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Determination of Analgesic Potential of Dibenzylidene Derivatives of Cyclohexanone

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Pain is significantly associated with most disease states, and the search for suitable analgesic alternatives with fewer side effects is continuous and urgent.
Aim of the study: This study is aimed at the evaluation of the analgesic potential of cyclohexanone derivatives which include; 2, 6 (P-dimethylaminobenzylidene) cyclohexanone, 2,6-bis[(4-methoxyphenyl) methylidene] cyclohexan-1-one, 2,6-diethylidenecyclohexan-1-one, 2,6-dibenzylidenecyclohexan-1-one, and 2,6-dibenzodioxylmethylidenecyclohexan-1-one (D_1-D_5 respective).
Methodology: The study measured analgesia potential using the hot plate and tail flick model. The mice were divided into five groups, (GP): GP I and V were control group (0.2 ml/kg distilled water) and standard group (50 mg/kg Tramadol Hydrochloride) respectively, GP II to IV were administered

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the different doses (500, 1000, and 1500 mg/kg) of the test compounds respectively, and evaluated 30 min afterward. The latency to pain was observed at 30 minutes, 60 minutes and 90 minutes at doses of 500, 1000, and 1500 mg/kg respectively.

Results: The hot plate model showed significance in pain inhibition with D_1 proven 45.5 %, 59% at 60 min,90 min respectively, and a significant ($p < 0.0008$) increase in latency to pain at 90 mins with the dose of 1500 mg/kg. D_5 proven 45.2%, 48.9%, and 79.8% pain inhibition at 30, 60 and 90 min respectively with 500 mg/kg; 75.4%, 71.9%, and 85.9% pain inhibition at 30,60 and 90 min respectively with 1000 mg/kg; 40.1%, 65.5% and 80.5% pain inhibition at 30, 60 and 90 min respectively with 1500 mg/kg and significant ($p < 0.0001$) increase latency to pain at 90 minutes with the doses, 500 mg/kg, 1000 mg/kg, and 1500 mg/kg.

Conclusion: The study gave an insight into the analgesic potential of the Cyclohexanone derivatives. D_1 and D_5 derivatives exhibited remarkable analgesic potential in the hot plate model, and the study outcomes suggest their useability as adjuvants in the management of pain, especially in veterinary patients.

Keywords: Analgesia; cyclohexanone derivatives; hot plate; pain inhibition; tramadol hydrochloride.

1. INTRODUCTION

Pain is an unpleasant sensory experience that can originate from any part of the body and be caused by inflammation or injury. Concerns or a need to find a solution by whatever means are always there among those impacted by either situation [1]. Pharmacological methods are the most commonly used techniques for pain relief. These medications come from different sources as well as classes but have side effects. These side effects are sometimes concerning and costly. Hepatic toxicity, depression, dysphoria, hallucinations, mydriasis, euphoria, tachycardia, miosis, drowsiness, disorientation, hormonal changes, bleeding, flushing, seizures, abortion, heartburn, nausea, vomiting, diarrhoea, dizziness, constipation, indigestion, hypoxia, hyperplasia, tolerance, dependency, and decreased testosterone levels are some of the many adverse effects. The urgent requirement of society in this area must thus be met by pharmaceutical and medical researchers. Since many phenomena and mechanisms underlying nociception processes have been developed, medicines can now be customised based on the mechanism underlying the development of pain [2]. Among these drug agents and their analogues is benzylidene acetophenone, a synthetic drug whose analogues have shown a structural activity relationship in the context of behavioural modulation and experimental seizure control [3]. The synthetic agent benzylideneacetone maintains an interesting molecule, an aromatic-ketone and enone. The compounds, benzaldehyde with acetone are combined in an aldol condensation with sodium hydroxide acting as a catalyst to produce dibenzylidene acetone. The natural compound flavonoids, are common in plants that are mostly safely consumed, can be recreated in the laboratory from dibenzylidene-acetone with various substitutions on the aromatic rings [4]. According to Kulkarni and Totre [4], most dibenzylidene-acetones, whether it is produced synthetically or natively, are relatively employed in human medicine. The compound dibenzylidene-acetone is said to be an intermediate laboratory based recreation of heterocyclic compounds, including -isoxazoles, -quinolones, -thiadiazines, and –flavones. It goes through a number of chemical processes [4]. The flavone cyclohexanone, often referred to as a pimelic ketone, ketohexamethylene, or oxycyclohexane, is a significant derivative of the dibenzylidene acetone derivative [5]. With the chemical formula $CO(CH_2)_5$, cyclohexanone is a compound with six-carbon and oxygen-atoms. It contains the effective group, α, β-unsaturated carbonyl compound, and is also known as Chalcone and has a broad spectrum of bio-activities due to chalcone composition, and as a result, plays a significant role in biochemistry and medicine. Its therapeutic properties include its use against viruses, cancerous cells, and infections [5]. Disubstituted benzimidazole derivatives were tested for *in vivo* analgesic efficacy in a recent study conducted by Saha *et al*.,[6]. It was found that at a dose of 25 mg/kg, the compounds showed encouraging analgesic action of about 88.81%, which was comparable to the analgesic effect of 25 mg/kg aceclofenac (88.81%). They also reduced writhing by 89.55%, respectively, at a dose of 50 mg/kg. The benzimidazole derivatives in this investigation had an antinociceptive effect similar to that of the NSAID aceclofenac [7]. The primary mechanism of action for this class of medications is the

