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Development of Novel Substituted 1,2,3,4-tetrahydro Cyclohex-1,2,3-trihydro Cyclopenta [B] Indole Derivatives as Potential Therapeutic Agents

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Abstract: ***The current study aims to synthesize, characterize, and evaluate a specific class of heterocyclic compounds called fused polycyclic indoles, in combination with carbazoles, carbolines, and their partially saturated counterparts. These compounds have been known to have potent biological activity. The study's procedures involve synthesizing these compounds and evaluating them for central nervous system activity. Results showed that all the compounds had CNS-depressing effects in mice. Some compounds, such as YA1 and YA5, were found to have a stronger CNS-depressing activity than others. All compounds tested, YA1 to YA7, caused more than 50% change in locomotor activity when compared to a standard drug. YA3 and YA5 were found to have the highest activity at 86.2% and 83.9% respectively after 120 minutes of administration at a dose of 100 mg/kg. In addition, the acute oral toxicity studies showed that YA3 was non-toxic and YA5 was found to be toxic. The findings of the study provide evidence that these title compounds have good CNS activity.***

Keywords: Heterocyclic compounds, Fused polycyclic indoles, Carbazoles, Carbolines, Central nervous system activity, CNS-depressing activity, Locomotor activity, Acute oral toxicity studies.

I. INTRODUCTION

Fused polycyclic indoles, which include carbazoles, carbolines, and their partially saturated versions, are a well-known group of heterocyclic compounds that have a wide range of biological activity. Some of these compounds have been used as anxiolytics, anticancer agents, antioxidants, and inhibitors of HIV integrase. Therefore, the creation and modification of indoles has been a focus of research for more than a century.[1], [2]

Carbazole derivatives are an important group of heterocyclic compounds that display a wide range of biological activity [3], [4]. These compounds, which include natural products with a carbazole skeleton, have received significant attention due to the excellent pharmacological properties of their analogues. Literature shows that carbazole derivatives have been linked to a wide range of biological activity, including antibacterial [5], [6], anti-inflammatory [7], analgesic, anti-viral [8], antifungal [9], anti-tubercular, and anti-depressant [10] activities.

Indolocarbazoles are a significant class of antibiotics that are effective against tumors, such as by inhibiting protein kinase C (PKC). Carbazole derivatives are also commonly used in organic materials for their ability to change in response to light (photorefractive), conduct electricity in response to light (photoconductive), and emit light (light-emitting). Therefore, the development of new methods to create modified carbazoles has been an area of interest. Among the various methods available, those that use indole derivatives as the starting material have often been found to be very successful[11]

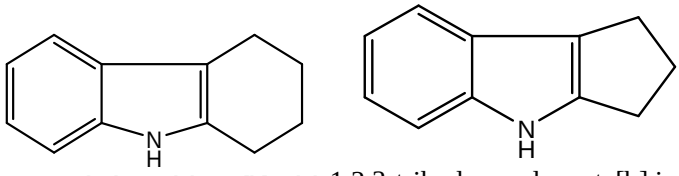
Anxiety is a complex emotional state characterized by feelings of worry, uneasiness, and fear. It can be triggered by psychological stress or an unknown source. The physical symptoms of anxiety are similar to those of fear and involve the activation of the sympathetic nervous system. Anxiety is associated with increased activity in the neurotransmitter GABA, which can lead to an opening of chloride channels that are activated by GABA[12]

The ability to move from one place to another, known as locomotor activity (LMA), is often studied in psychopharmacology by monitoring the movement of lab animals. This is done to understand the effects of drugs on the behavior of these animals. Locomotor activity is a useful and less complex method of evaluating behavior than other tests, such as the radial arm maze and operant conditioning. It is widely used in initial evaluations of drugs.

Previous research has shown that many derivatives of fused indoles have strong central nervous system activity [13]. Taking this into account, it was considered valuable to synthesize new versions of 1,2,3,4-tetrahydro cyclohexa/1,2,3-trihydro cyclopenta [b] indole derivatives and test their central nervous system activity.

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1,2,3,4-tetrahydro cyclohexa [b] indole 1,2,3-trihydro cyclopenta[b] indole

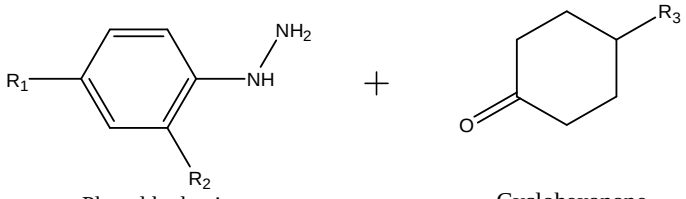
Fig. 1 1,2,3,4-tetrahydro cyclohexa/1,2,3-trihydro cyclopenta [b] indole

