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Design, Synthesis, and Neurobehavioral Assessment of Novel Piracetam Derivatives for Alleviating Peripheral Neuropathy

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ABSTRACT

Peripheral neuropathy is a common neurological disorder characterized by damage to the peripheral nerves, leading to symptoms such as pain, tingling, and numbness. Current treatment options are limited and often provide only symptomatic relief. This research paper explores the design, synthesis, and neurobehavioral assessment of novel piracetam derivatives as potential therapeutic agents for alleviating peripheral neuropathy. As peripheral neuropathy poses a considerable burden on affected individuals and lacks adequate treatment options, the study focuses on the design and synthesis of compounds with enhanced neuroprotective properties. The approach involves rational drug design to modify the piracetam structure, with subsequent in vitro and in vivo assessments of neuroprotective effects and neurobehavioral outcomes. The designed compounds are synthesized using established organic chemistry techniques, and their purity and identity are confirmed through rigorous spectroscopic and chromatographic methods. In vivo assessments on animal models of peripheral neuropathy include behavioral assays to measure pain thresholds, motor function, and cognitive performance. The anticipated results aim to provide insights into the potential therapeutic efficacy of the novel piracetam derivatives. Chemical structures, physicochemical properties, and neuroprotective outcomes will be discussed, considering the implications for developing innovative treatments for peripheral neuropathy. The abstract emphasizes the significance of addressing the unmet

clinical needs of individuals suffering from peripheral neuropathy through the development of safe and effective therapeutic interventions. The conclusion underscores the importance of future research to delve into mechanistic aspects, conduct additional preclinical assessments, and ascertain the long-term safety and efficacy of the synthesized compounds before advancing to clinical trials.

Keywords: Peripheral Neuropathy, Piracetam Derivatives, Neurobehavioral Assessment

1. INTRODUCTION

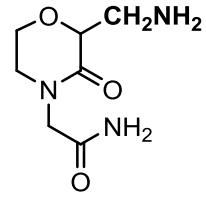
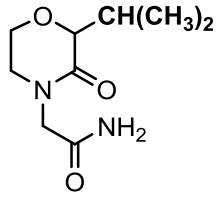
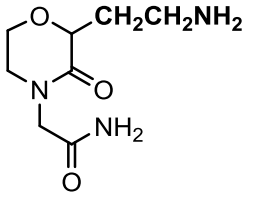
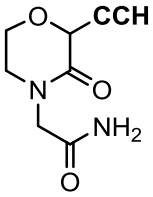
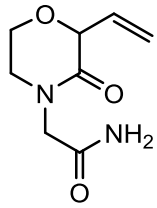
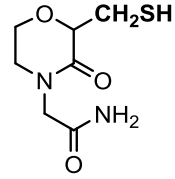
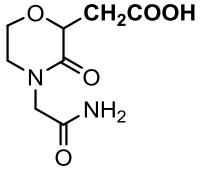
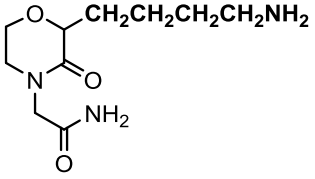
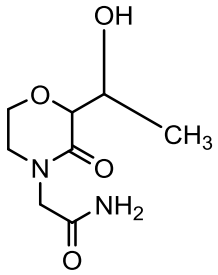
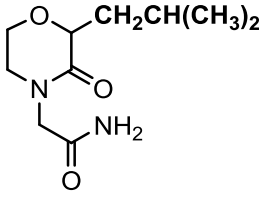
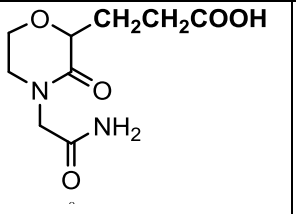
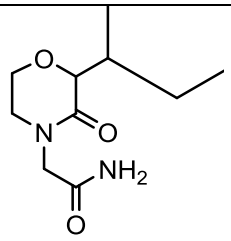
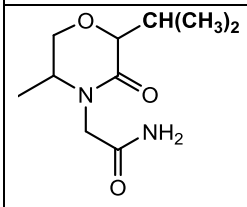
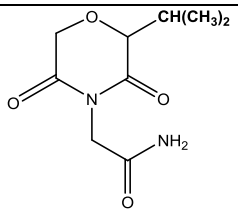
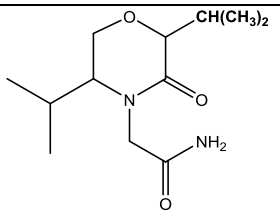
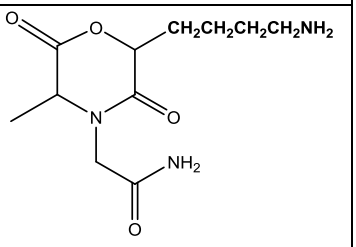
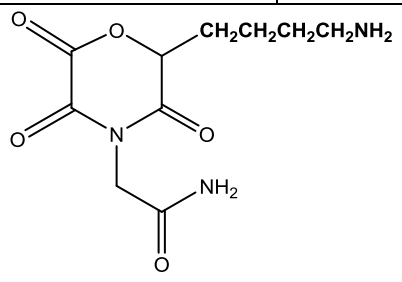
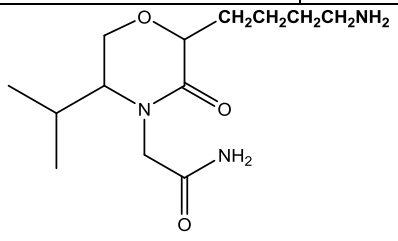
Peripheral neuropathy affects a significant portion of the global population, and its etiology includes various factors such as diabetes, chemotherapy, and traumatic injuries [1]. Despite the prevalence of this condition, effective therapeutic interventions are lacking. Piracetam, a nootropic compound known for its cognitive-enhancing properties, has shown promise in neuroprotection. This study aims to design and synthesize novel piracetam derivatives with enhanced neuroprotective properties for alleviating peripheral neuropathy. Peripheral neuropathy is a debilitating neurological disorder characterized by damage to the peripheral nerves, resulting in a range of symptoms such as pain, tingling, and numbness. The prevalence of peripheral neuropathy is substantial, with estimates suggesting that up to 20 million individuals in the United States alone are affected [1]. Etiological factors include diabetes, chemotherapy, and traumatic injuries, contributing to the complexity and heterogeneity of the condition [2]. Despite its widespread impact, therapeutic options for peripheral neuropathy are limited, often providing only symptomatic relief and failing to address the underlying mechanisms of nerve damage. In recent years, there has been a growing interest in exploring novel compounds with neuroprotective properties for the treatment of peripheral neuropathy. Piracetam, a prototypical nootropic agent, has demonstrated neuroprotective effects and has been investigated for its potential in various neurological disorders [3]. However, there is a need for innovative approaches to enhance its efficacy and tailor its properties for addressing the specific challenges presented by peripheral neuropathy.

