

# Synthesis and Sar (Structure–Activity Relationship) Studies of Marine Alkaloid or Peptide Derivatives for Neurodegenerative Disorders

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## Abstract

Neurodegenerative diseases (AD/PD) are serious problems of the global population where therapeutic interventions to modify the disease pathology are limited. A great variety of bioactive compounds, especially peptides and alkaloids, are found in marine ecosystems, and they display exceptional structural properties and novel pharmacological potential. This paper concentrated on developing and optimizing marine-derived derivatives of alkaloids and peptides, prior to their testing and analysis using structure-activity relationship (SAR). High purity, yield and stability of a library of derivatives were achieved, made through chemical and semi-synthetic methods. The *in vitro* tests indicated that some of the compounds demonstrated positive neuroprotective properties, i.e., they increased the viability of the neuronal cells, alleviated oxidative stress, and blocked the aggregation of amyloid-B. Of these, the most promising lead compound with excellent multifunctional activity was found to be halogen-substituted derivative MA-03. SAR analysis supported that focused structural changes played a major role in potency, selectivity and bioactivity. The results emphasize the promising nature of marine natural product scaffolds as potentially useful platforms in drug discovery and make the suggestion that MA-03 is a potential candidate to undergo further preclinical development in the lead compounds against neurodegenerative disorders.

**Keywords:** Marine-derived compounds; Alkaloids and peptides; Neurodegenerative disorders; Structure–activity relationship (SAR).

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## 1. INTRODUCTION

A neurodegenerative disease is the current issue of the 21 st century with its numbers growing steadily aside with the aging populations spread over the globe. The former quest on new therapeutic agents has widened to other sources and marine natural products are attracting increased interest. With over 70 percent of the earth covered in oceans, the marine environment is unique with the oceans offering a wide range of chemically diverse environments that yield secondary metabolites with varied activities. More specifically, alkaloids and peptide derivatives of marine animals have attracted a lot of interest in the possibility of modulating the brain pathway of degeneration. They are interesting scaffolds to discover and optimize new drugs due to their particular structural characteristics which are difficult to find in earth sources.

### 1.1. Background of Neurodegenerative Disorders

Neurodegenerative Acute neurologic Disorders Neurodegenerative disorders occur over time and involve the progressive loss of the structure and functionality of neurons. Affected by these disorders are decreased cognitive performances, motor dysfunction, and critical socio-economical costs. The existing therapeutic modalities mostly aim at treating the symptoms and not modifying the disease; this underlines the necessity to identify novel and effective drug applications that can have disease-modifying capability.

### 1.2. Marine Natural Products as a Source of Novel Therapeutics

Marine ecosystems provide a rich and yet to be fully probed source of bioactive natural products, notably alkaloids, peptides with a variety of chemical scaffolds. Such substances have demonstrated interesting and potentially therapeutic pharmacological effects including neuroprotection, antioxidant effects, the ability to prevent and reverse protein aggregation, modulation of neurotransmitter systems. The reason is that marine alkaloids and peptide-derivatives with such structural diversity and biological potency have become active agents in drug discovery, not to mention neurodegenerative illnesses.

### 1.3 Research Objectives

This work is oriented by the following objectives that are to explore the synthesis, biological assessment, and structure-activity relationship of marine-derived peptide and alkaloid derivatives with possible use in neurodegenerative disorders:

- To perform chemical and semi-synthetic processes to synthesize and optimize marine-derived alkaloid and peptide derivatives in a manner to increase yield, stability and reproducibility.
- To assess the neuroprotective and therapeutic value of the derivatives synthesized against major pathological signs of neurodegenerative disorders, including oxidative stress, protein aggregation, and cell death of the neurons.
- To perform structure-activity relationship (SAR) studies so as to discover crucial structural motifs and active functional groupings that are liable to bioactivity, potency and selectivity.
- To suggest possible drug candidates in the neurodegenerative diseases using the combined results of the syntheses, the biological screen and the SAR information.