II. MATERIALS AND METHODS

The study used chemicals obtained from commercial suppliers that were of Merck grade and were used without any further purification. The melting points of the compounds were determined using open capillary tubes on an electrical melting point apparatus, and the results were not corrected. The chemical shifts in the 1H-NMR spectra were recorded using a Bruker NMR 400 MHz spectrophotometer and DMSO-d6 as a solvent. The IR spectra of the synthesized compounds were recorded using a Bruker FT-IR spectrophotometer with KBr pellets. The progress of the reaction and the purity of the compounds were checked using TLC on pre-coated silica gel G plates and chloroform: methanol (19:1) as a mobile phase and visualized under UV light. Swiss albino mice weighing between 25-30 g of either sex were randomly selected, housed 8 per cage, and used in the study which was conducted at the Department of Pharmacology, Netaji Institute of Pharmaceutical Sciences, Warangal. The protocol was approved by the Institutional Animal Committee (IAEC Regd. No. 1287/PO/Re/S/2009/CPCSEA) and all experiments were carried out in compliance with guidelines for the care and use of laboratory animals. Statistical tests are performed using IBM SPSS software (Trial version) at 5% level of significance.

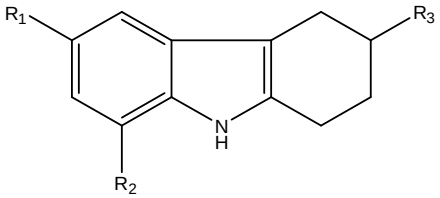
A. Procedure for the synthesis of 6,8-Dinitro-1,2,3,4-tetrahydro cyclohexa [b] indole:

A novel method was used in which a round-bottomed flask was equipped with a reflux condenser, and 0.01 moles of Cyclohexanone (1.03 ml) and 7 ml of acetic acid were added to it. The mixture was heated and stirred for 30 minutes at 120 degrees Celsius, then 0.01 moles of 2,4-dinitro phenyl hydrazine (1.98 g) was added and refluxed for another hour. The reaction was tracked using TLC. The mixture was poured into ice and stirred until it solidified. The resulting solid was filtered, dried and recrystallized from ethanol. The scheme and mechanism involved in the synthesis are shown below:



Phenyl hydrazine Cyclohexanone

120^0C, 2 hrs — Glacial acetic acid



1,2,3,4-tetrahydro cyclohexa [b] indole

R_1= -NO_2
R_2= -NO_2, -H
R_3= -CH_3, -H

Fig. 2 Experimental scheme

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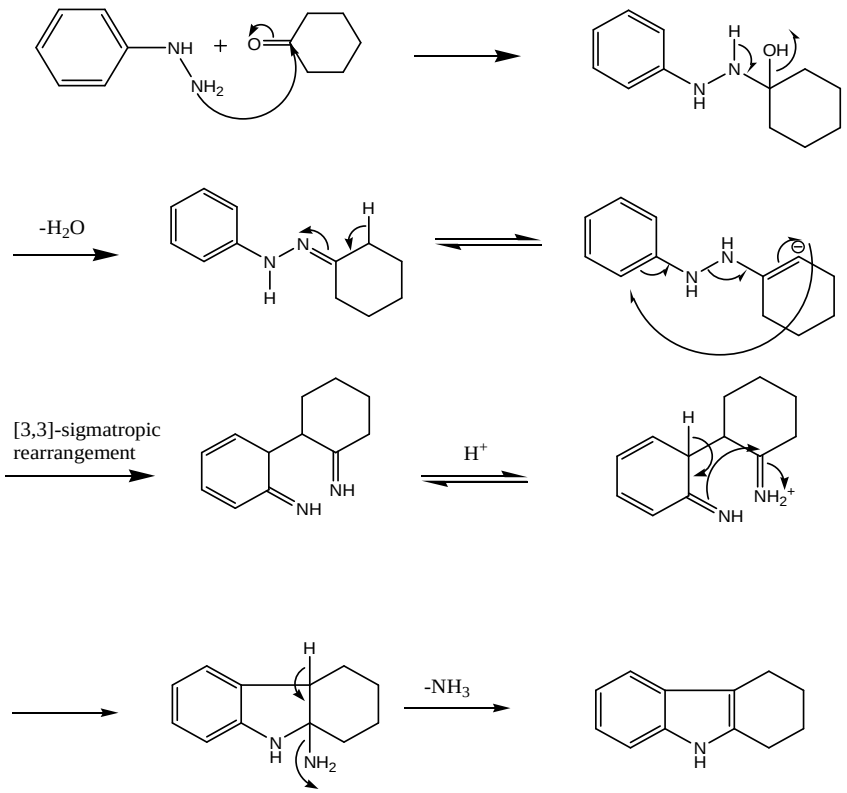


