Ind. J. Pharm. Edu. Res, 2023; 57(2):552-558.
https://www.ijper.org

Original Article

Synthesis and Biological Evaluation of the Selected Naphthalene Substituted Azetidinone Derivatives Targeting Parkinson's Disease

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ABSTRACT

Aim/Background: Parkinson's Disease (PD), the loss of dopaminergic neurons in the substantial nigra part of the brain leading to neurodegeneration. **Materials and Methods:** The objective of this study was to observe the neuroprotective effect of the synthesized derivatives in 6-hydroxydopamine (6-OHDA) induced rat model. Here, designed naphthalene substituted azetidinone compounds defended the lesions caused by 6-OHDA in rat model for PD. Male wistar rats (250g) were subjected into sham operated, controlled 6-OHDA, 6-OHDA treated L-dopa (Levodopa) and lesioned 6-OHDA with azetidinone derivatives (30mg/kg) where oxidative stress and behavioral characteristic were observed. **Results:** Induced synthesized derivatives partly have shown the reversed behavioral and neuronal changes compared to 6-OHDA lesioned rats. The free radical scavenging activity for the compound IVc, IVe and IVf were found to be 88, 70, 78 respectively as compared to that of 6-OHDA with L-dopa with 90%. **Conclusion:** The efficacy of the azetidinone derivatives was found to be promising in providing relief to oxidative stress and the derivatives could be used in the therapeutic approaches in preventing neurodegeneration.

Keywords: Schiff's bases, Azetidinone, Anti-Parkinson's activity, Neurodegeneration, 6-OHDA.

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Received: 23-11-2022;
Revised: 03-12-2022;
Accepted: 11-01-2023.

INTRODUCTION

Over the years heterocyclic compounds show a pivotal role in the field of medicinal chemistry.[1] Azetidinone is the simplest β-lactam ring and belongs to a class of heterocyclic compounds. It is the core structure of several antibiotics such as; penicillin, cephalosporin, and clavulanic acid. Now a day's researchers pay high attention to 2-azetidinone derivatives because of their versatile biological activities.[2] They act as an intermediate, for various chemical syntheses of different biologically active compounds an additional value for their remarkable attraction.[3] The contributions of heterocyclic 2-azetidinone to science and humanity are very valuable. These heterocyclic compounds have both industrial and physiological importance since these are the constituents of living organisms and also every year a large number of drugs are introduced in pharmacopeia.[4-6] Over the years azetidinone derivatives have been showing various neurological effects such as anticonvulsant various substituted azetidinone had shown potential activity in preventing convulsant.[7-8] Naphthalene derivatives has also shown potential activity against Alzheimer's disease.[9] In general, it is assumed that the therapeutic efficacy of the β-lactam skeleton is related to the chemical reactivity of its β-lactam ring and the nitrogen substituents in the 2-azetidinone ring particularly. The oxo group is at the 2nd position of 2-azetidinone, Figure 1. substituents at the N-1, C-3, and C-4 positions may be varied.[10]

Azetindin-2-one derivatives display interesting biological activities such as antifungal, antimicrobial;[11-14] antitubercular;[15-16] analgesic, anti-inflammatory;[17-18] chymase inhibitory, antitumoral;[19-21] antiviral, antidiabetic and cholesterol absorption inhibitory properties and also have anti-Parkinson's activity.[22]

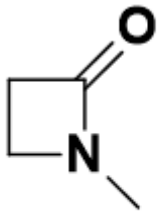

Figure 1:
2-Azetidinone.[10]

