recorded [5].

3.1.3 Behavioural test

Male Wistar rats with an average weight of 180–225 g were used to predict the catalepsy of experimental animals by using metallic bar test. Chlorpromazine was administered (10 mg/kg, orally) to induce the catalepsy in the standard group of animals, whereas synthesised compounds (7.5 mg/kg or 15 mg/kg, oral) were given to the test group of animals. To identify the catalepsy of the experimental animals, front paws were placed on the metallic bar, which was elevated to 9 cm above the base of the cage. Animals were maintained in the abnormal posture more than 20 s called as catalepsy. The severity of the catalepsy was estimated by awarding the points. The response of each animal was measured for 4 h at every 1-h interval on the seventh day of the experiment after administering standard and synthesised compounds [12].

3.1.4 Relative brain-body weight ration

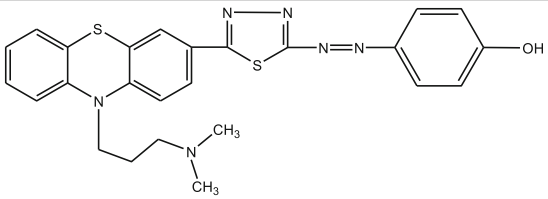
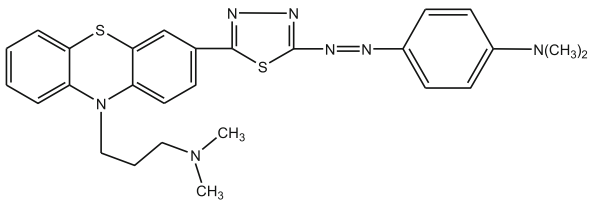
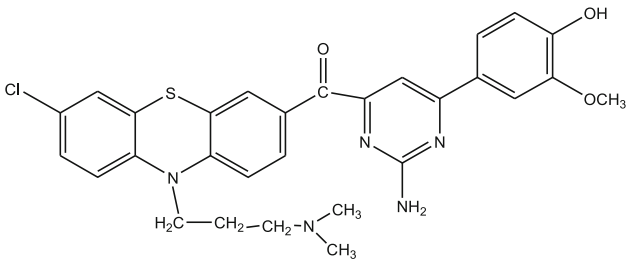
After the behavioural assessment, on the seventh day, animals were sacrificed with diethyl ether and the brains were separated, weighed and recorded. The relative brain-body weight ration of the experimental animals was calculated using the following formula [1].

$$\text{Relative brain body weight (RBW)} = \frac{\text{Absolute brain weight in grams}}{\text{Body weight of the animals on sacrified day in grams}}$$

3.1.5 Biochemical parameters

3.1.5.1 Condition 1 The aim of the first experiment was to identify the level of the dopamine in experimental animals after repeated administration of synthesised phenothiazine derivatives alone (7.5 mg/kg or 15 mg/kg, oral), twice daily at 9 AM and 5 PM for 1 week. The control and standard group of animals were administrated with 1% carboxymethyl cellulose (CMC) and chlorpromazine (10 mg/kg, oral route), respectively. The animals were sacrificed after

Table 1 Structure and name of the synthesised compounds

Compound name	Structure and name of the synthesised compounds
GC1	 (E)-4-((5-(10-(3-(*N,N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl phenol (E)-4-((5-(10-(3-(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl) diazenyl phenol
GC2	 (E)-4-((5-(10-(3-(*N,N*-Dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)-*N,N*-dimethylbenzenamine (E)-4-((5-(10-(3-(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3yl)-1,3,4-thiadiazole-2-yl)diazenyl)-*N,N*-dimethylbenzenamine
GC8	 2-Amino-6-(4-hydroxy-3-methoxyphenyl)pyrimidine-4-yl)(7-chloro-10-(3-(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) methanone. 2-Amino-6-(4-hydroxy-3-methoxyphenyl)pyrimidine-4-yl)(7-chloro-10-(3-(*N,N*-dimethylamino)propyl)-10*H*-phenothiazine-3-yl) methanone.

behavioural assessment and brains were collected and rinsed with 0.9% saline solution. The brain tissues were homogenised with phosphate buffer (pH -8) and centrifuged for 10 min at 2000 revolutions per minute (RPM). An aliquot supernatant clear solution was collected and stored at 5 °C.

