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Article

Design, synthesis and evaluation of pyrrolidone derivatives using Iodine as catalyst

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Abstract: In this study, a series of pyrrolidone derivatives were designed and synthesized using iodine as a catalyst, with the aim of evaluating their analgesic properties. The analgesic activity was assessed through two established methods: the hot plate test and the acetic acid-induced writhing test. The results from the hot plate test indicated that the control group showed stable response times, suggesting no analgesic effect. However, both the standard treatment (10 mg/kg) and Compound 10 (C10) (20 mg/kg) exhibited significant analgesic effects. While the standard treatment demonstrated a continuous and pronounced increase in response time over the 3-hour testing period, Compound 10 showed a notable, though slightly lesser, increase in response time. In the writhing test, the control group presented a baseline writhing count of 17.4 ± 2.50, while the standard treatment at 10 mg/kg reduced the writhing count to 6.2 ± 0.66, reflecting a 64.36% inhibition of pain. Compound 10 also demonstrated substantial analgesic activity, reducing the writhing count to 10.10 ± 0.41, corresponding to a 41.95% inhibition. Although the effect of Compound 10 was less pronounced than that of the standard treatment, it still showed significant analgesic potential. The structural analysis through NMR and mass spectrometry provided valuable insights into the structure-activity relationship, highlighting areas for further optimization. Overall, the findings underscore the promising analgesic properties of pyrrolidone derivatives, especially Compound 10, and suggest that these compounds could serve as potential candidates for future pain management therapies.

Keywords: Pyrrolidone derivatives, iodine catalyst, analgesic activity, hot plate test, writhing test, structure-activity relationship, NMR, mass spectrometry.

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1. Introduction

The discovery and development of bioactive compounds has been a central focus in medicinal chemistry, with heterocyclic compounds, particularly those containing nitrogen, oxygen, or sulfur atoms, being of great importance due to their pharmaceutical and industrial applications. Among these, pyrrolidone are widely studied for their significant pharmacological activities, including anti-inflammatory, antimicrobial, antitumor, neuroprotective, and antiviral effects. These compounds, featuring a five-membered lactam ring with a nitrogen atom, have demonstrated versatile interactions with biological macromolecules, making them valuable for therapeutic applications. Beyond their medicinal potential, pyrrolidone are also utilized in material science for the synthesis of polymers, resins, and membranes, underscoring their broad utility in both fields. The ability to modify the pyrrolidone ring through functionalization strategies further enhances their bioactivity and chemical stability, driving continued interest in the design and synthesis of novel derivatives.

Catalysis plays a vital role in organic synthesis, allowing selective product formation and improving efficiency while minimizing waste. Iodine has emerged as a promising green catalyst, recognized for its mild reaction conditions, selectivity, and minimal environmental impact. It facilitates a range of organic transformations, including electrophilic substitution, cyclization, and functional group transformations. Iodine catalysis is particularly useful in the synthesis of heterocyclic like pyrrolidone, promoting cyclization and functionalization reactions to generate a variety of substituted derivatives. This makes iodine an ideal candidate for developing a sustainable, simple, and efficient method for synthesizing pyrrolidone derivatives.

The design and synthesis of novel pyrrolidone derivatives is crucial for expanding the availability of bioactive compounds and advancing drug development. However, traditional synthesis methods can be challenging, often requiring toxic reagents, high temperatures, and complex multistep processes, limiting their scalability and environmental sustainability. Iodine catalysis offers a solution by enabling key reactions that facilitate the construction of pyrrolidone derivatives from various nitrogen-containing substrates. Additionally, iodine can aid in introducing functional groups to the pyrrolidone ring, enhancing the bioactivity and pharmacological profiles of the compounds. This study seeks to design, synthesize, and evaluate pyrrolidone derivatives using iodine as a catalyst, aiming to establish an eco-friendly, efficient synthetic route that yields high-purity compounds with potential for therapeutic applications.

The objectives of this study include the design of pyrrolidone derivatives with varying functional groups, optimizing the reaction conditions (such as iodine concentration, reaction time, and solvent choice), and characterizing the compounds using techniques like nuclear magnetic resonance (NMR), mass spectrometry (MS), and infrared (IR) spectroscopy. Furthermore, the study will evaluate the biological activity of the synthesized compounds, focusing on antimicrobial, anticancer, and anti-inflammatory properties, among others. The structure-activity relationship (SAR) will also be explored to identify the key structural features responsible for enhanced biological activity. [1-20]

This research is significant because it aims to streamline the synthesis of pyrrolidone derivatives, making the process more sustainable, cost-effective, and environmentally friendly by utilizing iodine as a catalyst. The findings could lead to the discovery of new drug candidates that target a range of diseases, including infections, cancer, and inflammatory conditions. Additionally, the study could provide valuable insights into the broader application of iodine catalysis in the synthesis of heterocyclic compounds, contributing to greener chemical processes in pharmaceutical, chemical, and material sciences. Ultimately, this work has the potential to advance the fields of organic chemistry, pharmacology, and drug development by creating novel bioactive pyrrolidone derivatives with diverse applications.

2. Materials and Method

List of chemicals

Every research chemical used in the experiments was bought from Merck or Cosmo Chem Pvt. Ltd. All solvents, with the exception of LR grade, were dried and refined as required by the literature. Borosil is used to make the glassware required in the reactions. Before being used, all of the glassware was cleaned using acetone and chromic acid.

Table No.1: List Of chemicals used for synthesis

. no.	Chemical Name	Supplied by
1.	Glacial Acetic Acid	Cosmo Chem Pvt. Ltd.
2.	cyclohexanone	Cosmo Chem Pvt. Ltd.
3.	Sulphur,	Cosmo Chem Pvt. Ltd.
4.	Ethyl cyano acetate	Cosmo Chem Pvt. Ltd.
5.	piperidine	Cosmo Chem Pvt. Ltd.
6.	ethanol	Merck
7.	aniline	Cosmo Chem Pvt. Ltd.

8.	diethyl acetylene dicarboxylate	Cosmo Chem Pvt. Ltd.
9.	4-chlorobenzaldehyde	Cosmo Chem Pvt. Ltd.
10.	citric acid monohydrate	Cosmo Chem Pvt. Ltd.

2. List of instruments

TLC was performed on microscopic slides (2×7.5 cms) coated with silica-gel-G and pre-coated silica gel strip. Spots were visualized under UV light and by exposure to iodine vapour. Mass spectra were recorded on ESI-MS Mass spectrometer at Cryogen MASS services, Mumbai. 1HNMR spectra were obtained in DMSO on Bruker Advance-II 400 MHz instrument and chemical shift were measured as parts per million downfield from tetramethylsilane (TMS) as internal standard at Cryogen NMR services, Mumbai.

Table 2: List if instruments required for synthesis

Sr. no.	Name of Instrument	Make
1	Magnetic stirrer	Remi 1MLH
2	Mass Spectroscopy	ESI-MS Mass spectrometer
3	NMR Spectroscopy	Bruker Advance-II 400 MHz
4	Microwave reactor	Anton Paar

SYNTHESIS & CHARACTERIZATION

1.1.1 S

CHEME OF PYRROLIDONE:

The synthesis of the target compound has been achieved by adopting following synthetic procedure

Step 1- Ethyl 2-Amino -4,5,6,7 Tetrahydro Benzothiopene 3 -Carboxylate

Step 2-Ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

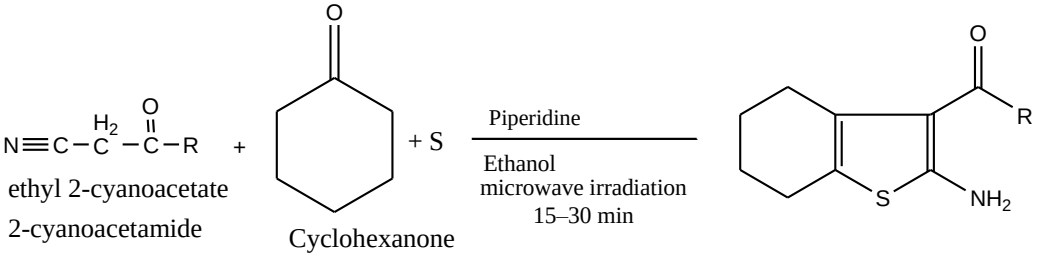
Step 3- *N*-(3-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamideethyl2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate

Preparation of Ethyl 2-Amino -4,5,6,7 Tetrahydro Benzothiopene 3 -Carboxylate

Chemicals: cyclohexanone, Sulphur, Ethyl cyano acetate, diethyl amine, ethanol

Apparatus: Glass beakers, Magnetic stirrer, water bath, filtration assembly, hot plate etc.

STEP 1



ethyl 2-cyanoacetate
2-cyanoacetamide
R= OC_2H_5, NH_2

Cyclohexanone

i) 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide

ii) ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

Step 1 Synthesis

Step-1: In a microwave-safe reaction vessel, a mixture of cyclohexanone (10 mL, 0.1 mol), sulfur (3.2 g, 0.1 mol), ethyl cyanoacetate (10 mL, 0.1 mol), piperidine (15 mL, 0.1 mol), and dry ethanol (20 mL) is irradiated in a microwave reactor at 300–500 W, maintaining a temperature of 80–100°C for 15–30 minutes. After cooling, the reaction mixture is poured into ice-cold water (100–150 mL) with stirring and left undisturbed for 3 hours. The resulting solid is filtered, washed with cold water, and dried at 40–50°C. If needed, the crude product is purified via recrystallization from ethanol-water (3:1). Characterization can be performed using standard techniques like NMR, FTIR, and mass spectrometry.