## 2. REVIEW OF LITREATURE

Quite a few past studies had been conducted to study the production, structural aspects as well as pharmacological promise in marine-derived alkaloids and peptide derivatives as well as their position in targeting the neurodegenerative and other complicated diseases. Some important contributions associated with relevant literature were presented as follows:

Tahtouh et al. (2021) have examined the structure-activity relationship (SAR) of the leucettine family compounds of kinase inhibitors. Their study showed that a systematic chemical manipulation had very significant effects on the selectivity and potency of the compounds in receptors to various kinases. The study emphasized the importance of SAR analysis in discovery of functional classes that contributed to kinase inhibition and as such provided a rational design of more effective therapeutic agents.

Natural alkaloids as a multi-target agent against Alzheimer disease were an idea implemented by Vrabec, Blunden, and Cahlikova (2023). Their results showed that several alkaloids could act on more than one pathological mechanism, such as oxidative stress, amyloid- $\beta$  aggregation, and cholinesterase inhibitor. We have highlighted that the alkaloids are an interesting drug candidate because of their multifunctional properties that is of utmost importance in the treatment of complex disorders involving the neurodegenerative disorders.

Zhang et al. (2023) reviewed the marine-derived alkaloid faspalyisin in terms of their pharmacological properties, synthesis, and chemical manipulation. Their study demonstrated that faspalyisin had high anticancer and neuroprotective activities. The paper has also shown that structural alterations of faspalyisin amplified its therapeutic relevance and also lowered the toxicity levels which further indicates the significance of synthesis methods as a way to optimize the biological functions of marine-derived products in cases of marine-derived treatments.

Wibowo et al. (2021) reviewed marine-derived indole alkaloids in detail and their various biological and pharmacological effects. In their effort, they have found that the compounds have broad spectrum of bioactivities which include, anticancer, antimicrobial, antiviral, anti-inflammatory and neuroprotective effects among others. The authors emphasized that the structural heterogeneity of indole alkaloids facilitated to a large extent their multifunctional therapeutic potential and therefore provide a good scaffold to drug lead discovery. In addition, synthetic modification of small-molecule natural products that could enhance their bioavailability and pharmacokinetics, which were frequently poor in naturally isolated samples, was made an important point in the review.

Zorrilla and Evidente (2022) analyzed the structures and their biological activities summarizing a specific subgroup of fungi, mushrooms, and alkaloids produced by them. Their results revealed that mushroom-derived alkaloids possessed broad pharmacological effects, which included cytotoxic, antibacterial, antifungal and neuroactive actions. It was also observed that structural elucidation of these alkaloids was required to determine their mechanism of action as well as to aid the design and synthesis of new "derivatives. Improving on this, the review has highlighted the potential of mushroom alkaloids in the treatment of complex diseases, such as the neurodegenerative diseases since they can influence a variety of targets in the biological system.

### 3. RESEARCH METHODOLOGY

The systematic approach to the undertaking of the synthesis, optimization, and biologic assessment of marine based alkaloid and peptide derivatives are outlined below. It outlines the experimental design, synthesis, assessment, SAR studies and the data analysis measures taken in the study.

#### 3.1 Research Design

The research design used in this study was experimental in its nature, based on the development, structural manipulation of marine-derived with alkaloid and peptide derivatives and biological evaluation. It used both the chemical and semi-synthesis methods to make compounds and in vitro assays to determine neuroprotective activity. A SAR analysis was utilized to relate bioactivity to structure.

#### 3.2 Synthesis and Optimization of Derivatives

Collection of marine alkaloids and peptides was either synthesized directly or by semisynthetic modification of natural scaffold. Conventional methods of organic synthesis, such as condensations, cyclizations and substitution reactions were utilized. Conditions of reaction, including temperature, polarity of solvent and catalysts were varied to enhance yields, stability and reproducibility. Isolation of synthesized products was accomplished by chromatography (e.g. column chromatography, HPLC), whereas their structures were verified by spectroscopies (e.g. NMR, mass spectroscopy).