3.1.5.2 Condition 2 The second experiment was to evaluate the induced level of dopamine by repeated administration of amphetamine (5 mg/kg, IP route) twice daily at 9 AM and 5 PM for one week. After the last dose, animals were sacrificed with ether; the brain

Table 2 Status of the animal's health prior to the treatment

Treatments (group)	Body weight of the Wistar rats	Microbial status	Drug effect
GC1 7.5 mg	184.2 ± 0.05*	Nil	Nil
GC1 15 mg	195.7 ± 0.07**	Nil	Nil
GC2 7.5 mg	220.4 ± 0.06**	Nil	Nil
GC2 15 mg	209.1 ± 0.08**	Nil	Nil
GC8 7.5 mg	210.3 ± 0.15*	Nil	Nil
GC8 15 mg	222.6 ± 0.10*	Nil	Nil
Control	205.1 ± 0.09*	Nil	Nil
Standard (chlorpromazine)	207.3 ± 0.11**	Nil	Nil
Amphetamine	211.6 ± 0.15**	Nil	Nil

**$P < 0.05$, *$P < 0.01$ as compared to standard and control respectively. Statistical analysis-One way ANOVA

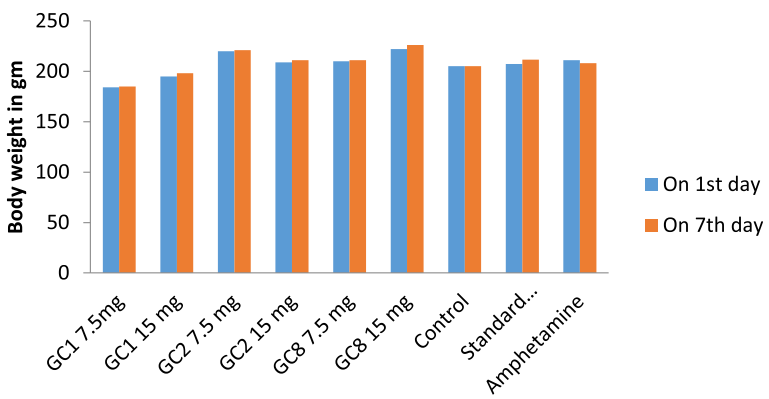


Fig. 1 Body weight of Wistar rats on the first and seventh day of the experiment

tissues were collected and rinsed with 0.9% saline solution. The brain tissues were homogenised with phosphate buffer (pH -8) and centrifuged for 10 min at 2000 RPM. An aliquot supernatant clear solution was collected and stored at 5 °C. Control rats were treated with 1% CMC suspension.

3.1.5.3 Condition 3 The purpose of the third experiments was to calculate the level of dopamine in the combined effect of synthesised phenothiazine derivatives and amphetamine (5 mg/kg), twice daily at 9 AM and 5 PM for. The test group of animals was treated with synthesised compounds (15 mg/kg, oral), whereas chlorpromazine was (10 mg/kg, oral) administered to the standard group of animals. Amphetamine was administered 30 min prior to synthesise compounds/ chlorpromazine. After the last dose, animals were sacrificed with ether; the brain tissues were collected and rinsed with 0.9% saline solution. The brain tissues were homogenised with phosphate buffer (pH 8) and centrifuged for 10 min at 2000 RPM. An aliquot supernatant clear solution was collected and stored at 5 °C. Control rats were treated with 1% CMC suspension.

