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Review Article

Uncovering Novel Anti-Lung Cancer Compounds: Insights from Marine Sponge-Derived Agents: A Bibliometric Review

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What's Known

- The existing literature indicates that marine sponges are a rich source of bioactive compounds, including alkaloids, sesquiterpenes, and quinones, which have shown promising anticancer properties. These compounds have been studied for their potential to target various cancer pathways and receptors.

What's New

- This study aims to build on existing knowledge by conducting a comprehensive bibliometric analysis to identify the most prominent anticancer components derived from marine sponges between 2018 and 2023. The study also includes molecular docking and toxicity prediction analyses to further explore the potential of these compounds as anti-lung cancer agents.

Abstract

Background: Lung cancer remains a leading cause of cancer-related mortality, necessitating improved treatment strategies. This study collectively highlights the valuable potential of marine sponges as a source for discovering new anti-tumor agents.

Methods: We conducted a bibliometric analysis to identify anticancer compounds from marine sponges using PubMed (2018–2023). The search included keywords such as "marine sponge," "cancer," "neoplasm," "proliferation," "cytotoxicity," "tumor," "sesquiterpene," "alkaloid," and "quinones." Inclusion criteria focused on studies related to lung cancer and marine sponge-derived compounds, excluding non-cytotoxic activities and unrelated species. Data were extracted in comma-separated values (CSV) format and analyzed via VOSviewer. Molecular docking identified compounds with strong binding to apoptotic receptors in lung cancer cells. PROTOX and Way2Drug tools predicted the pharmacological properties of selected compounds as potential drugs.

Results: The bibliometric analysis identified alkaloids, sesquiterpenes, and quinones as key keywords. Dactyloquinone B-D, dysidavarone D, smenohamien F, and sollasin E demonstrated strong binding to apoptotic receptors in lung cancer cells, suggesting potential as anti-lung cancer drugs. Pharmacological analyses revealed promising effects and potential side effects, highlighting their suitability for further drug development. These findings provide a foundation for novel targeted therapies for lung cancer.

Conclusion: This study highlights the potential of alkaloids and sesquiterpenes derived from marine sponges as promising anti-lung cancer agents, emphasizing the need for further *in vitro*, *in vivo*, and clinical investigations to validate their therapeutic efficacy.

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Keywords ● Lung neoplasms ● Porifera ● Antineoplastic agents ● Bibliometrics ● Apoptosis

Introduction

Lung cancer is a prevalent and highly fatal form of malignancy worldwide.[1] Consequently, the development of effective treatments for this disease is of paramount importance. Conventional therapeutic approaches such as chemotherapy, surgery, and immunotherapy have been utilized, albeit with

notable limitations including inadequate efficacy, lack of effectiveness, and suboptimal drug concentration at the tumor site due to uptake by healthy cells.[2, 3] Therefore, there is a pressing need to explore new therapeutic methods for lung cancer. Natural products derived from the environment have garnered significant interest among scientists, offering a vast array of potentially valuable biological compounds. These sources encompass plant and animal extracts, insect metabolites, microorganisms, and marine organisms, all of which present promising prospects for developing curative agents.[1]

Among natural environments, the marine ecosystem has emerged as a particularly promising source of bioactive compounds with anticancer properties.[4, 5] Marine sponges, in particular, have captured the attention of researchers in recent decades due to their remarkable anticancer effects.[6] Extensive research has demonstrated that these marine organisms harbor bioactive molecules and secondary metabolites that hold significant potential for the discovery of novel and sustainable anticancer components.[6] For example, stylissamide, a compound derived from the marine sponge *Stylissa carteri*, has exhibited potent anticancer activity against MCF-7 (human breast cancer cell line) and HepG2 (human liver cancer cell line) cells.[7] Likewise, *5-bromotrisindoline* extracted from the marine sponge *Callyspongia siphonella*, demonstrated cytotoxic effects against HT29 (human colorectal adenocarcinoma), OVCAR3 (ovarian adenocarcinoma), and MM.1S (multiple myeloma) cell lines.[8] Furthermore, alkaloid aaptamine derived from marine sponges has been identified as a promising anticancer agent with potentiality for the development of potent anti-tumor drugs.[9]

There is a study collectively highlighting the valuable potential of marine sponges as a source for discovering new anticancer agents.[6] Our objective was to identify the most frequently investigated anticancer compounds derived from marine sponges by conducting a bibliometric analysis of relevant keywords from previous studies. Subsequently, we focused on identifying anti-lung cancer compounds derived from marine sponges, based on our bibliometric analysis. We then employed molecular docking analysis to identify compounds that exhibited the highest affinity for apoptotic receptors involved in lung cancer cell apoptosis. Furthermore, we evaluated the pharmacological features of these identified compounds. Ultimately, this study presents the most promising anti-lung cancer compounds derived from marine sponges and provides insights into their pharmacological characteristics, which serves as a valuable resource for future research on the anti-lung cancer properties of marine sponges. Additionally, these findings may contribute to the identification and development of effective anti-lung cancer drugs in the near future.

Materials and Methods

Data Collection and Extraction

On June 12, 2023, a search was conducted in the PubMed/Medline-PMC online databases to identify the most frequent anti-lung cancer compounds from marine sponges, focusing on the MeSH keywords. The following search strategy was employed:

Search query: (marine sponge[Title/Abstract]) AND ((cancer*[Title/Abstract]) OR (cancer*[MeSH Terms]) OR (neoplasm*[MeSH Terms]) OR (neoplasm*[Title/Abstract]) OR (proliferat*[Title/Abstract]) OR (proliferat*[MeSH Terms]) OR (cytotoxic*[MeSH Terms]) OR (cytotoxic*[Title/Abstract]) OR (tumor*[Title/Abstract]) OR (tumor*[MeSH Terms])) Filters: from 2018-2023.

The inclusion criteria for this study encompassed research articles published between 2018 and 2023 that specifically investigated anti-lung cancer compounds from marine sponges, identified using MeSH keywords in the PubMed/ Medline-PMC database. Articles focusing on the biological activity of marine sponge compounds, such as sesquiterpenes, alkaloids, and quinones, about cancer, neoplasms, cytotoxicity, and tumor proliferation were included. In contrast, the exclusion criteria eliminated studies that discussed general topics unrelated to the specific compounds of interest, as well as those that mentioned keywords associated with animal and human models, proliferation, specific cell lines, molecular structures, demographic factors (such as gender and age), and other experimental methodologies, ensuring a focused bibliometric analysis on the most relevant anti-lung cancer agents derived from marine sponges.

Subsequently, relevant data were extracted in comma-separated values (CSV) format, and a bibliometric analysis was performed using the VOSviewer software (version 1.6.19, Centre for Science and Technology Studies, Leiden University, Netherlands). Specific keywords related to animals, humans, proliferation, neoplasm, cell lines, tumors, mice, rats, cell survival, molecular structures, gender, age, experimental methodologies, specific cell line names, and countries were eliminated from the bibliometric analysis.

Following the bibliometric analysis, a further in-depth search was conducted in the PubMed PubMed/ Medline-PMC online database based on the findings from the bibliometric analysis. The search strategies employed were as follows:

Search query: "marine sponge"[Title/Abstract] AND (("cancer*"[Title/Abstract] OR "cancer*"[MeSH Terms] OR "neoplasm*"[MeSH Terms] OR "neoplasm*"[Title/Abstract] OR "proliferat*"[Title/Abstract] OR "proliferat*"[MeSH Terms] OR "cytotoxic*"[MeSH Terms] OR "cytotoxic*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumor*"[MeSH Terms])) AND ((sesquiterpene*[Title/Abstract]) OR (sesquiterpene*[MeSH Terms])), Search: "marine sponge"[Title/Abstract] AND (("cancer*"[Title/Abstract] OR "cancer*"[MeSH Terms] OR "neoplasm*"[MeSH Terms] OR "neoplasm*"[Title/Abstract] OR "proliferat*"[Title/Abstract] OR "proliferat*"[MeSH Terms] OR "cytotoxic*"[MeSH Terms] OR "cytotoxic*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumor*"[MeSH Terms])) AND ((alkaloid[Title/Abstract]) OR (alkaloid[MeSH Terms])), and Search: "marine sponge"[Title/Abstract] AND (("cancer*"[Title/Abstract] OR "cancer*"[MeSH Terms] OR "neoplasm*"[MeSH Terms] OR "neoplasm*"[Title/Abstract] OR "proliferat*"[Title/Abstract] OR "proliferat*"[MeSH Terms] OR "cytotoxic*"[MeSH Terms] OR "cytotoxic*"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumor*"[MeSH Terms])) AND ((quinones[Title/Abstract]) OR (quinones[MeSH Terms])).

Molecular Interactions and Docking Studies of Lung Cancer Apoptotic Pathways and Anti-Lung Cancer Molecules of Marine Sponges

The selection method of the 18 most examined apoptotic receptors was based on a previous study.[10] To perform molecular docking analysis, AutoDock Vina software (version 1.2.0, The Scripps Research Institute, USA) was employed. Specifically, after identifying the alkaloids and sesquiterpenes with anti-lung cancer properties from previous studies (tables 1 and 2), the structures of all 16 alkaloids and 27 sesquiterpenes were obtained from the PubChem online database.[11] Additionally, the structures of the 18 apoptotic receptors were acquired from the Protein Data Bank (PDB) online database. The corresponding PDB IDs for each receptor were as follows: Caspase-3 (1cp3), Caspase-7 (1f1j), Caspase-8 (1f9e), Caspase-9 (1jxq), Cannabinoid receptor type 1 (CB1) (5u09), Cannabinoid receptor type 2 (CB2) (6pt0), Death receptor 4 (DR4) (5cir), Death receptor 5 (DR5) (1za3), Endothelial protein C receptor (EPCR) (1l8j), Fas receptor (3ezq), Insulin-like growth factor 1 receptor (IGF1R) (1igr), Metabotropic glutamate receptor 8 (mGluR8) (6bsz), Peroxisome proliferator-activated receptor-γ (PPAR-γ) (1i7i), Transforming growth factor beta receptor 2 (TGFBR2) (4kxz), Toll-like receptor 4 (TLR4) (2z64), Toll-like receptor 9 (TLR9) (3wpf), Tumor necrosis factor receptor 1 (TNFR1) (7k7a), and Prostaglandin D2 receptor (PGD2R) (6d27).

To prepare the receptors for docking, non-standard residues were excluded, and hydrogen atoms were added using AutoDockTools (version 1.5.7, The Scripps Research Institute, USA). Nonpolar hydrogens and ion pairs were merged, and Gasteiger partial charges were

Table 1: Cytotoxicity effects of sesquiterpenes and quinones derived from marine sponges on lung cancer cells

References	Compound	*Sources*	Lung cancer cells
Kwak et al., 2020[22]	Dactyloquinone B	*Dactylospongia elegans*	H460
	Ilimaquinone	*Smenospongia cerebriformis*	A549
	Nakijinol B		
	Nakijinol B diacetate		
	Smenospongine B		
	Smenospongine C		
Huyen et al., 2017[23]	Dactyloquinone D	*Smenospongia cerebriformis*	LU-1
	Smenohaimien F		
	Dactyloquinone C		
Ito et al., 2018[24] Nguyen et al., 2017[25]	Langconol C	*Spongia* sp.	A549
	Langcoquinone C		
	Langcoquinone D		

Table 2: The three most frequent keywords in surveys in which the anticancer features of marine sponges have been examined from 2018 to 2023

Keywords	Cluster	Link	Total Link Strength	Occurrence
Alkaloids	4	33	57	41
Sesquiterpenes	6	18	42	23
Quinones	6	14	32	15

assigned to each ligand atom. Grid boxes were generated using the Computed Atlas of Surface Topography of proteins (CASTp3.0, University of Illinois at Chicago, USA). Subsequently, docking was performed, and 10 conformations were obtained for each receptor-ligand pair. The docking conformations were ranked based on binding affinity, and the conformation with the lowest negative energy and RMSD≤2 Å was selected as the best conformation.

Visualization of Inter-Molecular Interactions

The visualization of the 3D structure of the best conformations was carried out using BIOVIA Discovery Studio Visualizer (version 2021, Dassault Systèmes, France). Furthermore, for a more detailed analysis of the intermolecular interactions between the ligand and the receptor, the data was visualized in 2D using PyMOL (version 2.5.4, Schrödinger, LLC, USA).

Prediction of Biological Availability and Various Pharmacological Effect of Anti-Lung Cancer Compounds Derived from Marine Sponges

The drug manufacturing safety and biological availability of elected compounds were predicted by SwissADME online tool (version 2023, Swiss Institute of Bioinformatics, Switzerland). The ProTox-II online tool (version 2023, Charité–Universitätsmedizin Berlin, Germany) was utilized to predict the LD50 (lethal dose 50%) and toxicity class of the anti-lung cancer compounds derived from marine sponges. Based on the predicted toxicity, each compound was assigned to one of six toxicity classes according to the globally harmonized system of classification and labeling of chemicals (GHS). The classification is as follows, with LD50 values given in milligrams per kilogram (mg/Kg):

Class I: Fatal if swallowed (LD50≤5)
Class II: Fatal if swallowed (5<LD50≤50)
Class III: Toxic if swallowed (50<LD50≤300)
Class IV: Harmful if swallowed (300<LD50≤2000)
Class V: May be harmful if swallowed (2000< LD50≤5000)
Class VI: Non-toxic (LD50>5000)

Furthermore, the ProTox-II online tool was employed to explore the various potential effects of the marine sponge-derived anti-lung cancer compounds as drugs on the human body. This analysis included their effects on organs, carcinogenicity, mutagenicity, cytotoxicity, immunotoxicity, as well as their impact on cytotoxic pathways in normal cells, such as nuclear receptor signaling pathways and stress response pathways. Additionally, the Way2Drug online tool (version 2023, Institute of Biomedical Chemistry, Russia) was used to predict the possible activities, adverse effects, and toxic effects of the mentioned components.