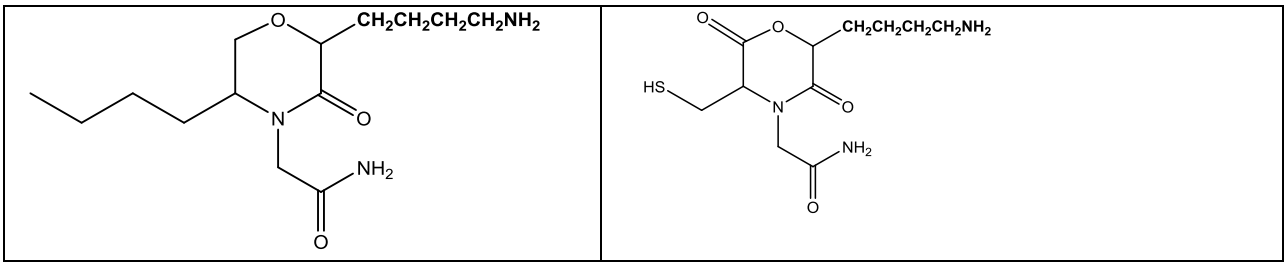
The rationale for investigating piracetam derivatives lies in their potential to modulate various cellular processes implicated in peripheral neuropathy pathogenesis. Previous studies have highlighted the role of oxidative stress, inflammation, and excitotoxicity in nerve damage associated with peripheral neuropathy [4]. Piracetam and its derivatives offer a unique pharmacological profile that may address these pathological processes, making them promising candidates for therapeutic development. Furthermore, advancements in computational methods and medicinal chemistry provide opportunities to design derivatives with optimized pharmacokinetic and pharmacodynamic properties. By strategically modifying the piracetam structure, it is possible to tailor these compounds to specifically target the pathways involved in

peripheral neuropathy, potentially leading to more effective and targeted therapeutic interventions.

The designed compounds illustrated in Table: -1 represent innovative hybrids, incorporating features from both Piracetam and other racetam compounds. Through their shared characteristics with Piracetam and related racetams, we anticipate that these compounds will exhibit pharmacological actions akin to groups known for their neuropathic effects and cognitive enhancement [5,6,7,8,9,10].

Table: -1 Deigned derivatives



2. Experimental section

2.1 Material

Melting Point was measured using ranges of Metals - visual equipment, open capillary tube - temperature range between initial melt and complete liquefaction.

Silica gel G adsorbents: TLC plates (20 x 5 cm), cleaned to 1 mm thickness, 30 minutes in an oven at 110°C; Silica gel G plates: substances investigated; and the TLC plate monitored reactions. Ethyl acetate:benzene:methanol (1.4:8.5:1), hexane:ethyl acetate (1:9), and chloroform:methanol (9:1) are the mobile phases. Iodine vapours and spot visualisation in a UV cabinet

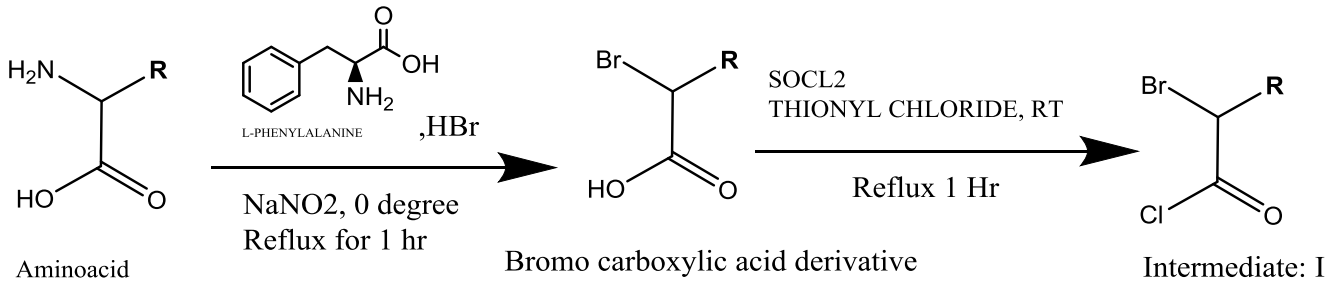
By examining the dissolution of intermediate and final compounds in water, methanol, ethanol, chloroform, dimethyl sulphoxide, benzene, and dichloromethane, the solubility of the compounds was determined. The analysis of infrared spectra is done using Bruker's FTIR. Bruker's NMR spectra recording for 1H NMR analysis Agilent Technology India Private Limited's model number 6230B is for mass spectral analysis.

2.2 Methods

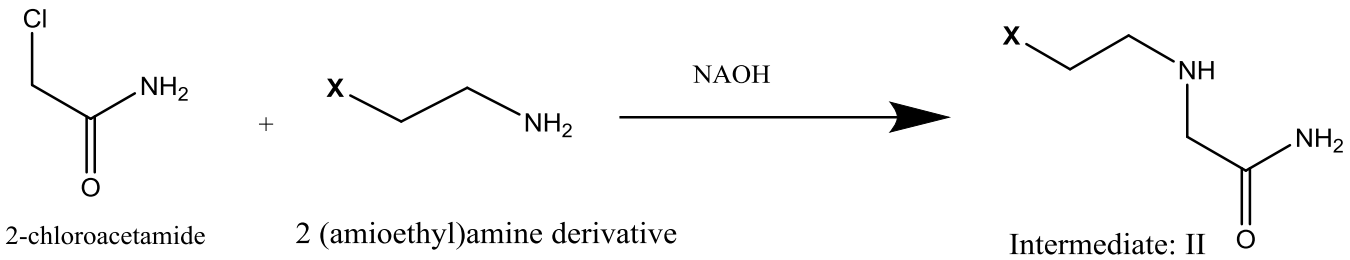
Structural alterations to improve neuroprotective characteristics were taken into consideration when designing novel derivatives of piracetam using a rational drug design approach. Standard organic chemistry procedures were used for the synthesis, and spectroscopic techniques were used to establish the compounds' identity.

2.3 General Scheme for Synthesis of Compound

STEP: 1

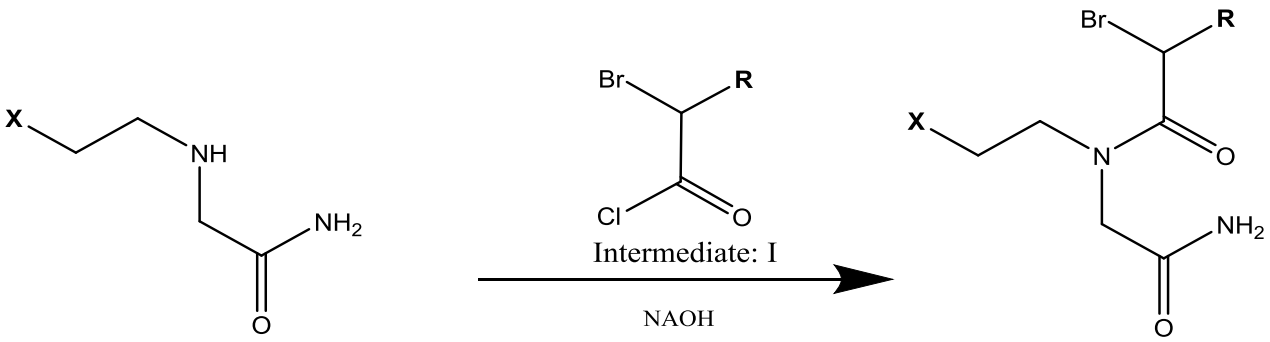


STEP: 2



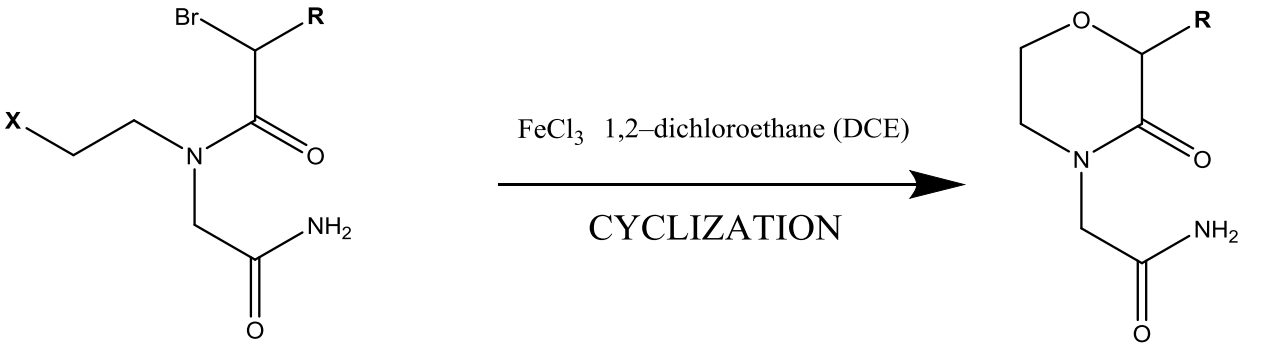
2-chloroacetamide 2 (amioethyl)amine derivative Intermediate: II