3.1.6 Procedure for estimation of brain dopamine

The level of dopamine in rat brain after repeated administration of the synthesised compounds either alone or in combined with amphetamine was evaluated by UV-visible spectrophotometer [10]. The dopamine level in rat brain was estimated by admixing of homogenised supernatant liquid (1 ml) with 1 ml of ferric chloride (1.5×10^{-2} M) and 1 ml of potassium ferricyanide (1.5×10^{-2} M) in 25 ml distilled water. It was kept aside for 30 min and the developed colour was estimated using the UV-visible double beam spectrophotometer at 735 nm [23].

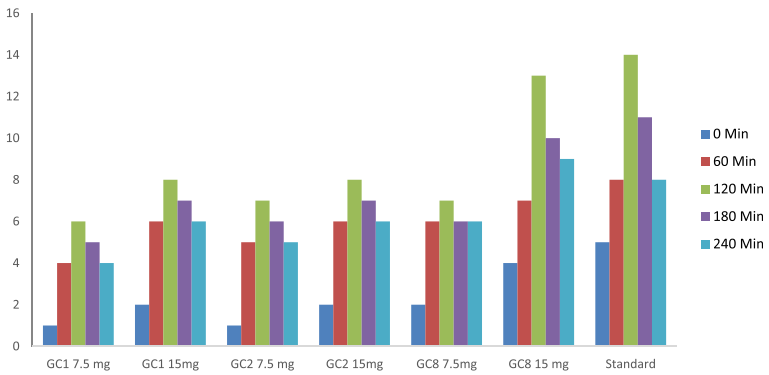


Fig. 2 Duration of catalepsy of Wistar rats on the seventh day of the experiment

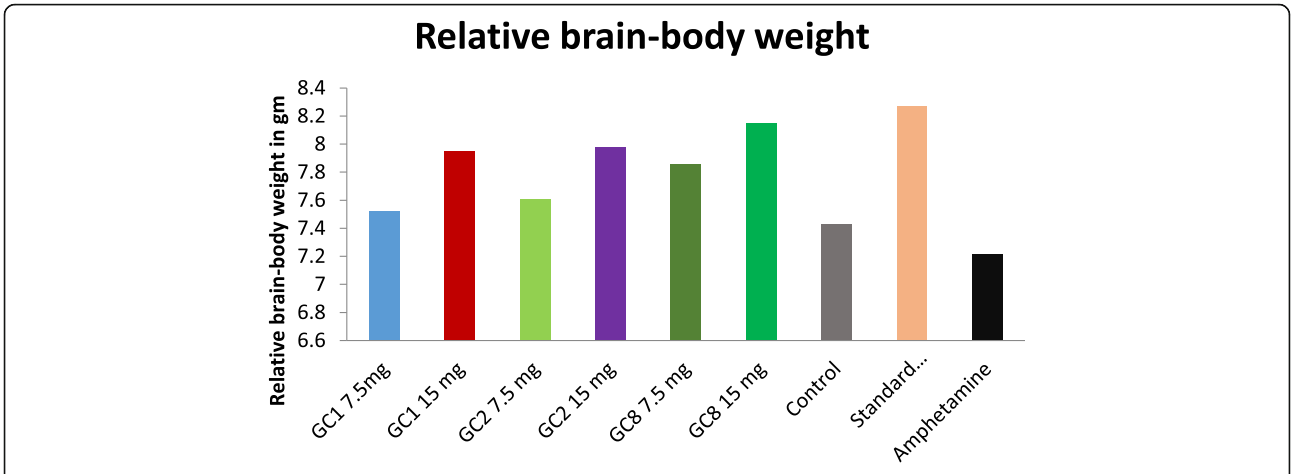


Fig. 3 Relative body weight of Wistar rats on the seventh day of the experiment

4 Results

4.1 Effect of synthesised compounds on body weight of Wistar rat

The body weight was increased in the tested animals when compared to the control group after the last dose of the standard and synthesised compounds. The increased body weight of the tested animals is due to more intake of food and fluid retention. The result of the body weight of the tested animals was summarised in Fig. 1.

