ChemBioChem

Review
doi.org/10.1002/cbic.202300346

Chemistry Europe
European Chemical Societies Publishing

www.chembiochem.org

Terpenoids as Human Neutrophil Elastase (HNE) Inhibitors: A Comprehensive Review of Natural Anti-inflammatory Isoprenoids

Muhammad Imran Tousif,[a] Mamona Nazir,[b] Naheed Riaz,[c] Muhammad Saleem,[c] Saba Tauseef,[d] Sheikh Muhammad Azam,[e] Mirza Arfan Yawer,[a] and Gokhan Zengin*[f]

Human neutrophil elastase (HNE) is an enzyme that plays a key role in the body's inflammatory response. It has been linked to several diseases such as chronic obstructive pulmonary disease (COPD), emphysema, and cystic fibrosis. As potential treatments for these diseases, HNE inhibitors are of great interest. Metabolites derived from plants, particularly terpenoids such as β-caryophyllene found in black pepper and other plants, and geraniol present in several essential oils, are recognized as significant sources of inhibitors for HNE. Because of their ability to inhibit HNE, terpenoids are considered promising candidates for developing novel therapies to treat inflammatory conditions such as COPD and emphysema. Furthermore, nature can serve as an excellent designer, and it may offer a safer drug candidate for inhibiting HNE production and activity in the future. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses were searched to get relevant and up-to-date literature on terpenoids as human neutrophil elastase inhibitors. This review focuses on the isolation, chemical diversity, and inhibition of human neutrophil elastase (HNE) of various terpenoids reported from natural sources up to 2022. A total of 251 compounds from various terpenoids classes have been reported. Further, it also provides a summary of HNE inhibitors and includes a thorough discussion on the structure-activity relationship.

1. Introduction

The enzyme elastase is a serine protease with a known structure and established sequence. In addition to several functions associated with elastase, it destroys collagen, elastin, fibronectin, and extra-cellular matrix components by breaking down the C terminus of hydrophobic amino acids such as glycine, alanine, and valine.[1] Elastase is initially synthesized as a zymogen in the pancreas and requires activation by trypsin in the duodenum. Once activated, it plays a substantial role in the digestion of elastin, a protein that provides elasticity to tissues.

Elastase has demonstrated its potential in medical science, particularly in the development of immunizations against the H1 N1 virus, commonly known as "swine flu." Elastase-dependent swine influenza virus (SIV) mutants have been identified as potential candidates for live-virus vaccines against swine influenza in pigs.[2] According to research, utilizing elastase as an adjuvant resulted in a stronger antibody response than using other proteases or nonproteases as adjuvants.[3]

Elastase can also assist in the easier digestion of milk caseins. Santillo's article, "Role of indigenous enzymes in proteolysis of casein in caprine milk," assesses the casein hydrolysis activity of the primary indigenous proteolytic enzymes in caprine milk as well as the potential significance of indigenous enzymes for goat milk and dairy product quality.[4] Based on their structural traits and roles, elastases 1 and 2 are just two of the many types of elastase that have been identified. Pancreatic elastase, also known as elastase 1, is primarily responsible for breaking down elastin in humans, while neutrophil elastase, also known as elastase 2, is crucial for destroying germs during inflammation.

According to Berg, elastase enzyme specifically cleaves peptide bonds after amino acids with small side chains, such as alanine, glycine, and serine. This property of elastase makes it well-suited for breaking down elastin protein by cleaving

[a] Dr. M. I. Tousif, Prof. Dr. M. Arfan Yawer
Department of Chemistry
Division of Science and Technology
University of Education
54770 Lahore (Pakistan)

[b] Dr. M. Nazir
Department of Chemistry
Government Sadiq College
Women University Bahawalpur
63100-Bahawalpur (Pakistan)

[c] Prof. Dr. N. Riaz, Prof. Dr. M. Saleem
Institute of Chemistry
Baghdad Campus the Islamia University of Bahawalpur
63100-Bahawalpur (Pakistan)

[d] S. Tauseef
Dr. Panjwani Center for Molecular Medicine and Drug Research
International Center for Chemical and Biological Sciences
University of Karachi
75270 Karachi (Pakistan)

[e] S. M. Azam
Department of Zoology
Division of Science and Technology
University of Education Lahore
75270 Lahore, Punjab (Pakistan)

[f] Prof. Dr. G. Zengin
Department of Biology
Science Faculty
Selcuk University
42130 Konya (Turkey)
E-mail: gokhanzengin@selcuk.edu.tr

peptide bonds within it, thus aiding in the digestibility of this elastic protein.[5] Elastase accelerates the cleavage of peptide bonds in elastin at an incredibly fast rate, completing the reaction within milliseconds, which is approximately 10^{17} times faster than the rate of reaction without the enzyme. This remarkable activity of elastase significantly aids in the digestion of elastin-rich foods, such as meat, by breaking down the protein into smaller, more manageable fragments that can be further digested and absorbed by the body.