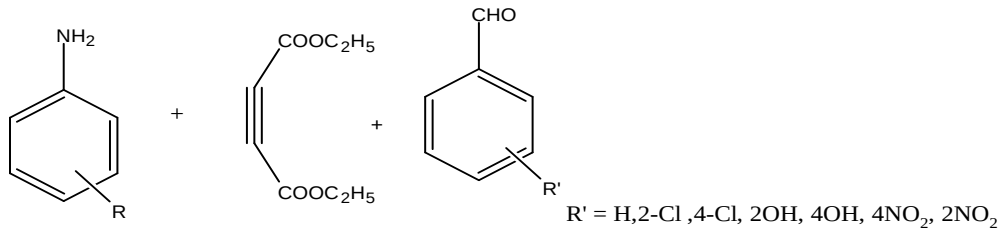
Step 2:

Chemicals: aniline, diethyl acetylene dicarboxylate, ethanol, 4-chlorobenzaldehyde, citric acid monohydrate

Apparatus:

Glass beakers, Magnetic stirrer, water bath, filtration assembly, hot plate etc

STEP 2



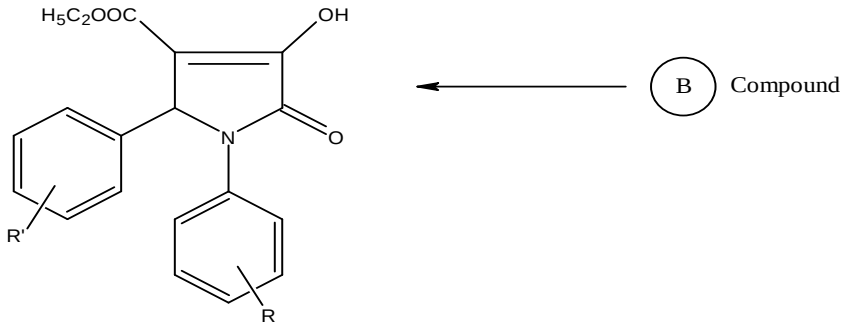
R' = H,2-Cl ,4-Cl, 2OH, 4OH, $4NO_2$, $2NO_2$

Aniline

R= H,2Cl ,4Cl

diethyl acetylene dicarboxylate

Ultrasound Irradiation or Reflux for 10-15 hrs



ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

Step 2 Synthesis

Procedure:

Aniline (0.091 ml, 1 mmol) and diethyl acetylenedicarboxylate (0.160 ml, 1 mmol) were combined with ethanol (4 ml) and magnetically agitated at room temperature. The mixture was sonicated under ultrasonic irradiation after 4-chlorobenzaldehyde (0.141 g, 1 mmol) and citric acid monohydrate (0.42 g, 2 mmol) were added. At ambient temperature, the identical process was also carried out without sonication. TLC was used to monitor the reactions' development (n-hexane: EtOAc, 10:7). Following the conclusion of the reactions, the solid product was filtered, and hot ethanol was recrystallized to produce the pure product.

Step 3:

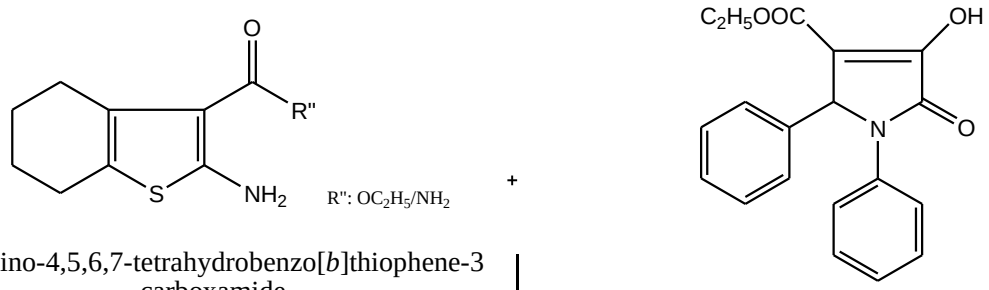
Chemicals:

Glacial Acetic Acid, ethanol

Apparatus:

Glass beakers, Magnetic stirrer, water bath, filtration assembly, hot plate etc.

Step 3



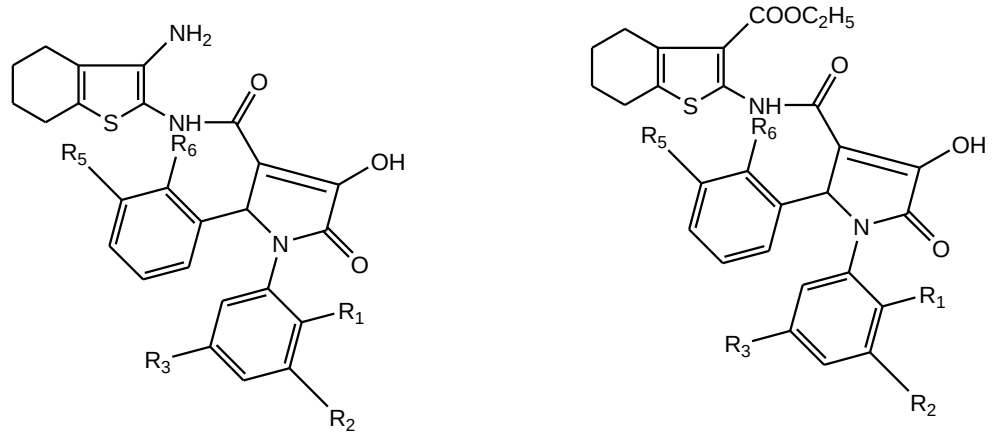
2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3 carboxamide

ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate

ethyl 4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate

Glacial acetic acid

Reflux at 60C for 4 to 5 hrs



N-(3-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)-4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide

ethyl 2-(4-hydroxy-5-oxo-1,2-diphenyl-2,5-dihydro-1*H*-pyrrole-3-carboxamido)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate

Step 3 Synthesis

Step 3: A compound (0.01 mol) and B compound (0.01 mol) refluxed at 60C for four to five hours in 50 ml of glacial acetic acid. To eliminate extra acetic acid by evaporation, the reaction mixture was distilled at low pressure. To create crystalline products, the yellow residue was filtered, dried, and recrystallized from ethanol[21-25]

3. Biological Activity

1. Analgesic activity

1. Hot plate Method

The analgesic effects of compound 10 (C10) in the central and peripheral nerve systems were assessed in albino male mice using the hot plate test and the acetic acid-induced writhing test,

respectively. Hot plate test The hot plate test was carried out in the manner previously mentioned. For this investigation, adult male Albino mice weighing between 20 and 25 grams were chosen. The mice were placed on the heated plate before the experiment. The heated plate was kept at 55 ± 0.5 °C. The latency between the placement and shaking or the licking of the hind paws or the jumping response of the animals was recorded as the latent response.For the experiment, the mice that showed latencies within five to thirty seconds were chosen. The chosen mice were split up into five groups of eight at random. Every mouse's pre-treatment response time was noted. For six days in a row, three dosages of compound 10 (C10) (0.8, 2.4, and 7.2 g/kg, p.o.), the control vehicle (distilled water, 20 mL/kg, p.o.), and the ASA positive control (100 mg/kg, p.o.) were given orally. Each animal's post-treatment response time was measured after 30, 60, 90, and 120 minutes on day 7, one hour after oral delivery. To prevent mouse foot scorching, the cut-off period was set at 60 seconds if the pain domain values were more than 60 seconds.

The percentage inhibition was calculated by using the following formula:

%Inhibition = [(Post-treatment Latency) − (Pre-treatment Latency)]/Pre-treatment Latency × 100.

2. Acetic acid-induced abdominal writhing in mice

The writhing research test was carried out as previously mentioned. Five treatment groups of eight mice each were randomly assigned to the mice: three dosages of compound 10 (C10) (0.8, 2.4, and 7.2 g/kg, p.o.), ASA positive control (100 mg/kg, p.o.), and vehicle control (distilled water, 20 mL/kg, p.o.). For six days in a row, these therapies were given orally. The mice were given an intraperitoneal injection of 0.6% acetic acid solution in normal saline at a dosage of 10 mL/kg on day 7, one hour after oral delivery, to elicit writhing. For fifteen minutes, the frequency of writhing (abdominal constrictions, pelvic rotation, and hind limb stretching) was noted. Additionally, the first instance of writhing following an acetic acid injection was noted (referred to as the latent phase).

The percentage analgesic activity was calculated using the following formula:

%Inhibition = [Numbers of writhes (control) − Numbers of writhes (test)]/Numbers of writhes (control) × 100.

Percentage Inhibition of Edema (Carrageenan-Induced Paw Edema Method)

The anti-inflammatory activity of the test compounds was evaluated using the carrageenan-induced paw edema model in rats**,** a widely accepted experimental method for the assessment of acute inflammation.

