

Synthesis, Characterization and Biological Evaluation of Some Heterocyclic Derivatives for Nootropic Activity

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ABSTRACT

Heterocycles are considered as the largest section of chemistry, especially organic chemistry. Coumarins are a class of compounds with benzopyrone ring widely used for their antioxidant, antibacterial, antifungal, antiviral, anti-HIV and anticancer activities [1-10]. Nootropic Activity of Coumarins. Antioxidant properties: Coumarins can exhibit antioxidant activity, which may contribute to neuroprotection and cognitive enhancement. The purpose of this investigation is to develop new heterocyclic derivatives containing nitrogen, sulphur and oxygen moiety with increased biological activities. The derivatives will be synthesized by conventional method. The structures of the final newly synthesized compounds will be confirmed from IR and ¹HNMR and Mass spectra. [1,2,20] The derivatives will be screened for their Nootropic and anti-oxidant activities by Cook's Pole climbing apparatus and Act photometer. The present studies focus on heterocycles in the treatment of various chronic diseases such as Alzheimer's disease, Dementia and memory related functions. Bacopa Monnieri, Rhodiola Rosea, Panax Ginseng, Ginkgo Biloba, Almond rich in proanthocyanidin polymers are some naturally occurring constituents for improved brain functions. [5-7]

Keywords: Heterocyclic nucleus, Coumarin ring, Nootropic activity, Cooke's pole climbing apparatus.

INTRODUCTION

A greater part of the natural compounds produced by biotic component has heterocyclic rings as a constitutional part of their molecules. Coumarins are becoming an attractive target of extensive research due to its inherent diverse properties. The most widely reported activities are anti-inflammatory, antibacterial, anti-oxidant, anti-cancer, anti-coagulant, etc. Nitrogen, Sulphur containing heterocycles have specific properties due to which they can be used as a potential material in a different type of industries such as medicinal/pharmaceutical, required for various chemical, physical operations and their use as products. Especially dyes, paint, agrochemicals, medicine, etc. Make them more significant. In present days, Nitrogen-Sulphur heterocycles are repeatedly attracting the interest of chemists due to their exceptional bioactive behaviour.

6,7-Substitution patterns are common in coumarins with activity against neurodegenerative conditions.

The presence of hydroxyl or methoxy groups at C-6 and C-7 is crucial for the free radical scavenging effects of coumarins. Coumarins are a class of compounds known for their diverse biological activities, including nootropic effects. Research suggests that certain coumarin derivatives exhibit promising nootropic activity by:

- 1. Inhibiting acetylcholinesterase (AChE):** Coumarins can enhance cholinergic transmission, improving memory and cognitive function.
 - 2. Antioxidant activity:** Coumarins' antioxidant properties may protect against oxidative stress, contributing to their nootropic effects.
 - 3. Modulating neurotransmitters:** Some coumarins interact with serotonin, dopamine, and other neurotransmitters, influencing mood and cognition.
- Some notable coumarin derivatives with reported nootropic activity include:

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

- **Scopolamine-induced amnesia reversal:** Certain coumarins have shown potential in reversing scopolamine-induced memory impairment.

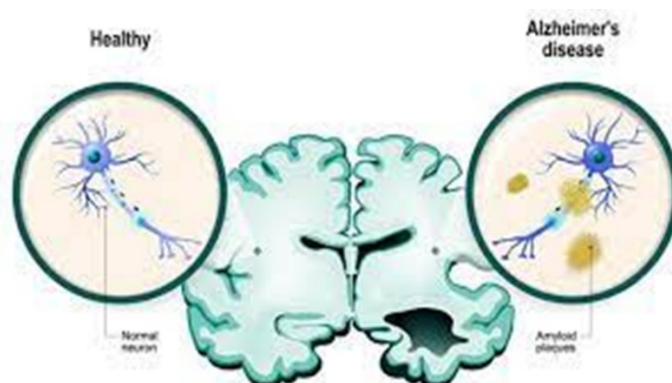
- **Anxiolytic and antidepressant effects:** Coumarins may exhibit anxiolytic and antidepressant properties, contributing to their nootropic profile.^[21]

The majority of the important advances have been developed by synthesizing new heterocycles which imitate natural products with similar biological activities. For that reason, scientists/researchers/chemist communities are on a nonstop search to develop better pesticides, pharmaceuticals, fungicides, compost material, weed killers, insecticides, etc.^[15-17]