Results

Alkaloids, Sesquiterpenes, and Quinones Are the Most Frequent Components in Anticancer Studies of Marine Sponges

A comprehensive search of the PubMed/Medline-PMC online database was conducted to identify prominent anticancer components derived from marine sponges between 2018 and 2023, resulting in a total of 314 relevant studies. Subsequently, these studies were subjected to bibliometric analysis using VOSviewer software. The analysis revealed 56 distinct items, which were organized into six clusters, with a total of 304 connections and a link strength of 404. Among the identified keywords, alkaloids, sesquiterpenes, and quinones emerged as the

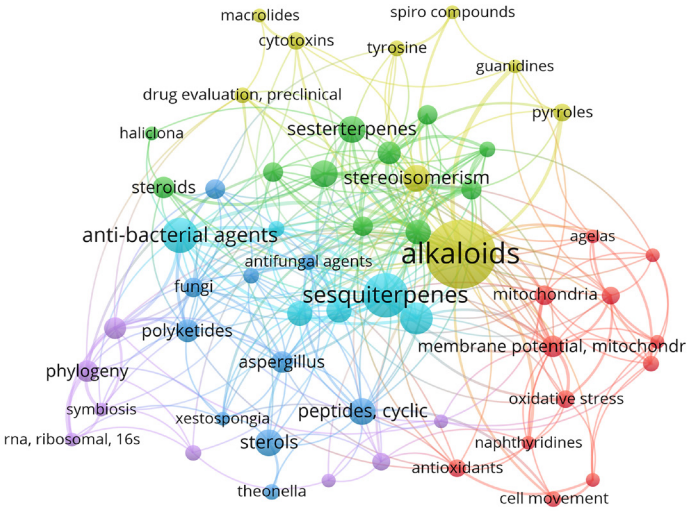


Figure 1: The most frequently occurring keywords from surveys focused on the anticancer properties of marine sponges. The size of each keyword corresponds to its frequency, with larger keywords representing those mentioned more often in the studies.

most prominent and highly studied in the context of anticancer properties associated with marine sponges (table 2 and figure 1).

Alkaloids in the Marine Sponges Extract with Anti-Lung Cancer Properties

Table 3 presents a comprehensive list of 16 Alkaloids derived from marine sponges, which have exhibited notable anti-lung cancer properties since 1991.

In our investigation, we identified a total of 27 sesquiterpenes that have demonstrated inhibitory effects on lung cancer cells, and these findings date back to 1985 (table 1). Notably, our analysis revealed that quinones, which possess anti-lung cancer properties, are structurally associated with sesquiterpenes and other components found in marine sponges. Intriguingly, it was observed that quinones with anti-lung cancer effects exhibit a close association with sesquiterpenes (table 1).

19-oxofasciospongine A, Araguspongine C, Hyrtiocarboline, Hyrtioerectine F, Ingenine E, Ingenine F, Pyronaamidinev, Renieramycin T, and Sceptrin Were Nine Alkaloids with the Most Affinity to Receptors Involved in the Apoptosis of Lung Cancer Cells

Through molecular docking analysis, it was determined that 19-oxofasciospongine A exhibited the highest binding affinity to caspase 3, Araguspongine C had the strongest binding affinity to multiple apoptotic receptors in lung cancer cells, including caspase 8, Insulin-like growth factor 1 receptor (IGF1R), PGD2R, PPAR-γ, TGFBR2, TLR-4, and TLR-9. Besides, hyrtiocarboline showed the most *in-silico* binding affinity to caspase 9, DR5, mGluR8, and TLR-9. Furthermore, hyrtioerectine F demonstrated the highest tendency to Fas R and CB2. Moreover, ingenine E, ingenine F, pyronaamidine, and renieramycin T displayed the highest binding affinity to CB1, TLR-4, EPCR, and TNFR1. Finally, sceptrin demonstrated the strongest binding affinity to caspase 7 and DR4. The molecular interaction between all mentioned nine alkaloids and the receptor involved in the apoptosis in lung cancer cells is demonstrated in figure 2.

Dactyloquinone B, C, and D, Dysidavarone D, Nakijinol B, Smenohaimien F, Sollasin C and Sollasin E Were Seven Sesquiterpenes with the Highest Affinity to Receptors Involved in the Apoptosis of Lung Cancer Cells

Based on our *in-silico* analysis, it was determined that dactyloquinone B exhibited the highest binding affinity to several apoptotic receptors, including caspase 9, CB2, and mGluR8. Dactyloquinone C demonstrated a notable tendency to bind with caspase 8, DR4, DR5, PPAR-γ, and TLR9. Furthermore, dactyloquinone D displayed the strongest binding affinity to caspase-3 (table 4).

Additionally, dysidavarone D exhibited the highest tendency to caspase 7. Nakijinol B had the strongest *in-silico* tendency to Fas receptor and PGD2R. Smenohaimien F mirrored the highest *in-silico* tendency to IGFR1 and TNFR1. Sollasin C had the strongest binding affinity to EPCR, TGFB2R, and TLR4. Ultimately, sollasin E showed the highest *in-silico* tendency to CB1 (table 4). For a more comprehensive understanding, detailed information regarding the binding sites between these mentioned sesquiterpenes and the identified apoptotic receptors is provided in figure 3.

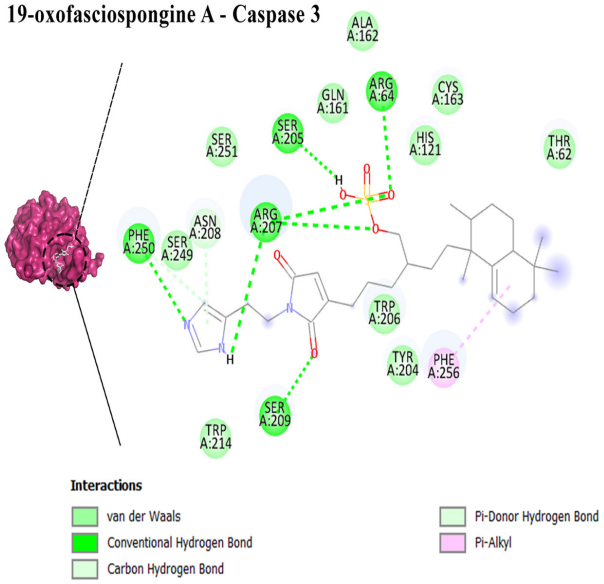
Pharmacological Prediction Analysis of Alkaloids and Sesquiterpenes with the Highest Binding Affinity to Apoptotic Receptors in Lung Cancer Cells

Drug Manufacturing Safety and Bioavailability Assay: Based on the bioavailability analysis of SwissADME online tool, araguspongine C, dactyloquinone B, C, and D, dysidavarone D, ingenine E, ingenine F, nakijinol B, pyronaamidine, sceptrin, smenohaimien F, sollasin C, and sollasin F have shown various favorable bioavailable features (LIPO: lipophility, SIZE: size, POLAR: polarity, INSOLU: solubility, INSATU: saturation, FLEX: flexibility). In other words, remarked analysis displayed that all of these compounds are safe to be utilized for manufacturing curative drugs (figure 4).

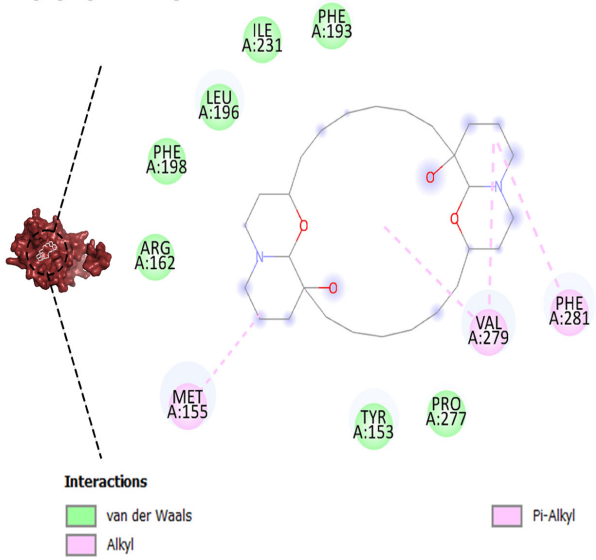
Table 3: Cytotoxicity effects of alkaloids derived from marine sponges on lung cancer cells

References	Compound	Sources	Lung cancer cells
Ki et al., 2020[12]	1H-indole-3-carboxylic acid	*Gelliodes* sp.	A549
Zhang et al., 2016[13]	3-dodecyl pyridine	*Haliclona* sp.	A549
Sirimangkalakitti et al., 2016[14]	Acanthodendrilline	*Acanthodendrilla* sp.	H292
Dung et al., 2019[15]	Araguspongine C	*Xestospongia muta*	LU-1
Lhullier et al., 2019[16]	Clerodane diterpene	*Raspailia bouryesnaultae*	A549
Ibrahim et al., 2018[17] Ibrahim and Mohamed, 2017[18]	Ingenine F and E	*Acanthostrongylophora ingens*	A549
Tang et al., 2018[19]	Pyronaamidine	*Leucetta chagosensis*	A549
Petsri et al., 2019[20]	Renieramycin T	*Xestospongia* sp.	H460
Kwon et al., 2018[21]	Sceptrin	*Agelas kosrae*	A549