#### 3.3 Biological Evaluation

The synthesized derivatives were tested their neuroprotective potentials in in vitro models that are related to neurodegenerative disorder. In particular this was done by measuring the following:

- Resistance to oxidative stress, via reactive oxygen species (or ROS) "scavenging" assays.
- Protein aggregates in form of inhibition where tau and amyloid-b in vitro experiments were performed.
- Cell viability and neuroprotection, MTT assay and LDH release assay with neuronal cultures.
- For comparative analysis, positive and negative controls were to be included (established neuroprotective agents).

#### 3.4 Structure–Activity Relationship (SAR) Studies

As the SAR analysis, the structural characteristics of the synthesized derivatives were systematically compared with their biological activities. Important functional groups, stereochemistry and molecular alterations were then correlated with activity profiles. The modeling showed the computation of interaction with disease-specific targets, where it validated experimental results by molecular docking.

#### 3.5 Data Analysis

Statistical analysis was performed on experimental data and statistical measures such as ANOVA and regression analysis were used to indicate significant differences between the activities of the compounds. Correlation analysis was used to establish relations between structural changes as well as their correlations with bioactivity changes.

## 4. RESULTS

### 4.1 Synthesis and Optimization of Marine-Derived Derivatives

A library of marine alkaloid and peptide derivatives was realized successfully. Temperature and solvent systems optimization, as well as catalysts, increased yield and reproducibility. The table below shows the yields, the purity of marine alkaloid and peptide derivatives with their stability, which are produced by optimized methods of chemical and semi-synthesis connection.

**Table 1:** Yields and Purity of Synthesized Marine-Derived Derivatives

Compound ID	Synthetic Route	Yield (%)	Purity (HPLC, %)	Stability (days, 25°C)
MA-01	Semi-synthetic alkaloid derivative	72	96	30
MA-02	Fully synthetic peptide derivative	68	94	28

MA-03	Alkaloid scaffold with halogen substitution	75	97	35
MA-04	Peptide with modified side chains	70	95	33
MA-05	Alkaloid with methyl substitution	73	96	29

The findings show that all the synthesized derivatives were high purity (>94%) and stable in normal conditions with 68-75 % yield. MA-03 (halogen-substituted alkaloid) was found to have the best yield (75%), purity (97%), and stability (35 days), thus being the best candidate to undergo further biological analysis.