Fig. 3 Mechanism of reaction involved in the synthesis of indole derivatives

B. CNS Activity

1) *Animals:* The study used Swiss albino mice (both male and female), weighing 25-30 g, which are chosen randomly and housed 8 per cage. The experiments were carried out in the Department of Pharmacology at Netaji Institute of Pharmaceutical Sciences, at Warangal. The protocol for the study had been approved by the Institutional Animal Committee (IAEC Regd. No. 1287/PO/Re/S/2009/CPCSEA) and all experiments were carried out in compliance with guidelines for the handling and use of laboratory animals [14].
2) *Preparation of animals:* The animals were grouped and given a set dose of the test compounds suspended in 0.1% Sodium CMC, orally at a dose of 100 mg/kg body weight. The control group animals received only the vehicle (0.1% Sodium CMC). The response, or counts, were recorded 30 minutes after the administration of the drug or test compound. The scores or number of deflections were recorded and then compared to the standard by placing the animals in the actophotometer for 10 minutes. The gross behavioral changes were also continuously observed for 5 hours at 1 hour intervals after the administration of the compounds. The observations were then recorded intermittently for 24 hours and compared with the control group.
3) *Preparation of 0.1% w/v carboxy methyl cellulose:* A 0.1% w/v solution of sodium carboxy methyl cellulose (sodium CMC) was prepared by dissolving 100mg of the substance in 100ml of distilled water.
4) *Preparation of standard drug solution:* Diazepam as the standard drug, it was at a concentration of 5mg/ml. Dilutions were created by using a 0.1% w/v solution of carboxy methyl cellulose.
5) *Preparation of doses:* Diazepam as the standard drug, it was at a concentration of 5mg/ml. Dilutions were created by using a 0.1% w/v solution of carboxy methyl cellulose.
6) *Testing procedure:* A device known as an actophotometer was used to observe the movement of lab animals, which uses photoelectric cells connected to a counter. When the light beam on the cells is interrupted by the animals' movement, a count is recorded. Healthy mice were used in the study, and were fasted overnight and divided into groups of 5. The standard drug Diazepam was used, and the test compounds were given at a dose of 100 mg/kg orally. The control group only received the vehicle. The response was recorded after 30 minutes and compared to the standard. Behavioral changes were also observed for 5 hours at 1 hour intervals and recorded intermittently for 24 hours, and compared to the control group [14].

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B. Acute oral toxicity studies-OECD423:

The outcome of one step, whether there is compound-related mortality or not, determines the next step in the process. This may involve continuing to the next dose level, repeating the same dose level with additional animals, or discontinuing the study if no toxicity is observed [15]. The presence or absence of compound-related mortality in animals dosed at one step determines the next step in the process.

1) If no mortality occurs, no further testing is needed
2) If mortality occurs, three additional animals will be dosed with the same dose
3) If mortality still occurs, three additional animals will be dosed at the next lower or higher dose level.

a) *Administration of Doses:* The test substance was administered in a single dose by using a stomach gavage technique. However, in certain circumstances, where a single dose is not feasible, the dose can be given in smaller portions over a period of not more than 24 hours. However, in this study, it was not required as the dose was given at once. The animals were kept without food overnight during the drug administration period and had unrestricted access to water. After the fasting period, the weight of the animals was recorded and then the test substance was administered. The animals were given food three hours later.

b) *Nature of Animals and Dose Levels:* The study used three animals for each step of the process. The initial dose was selected from a set of four fixed levels: 5, 50, 300, and 2000mg/kg body weight. The chosen starting dose was the one that was most likely to cause death in some animals. The time interval between treatment groups was established based on the duration, onset and severity of toxic effects. The next dose was not administered until the survival of the previous group was confirmed. The dose level of 2000 mg/kg was selected as the starting point.

c) *Observation:* The animals were closely monitored after receiving the dose, with special focus on the first 30 minutes and the first 24 hours, as well as daily for 14 days. The length of observation period may be extended if necessary, based on the severity of the toxic reactions, when they occur, and how long it takes for the animals to recover. All the data collected was recorded and kept for each individual animal.

III.RESULTS AND DISCUSSION

A series of novel substituted 1,2,3,4-tetrahydro cyclohexa / 1,2,3-trihydro cyclopenta [b] indole derivatives has been synthesized using the appropriate synthetic procedures. The physical data of the compounds is shown in Table I.

1) *Spectral data of novel substituted 1,2,3,4-tetrahydro cyclohexa / 1,2,3-trihydro cyclopenta [b] indole derivatives:* The IR spectra exhibited a prominent single peak at (3500-3200 cm-1), which is characteristic of a secondary amino group, indicating the formation of the expected product. The ^{1}H NMR (400 MHz, CDCl3) showed peaks at δ 1.73-1.69 multiplet with four protons at 2nd & 3rd position, δ 1.80-1.78 triplet with four protons at 1st& 4th position, δ 7.95 singlet with one proton at 9th position, δ 8.27 with singlet at 7th position, δ 11.201 singlet with one proton -NH, indicating the formation of 6,8-Dinitro-1,2,3,4-tetrahydro cyclohexa [b] indole (YA1).

