

Neuroprotective effects of 2-(2-thienyl) benzothiazoline on gross motor skill deficits in rotenone induced rat model of Parkinson's disease

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Abstract: In elderly aged people, Parkinson's disease is reported as 2nd most prevailing neuro-degenerative disease. Presently benzothiazole derivatives are gaining attention after showing positive results in various animal models for the investigation of different motor-diseases. In Current work, the 2- (2 Thienyl)Benzothiazoline is synthesized and its therapeutic effect was evaluated against rotenone-induced Parkinson's disease. It was expected to obtain the positive results in the treatment because thiophen group has been successfully reported in various literature as effective agent in the treatment of cognitive and locomotory disease. So, we used a Parkinson's inducive compound rotenone and injected it intraperitoneally. The dose that we were used was 1.5mg/kg and treatment proceeded for 8 days in rats as rotenone inhibit the functioning of mitochondrial complex I. Administration of 2- (2 Thienyl)Benzothiazoline (10mg/kg per day) was already started 15 days prior to rotenone dose injection. The effects of both pre-treatment and without pre-treatment of 2- (2 Thienyl)Benzothiazoline were assessed by the use of various motor parameters of behavior such as pole test and Konziela's inverted screen test for checking muscular strength, whereas inclined plane test, open field test and Rota rod test for motor coordination. Pre-treatment with drug reversed the gross motor impairments which were produced by rotenone. We conclude that 2- (2 Thienyl)Benzothiazoline, like its other candidate drug also protects against destructive effects of the compound rotenone and it can be used as beneficial drug against various neurodegenerative diseases.

Keywords: Neurodegenerative disease, Parkinson disease, benzothiazole derivatives, rotenone, toxicity.

INTRODUCTION

Parkinson disease (PD) is one of the neurodegenerative diseases that comes after Alzheimer's disease. The clinical sign and symptoms involves tremor, rigidity and instability of postural muscles. It is also defined by bradykinesia and akinesia (Berganzo *et al.*, 2016; Wang T *et al.*, 2020). Parkinson disease (PD) is recognized by slow body movements, persistent shaking of resting limbs and loss of postural balance along with change in speech. The motor impairments associated with dopamine (DA), involves cognitive dysfunctions, neuro-psychiatric disorder, bradykinesia, continuous and excessive involuntary muscular movement and some non-motor symptoms such as gastrointestinal autonomic nervous problems, sleepwalking, reduced sleep and so on (Lin *et al.*, 2018). It is the 2nd most prevailing neuro-degenerative disease after Alzheimer disease. It has been reported that 2% of (Priyadarshi *et al.*, 2001) people above the age of 65 is suffering from this disease (Bose and Beal 2019). In 2015, PD affected 6.2 million people and resulted in 117400 deaths globally. Parkinson disease has become a communal-global disease having 7 to 10 million patients worldwide. It is approximated that 8.7 to 9.3 million patients of this disease will be domiciled in the top 10 most densely populated nation in the world by the year 2030 (Farombi *et al.*, 2019).

Pakistan estimated to be involve 450,000 persons suffering with the disease Genetic mutation and environment factors, combines with the effect of aging, Play a crucial part in the development of PD (Imtiaz *et al.*, 2016). The prevalence of genetically linked PD is ~10 to 15% of all PD's cases.

where as remaining is the classified as sporadic (idiopathic) (Ball *et al.*, 2019). 100-219 people daily fall prey to PD and 0.45-1 million Pakistanis suffer from PD according to the data from Agha Khan University, Karachi. There are genetic as well as many environmental factors for example, specifically those used in agriculture i.e. pesticides (Zeb *et al.*, 2016) playing their role in development of various neurogenerative diseases. Rotenone is one of widely used pesticide and has botanical origin and the source of this compound is roots of several plants that are used as an insecticide. Long term or chronic exposure to this drug droves to the signs of Parkinson disease (Peng *et al.*, 2017).

Rotenone is the major of the inactivation of the complex I that results in depletion of cells fuel (energy) & causes essential malfunctions in the normal mechanism of mitochondria thus causes human diseases related to mitochondria. Behavioral experiments showed catalepsy in dose dependent manner in the two treated groups of rats. Data indicates that in rats rotenone also start the degeneration of dopamine producing neurons and

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induction of Parkinson symptoms (Madiha *et al.*, 2018). Benzothiazole ring system chemical formula $C_7H_5N_2S$ that are involved in many influential bio-active drugs; such as many N-p-bromophenyl-N' (substituted) benzothiazole-N''-(n-butyl) guanidine components are used as anticonvulsant, relaxant for muscles, central nervous system (CNS) sedative, pain relieving & anti-inflammation (Gagoria *et al.*, 2015).