STEP: 3



Intermediate: II Intermediate: III

STEP: 4



Intermediate: III Piracetam derivatives A1 to A20

2.4 The synthesis of designed compounds

it involves a multi-step process aimed at achieving the desired molecular structure. In Step 1, L-Phenylalanine reacts with hydrobromic acid, and sodium nitrite is added to the solution. Amino acid incorporation at 0°C, followed by reflux for an hour, is performed. Thionyl chloride is then introduced, with the solution stirred and heated until the evolution of SO2 and HCl gases ceases. After cooling, toluene is added and evaporated to remove excess thionyl chloride, and reaction completion is assessed using TLC. The resulting intermediate is analyzed via IR spectroscopy [6].

Moving to Step 2, an acetamide substituent solution in 10% sodium hydroxide reacts with ethanolamine, undergoes filtration, and is recrystallized. TLC determines the completion of the reaction, and IR spectroscopy analyzes the resulting intermediate [7,8].

In Step 3, solutions from Steps 1 and 2 are combined at 0°C, stirred, and then refluxed. After cooling, the reaction is quenched, and volatiles are evaporated. The resulting intermediate is analyzed using IR spectroscopy.

Finally, in Step 4, the intermediate from Step 3 undergoes cyclization with FeCl3 in 1,2–dichloroethane at room temperature and reflux. The final product is filtered and analyzed using spectroscopy. This intricate procedure ensures the synthesis of the designed compounds (Table: -2) with specific molecular attributes [9,10].

Table: 2 List of synthesized compounds.

S.NO.	R	X	PIRACETAM DERIVATIVES (COMPOUND CODE)
1.	-CH2NH2.HCL DL-2,3 diamino propionic acid monohydrochloride	X(-OH) Ethanolamine	**A1**
2.	-$CH(CH_3)_2$ DL- Valine	X(-OH) Ethanolamine)	**A2**
3.	-CH2CH2NH2 2,4 Diamino-butanoic acid	X(-OH) Ethanolamine)	**A3**

4.	-CCH DL-Propargylglycine	X(-OH) Ethanolamine)	**A4**
5.	-CCH2 DL-2-Allyl-glycine	X(-OH) Ethanolamine)	**A5**
6.	-CH2SH DL-Homo-cysteine	X(-OH) Ethanolamine)	**A6**
7.	-CH2COOH DL-Aspartic acid	X(-OH) Ethanolamine)	**A7**
8.	-CH2CH2CH2CH2NH2 L-Lysine	X(-OH) Ethanolamine)	**A8**
9.	-CH (OH, CH3) L-Threonine	X(-OH) Ethanolamine)	**A9**
10.	-CH2CH$(CH3)_2$ DL-Leucine	X(-OH) Ethanolamine)	**A10**
11.	-CH2CH2COOH D-Glutamic acid	X(-OH) Ethanolamine)	**A11**
12.	-CH(CH3)CH2CH3 DL-Isoleucine	X(-OH) Ethanolamine)	**A12**
13.	-CH$(CH3)_2$ DL- Valine	2-Amino-1-Propanol	**A13**
14.	-CH$(CH3)_2$ DL- Valine	GLYCOLAMIDE	**A14**
15.	-CH$(CH3)_2$ DL- Valine	2-Amino-3-methyl-1-butanol	**A15**
16.	-CH2CH2CH2CH2NH2 L-Lysine	DL Alanine	**A16**

17.	-CH2CH2CH2CH2NH2 L-Lysine	OXAMIC ACID	**A17**
18.	-CH2CH2CH2CH2NH2 L-Lysine	2-Amino-3-methyl-1-butanol	**A18**
19.	-CH2CH2CH2CH2NH2 L-Lysine	2-Amino-1-hexanol	**A19**
20.	-CH2CH2CH2CH2NH2 L-Lysine	DL-Cysteine	**A20**

2.5 Biological Activity of Synthesized Compounds

Male albino Wistar rats (150–200 g) were subjects in experiments conducted under standard laboratory conditions (temperature: 25±2℃, relative humidity: 50±15%, 12 h dark/12 h light period). They received a commercial pellet diet and water ad libitum. Animal procedures followed National Institutes of Health guidelines. The 80 rats were randomly divided into four groups: a negative control (Group 1), positive control with diabetic neuropathy induction (Group 2), a reference group treated with a marketed drug (Group 3), and test groups treated with various synthesized compounds (Group 4). [11,12]

2.5.1 Initiation of Diabetes

Inducing diabetes involved intraperitoneal injection of a single 60 mg/kg dose of streptozotocin, freshly dissolved in ice-cold 0.1 M citrate buffer (pH 4.5). The physiological parameters of male albino Wistar rats were monitored at 0, 7, 14, and 21 days following the streptozotocin injection, as detailed in Table 13-22. [13,14,15]

2.5.2 Medication Treatment

After assessing neuropathic pain baseline on the 7th day of diabetes induction, animals (n=5/group) were randomly assigned to four groups. The first group served as a negative non-diabetic control with no treatment, the second as a positive control with diabetic neuropathy induction, and the third as a reference group treated with Pregabalin. The fourth group received various synthesized compounds (A1 to A20). Pregabalin (150 mg/kg) was administered 30 min before behavioral assessment in the reference group, while the test groups received synthesized compounds once daily from days 0, 7, 14, to 21. Experimental animals were given intraperitoneal injections of pregabalin and derivatives of piracetam in a fine suspension produced in a 0.9% NaCl solution (CDH laboratory). [16,17]

2.5.3 Neuropathic pain behavioral tests

Neuropathic pain was assessed through behavioral tests, measuring hyperalgesia to noxious thermal stimuli and allodynia to mechanical stimuli using the radiant heat plantar and von Frey tests, respectively. Tests were conducted during the day (09:00–16:00h) after the cessation of cage exploration and grooming. Measurements included neuropathic pain scores, body weight, and plasma glucose levels at baseline and 7^{th}, 14^{th}, and 21^{st} days post-diabetes induction. [18,19]

A. Mechanical allodynia assessment (von Frey test)

Mice were individually placed in a plastic cage (13x7x7 cm) with a wire mesh bottom. After 15 minutes of acclimatization, von Frey's hair aesthesiometer (15 mm) was gently pressed perpendicularly to hind paw plantar surfaces. Responses were ranked from 0 to 2. Stimulations were applied five times per paw with a 30-second interval, and the sum of ten values served as the paw withdrawal response score.[17]