Acute inflammation was induced by the subplantar injection of carrageenan (1% w/v in normal saline, 0.1 mL) into the right hind paw of each animal. The animals were divided into different groups consisting of a normal control group, a carrageenan control (disease control) group, test groups receiving the synthesized compounds at the dose of 50 mg/kg, p.o.**,** and a standard group treated with indomethacin (10 mg/kg, p.o.)**.** Test compounds and standard drug were administered orally 1 h prior to carrageenan injection**.**

Paw volume was measured using a plethysmometer immediately before carrageenan administration (0 min) and at 1, 2, 3, 4, and 5 h after carrageenan injection. The increase in paw volume was considered as edema and expressed as mean ± SEM.

The percentage inhibition of edema produced by the test compounds was calculated using the following formula:

Percentage Inhibition of Edema

Percentage Inhibition of Edema

$$\% \text{ Inhibition} = \frac{(E_c - E_t)}{E_c} \times 100$$

Where:
Ec = Mean edema of carrageenan control
Et = Mean edema of treated group

3. Results and Discussion

1. Physicochemical data of the synthesized compounds

The number of pyrrolidone derivatives has been synthesized as per the procedure mentioned in the experimental section. The structure of the synthesized compounds was established by using NMR, MS.

Table no.3 Physicochemical data of the synthesized compounds

COMPOUND CODE	R 1	R 2	R 3	R4	R5	MOLECULAR FORMULA (M.W)	MP (ºC)	YIELD (%)	Rf values
Compound 1	H	H	H	H	H	C28H26N2O5S (502.44)	201 - 203	52.12	0.21
Compound 2	H	H	H	Cl	H	C28H25ClN2O5S (536.31)	210 - 212	61.17	0.23
Compound 3	H	H	H	H	Cl_4	C28H25ClN2O5S (536.12)	215 - 217	57.21	0.22
Compound 4	H	H	H	NO_2	H	C28H25N3O7S (547.04)	199 - 202	50.12	0.24
Compound 5	H	H	H	H	NO_2	C28H25N3O7S (547.10)	212 - 214	62.17	0.25
Compound 6	H	H	H	Cl_4	H	C25H22ClN3O3S (479.10)	218 - 219	58.21	0.26
Compound 7	H	H	H	H	Cl_4	C25H22Cl4N3O3S^{3+} (584.31)	235 - 237	59.35	0.26
Compound 8	H	H	H	H	NO_2	C25H22N4O5S (490.10)	235 - 237	60.12	0.28
Compound 9	H	H	H	NO_2	H	C25H22N4O5S (490.02)	212 - 214	54.44	0.33

Compound 10	H	H	H	H	CO_4 H	C25H23N3O7S (509.13)	220 - 222	61.10	0.17

2. Spectral characterization

A. NMR

Compound 1

ethyl2-(3-hydroxy-2-oxo-1,5-diphenyl-2,5-dihydro-1H-pyrrole-4-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

1H NMR δ (d, J = 8.47, 7.93, 7.93, 7.70, 7.50, 7.29, 7.28, 7.27, 7.25, 7.23, 7.08 Hz), (s, J = 5.79, 5.75, 5.56, 4.94 Hz), (d, J = 2.83, 2.83, 2.60, 2.60, 1.65, 1.65, 1.64, 1.64 Hz).

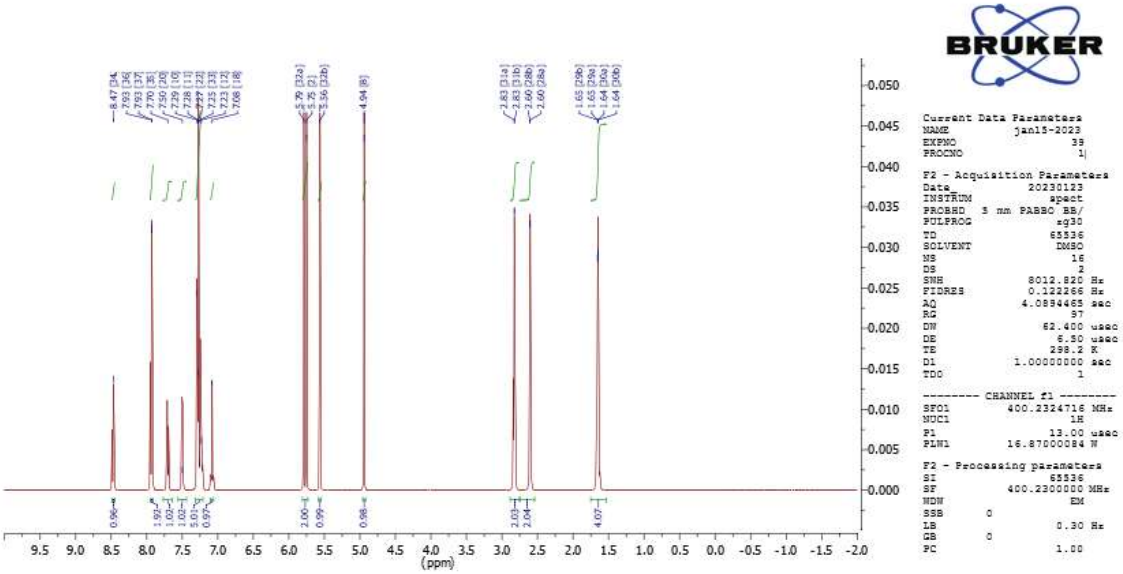


Figure 1 NMR Spectra of Compound 1

Compound 2

ethyl2-(5-(2-chlorophenyl)-3-hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-4-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

1H NMR δ (d, J = 8.58, 7.97, 7.97, 7.61, 7.50, 7.43, 7.07, 7.05, 7.02, 6.91 Hz), (s, J = 5.65, 5.55, 5.55, 3.87 Hz), (d, J = 2.83, 2.83, 2.60, 2.60, 1.66, 1.66, 1.64, 1.64 Hz).

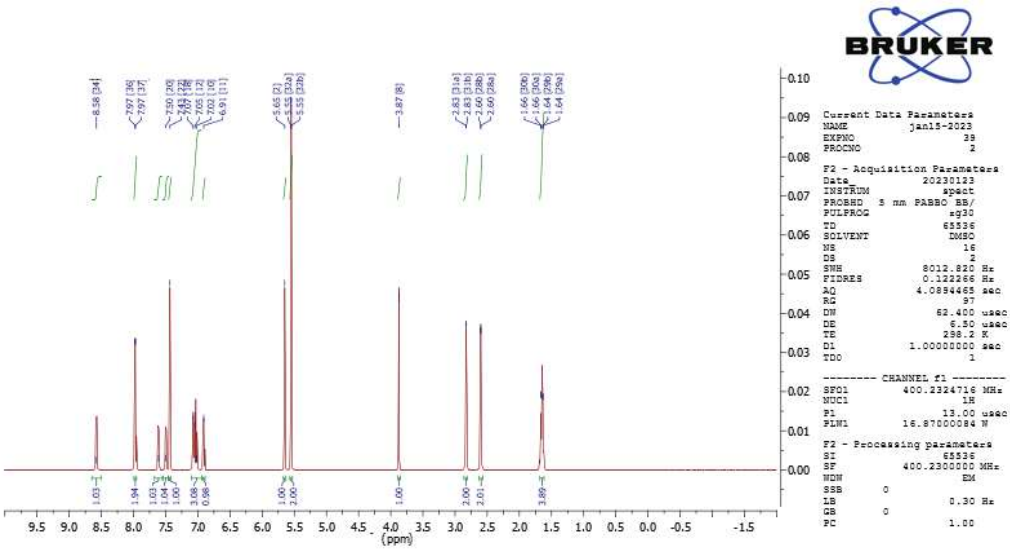


Figure 2 NMR Spectra of Compound 2

Compound 3

Ethyl 2-(5-(3-chlorophenyl)-3-hydroxy-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-4-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

1H NMR δ (s, J = 8.91 Hz), (d, J = 7.67, 7.67, 7.58, 7.47 Hz), (m, J = 7.31, 7.24, 7.19, 7.08, 7.08 Hz), (d, J = 5.57, 5.57 Hz), (m, J = 5.36, 4.90, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

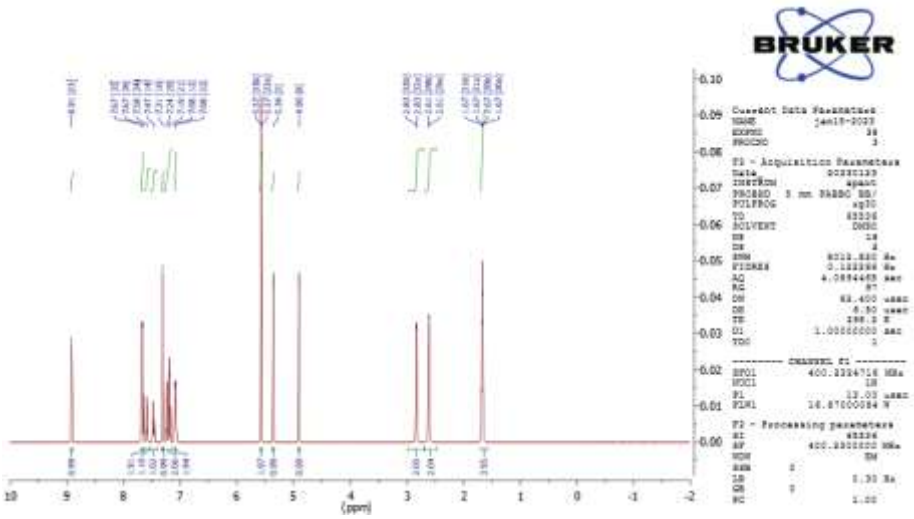


Figure 3 NMR Spectra of Compound 3

Compound 4

Ethyl2-(3-hydroxy-5-(3-nitrophenyl)-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-4-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