4.2 Effect of synthesised compounds on behavioural assessment

The behaviour assessment of the experimental animals was observed for 4 h at the interval of 0, 60, 120, 180 and 240 min. The severity of the catalepsy increased gradually in the tested animals between 60 to 120 min. The highest catalepsy was obtained at 120 min after administration of the last dose of standard and test compounds. The result proved that our synthesised compounds controlled the dopaminergic neurotransmitter effectively and brought the behavioural changes in the experimental animals. Among the synthesised compounds, GC8 had shown excellent activity at various periods of behavioural assessment and the result was close to the standard drug. The result of the behaviour assessment of tested animals was summarised in Fig. 2.

4.3 Effect of synthesised compounds on relative brain-body weight

There is a significant relative brain-body weight was observed in the experimental animals after administering the dose of synthesised compounds and standard drug. The level of relative brain-body weight of experimental animals was compared to the control group. The result

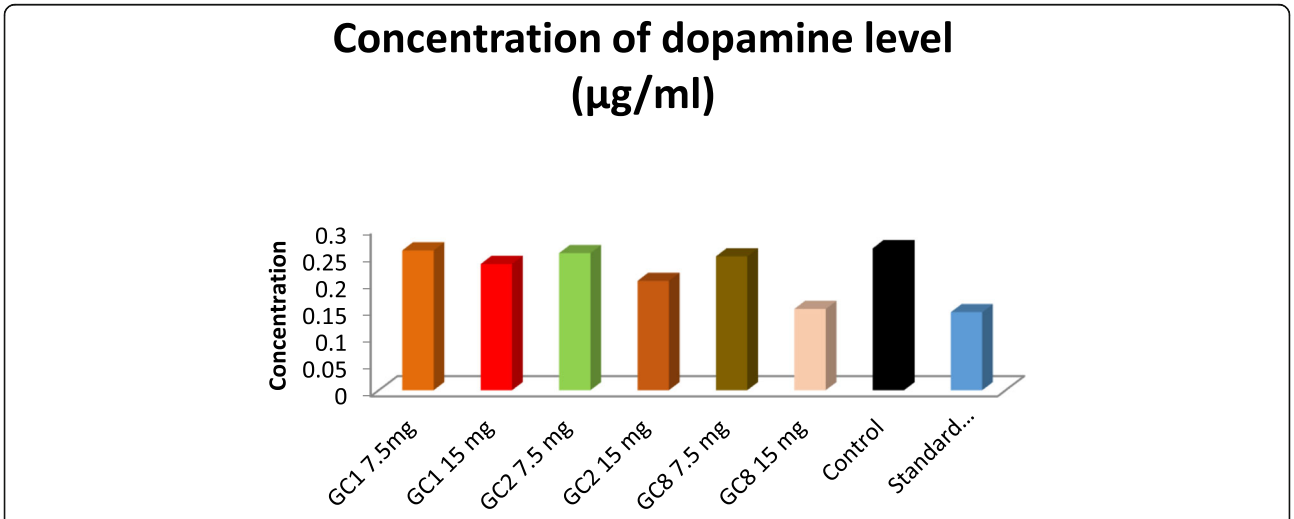


Fig. 4 The concentration level of dopamine in the separated brain after being administered with synthesised compounds/chlorpromazine/1% CMC suspension

