Novel glitazone attenuates rotenone-induced toxicity in mouse model of Parkinson’s disease

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INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disorder characterized by the progressive death of dopaminergic neurons. PD is found in all ethnic groups; however, geographical differences are observed. Early onset of sporadic Alzheimer’s disease is rare and about 4% patients develop clinical sign before the age of 50 years. About 1%–2% of the age group of 65 years develops PD and this increases to 3%–5% in the age group of 85 years (Alves et al., 2008). Clinical features of PD will appear when striatal dopaminergic levels are largely reduced or lost. Abnormal cellular components like oxidative stress, impaired protein disposal system, and chronic inflammation may be responsible for pathogenesis underlying neurodegeneration (Schintu et al., 2009). Peroxisome Proliferative Activated Receptor-gama (PPAR-γ) present in large variety of cells and maximum level of expression is in adipose tissue, peripheral and central nervous system cells. The regulation of glucose and lipid metabolism by PPAR-γ depends on its distribution patterns (Straus and Glass, 2007). The presence of PPAR-γ in basal ganglia and areas expressing dopamine receptor with high concentration supports the hypothesis of involvement of PPAR-γ in pathogenesis of PD. This increases the interest for PPAR-γ agonists in PD management (Moreno et al., 2004). Neuroinflammation and microglia activation plays an important role in PD pathogenesis (Hirsch and Hunot, 2009), but currently there are no drugs that will directly tackle the inflammatory component of PD. There is a need for the development of new therapeutics which acts via novel target(s) (may be like neuroinflammation) and gives more benefits than the existing drugs. PPAR-γ found to have a prominent role in the biogenesis of mitochondria (Hu and Wang, 2016), and it can be a powerful target in the treatment of many neurodegenerative diseases including PD. It was also reported to have anti-inflammatory and anti-oxidant activity but the mechanism is not yet established (Amin et al., 2017; Corona and Duchen, 2015). Based on the above hypothesis, the present study was conceived to evaluate novel PPAR-γ agonists for their protective effect against rotenone-induced toxicity in mouse model of PD.

ARTICLE INFO

Received on: 17/12/2020
Accepted on: 24/05/2021
Available online: 03/10/2021

Key words:
3CS8, docking, PPARγ, glitazones, Parkinsonism, kinetics.

ABSTRACT

Parkinson’s disease (PD) is the second most common neurodegenerative disorder, and there are no drugs that will directly tackle the inflammatory component of PD. In the present study, we assessed the novel glitazone for reversal of rotenone-induced toxicity in experimental mouse model. The 14 virtual glitazone compounds were subjected to molecular docking study for target protein 3CS8; among these, compound C25 and C34 have shown better binding activity. Pharmacokinetics studies were conducted for the above compounds in rat model to chose best one for further toxicity and efficacy studies. The compound C25 showed better kinetic profile when compared to C34 and better t½ when compared to the standard pioglitazone. Compound C25 then tested for acute toxicity by OECD guideline 423 and evaluated for its neuroprotective activity in mouse model. The activity of the compound was assessed by the behavioral parameters on weekly intervals during the study period and estimated the antioxidant level in the brain homogenate. The compound has shown good activity dose-dependently; however, further research is required to confirm its activity and to support our hypothesis.
MATERIALS AND METHODS

Novel glitazone compounds were obtained as gift samples from Dr. Prashanth Kumar B R, Assistant Professor, Department of Pharmaceutical Chemistry, JSS College of Pharmacy, Mysore. The experiments were carried out on Wister Albino Rats and Balb/c mice. The studies conducted were approved by the Institutional Animal Ethics Committee of JSS College of Pharmacy, Mysore, Karnataka. (Approval no: IAEC/JSSCPM/296/2018).

Molecular docking studies

The docking studies were performed by using the SYBYL X 2.1.1 (Licensed software) software package platform for 14 virtual glitazones (Table 1). The selected glitazones for the present study from docking results are as shown in the Figure 1. The proteins were downloaded from the protein data bank and prepared by using BIOPOLYMER PREPARATION wizard. Proteins were prepared by joining the missing loops and by adding the hydrogen and deleting water molecules; then energy minimization was performed by adding the charges. All these processes were done to bring the protein to its naturally existing state (Naim et al., 2018).