Newly synthesized benzothiazole derivative i.e., 2- (2 Thienyl)Benzothiazoline was used as therapeutic drug. 2- (2 Thienyl)Benzothiazoline was synthesized by adding the thiophen at the position 2 in the benzene ring that increased the therapeutic effects of benzothiazole group the therapeutic effects of the 2- (2 Thienyl) Benzothiazoline is expected to give the positive results in the treatment of Parkinson's disease because thiophen group has been reported to be extensively used in the treatment of cognitive disease such as Alzheimer and other various disease in which memory and locomotion is affected. Thiophen Group has been used in various animal models for different diseases and have shown positive results. So, when the therapeutic effects of thiophen and the benzothiazole groups are combined they will result in producing better effects against the cataleptic effects that are produce as a result of inducing of Parkinson's disease in rats.

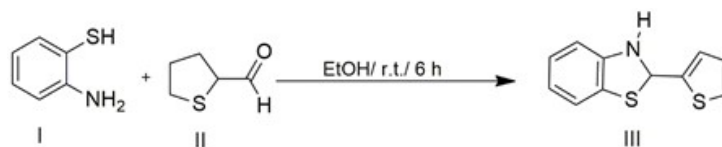
MATERIALS AND METHODS

Experimental model animals

Adult Sprague Dawley rats (9 weeks old, $200 \pm 30g$) were used as experimental animals (Shin *et al.*, 2017). Breeding pairs of Sprague Dawley rats were procured by Dr Imran from department of Pharmacy, Bahauddin Zakariya University Multan. Rats were retained in individual crates full with white wood chips. Rats were provided with regular rat regime and water *ad libitum*. Room-temperature was sustained at standard $22 \pm 1^\circ C$ (Michel *et al.*, 2017). Animal house was lightened with artificial-light at the time 8:00 a.m. to 6:00 p.m. The relative humidity was maintained at 40-60% (Guide for the Care and Use of Laboratory Animals. 8th edition). The University Research Ethics Committee (UREC) of The Women University, Multan granted the ethical approval under the letter no WUM/UREC/20-00016.

Synthesis and characterization of 2- (2-thienyl) benzothiazoline

2- (2-Thienyl)Benzothiazoline (III) was prepared by a



Scheme 1: Synthesis of 2- (2-thienyl)benzothiazoline

reported procedure (Capitan-Vallvey LF and Espinosa P 1983) condensation of the 2-aminobenzenethiol (I) (0.05 M) with thiophen 2-aldehyde (II) in a 1:1 molar ratio in pure ethanol (20mL). The mixture was undergone the process of reflux for 6 h and then it was allowed to cool and 20 ml distilled water was added gradually with continuous stirring. The mixture was allowed to stand for couple of hours to get yellow crystals which were finally washed with water-ethanol (1:1). Synthesis of target compound is given in scheme 1.

Synthesized compound was characterized by IR, NMR spectroscopic techniques. The IR spectrum of compound exhibited a band at $3274cm^{-1}$, assigned to N-H stretching Vibration and an intense band at $916cm^{-1}$ to the C-S-C linkage. Bands appearing at $1580cm^{-1}$ and $1544cm^{-1}$ can be made to the vibrations of the thiazoline ring. The NMR spectrum of compound shows that the NH proton signal that was as a broad signal at δ 4.5 ppm. The other protons appear as a complex multiplet at δ 7.32 ppm.

Experiment design

Rat-Pups were separated from their mother after dissuading and were housed individually. When they were 9-week-old, four groups were made from these adult female Sprague Dawley rats. Groups were named as Group 1: control that received (sunflower oil), Group 2: 2- (2 Thienyl) Benzothiazoline, Group 3: rotenone and Group 4: 2- (2 Thienyl)Benzothiazoline + Rotenone all groups have six-rats i.e. (n=6). Treatment was initiated by the injection of 2- (2 Thienyl)Benzothiazoline after dissolving in Dimethyl sulfoxide (DMSO) at the dose of 10 mg/kg to the 2- (2 Thienyl) Benzothiazoline (group 2) and 2- (2 Thienyl) Benzothiazoline + Rotenone group (group 4) (umide Demir ozkaya *et al.*, 2017). Remaining other groups were supplied with tap-water. After fifteen days' of 2- (2 Thienyl) Benzothiazoline administration, rotenone was injected intraperitoneally (i.p) to rotenone (group 3) and 2- (2 Thienyl) Benzothiazoline + Rotenone-groups (group 4). The dose of rotenone given to group 3 and 4 was 1.5mg/kg and it was completely dissolved in pure sunflower oil (Abdelkader *et al.*, 2017).