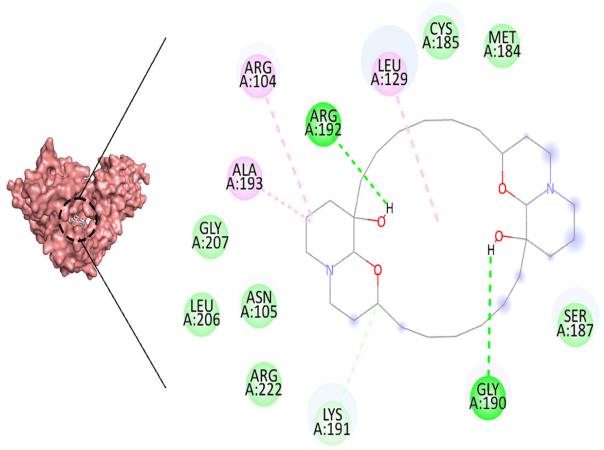
19-oxofasciospongine A - Caspase 3



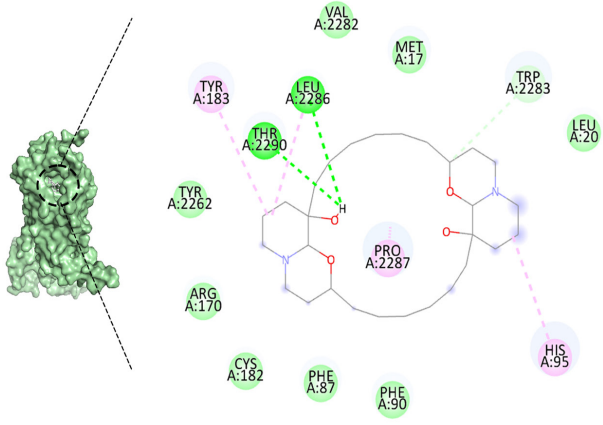
Araguspongine C - caspase8



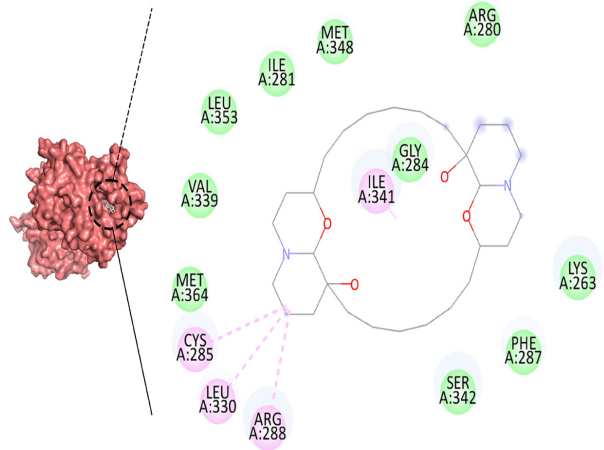
Araguspongine C - IGFR1



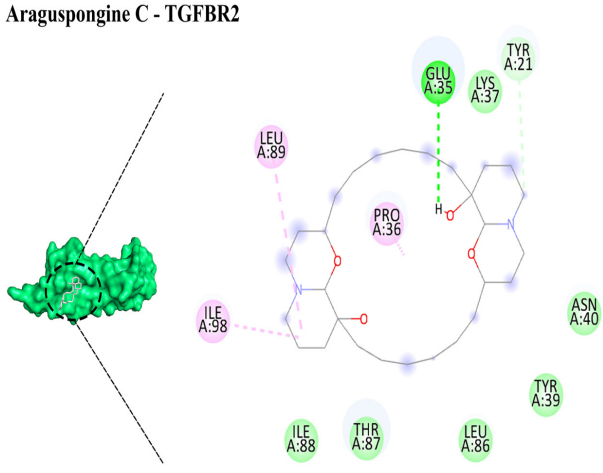
Araguspongine C - PGD2R



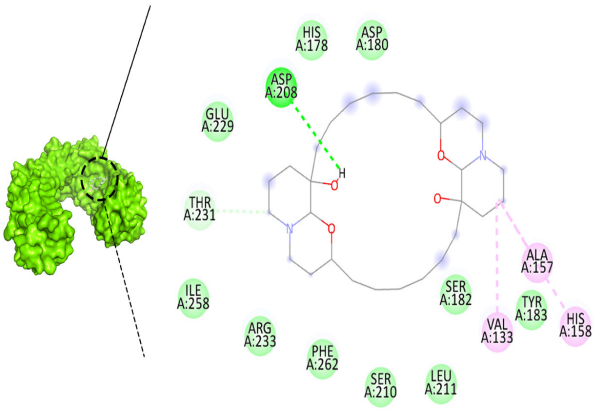
Araguspongine C - PPAR-γ



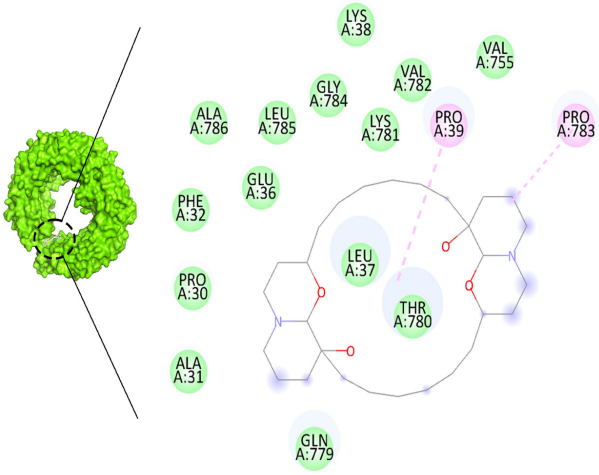
Araguspongine C - TGFBR2



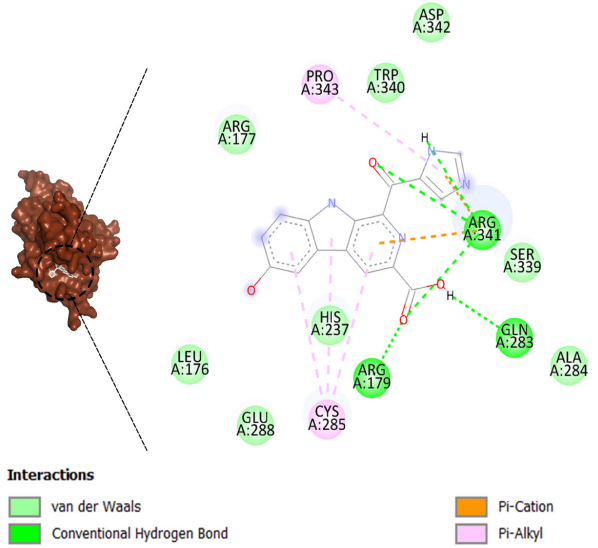
Aragusponginе C - TLR4



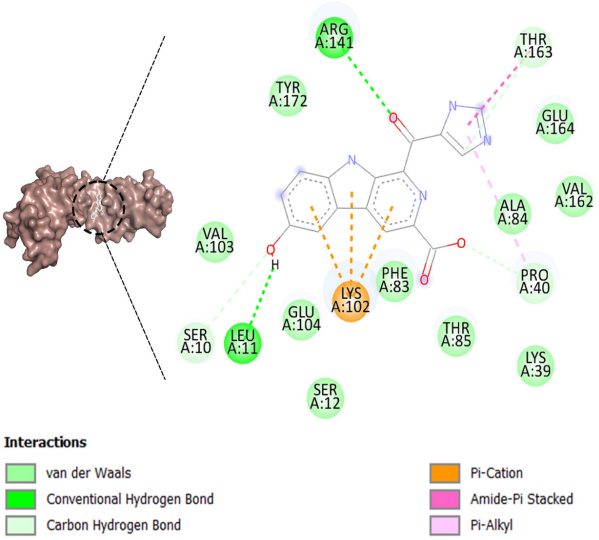
Aragusponginе C - TLR 9



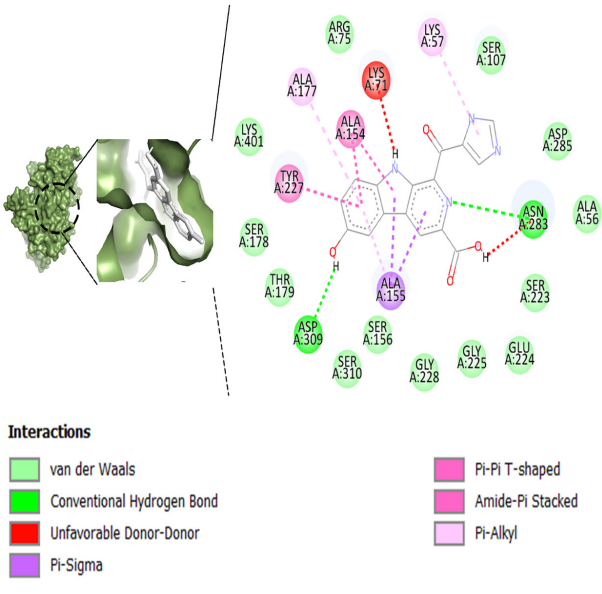
Hyrtiocarboline - Caspase 9



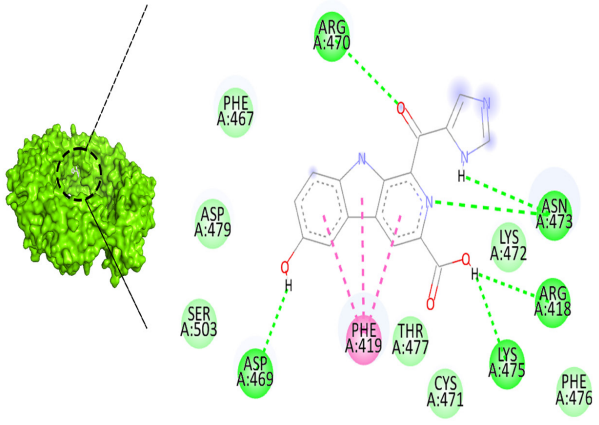
Hyrtiocarboline - DR5



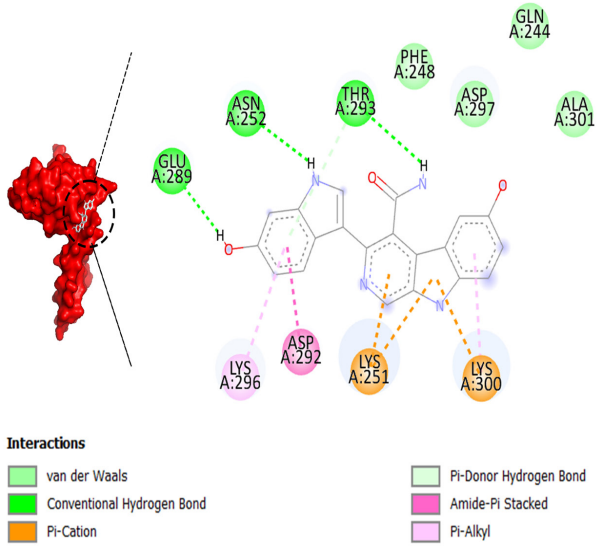
Hyrtiocarboline - mGluR8



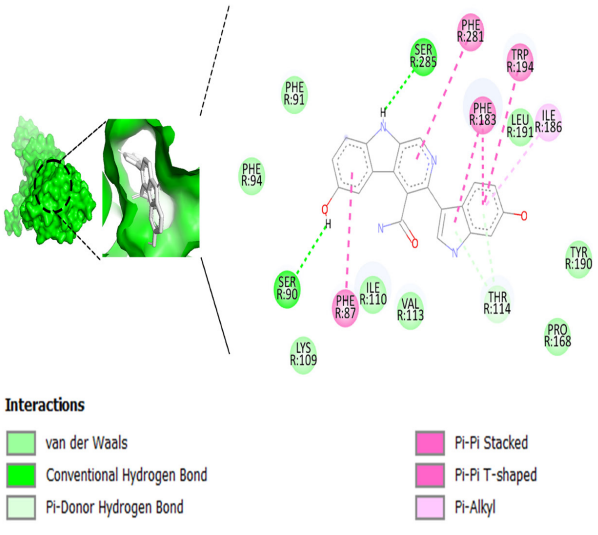
Hyrtiocarboline - TLR9



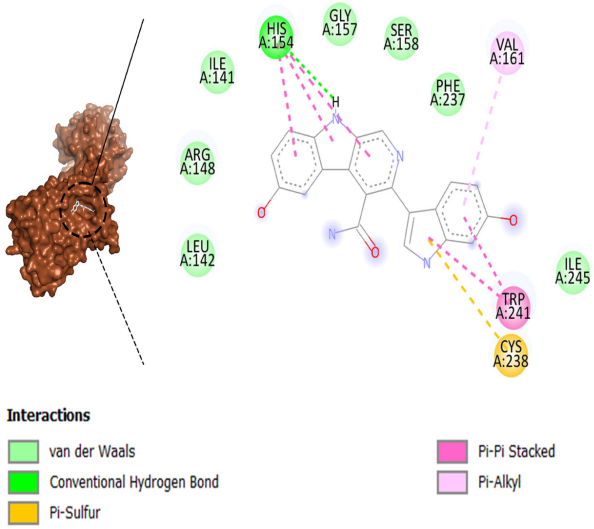
Hyrtioerectine F - FAS Receptor



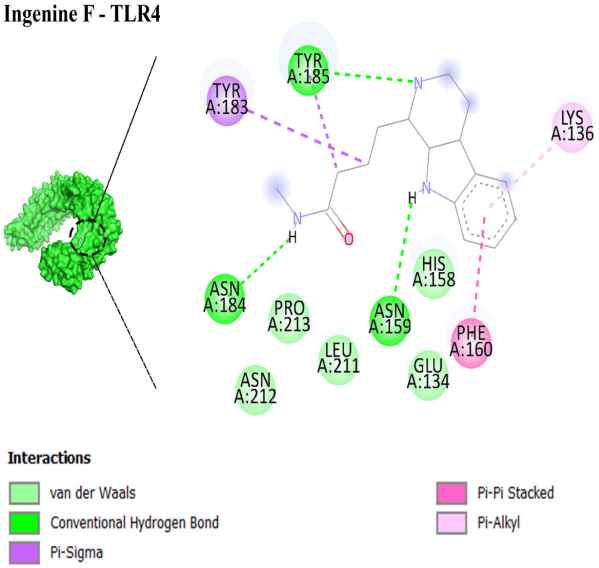
Hyrtioerectine F - CB2



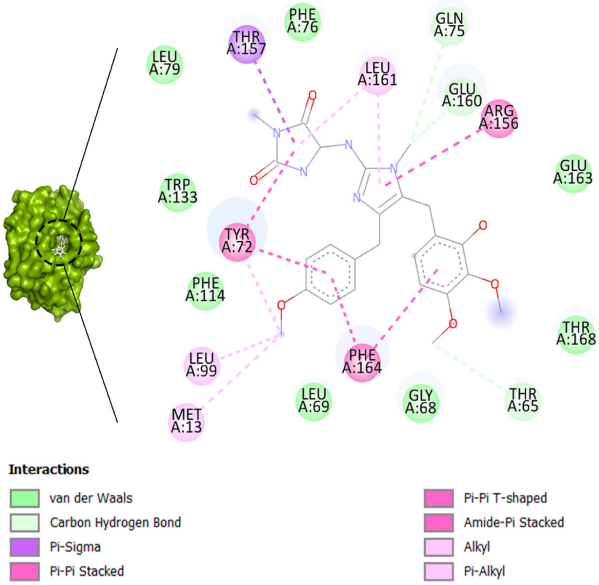
Ingenine E - CB1



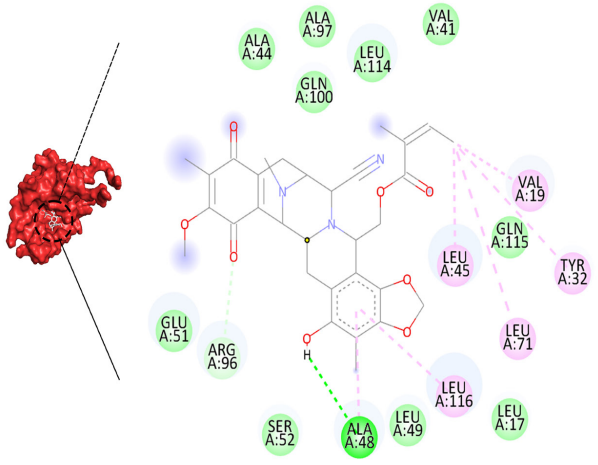
Ingenine F - TLR4



Pyronaamidine - EPCR



Renieramycin T - TNFR1



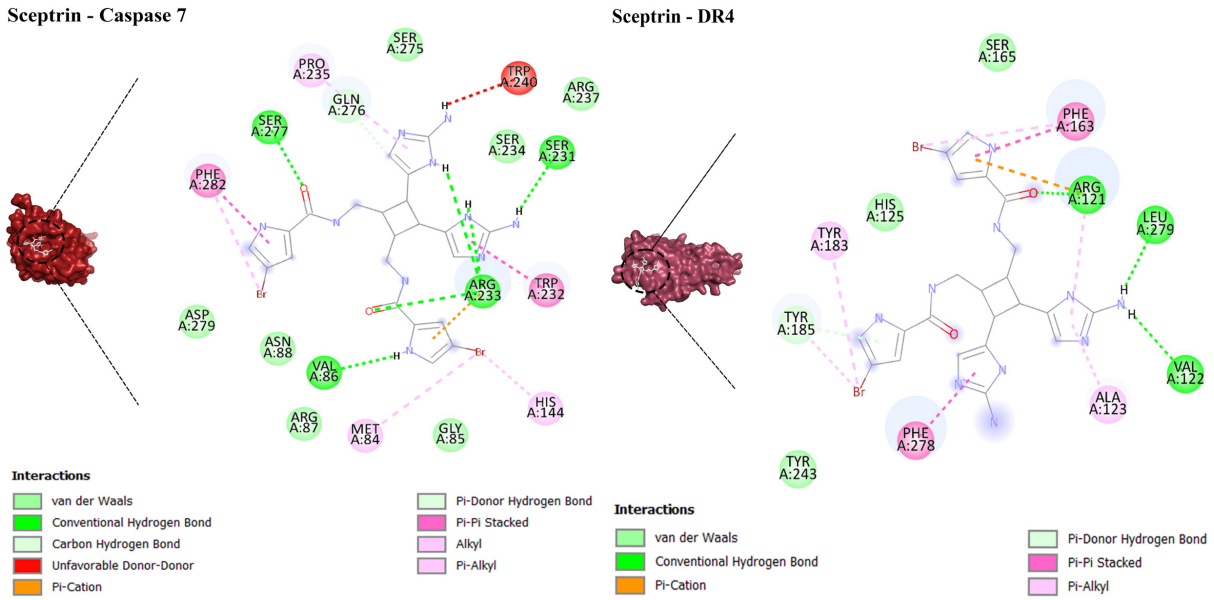
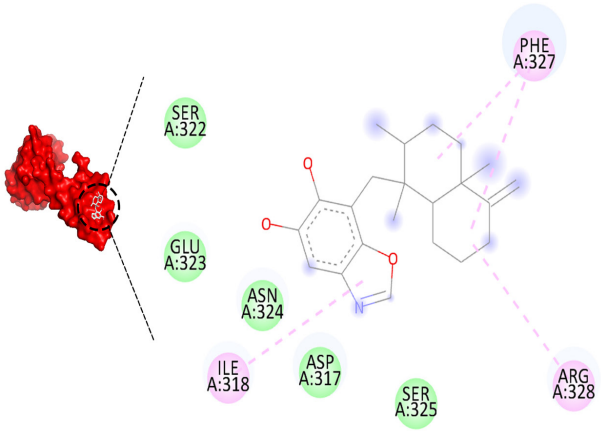


Figure 2: The molecular interactions at the binding sites of the top binding conformations between selected marine sponge-derived compounds and their respective targets. The interactions shown include 19-oxofasciospongine A with caspase 3; araguspongine C with caspase 8, IGF1R, PGD2R, PPAR-γ, TGFBR2, TLR-4, and TLR-9; hyrtiocarboline with caspase 9, DR5, mGluR8, and TLR-9; hyrtioerectine F with Fas receptor (FasR) and CB2; ingenine E, ingenine F, pyronaamidine, and renieramycin T with CB1, TLR-4, EPCR, and TNFR1; and sceptrin with caspase 7 and DR4.