Although elastase has several positive attributes in terms of its role in digestion and immune response, when it is not functioning correctly, it can have devastating effects and cause significant damage to the host. In this regard, elastase is known to be one of the most destructive enzymes as it can degrade almost all of the connective components present in the body. This unrestricted activity of elastase can lead to tissue damage and various pathological conditions, including emphysema; which is characterized by the loss of elasticity in the lungs and

Muhammad Imran Tousif is an Associate Professor at the Department of Chemistry, University of Education in Lahore. He obtained his PhD degree from Institute of Chemistry, The Islamia University of Bahawalpur. His field of research is natural product chemistry of medicinal plants, endophytic fungi and bacteria. He has published more than 47 scientific papers in peer reviewed international journals, supervised several MS and PhD students. He is a reviewer for several leading scientific journals

Mamona Nazir has worked as an Assistant Professor in the Department of Chemistry, Government Sadiq College Women University (GSCWU) Bahawalpur since 2016. She obtained her PhD degree in 2015 from University of Bonn, Germany, where she also worked for few months as research assistant and as a consultant with a pharmaceutical company, Truesaffaron, for two years. She is supervising several PhD and MS students. Her field of interest is medicinal chemistry/organic and biosynthesis. She has published 39 research articles and also serves as an editorial member of chemistry journals.

Naheed Riaz has been a Professor of Chemistry at the Institute of Chemistry, The Islamia University of Bahawalpur (IUB) since 2007. He has worked in different institutions in Pakistan as well as in Germany. His field of research is natural product chemistry of medicinal plants, bacteria and fungi. He has supervised several MPhil and PhD students and published more than 120 research articles with >2200 citations and has an h-index of ~23.

Muhammad Saleem has been working as a full Professor at the Institute of Chemistry, The Islamia University of Bahawalpur (IUB) since 2007. He also worked in different institutions in Germany and South Korea. His field of research is the natural product chemistry of medicinal plants, marine algae and endophytic fungi. He has supervised several MPhil and PhD students and published more than 160 research/review articles with >3600 citations; he has a research interest score of ~2295 and an h-index of >28.

Saba Tauseef is a doctoral student at the Dr Panjwani Centre for Molecular Medicine and Drug Research, University of Karachi. Her master's dissertation focused on expression studies of site-directed mutations on the human epidermal growth factor expressed by Pichia pastoris. She has written 14 scientific publications. Her current research focuses on computational approaches to discovering possible enzyme inhibitors and computational analysis of peptides and analogues against drug resistance pathogens.

Sheikh Muhammad Azam is a Lecturer at the Department of Zoology, University of Education Lahore. His MS thesis was on the breeding and mortality of lions and tigers in captivity and PhD thesis was on Talang queenfish exploring its digestive enzymes, body composition, morphometrics & elemental composition. He has authored 45 original scientific papers. His current scientific interest includes ethnozoology, fisheries and wildlife management. He is also reviewer of various scientific journals.

Mirza Arfan Yawer (Wv.S.A) is a Professor of Chemistry at the University of Education Lahore. He obtained his PhD in chemistry from University of Rostock, Germany, in 2008 and did a postdoc at Erlangen University, Nuremberg, Germany, under the DFG program, He also worked at Masaryk University Research Center for Toxic Compounds in the Environment (RECETOX) in Brno, Czech Republic, as a senior researcher from 2012 to 2017. He was honored with the Werner von Siemens Excellence Award 20015/16 in Prague, Czechia, on the development of receptors for the recognition and transportation of inorganic anions in water. He has published 35 papers.