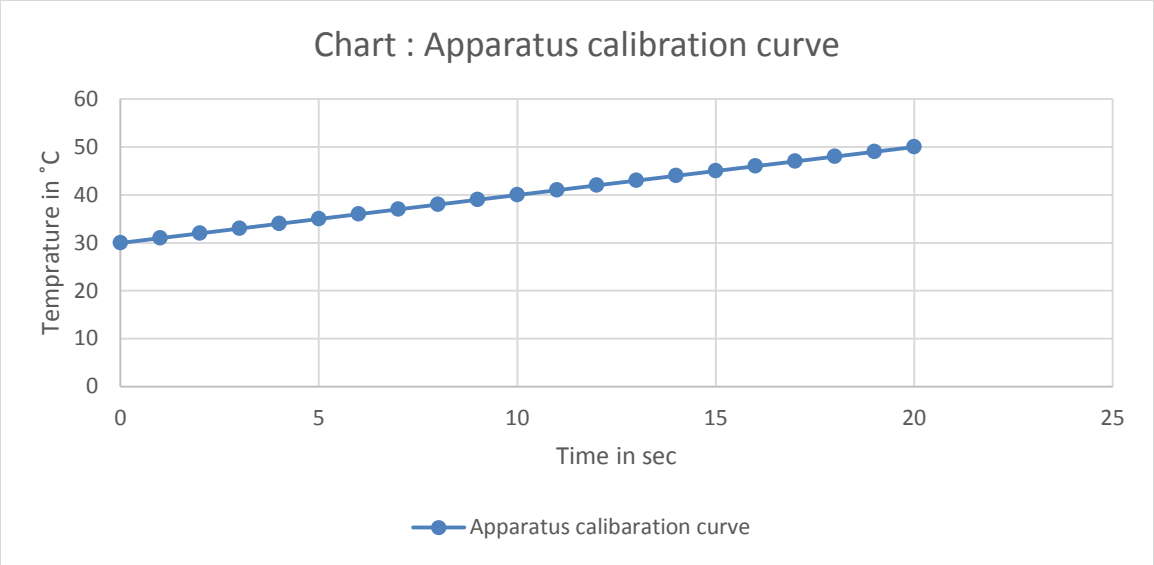
B. Latency of paw thermal response measurement

The assessment of small sensory fiber dysfunction in diabetic rats involved quantifying behavioral responses to heat, correlating with nerve fiber density in the skin and cornea. Utilizing a validated thermal nociception test device, we measured thermal hyperalgesia using a plantar test apparatus. Rats were acclimated in individual chambers with constant "white noise" to minimize startle responses. Measurements excluded grooming or urination periods, with surfaces cleaned post-urination. Three latency measurements per paw were taken, and the mean response latency was calculated, converted to response temperature using a calibration curve (Fig. 1). Diabetic rats were not kept in testing chambers for over an hour to prevent dehydration and reduced responsiveness. [20,21]

2.6 Statistical evaluation

Data is expressed as Mean ± S.D., with significance assessed at $P < 0.05$. Behavioral responses were analyzed using repeated measures ANOVA followed by Tukey's HSD test through Prism 5 software. Group served as the between-subjects factor, and day as the within-subjects factor in the statistical analysis. [14,15]

Fig. 1: Apparatus calibration curve



3. RESULT

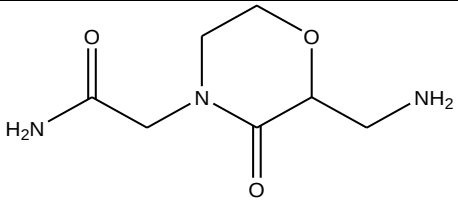
3.1 Chemistry

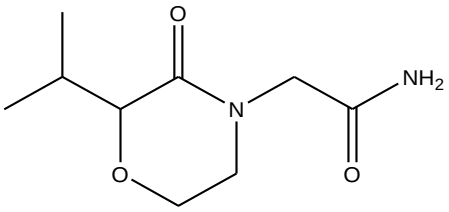
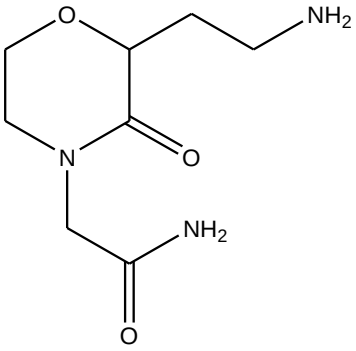
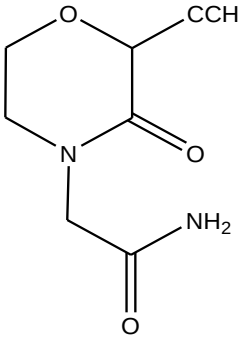
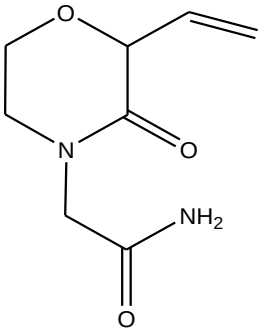
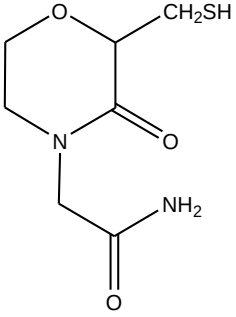
The synthesis involves initial reaction of L-Phenylalanine with hydrobromic acid and sodium nitrite, followed by incorporation at 0°C and reflux. Thionyl chloride is introduced, and after cessation of SO2 and HCl evolution, toluene is added to remove excess thionyl chloride. The resulting intermediate is analyzed. Subsequently, an acetamide substituent reacts with ethanolamine, undergoes filtration, and is recrystallized. The solutions from both steps are combined, stirred, and refluxed, and the resulting intermediate is analyzed. Finally, the intermediate undergoes cyclization with FeCl3, producing the final product analyzed using spectroscopy, ensuring specific molecular attributes.

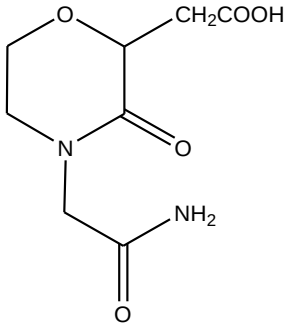
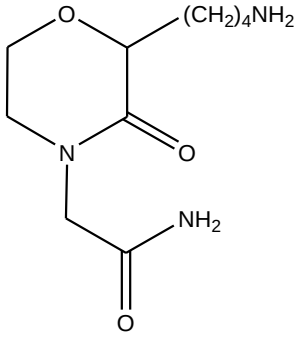
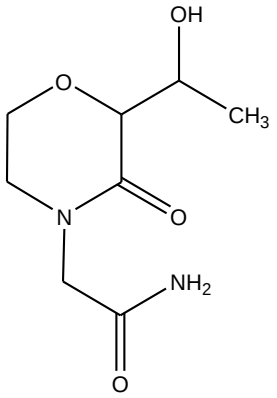
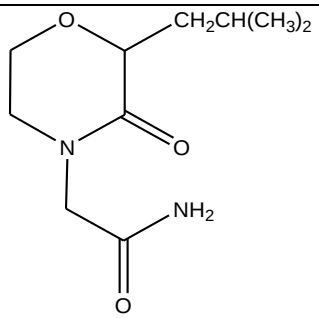
3.2 Characterization

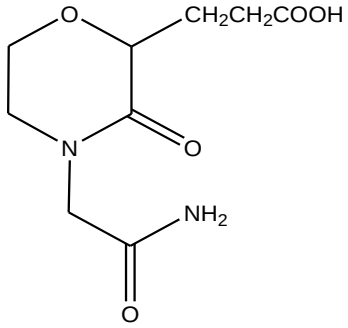
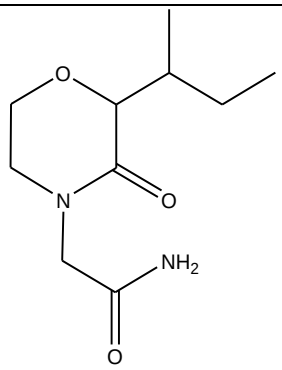
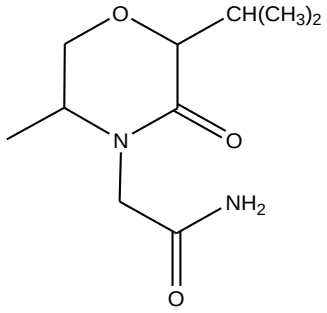
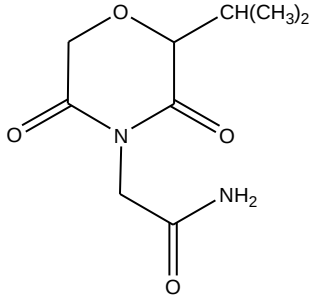
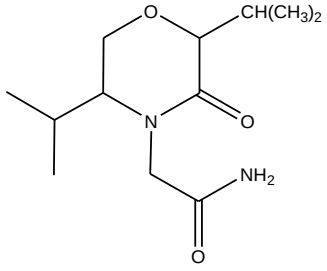
Compound 1 to 20 synthesized with optimum yield. Tables 3 and 4 detail their structure, IUPAC nomenclature, physiochemical properties, and spectral analysis (FT-IR, 1H-NMR, MASS).