a) *YA_1: 6,8-Dinitro-1,2,3,4-tetrahydro cyclohexa [b] indole*
^{1}H NMR (400 MHz, $CDCl_3$)δ: 1.73-1.69 (m, 4H, CH_2 at 2,3), 1.80-1.78 (t, *J* =2.8 Hz, 4H, C<u>H</u>$_2$ at 1,4), 7.95 (s, 1H, CH at 9), 8.27 (s, 1H, CH at 7), 11.2 (s, 1H, -N<u>H</u>).
IR [Cm^{-1}, KBr]: 3307.67 (-NH), 2924.52 (CH_2, C-H stretch), 1588.21 (Ar.C=C), 1333.78 (C-N),1500 (Ar.C-NO_2).
The ^{1}H NMR (400MHz, $CDCl_3$) showed peaks at δ 1.91-1.84 multiplet with two protons at 3rd position, δ 2.02-1.96 multiplet with two protons at 2nd position, δ 2.49-2.45 triplet with two protons at 1st position, δ 7.91 singlet with one proton at 8th position, δ 9.12 singlet with one proton at 6th position, δ 10.81 singlet with one proton -NH indicating formation of 5,7-Dinitro-1,2,3-trihydro cyclopenta [b] indole (YA_2).

b) *YA_2:5,7-Dinitro-1,2,3-trihydro cyclopenta [b] indole*
1H NMR (400 MHz, CDCl3) δ: 1.91-1.84 (m, 2H, CH2 at 3), 2.02-1.96 (m, 2H, CH2 at 2), 2.49-2.45 (t, J =7.2 Hz, 2H, CH2 at 1), 7.91 (s,1H, CH at 8), 9.12 (s, 1H, CH at 6), 10.81 (s, 1H, -NH).
IR [Cm-1, KBr]: 3309.5 (-NH),1585.79 (Ar.C=C), 1306.74 (C-N),1503.32 (Ar.C-NO2).
MASS (m/z):247 (M+), 248 (M+1).
The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.91-1.84 pentet with two protons at 3rd position, δ 2.02-1.96 pentet with two protons at 2nd position, δ 2.49-2.45 triplet with two protons at 4th position, δ 2.60-2.56 triplet with two protons at 1st position, δ 7.96-7.93 doublet with one proton at 7th position, δ 8.30-8.37 doublet of doublet with one proton at 6th position, δ 9.13 singlet with one proton at 9th position, δ 10.81 singlet with one proton -NH indicating formation of 8-Nitro-1,2,3,4-tetrahydro cyclohexa [b] indole (YA3).

c) *YA_3: 8-Nitro-1,2,3,4-tetrahydro cyclohexa [b] indole*

1H NMR (400 MHz, CDCl3) δ: D.1.91-1.84 (p, J = 6.9 Hz, 2H, CH2 at 3), 2.02-1.96 (p, J = 6.9 Hz, 2H, CH2 at 2), 2.49-2.45 (t, J =7.2 Hz, 2H, CH2 at 4), 2.60-2.56 (t, J =7.2 Hz, 2H, CH2 at 1), 7.96-7.93 (d, J = 9.6 Hz, 1H, CH at 7), 8.30-8.37 (dd, J = 9.3 Hz, 1H, CH at 6), 9.13 (s, 1H, CH at 9), 10.81 (s, 1H, -NH).

IR [Cm-1, KBr]: 3310.96 (-NH), 2930 (CH2, C-H stretch), 1521 (Ar.C=C), 1306 (C-N),1501.56 (Ar.C-NO2).

The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.01-1.00 doublet with three protons -CH3, δ 1.34-1.19 multiplet with two protons at 4th position, δ 1.82-1.72 multiplet with two protons at 2nd position, δ 2.03-1.95 multiplet with two protons at 3rd position, δ 2.17-2.09 multiplet with one proton at 1st position, δ 2.39-2.31 multiplet with one proton at 1st position, δ 8.02 singlet with one proton at 9th position, δ 8.31-8.28 doublet of doublet with one proton at 6thposition, δ 9.15-9.14 doublet with one proton at 7th position, δ 11.18 singlet with one proton -NH indicating formation of 2-Methyl-8-nitro-1,2,3,4-tetrahydro cyclohexa [b] indole(YA4).

d) *YA_4: 2-Methyl-8-nitro-1,2,3,4-tetrahydro cyclohexa [b] indole*

1H NMR (400 MHz, CDCl3) δ:1.01-1.00 (d, J = 6.8 Hz, 3H, -CH3), 1.34-1.19 (m, 2H, -CH2 at 4), 1.82-1.72 (m, 1H, -CHat 2), 2.03-1.95 (m, 2H, CH2 at 3), 2.17-2.09 (m, 1H, CH2 at 1), 2.39-2.31 (m, 1H, CH2 at 1), 8.02 (s, 1H, -CH at 9), 8.31-8.28 (dd, J = 4 Hz, 1H, -CHat 6), 9.15-9.14 (d, J = 4 Hz, 1H, -CH at 7), 11.18 (s,1H,-NH).

IR [Cm-1, KBr]: 3278.02(-NH), 1599.12 (Ar.C=C), 1333 (C-N),1504 (Ar.C-NO2).