Behavioral analysis

Food intake & Weight of body were observed during the treatment of 2- (2 Thienyl) Benzothiazoline and rotenone administration. The compound Rotenone was injected for continuous eight days during which 2- (2 Thienyl) Benzothiazoline administration was also continued. After 8 days, rats were taken to test room to perform open-field

test, Rota-Rod and Pole-test to check their motor coordination as well as their balance. The muscular strength (after treating with rotenone) was determined by Kondziela's-inverted screen test and by inclined-plane test.

Pole test

Pole test gives the information about basal ganglia-related disorders that leads to movement difficulty in rodents. In fleeing, rats were placed at vertical wooden pole top (the dimensions of pole were: 2.5 cm was the diameter of pole and 100 cm was the height) and pole was located in their cage. The total time-period in which rat comes back to ground-floor was observed (Song et al., 2014).

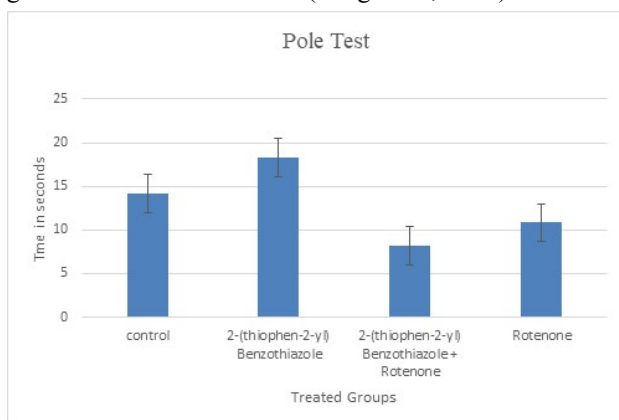


Fig. 1:Result of pole Test

Kondziela's inverted screen test

This test is being used for examination of power of muscles of animals while using their all four limbs. It is performed by simply taking the individual rat and placing in the center of screen. The Screen was kept inverted for total 120 seconds in which the rat's head was declining for first. The total time taken by rat to fall was monitored. (Kondziella et al., 1964).

Inclined plane test

The simple test was done in a way that rat was placed with care on any inclined surface. The maximum time for this test is three minutes. The total duration of time that the rat took to change its position was recorded. (Costall et al., 1974).

Open field test

This test is widely used to study the behavior of rat when left in open field. The behavior included is both exploratory as well as locomotory. For every single trial, the individual rat was put in the mid of an open field box (dimension: 40cm is the length; 70cm is height of walls) for 10min. Various parameters of their locomotory activities including time in corner, time in centre, mobile episode, immobile episode, clockwise rotation, anticlockwise rotation, rearing frequency, urination and defecation) were observed (Sun et al., 2019; Weitzdoerfer et al., 2004).