DOI: 10.5530/ijper.57.2.68

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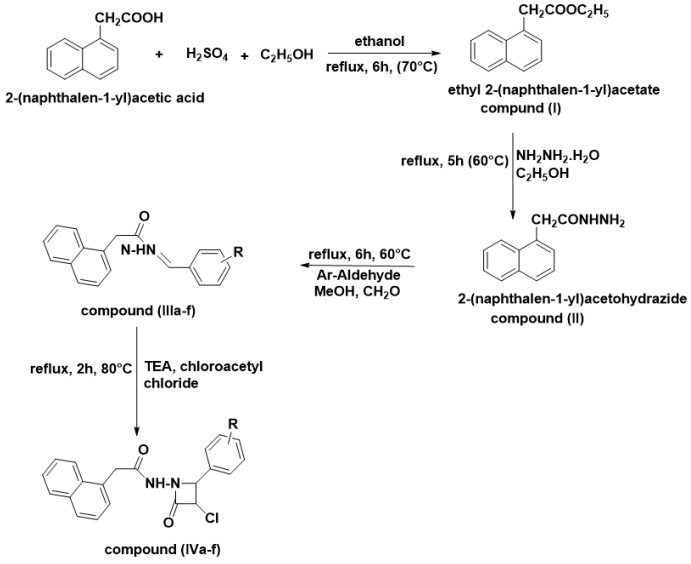
MATERIALS AND METHODS

Thin-Layer Chromatography (TLC) was performed using the required mobile phase (Methanol and chloroform) and was visualized under ultraviolet rays on microscopic glass sliders (2 x 7.5 cm) covered with silica-G. Melting points were obtained using Veego VMP-1 apparatus in an open capillary tunnel. Fourier Transform Infrared Spectroscopy (FT-IR) Shimadzu 8400-S was performed using Potassium Bromide (KBr) pellets and, IR spectra were obtained in the range of 4000-400 cm^{-1} for the synthesized compounds and were reported. Nuclear Magnetic Resonance (NMR) Bruker 400 MHz spectrometer was used to obtain Proton (^1H) NMR under dimethyl sulfoxide-d_6 solvent and the Peaks were reported. Mass spectrometry was performed (MS) with Electron impact ionization mode and spectrum were derived for the synthesized compounds.

General Scheme for the synthesis of N-(3-chlor o-2-oxo-4-phenylazetidin-1-yl)-2-(naphthalen-1-yl) acetamide substituted derivatives

Procedures for the synthesis of substituted

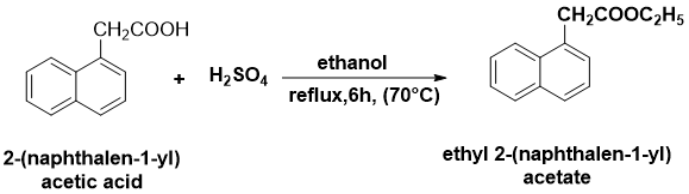


(E)-N'-benzylidene-2-(naphthalen-1-yl) acetohydrazide derivatives

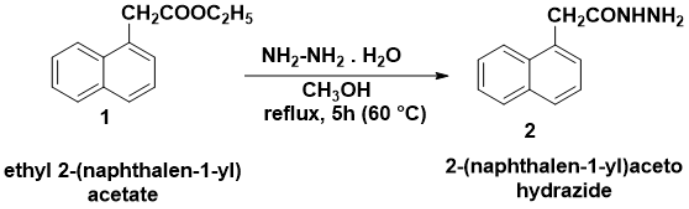
Synthesis of ethyl naphthalen-1-ylacetate (I)[23]

Step 1

To a solution of naphthalene-1-yl acetic acid (0.1 mmol) in ethanol (50 mL) and conc. H_2SO_4 (12 mL) was added dropwise using separating funnel under 0-5° and the reaction mixture was refluxed for 6 hr under 70°. Reaction was monitored with TLC (5% Methanol and n-hexane), It was neutralized using 5% of ammonia solution to get pH of 8-9. The developed precipitation



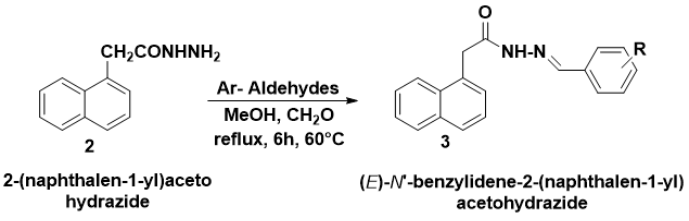
was filtered with vacuum pump and was recrystallized using ethanol (25 mL) in 65°. The precipitate was dried and washed with water and dried to obtain ethyl naphthalene-1-yl acetate (I).