The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.017-1.000 doublet with three protons -CH3, δ 1.34-1.19 multiplet with two protons at 4th position, δ 1.82-1.72 multiplet with two protons at 2nd position, δ 2.03-1.95 multiplet with two protons at 3rd position, δ 2.17-2.09 multiplet with one proton at 1st position, δ 2.39-2.31 multiplet with one proton at 1st position, δ 7.97 singlet with one proton at 9th position, δ 9.12 singlet with one proton at 7th position, δ 11.18 singlet with one proton -NH indicating formation of 2-Methyl-6,8-dinitro-1,2,3,4-tetrahydro cyclohexa [b] indole(YA5).

e) *YA_5: 2-Methyl-6,8-dinitro-1,2,3,4-tetrahydro cyclohexa [b] indole*

1H NMR (400 MHz, CDCl3)δ: 1.01-1.00 (d, J = 6.8 Hz, 3H, -CH3), 1.34-1.19 (m, 2H, -CH2 at 4), 1.82-1.72 (m, 1H, -CHat 2), 2.03-1.95 (m, 2H, CH2 at 3), 2.17-2.09 (m, 1H, CH2 at 1), 2.39-2.31 (m, 1H, CH2 at 1), 7.97 (s, 1H, -CH at 9), 9.12 (s,1H,-CH at 7), 11.18 (s,1H,-NH).

IR [Cm-1, KBr]: 3355.34 (-NH), 2854 (CH2), 2924 (CH3), 1596 (Ar.C=C), 1304.97 (C-N), 1504 (Ar.C-NO2).

The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.44-1.40 triplet with two protons at 3rd position, δ 2.72-2.69 triplet with two protons at 2nd position, δ 2.83-2.80 triplet with two protons at 1st position, δ 8.19-8.17 doublet with one proton at 5th position, δ 8.38-8.36 doublet with one proton at 6th position, δ 8.56 singlet with one proton at 8th position, δ 12.55 singlet with one proton -NH indicating formation of 7-nitro-1,2,3-trihydro cyclopenta [b] indole (YA_6).

f) *YA_6:7-nitro-1,2,3-trihydro cyclopenta [b] indole*

1H NMR (400 MHz, CDCl3)δ:1.54-1.40 (t , J = 7.2 Hz, 2H, CH2 at 3), 2.72-2.69 (t, J = 6.2 Hz, 2H, CH2 at 2), 2.83-2.80 (t, J = 5.8 Hz, 2H, CH2 at 1), 8.19-8.17 (d, J = 8.4 Hz, 1H, CHat 5), 8.38-8.36 (d, J = 8.4 Hz, 1H, -CH at 6), 8.56 (s, 1H, -CH at 8), 12.55 (s,1H,-NH).

IR [Cm-1, KBr]: 3363.41 (-NH), 1480 (CH2, C-H stretch), 1598 (Ar.C=C), 1303 (C-N),1503 (Ar.C-NO2).

The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.82-1.80 triplet with two protons at 3rd position, δ 2.70-2.67 triplet with two protons at 2nd position, δ 2.82-2.80 triplet with two protons at 1st position, δ 7.53-7.50 triplet with one proton at 7th position, δ 7.59-7.56 triplet with one proton at 6th position, δ 8.03-8.01 doublet with one proton at 5th position, δ 8.10-8.09 doublet with one proton at 8th position, indicating formation of 1,2,3-trihydro- cyclopenta [b] indole (YA_7).

g) *YA7: 1,2,3-trihydro cyclopenta [b] indole*

1H NMR (400 MHz, CDCl3) δ:1.82-1.80 (t , J = 2.4 Hz, 2H, CH2 at 3), 2.70-2.67 (t , J = 5.2 Hz, 2H, CH2 at 2), 2.82-2.80 (t, J = 4.6 Hz, 2H, CH2 at 1), 7.53-7.50 (t, J = 7.2 Hz, 1H, CHat 7), 7.59-7.56 (t, J = 6.8Hz, 1H, -CH at 6), 8.03-8.01 (d, J = 7.2 Hz, 1H, -CH at 5), 8.10-8.09 (d, J = 7.2 Hz, 1H, -CH at 8).

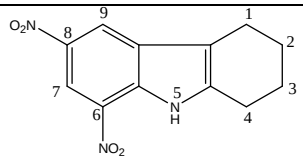
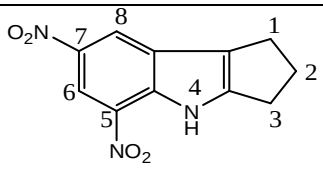
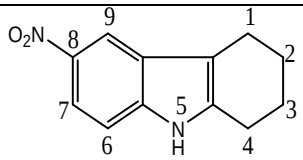
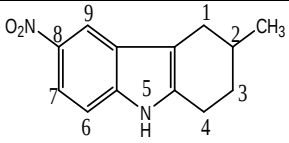
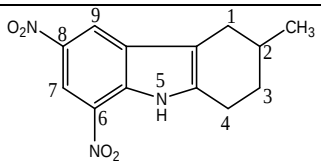
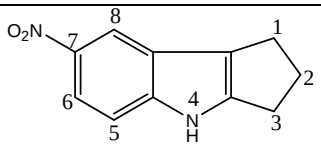
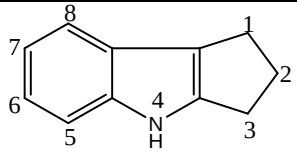
IR [Cm-1, KBr]: 3463.77 (-NH), 1561 (Ar.C=C), 1339 (C-N).