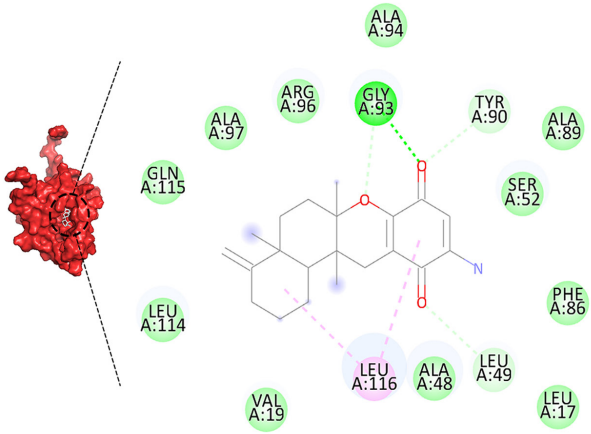
Table 4: Various binding affinities between each sesquiterpene and apoptotic receptor in lung cancer cells

Sesquiterpenes	Receptors																	
	Fas R	TNFR1	DR4	DR5	IGFR1	PPAR-γ	Caspase-3	Caspase-7	Caspase-8	Caspase-9	CB1	CB2	TLR-4	TLR-9	EPCR	mGluR 8	PGD2R	TGFBR2
Arenaran A	-5.7	-5.8	-5.5	-5.6	-6.4	-6.4	-6.5	-6.3	-5.9	-5.6	-7.9	-8.5	-6.3	-6.8	-8.3	-5.5	-7.3	-5.0
Dactyloquinone B	-6.8	-8.2	-6.7	-7.1	-7.5	-7.9	-7.8	-8.7	-6.7	-8.2	-8.4	-11.0	-7.4	-7.6	-8.2	-7.2	-9.5	-6.4
Dactyloquinone C	-7.1	-8.0	-7.1	-7.7	-8.9	-8.9	-8.6	-8.5	-7.1	-6.8	-8.6	-9.7	-7.4	-8.4	-8.0	-6.9	-9.9	-7.0
Dactyloquinone D	-6.2	-7.3	-7.0	-6.7	-8.9	-8.4	-8.7	-7.7	-6.7	-6.9	-8.0	-10.2	-7.1	-7.4	-8.6	-7.1	-10.4	-6.3
Dysidavarone D	-6.8	-7.6	-6.9	-7.0	-7.3	-8.1	-8.1	-9.1	-6.4	-7.4	-8.3	-9.4	-6.8	-8.0	-8.3	-6.9	-6.8	-6.2
Ilimaquinone	-6.0	-6.9	-6.4	-7.0	-7.9	-8.0	-7.6	-7.5	-6.3	-6.6	-7.9	-7.1	-7.1	-7.7	-8.4	-6.7	-9.4	-6.0
Langconol C	-5.5	-7.3	-5.7	-6.1	-7.5	-7.8	-7.1	-7.5	-5.6	-6.2	-6.2	-8.7	-6.1	-6.6	-6.6	-6.0	-9.1	-5.6
Langcoquinone C	-6.4	-7.9	-6.7	-6.7	-6.9	-7.8	-7.4	-7.5	-6.0	-6.2	-7.3	-9.6	-6.9	-7.5	-8.2	-6.3	-9.5	-6.1
Langcoquinone D	-6.6	-6.3	-6.6	-6.6	-7.2	-6.7	-7.6	-7.1	-6.4	-6.8	-7.5	-7.0	-6.6	-7.2	-8.5	-6.2	-9.4	-6.1
Nakijinol B	-7.2	-7.4	-6.7	-7.1	-8.1	-8.1	-8.1	-7.7	-6.8	-6.9	-7.9	-7.4	-7.4	-7.9	-7.9	-6.9	-10.5	-6.2
Nakijinol B Diacetate	-5.8	-7.1	-6.7	-6.6	-8.1	-7.5	-8.2	-7.6	-6.2	-6.8	-6.9	-7.3	-6.8	-8.0	-7.8	-6.7	-8.1	-6.0
Parahigginic acid	-6.0	-6.8	-5.7	-6.2	-7.2	-7.4	-7.2	-6.6	-5.5	-6.0	-8.6	-8.1	-5.9	-7.8	-8.7	-6.5	-7.7	-5.5
Parahigginol B	-5.4	-6.2	-5.1	-6.1	-6.9	-5.9	-6.2	-5.8	-5.3	-5.6	-6.2	-7.3	-5.7	-7.0	-7.9	-6.3	-7.5	-4.9
Parahigginol C	-5.8	-6.8	-5.3	-5.7	-6.3	-6.0	-6.2	-6.2	-5.1	-5.5	-6.1	-6.4	-5.3	-6.7	-8.4	-6.6	-7.8	-4.7
Parahigginol D	-6.0	-6.0	-5.4	-6.2	-7.0	-7.1	-7.1	-6.8	-5.9	-5.6	-8.1	-7.9	-6.2	-8.1	-8.7	-6.2	-7.7	-5.3
Polyfibrospongol A	-6.4	-8.2	-6.6	-7.0	-7.7	-8.3	-8.3	-6.5	-6.5	-7.2	-7.2	-9.8	-7.0	-7.8	-8.5	-6.5	-9.7	-6.3
Polyfibrospongol B	-5.9	-7.9	-6.2	-7.4	-7.3	-8.0	-7.8	-7.7	-6.2	-6.1	-7.1	-7.0	-6.5	-7.7	-8.1	-6.4	-9.2	-5.8
Smenohaimien F	-6.9	-8.8	-7.0	-6.7	-9.0	-8.2	-8.5	-7.8	-6.8	-6.9	-8.1	-10.2	-7.1	-7.9	-8.3	-7.1	-10.0	-6.4
Smenospongine	-6.0	-6.8	-6.6	-6.8	-7.8	-7.7	-7.5	-7.4	-6.8	-6.8	-7.9	-9.1	-7.2	-7.9	-7.5	-6.8	-9.7	-6.6
Smenospongine B	-6.4	-7.4	-7.0	-6.7	-7.5	-7.3	-8.5	-8.5	-7.0	-7.3	-7.1	-9.2	-6.9	-8.0	-8.6	-6.4	-9.7	-6.3
Smenospongine C	-6.3	-7.0	-6.6	-6.8	-7.0	-7.3	-8.1	-8.0	-6.0	-6.7	-7.4	-8.7	-6.8	-7.7	-7.6	-6.3	-9.7	-6.2
Sollasin A	-6.0	-6.1	-5.5	-5.8	-5.9	-7.1	-6.5	-5.9	-5.5	-5.4	-6.6	-8.5	-5.7	-5.9	-8.9	-5.5	-7.0	-5.0
Sollasin B	-6.2	-6.7	-6.6	-6.9	-7.1	-7.0	-7.6	-7.1	-6.2	-6.3	-8.2	-7.5	-7.0	-7.7	-10.4	-7.1	-8.2	-6.8
Sollasin C	-6.7	-6.7	-6.7	-6.9	-7.2	-7.2	-7.5	-7.4	-6.7	-6.9	-8.0	-9.7	-7.5	-7.5	-10.9	-6.7	-8.5	-7.3
Sollasin D	-6.2	-7.0	-6.4	-6.5	-7.1	-7.7	-7.7	-6.9	-6.0	-6.4	-7.6	-7.3	-6.8	-7.4	-10.3	-6.5	-8.1	-6.0
Sollasin E	-5.0	-6.7	-5.9	-6.4	-6.6	-7.1	-7.0	-7.0	-5.8	-6.3	-8.7	-9.1	-6.1	-6.8	-8.2	-6.1	-7.9	-5.2
Sollasin F	-5.9	-6.9	-6.0	-6.3	-7.2	-6.9	-6.8	-6.6	-6.0	-6.3	-7.4	-9.0	-6.2	-8.0	-7.5	-6.1	-8.9	-5.7

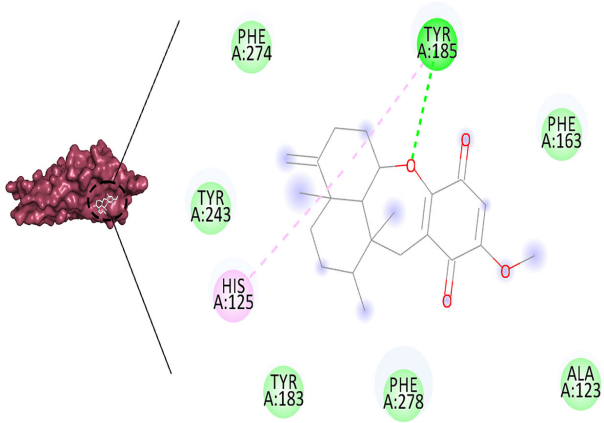
Nakijinol B - FAS Receptor



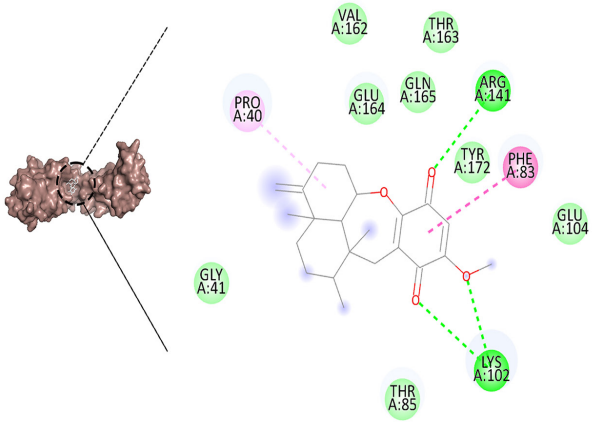
Smenohaimien F - TNFR1



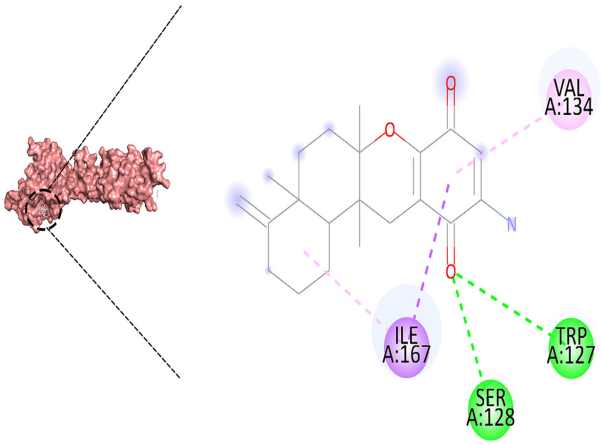
Dactyloquinone C - DR4



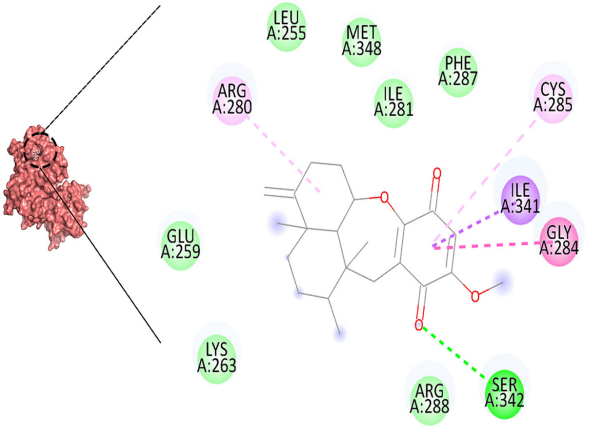
Dactyloquinone C - DR5



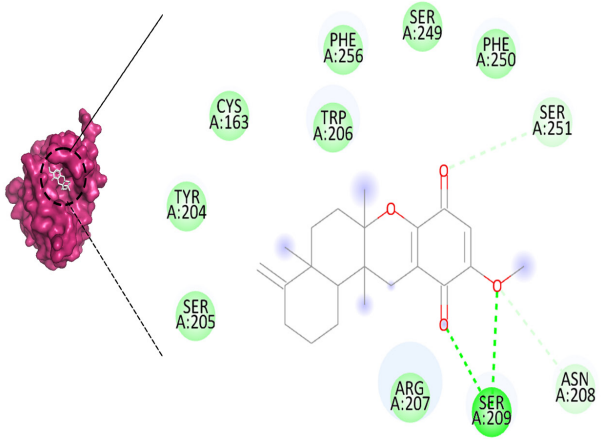
Smenohaimien F - IGFR1



Dactyloquinone C - PPAR-γ

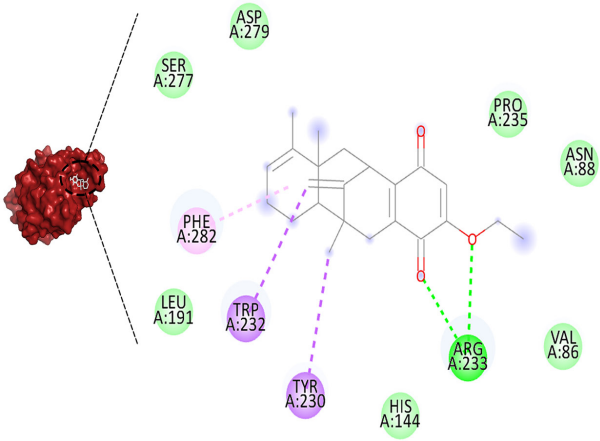


Dactyloquinone D - Caspase 3



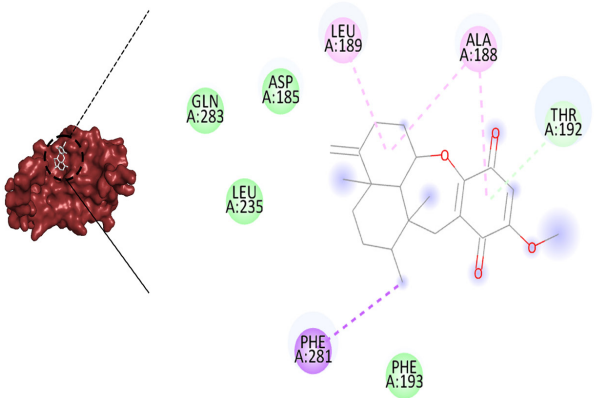
Interactions
van der Waals
Conventional Hydrogen Bond
Carbon Hydrogen Bond