Synthesis of 2-(naphthalene-1-yl) acetohydrazide (II)[24]

Step 2

Compound 1 (2 mmol) was dissolved in 10 mL of methanol, and to this equimolar of hydrazine hydrate (2 mmol) was added and stirred for 5-10 min. The mixture was refluxed for 5 hr under 60° until the clear solution appeared. TLC was checked using a 5% methanol: chloroform solvent system. The precipitate was separated using column chromatography, the separated product was filtered and dried. It was recrystallized using ethanol (25 mL) under 65°.

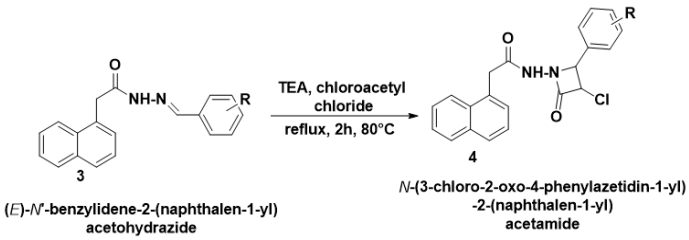


MeOH; methanol : CH_2O; formaldehyde

Synthesis of (E)-N'-benzylidene-2-(naphthalen-1-yl) acetohydrazide (IIIa-f)

Step 3

Compound II (1 mmol), was dissolved in 10 mL of methanol with equimolar quantity of formaldehyde and substituted aldehydes (1 mmol), which were added to the reaction mixture. The reaction mixture was refluxed for 6 hr under 60° until the clear solution appeared. The reaction was monitored by TLC using a 5% methanol: chloroform solvent system. The precipitate was filtered, and washed with diethyl ether. The recrystallization was done with 25 mL of ethanol. The recrystallized product was



dried in room temperature to obtain (E)-N'-benzylidene-2-(naphthalen-1-yl) acetohydrazide.

Synthesis of N-(3-chloro-2-oxo-4-substitutedphenyl azetidinone-1- yl)-2-(naphthalen-1-yl) acetamide (IVa-f)

Step 4

To a stirred solution of compound IIIa-f (0.05 mmol), triethyl amine (TEA) (0.01 mmol) in dioxane (50 mL), chloroacetyl chloride (0.01 mmol) was added dropwise using separating funnel under ice cold condition at 0-5°C. The reaction mixture was continuously stirred for 2 hr, under 80°C. The reaction condition was monitored using TLC 5% of methanol and *n*-hexane. The precipitates were filtered and washed with diethyl ether under vacuum. The filtrate was collected and the remaining solvent was evaporated. The solid precipitate was washed with water, filtered under vacuum pump and was dried with diethyl ether.

RESULTS AND DISCUSSION

The synthesized compounds were subjected to physicochemical and spectral characterization (Table 1). The purity of the compound was determined by the appearance of a single spot in TLC. Compounds IVa-f showed molecular weight ranged from 316.78 to 473.74 Daltons with percentage yield was obtained in the range of 50-70%. All the compounds were confirmed by TLC with 5% methanol and n-hexane and the retention factor (Rf) was obtained, the detailed results obtained are mentioned in Table 2. Further the synthesized compounds were confirmed by melting point. IR Spectral range for compound I showed aromatic CH (3036.3 cm^{-1}), aromatic C=C (1494.98 cm^{-1}), aliphatic C-H (2887.53 cm^{-1}), whereas for compounds II and IIIa-f showed functional group such as N-H amide (3140.22 cm^{-1}), N-N hydrazine (1113.93 cm^{-1}). Substituted derivatives of compound IIIa-f showed functional group C=N (1652.09 cm^{-1}), C-F (1310 cm^{-1}), C-Cl (890 cm^{-1}), C-O (1050 cm^{-1}), C-OCH_3 (2860 cm^{-1}). As for the final derivatives compound IVa-f displayed functional groups containing azetidinone C-N (1035 cm^{-1}), C-Cl (615.31 cm^{-1}), C-F (1310 cm^{-1}), C-Cl (890 cm^{-1}), C-O (1050 cm^{-1}), C-OCH_3 (2860 cm^{-1}), these peaks gave the confirmation for the synthesized compounds, the detailed functional group has been shown in Table 3.