Prof. Dr. Gokhan Zengin PhD is a full professor at the Department of Biology, Science Faculty, Selcuk University, Konya. His MSci thesis was on the genus Centaurea and PhD thesis was about the genus Asphodeline. He has authored more than 700 original scientific papers (h-index WoS = 52). His current scientific interests include the biological properties and chemical characterization of medicinal plants, especially Turkish, as well as the antioxidant capacity and inhibition of key enzymes linked to global health problems. He is a reviewer for several leading scientific journals.

pulmonary fibrosis.[5] It is widely believed that uncontrolled elastase activity is a significant contributor to the lung pathology associated with emphysema. The excessive activity of elastase can lead to the destruction of lung tissue, including the alveoli, which are responsible for the exchange of oxygen and carbon dioxide. This damage results in the loss of lung elasticity, reduced lung function, and breathing difficulties.[6] It is also linked to a number of chronic inflammatory disorders, including cystic fibrosis, asthma, chronic obstructive pulmonary disease (COPD), and systemic inflammatory response syndrome, in which the protease-antiprotease system is out of balance.[1,7] Intratracheal elastase instillation has been shown in animal models to elicit alterations such as alveolar space enlargement, alveolar septal thickening, and mucus hypersecretion, which are the same as clinical observations.[8] Furthermore, elastase has been linked to a variety of cellular processes, including cell death, transcriptional and translational regulation, and the processing of pro-inflammatory cytokines, chemokines, and adhesion molecules, all of which contribute to downstream physiological consequences. The dysregulation of elastase activity and its proteolytic products can result in tissue damage, inflammation, and contribute to the pathogenesis of these chronic inflammatory diseases.[7]

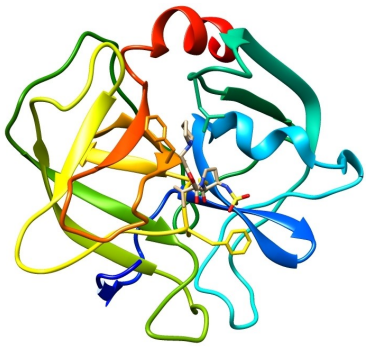
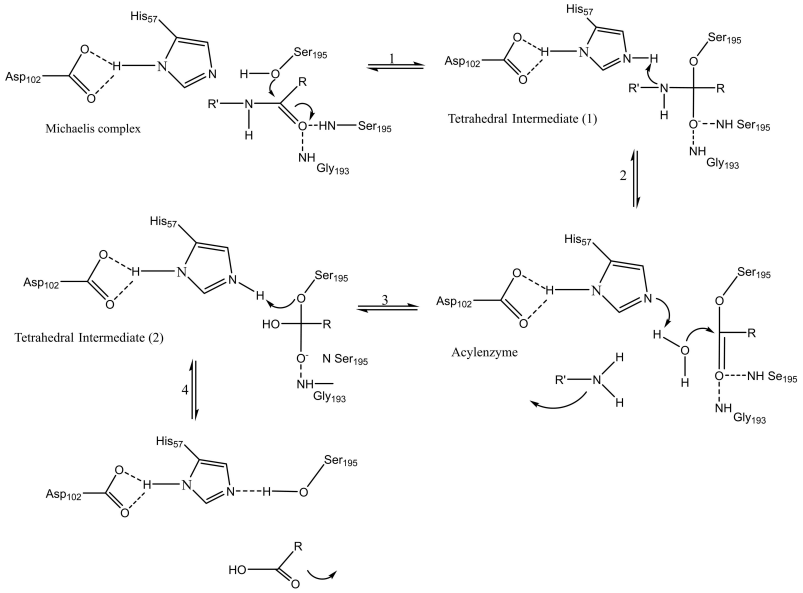


Figure 1. Crystal structure of human neutrophil elastase retrieved from Protein Data Bank (PDB ID: 1H1B).

Human neutrophils have been linked to the pathophysiology of a variety of disorders, including rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ischemia-reperfusion injury, and asthma, as well as host defense against pathogens.[9] However, activated neutrophils release granule proteases, bioactive lipids, neutrophil elastase, a precursor to other reactive oxygen species (ROS), the superoxide anion radical ($O_2^{\bullet-}$), which is a prominent contributor to tissue destruction in chronic inflammatory disorders, in response to diverse stimuli.[9–10] Additionally, it has been suggested that using medications to inhibit elastase, stop neutrophils from activating excessively or inappropriately, and quench superoxide anion radicals could help treat inflammatory diseases.