Table: 3 physicochemical parameters of the synthesized compounds

Comp. code	**Chemical Structure**	**IUPAC name**	**Mol. Formula**	**Yield (%)**
A1		**2-(2-(aminomethyl)-3-oxomorpholino) acetamide**	C7H13N3O3	93.01

A2		**2-(2-(isopropyl)-3-oxomorpholino) acetamide**	C9H16N2O3	89.2
A3		**2-(2-(2-aminomethyl)-3-oxomorpholino) acetamide**	C8H15N3O3	88.7
A4		**2-(2-ethynyl)-3-oxomorpholino) acetamide**	C8H10N2O3	91.07
A5		**2-(3-oxo-2-vinylmorpholino) acetamide**	C8H12N2O3	94.8
A6		**2-(2-(mercaptomethyl)-3-oxomorpholino) acetamide**	C7H12N2O3S	82.3

A7		**2-(4-(2-amino-2-oxoethyl)-3-oxomorpholin-2-yl) acetic acid**	C8H12N2O5	91
A8		**2-(2-(4-aminobutyl)-3-oxomorpholino) acetamide**	C10H19N3O3	92.3
A9		**2-(2-(1-hydroxyethyl)-3-oxomorpholino) acetamide**	C8H14N2O4	88.9
A10		**2-(2-isobutyl-3-oxomorpholino) acetamide**	C10H18N2O3	92.8

A11		**3-(4-(2-amino-2-oxoethyl)-3-oxo morpholin-2-yl) propanoic acid**	C9H14N2O5	94.1
A12		**2-(2-sec-butyl-3-oxomorpholino) acetamide**	C10H18N2O3	88.9
A13		**2-(2-isopropyl-5-methyl-3-oxomorpholino) acetamide**	C10H18N2O3	80.9
A14		**2-(2-isopropyl-3,5-dioxomorpholino) acetamide**	C9H14N2O4	83.7
A15		**2-(2,5-diisopropyl-3-oxomorpholino) acetamide**	C12H22N2O3	94.3

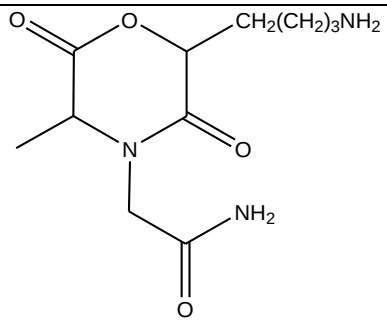
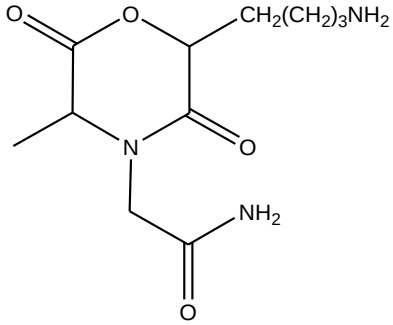
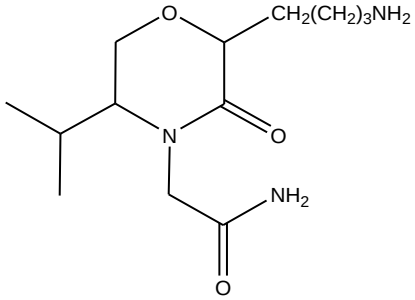
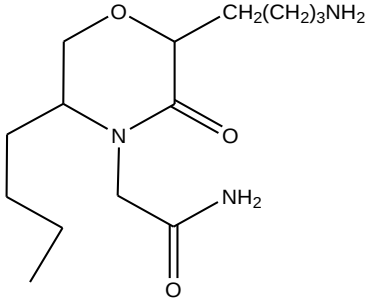
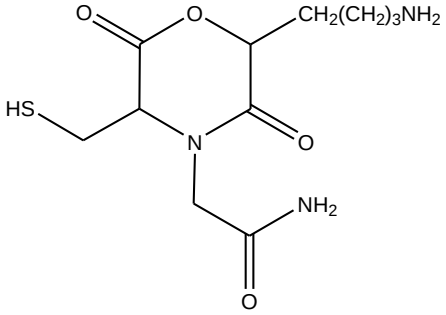
A16		**2-(2-(4-aminobutyl)-5-methyl-3, 6-dioxomorpholino) acetamide**	C11H19N3O4	81
A17		**2-(2-(4-aminobutyl)-5-methyl-3, 6-dioxomorpholino) acetamide**	C11H19N3O4	94.7
A18		**2-(2-(4-aminobutyl)-5-isopropyl-3-oxomorpholino) acetamide**	C13H25N3O3	84.8
A19		**2-(2-(4-aminobutyl)-5-butyl-3-oxomorpholino) acetamide**	C14H27N3O3	89.9
A20		**2-(2-(4-aminobutyl)-5-(mercaptomethyl)-3,6-dioxomorpholino) acetamide**	C11H19N3O4S	88.7

Table: 4 Spectro analytical data of synthesized compounds

Comp. Code	IR(cm-1)	1HNMR(δ(ppm))	Mass(m/z)
A1	FT IR [KBR (v, cm^{-1})] 960 (CH), 1160 (CO), 1620 (NH), 1710 (CO)	1H NMR: δ 2.96-3.07 (2H, 3.01 (d, *J* = 6.2 Hz), 3.01 (d, *J* = 6.2 Hz)), 3.16 (1H, ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.33-3.64 (3H, 3.42 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.49 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.57 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.16 (1H, t, *J* = 6.2 Hz)	MS C7H13N3O3(m/z) = 188.1116 [M+H]
A2	FT IR [KBR (v, cm^{-1})] 850 (CH), 1620 (NH), 1710 (CO), 3350 (NH),	1H NMR: δ 0.95-1.06 (6H, 1.01 (d, J = 6.9 Hz), 1.01 (d, J = 6.9 Hz)), 2.09 (1H, septd, J = 6.9, 2.9 Hz), 3.26 (1H, ddd, J = 15.1, 3.7, 2.1 Hz), 3.34-3.68 (3H, 3.43 (ddd, J = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, J = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, J = 13.5, 3.7, 2.1 Hz)), 3.83-3.93 (2H, 3.88 (s), 3.88 (s)), 4.25 (1H, d, J = 2.9 Hz).	MS C9H16N2O3(m/z) =201.1325 [M+H]
A3	FT IR [KBR (v, cm^{-1})] 750, 860,950 (CH), 1240 (CN), 1670 (NH), 1770 (CO), 3100 (CC), 3450 (NH)	1H NMR: δ 1.66-1.80 (2H, 1.73 (td, J = 6.7, 6.2 Hz), 1.73 (td, J = 6.7, 6.2 Hz)), 2.62-2.74 (2H, 2.68 (t, J = 6.7 Hz), 2.68 (t, J = 6.7 Hz)), 3.26 (1H, ddd, J = 15.1, 3.7, 2.1 Hz), 3.34-3.68 (3H, 3.42 (ddd, J = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, J = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, J = 13.5, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.33 (1H, t, J = 6.2 Hz).	MS C8H15N3O3(m/z) =202.1278 [M+H]
A4	FT IR [KBR (v, cm^{-1})] 870, 2950 (CH), 3150 (NH)	^{1}H NMR: δ 2.84 (1H, s), 3.22 (1H, ddd, *J* = 15.0, 3.7, 2.1 Hz), 3.40-3.71 (3H, 3.48 (ddd, *J* = 15.0, 10.1, 3.7 Hz), 3.62 (ddd, *J* = 13.6, 10.1, 3.7 Hz), 3.62 (ddd, *J* = 13.6, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.47 (1H, s).	MS C8H10N2O3(m/z) =183.0848 [M+H]
A5	FT IR [KBR (v,	^{1}H NMR: δ 3.16 (1H, ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.33-3.72 (3H,	MS