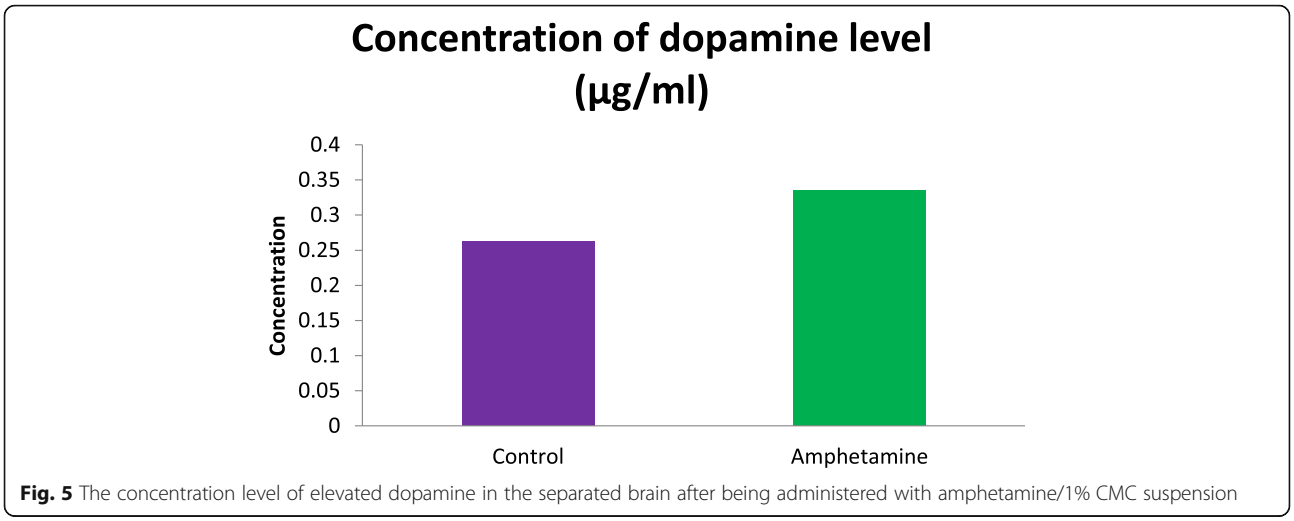


Fig. 5 The concentration level of elevated dopamine in the separated brain after being administered with amphetamine/1% CMC suspension

of the relative brain-body weight ratio of the tested animals was summarised in Fig. 3.

4.4 Biochemical parameters

4.4.1 Condition 1

The concentration of brain dopamine in a test animal has been decreased significantly by repeated administration of synthesised compounds. The experimental result indicated that some of the tested compounds blocked the dopaminergic neurotransmitter in the brain effectively and the activity was similar to that of the standard drug. The result of the dopamine-inhibiting effect of the test compound was summarised in Fig. 4.

4.4.2 Condition 2

The result indicated that repeated administration of amphetamine twice daily increased the brain dopamine level in experimental animals. The elevated level of brain dopamine had been compared against the control group and was depicted in Fig. 5.

4.4.3 Condition 3

Mixed effect of synthesised compound (15 mg/kg) and amphetamine (5 mg/kg) have been marked with the different level of dopamine in the brain tissue of experimental animals. The level of dopamine in the combined effect of synthesised phenothiazine derivatives and amphetamine has been compared with the standard drug