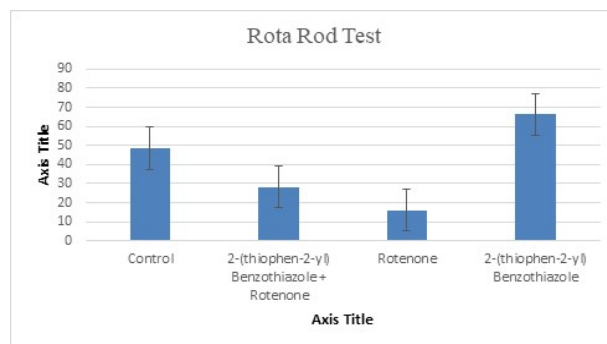


Fig. 2: Result of Rota Rod Test

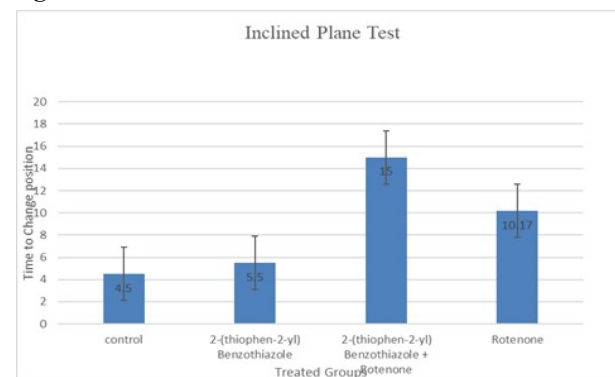


Fig. 3: Result of Inclined Plane

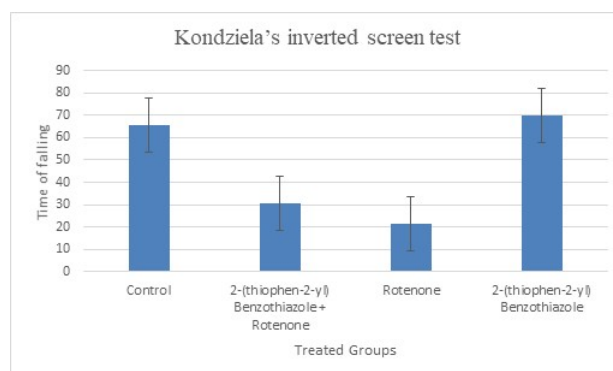


Fig. 4: Result of Kondziela's inverted screen test

Rota rod test

The test is done by using the rotating rod. (usually locally manufactured). It tests the balance as well as coordination in rat limbs. It consists of rotating drum, which is continuously accelerating at fixed speed of 40 rpm. The time at which each rat falls was noted (Gillani et al., 2014).

STATISTICAL ANALYSIS

The result for behavioral analysis of all four groups was analysed that contained Group 1: Control (sunflower oil), Group 2: 2-(thiophen-2-yl) benzothiazole, Group 3: rotenone and Group 4: 2-(thiophen-2-yl) benzothiazole + rotenone. Data is presented in form of Mean ± SD (Standard Deviation). The Mean differences calculation

was done by using one-way ANOVA test using the software Minitab 18, (LLC, USA).

RESULTS

On characterization of synthesized drug 2-(thiophen-2-yl) benzothiazoline light yellow shiny crystals were obtained. Yield: 32%; m.p 86°C; IR (ATR) cm-1: 3274, 2962, 2928, 2469, 1622, 1575, 1544, 1475, 1138, 1078, 1014, 916; ¹H-NMR: (600 MHz, CDCl₃) ppm: δ 4.5 (s, 1H, NH), 7.32 (m, 8H, Ar-H).

Pole test

This test was used in order to assess basal ganglia movement related disorders in rodents. Time taken by rat to come down on the floor from pole was noted. Mean, SD and standard error of mean was calculated by applying one sample t-test to the data. When the result of Rota Rod Test was analyzed, it showed that the result was highly significant when 2-(2 Thienyl) Benzothiazoline* was compared to control (p<0.01) and the cataleptic effect was more in rotenone group when compared with that of the combination group of 2-(2 Thienyl)Benzothiazoline plus rotenone. One-way ANOVA showed considerable effect of administration of 2-(2Thienyl) Benzothiazoline* when compared to control (p<0.01) whereas the the group with administration of rotenone showed that the rats spend more time on pole as compared to combination group of 2-(2 Thienyl) Benzothiazoline plus rotenone.

Rota rod test

In this test rats were placed on drum and time taken by rat that it spent on the drum was monitored. Mean value and SD were calculated by one sample t-test. Then One-way ANOVA was applied to check the significance of result. The Rotenone group 3* showed the significant difference when compared with control.

Inclined plane test

The cataleptic test was performed by placing rats on

inclined plane surface for the time duration of three minutes and the total time taken by rat to remained in one position was recorded. Mean, SD and standard error of mean was calculated by applying one sample t-test to the data. The graph was made between the time taken by the rat to change position and treated groups. Mean and standard error of mean value were used to make the bar graph. The significant result was shown when the 2-(2 Thienyl) Benzothiazoline group * was compared with the control (p<0.01). The cataleptic score of rotenone was overcome by the use of 2-(2 Thienyl) Benzothiazoline when the result of combination and the rotenone group was compared.

Kondziela's inverted screen test

In this test individual rat were allowed to hold the screen that was inverted screen and time taken by rat to descend was monitored. Mean value and SD were calculated by one sample t-test. One-way ANOVA was applied to check the significance. Effects of 2-(2 Thienyl) Benzothiazoline on strength of muscles of four paws wastested by Kondziela's test. Rotenone had bad effects on the muscular grip of rats. It decreased their time significantly to hold the inverted screen when compared to that of the combination of rotenone plus 2-(2 Thienyl) Benzothiazoline *(p<0.01). While comparing the control with 2-(2 Thienyl)Benzothiazoline group, it was shown that 2-(2 Thienyl)Benzothiazoline group had grip to screen for longer time as compared to control.