1H NMR δ (s, J = 9.61 Hz), (d, J = 8.01, 7.75, 7.75, 7.57, 7.52, 7.50, 7.48 Hz), (m, J = 7.34, 7.08 Hz), (d, J = 5.57, 5.57 Hz), (m, J = 5.49, 5.13, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

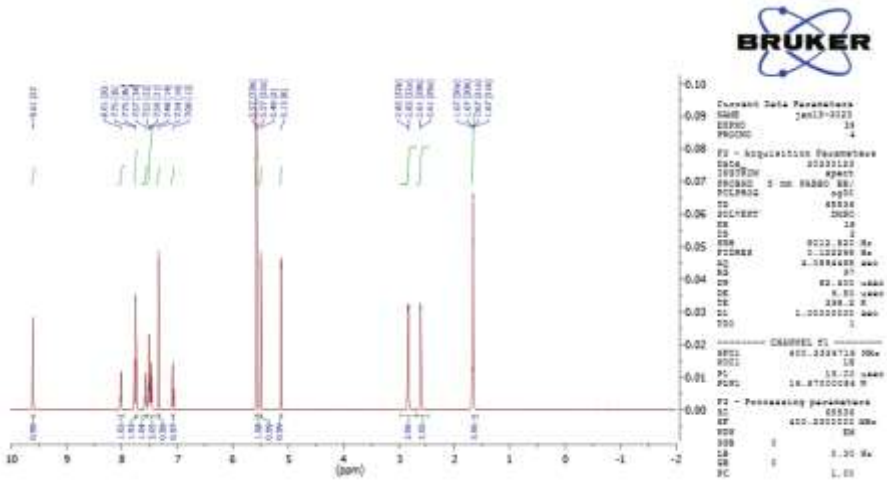


Figure 4 NMR Spectra of Compound 4

Compound 5

Ethyl2-(3-hydroxy-5-(2-nitrophenyl)-2-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-4-carboxamido)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate

1H NMR δ (s, J = 9.61 Hz), (d, J = 8.01, 7.75, 7.75, 7.57, 7.52, 7.50, 7.48 Hz), (m, J = 7.34, 7.08 Hz), (d, J = 5.57, 5.57 Hz), (m, J = 5.49, 5.13, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

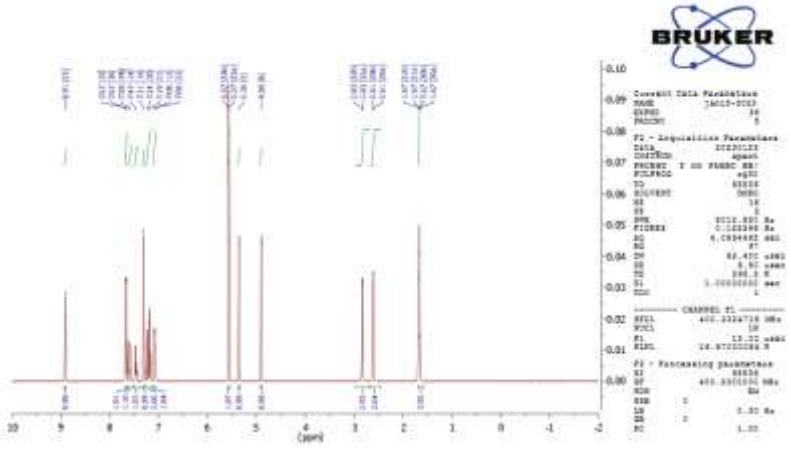


Figure 5 NMR Spectra of Compound 5

Compound 6

N-(3-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-2-(2-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamide

1H NMR δ (s, J = 8.87 Hz), (d, J = 7.85, 7.81, 7.58, 7.36 Hz), (m, J = 7.22, 7.18, 7.14, 7.12, 7.04, 6.06 Hz), (d, J = 5.80, 5.70 Hz), (m, J = 3.74, 2.83, 2.83, 2.60, 2.60, 1.66, 1.66, 1.66, 1.66 Hz).

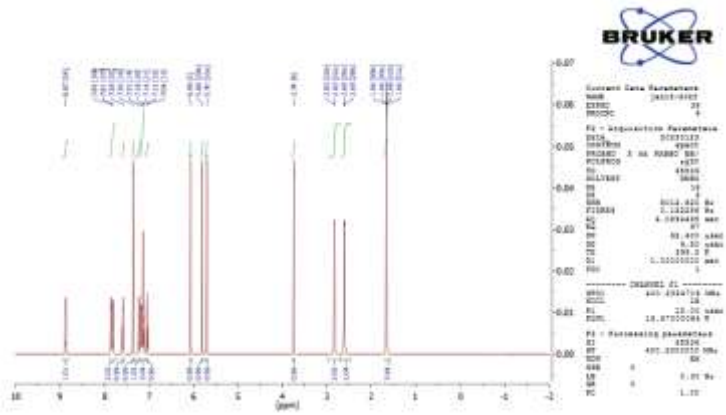


Figure 6 NMR Spectra of Compound 6

Compound 7

N-(3-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-2-(3-chlorophenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamide

1H NMR δ (s, J = 8.87 Hz), (d, J = 7.85, 7.81, 7.58, 7.36 Hz), (m, J = 7.22, 7.18, 7.14, 7.12, 7.04, 6.06 Hz), (d, J = 5.80, 5.70 Hz), (m, J = 3.74, 2.83, 2.83, 2.60, 2.60, 1.66, 1.66, 1.66, 1.66 Hz).

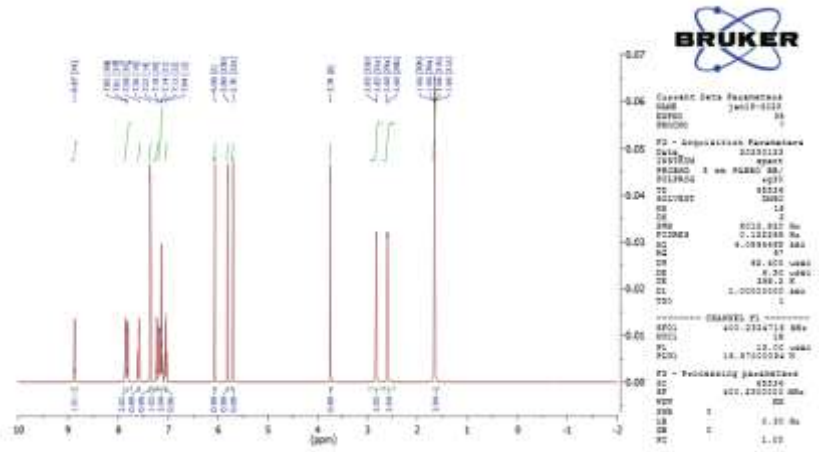


Figure 7 NMR Spectra of Compound 7

Compound 8

N-(3-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-4-hydroxy-2-(3-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamide

1H NMR δ (s, J = 9.61 Hz), (d, J = 8.01, 7.75, 7.75, 7.57, 7.52, 7.50, 7.48 Hz), (m, J = 7.34, 7.08 Hz), (d, J = 5.57, 5.57 Hz), (m, J = 5.49, 5.13, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

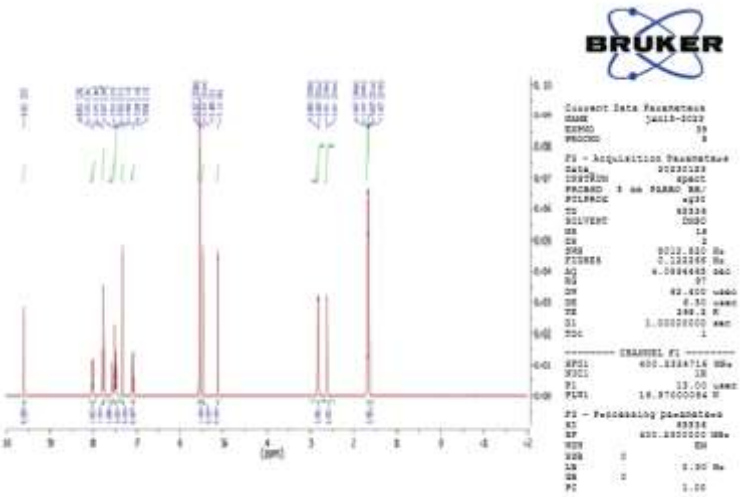


Figure 8 NMR Spectra of Compound 8

Compound 9

N-(3-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-4-hydroxy-2-(2-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamide

1H NMR δ (s, J = 9.61 Hz), (d, J = 8.01, 7.75, 7.75, 7.57, 7.52, 7.50, 7.48 Hz), (m, J = 7.34, 7.08 Hz), (d, J = 5.57, 5.57 Hz), (m, J = 5.49, 5.13, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

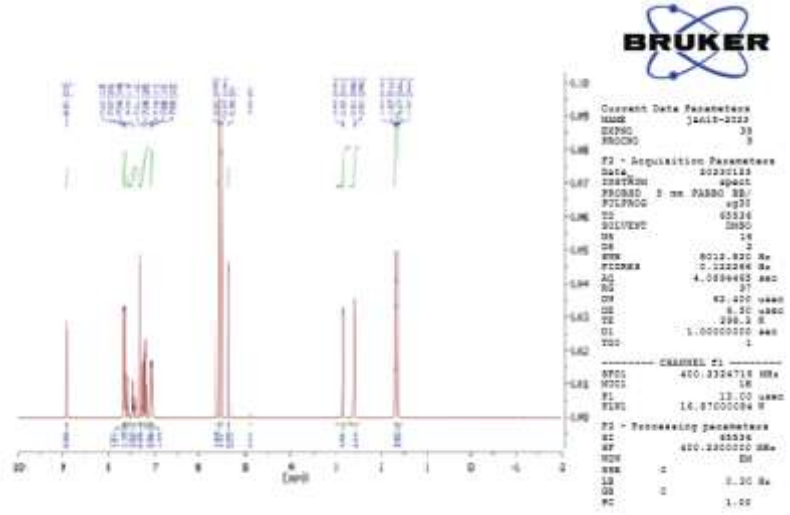


Figure 9 NMR Spectra of Compound 9

Compound 10

N-(3-amino-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-2-(3-(hydroperoxyperoxy)phenyl)-4-hydroxy-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxamide

1H NMR δ (s, J = 12.78 Hz), (d, J = 7.79, 7.67, 7.45, 7.41 Hz), (m, J = 7.20, 7.10, 7.09, 7.06, 6.80, 6.74 Hz), (d, J = 5.56, 5.56 Hz), (m, J = 5.36, 4.63, 2.83, 2.83, 2.61, 2.61, 1.67, 1.67, 1.67, 1.67 Hz).

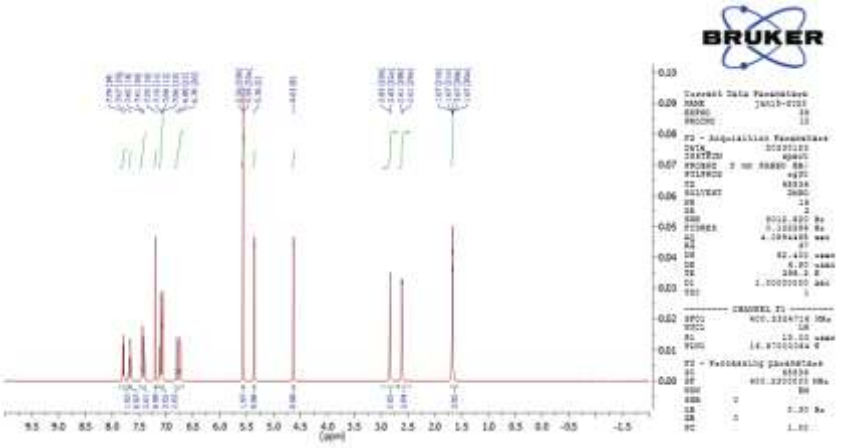


Figure 10 NMR Spectra of Compound 10

B. Mass Spectroscopy

Compound 1

The suggested structure with C28H26N2O5S matched the MS's molecular ion signal at m/z 502.44 (M] +). Thus, spectroscopic investigations led to the conclusion that chemical 1 may be classified as a pyrrolidone derivative.

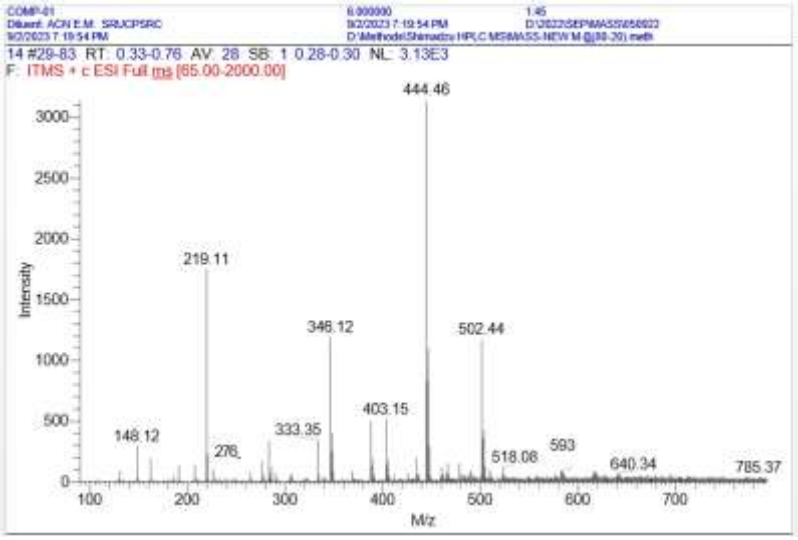


Figure 11 Mass Spectra of Compound 1

Compound 2

The suggested structure with C28H25ClN2O5S was consistent with the MS's molecular ion signal at m/z 536.31 (M] +). Thus, spectroscopic analysis led to the conclusion that chemical 2 may be classified as a pyrrolidone derivative.

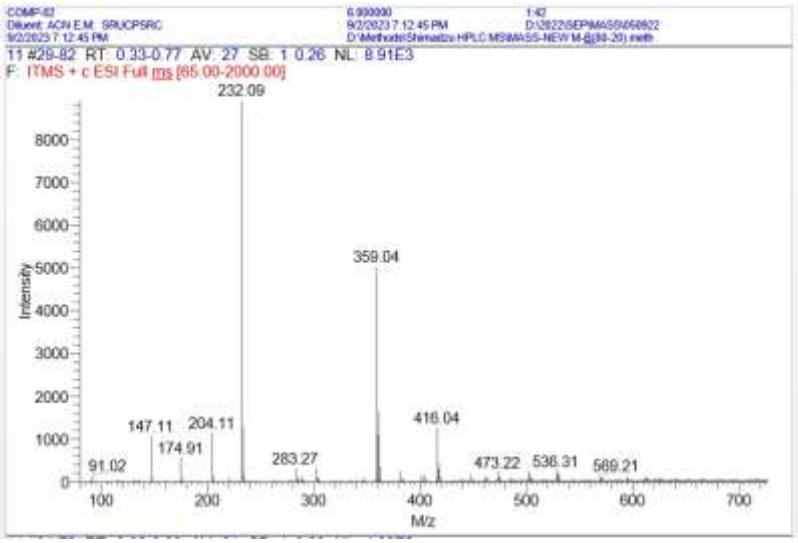


Figure 12 Mass Spectra of Compound 2

Compound 3

At m/z 536.12 (M] +, the MS displayed a molecular ion peak that matched the suggested structure with C28H25ClN2O5S. Thus, spectroscopic investigations led to the conclusion that chemical 3 may be classified as a pyrrolidone derivative.

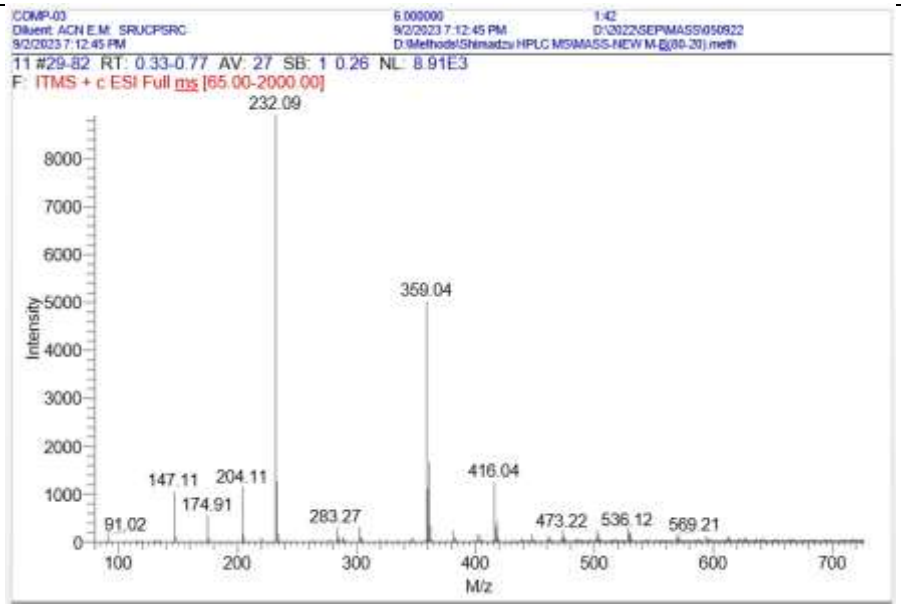


Figure 13 Mass Spectra of Compound 3

Compound 4

At m/z 547.40 (M] +, the MS revealed a molecular ion peak that matched the suggested structure with C28H25N3O7S. Thus, spectroscopic analysis led to the conclusion that chemical 4 may be classified as a pyrrolidone derivative.