Memory is critical to both human survival and personal identity. Non-conscious emotional memory of fearful or threatening events enables us to recognise and respond appropriately to real threats in the natural and social environment. Episodic memory of events involving personal experience is necessary for the psychological connectedness and continuity that gives one the feeling of persisting through time as the same person. Other forms of memory include non-conscious procedural memory, which enables us to perform basic motor skills and tasks of daily life, and semantic memory, which enables us to recall and use concepts and facts. Semantic and episodic memory are two forms of declarative memory, which enables us to consciously recall facts and events. Working memory is a short-term version of declarative memory and is involved in such complex cognitive

tasks as reasoning and decision making.^[20] Nootropic represents a new class of psychotropic agents with selective facilitatory effect on integrative functions of the central nervous system, particularly in intellectual performance, learning capability and memory (Joshi et al., 2006). Nootropic agents such as Piracetam, Pramiracetam, Aniracetam, Oxiracetam and Choline esterase inhibitors like Donepezil, Metrifonate, Physostigmine, Tacrine, Rivastigmine and Galantamine are being primarily used to improve memory, mood and behaviour. But they have many side-effects like loss of appetite, nausea, vomiting, diarrhoea, stomach cramps, headache, dizziness, fatigue and insomnia (Dubey et al., 2004). So, there are drugs like Antipsychotics, that ameliorate mental aberrations that are characteristic of the psychoses. Derivatives like Phenothiazine are most focusing on people with seizures, dementia, concussion or other neurological problems.^[20,21]

Many of the peoples are suffering from various head injuries due to accident and may suffer from dementia, some older patients are suffering from Alzheimer's and other inflammatory diseases so there is a need to synthesize some new derivatives containing sulphur, nitrogen and oxygen derivatives which may acts as nootropic (i.e. memory enhancing) drug and some may act as anti-inflammatory. Here our main aim is to synthesize a new drug which may acts as nootropic drug and it may be useful for Alzheimer's and in dementia etc.



SCOPE OF STUDY:

➤ Nootropics are a heterogeneous group of compounds of diverse chemical composition and

biological function that facilitate learning and memory or overcome natural or induced cognitive impairments.

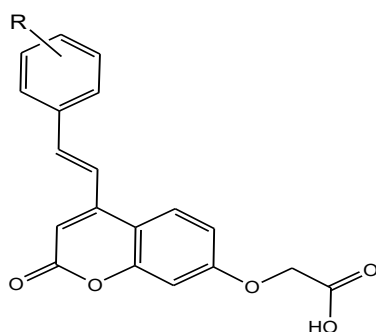


- The development of effective drugs for the treatment of dementia is an important therapeutic target. Drugs which stop the progression of dementia have not been developed.
- The learning and memory deficits have been recognized as severe and consistent neurological disorders associated with numerous neurodegenerative states.
- Many therapeutic strategies to augment the concentration of neurotransmitters in brain such as cholinergic agents, biogenic amines and neuropeptides etc. have been evaluated in cognitive deficits.
- They improve the brain's supply of glucose and oxygen and also remove free radicals from brain.

REVIEW OF WORK:

- A specific class of heterocycles having sulphur-nitrogen heteroatoms includes very important aromatic compounds that show physicochemical properties with significance in the development of futuristic materials such as magnets and molecular conductors.
- Heterocyclic compounds can be potent regulators of the nitro oxidative stress and targeting free nitrogen and oxygen radicals.

SYNTHETIC DERIVATIVE:



RESULTS AND DISCUSSION:

The target compounds were synthesized for their nootropic activity. For nootropic activity male/female albino rats weighing 20-25 grams. Animals were observed in a group of five per cage under standard laboratory conditions with food and water

continuously available in a 12h: cycle used with light on from 7:00am to 5:00pm. ^[2,20] All behavioural testing were done during the daytime. The compounds were screened for nootropic activity both for learning and memory enhancing by Cook's pole climbing apparatus. The experimental protocol was approved by institutional animal ethics committee (protocol no. APJ/IAEC/2023/12)

IDENTIFICATION AND CHARACTERIZATION

The Identification and Characterization of the compounds was carried out by the following methods.

1. Melting point
2. Thin layer chromatography
3. Infrared spectroscopy
4. Nuclear magnetic resonance spectroscopy
5. Mass spectroscopy

MELTING POINT (M.P.)

The melting points of the organic compounds were determined by open capillary tube method. Melting points were determined by using Veego electronic (VMP-D) apparatus.