NMR spectra were taken with dimethyl sulfoxide-d_6 for all the synthesized compounds. Compound IVc naphthalene ring showed multiplet proton peaks at 8.2 δ/ppm, followed by NH (secondary amine) peak at 3.8 δ/ppm, compound IVe naphthalene ring showed multiplet proton rings NH peak appeared at 3.8 δ/ppm. Whereas, compound IVa-f, displayed methoxy peak at 2.2 δ/ppm and NH-peak appeared at 3.8 δ/ppm, the detailed peaks are mentioned on Table 4.

In vitro Study

The anti-Parkinson's activity screening was performed using *in vitro* free radical scavenging assay.[25] This screening was done to obtain the potent compounds out of synthesized one for further screening of *in vivo* study. *In vitro* studies were performed on male wistar rat brain of sagittal slices having uniform thickness around 1mm. Prepared cerebrospinal fluid with the pH-7 and was used as 1.2 mL per slice and the slices were incubated at 37°C. Along with sodium chloride and potassium chloride, Magnesium sulfate, calcium chloride and glucose. The administration of 6-*OHDA* (1nM-10μM) (with and without) was done on the oxygen rich area in brain. After incubation the slices were processed for reactive oxygen species assay. The results are presented in Table 5.

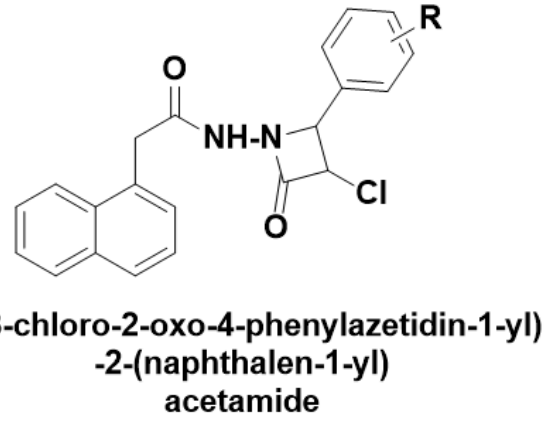


Figure 2: Compound IVa-f.

Based on *in vitro* study by free radical scavenging assay, it was found that compounds IV(c), IV(e) and IV(f) showed potent free radical scavenging activity giving 88%, 70% and 78% respectively. These three derivatives were subjected to *in vivo* studies for their anti-Parkinson's activity.

In vivo Study

Three compounds IV(c), IV(e), and IV(f) were taken for anti-PD studies. These were given orally after 48 hr of induction for 45 d at the dose of 30mg/kg to Wistar rat. After 45 d, treatment checked the parameter as circulating behavior, grip strength, catatonia, complex-I activity[26-28] and the results were tested for their significance using one-way ANOVA followed by Dunnett's multiple comparisons test. The azetidinone ring 4th position having an aromatic aldehydes side chain was proposed to have anti-Parkinson's activity. L-dopa has been exerting potential activity by reloading dopamine quantity in striatum of brain by decarboxylation of enzymes in synaptic neurons.[29] Here we used rat animal model with induced 6-OHDA. Where 6-OHDA lesion eliminated most of the dopamine receptors in the nigra part of brain leading to loss of dopamine levels in brain. It was seen that L-dopa gets elevated in the brain for a shorter period of time when 6-OHDA is induced. Here 6-OHDA (2mg/1mL) was induced with azetidinone derivatives in the striatal ipsilateral of nigra where moderate reduction of L-dopa persuaded circling behavior was observed as shown in Table 6 and Figure 3. It was seen that administration of L-dopa increased dopamine quantity in the ipsilateral striatum, although it remained for a shorter period of time, further administration of 6-OHDA (1nM-10μM) caused lesion in the neurons and synthesized compounds interestingly reduced rotational behavior caused by L-dopa which has been shown in Table 7. The auto-oxidation of 6-OHDA generates free radicals such as hydrogen peroxides, free hydroxyl groups (ROS) which leads to oxidative stress and neuronal death, administration of 6-OHDA in the substantia nigra of brain leads to the accumulation of the 6-OHDA and prevents the activity of electron transport chain in mitochondrial. Mitochondrial uncoupling was observed in 6-OHDA rat model of PD, where it may be due to uncoupling of oxidative phosphorylation which helps in producing reactive oxygen species resulting in mitochondrial opening by which neuronal death occurred.