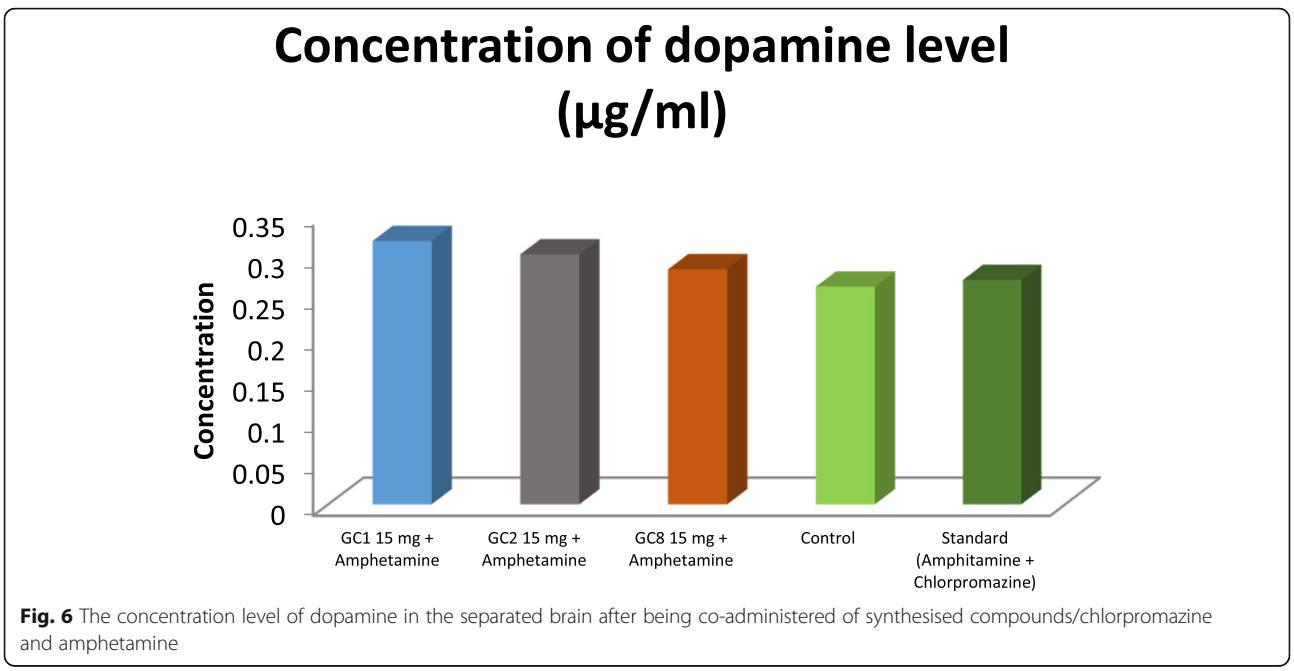
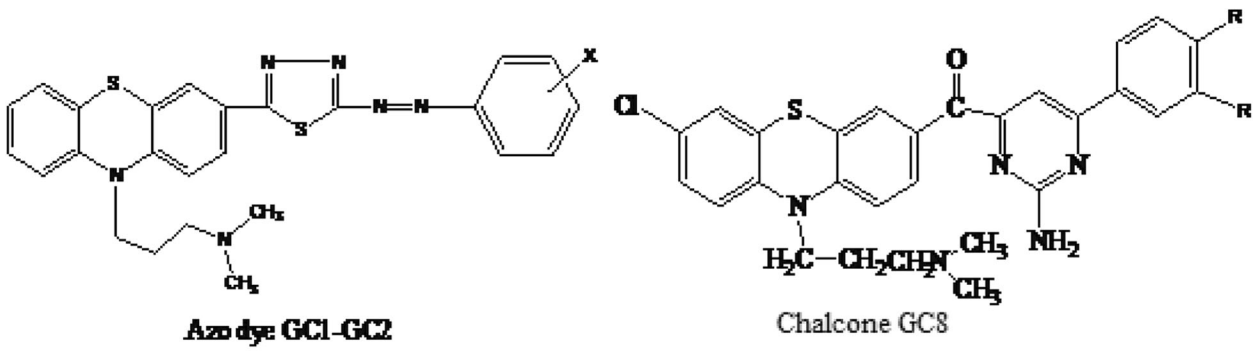


Fig. 6 The concentration level of dopamine in the separated brain after being co-administered of synthesised compounds/chlorpromazine and amphetamine



Compounds	Activity
GC8	Significant
GC2	Interesting
GC1	Least

Fig. 7 Structural activity relationship of synthesised compounds related to brain dopamine level

(chlorpromazine 10 mg/kg). The level of brain dopamine in test animals was summarised in Fig. 6.

4.5 Statistical analysis

The results obtained in the experiment were assessed by one-way ANOVA. The results of the test groups were compared to control and standard, respectively [11, 13, 15, 19, 20].