The 1H NMR (400MHz, CDCl3) showed peaks at δ 1.82-1.80 triplet with two protons at 3rd position, δ 2.70-2.67 triplet with two protons at 2nd position, δ 2.82-2.80 triplet with two protons at 1st position, δ 7.53-7.50 triplet with one proton at 7th position, δ 7.59-7.56 triplet with one proton at 6th position, δ 8.03-8.01 doublet with one proton at 5th position, δ 8.10-8.09 doublet with one proton at 8th position, indicating formation of 1,2,3-trihydro- cyclopenta [b] indole (YA7).

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TABLE I

PHYSICAL DATAOF NOVEL SUBSTITUTED 1,2,3,4-TETRAHYDRO CYCLOHEXA / 1,2,3-TRIHYDRO CYCLOPENTA [B] INDOLE DERIVATIVES

Compd. Code	Compound structure	Mol. Formula	Mol.Wt	Recrys. Solvent	M.P	Yield	R_f Value*
YA_1		$C_{12}H_{11}N_3O_4$	261.23	Ethanol	160^0	76%	0.82
YA_2		$C_{11}H_9N_3O_4$	247.21	Ethanol	146^0	87%	0.88
YA_3		$C_{12}H_{12}N_2O_2$	216.24	Ethanol	135^0	68%	0.94
YA_4		$C_{13}H_{14}N_2O_2$	230.26	Water	205	43%	0.40
YA_5		$C_{13}H_{13}N_3O_4$	275.26	Water	135^0	63%	0.58
YA_6		$C_{11}H_{10}N_2O_2$	202	Water	220^0	69%	0.63
YA_7		$C_{11}H_{11}N$	157	Water	126^0	82%	0.85

*Solvent system: Chloroform: Methanol(19:1)

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2) Gross Behavioral studies

The newly synthesized compounds were screened for their gross behavioral effects. The studies found that all the compounds exhibited CNS depression in mice. Results are summarized in Table II. YA1 and YA5 were found to have stronger CNS depression activity when compared to the other compounds.

TABLE II

GROSS BEHAVIORAL STUDIES OF NOVEL SUBSTITUTED 1,2,3,4-TETRAHYDRO CYCLOHEXA/1,2,3 TRIHYDRO CYCLOPENTA[B] INDOLE DERIVATIVES.

Compound	Time-hrs	Awareness					Mood			
		Alertness	Visual placing	Stereo type	Passivity	Writhing	Grooming	Vocalization	Restlessness	Irritability
YA_3	1/2	+	+	-	-	+	+	-	-	-
	1	+	+	-	-	+	+	-	-	-
	2	+	+	-	-	+	+	-	-	-
	3	+	+	-	-	+	+	-	-	-
	4	+	+	-	-	+	+	-	-	-
	5	+	+	-	-	+	+	-	-	-
	24	+	+	-	-	+	+	-	-	-
YA_5	1/2	+	+	+	-	+	+	-	-	-
	1	+	+	+	-	+	+	-	-	-
	2	+	+	+	-	+	+	-	-	-
	3	+	+	+	-	+	+	-	-	-
	4	+	+	+	-	+	+	-	-	-
	5	+	+	+	-	+	+	-	-	-
	24	+	+	+	-	+	+	-	-	-

The YA_3 & YA_5 compounds were screened for their gross behavioral studies. The studies revealed that YA_5 shows stereo type behavior on mice and YA_3 was found to be non-toxic.

3) Locomotor activity

The newly synthesized compounds were evaluated for their effects on locomotor activity in mice. Diazepam was used as a reference drug (Table III). All the compounds (YA1-YA7) caused more than 50% change in activity compared to the standard drug (Table IV). YA3 and YA5 had the highest activity at 86.2% and 83.9% respectively, after 120 minutes of administration at a dose of 100 mg/kg by the intraperitoneal route. Therefore, toxicity studies were conducted on these two compounds (Results are shown in Figure 1).

TABLE III

LOCOMOTOR ACTIVITY RESULTS OF NOVEL SUBSTITUTED 1,2,3,4-TETRAHYDRO CYCLOHEXA/1,2,3-TRIHYDRO CYCLOPENTA[B] INDOLE DERIVATIVES .

S.NO	CPD CODE	MEAN+SEM				
		Control	30 min	60 min	90 min	120min
1	YA1	859.2±93.78	471.8±78.29	338.2±29.17	240.4±4.308	238.4±11.17
2	YA2	830±125.3	534±120	382.2±93.49	277.2±74.93**	172.2±16.61
3	YA3	887.6±45.28	527±90.51	362.2±63.68	196.4±36.51*	133.4±28.54**
4	YA4	805.8±101.5	434±38.22	320.2±23.02	190.4±34.98*	95.8±19.37*
5	YA5	874.6±45.38	475.4±63.83	363.8±66.44	239±17.91	140.2±9.60
6	YA6	857.2±36.76	644.4±79.11	494.6±102.7	460.4±65.75**	407.4±87.13***
7	YA7	818.6±51.75	645.2±56.57	594.2±68.37	536.6±33.83	470.4±16.03
Std	Diazepam	901.4±52.71	262.6±76.15	146.2±49.18	58.0±11.08	26.80±5.928

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Each values represents the mean ± SEM .Significance levels n=5.Significance at $^{***}P<0.0001$, $^{**}P<0.001$, $^{*}P < 0.05$ and ns =not significant compared with standard group.