Dysidavarone D - Caspase 7



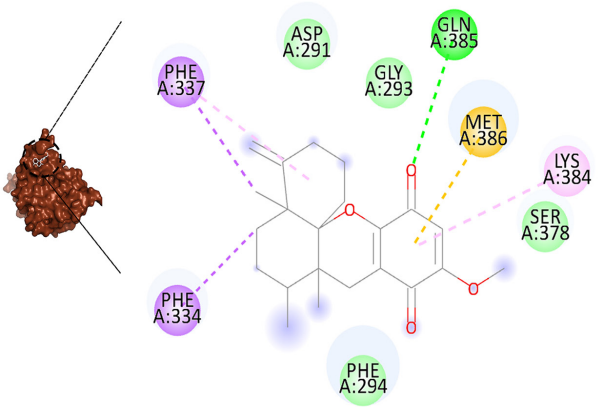
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Alkyl

Dactyloquinone C - Caspase 8



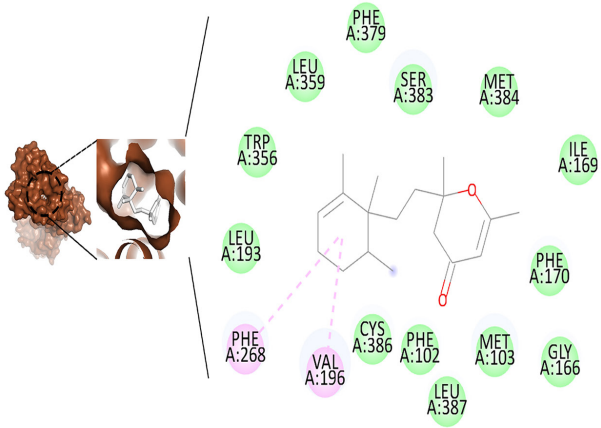
Interactions
van der Waals
Pi-Donor Hydrogen Bond
Pi-Sigma
Alkyl
Pi-Alkyl

Dactyloquinone B - Caspase 9



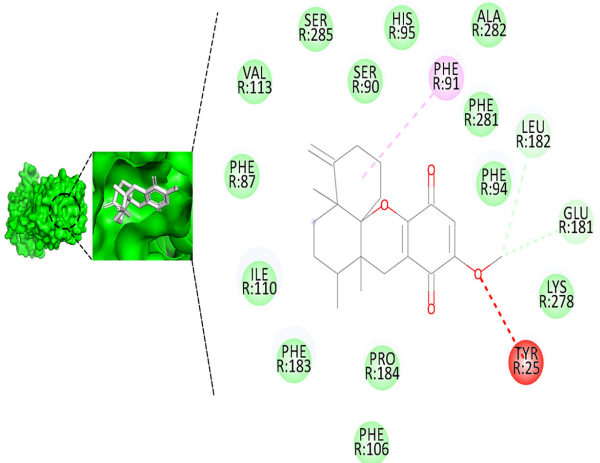
Interactions
van der Waals
Conventional Hydrogen Bond
Pi-Sigma
Pi-Sulfur
Pi-Alkyl

Sollasin E - CB1



Interactions
van der Waals
Alkyl
Pi-Alkyl

Dactyloquinone B - CB2



Interactions
van der Waals
Carbon Hydrogen Bond
Unfavorable Acceptor-Acceptor
Pi-Alkyl

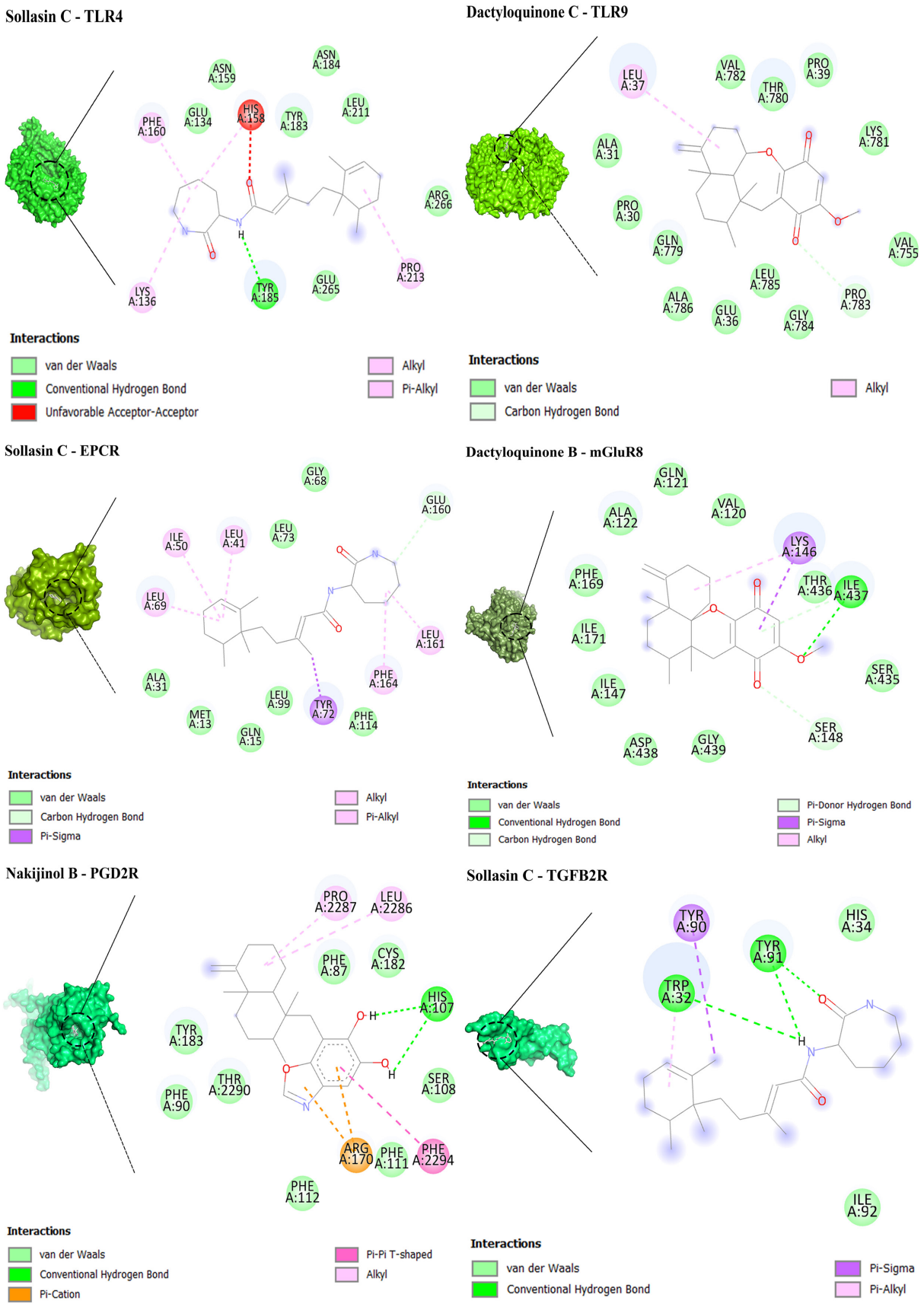


Figure 3: The molecules and interactions at the binding sites of the optimal binding conformations between dactyloquinone B, C, and D; dysidavarone D; nakijinol B; smenohaimien F; sollasin C; and sollasin E with apoptotic receptors in lung cancer cells. The interactions illustrated involve these sesquiterpenes and the following receptors: Fas receptor, TNFR1, DR4, DR5, IGF1R, PPAR-γ, caspase-3, caspase-7, caspase-8, caspase-9, CB1, CB2, TLR4, TLR9, EPCR, mGluR8, PGD2R, and TGFBR2.

On the contrary, figure 4 portrays that 19-oxofasciospongine A, hyrtiocarboline, hyrtioerectine F, and renieramycin T did not display proper features of a bioavailable compound.

Finally, related analysis showed different bioavailability characteristics of mentioned alkaloids and sesquiterpenes that demonstrated the strongest binding affinity to apoptotic receptors in lung cancer (table 5). Based on the analysis of SwissADME online tool, dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E demonstrated the highest bioavailable score between all selected alkaloids and sesquiterpenes with the highest binding affinity to apoptotic receptors in lung cancer cells with the bioavailable score of 85% (table 5). Thus, based on the information obtained from figure 4 and table 5, we chose these six components for further analysis.

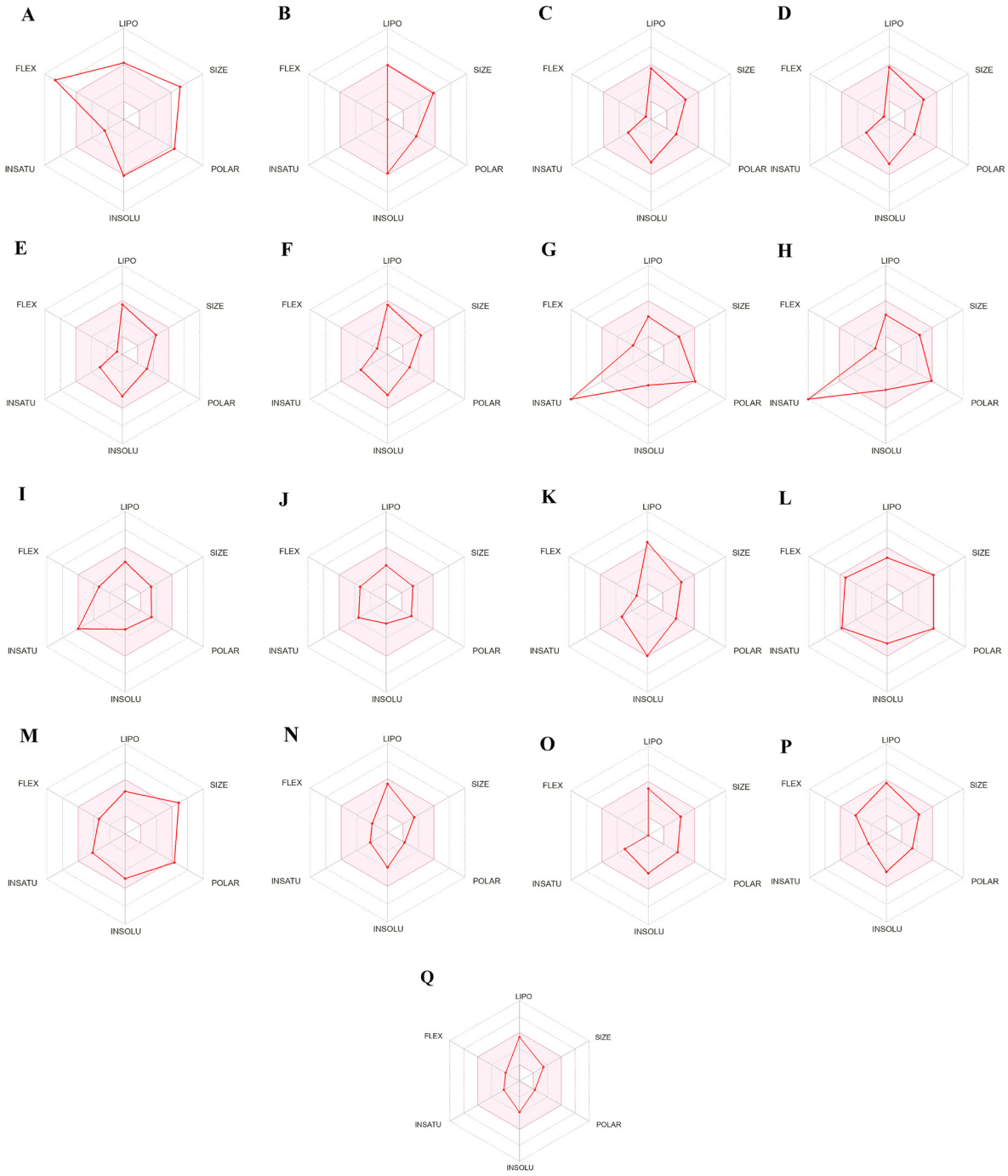


Figure 4: The safety analysis of the manufacturing potential of various compounds as potential drug candidates, including A) 19-oxofasciospongine A, B) araguspongine C, C) dactyloquinone B, D) dactyloquinone C, E) dactyloquinone D, F) dysidavarone D, G) hyrtiocarboline, hyrtioerectine F (H), ingenine E (I), ingenine F (J), nakijinol B (K), pyronaamidine (L), renieramycin T (M), sceptrin (N), smenohaimien F (O), sollasin C (P), and (Q) sollasin F. The analysis evaluates various drug safety parameters, including lipophilicity (LIPO), molecular size (SIZE), polarity (POLAR), solubility (INSOLU), saturation (INSATU), and molecular flexibility (FLEX).