Table 1: Substituted phenyl methanimine derivatives.

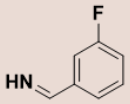
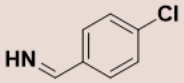
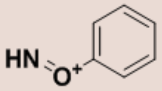
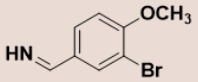
Sl. NO	Compounds	Substitutions-R
1	a	$N=CH_2-CH_3$
2	b	
3	c	
4	d	
5	e	
6	f	

Table 2: Physical parameters of synthesized compounds.

Compound No.	Molecular weight	Melting point °	Practical yield (g)	% Yield	R_f value (5% methanol and *n*-hexane)
I	214.26	146-148	4.3	74.7	0.372
II	200.24	278-280	1.49	62.3	0.851
III(a)	240.30	140-142	0.99	55	0.789
III(b)	280.36	282-284	1.03	45	0.543
III(c)	306.33	278-280	1.6	60	0.698
III(d)	322.78	240-242	1.4	57.6	0.510
III(e)	296.36	220-222	1.43	58.8	0.601
III(f)	411.29	230-232	1.5	56.2	0.421
IV(a)	316.78	104-106	0.3	50	0.41
IV(b)	356.84	232-234	0.148	40	0.45
IV(c)	382.81	200-202	0.67	60	0.51
IV(d)	399.26	224-226	0.43	66	0.57
IV(e)	372.84	212-214	0.23	60	0.45
IV(f)	473.74	206-208	0.27	64	0.54

Table 3: IR (cm^{-1}) data of synthesized compounds I-IVa-f.

Compounds	IR Spectral ranges (cm^{-1})
I	Ar C-H (303636), Ar C=C (1494.98), C-H aliphatic (2887.53), C=O ester (1735.03), C-O ester (1113.93)
II	Ar C-H (3036.06), Ar C=C (1494.88), C-H aliphatic (2979.16), C=O amide (1643.31), N-H amide (3140.22), N-N hydrazine (1113.93)
III (a)	Ar C-H (3030.27), Ar C=C (1401.33), C-H aliphatic (2856.67), N-H amide (3155.65), N-N hydrazine (1115.86)
III (b)	Ar C-H (3120.93), Ar C=C (1401.33), C-H aliphatic (2853.78), C=O amide (1699.34), N-H amide (3156.61), N-N hydrazine (1115.86), C=N (1652.09)
III (c)	Ar C-H (3033.16), Ar C=C (1465.95), C-H aliphatic (2932.86), C=O amide (1684.88), N-H amide (3107.43), N-N hydrazine (1173.72), C=N (1513.21), C-F (1310)
III (d)	Ar C-H (3005.20), Ar C=C (1457.27), C-H aliphatic (2956.01), C=O amide (1653.05), N-H amide (3197), N-N hydrazine (1170.83), C=N (1559.50), C-Cl (890)
III (e)	Ar C-H (3005.20), Ar C=C (1457.27), C-H aliphatic (2956.01), C=O amide (1653.05), N-H amide (3197), N-N hydrazine (1170.83), C=N (1559.50), C-O (1050)
III(f)	Ar C-H (3005.20), Ar C=C (1457.27), C-H aliphatic (2956.01), C=O amide (1653.05), N-H amide (3197), N-N hydrazine (1170.83), C=N (1559.50), C-Br (650), C-OCH_3 (2860)
IV (a)	Ar C-H (3199.05), Ar C=C (1442.80), C-H aliphatic (2881.75), C=O (1690.66), N-H amide (3199.05), Azd C-N (1035), Azd C=O (1749.49), C-Cl (615.31)
IV (b)	Ar C-H (3051.49), Ar C=C (1446.66), C-H aliphatic (2849.49), C=O (1623.15), Azd C-N (1019), Azd C=O (1709.95), C-Cl (753.23)
IV (c)	Ar C-H (3087.17), Ar C=C (1525.74), C-H aliphatic (2954.08), C=O amide (1675.23), Azd C-N (1075.35), Azd C=O (1748.53), C-Cl (700.18), C-F (1310)
IV (d)	Ar C-H (3026.71), Ar C=C (1506.46), C-H aliphatic (2924.18), C=O Amide (1652.09), N-H amide (3126.71), Azd C-N (1029.41), Azd C=O (1722.49), C-Cl (890)
IV (e)	Ar C-H (3199.05), Ar C=C (1442.80), C-H aliphatic (2881.75), C=O (1690.66), N-H amide (3199.05), Azd C-N (1035), Azd C=O (1749.49), C-O (1050)
IV (f)	Ar C-H (3199.05), Ar C=C (1442.80), C-H aliphatic (2881.75), C=O (1690.66), N-H amide (3199.05), Azd C-N (1035), Azd C=O (1749.49), C-Br (650), C-OCH_3(2860)