inhibition of COX enzyme, specifically COX-2 in the case of aceclofenac, which prevents prostaglandin formation.

2. METHODOLOGY

2.1 Drugs and Chemicals

The standard drug used in this study was Tramadol Hydrochloride BP, 50 mg with brand name, WIZTRAM-100 capsules, with NAFDAC REG NO- C4-1529, with BATCH No. CE1023 purchased from a community pharmacy (Keto-divine, Amassoma, Bayelsa State, Nigeria).

The chemicals used in this study are cyclohexanone derivatives of Dibenzylidene analogs which include:

1. 2,6 (P-dimethylaminobenzylidene) cyclohexanone (D_1)
2. 2,6-bis[(4-methoxyphenyl) methylidene] cyclohexan-1-one (D_2)
3. 2,6-diethylidenecyclohexan-1-one (D_3)
4. 2,6-dibenzylidenecyclohexan-1-one (D_4)
5. 2,6-dibenzodioxylmethylidenecyclohexan-1-one (D_5)

2.2 Animal

The animals used in this study were mainly male mice sourced from the animal house unit of Pharmacology and Toxicology, Niger Delta University. The animals were kept under healthy conditions of light and dark cycle 12:12 hours, with relative humidity of 55-65% and temperature of 24.0±0°C. The mice were taken to the laboratory on daily basis for acclimatization. The animals were exposed to the hot plate without switching on the power as orientation for three days before the practicals commenced, so was the animals for the tail flick model. These were done in accordance with the animal handling rules [8].

2.3 Study Design

Male mice were weighed and divided at random into five (5) with six (6) in each group, this was done for both hot plate and tail flick model respectively. Group I was used as the control group and was administered 0.2 ml/kg of distilled water orally. Group II, III, and IV were orally administered 500 mg/kg, 1000 mg/kg and 1500 mg/kg of the respective test compounds, while Group V was administered 50 mg/kg of the standard drug (Tramadol Hydrochloride). This process was repeated for all the five test compounds which include, D_1 (2,6-bis [(4-dimethylaminophenyl) methylidene] cyclohexan-1-one), D_2 (2,6-bis [(4-methoxyphenyl) methylidene] cyclohexan-1-one), D_3 (2,6-diethylidenecyclohexan-1-one), D_4 (2,6-dibenzylidenecyclohexan-1-one), and D_5 (2,6-dibenzodioxylmethylidenecyclohexan-1-one).

2.3.1 The hot plate model

The hot plate method that was described by Eddy and Leinbach [9], was adopted with modification. Each mouse was orally administered the test compound. After which, it was placed on the hot plate which was electrically heated and was maintained at the temperature of 55 ± 1^0 C and the pain reaction time *(PRT) was recorded per mouse. Each mouse was tested for pain at an interval of 30 minutes, 60 minutes and 90 minutes after administration of the test drugs, respectively. Reactions to pain includes; -jumping, -raising, and –licking of hind/fore paw. This model evaluates central pain [10,11]. Percentage increase in reaction time was calculated as follows:

$$\%\ Inhibition = \frac{Latency\ test\ -\ Latency\ control}{Latency\ test} * 100$$