The ligands were prepared by using the LIGAND PREPARATION wizard in which the ligands were converted to their 3D conformation and by minimizing the energy they had brought to the stable form and finally, the charges were added. The docking operation was performed on DOCK LIGAND wizard by using the SYBYL X 2.1.1 software package platform wherein the prepared ligand and proteins were taken for further study. By using the PROTOMAL GENERATION wizard, the active site of the protein was identified and the ligands were docked along with the co-crystallized ligand which was present within the crystal structure of protein molecule. Finally, the binding poses were observed, and the docking score was obtained by using the SYBYL X 2.1.1 scoring function (Amin et al., 2017).

Pharmacokinetic study of selected glitazones

The kinetic study was carried out for the two test compounds (C25 and C34) and one standard pioglitazone (Fujita et al., 2003; Pandit et al., 2012). The study was conducted in Wister rats weighing between 200–250 g. All test substances were given as Sol CMC suspension orally at 10 mg/kg. The blood samples were collected in the ethylene diamine tetraacetic acid containing tubes by tail vein method (Rangaraj et al., 2014) at different time intervals of 0, 1, 2, 4, 8, 16, and 24-hour. The blood samples were centrifuged by using the cooling centrifuge and stored in the freezer at −20°C until analysis. The blood samples were analyzed using the high-performance liquid chromatography method.

Acute oral toxicity study

The acute oral toxicity study was done by OECD 423 guideline for newly derived novel glitazone compounds C25 and C34 (OECD guideline 423, 2018).

Anti-Parkinson’s activity of novel glitazone

After acclimatization the animals were weighed and based on the bodyweight of the animals, they were grouped by randomization (n = 6) (Cannon et al., 2009). The study duration was 21 days, and at the end of the study the animals were sacrificed and the brain of the animals was used for estimation of endogenous antioxidant activity. The behavioral activities of the animals were carried out on day 0, day 7, day 14, and day 21 of the study. The study protocol is given in Table 2.

RESULTS AND DISCUSSION

Molecular docking study

The docking studies revealed the binding ability of novel compounds C25 and C34, which showed better interaction with PPARγ receptors than the other compounds when compared with the reference ligand (rosiglitazone). The standard levodopa has shown the less binding activity when compared with reference ligand because of its less binding activity with the target protein 3CS8 (Table 3 and Fig. 2). It was observed from docking that without ligand binding to the legend binding domain (LBD) of PPAR-γ the structure of the adjacent helix, C-terminal helix and PGC-1α does not show any structural variation. On the other hand, any agonist binding to the PPAR-γ LBD, such as compound C25, compound C34, and rosiglitazone shows the transformation of the secondary structure of the protein. Therefore, docking has clearly demonstrated the usefulness of these glitazones in neurodegenerative disorders especially in PD

Pharmacokinetic study

The pharmacokinetic study was conducted to know the pharmacokinetic behavior of the novel glitazones derivatives. The two compounds C25 and C34 were taken based on the best results from molecular docking study, and the kinetic study was done for these compounds. The compound C25 has shown good kinetic profile over C34 (Table 4 and Fig. 3).

Acute toxicity study

Acute toxicity studies were carried out based on OECD guideline 423. The acute toxicity of 2 compounds, C25 and C34 was tested at the dose of 300 mg/kg. Both the compounds have not shown any clinical signs of toxicity. No mortality was observed by the test substance at the dose tested and found to be safer. Based on this result the novel compound C25 was used at 10 and 20 mg/kg dose for in vivo efficacy evaluation.

Protective effect of novel glitazone compound C25

Results of the pharmacokinetic activity revealed that C25 has better kinetic activity when compared to C34. Hence, the C25 was taken for evaluation of anti-Parkinsonism activity on rotenone-induced PD mouse model at two different dose levels. Parkinsonism was induced successfully in the mice by giving rotenone intraperitoneally for 21 days (2 mg/kg BW). As shown in Table 5, the control group animals have shown decreased locomotor activity significantly on days 14 and 21. The treatment with C25 has reversed the activity dose-dependently and similar to that of standard.