Table 4: ^{1}H-NMR (δ/ppm) data of synthesized compounds IVa-f.

Compounds	NMR data ^{1}H-NMR (δ/ppm)
IV (a)	7.2 (m, 7H, Ar-H), 1.4 (t, 1H, CH-Cl), 2.2 (s-1H, N-CH), 0.8 (s, 2H, CH_2), 3.5 (s, 1H, NH)
IV (b)	7.8 (m, 7H, Ar-1H), 7.7 (m, 5H, Ar-2H), 1.7 (t, 1H, CH-Cl), 2.2 (s, 1H, N-CH), 1.1 (s, 2H, CH_2), 3.8 (s, 2H, CH_2)
IV (c)	8.2 (m, 7H, Ar-1H), 8.3 (m, 4H, Ar-2H), 1.5 (t, 1H, CH-Cl), 1.5 (s, 2H, CH_2), 3.7 (s, 1H, NH)
IV (d)	6.8 (m, 7H, Ar-1H), 7.9 (m, 4H, Ar-2H), 1.5 (s, 1H, CH-Cl), 0.8 (s, 2H, CH_2), 3.8 (s, 1H, NH), 8.5 (s, 1H, OH)
IV (e)	7.8 (m, 7H, Ar-1H), 7.7 (m, 5H, Ar-2H), 1.7 (t, 1H, CH-Cl), 2.2 (s, 1H, N-CH), 1.1 (s, 2H, CH_2), 3.8 (s,C-NH)
IV (f)	6.8 (m, 7H, Ar-1H), 7.9 (m, 4H, Ar-2H), 1.5 (s, 1H, CH-Cl), 0.8 (s, 2H, CH_2), 3.8 (s, 1H, NH), 2(t, C-Br), 3.8 (s,O-CH_3)

Table 5: Effect of azetidinone derivatives on reactive oxygen species.

Sl. No.	Samples	Free radical scavenging activity %
1	Sham-operated control	100
2	6-OHDA	56
3	6-OHDA+L-dopa	90
4	6-OHDA+ Compound IV a	42
5	6-OHDA+ Compound IV b	48
6	6-OHDA+ Compound IV c	88
7	6-OHDA+ Compound IV d	44
8	6-OHDA+ Compound IV e	70
9	6-OHDA+ Compound IV f	78

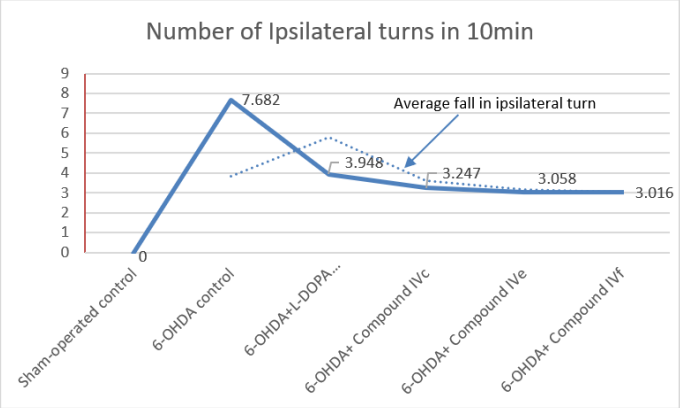


Figure 3: Effect of Azetidinone derivatives on quantification of circling behavior in rats.

Table 6: Effect of azetidinone derivatives of experimental groups by using rotarod apparatus.