	cm^{-1})] 1640 (NH), 1715 (CO), 2970 (CH)	3.41 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.49 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.65 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.67 (1H, d, *J* = 3.8 Hz), 5.07-5.29 (2H, 5.14 (dd, *J* = 16.9, 1.1 Hz), 5.22 (dd, *J* = 10.9, 1.1 Hz)), 6.19 (1H, ddd, *J* = 16.9, 10.9, 3.8 Hz).	C8H12N2O3(m/z) =185.1005 [M+H]
A6	FT IR [KBR (v, cm^{-1})] 1620 (NH), 1720 (CO), 2950 (CH), 3110 (NH)	^{1}H NMR: δ 3.23 (1H, ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.34-3.68 (5H, 3.42 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.60 (ddd, *J* = 13.5, 3.7, 2.1 Hz), 3.63 (d, *J* = 4.4 Hz), 3.63 (d, *J* = 4.4 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.43 (1H, t, *J* = 4.4 Hz).	MS C7H12N2O3S(m/z) =205.0735 [M+H]
A7	FT IR [KBR (v, cm^{-1})] 880 (CH, 1510, 1670 (NH), 1720 (CO), 2860 (CH)	^{1}H NMR: δ 1.36-1.53 (4H, 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.46 (tt, *J* = 7.4, 7.0 Hz), 1.46 (tt, *J* = 7.4, 7.0 Hz)), 1.61-1.73 (2H, 1.67 (td, *J* = 7.0, 4.9 Hz), 1.67 (td, *J* = 7.0, 4.9 Hz)), 2.57-2.69 (2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 3.25-3.69 (4H, 3.32 (ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.43 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.83-3.93 (2H, 3.88 (s), 3.88 (s)), 4.39 (1H, t, *J* = 4.9 Hz).	MS C10H19N3O3(m/z) =230.1603 [M+H]
A8	FT IR [KBR (v, cm^{-1})] 1210 (CO), 1225 (CN), 1570(NH)	^{1}H NMR: δ 1.17 (3H, d, *J* = 6.2 Hz), 3.16 (1H, ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.32-3.63 (3H, 3.40 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.49 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.56 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.85-4.08 (4H, 3.90 (s), 3.90 (s), 4.00 (qd, *J* = 6.2, 4.6 Hz), 4.02 (d, *J* = 4.6 Hz)).	MS C8H14N2O4(m/z) =203.1119 [M+H]
A9	FT IR [KBR (v, cm^{-1})] 1720 (CO), 2950	^{1}H NMR: δ 0.81-0.93 (6H, 0.87 (d, *J* = 6.7 Hz), 0.87 (d, *J* = 6.7 Hz)), 1.50 (1H, tsept, *J* = 8.3, 6.6 Hz), 1.60-1.73 (2H, 1.67 (dd, *J* = 8.3, 4.3 Hz), 1.67 (dd, *J* = 8.3, 4.3 Hz)), 3.23-3.68 (4H,	MS C10H18N2O3(m/z)

	(CH), 3250 (NH)	3.30 (ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.43 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.83-3.93 (2H, 3.88 (s), 3.88 (s)), 4.39 (1H, t, *J* = 4.3 Hz).	=215.1488 [M+H]
A10	FT IR [KBR (v, cm^{-1})] 660 (CH), 1505 (NH), 1710 (CO)	^{1}H NMR: δ 0.79-1.02 (6H, 0.85 (t, *J* = 7.1 Hz), 0.96 (d, *J* = 6.8 Hz)), 1.20-1.32 (2H, 1.26 (quint, *J* = 7.1 Hz), 1.26 (quint, *J* = 7.1 Hz)), 2.06 (1H, tqd, *J* = 7.1, 6.8, 2.9 Hz), 3.23-3.68 (4H, 3.30 (ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.43 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.83-3.93 (2H, 3.88 (s), 3.88 (s)), 4.22 (1H, d, *J* = 2.9 Hz).	MS C10H18N2O3(m/z) =215.1488 [M+H]
A11	FT IR [KBR (v, cm^{-1})] 830(CH), 1240 (CN), 1720 (CO), 3250 (NH)	^{1}H NMR: δ 0.95-1.07 (6H, 1.01 (d, *J* = 6.9 Hz), 1.01 (d, *J* = 6.9 Hz)), 1.14 (3H, d, *J* = 6.6 Hz), 2.10 (1H, septd, *J* = 6.9, 2.9 Hz), 3.38 (1H, dd, *J* = 13.9, 3.7 Hz), 3.47-3.63 (2H, 3.54 (dd, *J* = 13.9, 2.1 Hz), 3.57 (qdd, *J* = 6.6, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.25 (1H, d, *J* = 2.9 Hz).	MS C10H18N2O3(m/z) =215.1488 [M+H]
A12	FT IR [KBR (v, cm^{-1})] 1360 (CN), 1630 (NH), 1715(CO)	^{1}H NMR: δ 0.90-1.02 (6H, 0.96 (d, *J* = 6.9 Hz), 0.96 (d, *J* = 6.9 Hz)), 2.05 (1H, septd, *J* = 6.9, 3.4 Hz), 3.86-3.96 (2H, 3.91 (s), 3.91 (s)), 4.02-4.17 (2H, 4.09 (d, *J* = 15.9 Hz), 4.10 (d, *J* = 15.9 Hz)), 4.74-4.86 (2H, 4.79 (d, *J* = 2.3 Hz), 4.81 (d, *J* = 3.4 Hz)), 5.16 (1H, d, *J* = 2.3 Hz).	MS C9H14N2O4(m/z) =215.1124 [M+H]
A13	FT IR [KBR (v, cm^{-1})] 730 (CH), 1660 (NH), 1710 (CO)	^{1}H NMR: δ 0.77-0.89 (6H, 0.83 (d, *J* = 6.8 Hz), 0.83 (d, *J* = 6.8 Hz)), 0.92-1.04 (6H, 0.98 (d, *J* = 6.9 Hz), 0.98 (d, *J* = 6.9 Hz)), 1.90 (1H, septd, *J* = 6.8, 6.0 Hz), 2.10 (1H, septd, *J* = 6.9, 2.9 Hz), 3.38 (1H, dd, *J* = 13.4, 3.7 Hz), 3.52 (1H, ddd, *J* = 6.0, 3.7, 2.1 Hz), 3.68 (1H, dd, *J* = 13.4, 2.1 Hz), 3.89-3.99 (2H, 3.94 (s), 3.94 (s)), 4.25 (1H, d, *J* = 2.9 Hz).	MS C12H24N2O2(m/z) =229.2014 [M+H]