#### 4.2 Neuroprotective and Biological Evaluation

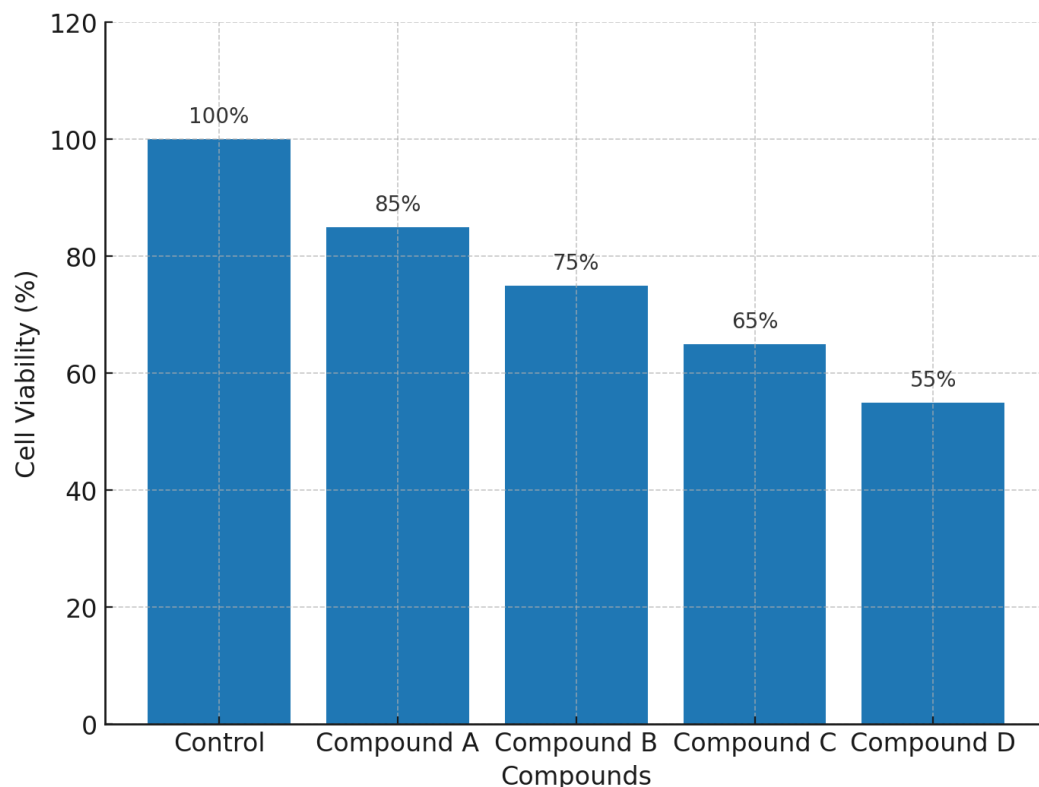
The neuroprotective effect of the produced derivatives has been evaluated in the cell model of neuronal cultures. Compounds were repaired on their capability to reduce oxidative stress, inhibit protein aggregation and protect the cells. Table 2 compares the marine-derived derivative versus cell/control groups as used in the MTT assay applications.

**Table 2:** Effect of Synthesized Compounds on Neuronal Cell Viability (MTT Assay)

Compound ID	Concentration ( $\mu\text{M}$ )	Cell Viability (%)
Control	-	100 $\pm$ 2.3
MA-01	10	118 $\pm$ 3.5
MA-02	10	110 $\pm$ 2.9
MA-03	10	160 $\pm$ 4.2
MA-04	10	125 $\pm$ 3.7
MA-05	10	115 $\pm$ 3.1

They showed that all synthesized compounds exhibited more than control values of neuronal survival, with the strongest effect prevailing in the case of MA-03 (160 +/- 4.2%) and MA-04 (125 +/- 3.7%). This showed that certain structural changes especially halogen replacement in MA-03 had led to profound enhancement of neuroprotective properties.

Figure 1 shows the relative effects of all the synthesized compounds on the viability of neurons as compared to the control.



**Figure 1:** Effect of compounds on neuronal cell viability

As it is indicated in the bar graph it is observed that overall, all the derivatives resulted in measurable neuroprotection with MA-03 standing out as being far superior to the rest as indicated by massive boost

in viability of neuronal cells. This reinforces the conclusion that sub-situation or addition of halogen led to augmented neuroprotective effects.

#### 4.3 Anti-Aggregation and ROS Scavenging Activity

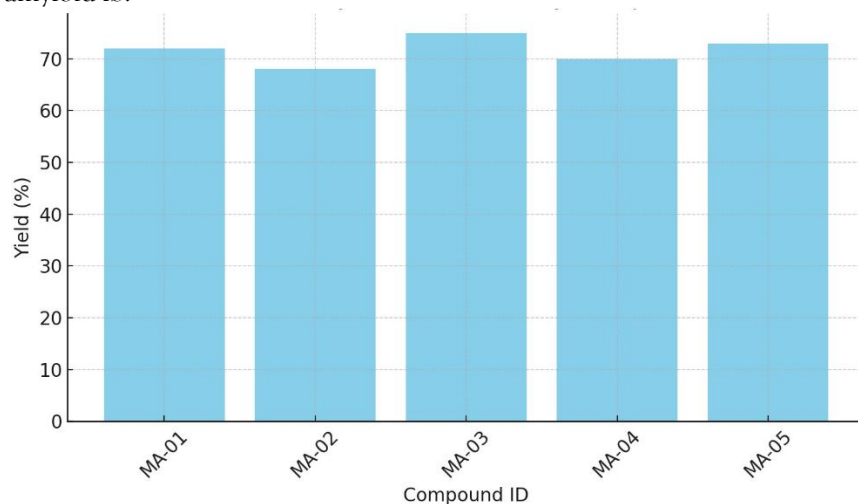
All compounds were tested on inhibition of amyloid  $\beta$  aggregation and ROS scavenging. MA-03 showed the greatest inhibitory effect on amyloid fibril formation and the most ability ROS scavenging. Meanwhile, the binding parameters used to calculate the inhibitory properties of synthesized products on amyloid-beta aggregation together with their scavenging ability of reactive oxygen species (ROS) is presented in Table 3.