HNE belongs to the serine protease family and has a compact, globular structure (Figure 1). The enzyme has this characteristic because it is monomeric, or composed of only one polypeptide chain. Polymorphonuclear neutrophils deposit HNE as an active enzyme in their azurophilic granules.[11] The catalytic triad, which consists of the amino acids Asp102, His57, and Ser195, is the catalytic site of this enzyme. During the protease process, His57 functions as a base, Asp102 as an acid, and Ser195 as a nucleophile. It is necessary for the enzyme to have this configuration of residues for it to catalyze the breakdown of proteins.[1] Scheme 1 represents the complete mechanism of action for HNE active site residues. Designing inhibitors that specifically target HNE can be challenging since HNE is one of several serine proteases with similar active sites.[12]

Unfortunately, the present drugs used to treat chronic inflammatory diseases like COPD, asthma, cystic fibrosis, and systemic inflammatory response syndrome only offer symptomatic relief and do not address disease progression, which



Scheme 1. Systematic representation mechanism of action of HNE.[12]

might be linked to the activity of elastase or reactive oxygen species (ROS).[13] Sivelestat is an approved drug that specifically targets and inhibits neutrophil elastase, making it a selective neutrophil elastase inhibitor that can be used to treat inflammatory diseases.[14] Finding new small molecule therapeutics for COPD is critical because the disease has been recognized as a major public health problem, and the World Health Organization (WHO) reports that chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, accounting for 3.23 million deaths in 2019.[15] Designing inhibitors for elastase has proven to be a challenging task due to the shared functions with other serine proteases and a lack of understanding about its role in disease progression. This review article provides a comprehensive overview of natural elastase inhibitors from a variety of natural sources. The inhibitors, classified by their respective classes, have been discussed as potential anti-inflammatory drug candidates.

2. Review Methodology

The use of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards has made for a detailed investigation of scientific literature. Databases such as Ovid (Books, Journals, Cochrane, AMED, Embase, and MEDLINE), Scopus, Google Scholar, PubMed, and Science Direct have been searched up to 2022. Terpenoids, sesquiterpenoids, diterpenoids and triterpenoids as HNE inhibitors were used as search terms to ensure the inclusion of relevant literature. Later, biological activity, pharmacological activity and traditional medical use were added. Boolean operators were used to combine the search terms. Additionally, a comprehensive search of the literature was conducted in an effort to better understand the gray area.

3. Mechanism of Neutrophil Inhibitors

The mechanism of action of neutrophil elastase inhibitors involves the inhibition of the activity of the neutrophil elastase enzyme. Neutrophil elastase is an enzyme that is produced and released by neutrophils, a type of white blood cell, during inflammation. This enzyme can degrade proteins in the extracellular matrix and contribute to lung tissue deterioration in disorders such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, and emphysema.[16] Neutrophil elastase inhibitors work by binding to the active site of the enzyme and preventing it from cleaving and breaking down target proteins. This helps to reduce inflammation and prevent further tissue damage. Some neutrophil elastase inhibitors are designed to mimic the structure of the substrate proteins that the enzyme cleaves, thereby competing with these proteins for binding to the active site of the enzyme. Others are designed to directly bind to the active site of the enzyme and prevent it from cleaving proteins.[17]

4. Terpenoids as HNE Inhibitors

Terpenoids are a class of compounds that are derived from terpenes and are the building blocks of essential oils. These compounds have been found to have various pharmacological activities, including the ability to inhibit neutrophil function, anti-inflammatory activity, antiviral, antibacterial activity as well as aiding in immunomodulation. Neutrophils are a type of white blood cell that play an important part in the immunological response of the body. They are involved in phagocytosis, the process of engulfing and destroying invading microorganisms.[18] Further, terpenoids have been shown to have inhibitory effects on Neutrophil Elastase. They are found in a variety of plants and have a wide range of biological activities, including anti-inflammatory and anti-tumor effects.[19]

Studies have shown that some terpenoids have the ability to bind to and inhibit the activity of Neutrophil Elastase. For example, compounds such as eucalyptol, found in eucalyptus oil, have been shown to have inhibitory effects on neutrophil elastase in vitro.[20] Similarly, compounds such as ursolic acid and oleanolic acid, found in plants such as rosemary and olive oil, have been shown to inhibit the activity of this enzyme.[21] In addition to their inhibitory effects on Neutrophil Elastase, some terpenoids also have antioxidant properties and may help reduce oxidative stress in the lungs, which can further improve lung function in patients with respiratory diseases such as COPD.[22]

Another important feature of terpenoids is immunomodulatory effects, meaning they can help regulate the immune system and maintain its balance.[23] This can be beneficial in conditions where there is an overactive immune response, such as allergies or autoimmune disorders.