Table 5: The results of bioavailability analysis performed by SwissADME about bioavailability characteristics of all elected alkaloids and sesquiterpenes with the highest binding affinity to apoptotic receptors in lung cancer cells

Compounds	Bioavailability criterion												
	Lipophilicity	Water Solubility	Pharmacokinetics				Drug likeness						Medicinal Chemistry
	Consensus Log $P_{o/w}$	Log *S* (ESOL)	GI absorption	BBB permeant	P-gp substrate	Log Kp (skin permeation)	Lipinski	Ghose	Veber	Egan	Muegge	Bioavailability Score	Synthetic accessibility
19-oxofasciospongine A	2.04	-6.15	Low	No	Yes	-6.15 cm/s	Yes	No	No	No	No	0.55	5.82
Araguspongine C	3.76	-5.89	High	Yes	Yes	-5.74 cm/s	Yes	No	Yes	Yes	Yes	0.55	7.36
Dactyloquinone B	3.71	-4.67	High	Yes	No	-5.45 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	5.90
Dactyloquinone C	3.67	-4.83	High	Yes	No	-5.27 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	5.58
Dactyloquinone D	3.71	-4.67	High	Yes	No	-5.44 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	5.43
Dysidavarone D	4.14	-4.56	High	Yes	No	-5.44 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	5.18
Hyrtiocarboline	1.14	-3.44	High	No	No	-6.87 cm/s	Yes	Yes	Yes	No	Yes	0.55	2.53
Hyrtioerectine F	2.04	-3.96	High	No	No	-6.87 cm/s	Yes	Yes	Yes	Yes	Yes	0.55	2.78
Ingenine E	2.46	-3.05	High	Yes	Yes	-6.35 cm/s	Yes	Yes	Yes	Yes	Yes	0.55	2.15
Ingenine F	1.70	-2.39	High	Yes	Yes	-6.88 cm/s	Yes	Yes	Yes	Yes	Yes	0.55	3.26
Nakijinol B	4.76	-5.99	High	No	Yes	-4.17 cm/s	Yes	Yes	Yes	Yes	No	0.55	4.63
Pyronaamidine	2.56	-4.62	High	No	Yes	-7.17 cm/s	Yes	No	Yes	Yes	Yes	0.55	4.16
Renieramycin T	2.22	-4.92	High	No	No	-7.86 cm/s	No	No	Yes	No	No	0.17	6.50
Sceptrin	1.93	-5.66	Low	No	No	-8.51 cm/s	No	No	No	No	No	0.17	4.75
Smenohaimien F	3.16	-4.24	High	Yes	Yes	-5.81 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	5.31
Sollasin C	3.66	-4.36	High	Yes	Yes	-5.30 cm/s	Yes	Yes	Yes	Yes	Yes	0.55	4.46
Sollasin E	4.04	-3.90	High	Yes	No	-5.12 cm/s	Yes	Yes	Yes	Yes	Yes	0.85	4.97

Drug Safety and Toxicity: According to the predictions made by the ProTox-II online tool, dactyloquinone B, if taken orally, would fall under the class V toxicity category, indicating potential harm if swallowed (figure 4). The analysis resulted in an average similarity of 72.56% and a prediction accuracy of 69.26% (figure 5). Further details regarding the use of dactyloquinone B as an oral anti-lung cancer agent are provided in figure 5.

Furthermore, the analysis conducted using the Way2Drug online tool indicated that dactyloquinone B exhibits potential activities such as anti-neoplastic, anti-eczematic, and phosphatase inhibition, with respective probabilities (Pa) of 89%, 81%, and 73% (figure 5). Additionally, this analysis suggested that the drug may have certain side effects, including sensitization and withdrawal (figure 5). Figure 5 presents additional potential effects and side effects associated with the use of dactyloquinone B as a drug.

As a drug, dactyloquinone C was categorized under class V toxicity by the ProTox-II online tool, indicating potential harm if swallowed (figure 5). The analysis yielded an average similarity of 74.23% and a prediction accuracy of 69.26% (figure 5).

Conversely, according to the predictions made by the Way2Drug online tool, dactyloquinone C is likely to exhibit antineoplastic, anti-eczematous, and phosphatase inhibition effects, while its potential adverse effects include sensitization, toxicity, and cataract formation (figure 5).

The ProTox-II online tool classified dactyloquinone D as a class V toxicity when used as an oral drug, indicating the potential for harm if swallowed (figure 5). The analysis yielded an average similarity of 73.39% and a prediction accuracy of 69.26% (figure 5).

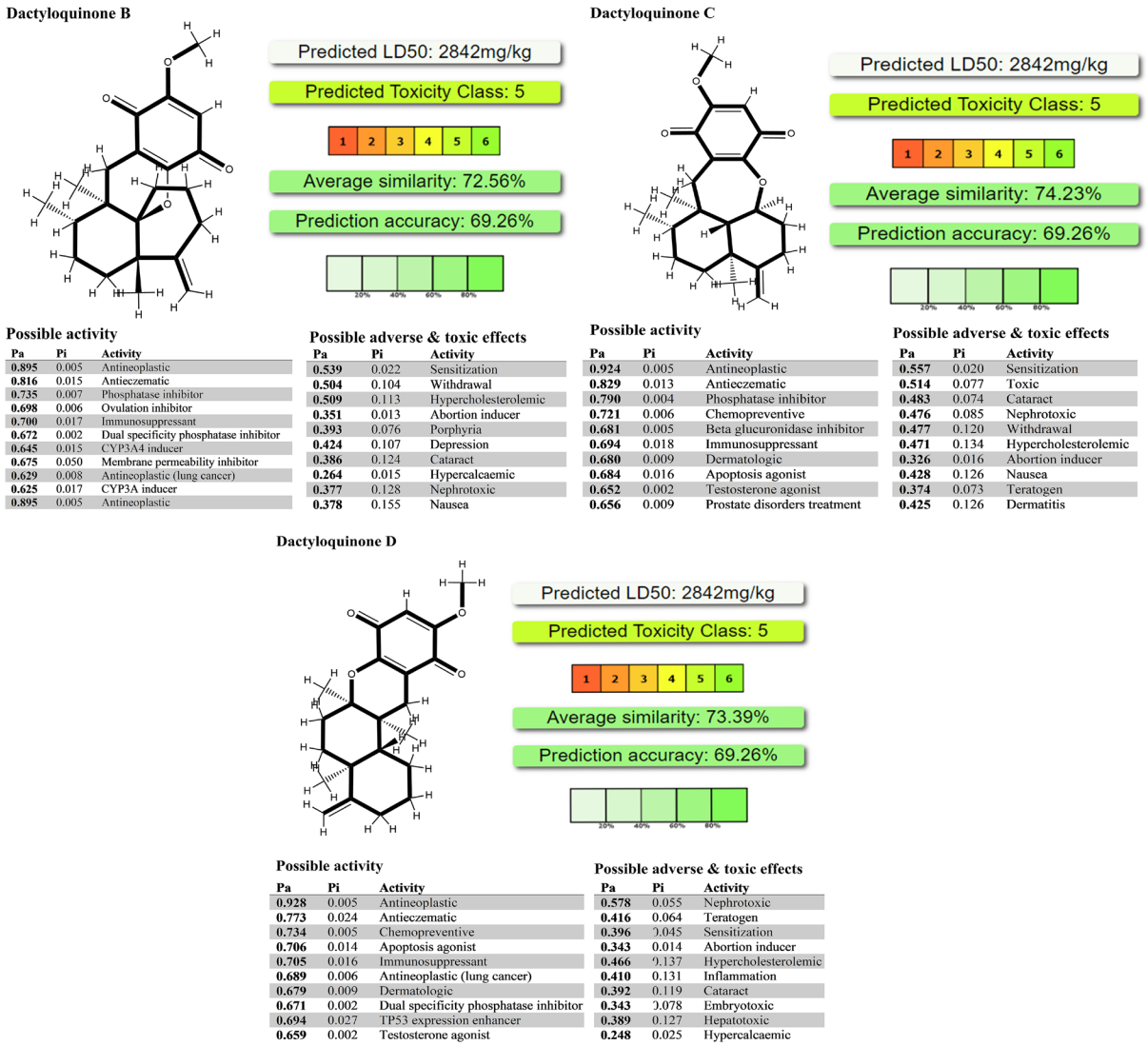


Figure 5: The 2D structures, toxicity classifications, potential activities, and possible side effects of dactyloquinone B, C, and D as prospective anti-lung cancer drugs. The figure includes the probability of activity (Pa) and the probability of inactivity (Pi) for each predicted activity and toxic effect.

Furthermore, the analysis conducted using the Way2Drug online tool identified antineoplastic, anti-eczematous, and chemo-preventive effects as the most probable activities of dactyloquinone D (figure 5). Additionally, nephrotoxicity, teratogenicity, and sensitization were determined to be the most likely toxic effects associated with this compound (figure 5). The respective Pa for each of these potential effects and side effects of dactyloquinone D are presented in figure 5.

Each of the compounds dysidavarone D, smenohaimien F, and sollasin E demonstrated a strong affinity towards a specific apoptotic receptor (table 4). These compounds underwent pharmacological prediction analysis using the ProTox-II and Way2Drug online tools, and the results of this analysis are presented in figure 6.

All mentioned compounds exhibited antineoplastic properties (figure 6), and some, such as dysidavarone D and smenohaimien F, showed potential as anti-lung cancer drugs (figure 6). On the other hand, these components were found to have different toxic effects based on the analysis conducted using the Way2Drug online tool, including toxicity, nephrotoxicity, sensitization, and dermatotoxicity (figure 6). Additionally, the ProTox-II analysis classified dysidavarone D, smenohaimien F, and sollasin E into toxicity classes V, V, and IV, respectively (figure 6). Detailed information regarding the pharmacological analysis can be found in figure 6.

Evaluation of the Effects of All Mentioned Alkaloids and Sesquiterpenes on the Mechanism of Activation of Toxicity Pathways in Normal Cells

Table 6 presents a comprehensive list of diverse effects associated with the use of dactyloquinone B, C, and D, smenohaimien F, as well sollasin E as drugs, as analyzed by the ProTox-II online tool.

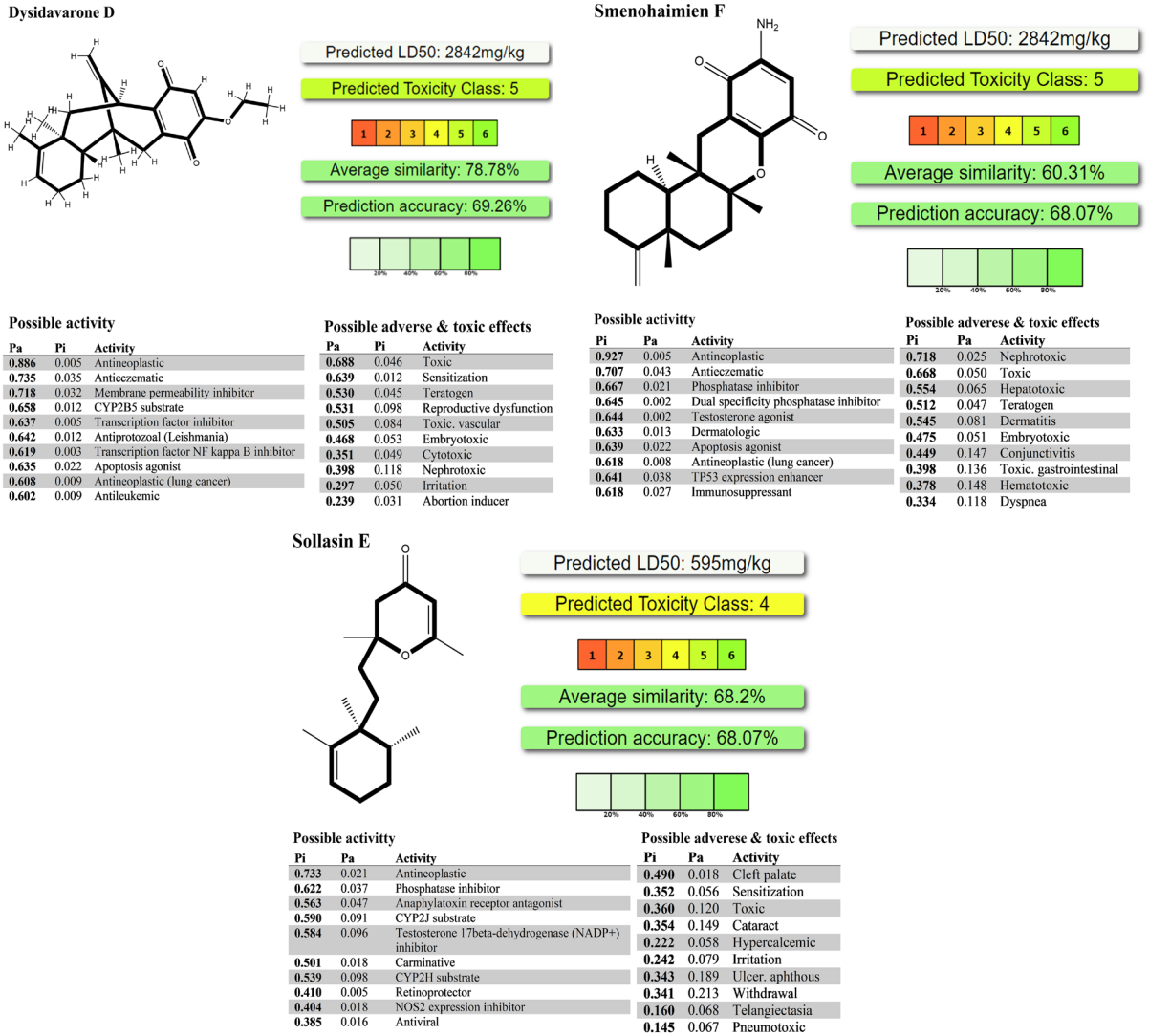


Figure 6: The 2D structures, toxicity classifications, potential activities, and possible side effects of dysidavarone D, smenohaimien F, and sollasin E as potential drug candidates. The figure displays the probability of activity (Pa) and the probability of inactivity (Pi) for each predicted activity and toxic effect.