2.3.2 Tail flick model

This method was described by Uma-Devi [12,11] and was applied with modification. Each mouse was orally administered with the test compound according to prescribed dose in the study design and was observed for reaction to pain in an interval 30 minutes, 60 minutes and 90 minutes after administration. The tail (1-1.5 cm) of every mouse in this study model was immersed into a water bath of temperature 55±1°C and the pain reaction time (PRT) was recorded for all mice in this study. Percentage of increase in reaction time or pain threshold, was calculated as follows [13]:

$$\%\ Inhibition\ = \frac{Latency\ test\ -\ Latency\ control}{cut\ off\ tail\ latency\ -\ Latency\ control} * 100$$

2.4 Statistical Analysis

The laboratory data derived from this study were analysed using Graph Pad Prism 10.2, followed with two way of ANOVA in multiple comparison post hoc test (dunnett). All statistical outcome were presented in the form of Mean ± Standard Error of Mean (SEM) in table form or graph and significant levels were taken as $p < 0.05$.

3. RESULTS

3.1 Hot Plate Model

3.1.1 Latency to pain in hot plate model

The result indicated remarkable analgesic potential in D_1 and D_5 using the hot plate model (Figs. 1 and 5). However, Figs. (2, 3 and 4) did not show statistical significance, but have little biological indication for increase in latency to pain.

3.1.2 Percentage pain inhibition

The result indicated remarkable pain inhibition in D_1 and D_5 using the hot plate model (Table 1 and 5). It is worthy of note that D_5 showed analgesic potential similar to the standard drug especially in time dependent trend in the action (Table 5).

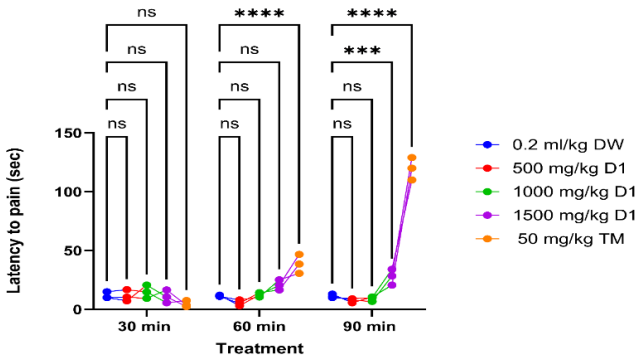

Fig. 1. Showed D_1 at 90 mins; 1500 mg/kg indicated ***significant increase ($p < 0.0008$) latency to pain when compared to the control. D_1= (2,6-bis[(4-dimethylaminophenyl) methylidene] cyclohexan-1-one), TM= Tramadol Hydrochloride

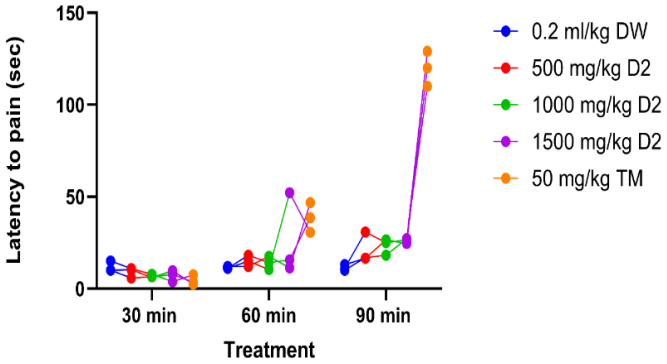

Fig. 2. Showed D_2 indicated no statistically significant increase when compared to the control. D_2= (2,6-bis [(4-methoxyphenyl) methylidene] cyclohexan-1-one).TM= Tramadol Hydrochloride

Table 1. Percentage pain inhibition of 2,6-bis[(4-dimethylaminophenyl) methylidene] cyclohexan-1-one (D_I)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-1.478	-107.243	-50.404
1000	22.044	8.849	-24.958
1500	-6.090	45.528	59.200**
Standard	-159.333	70.700***	90.000****

*Results showed statistical significance, ** = $p < 0.04$, *** = $p < 0.001$ and, **** = $p < 0.0001$*