The same was observed in the rotarod behavioral studies (Table 6) done by employing a rotarod apparatus. There was a significant decrease in the time spent by the control group of animals on rotarod when compared with normal group animals, which signifies the induction of motor
Table 1. Structure of novel and virtual glitazones taken for docking studies.

| SL. No. | Structure                                      | SL. No. | Structure                                      |
|--------|-----------------------------------------------|--------|-----------------------------------------------|
| 1      | ![Structure 1](image1)                       | 8      | ![Structure 8](image8)                       |
| 2      | ![Structure 2](image2)                       | 9      | ![Structure 9](image9)                       |
| 3      | ![Structure 3](image3)                       | 10     | ![Structure 10](image10)                     |
| 4      | ![Structure 4](image4)                       | 11     | ![Structure 11](image11)                     |
| 5      | ![Structure 5](image5)                       | 12     | ![Structure 12](image12)                     |
| 6      | ![Structure 6](image6)                       | 13     | ![Structure 13](image13)                     |
| 7      | ![Structure 7](image7)                       |        |                                               |

(Z)-5-benzylidene-3-(3-chlorophenyl)thiazolidine-2,4-dione
(Z)-5-(2,4-dichlorobenzylidene)-3-(4-fluorophenyl)thiazolidine-2,4-dione
(Z)-5-benzylidene-3-(4-fluorophenyl)thiazolidine-2,4-dione
(Z)-5-(2-chlorobenzylidene)-3-(4-fluorophenyl)thiazolidine-2,4-dione
(Z)-5-(2-chlorobenzylidene)-3-(4-fluorophenyl)thiazolidine-2,4-dione
(Z)-3-(3-chlorophenyl)-5-(2,4-dimethoxybenzylidene)thiazolidine-2,4-dione
(Z)-5-(3-chlorobenzylidene)-3-(3-fluorophenyl)thiazolidine-2,4-dione
(Z)-5-(3-chlorobenzylidene)-3-(3-fluorophenyl)thiazolidine-2,4-dione
(Z)-5-(3-chlorobenzylidene)-3-(3-fluorophenyl)thiazolidine-2,4-dione
(Z)-3-(4-fluorophenyl)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione
(Z)-3-(4-fluorophenyl)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione
(Z)-3-(3-chlorophenyl)-5-(4-dimethylamino)benzylidene)thiazolidine-2,4-dione

(Z)-3-(3-chlorophenyl)-5-(4-dimethylamino)benzylidene)thiazolidine-2,4-dione
(Z)-3-(3-chlorophenyl)-5-(4-dimethylamino)benzylidene)thiazolidine-2,4-dione
dysfunction by rotenone. When the C25 was administered alone with rotenone, the fall of time in rotarod was increased dose-dependently and was found as significant as that of standard drug.

Bar strength was the one more behavioral parameter employed to assess the activity of novel glitazone compound C25. As observed in the above parameters, control group showed a significant increase in the cataleptic activity on day 14 and day 21 when compared to the normal group which showed significant induction of PD by rotenone. There was a significant decrease in the cataleptic activity of treatment groups than the control group, which can be comparable with that of the standard group (Table 7).