TABLE IV

% CHANGE IN LOCOMOTOR ACTIVITY OF NOVEL SUBSTITUTED 1,2,3,4-TETRAHYDRO CYCLOHEXA/1,2,3-TRIHYDRO CYCLOPENTA[B] INDOLE DERIVATIVES ON MICE.

S.No	Cpd code	Percent change in activity			
		30 min	60 min	90 min	120 min
1	YA1	60.6	68.9	73.3	70.9
2	YA2	46.3	59.2	65.5	75.2
3	YA3	56.4	69.5	81.9	86.2
4	YA4	58.2	64.3	72.9	81.1
5	YA5	62.4	67.6	75.3	83.9
6	YA6	33.3	48.0	47.0	51.4
7	YA7	27.1	29.7	33.4	39.8
8	Std	100	100	100	100

4) Oral acute toxicity studies OECD-423

Acute oral toxicity studies were conducted in accordance with the Organization of Economic Cooperation and Development (OECD-423) guidelines for the synthesized compounds YA3 and YA5. No toxicity or death was observed for the synthesized compounds when administered at dose levels of 5, 50, and 300 mg/kg body weight. However, at a dose of 2000 mg/kg, the synthesized compound YA5 was found to be toxic as death occurred within 1 hour of drug administration. In contrast, the synthesized compound YA3 was found to be non-toxic at the 2000 mg/kg dose level (Table 5).

TABLE V

ORAL ACUTE TOXICITY STUDIES: OECD-423

GROUPS	BEHAVIOURAL STUDIES		MORTALITY	
	YA_3	YA_5	YA_3	YA_5
Group I (5mg/kg)	No Change	No Change	No	No
Group II (50mg/kg)	No Change	No Change	No	No
Group III (300mg/kg)	No Change	Stereo type	No	No
Group IV (2000mg/kg)	No Change	Stereo type	No	Yes

LD_{50} = 2000 mg/kg, ED_{50} = 100 mg/kg, Therapeutic index = LD_{50} / ED_{50} = 20.

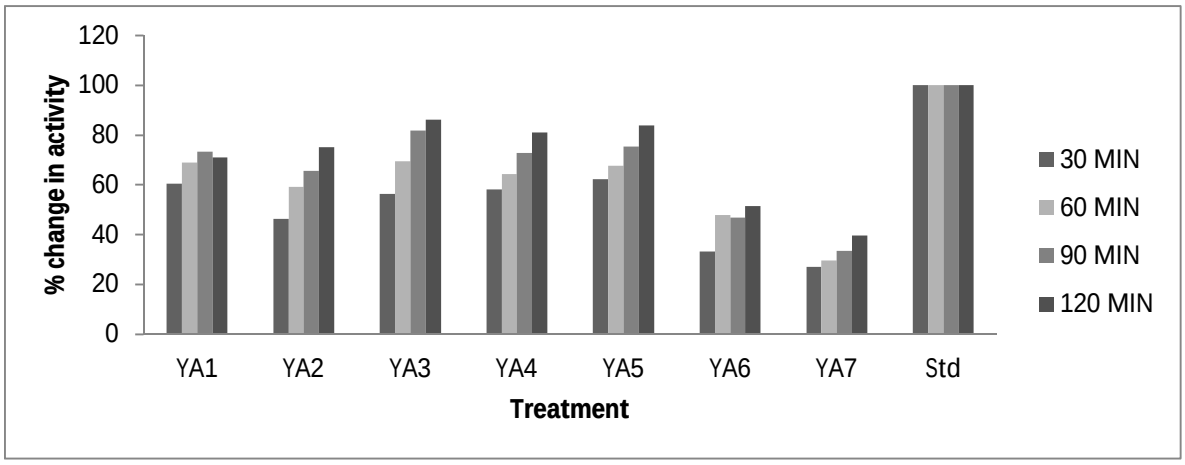


Fig. 2 % change in activity of novel substituted 1,2,3,4-tetrahydro cyclohexa/1,2,3-trihydro cyclopenta[b] indole derivatives on mice.

Diazepam is used as a standard reference drug. All the compounds (YA_1-YA_7) showed above 50% change in activity when compared to standard drug.