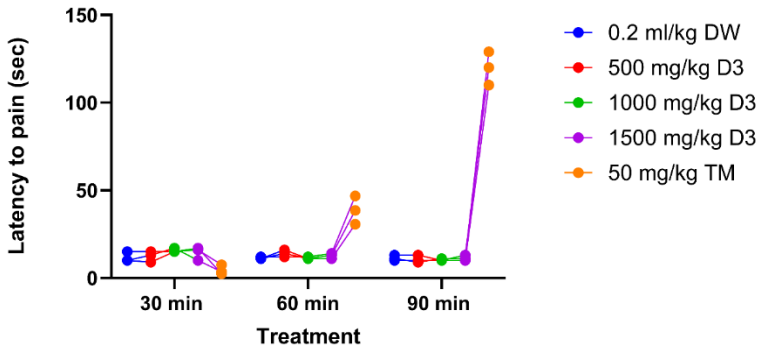

Fig. 3. Showed D_3 indicated no statistically significant increase when compared to the control. D_3 indicated no significance when compared to the control. D_3= (2,6-diethylidenecyclohexan-1-one), TM= Tramadol Hydrochloride

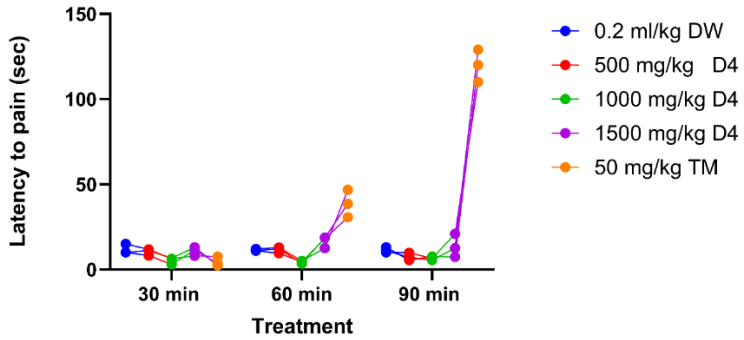

Fig. 4. Showed D_4 indicated no statistically significant increase when compared to the control. D_4 indicated no significance when compared to the control. D_4= (2,6-dibenzylidenecyclohexan-1-one).TM= Tramadol Hydrochloride

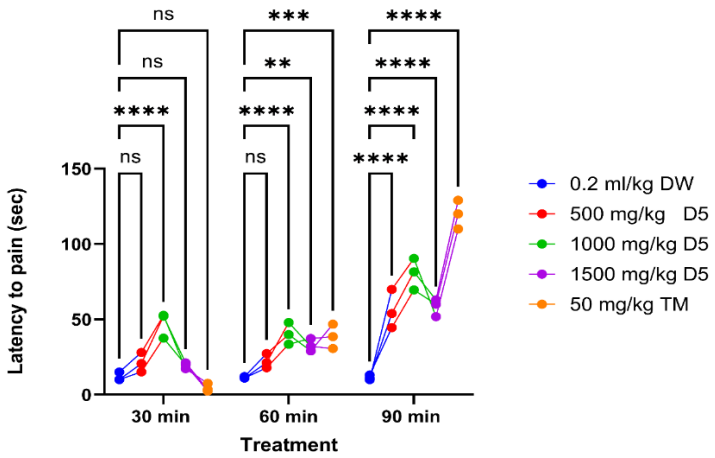

Fig. 5. Showed D_5 at 30 min: 1000 mg/kg indicated * Significantly increased ($p < 0.0001$) latency to pain when compared to the control. 60 min: 1000 mg/kg, 1500 mg/kg of D_5 indicated ****, ** Significance ($p < 0.0001$, 0.002) when compared to the control. 90 min: 500 mg/kg, 1000 mg/kg, 1500 mg/kg of D_5 indicated *** Significance ($p < 0.0001$) when compared to the control. D_5=(2,6-dibenzodioxylmethylidenecyclohexan-1-one). TM= Tramadol Hydrochloride**

Table 2. Percentage pain inhibition of 2,6-bis[(4-methoxyphenyl) methylidene] cyclohexan-1-one (D_2)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	46.970	21.278	11.851
1000	29.161	15.203	15.970
1500	49.341**	49.977**	36.268
Standard	-159.333	70.700***	90.534****

*Results showed statistical significance, ** = p < 0.04, *** = p < 0.001 and, **** = p < 0.0001*

Table 3. Percentage pain inhibition of 2,6-diethylidenecyclohexan-1-one (D_3)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-29.666	24.817	-6.185
1000	-72.454	19.244	-9.680
1500	-63.605	57.083**	28.333
Standard	-159.333	70.700***	90.534****

*Result showed statistical significance, ** = p < 0.04, *** = p < 0.001 and, **** = p < 0.0001*

Table 4. Percentage pain inhibition of 2,6-dibenzylidenecyclohexan-1-one (D_4).