Table 6: A comprehensive list of diverse effects associated with the use of bioactive compounds from marine sponges as potential anti-lung cancer drugs

Compound	Type	Classification	Target	Probability
Dactyloquinone B	Sesquiterpenes	Toxicity end points	Carcinogenicity	0.51
			Immunotoxicity	0.97
		Nuclear receptor signaling pathways	Aromatase	0.56
Dactyloquinone C	Sesquiterpenes	Toxicity end points	Carcinogenicity	0.51
			Immunotoxicity	0.98
		Nuclear receptor signaling pathways	Aromatase	0.56
Dactyloquinone D	Sesquiterpenes	Toxicity end points	Carcinogenicity	0.53
			Immunotoxicity	0.99
		Toxicity end points	Cytotoxicity	0.70
Dysidavarone D	Sesquiterpenes	Toxicity end points	Carcinogenicity	0.55
			Immunotoxicity	0.98
Smenohaimien F	Sesquiterpenes	Toxicity end points	Carcinogenicity	0.53
			Immunotoxicity	0.89

These effects include the potential to induce carcinogenicity and immunotoxicity in normal cells (table 6). Additionally, dactyloquinone B and C were found to impact nuclear receptor signaling pathways, leading to the activation of aromatase and subsequent cell toxicity (table 6). Moreover, dactyloquinone D exhibited cytotoxic effects, while all these five compounds showed immunotoxic impacts (table 6). The table also provides the Pa associated with each of these effects.

Furthermore, the impacts of dactyloquinone B, C, and D, smenohaimien F, as well sollasin E on various organs, their effects on cytotoxic pathways in normal cells (such as nuclear receptor signaling pathways and stress response pathways), and their toxicity endpoints are listed in supplementary tables (S1-S6). These tables provide a comprehensive overview of the toxicological effects and pathways associated with these compounds in the context of anti-lung cancer activity.

Detailed information about the mechanism of apoptosis induction in lung cancer cells by these alkaloids and sesquiterpenes is presented in figure 7.

Discussion

Alkaloids are a significant group of compounds derived from marine sponges, known for their diverse biological activities such as anticancer, antimicrobial, and anti-inflammatory effects. Several alkaloids, including manzamine A, aaptamine, and aeroplysinin-1, have been extensively studied for their biological functions, particularly their anticancer properties.[26] Previous research has consistently highlighted alkaloids derived from marine sponges as valuable sources of bioactive compounds with potential anticancer properties, drawing the attention of researchers in recent years.[9] Our study reinforces this finding, as alkaloids emerged as an attractive keyword in investigations exploring the anticancer features of marine sponge-derived compounds.

Sesquiterpenes, another group of marine-derived components, have also demonstrated remarkable anticancer effects. For instance, ilimaquinone, extracted from Halichondria sp., has exhibited anti-tumoral effects against various types of cancer cells, including multiple myeloma, colon, breast, and prostate cancer.[27] A previous study has shown that sesquiterpenes possess anticancer activities against different tumor types, such as eye, stomach, kidney, and brain cancers.[28] Our study highlights the growing interest in evaluating the role of sesquiterpenes in the anticancer properties of marine sponge-based compounds.

Furthermore, quinones have shown their anticancer potential when combined with other components. These compounds have exhibited various biological effects, including cytotoxic effects.[29] Consequently, they have emerged as one of the most frequently studied keywords in research exploring the anticancer impacts of marine sponges.

Previous studies have highlighted the importance of activating specific receptors to trigger an apoptotic cascade in lung cancer cells. These receptors include Fas receptor, TNFR1, DR4, and DR5. The initiation of this cascade involves the activation of Fas-associated death domain protein (FADD), which ultimately leads to the activation of caspase-3, -6, -7, -8, and -9 and the induction of apoptosis.[30] Among alkaloids, hyrtioerectine F and between the sesquiterpenes, nakijinol B demonstrated the strongest binding affinity to Fas receptor).

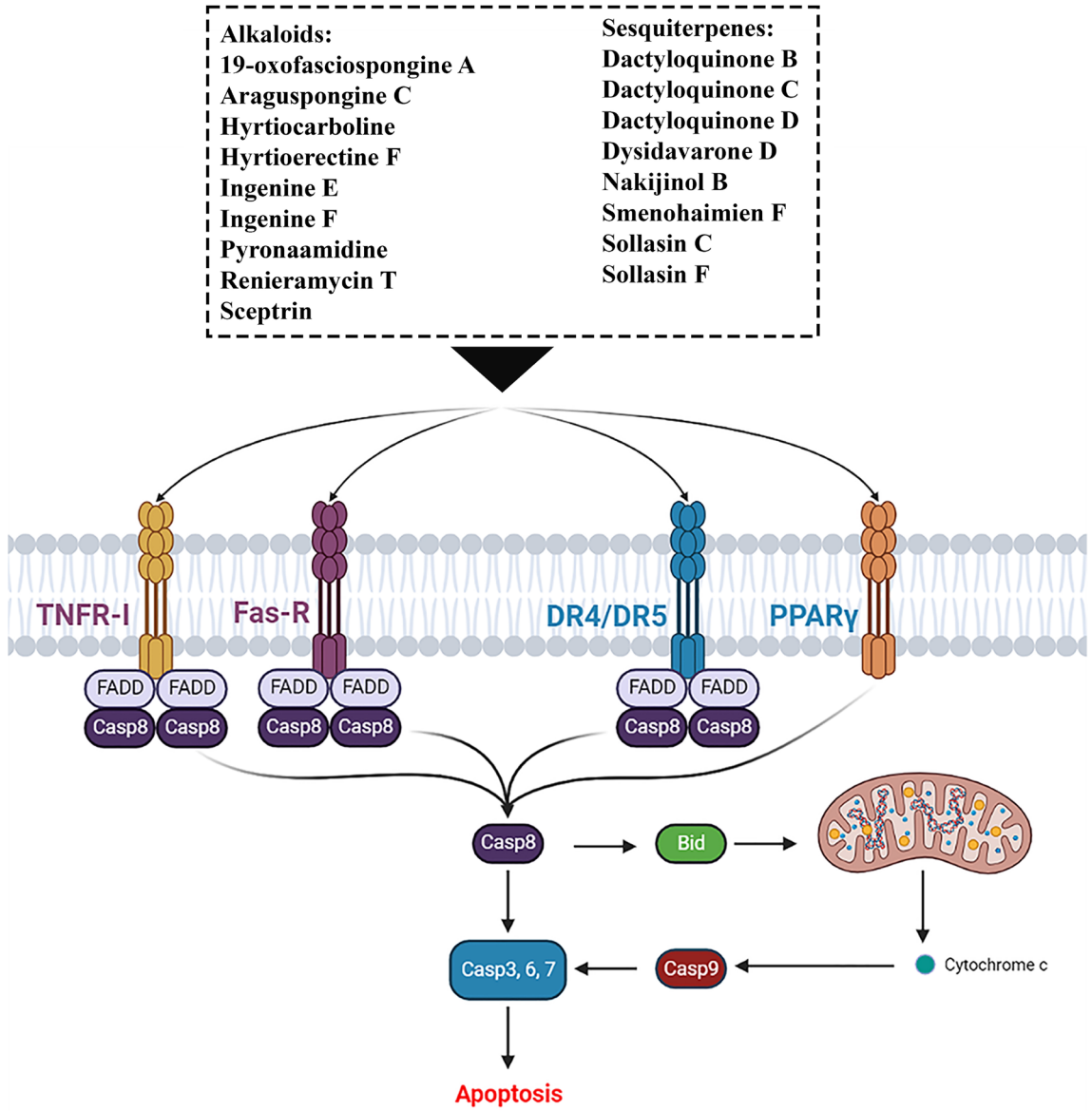


Figure 7: The mechanisms of apoptosis induction in lung cancer cells by alkaloids and sesquiterpenes derived from marine sponges. The figure illustrates the pathways through which these compounds trigger apoptosis in lung cancer cells.

Moreover, between all chosen alkaloids and sesquiterpenes, sceptrin, and hyrtiocarboline showed the highest affinity to DR4 and DR5, respectively. While dactyloquinone C had the highest *in-silico* tendency to both mentioned receptors. Furthermore, renieramycin T and smenohaimien F displayed the highest *in-silico* tendency towards TNFR1.

Furthermore, the activation of certain receptors such as PPAR-γ can induce apoptosis in various cells, including lung cancer cells, through both PPAR-γ-dependent and PPAR-γ-independent pathways. However, the mechanism of apoptosis induction in lung cancer cells by marine-derived alkaloids and sesquiterpenes is through the PPAR-γ-independent pathway.[31] In this pathway, PPAR-γ activation leads to the initiation of a caspase cascade, resulting in apoptosis in lung cancer cells.[32] Interestingly, both araguspongine C and dactyloquinone C exhibited high affinity to PPAR-γ, suggesting that these two components can stimulate apoptosis in lung cancer cells by activating these receptors.

Moreover, both CB1 and CB2 receptors can trigger apoptosis in lung cancer cells by inducing the activation of Fas and PPAR-γ receptors, creating an apoptotic environment in these cells.[30] Molecular docking analysis revealed that among all elected alkaloids, ingenine E, and hyrtioerectine F displayed the strongest binding affinity to CB1 and CB2, respectively. On the other side, among selected sesquterpenes, sollasin E, and dactyloquinone B had the most tendency to CB1 and CB2, respectively.

This finding aligns with previous studies highlighting the anti-lung cancer properties of these two components.

Furthermore, caspase-3, -7, -8, and -9 have been known to play crucial roles in the apoptosis process in various cell types, including lung cancer cells. These apoptotic factors have been valuable targets for the development of anticancer drugs due to their involvement in triggering apoptosis.[33] Among the alkaloids analyzed in our research, 9-oxofasciospongine A, sceptrin, araguspongine C, and hyrtiocarboline exhibited the highest binding affinity to caspase 3, 7, 8, and 9, respectively. Among the analyzed sesquiterpenes, dactyloquinone C showed the strongest tendency towards caspase-3 and -8, while dactyloquinone D had the highest *in-silico* affinity to caspase 3. Moreover, langcoquinone D showed the greatest affinity to caspase-7, and sollasin C demonstrated the highest tendency towards caspase-9.

Our findings highlight the involvement of various apoptotic receptors in the apoptosis process of lung cancer cells, including TLR9, mGluR8, PGD2R, and TGFBR2, with their activation promoting apoptosis.[30] In our *in-silico* analysis, among the alkaloids, araguspongine C and hyrtiocarboline exhibited the highest affinity to TLR9; hyrtiocarboline had the strongest tendency to mGluR8, and araguspongine C demonstrated the highest binding affinity to both PGD2R, and TGFBR2. While among the sesquiterpenes, dactyloquinone C and B showed the highest affinity to TLR9 and mGluR8, and nakijinol B and sollasin C displayed the highest affinity to PGD2R and TGFBR2, respectively.

Conversely, certain receptors can enhance the survival of lung cancer cells, such as IGFR1, which is associated with cell survival, metastasis, and drug resistance in lung cancer.[34] Other receptors, including TLR4 and EPCR, can also promote cell survival in lung cancer through different pathways.[35] Araguspongine C exhibited the highest binding affinity to IGFR1, TLR4, and EPCR (table 7), while dactyloquinone C showed the highest affinity to IGFR1 and TLR4, and pyronaamidine demonstrated the highest affinity to EPCR. On the other side, smenohaimien F showed the most tendency to IGFR1, and sollacin C had the highest affinity to both TLR4 and EPCR. Therefore, we

Table 7: Various binding affinities between each alkaloid and apoptotic receptor in lung cancer cells

Alkaloids	Receptors																	
	Fas R	TNFR1	DR4	DR5	IGFR1	PPAR-γ	Caspase-3	Caspase-7	Caspase-8	Caspase-9	CB1	CB2	TLR- 4	TLR- 9	EPCR	mGluR 8	PGD2R	TGFBR2
19-oxofascio-spongine A	-6.2	-6.8	-6.7	-7.2	-8.5	-7.8	-9.0	-7.6	-6.4	-7.9	-7.8	-7.4	-7.3	-7.9	-10.0	-7.1	-9.6	-6.4
1H-indole-3-carboxylic acid	-5.2	-5.3	-5.7	-5.4	-5.8	-6.4	-5.9	-5.6	-4.9	-5.5	-6.4	-6.5	-6.7	-6.8	-7.7	-5.3	-6.1	-4.9
3-dodecyl pyridine	-4.6	-5.3	-4.3	-4.8	-5.0	-6.2	-4.8	-4.9	-4.5	-4.8	-6.4	-6.5	-4.5	-5.1	-8.1	-4.9	-6.1	-4.3
Acanthodendr illine	-5.4	-5.7	-5.9	-5.4	-6.1	-6.0	-6.8	-6.4	-5.0	-5.4	-6.4	-8.1	-6.0	-6.5	-7.5	-6.1	-7.5	-5.4
Araguspongine C	-7.1	-7.3	-7.4	-7.3	-9.2	-9.6	-8.7	-7.7	-7.3	-8.0	-8.4	-9.2	-7.7	-8.8	-8.3	-9.0	-10.3	-6.9
Clerodane Diterpene	-6.0	-6.8	-6.1	-6.5	-6.5	-6.7	-6.7	-6.8	-6.0	-6.0	-7.8	-9.4	-6.3	-6.9	-8.5	-6.0	-8.4	-5.5
Hyrtiocarboline	-6.6	-7.2	-6.9	-7.9	-8.8	-8.1	-8.5	-8.0	-6.7	-8.1	-7.4	-9.4	-7.5	-8.8	-8.7	-9.3	-7.8	-6.2
Hyrtioerectine D	-7.2	-7.5	-6.7	-7.6	-8.2	-8.5	-8.5	-7.6	-6.9	-7.0	-8.7	-9.3	-7.1	-8.4	-9.9	-7.5	-8.9	-6.3
Hyrtioerectine E	-7.2	-7.0	-6.9	-7.6	-7.8	-8.7	-8.5	-7.9	-6.8	-7.2	-8.6	-9.5	-7.5	-8.3	-8.6	-7.3	-9.0	-6.3
Hyrtioerectine F	-7.4	-7.0	-6.9	-7.7	-7.7	-8.0	-8.5	-7.6	-7.0	-7.3	-8.9	-9.7	-7.3	-8.6	-8.8	-7.1	-9.2	-6.5
Ingenine E	-7.3	-8.0	-6.9	-7.7	-8.1	-8.2	-8.5	-7.6	-7.1	-7.3	-9.0	-9.5	-7.1	-8.6	-8.8	-7.1	-9.2	-6.5
Ingenine F	-6.2	-7.1	-6.2	-6.8	-6.6	-7.2	-6.9	-6.7	-6.2	-6.4	-8.4	-8.6	-7.7	-8.1	-8.6	-6.8	-7.9	-5.9
Pyronaamidine	-6.3	-7.3	-6.6	-6.8	-8.4	-7.5	-8.2	-7.5	-6.0	-7.2	-7.5	-7.3	-6.5	-6.8	-10.4	-7.6	-8.7	-6.0
Renieramycin M	-6.5	-7.4	-7.3	-6.7	-7.6	-7.9	-7.6	-7.3	-6.2	-6.5	-7.3	-7.4	-6.2	-7.0	-7.7	-6.6	-8.5	-6.1
Renieramycin T	-7.2	-8.6	-7.3	-6.6	-7.2	-8.3	-8.0	-7.8	-7.1	-6.7	-8.0	-7.2	-6.5	-7.8	-8.3	-6.8	-8.5	-6.1
Sceptrin	-7.3	-7.7	-7.7	-7.4	-8.1	-8.3	-8.2	-8.1	-7.1	-7.3	-7.7	-9.3	-7.5	-8.3	-10.1	-7.3	-9.5	-6.8

propose that araguspongine C, dactyloquinone C, smenohaimien F, and sollacin C may exert their anti-lung cancer effects by targeting these apoptotic receptors or inhibiting IGFR1, EPCR, and TLR4.