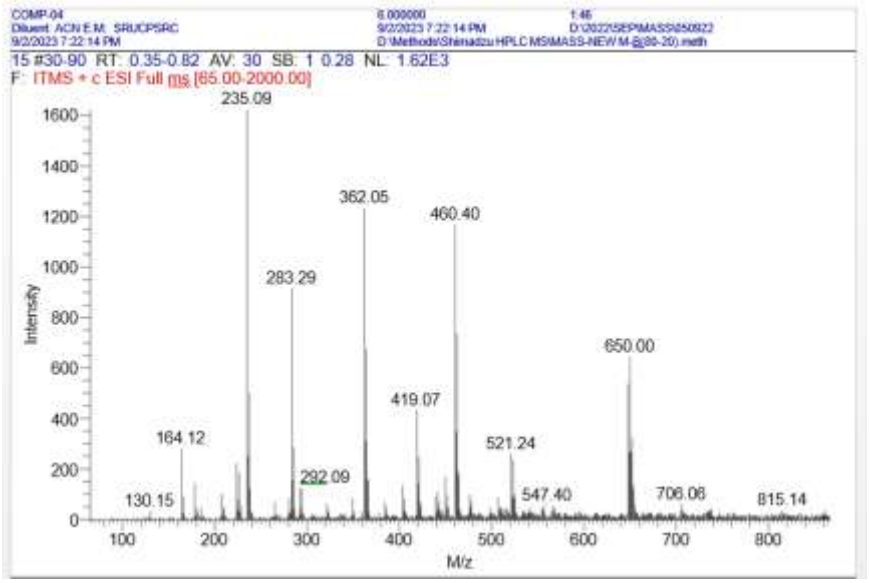


Figure 14 Mass Spectra of Compound 4

Compound 5

At m/z 547.10 (M] +, the MS revealed a molecular ion peak that matched the suggested structure of C28H25N3O7S. Thus, spectroscopic analysis led to the conclusion that chemical 5 may be classified as a pyrrolidone derivative.

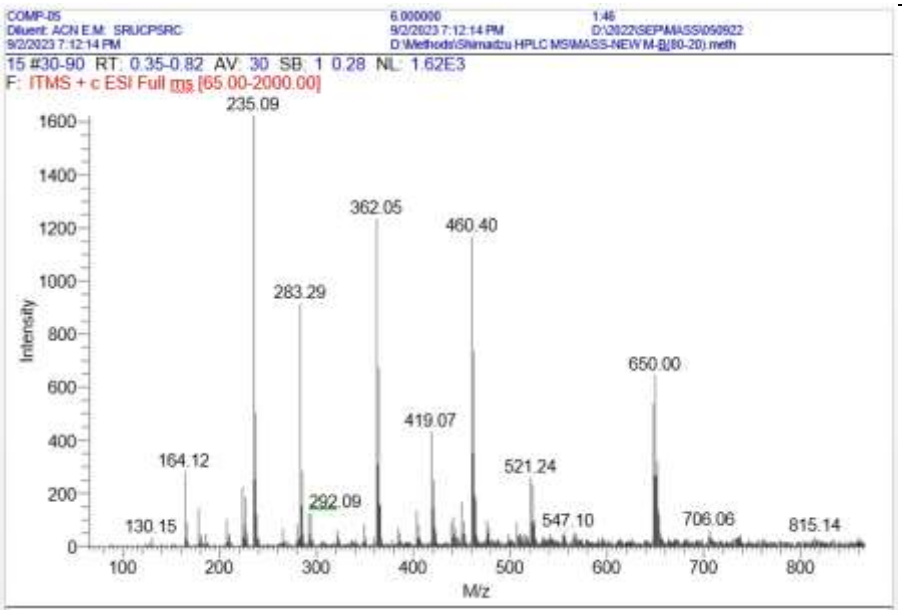


Figure 15 Mass Spectra of Compound 5

Compound 6

The MS showed a molecular ion peak at m/z 479.10 (M] + and was in match with the proposed structure with C25H22ClN3O3S. Thus, spectroscopic analyses led to the conclusion that chemical 6 may be classified as a pyrrolidone derivative.

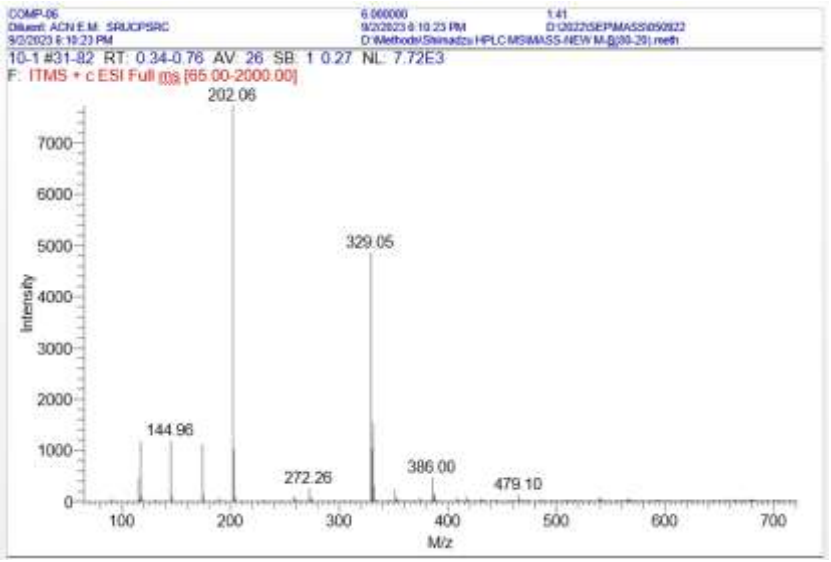


Figure 16 Mass Spectra of Compound 6

Compound 7

The MS showed a molecular ion peak at m/z 584.31 (M] + and was in match with the proposed structure with $C25H22Cl4N3O3S^{3+\cdot}$ Hence, it was concluded through spectroscopic studies that the compound 7 could be characterized as pyrrolidone derivative.

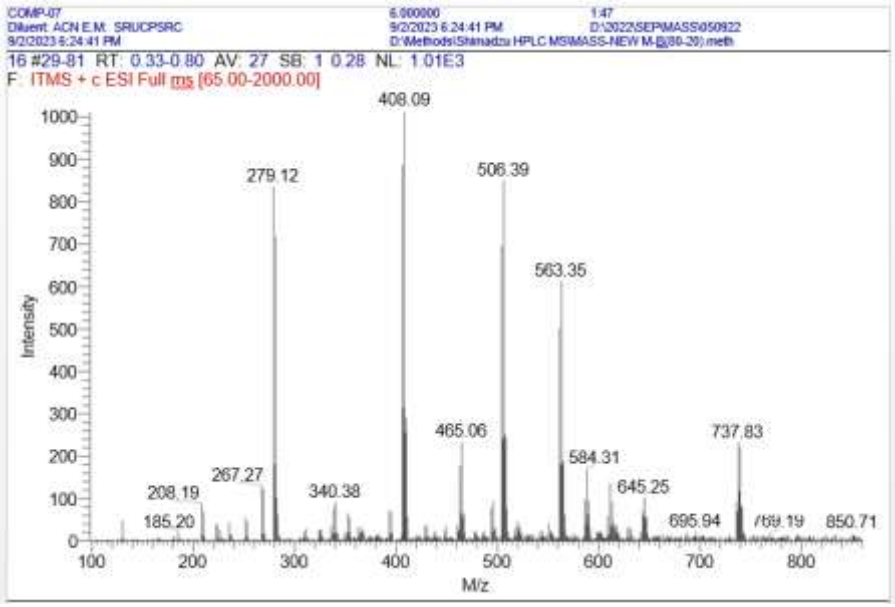


Figure 17 Mass Spectra of Compound 7

Compound 8

The MS showed a molecular ion peak at m/z 490.10 (M] + and was in match with the proposed structure with $C_{25}H_{22}N_4O_5S^{\cdot}$ Hence, it was concluded through spectroscopic studies that the compound 8 could be characterized as pyrrolidone derivative.