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-12.211	2.074	-50.404
1000	-17.44	-16.482	-73.427
1500	-7.756	31.202	16.691
Standard	-159.333	70.700***	90.534****

*Result showed with statistical significance, *** = p < 0.001 and, **** = p < 0.0001*

Table 5. Pain inhibition of 2,6-dibenzodioxylmethylidenecyclohexan-1-one (D_5)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	45.211	48.894	79.814****
1000	75.416***	71.976***	85.920****
1500	40.061	65.457**	80.542****
Standard	-159.333	70.700***	90.534****

*Result showed statistical significance, ** = p < 0.04, *** = p < 0.001 and, **** = p < 0.0001*

3.2 Tail flick Model

3.2.1 Latency to pain in tail flick model

The result indicated no analgesic potential in D_1 to D_5 using the tail flick model (Figs. 6-10). However, Figs. 6 – 10 indicated significant statistical decrease in latency to pain compared to the control.

3.2.2 Percentage pain inhibition in tail flick model

The percentage pain inhibitions are presented in Tables 6-10 below, and corresponds with results as shown in Figs. 6- 10, as no derivative showed any significant increase in the tail flick model test.

Table 6. Percentage pain inhibition of 2,6-bis[(4-dimethylaminophenyl) methylidene] cyclohexan-1-one (D_I)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-322.845	16.55ns	11. 000ns
1000	-326.555	-81.765	-282.444
1500	-339.545	-118.144	-163.400
Standard	-110.217ns	-49.687ns	46.481ns

Result showed no statistical significance = ns

Table 7. Percentage pain inhibition of 2,6-bis[(4-methoxyphenyl) methylidene] cyclohexan-1-one (D_2)

Treatment (mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	).000	0.000
500	-233.256	774.414	-642.931
1000	-106.860	483.125	-242.282
1500	-262.580	-233.214	-182.687
Standard	-110.217^{ns}	-49.687^{ns}	46.481^{ns}

Result showed no statistical significance = ns

Table 8. Percentage pain inhibition of 2,6-diethylidenecyclohexan-1-one (D_3)

Treatment(mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-2333.256	-774.414	-642.931
1000	-1060.861	-483.125	-242.282
1500	-262.583	-233.214	-182.687
Standard	-110.217^{ns}	-49.687^{ns}	46.481^{ns}

Result showed no statistical significance = ns

Table 9. Percentage pain inhibition of 2,6-dibenzylidenecyclohexan-1-one (D_4).

Treatment(mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	0.000	0.000	0.000
500	-559.168	-200.968	-364.381
1000	-383.523	-599.925	-465.558
1500	-867.000	-1650.472	-1082.814
Standard	-110.217^{ns}	-49.687^{ns}	46.481^{ns}