A14	FT IR [KBR (v, cm^{-1})] 670 (CH), 1140 (CO), 1320 (CN), 1660 (NH)	^{1}H NMR: δ 1.29 (3H, d, *J* = 7.0 Hz), 1.36-1.54 (4H, 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.47 (tt, *J* = 7.4, 7.1 Hz), 1.47 (tt, *J* = 7.4, 7.1 Hz)), 1.70-1.84 (2H, 1.77 (dt, *J* = 8.5, 7.1 Hz), 1.77 (dt, *J* = 8.5, 7.1 Hz)), 2.57-2.69 (2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 3.87-3.97 (2H, 3.92 (s), 3.92 (s)), 4.28 (1H, q, *J* = 7.0 Hz), 5.67 (1H, t, *J* = 8.5 Hz).	MS C11H19N3O4(m/z) =258.1564 [M+H]
A15	FT IR [KBR (v, cm^{-1})] 820, 2960 (CH), 1650 (NH), 1718(CO)	^{1}H NMR: δ 1.36-1.54 (4H, 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.47 (tt, *J* = 7.4, 7.1 Hz), 1.47 (tt, *J* = 7.4, 7.1 Hz)), 1.73-1.86 (2H, 1.79 (dt, *J* = 8.1, 7.1 Hz), 1.79 (dt, *J* = 8.1, 7.1 Hz)), 2.57-2.69 (2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 4.29-4.39 (2H, 4.34 (s), 4.34 (s)), 5.39 (1H, t, *J* = 8.1 Hz), 6.13 (1H, d, *J* = 1.6 Hz), 6.28 (1H, d, *J* = 1.6 Hz).	MS C10H15N3O5(m/z) =258.1201 [M+H]
A16	FT IR [KBR (v, cm^{-1})] 830 (CH), 1330 (CN), 1715 (CO), 3350 (NH)	^{1}H NMR: δ 0.77-0.89 (6H, 0.83 (d, *J* = 6.8 Hz), 0.83 (d, *J* = 6.8 Hz)), 1.36-1.53 (4H, 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.47 (tt, *J* = 7.4, 7.0 Hz), 1.47 (tt, *J* = 7.4, 7.0 Hz)), 1.61-1.74 (2H, 1.68 (td, *J* = 7.0, 4.6 Hz), 1.68 (td, *J* = 7.0, 4.6 Hz)), 1.90 (1H, septd, *J* = 6.8, 6.0 Hz), 2.57-2.69 (2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 3.38 (1H, dd, *J* = 13.4, 3.6 Hz), 3.52 (1H, ddd, *J* = 6.0, 3.6, 2.1 Hz), 3.68 (1H, dd, *J* = 13.4, 2.1 Hz), 3.89-3.99 (2H, 3.94 (s), 3.94 (s)), 4.43 (1H, t, *J* = 4.6 Hz).	MS C13H25N3O3(m/z) =272.2091 [M+H]
A17	FT IR [KBR (v, cm^{-1})] 810(CH), 1310 (CN), 1710 (CO), 3320 (NH)	^{1}H NMR: δ 0.87 (3H, t, *J* = 6.5 Hz), 1.24-1.58 (10H, 1.30 (h, *J* = 6.5 Hz), 1.30 (h, *J* = 6.5 Hz), 1.32 (tt, *J* = 7.2, 6.5 Hz), 1.32 (tt, *J* = 7.2, 6.5 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.43 (tt, *J* = 7.4, 7.3 Hz), 1.47 (tt, *J* = 7.4, 7.0 Hz), 1.47 (tt, *J* = 7.4, 7.0 Hz), 1.52 (td, *J* = 7.2, 6.7 Hz), 1.52 (td, *J* = 7.2, 6.7 Hz)), 1.61-1.74 (2H, 1.68 (td, *J* = 7.0, 4.6 Hz), 1.68 (td, *J* = 7.0, 4.6 Hz)), 2.57-2.69	MS C14H27N3O3(m/z) =286.2253 [M+H]

		(2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 3.35 (1H, dd, *J* = 13.3, 3.6 Hz), 3.56-3.72 (2H, 3.63 (dd, *J* = 13.3, 2.1 Hz), 3.65 (tdd, *J* = 6.7, 3.6, 2.1 Hz)), 3.89-3.99 (2H, 3.94 (s), 3.94 (s)), 4.40 (1H, t, *J* = 4.6 Hz).	
A18	FT IR [KBR (v, cm^{-1})] 790(CH), 1550 (NH), 1680 (CN), 1710 (CO)	^{1}H NMR: δ 1.40-1.54 (4H, 1.46 (tt, *J* = 7.4, 7.3 Hz), 1.46 (tt, *J* = 7.4, 7.3 Hz), 1.48 (tt, *J* = 7.4, 7.1 Hz), 1.48 (tt, *J* = 7.4, 7.1 Hz)), 1.70-1.84 (2H, 1.77 (dt, *J* = 8.6, 7.1 Hz), 1.77 (dt, *J* = 8.6, 7.1 Hz)), 2.57-2.69 (2H, 2.63 (t, *J* = 7.3 Hz), 2.63 (t, *J* = 7.3 Hz)), 3.71-3.82 (2H, 3.76 (d, *J* = 4.0 Hz), 3.76 (d, *J* = 4.0 Hz)), 3.87-3.97 (2H, 3.92 (s), 3.92 (s)), 4.62 (1H, t, *J* = 4.0 Hz), 5.75 (1H, t, *J* = 8.6 Hz).	MS C11H19N3O4S(m/z) =290.1299 [M+H]
A19	FT IR [KBR (v, cm^{-1})] 661, 792 (CH), 1713(C=0), 3450(NH), 1345 (CN)	^{1}H NMR: δ 2.88-2.99 (2H, 2.94 (d, *J* = 6.6 Hz), 2.94 (d, *J* = 6.6 Hz)), 3.14-3.66 (4H, 3.21 (ddd, *J* = 15.1, 3.7, 2.0 Hz), 3.36 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.49 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.58 (ddd, *J* = 13.5, 3.7, 2.0 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.63 (1H, t, *J* = 6.6 Hz).	MS C8H12N2O5(m/z) =217.0917 [M+H]
A20	FT IR [KBR (v, cm^{-1})] 684 (CH), 1080 (CO), 1310 (CN), 1600, 3104 (NH),	^{1}H NMR: δ 1.98-2.11 (2H, 2.04 (td, *J* = 7.4, 7.1 Hz), 2.04 (td, *J* = 7.4, 7.1 Hz)), 2.40-2.52 (2H, 2.46 (t, *J* = 7.4 Hz), 2.46 (t, *J* = 7.4 Hz)), 3.26 (1H, ddd, *J* = 15.1, 3.7, 2.1 Hz), 3.34-3.68 (3H, 3.43 (ddd, *J* = 13.5, 10.1, 3.7 Hz), 3.50 (ddd, *J* = 15.1, 10.1, 3.7 Hz), 3.61 (ddd, *J* = 13.5, 3.7, 2.1 Hz)), 3.85-3.95 (2H, 3.90 (s), 3.90 (s)), 4.38 (1H, t, *J* = 7.1 Hz).	MS C11H20N2O3S(m/z) =261.1385 [M+H]

3.3 Treatment's impact on body weight and blood sugar level

STZ injection increased plasma glucose significantly compared to control. Pregabalin and piracetam derivatives (A1 to A20) didn't reduce hyperglycemia or prevent body weight decline in diabetic rats. (Fig. 2)