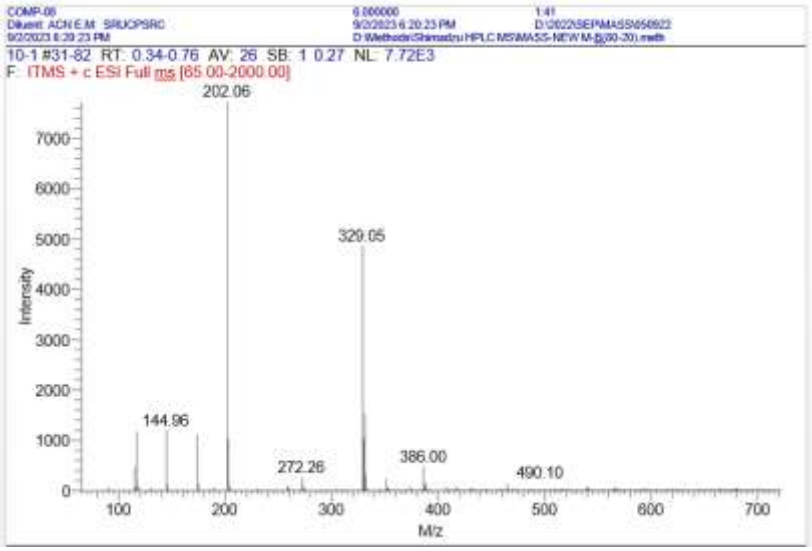


Figure 18 Mass Spectra of Compound 8

Compound 9

The MS showed a molecular ion peak at m/z 490.02 (M] + and was in match with the proposed structure with $C_{25}H_{22}N_4O_5S^{\cdot}$ Hence, it was concluded through spectroscopic studies that the compound 9 could be characterized as pyrrolidone derivative.

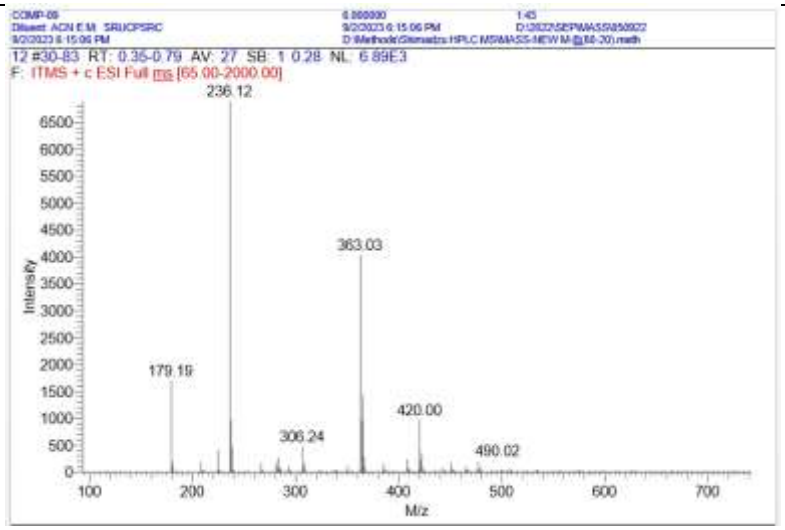


Figure 19 Mass Spectra of Compound 9

Compound 10

The MS showed a molecular ion peak at m/z 509.13 (M] + and was in match with the proposed structure with C25H23N3O7S· Hence, it was concluded through spectroscopic studies that the compound 10 could be characterized as pyrrolidone derivative.

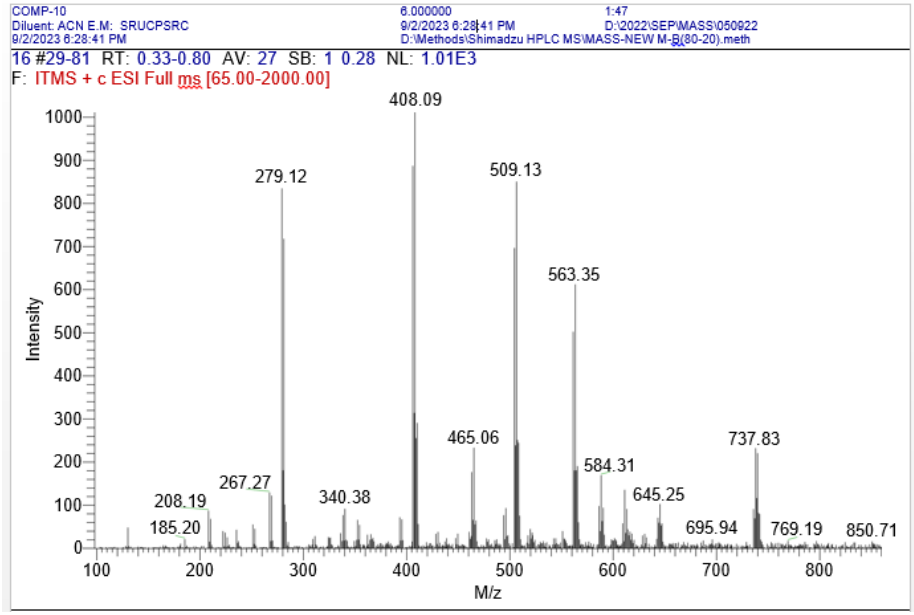


Figure 20 Mass Spectra of Compound 10

C. Biological Activity

Table3Effectof compound 10 (C10) on hotplatetest:

Treatment	Responsetime(sec)				
	0h	0.5h	1h	2h	3h
Control(10ml/kg)	8.30±0.63	7.42±0.42	7.50±0.39	7.50±0.45	7.18±0.33
Standard(10mg/kg)	8.42±0.29	11.59±0.32**	13.58±0.38**	14.98±0.48***	16.38±0.27***
compound 10 (C10) (20mg/kg)	8.27±0.32	10.25±0.31**c	10.94±0.13***a	11.27±0.58**a	11.98±0.37***b

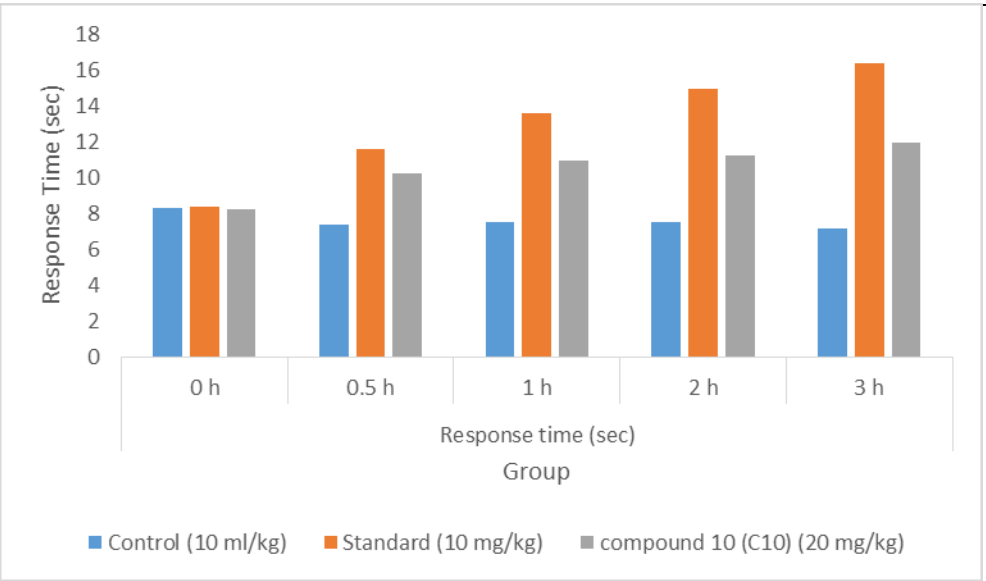


Figure 21 Effectof compound 10 in Hot Plate method

Valuesareexpressedasmean±SEM(Standarderrormean);Valuesarecalculatedusingone-wayANOVAfollowedbyDennett'stest;***indicatesP<0.001and **indicatesP<0.01whencomparedtocontrol;^{a}indicatesP<0.001,^{b}indicatesP<0.01and^{c}indicatesP<0.05whencomparedtostandarddrug;p.o.;n=6.

The analgesic activity test using the hot plate method indicates that the control group shows consistent response times with minimal changes. The standard treatment (10 mg/kg) demonstrates a significant and continuous increase in response time over the 3-hour period, suggesting a strong analgesic effect. Similarly, the Compound 10 (C10) treatment (20 mg/kg) also results in a notable increase in response time, though to a slightly lesser extent than the standard treatment. Overall, both treatments exhibit significant analgesic properties, with the standard treatment having a more pronounced effect on response times compared to Compound 10.

Table 4 Effect of compound 10 (C10) on acetic acid induced writhing in mice

Treatment	Totalwrithingcount (Mean±SEM)	%Inhibition
control	17.4±2.50	-
Standard	6.2±0.66***	64.36
compound 10 (C10) (20mg/kg)	10.10±0.41**	41.95

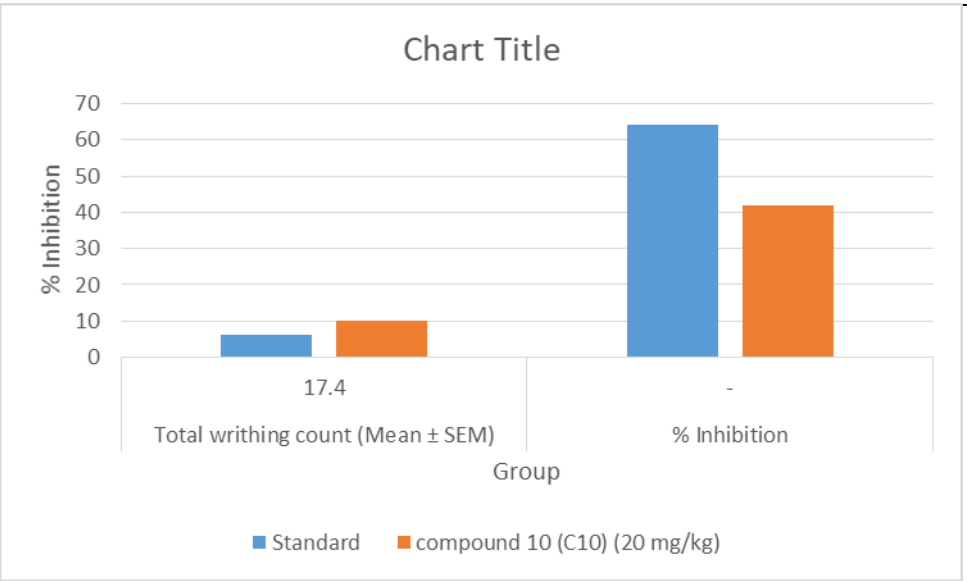


Figure 22 Effect of compound 10 (C10) on acetic acid induced writhing in mice

Valuesareexpressedasmean±SEM(Standarderrormean);Valuesarecalculatedusingone-wayANOVAfollowedbyDennett'stest;***indicatesP<0.001and **indicatesP<0.01whencomparedtocontrol;^{a}indicatesP<0.001,^{b}indicatesP<0.01and^{c}indicatesP<0.05whencomparedtostandarddrug;p.o.;n=6.