Result showed no statistical significance = ns

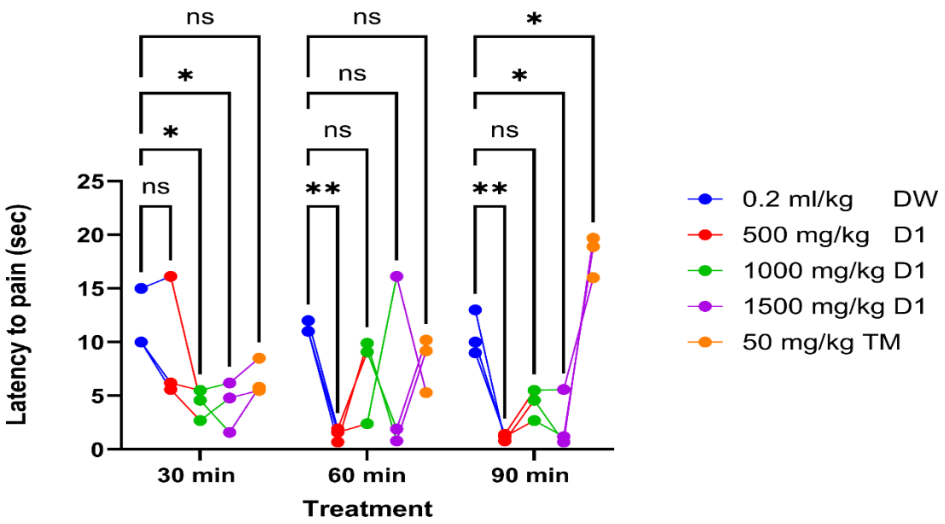

Fig. 6. Showed D_1 at 30 min: 1000 mg/kg indicated * significantly reduced when compared to the control with Adjusted p<0.02; 60 min: 500 mg/kg of D1 indicated ** Significantly reduced latency to pain when compared to the control with Adjusted p<0.002.; 90 min: 500 mg/kg and 1500 mg/kg of D_1 indicated **, * Significantly reduced when compared to the control with Adjusted p<0.002, 0.02. D1=(2,6-bis[(4-dimethylaminophenyl) methylidene] cyclohexan-1-one), TM= Tramadol Hydrochloride

Table 10. Percentage pain inhibition of 2,6-dibenzodioxylmethylidenecyclohexan-1-one (D_5).

Treatment mg/kg)	30 minutes (%)	60 minutes (%)	90 minutes (%)
Control	). 000	0.000	0.000
500	57.480	-39.042	-19.023^{ns}
1000	56.9042	-71.150	-30.092^{ns}
1500	29.203^{ns}	-13.825^{ns}	-7.000^{ns}
Standard	110.217	-49.687	46.481^{ns}

Result showed no statistical significance = ns

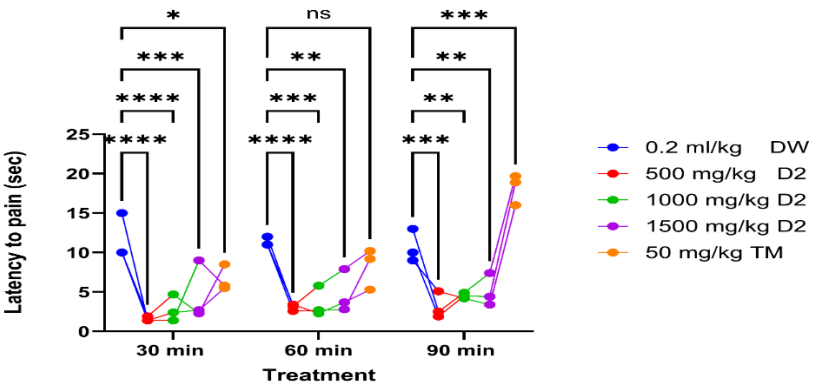

Fig. 7. Showed D_2 at 30 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg of D_2 indicated **, ****, *** significantly reduced latency to pain when compared to the control with adjusted p<0.0001, 0.0001, 0.0008. At 60 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ****, ***, ** significantly reduced when compared to control with adjusted p< 0.0001, 0.0002, 0.0017. At 90 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ***, **, **, significantly reduced when compared to the control with adjusted p <0.0003. 0.0032. 0.0073. D_2= (2,6-bis [(4-methoxyphenyl) methylidene] cyclohexan-1-one). TM= Tramadol Hydrochloride**