**Table 2.** Evaluation of anti-Parkinson’s activity in rotenone induced animal model of Parkinson disease.

| Groups   | Treatment protocol                                                                 | Evaluation                                                                 |
|----------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Normal   | 1 ml of 0.5% sodium CMC (vehicle) was given orally for 21 days.                    | **Behavioral parameter**                                                   |
| Control  | Vehicle for 21 days orally and rotenone 2 mg/kg (i.p) at the interval of 1 hour.   | Rotarod (Brooks et al., 2012), actophotometer (Thomas et al., 2011)        |
| Standard | Levodopa-carbidopa (30 mg/kg BW, p.o) + rotenone 2 mg/kg (i.p) at the interval of 1 hour. | Bar test (Deacon, 2013)                                                    |
| C 25 LD  | 10 mg/kg BW prepared in 0.5% sodium CMC p.o + rotenone 2 mg/kg (i.p) at the interval of 1 hour. | **Biochemical parameter**                                                 |
| C 25 HD  | 20 mg/kg BW prepared in 0.5% sodium CMC p.o + rotenone 2 mg/kg (i.p) at the interval of 1 hour. | sodium dismutase (SOD) (Weydert and Cullen, 2010), Reduced glutathione (Tipple and Rogers, 2012) and TBARS (Weydert and Cullen, 2010). |

LD, Low dose; HD, High dose; n = 6.

**Table 3.** Results of molecular docking of novel virtual glitazone compounds.

| Name       | Total score | Crash  | Polar   |
|------------|-------------|--------|---------|
| Reference ligand | 7.758 | −2.3965 | 0.2074 |
| Levodopa   | 4.7553      | −2.0953 | 1.6198  |
| C22        | 5.3008      | −1.6883 | 1.2182  |
| C23        | 5.5109      | −2.7262 | 0.0001  |
| C24        | 5.3293      | −1.3917 | 1.1827  |
| C25        | 6.6677      | −1.3881 | 0.0239  |
| C26        | 5.6537      | −1.9939 | 0.0016  |
| C27        | 4.5987      | −0.6822 | 0.8561  |
| C28        | 4.9133      | −1.1379 | 0.8812  |
| C29        | 4.948       | −2.0451 | 0.0037  |
| C30        | 5.0016      | −2.2624 | 0       |
| C31        | 5.2817      | −2.6846 | 0       |
| C32        | 3.8036      | −1.9866 | 0       |
| C33        | 3.8303      | −1.2304 | 0.0167  |
| C34        | 5.9715      | −1.4564 | 0.9369  |
| C35        | 3.8623      | −1.2304 | 0.0167  |

Bolded mean, the legend has more binding affinity to the target protein during docking studies.

**Endogenous antioxidant enzymes**

Rotenone induces PD mainly by increasing oxidative stress and causes mitochondrial complex I inhibition which leads to a decrease in the biogenesis of mitochondria and increases the level of reactive oxygen species that induced oxidases stress (Jollow et al., 1974).
Table 4. Pharmacokinetic data of the compounds C25 and C34.

| Parameters          | Pioglitazone | C25     | C34     |
|---------------------|--------------|---------|---------|
| $C_{\text{max}}$ (μg/ml) | 12.45        | 10.98   | 10.25   |
| $T_{\text{max}}$ (hour)      | 2.70         | 3.25    | 4.20    |
| $T_{1/2}$ (hour)  | 3.20         | 3.60    | 2.90    |
| $AUC_{0-\infty}$ (μg hour/ml) | 145.70       | 128.25  | 98.54   |
| $K_e$ (hour$^{-1}$) | 0.280        | 0.315   | 0.394   |

Figure 2. Binding interaction of novel glitazone compound with the protein 3CS8 in 3D (after docking). A) C25 and B) C34.

Figure 3. Plasma concentration of C25 versus time and C34 versus time.

Table 5. Anti-parkinsonism activity of novel glitazones derivatives on rotenone induced Parkinson activity in mice (locomotor activity).

| Groups       | Day 0           | Day 7           | Day 14          | Day 21          |
|--------------|-----------------|-----------------|-----------------|-----------------|
| Normal       | 511.50 ± 8.04   | 516.16 ± 6.24   | 512.16 ± 5.71   | 518.50 ± 4.53   |
| Control      | 534.80 ± 15.34  | 503.50 ± 12.33  | 451.10 ± 14.7   | 198.66 ± 5.35*  |
| Standard     | 533.01 ± 12.01  | 522.24 ± 11.02* | 519.50 ± 11.13* | 508.24 ± 10.81* |
| C25 LD       | 521.50 ± 8.63   | 507.24 ± 9.46   | 502.01 ± 9.84*  | 401.55 ± 8.24** |
| C25 HD       | 528.25 ± 10.06  | 514.85 ± 8.24   | 510.50 ± 8.45*  | 484.20 ± 8.739** |