The data on total writhing count suggests notable analgesic effects for both the standard treatment and Compound 10 (C10). The control group has a mean writhing count of 17.4 ± 2.50, serving as the baseline with no inhibition. The standard treatment significantly reduces the writhing count to 6.2 ± 0.66, representing a 64.36% inhibition, indicating a strong analgesic effect. Similarly, Compound 10 (C10) at 20 mg/kg shows a reduction in writhing count to 10.10 ± 0.41, resulting in a 41.95% inhibition, demonstrating considerable analgesic activity though slightly less pronounced than the standard treatment. These results underscore the efficacy of both treatments in reducing pain responses.

TABLE 5 Effectof compound 10 (C10) on Carrageenan-Induced Paw Edema

Sr. No	Group / Treatment	0 min	1 h	2 h	3 h	4 h	5 h
1	**Normal Control**	0.24 ± 0.01 NS	0.24 ± 0.01 NS	0.25 ± 0.01 NS	0.25 ± 0.01 NS	0.25 ± 0.01 NS	0.26 ± 0.01 NS
2	**Disease Control (1% Tween 80, p.o.)**	0.24 ± 0.01 NS	0.38 ± 0.02 NS	0.49 ± 0.02 NS	0.63 ± 0.03 NS	0.72 ± 0.02 NS	0.75 ± 0.03 NS
3	**Standard Indomethacin (10 mg/kg)**	0.25 ± 0.02 NS	0.28 ± 0.02**	0.30 ± 0.02**	0.32 ± 0.02**	0.33 ± 0.02**	0.34 ± 0.02**
4	**Compound 10 (10 mg/kg)**	0.24 ± 0.02 NS	0.32 ± 0.02**	0.36 ± 0.02**	0.41 ± 0.02**	0.45 ± 0.02**	0.48 ± 0.02**

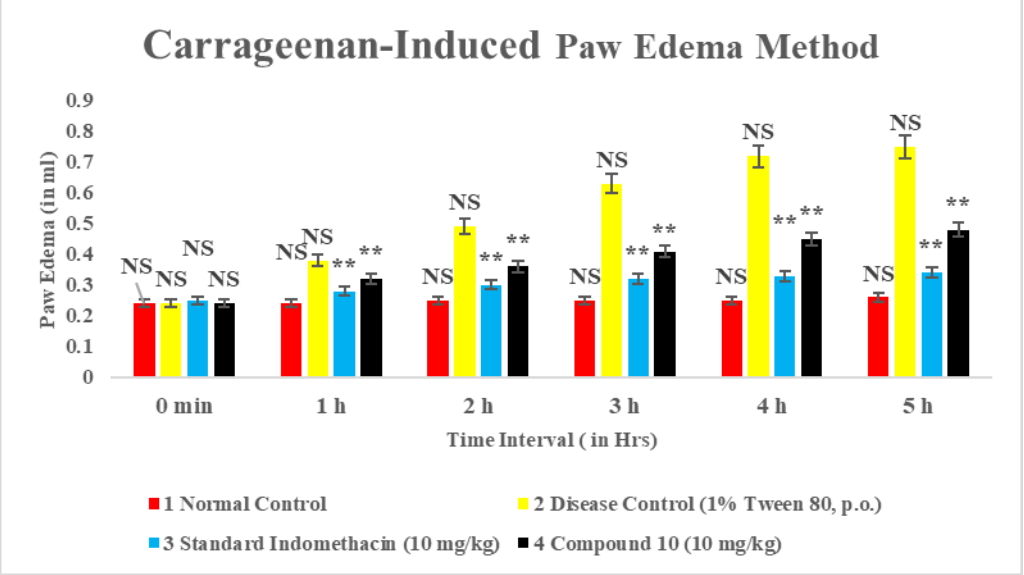


Figure 23 Effectofcompound 10 (C10) on Carrageenan-Induced Paw Edema in mice

Valuesareexpressedasmean±SEM(Standarderrormean);Valuesarecalculatedusingone-wayANOVAfollowedbyDennett'stest;***indicatesP<0.001and **indicatesP<0.01whencomparedtocontrol;^{a}indicatesP<0.001,^{b}indicatesP<0.01and^{c}indicatesP<0.05whencomparedtostandarddrug;p.o.;n=6.

The present study demonstrates that Compound 10 (10 mg/kg)exhibits significant anti-inflammatory activity in the carrageenan-induced paw edema model. The disease control group showed a progressive and marked increase in paw volume from 1 to 5 h, confirming successful induction of acute inflammation. In contrast, the normal control group maintained a nearly constant paw volume throughout the experimental period.Treatment with the standard drug Indomethacin (10 mg/kg) produced a significant ($P < 0.01$) reduction in paw edema from the 1st hour onward, validating the sensitivity of the experimental model. Similarly, Compound 10 (10 mg/kg) significantly suppressed paw edema at all post-carrageenan time points (1–5 h) when compared with the disease control group.Although the inhibitory effect of Compound 10 was less pronounced than Indomethacin, it showed a consistent and time-dependent reduction of inflammation**,** particularly during the late phase (3–5 h), which is mainly mediated by prostaglandins. These findings suggest that Compound 10 possesses appreciable anti-inflammatory potential**,** possibly through inhibition of inflammatory mediators involved in the acute inflammatory response.Overall, the results indicate that Compound 10 may serve as a promising lead compound for further anti-inflammatory drug development**,** warranting additional mechanistic and dose-dependent studies.

4. Conclusion:

In this study, we designed and synthesized a series of pyrrolidone derivatives using iodine as a catalyst, and evaluated their analgesic activity through two methods: the hot plate test and the writhing test.

The hot plate test showed that the control group exhibited stable response times with minimal changes, indicating no analgesic effect. However, both the standard treatment (10 mg/kg) and Compound 10 (C10) (20 mg/kg) demonstrated significant analgesic effects, with Compound 10 showing a notable but slightly lesser increase in response times compared to the standard treatment. The standard treatment exhibited a pronounced and continuous increase in response time over the 3-hour testing period, reinforcing its strong analgesic potential. Compound 10 also showed an increase in response time, highlighting its analgesic properties, though not as substantial as the standard treatment.

In the writhing test, the control group had a baseline mean writhing count of 17.4 ± 2.50, confirming a lack of analgesic effect. The standard treatment at 10 mg/kg showed a significant reduction in writhing count to 6.2 ± 0.66, representing a 64.36% inhibition of pain, which points to a potent analgesic effect. Compound 10 (20 mg/kg) also demonstrated substantial analgesic

activity with a reduction in writhing count to 10.10 ± 0.41, corresponding to a 41.95% inhibition. While the analgesic effect of Compound 10 was less pronounced than the standard treatment, it still exhibited considerable efficacy in reducing pain.

These findings highlight the analgesic potential of pyrrolidone derivatives, particularly Compound 10, which, while slightly less effective than the standard treatment, still demonstrates promising analgesic activity. The structure-activity relationship of these derivatives, as analyzed through NMR and mass spectrometry data, could be further optimized to enhance their efficacy. Overall, the results of both the hot plate and writhing tests underscore the promising analgesic properties of these compounds, paving the way for future developments in pain management therapies.

The disease control group exhibited a progressive increase in paw edema, confirming the successful induction of acute inflammation, while the normal control group showed no significant change in paw volume throughout the experimental period. Treatment with the standard drug Indomethacin (10 mg/kg) resulted in a significant reduction in paw edema from 1 to 5 h, thereby validating the sensitivity of the carrageenan-induced inflammation model. Compound 10 (10 mg/kg) also produced a significant and time-dependent reduction in paw edema at all observed time points when compared with the disease control group. Although the anti-inflammatory effect of Compound 10 was less pronounced than that of Indomethacin, it remained consistently significant during the late phase of inflammation. The observed inhibition suggests an effect on mediators involved in the prostaglandin-dependent phase of acute inflammation. Overall, the findings indicate that Compound 10 possesses notable anti-inflammatory activity and merits further pharmacological evaluation.

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