5 Discussion

A new series of novel phenothiazine derivatives were synthesised as a dopamine antagonist by performing the interacting between 5-(10-(3-(*N*,*N*-dimethylamino) propyl-10H-phenothiazine-3-yl)-1,3,4-thiadiazole-2-amine, sodium nitrite, Con. HCl and the different coupling reagents. The highly potent compounds were selected through molecular docking and were utilised to identify the level of the dopamine inhibition effect in the experimental animals after repeated administration either alone or in combination with amphetamine, twice daily at 9 AM and 5 PM for 1 week. The body weight, relative brain-body weight and behaviour assessment of the animals were also observed on the seventh day of the experiment. Later, each group of animals was sacrificed and their brains were utilised for the dopamine-inhibition study. The results revealed that these derivatives blocked the brain effectively and decreased the dopamine level significantly. The obtained result proved that the concentration level of dopamine in rat brain has been decreased by repeated administration of synthesised phenothiazine derivatives (7.5 mg/kg and 15 mg/kg) by blocking the dopaminergic receptor on the basis of the substituent present in the phenothiazine nucleus. Therefore, all the synthesised compounds exhibited a varying degree of anti-dopaminergic activity and are listed in Fig. 7. The induced level of dopamine was observed in the tested rats after repeated administration of amphetamine. The above results were observed in some other studies performed by scientists on phenothiazine derivatives which are involved in the mechanism of inhibiting the brain dopamine level in the tested animals after repeated administration. In fact, [32] observed that a clear system exists between the structure of the phenothiazine derivatives and the capacity to inhibit the dopamine level in the brain. Likewise, it has been proved that amphetamine induced effect on neuropeptide in the rat brain [35]. Compound GC8 (15 mg/kg) significantly reduced the level of dopamine as similar to that of chlorpromazine-treated animals. Furthermore, compound GC2 (15 mg/kg) and GC1 (15 mg/kg) exhibited a varying level of dopamine inhibition activity and have been found to be 0.203 ± 0.06 μg/ml and 0.234 ± 0.02 μg/ml, respectively. The levels of dopamine present in the synthesised compound-treated animals were summarised in Fig. 4. Amphetamine-treated animals were shown with an enhanced level of dopamine in rat brain which has been found to be 0.336 ± 0.03 μg/ml as mentioned in Fig. 5. The result showed that the mixed administration of

synthesised phenothiazine derivatives and amphetamine-treated animals maintained the different levels of dopamine in the brain which were found to be 0.318 ± 0.07 μg/ml, 0.302 ± 0.04 μg/ml, 0.284 ± 0.03 μg/ml and 0.263 ± 0.05 μg/ml, respectively. Mixed effect of synthesised phenothiazine derivatives and amphetamine on dopamine levels in testing animals were mentioned in Fig. 6. The order of dopamine-inhibiting effect of the selected synthesised compound was found to be GC8 > GC2 > GC1. Furthermore, these derivatives had changed the body weight, behaviour and relative brain-body weight of experimental animals and were summarised in Figs. 1, 2 and 3. There are no adverse effects that have been found in the experimental animals.

6 Conclusion

The present study proves that the synthesised phenothiazine derivatives are exhibiting an excellent activity against the brain dopamine in Wistar rats. The results revealed that these derivatives blocked the rat brain dopamine level significantly after repeated administration of either selected synthesised phenothiazine derivatives alone or in combination with amphetamine. The compound 2-amino-6-(3-hydroxy-4-methyl phenyl) pyrimidine-4-yl) (7-chloro-10-(3-(N,N-dimethylamino) propyl)-10H-phenothiazine-3-yl) methanone (GC8, 15 mg/kg) considerably reduces the level of dopamine in rat brain as similar to that of the standard drug.

Abbreviations

CMC: Carboxymethyl cellulose; IP: Intraperitoneal; RPM: Revolutions per minute

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Authors' contributions

CG synthesised the compounds from the respective raw materials and is involved in the estimation of brain dopamine in Wistar rats. VGS monitored the compound synthesis and interpreted the data obtained from the results. MDD has contributed the major work in writing the manuscript, alignment and the pharmacological part of the manuscript. All the authors read and approved the final manuscript.

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Availability of data and materials

All the data generated and analysed during the study are included in the main manuscript.

Ethics approval and consent to participate

The whole experimental protocol was approved by the institutional animal ethics committee at GIET School of Pharmacy, Rajahmundry, India (GSP/IEAC/2018/02/04).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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