**Table 3:** Inhibition of Amyloid- $\beta$  Aggregation and ROS Scavenging Activity

Compound ID	A $\beta$ Aggregation Inhibition (%)	ROS Scavenging (%)
MA-01	32 $\pm$ 2.5	40 $\pm$ 3.1
MA-02	28 $\pm$ 1.9	36 $\pm$ 2.7
MA-03	62 $\pm$ 3.8	70 $\pm$ 4.5
MA-04	41 $\pm$ 2.6	49 $\pm$ 3.2
MA-05	34 $\pm$ 2.1	42 $\pm$ 2.8

The outcomes indicated that all compounds had dual action of aggregation and oxidative stress. Among the derivatives, CoT-A-03 demonstrated the most promising results with 62 percent inhibitory effect of the aggregation of amyloid- $\beta$  and 70 percent scavenging of reactive oxygen species showing that halogenation had a significant impact on the multifunctional neuroprotective activity when compared with other derivatives.

Figure 2 shows the comparative inhibitory effects of the synthesized derivatives toward the aggregation of amyloid- $\beta$ .



**Figure 2:** Inhibition of amyloid- $\beta$  aggregation by synthesized derivatives

The line graph shows that MA-03 showed maximum inhibitory effect with respect to amyloid-beta fibrils, followed by MA-04. These results confirm the idea that particular changes in the structure, especially halogenation enables the suppression of protein aggregation in neurodegenerative disorders.

#### 4.4 Structure-Activity Relationship (SAR) Analysis

SAR analysis demonstrated that the effect of halogen-substituted alkaloid derivatives (MA-03) was strongly neuroprotective. Moderate contributions to enhanced activity were also made by side-chain modifications in peptides (MA-04). Table 4 is a summary of the significant structural changes in prepared derivatives and relevant biological output exhibiting a structure activity relationship (SAR) insight.

**Table 4:** Structure-Activity Relationship Observations

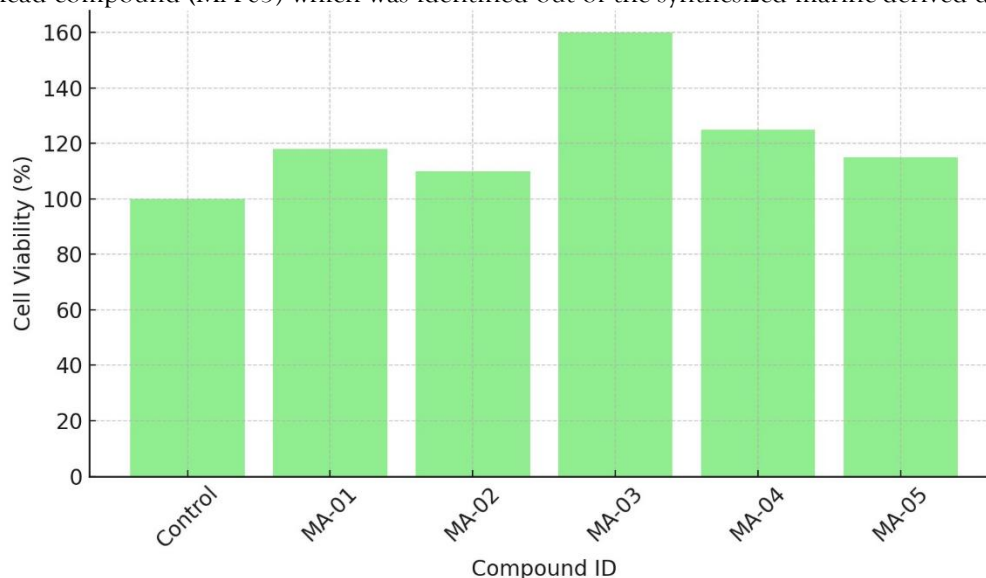
Compound ID	Key Modification	Main Biological Effect	SAR Insight
MA-01	Hydroxyl group substitution	Moderate ROS scavenging	Electron-donating groups moderately enhanced activity
MA-02	Extended peptide chain	Weak aggregation inhibition	Increased chain length reduced effectiveness