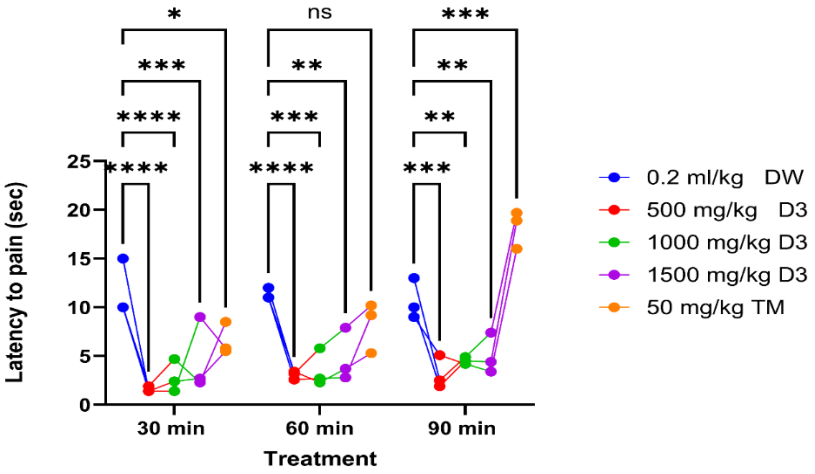

Fig. 8. Showed D_3 at 30 mins; 500 mg/kg, 1000 mg/kg. 1500 mg/kg indicated **, ****, *** significantly reduced latency to pain compared to the control with adjusted p<0.0001, <0.0001, 0.0008. At 60 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ****, ***, ** significantly reduced compared to the control with adjusted p<0.0001, 0.0002, 0.0017. At 90 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ***, **, ** significantly reduced compared to the control with adjusted p<0.0003, 0.0032, 0.0073. D3= (2,6-diethylidenecyclohexan-1-one), TM= Tramadol Hydrochloride**

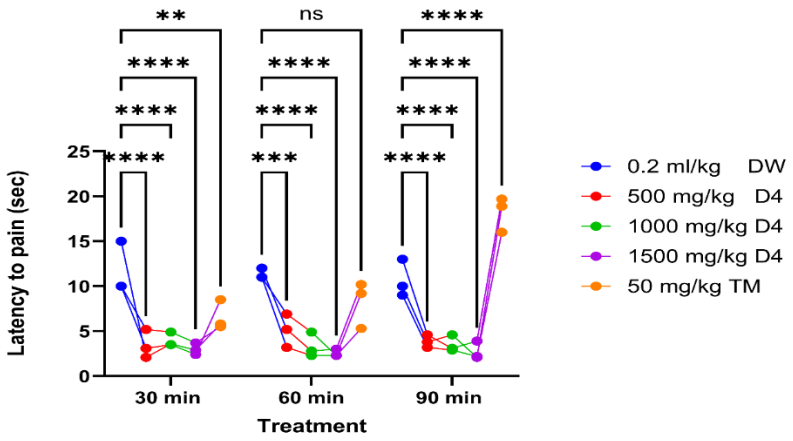

Fig. 9. Showed D_4 at 30 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated **, ****, **** significantly reduced latency to pain compared to the control DW 0.2 ml/kg, with adjusted p < 0.0001, < 0.0001, < 0.0001. At 60 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ***, ****, **** significantly reduced with adjusted p < 0.0001, < 0.0001, < 0.0001. At 90mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ****, ****, **** significantly reduced compared to the control DW 0.2 ml/kg, with adjusted p<0.0001, <0.0001, <0.0001. D_4= (2,6-dibenzylidenecyclohexan-1-one).TM= Tramadol Hydrochloride.**

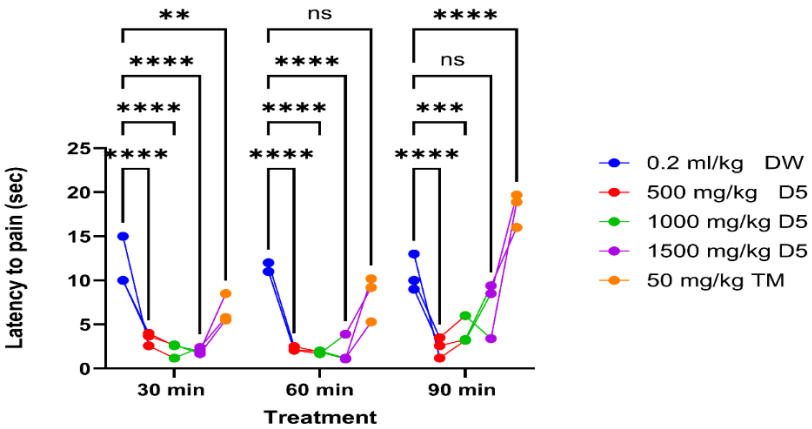

Fig. 10. Showed D_5 at 30 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated **, ****, **** significantly reduced latency to pain compared to the control DW 0.2 ml/kg with adjusted p < 0.0001, < 0.0001, < 0.0001. At 60 mins; 500 mg/kg, 1000 mg/kg, 1500 mg/kg indicated ****, ****, **** significantly reduced compared to the control DW 0.2 ml/kg with adjusted p < 0.0001, < 0.0001, < 0.0001. At 90 mins; 500 mg/kg, 1000 mg/kg indicated ****, **** significantly reduced compared with the control DW 0.2 ml/kg with adjusted p < 0.0001, < 0.0003. D_5=(2,6-dibenzodioxylmethylidenecyclohexan-1-one). TM= Tramadol Hydrochloride**