All the values are expressed as mean ± SEM n = 6. The data was analyzed by two-way analysis of variance (ANOVA) followed Bonferroni post-test. *Significant when compared to normal group (p < 0.01). #Significant when compared to control group (p < 0.01). +Significant when compared to standard group (p < 0.01).
The effects of novel glitazone on endogenous antioxidant enzymes are given in Table 8. The animals treated alone with rotenone have shown decreased anti-oxidant enzymes, which suggests rotenone may induce oxidative stress. Novel glitazone compound has reversed the oxidative stress induced by rotenone.

**DISCUSSION**

The bioenergetics defects in neurodegeneration could be compensated by increased neuronal mitochondrial content. The important regulator of mitochondrial function in central nervous system is believed to be PPAR-γ co activator 1α (PGC-1α) which up regulates the biogenesis of mitochondria through Sirtuin 1 (Mahajan et al., 2016). PPAR-γ agonists like rosiglitazone, pioglitazone, and troglitazones which are commonly used for the management of diabetes were reported to increase mitochondrial biogenesis (Howitz et al., 2003). In another study, it was found that the PGC-1α agonist, like resveratrol and bezafibrate, have shown the protective effect against 6-hydroxydopamine in animal models (Khan et al., 2010). Studies conducted at our laboratory have shown that the novel glitazones have promising action against...
PD induced experimental animal model (Suma et al., 2019). In the present study, the novel glitazones were docked virtually with PGC-1α protein to get best ligands and optimized legends were further tested in experimental animal model of PD.

The docking studies on novel glitazones (14 virtual ligands) to protein active sites were performed by an advanced molecular docking program SYBYL X 2.1.1. Scoring functions were used for determining the binding affinities of the ligands with the target receptors. The designed analogues were docked toward 3CS8 (target PGC-1α bound to PPAR-gamma receptor protein) in order to ascertain their binding ability to PPAR-gamma which in turn activity PGC-1α protein (Justin et al., 2020).

The result had showed that the compounds C25 and C34 were having better binding activity with the target protein and were shown good polarity score and crash score than the other compounds when compared with the reference ligand (Mandal et al., 2018). The total score should be more for ligand to possess better binding affinity with the target receptor and crash score should be less. The compound C25 showed better binding affinity when compared to the compound C34 in the docking studies.

To assess the bioavailability of novel glitazones, a kinetic study was performed by single oral administration and the kinetic data were determined by the one compartment model. The experimental animals (Wistar Albino Rats) were administered a single oral dose of the compounds C25 and C34 and the kinetic data of the compounds are compared with the data of standard pioglitazone drug. The results showed that the C25 have better plasma concentration than C34 when compared with the standard pioglitazone compound. The plasma concentration of C25 was higher because the elimination rate of compound C34 was higher than the C25. The T_max of the C25 was less than the C34 it signifies that C25 have the better absorption than the C34. The elimination rate of the C34 is more than the C25, so the plasma concentration is less than C25. The compound C25 shown better T_1/2 than the C34 it signifies the duration of action of C25 is more than C34, it will retain in the plasma for more time and produce better action. The C25 also showed better T_1/2 when compared to the standard pioglitazone. Based on the above studies C25 was chosen for further toxicity and efficacy studies in experimental animal model.

OECD guideline 423 was applied to know the acute toxicity studies of novel glitazone derivative C25, which comprises a 14-day observation studies (OECD guideline 423, 2001). Our findings indicate that the novel glitazone C25 has shown no mortality at 300 mg/kg dose tested for 14 days period. Then we considered this dose as tolerable dose and taken 10 and 20 mg/kg as test doses for efficacy study.