THIN LAYER CHROMATOGRAPHY (TLC)

In the present work, silica gel G (Loba) is used as coating material. The mobile phase used for development of TLC was chloroform: acetone: toluene in ratio of (7:3:1) and chloroform: ethanol in a ratio of (9:2).

SPECTRAL DATA:

INFRARED SPECTROSCOPY

The infrared radiation spectroscopy is concerned about the absorption of infrared radiation by a molecule and exhibits characteristics absorption spectra. The most useful range for analytical purpose lies between 4000 and 400 cm^{-1} . Different bonds (C-C, C-O, C=O, O-H, N-H etc.) have different vibrational frequencies, and we can detect the



presence of these bands in an organic molecule by identifying this characteristic frequency as an absorption band in the infrared spectrum. The IR spectra of compounds were recorded on a JASCO FT-IR 4100 spectrometer.

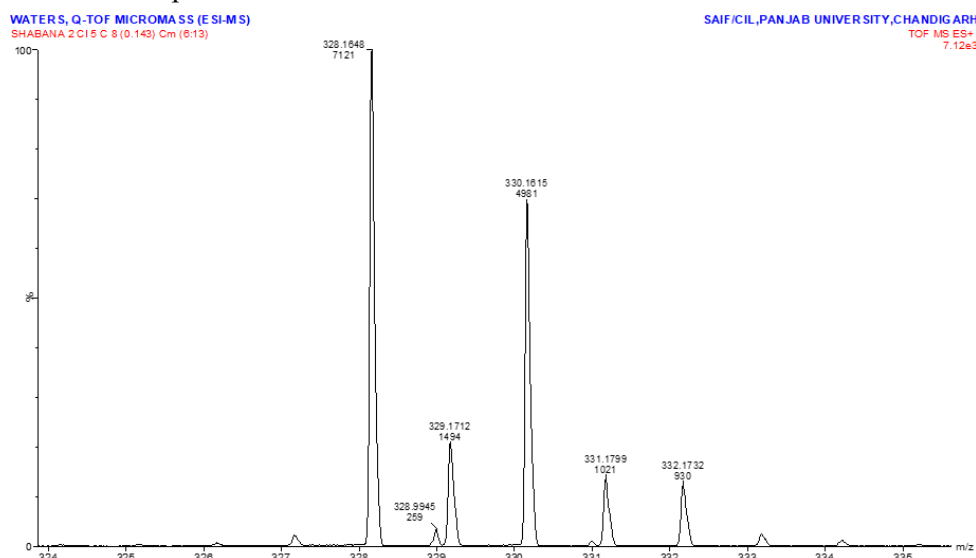
NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

The ^1H NMR spectra were obtained on a BRUKER AVANCEV II 400 NMR Spectrometer in DMSO as

solvent and TMS as internal standard, chemical shifts are given in ppm.

MASS SPECTROSCOPY

Mass spectra are obtained after ionization of samples by different ionization techniques. Molecular mass of the compound is determined by mass to charge (m/z) ratio. The mass spectra were obtained on WATERS Q-TOF MICROMASS (ESI-MS).



EVALUATION OF NOOTROPIC ACTIVITY:

DRUGS AND CHEMICALS:

In this study the pharmacological evaluation of novel derivatives was carried out for nootropic activity. List of drugs used in the present study are Piracetam (UCB India Pvt. Ltd.) and Scopolamine (Cadila Healthcare Ltd., India) dissolved in distilled water. The newly synthesized compounds were dissolved in Corn oil and administered orally. All required chemicals were procured from Loba Chemie PVT. Ltd., Mumbai.

ACUTE ORAL TOXICITY:

The test material in corn oil was given orally at a limit dose of 2000 mg per kg body weight to male Albino

rats weighed between 180 to 250 gm. The acute oral toxicity for the compounds reveals that it is safe at the dose level of 2000 mg per kg body weight. Acute oral toxicity test for the novel derivatives was carried out as per OECD guidelines 420.^[21]

MATERIALS AND METHODS

COOK'S POLE CLIMBING RESPONSE APPARATUS:

Cooks pole climbing apparatus is the behavioural model used to evaluate memory in animals. In this model all animals were trained for 10 days to attend continuous transition (90-95%) CAR (Conditioned Avoidance Response) as described in following table:

Group No.	Group	Dose(mg/kg)	No. of Animals	Route of Administration
1	Control (Vehicle)	0.5 ml	5	Oral
2	Piracetam	100	5	intraperitoneal
3	Scopolamine	0.3	5	intraperitoneal
4	Drug 1	100	5	Oral



5	Drug 1	150	5	Oral
6	Drug 1	200	5	Oral
7	Piracetam + Scopolamine	100 + 0.3	5	intraperitoneal
8	Drug 1 + Scopolamine	100 + 0.3	5	Oral + intraperitoneal
9	Drug 1 + Scopolamine	150 + 0.3	5	Oral + intraperitoneal
10	Drug 1 + Scopolamine	200 + 0.3	5	Oral + intraperitoneal

STATISTICAL ANALYSIS:

Scopolamine (0.3~mg/kg b.w., i.p.) treated groups show decrease in condition avoidance response blocked (4.4 ± 1.06) compare to normal groups (10.00 ± 0.00) indicating impairment of memory in animals. Piracetam (i.p.) and at all the doses (100, 200, and 400 mg/kg b.w. p. o.) administered orally for 6th day significantly ($P < 0.001$) reversed amnesia induced by scopolamine when compared to the scopolamine treated animals (9.5 ± 0.20 , 5.1 ± 0.91 , 5.3 ± 0.67 , 7.00 ± 0.51 , 0.51 ± 0.97 , 7.00 ± 0.57 , 7.14 ± 0.50)

(Indicate novel derivatives at varying doses***
 $p < 0.001$, $p < 0.05$ comparison with control.)

RESULTS:

Cooks pole climbing apparatus is the behavioural model used to evaluate memory in animals. In this model all animals were trained for 10 days to attend continuous transition (90-95%) CAR (Conditioned Avoidance Response) as described in following table:

Groups	CAR blocked
Normal	10.00 ± 0.00
Positive Control (Scopolamine)	4.428 ± 1.067
Standard treatment (Piracetam i.p.+ Scopolamine)	$9.572 \pm 0.200^{***}$
Drug 1 (100 mg/kg) + Scopolamine	$5.142 \pm 0.911^{***}$
Drug 1 (200 mg/kg) + Scopolamine	$5.855 \pm 0.799^{***}$
Drug 1 (100 mg/kg) + Scopolamine	$7.001 \pm 0.534^*$

*** $p < 0.001$, * $p < 0.05$ comparison with control

Scopolamine treated groups show decrease in Condition Avoidance Response blockade compared to normal groups indicating impairment of memory in animals. Piracetam and synthesized drugs at all doses administered orally for 6 days significantly reversed amnesia induced by Scopolamine when compared to the scopolamine treated animals.

CONCLUSION

The findings of the present study reveal the nootropic activity of newly synthesized novel Coumarin derivatives.

ANIMAL MODEL USED FOR ANTI-INFLAMMATORY ACTIVITY:

RAT PAW EDEMA MODEL:

Paw swelling, or paw edema, is a convenient method for assessing inflammatory responses to antigenic challenges and irritants. The protocol described in this unit uses carrageenan as the irritant to induce paw edema. This model has long been used to assess the anti-inflammatory properties of agents that inhibit prostaglandin production.

BIOLOGICAL EVALUATION:



All the synthesized compounds were subjected to Anti-inflammatory activity at a dose of 10 mg/kg

body weight using carrageenan induced rat paw edema model.

Group	Drug	Dose (mg./kg.)	Mean increase in Paw edema vol.(ml)± SEM After 3 hrs.	Inhibition of Paw edema (%)
1.	Control	10mg./kg.	0.85±0.02ns	-
2.	Standard	5mg./kg.	0.11±0.02***	73
3.	A	10mg./kg.	0.41±0.02	44
4.	B	10mg./kg.	0.27±0.02**	58
5.	C	10mg./kg.	0.19±0.02***	66
6.	D	10mg./kg.	0.28±0.01*	57
7.	E	10mg./kg.	0.20±0.02**	65

STATISTICAL ANALYSIS:

N=6; One way ANOVA followed by multiple Tukey's comparison test. * P<0.05; **

P<0.01; ***P<0.001 when compared with control, ns-nonsignificant.

Inhibition of Paw edema (%) = $V_c - V_t / V_c \times 100$

Where, V_c = Mean increase in Paw volume in the control group of rats.

V_t = Mean increase in Paw volume in rats treated with test compound group of rats.

CONCLUSION:

Compounds A, B, C, D and E showed significant anti-inflammatory activity in comparison to standard drug Ibuprofen.

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