IV. CONCLUSIONS

Different cyclic ketones were treated with various substituted phenylhydrazines in the presence of acetic acid to give corresponding tetrahydro carbazole derivatives which resulted in good practical yields. A facile method under mild conditions has been developed for the synthesis of the title compounds. All the compounds synthesized were characterized by physical (Rf values, Melting point, Molecular weight, Molecular formula) and spectral data (1H NMR, IR, Mass spectra).The title compounds were screened for CNS activity (Locomotor activity and gross behavioural studies). The obtained results were analyzed statistically. Among the synthesized compounds the percent change in activity of YA 3 & YA 5 in comparision with standard drug (Diazepam, 2 mg/kg dose) at 120 minutes was found to be 86.5 & 83.9 respectively. Toxicity studies of YA 3 & YA 5 were performed.YA 3 was found to be non-toxic and YA 5 was found to be toxic. From these studies 8-Nitro-1,2,3,4-tetrahydro cyclohexa [b] indole (YA3)is the most active compound and it serves as a lead to further optimization in drug discovery process

In conclusion, this study has successfully synthesized new derivatives of 1,2,3,4-tetrahydro cyclohexa/1,2,3-trihydro cyclopenta [b] indole and evaluated their central nervous system activity. The synthesized compounds exhibited CNS depression in mice, with YA1 and YA5 showing the strongest activity. The compounds were also evaluated for their effects on locomotor activity in mice, with YA3 and YA5 showing the highest activity. Acute oral toxicity studies were conducted in accordance with OECD-423 guidelines, with YA3 being non-toxic and YA5 [1], [2] being toxic at high doses. Overall, the study has identified 8-Nitro-1,2,3,4-tetrahydro cyclohexa [b] indole (YA3) as the most active compound and serves as a potential lead for further drug discovery optimization.

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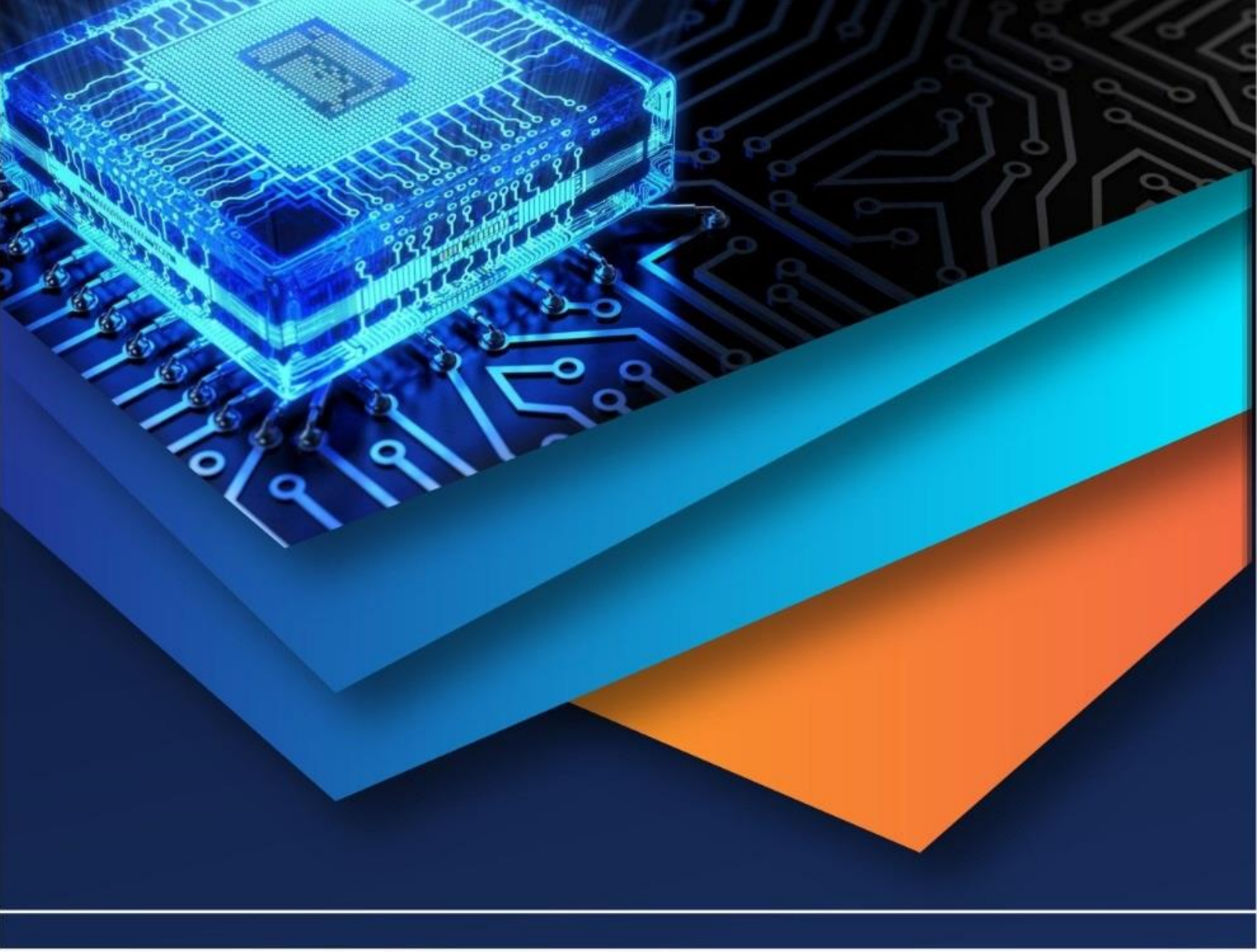
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