Based on previous surveys about the analysis of SwissADME online tool,[36] if all four criteria (LIPO: lipophility, SIZE: size, POLAR: polarity, INSOLU: solubility, INSATU: saturation, FLEX: flexibility) of the selected compound were located inside the pink hexagon, the manufacturing of this compound as a drug, will be safe. On the other side, figure 5 demonstrates that all four mentioned criteria for dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E are located in pink hexagon. This demonstrates that all of these four components have an acceptable safety.[36]

Moreover, earlier studies have mentioned that if the amount of Consensus Log Po/w and Log S (ESOL) for a compound is less than 5 and -10, respectively, that component has good lyophilization and water solubility.[36] Notably, the analysis of SwissADME demonstrated that dactyloquinone B, C, and D, dysidavarone D, smenohaimien F, as well as sollasin E, have a good capability for lyophilization and water solubility because the range of their Consensus Log Po/w and Log S (ESOL) is less than 5 and less than -10.

Besides, all mentioned compounds demonstrated a high gastrointestinal (GI) absorption. This result confirms some of the findings of the ProTox-II online tool, which are displayed in figures 5 and 6. For instance, the toxicity class of sollasin E is IV, which means it will be harmful if swallowed. The toxicity grade for dactyloquinone B, C, and D, dysidavarone D, as well as smenohaimien F, is V, which means they may be harmful if swallowed. Interestingly, these findings are confirmed by the results of the analysis of SwissADME (table 5). In other words, all of the mentioned components have a high GI absorption, which can be harmful or even toxic if an excessive amount of them is used orally.

Another remarkable finding in the analysis of SwissADME is the blood-brain barrier (BBB) permeability of dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E. All of them can cross the BBB. These results endorse the findings about the adverse and toxic effects of the mentioned compounds as a drug. In other words, dactyloquinone B, C, D, dysidavarone D, and sollacin E have some side effects including withdrawal, dependence, irritation, and depression. Briefly, the probability of some complications in the mentioned compounds as a drug are confirmed by the analysis of SwissADME.

On the other side, four components including dactyloquinone B, C, D, dysidavarone D, and sollacin E have negative P-gp substrate (which represents the ability of the compound to exit from cells through attaching to the glycoproteins of plasma membrane). This means that when these five compounds enter the cells, they cannot go out easily through the plasma membrane, and their concentration in cells will not be decreased, and cells can keep them for a long time. On the other side, smenohaimien F has a positive P-gp substrate, and this component as a drug will easily flow out of cells. Thus, its concentration in various cells will be low, and they need higher dosages to exert their effect.[37]

Another result obtained from the analysis of SwissADME was skin permeability. Based on surveys, the more negative the log Kp (cm/s) is, the less skin permeant is the molecule.[36] Therefore, the log Kp for dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E was between -4 to -6. On the other side, the analysis of all remarked compounds with Way2Drug online tool showed that dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E may cause sensitization, ulcer, aphtus, and dermatitis as a drug. Hence, the results of SwissADME conform to the findings from Way2Drug online tool.

Furthermore, based on the analysis of SwissADME, three components of dactyloquinone B, C, and D, dysidavarone D, smenohaimien F as well as sollasin E have an acceptable drug-likeness. Besides, these six compounds have a bioavailability score of 85%, which means that they have a great bioavailability for manufacturing drugs. Notably, 19-oxofasciospongine A, araguspongine C, hyrtiocarboline, hyrtioerectine F, ingenine E, ingenine F, nakijinol B, pyronaamidine, and sollasin C have a good drug-likeness according to three of four remarked methods. They have also a bioavailability score of 55%, which is an acceptable bioavailability score, based on previous surveys.

Finally, another fascinating result of SwissADME analysis about selected compounds is their synthetic accessibility (SA). Based on prior surveys, synthetic accessibility is defined as the ease of synthesis and obtaining the mentioned molecule, which is scored from 1 to 10 (1 means easy to produce and 10 means very hard to manufacture).[36] Thus, based on table 5, the SA for all selected compounds is between 4 to 6. This means that all remarked components have a moderate hardship in being produced.

Dactyloquinone B, C, and D exhibit antineoplastic properties with significant Pa. Previous studies have highlighted their effectiveness against various cell lines, indicating their potential for lung cancer treatment.[23] Furthermore, these compounds show additional potential effects such as antieczematous activity, phosphatase inhibition, apoptosis agonist, and chemoprevention. Interestingly, the pharmacological analysis conducted using the Way2Drug online tool reveals that dactyloquinone B, C, and D have the ability to suppress the immune system in humans. This finding aligns with the results from the ProTox-II online tool analysis, which indicates a high probability (97% to 99%) of toxic effects on normal human cells. While dactyloquinone B, C, and D demonstrate potent potential for inhibiting lung cancer cells, their immunosuppressive properties may impact their future use as anticancer drugs.

Dysidavarone D is a notable compound derived from marine sponges that show potential as drugs against various cancers, as indicated by the analysis conducted using the Way2Drug online tool. Previous studies have demonstrated the anticancer effects of these compounds *in vitro* conditions, with dysidavarone D exhibiting cytotoxic effects on HeLa, A549, MDA231, and QGY7703 cell lines.[38] Therefore, our analysis aligns with these previous *in vitro* studies. Furthermore, the analysis reveals that dysidavarone D has the potential to be utilized as an anti-lung cancer agent, with Pa of 60%. In conclusion, this marine-derived compound demonstrated a striking potential for being used as future anti-lung cancer drug. *In-vitro* and *in-vivo* experiments are needed to endorse this *in-silico* finding.

Our pharmacological prediction analysis using the Way2Drug online tool revealed that smenohaimien F shows potential as a future drug with diverse activities, including enhancement of TP53 expression. A previous study has highlighted the role of TP53 expression in suppressing different kinds of cancer, including lung cancer, suggesting that increasing the expression of TP53 could be important for inhibiting lung cancer cells.[39]

Additionally, smenohaimien F demonstrated dual specificity phosphatase inhibition properties with a probability of 64%. Dual specificity phosphatases (DUSPs) promote the activity, proliferation, and migration of lung cancer cells, and inhibiting this factor has been shown to enhance the immune system's response against lung cancer cells.[40]

Furthermore, other possible effects of smenohaimien F are displayed in figure 6. Based on previous studies and the analysis from the Way2Drug online tool, smenohaimien F appears to hold promise as a potent anti-lung cancer compound. Although further *in vitro* and *in vivo* research is needed to fully evaluate its potential.

According to the pharmacological prediction analysis conducted using the Way2Drug online tool, sollasin E shows potential activities as a drug, including phosphatase inhibition, anaphylatoxin receptor antagonist, and nitric oxide synthase (NOS2) expression inhibition with Pa of 62%, 56%, and 40%, respectively. Phosphatases, including protein phosphatase 2A (PP2A), is involved in the progression of chronic obstructive pulmonary disease (COPD) to lung cancer. Thus, early surveys have displayed that these sorts of enzymes can facilitate cancer in the human lung.[41] Besides, based on previous surveys, the trigger of anaphylatoxin receptor creates a favorable microenvironment for lung cancer progression.[42] Furthermore, NOS2 can raise lung carcinogenesis and inflammation through induction of KRAS pathway.[43] Therefore, our results are in line with the findings of prior research. However, it is important to note that although the Pa of these activities range from 42% to 65%, further *in vitro* and *in vivo* studies are needed to determine the exact impacts of sollasin E. Overall, this analysis highlights the potential of sollasin E as a valuable anticancer agent that has the ability to induce apoptosis in lung cancer cells.

Based on our analysis, the potential adverse and toxic effects of the selected alkaloids and sesquiterpenes as drugs can be categorized into seven groups, as listed in table 8. Additionally, a previous study has shown that eribulin mesylate (EM),[26] derived from the marine sponge Porifera *Halichondria okadai*, is the only anticancer drug approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of metastatic and locally advanced breast cancer. However, EM is associated with adverse effects such as neutropenia, leukopenia, anemia, and febrile neutropenia in cancer patients.[44] These findings are consistent with our present results. Furthermore, our analysis using the ProTox-II online tool indicates that dactyloquinone B, C, and D, as well as smenohaimien F have a high probability (97-99%) of immunotoxic effects. EM, E7974, and PM060184 are three agents with anticancer effects that have been associated with toxic effects such as neutropenia and thrombocytopenia.[26]

Despite the numerous studies conducted on the anti-lung cancer effects of marine sponge-derived compounds, including the present study, there is a lack of sufficient clinical trials in this

Table 8: The most possible adverse and toxic effects of both chosen sesquiterpenes as a drug

Compounds	Respiratory toxicity		Eye toxicity		Nephrotoxicity		Sensitization		Toxic/Cytotoxic		Electrolyte/ Metabolic disorders		Reproductive/ Gynecologic disorders		Psychological disorders	
	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)	Active (%)	Possibility (%)
Dactyloquinone B			+	38	+	37	+	53	+		+	50	+	35	+	50
Dactyloquinone C			+	48	+	47	+	55	+	51	+	47	+	32	+	47
Dactyloquinone D			+	39	+	57	+	39	+		+	46	+	41		
Dysidavarone D	+	53			+	39	+	63	+	68			+	53		
Smenohaimien F	+	33	+	44	+	71			+	66			+	51		
Sollasin E	+	14	+	35			+	35	+	36	+	22	+	49	+	24

field.[26] Although our study demonstrated the potential anti-lung cancer properties of marine sponge-derived compounds through *in-silico* analysis and pharmacological predictions using online tools, further *in vitro*, *in vivo*, and clinical trials are essential to validate these findings.

Additionally, this study has provided valuable insights into the anti-lung cancer compounds derived from marine sponges, which can guide researchers in the development of novel anti-lung cancer agents. This is particularly significant considering the limited number of anticancer drugs approved by the FDA for cancer treatment.[26]

The advantages of this study are underscored by the explicit application of *in-silico* tools, which offer significant strengths for preliminary assessments of anti-lung cancer compounds derived from marine sponges. Utilizing platforms such as SwissADME, ProTox-II, and Way2Drug enables the evaluation of critical pharmacokinetic properties, including bioavailability, solubility, and toxicity profiles, thereby streamlining the drug discovery process. Additionally, the uniqueness of the compounds investigated, particularly the alkaloids and sesquiterpenes, contributes to the novelty of this research, as these classes of marine-derived compounds have demonstrated compelling binding affinities to apoptotic receptors in lung cancer cells. By clearly enumerating these strengths, we highlight the potential for these compounds to serve as innovative therapeutic agents, setting the stage for further exploration and development in clinical applications.

The limitations of this study primarily stem from its reliance on *in-silico* analysis and the inherent challenges associated with such methods. While molecular docking provides valuable insights into the binding affinities of marine-derived compounds to various receptors, it does not fully replicate the complexities of biological systems. Consequently, the findings regarding the anticancer properties of alkaloids, sesquiterpenes, and quinones should be interpreted with caution. Moreover, the study does not include experimental validation of the predicted interactions and effects, which is critical for establishing the clinical relevance of the compounds. Furthermore, the analysis primarily focuses on a specific subset of marine sponge-derived compounds, potentially overlooking other bioactive constituents that may contribute to their anticancer activities. Future studies should aim to integrate *in vitro* and *in vivo* experiments to substantiate the findings and explore the broader spectrum of marine-derived bioactive compounds.

Conclusion

Our bibliometric analysis revealed a growing interest in the anticancer properties of marine sponge-derived compounds, particularly in the classes of alkaloids and sesquiterpenes. Notably, compounds such as dactyloquinone B, C, and D, along with dysidavarone D, smenohaimien F, and sollasin E, exhibited exceptional binding affinities to receptors associated with apoptosis in lung cancer cells. The *in-silico* analysis using tools such as SwissADME, ProTox-II, and Way2Drug further illustrated the favorable bioavailability and potential therapeutic activities of these compounds, alongside possible side effects. Collectively, these findings underscore the importance of these marine-derived agents as promising candidates for developing novel anti-lung cancer therapies. However, to fully harness their therapeutic potential, comprehensive *in vitro* and *in vivo* studies, followed by clinical trials, are essential. This research not only paves the way for future studies but also emphasizes the urgent need for innovative approaches in the fight against lung cancer.

Authors' Contribution

A.Z: Study concept, data gathering, investigation, data analysis, study design, software, validation, and drafting; A.A: Study concept, investigation, data analysis, and reviewing the manuscript; NM.M: Study concept, investigation, resources, and reviewing the manuscript; AA.K: Data gathering, study design, resources, validation, and reviewing the manuscript; RA.A: Study concept, study design, and reviewing the manuscript; N.T: Study concept and reviewing the manuscript; M.M: Study concept and reviewing the manuscript; F.R: Study concept, supervision and reviewing the manuscript; Zh.Zh: Project administration and reviewing the manuscript; B.BT: Resources, software, and reviewing the manuscript; A.T: Study concept, data gathering, study design, project administration, software, supervision, validation, and reviewing the manuscript; All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Conflicts of Interest

The authors Afshin Zare, Alireza Afshar, Nader Tanideh, and Amin Tamadon are employed by PerciaVista R&D Co. The remaining authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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