Sl. No.	Samples	Retention Time (sec)
1	Sham-operated control	177.4±4.343
2	6-OHDA control	65.60±3.415
3	6-OHDA+L-dopa treated group	146.6±2.731***
4	6-OHDA+ Compound IVc	94.00±3.362**
5	6-OHDA+ Compound IVe	110.8±3.652***
6	6-OHDA+ Compound IVf	89.60±4.501***

Table 7: Effect of azetidinone derivatives on catatonia activity of experimental groups.

Sl. No.	Samples	Catalepsy score
1	Sham-operated control	00
2	6-OHDA control	3.05±0.10
3	6-OHDA+L-dopa treated group	0.82±0.12***
4	6-OHDA+ Compound IVc	2.060±0.13**
5	6-OHDA+ Compound IVe	1.420±0.16***
6	6-OHDA+ Compound IVf	2.780±0.24

Monoamine oxidase dysfunctioning increased the 6-OHDA lesion on electron transport chain, causing neurotoxicity, all these events could lead to protein and DNA oxidation resulting on mitochondrial dysfunctioning. Where, treatment with the compounds IV c, e and f helped in the survival of the electron transport chain which indicated less production of reactive oxygen species, which resulted proper functioning of complex I-IV shown in Table 8.

Table 8: Effect of azetidinone derivatives IVc, IVe and IVf on mitochondrial complex I activity in brain homogenate of treatment groups.

Sl. No.	Samples	Catalepsy score
1	Sham-operated control	00
2	6-OHDA control	3.05±0.10
3	6-OHDA+L-dopa treated group	0.82±0.12***
4	6-OHDA+ Compound IVc	2.060±0.13**
5	6-OHDA+ Compound IVe	1.420±0.16***
6	6-OHDA+ Compound IVf	2.780±0.24

Sham-operated group showed no effect. Controlled administration of 6-OHDA reduced the dopamine level in ipsilateral part of brain lesion in ipsilateral where it eliminated movement regulation with 7.68±0.52. Treated group of 6-OHDA with L-dopa showed exaggerated effect in motor symptoms, here 6-OHDA lesion was countered by L-dopa compared to controlled group with 3.948±0.3623. Compound IVc administration showed moderate activity with 3.24±0.5 ipsilateral turn in 10 min, whereas compound IVe-f showed significant activity with 3.05±0.5 and 3.01±0.3 number of ipsilateral turns in 10 min, (30 mg/kg) helped in reducing circling behavior caused by L-dopa. It was also observed that higher dose of synthesized compounds could minimize more L-dopa induced circling behavior.

CONCLUSION

Based on the scheme outlined, compounds IV (a-f) were synthesized and acquired a good synthetic yield. IR and ^{1}H-NMR for the synthesized compounds were done and structures were identified. The synthesized compounds were screened for anti-Parkinson's activity. Compounds IVa-f were subjected to *in vitro* free radical scavenging assay. Among that, compounds IV (c, e, f) have shown a good result and further taken for *in vivo*, 6-OHDA lesioned rat model studies. Based on our observations, we appreciate and anticipate more detailed research in anti-Parkinson's and toxicology with these compounds and believe that these compounds could be a potential treatment to be chosen for clinical Parkinsonism.

ACKNOWLEDGEMENT

We acknowledge the generous research infrastructure and supports from JSS College of Pharmacy, JSS Academy of Higher Education and Research, Rocklands, Ooty, The Nilgiris, Tamil Nadu, India.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PD: Parkinson disease; **g:** Gram; **kg:** Kilogram; **H_2SO_4:** Sulfuric acid; **h:** Hour; **d:** Day; **mL:** Milliliter; **µl:** Microliter; **C:** Celsius; **mg:** Milligram**; nm:** Nanomolar; **mol:** Mole; **TLC:** Thin Layer chromatography; **mmol:** Millimole; **NMR:** Nuclear Magnetic Resonance; **ANOVA:** Analysis of variance; **min:** Minute; **IR:** Fourier transform infrared spectrometer.

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Cite this article: Subramanian G, Chand J, Jupudi S, Prudviraj P. Synthesis and Biological Evaluation of the Selected Naphthalene Substituted Azetidinone Derivatives Targeting Parkinson's Disease. Indian J of Pharmaceutical Education and Research. 2023;57(2):552-8.