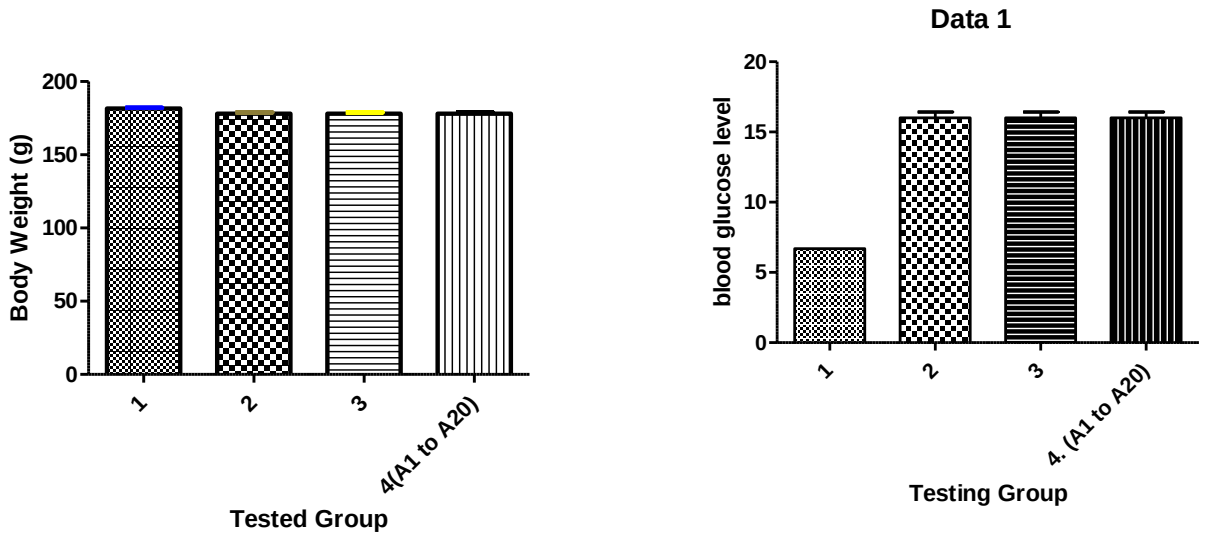


Fig. 2: STZ, pregabalin, and piracetam derivatives' impact on body weight and blood glucose was assessed at 0, 7th, 14th, and 21st days post-STZ injection. Results: Mean ± S.D. (n=5/group). *P<0.05.

3.4 Effects of treatment on mechanical allodynia

Fig. 3 depicts a significantly lower von Frey filament withdrawal threshold in diabetic rats compared to controls. Mechanical allodynia initiated post-STZ injection, persisting on the 7th, 14th, and 21st testing days. Pregabalin and Piracetam derivatives (A1 to A20) administration notably attenuated mechanical allodynia.

3.5 Effects of treatment on heat hyperalgesia

STZ-induced diabetes increased hind paw withdrawal threshold to thermal stimuli. Treatment with Pregabalin and synthesized compounds reduced withdrawal latency compared to diabetic rats Fig. 4

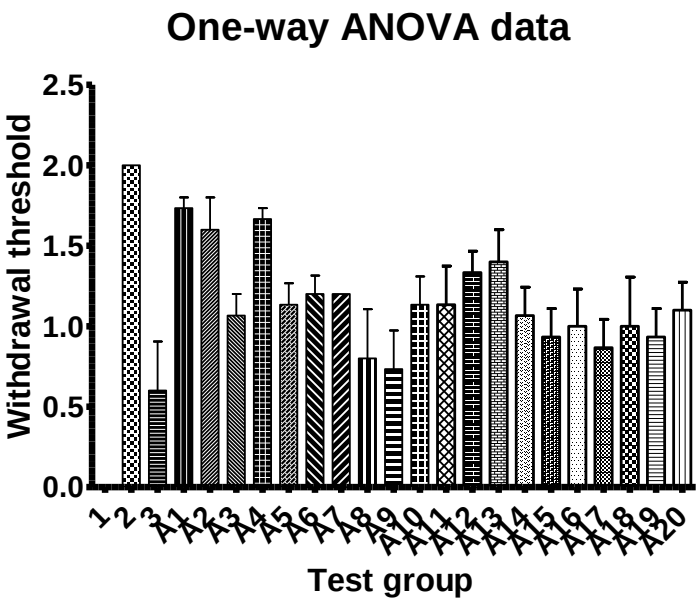


Fig. 3: piracetam derivatives' impact on mechanical allodynia was assessed at 7th, 14th, and 21st days post-STZ injection. Results: Mean ± S.D. (n=5/group). *P<0.05.

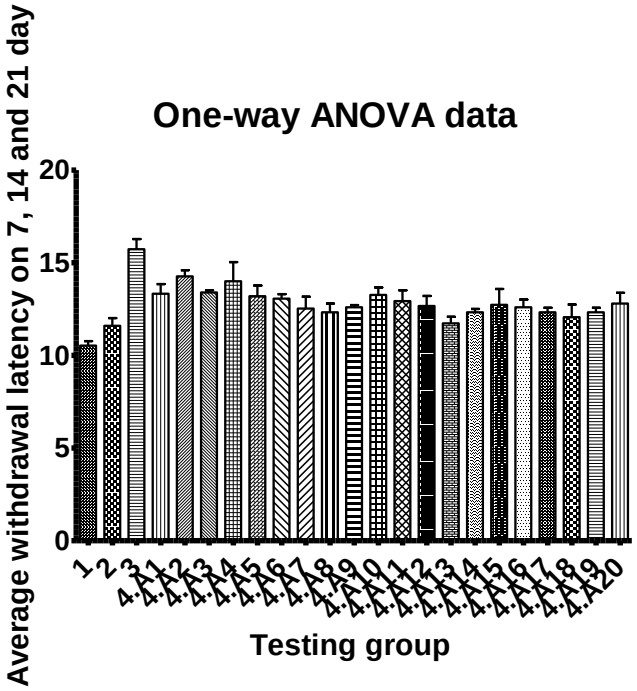


Fig. 4: Assessment of Pregabalin and Piracetam Derivatives (A1 to A20) on STZ-Induced Diabetic Neuropathy through Radiant Heat Plantar Test, measuring withdrawal latency (assessed at 7th, 14th, and 21st days post-STZ injection. Results: Mean ± S.D. (n=5/group). *P<0.05.

4. DISCUSSION

The synthesized compounds (A1 to A20) showcase diverse chemical structures and functional groups, hinting at potential biological activities. Notably, the inclusion of moieties like morpholino, acetamide, and amino groups suggests possible interactions with biological targets. To ascertain their pharmacological relevance, a focus on peripheral neuropathy is proposed for biological evaluations. Spectroscopic analysis highlights key functional groups (NH, CO, CH) that likely play pivotal roles in mediating biological interactions. Variations in molecular formulas, as evident in Table 3, signify differences in molecular weights, influencing pharmacokinetic properties. The study underscores the need for comprehensive biological assays and further investigations to unravel the therapeutic applications of these compounds. The data presented establishes a groundwork for future research, offering insights into the potential medicinal applications of the synthesized compounds and contributing to the development of novel pharmaceutical agents.

5. CONCLUSION

In conclusion, this thesis focused on designing, synthesizing, and evaluating 20 piracetam derivatives for peripheral neuropathy, meticulously characterized through spectroscopy. Biological evaluation in streptozotocin-induced diabetic rats revealed no antidiabetic effect but demonstrated a significant reduction in mechanical allodynia in the Von Frey test, derivatives A8, A9, A15, A17, and A19. Unexpectedly, hind paw withdrawal thresholds increased in the Plantar test, reversed by treatment. The complex outcomes underscore the need for further exploration into mechanisms, emphasizing the potential of these derivatives in addressing diabetic neuropathic pain.

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