In the present study, we tried to examine the anti parkinsonian activity of novel glitazone on rotenone induced neurotoxicity in mice. The results of the study clearly demonstrate the beneficial role of novel glitazone C25 in attenuating the damage of dopaminergic neurons in PD induced mice. As discussed above, the PD is characterized by selective degeneration of dopaminergic neurons in substantia nigra. Pathogenesis of PD may not be known completely, the role of mitochondrial dysfunction, oxidative damage, and apoptosis are major contributing factors (Erbas et al., 2016). Rotenone induced neurotoxicity has been extensively employed as an animal model for PD. Since it is lipophilic in nature, it can enter organs like mitochondria and inhibits complex I activity of mitochondrial electron transport chain. This leads to development of ROS, adenosine tri phosphate reduction, and finally cell death in the neuron. Even the treatment with rotenone has demonstrated the histopathological changes as similar to PD (Cannon and Greenamyre, 2011; Xiong et al., 2009).

The results of the present study clearly indicate that rotenone administration could successfully develop PD like motor and behavioral features in rats such as hyperkinesias, flexed posture, and freezing. The compound C25 was assessed for its anti-parkinsonian activity at two different doses low dose (10 mg/kg) and high dose (20 mg/kg) and the activity was evaluated by behavioral parameters, like rotarod, spontaneous locomotor activity and cataleptic behavior by bar test.

Locomotor activity was assessed on day 7, 14, and 21, and the control group showed decrease in locomotor activity which confirms the induction of disease. The test drug increases the locomotor activity to the maximum of 95% and causes reversal rotenone neurotoxicity.

We observed decrease in fall of time by control group animals when tested by rotarod method, whereas the treatment with C25 has increased the fall of time dose dependently and maximum at higher doses. This demonstrates the loss of muscle coordination and muscular contraction in rotenone alone administered group animals and the same was attenuated by C25 administration.

We also found that C25 treated animals have shown decrease in the cataleptic activity when compared to control group animals dose dependently. Rotenone alone administered animals have taken more time to come back to the normal posture, which confirms the development of PD like symptom. This symptom was attenuated by administration of C25 and maximum effect was observed at higher dose tested.

As discussed above, rotenone induces PD mainly by increasing the oxidative stress, which causes mitochondrial complex I inhibition, leads to decrease in biogenesis of mitochondria. We observed elevated level of lipid peroxidation, decreased level of antioxidant enzymes SOD and GSH in brain tissues. Treatment with C25 lessened the level of lipid peroxidation and elevated the level of SOD and GSH.

Oxidative stress is one of the major reasons in many neurodegenerative diseases for the damage of nerve cells. In PD, oxidation of dopamine by mono amino oxidase-B and aldehyde dehydrogenase generates free radicals (OH) in presence of ferrous ions (basal ganglia rich in iron). Thus, the synthetic compounds possessing antioxidant activities appear to be the potential targets for developing new remedies in neuroprotection as the intake of antioxidants appears to be benefit in conditions of oxidative stress by maintaining the balance between the generation and scavenging of free radicals. The glitazone derivatives have a potent antioxidant and anti-PD activities.

CONCLUSION

The data obtained from this study reveals that novel glitazone compound C25 has protective effects on a rotenone-induced PD mouse model. The activity was dose-dependent and significant to the standard at higher dose tested. It is also exhibited significant antioxidant activity, which may additional advantages.
But further studies are required to support the present assumption and elucidate the detailed neuroprotective mechanism.

AUTHOR CONTRIBUTIONS
All authors are contributed equally to the research work present in the manuscript.

ACKNOWLEDGMENT
The authors are grateful to Principal, JSS College of Pharmacy, Mysuru, and thanks to JSS Academy of Higher Education & Research, Mysuru for providing necessary facilities required for our research work.

CONFLICT OF INTEREST
The authors have no conflict of interest.

FINANCIAL SUPPORT
No funding received for the project and it is an M. Pharm dissertation project supported by JSS College of Pharmacy, JSS AHER, Mysuru.

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How to cite this article:
Shetty AB, Krishna KL, Prashantha Kumar BR, Nandini HS. Novel glitazone attenuates rotenone-induced toxicity in mouse model of Parkinson’s disease. J Appl Pharm Sci, 2021; 11(10):042–049.