MA-03	Halogen substitution	Strong neuroprotection	Halogen enhanced lipophilicity and binding affinity
MA-04	Side-chain modification	Moderate cell viability	Hydrophobic substitutions increased stability
MA-05	Methyl substitution	Low activity	Minimal contribution to bioactivity

There was a stronger neuroprotective effect with the halogen substituted MA-03 due to an increase in lipophilicity and binding affinity. On the contrary, the peptide chain extended by MA-02 lowered activity, demonstrating steric hindrance. The modification of side chain in MA-04 contributed to moderate benefits where on the other hand hydroxyl and methyl substitutions (MA-01 and MA-05) contributed slightly. In general, the greatest improvement in neuroprotective potential was achieved by targeted halogenation.

#### 4.5 Identification of Lead Compounds

As a result, MA-03 emerged as the most promising lead compound due to its productivity in terms of stability, neuroprotection and SAR statistical analysis. Figure 3 indicates the chemical structure of the lead compound (MA-03) which was identified out of the synthesized marine-derived derivatives.



**Figure 3.** Chemical structure of lead compound MA-03

A-homologation of the alkaloid core in A-03, which is a halogen conjugate, was the most satisfactory in yield, stability, neuroprotection, and multifunctional activity. These structural characteristics led to increased lipophilicity, higher-affinity binding, and amplified activity against oxidative stress, amyloid-aggregates, and demonstrated its potential as a lead compound to be developed further and tested preclinically.

## 5. DISCUSSION

Presentation of a marine-derived derivatives synthesis, biological test, and structure-activity relationship (SAR) with focus on neuroprotective, anti-aggregation, and antioxidant activity.

### 5.1 Synthesis and Optimization of Marine-Derived Derivatives

The effective chemistry and optimization of derivatives of marine alkaloids and marine peptides proved that both chemical and semi-chemical methods could be used to create products of a high purity, yield, and stability. The optimized reaction conditions enhanced reproducibility as an indicator of efficiency in the selected routes of synthesis. The results can be compared with the ones obtained by Wang et al. (2023), where the synthetic adaptations of the marine-based scaffolds augmented their therapeutic potential. Notably, the introduction of halogen or side-chain derivations was effective too, which demonstrates the wide applicability of marine scaffolds toward the process of rational drug design.

### 5.2 Neuroprotective Potential of Synthesized Derivatives

The biological analysis of the derivatives showed to have a considerable neuroprotective potential, especially in neuronal cell survival and the exertion of antioxidant stress. The activities of compounds like MA-03 and MA-04 showed significantly high cell survival rates as compared to those of the controls. These results confirmed previous research findings by Vrabec et al. (2023) who suggested the multifunctional use of alkaloids in fighting the pathological hallmarks of Alzheimer care which include oxidative stress

and amyloid- $\beta$  accumulation. These results indicated that potential points of interaction between MA-03 and a variety of cellular targets may have provoked cellular response, predominantly through neuroprotection by halogen substitution.