Open field test

Comparison of various studied parameters in open field test between control, 2-(2 Thienyl) Benzothiazoline group, rotenone and the combination group of rotenone and 2-(2 Thienyl) Benzothiazoline group are shown in table 1. All values are expressed as mean ± of standard error of mean. P-value represents the 2-sample t test for each studied parameter of 2 groups showed the result. The clock wise rotation and defecation showed significant result*.

Table 1: Open field test

Parameters	Control	2-(2 Thienyl) Benzothiazoline	P-value	2-(2 Thienyl) Benzothiazoline plus rotenone	Rotenone	P-value
Time in corner (sec)	555.30±14	544.50±12	0.56	538.01±11	524.40±19	0.55
Time in center (sec)	44.80±14	55.50±12	0.56	62.01±11	75.6±19	0.55
Mobile Episode	138.30±16	139.80±17	0.94	159.80±6.5	148.90±10	0.38
Immobile Episode	137.80±16	139.00±19	0.95	159.50±6.4	149.40±10	0.41
Clockwise rotation	21.13±2.5	24.50±2.5	0.35	29.75±2.4	17.63±3.3	0.01*
Anticlockwise rotation	18.50±3.2	21.50±1.9	0.47	30.88±3.2	22.50±5.0	0.18
Urination	1.38±0.8	0.37±0.3	0.30	0	0	0
Defecation	3.25±0.5	3.50±0.6	0.77	4.01±0.7	2.1±0.4	0.04*

The data of various parameters had significant value if the P-value is P≥0.05. So, the result was not significant for Time in corner, Time in center, Mobile Episode, Immobile Episode Clockwise, rotation, Anticlockwise rotation, Urination and Defecation.

DISCUSSION

Derivatives of benzothiazole are also used as a treatment for various disorders in which nervous system is degenerated like as namely amyotrophic lateral sclerosis (ALS) Alzheimer's disease (AD), Parkinson's disease (PD), as well as degeneration of fronto temporal lobar degeneration. 1-(Benzo[d]thiazol-2-yl)-3-phenylureas has been used successfully as the inhibitor of enzyme casein kinase 1 (CK1) if over expressed, leads to the Alzheimer's disease. (Benek *et al.*, 2018). It is also used in convulsions and other brain diseases (Tariq *et al.*, 2018).

In present work Effects of 2- (2 Thienyl) Benzothiazoline on strength of muscles for paws was checked by Kondziela's test. In our experiment from behavioral analysis, it was experiential that rats treated with rotenone had increased rigidity and decreased motor actions. Our results are consistent with study of Alam demonstrated that motor impairments that also had decreased motor activity (Alam *et al.*, 2012). After administration of rotenone impaired muscular strength monitored by Kondziela's inverted screen test. Rotenone decreased the muscle grip of rats significantly and decreased their time to hold that inverted screen when compared to that of the combination of rotenone plus 2- (2 Thienyl) Benzothiazoline. In benzothiazole-treated groups had the different kind of behavior, their motor as well as the cognitive abilities are improved and they also reverse certain effects of rotenone catalepsy.

While discussing the *in vivo* therapeutic effects of benzothiazole rings, there are several compounds that have shown significant results in case of animal model. A element (E)-5-((benzo[d]thiazol-2-ylimino)(methyl thio) methylamino)-2-hydroxybenzoic acid rapidly increase the decreased glutathione content and it also lowered the malondialdehyde levels by decreasing the reactive oxygen species in the liver tissues of mice (Cabrera-Perez *et al.*, 2019) Thioflavin T (ThT) also has benzothiazole core structure, its administration to diabetic rats improved their blood glucose levels and lipid profiles significantly (Najafian *et al.*, 2015).

In our work a good change was observed tested by rota rod test after the administration of 2- (2 Thienyl) Benzothiazoline to rotenone treated group showing basal ganglia movement related disorders.

Keeping in View the therapeutic importance of benzothiazoline group as the potential neuroprotective (Ramaiah MJ *et al.*, 2020) when we performed our experiments we also found that the cataleptic effects of rotenone are minimized when we administrate the 2- (2 Thienyl) Benzothiazoline as supplementary drug.

CONCLUSION

Keeping in View the therapeutic importance of benzothiazoline group when we performed our experiments we also found that the cataleptic effects of rotenone are minimized when we administrate the 2- (2 Thienyl) Benzothiazoline as supplementary drug. However further perspectives of the project could be checking the neurotransmitters by doing HPLC and antioxidant activities of the similarly designed group samples.

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