4. DISCUSSION

The medicines that are employed in pain management, do so without affecting consciousness as they act selectively on the central or peripheral neural systems. These medications which are also referred to as analgesics raises the pain threshold, hence prolonging pain reaction time apparently. On the other hand, medications with peripheral actions, like aspirin and naproxen, work by preventing the chemoreceptors from producing pain signals. The tail flick and hot plate models were used to examine the analgesic properties of the test compounds [14]. The hot plate is useful for evaluating centrally acting analgesics, which are widely used to raise the heat-induced pain in mice. It is known to provide primarily supra-

spinally integrated response [15]. The hot plate model, D_1 (2,6-bis [(4-dimethylaminophenyl) methylidene] cyclohexan-1-one), showed that there was a significant increase ($p < 0.0008$) at 90 mins with the dose of 1500 mg/kg compared to the control group, Fig. 1. Correspondingly, the percentage pain inhibition also reflected a remarkable value of 59.2% when compared to the control group as seen in Table 1. This result suggested that D_1 could obviously prolong latency to pain induced by heat, revealing that D_1 has effective analgesic activity at a high dose, although the onset of action was prolonged, this may gives an advantage of its use as an adjuvant in management of sub-chronic or chronic pain [16]. It is widely believed that delayed withdrawal reactions typically involve higher processes of the central nervous system, that are thought to be required for the processing of "pain"[17]. Similarly, in the hot plate model, the test compound D_5 (2,6-dibenzodioxylmethylidenecyclohexan-1-one), showed significant ($p< 0.0001$) increased latency to pain compared to the control at an interval of 30 minutes with the dose 1000 mg/kg; significant ($p< 0.0001$, 0.002) increased latency to pain at an interval of 60 minutes with the doses 1000 mg/kg, 1500 mg/kg respectively. Significant ($p< 0.0001$) increase latency to pain at an interval of 90 minutes with the doses, 500 mg/kg, 1000 mg/kg, and 1500 mg/kg as shown in Fig. 5. The pain inhibition percentage gave values of 45.2%, 48.9% and 79.8% at an interval of 30, 60 and 90 minutes respectively, for 500 mg/kg. For dose 1000 mg/kg, 75.4%, 72.0%, 85.9% at an interval of 30, 60 and 90 minutes respectively were found. While for dose 1500 mg/kg, 40.1%, 65.5%, and 80.5% at an interval of 30, 60, and 90 minutes respectively, were found (Table 5). The dose of 1500 mg/kg showed consistency in significant increase at all levels. One plausible explanation for the test chemicals' propensity to operate centrally as an analgesic could be that they activate the periaqueductal grey matter (PAG), which releases endogenous peptides like enkephalin and endorphin. According to Yimer *et al*.,[16], these endogenous peptides act as inhibitors of pain impulse transmission at the synapse in the dorsal horn of the descending spinal cord. The tail flick result showed significant reduction in pain threshold as shown in Figs. 6-10 of the test substances, 2,6-bis [(4-dimethylaminophenyl) methylidene] cyclohexan-1-one (D_1), 2,6 dimethoxybenzylidene (D_2), 2-methylidene-1, 3-bis (propan-2-ylidene) cyclohexane (D_3), 2,6-dibenzylidenecyclohexan-1-one (D_4), 2,6-dibenzodioxylmethylidene cyclohexan-1-one (D_5). Other reasons could be responsible for such results as well, being that pain threshold depends on the state of an animal, a state of distraction, strong emotion and depression evokes a lowered pain threshold. Also, pain can be said to be heterogenous, regarding etiological factors, mechanism and temporal characteristics [18].

5. CONCLUSION

The study results showed D_1 (2,6-bis [(4-dimethylaminophenyl) methylidene] cyclohexan-1-one) and D_5 (2,6-dibenzodioxylmethylidene cyclohexan-1-one) to have remarkable analgesic potential. This study outcomes suggest that the cyclohexanone derivatives are potential agents that can be further developed as adjuvants in the management of pain.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

ETHICAL APPROVAL

The study protocol was ethically approved by the Department of Pharmacology Ethical Committee, with registration identity as NDU /PHARM /AEC /043a.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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