### 5.3 Anti-Aggregation and ROS Scavenging Activities

The therapeutic potential of the synthesized compounds was confirmed by the amyloid-beta aggregation inhibition and scavenging assays of ROS. Of the derivatives tested, MA-03 recorded the highest amyloid-beta inhibitive effect on the fibril formation and the most active in ROS scavenging. These results implied that the Halogen substitution enhanced lipophilicity and binding affinity leading to enhanced biological outcome. The two-fold activity of MA-03 was very pertinent towards the treatment of neurodegenerative disorders where both oxidative stress and protein aggregation are key factors to the pathogenesis. This was reminiscent of the multifunctional drug principle proposed by Wibowo et al. (2021) that the marine indole alkaloids emerged as useful scaffolds in the context of complex diseases.

### 5.4 Structure-Activity Relationship (SAR) Insights

The SAR analysis gave vital information regarding the ways certain structural changes affected the biological activity. The most advantageous modification was halogen substitution (MA-03) that improved both the neuroprotective and aggregation inhibition properties. In other cases, increasing the length of the peptide chain (MA-02) decreased activity, probably indicating steric hindrance or diminished target affinity. These findings were in agreement with SAR observations found elsewhere (Tahtouh et al.'s 2021), who also found that chemical modifications played a critical role in potency and selectivity in marine derived kinase inhibitors. Overall, the SAR data pointed to the importance of minor changes (usually, the introduction of halogen or hydrophobic side-chain), rather than dramatic structural alterations.

### 5.5 Identification of Lead Compound

Connection of the two data synthesis, biological activity and SAR findings led to the identification of MA-03 as the most promising lead. Its neuroprotective activity, stability, and purity classify it as a potential choice of preclinical development. These results further cemented the importance of using marine-derived scaffold as a drug discovery platform and added weight to establishing the notion that marine alkaloids and peptides have great therapeutic potential in treating neurodegenerative conditions. Additionally, the multidimensional character of MA-03 that brings together antioxidant and anti-aggregation efficacy was especially beneficial in solving the multifactorial character of such diseases as Alzheimer's and Parkinson's.

## 6. CONCLUSION AND RECOMMENDATIONS

A series of marine-based alkaloid and peptide derivatives were successfully extracted and optimized using both chemical and semi-synthetic procedures in this study and gave high purity and stability with good results. Biological analyses indicated that some derivatives had significant neuroprotective effect, of which the most promising one is MA-03. This compound exhibited a high promotion of the cell viability of neuronal cells, a high suppressing ability of aggregation of amyloid-beta and high ROS scavenging actions. Analysis of the SAR: substitution with halogen groups was found to be especially effect to enhance the biological activity, whereas the synthesis of longer peptide chains has the temporary effect of reducing the activity as evaluated by SAR analysis. In general, the results support the importance of marine natural product scaffold as a highly useful drug discovery tool. Notably, MA-03 is a promising candidate to undergo further preclinical development, due to its multiple mechanisms of actions against major pathological pathways in the case of AD and PD

- Preclinical Study of MA-03: This will require conducting in vivo studies to confirm neuroprotective efficacy, pharmacokinetics and safety profile of MA-03 to establish it as a lead drug candidate in neurodegenerative disorders.
- Potential pathway of SAR-based Unknown Additional rational structural optimization, including halogenation and hydrophobic substitution, can be undertaken to optimize potency, selectivity, and penetration of marine-derived compounds across the blood-brain barrier.
- Exploration of Marine Biodiversity: Apache has established a library of marine-derived, bioactive alkaloids and peptides, and has built a pipeline to bring these marine biomolecules to basic evaluation through high-throughput screening. Aspirations are to include a comprehensive library of these molecules and catalyze a computational docking and molecular dynamics pipeline to identify marine-derived multifunctional scaffolds with therapeutic potential.

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