In conclusion, terpenoids have the potential to be useful in the treatment of various inflammatory diseases by inhibiting neutrophil function. Further studies are needed to fully understand the mechanisms behind these effects and to determine the optimal dose and administration methods for these compounds. Overall, the research suggests that terpenoids may have potential as therapeutic agents for conditions involving chronic inflammation and overactive immune responses. However, further research is needed to fully understand the mechanism of action and potential therapeutic applications of terpenoids as inhibitors of neutrophils.

4.1. Sesquiterpenoids as HNE inhibitors

A documented anti-inflammatory plant *Inula viscosa* (Asteraceae) produces an anti-inflammatory compound, dehydrocostic acid (**1**), that inhibits elastase activity ($IC_{50} = 43\ \mu M$) and leukotriene B_4 production ($IC_{50} = 22\ \mu M$) in UV/Vis absorbance measuring assay of proteolytic products. Compound **1** fully inhibits the human elastase activity at 100 μM, whereas, the reference drug α-1-antitrypsin showed 84% inhibition at 90 $\mu g\,mL^{-1}$. Further, a comparison of the activity of **1** with another similar sesquiterpene, ilicic acid (**2**) firmly suggests that the presence of a semiplanar ring A in **1** is essential for an

improved inhibitory activity on inflammatory mediators. However, the propenoic chain would not constitute a pharmacophore since it is present in both the compounds **1** and **2** (Figure 2). It is suggested that hydration of the double bond at 4–15 are detrimental for anti-inflammatory, perhaps due to the annulment of the C-15 exomethylene.[24] Although the current data only pertains to dehydrocostic acid (**1**), it is possible that future research on sesquiterpenoids should take into account the presence of multiple olefinic clouds as potential nucleophiles that could enhance their pharmacological activity. This assumption has already been established for sesquiterpene lactones containing an α-methylene function,[25] and it may be necessary to extend it to other unsaturated structures such as sesquiterpene conjugated dienes.

In the Indo-Pacific Ocean, the genus Rumphella (Gorgoniidae) was identified and it contains four species namely *R. aggregata*, *R. antipathies*, *R. attenuata*, and *R. torta*. The most common names of *Rumphella*, are bushy sea rod, gorgonian, sea fan and sea whip.[26] It has a symbiotic association with zooxanthellae, which are micro-marine algae that provide some of their nutrition. This genus is a rich source of caryophyllane-type sesquiterpenes which are usually present in terrestrial plants.[27] A nor-sesquiterpenoids, of caryophyllane-derived class named as kobusone (**3**) is a first isolate of *R. antipathies*.[28] The same source also produces *nor*-sesquiterpenoid, rumphellolide I (**4**; 32.3%inhibited human neutrophil elastase release at 10 $\mu g\,mL^{-1}$), having an ether bridge between C-4 and C-8 as a tetrahydropyran ring.[29] The same source produces rumphellatin D (**5**; having 27.2% inhibition on human neutrophil elastase release at 10 $\mu g\,mL^{-1}$) contains an epoxide between C-3 and C-4 together with primary chloride (Figure 2).[30] Rumphellolide H (**6**) also known ascaryophyllane (synthetic name[31]) having a tetrahydropyran moiety in its structure (was found to show 32.7% inhibitory effect on human neutrophil elastase release at 10 $\mu g\,mL^{-1}$).[32] Clovan-2,9-dione (**7**), displayed significant inhibitory effects ($IC_{50} = 6.73\ \mu g\,mL^{-1}$) on the release of elastase by human neutrophils.[33] Rumphellaoic acid A (**8**), a member of a novel class of sesquiterpenoid a bicyclic compound (containing an eight-membered ring merge with five membered ring) display inhibitory effect on the release of elastase 29.2% at a concentration of 10 $\mu g\,mL^{-1}$.[34] Rumphellols A and B (**9** and **10** Figure 2) exhibited the release of elastase (inhibition rates = 51.64 and 42.10%, respectively) by human neutrophils at concentrations of 42.4 and 37.6 μM (Table 1).[35] The SAR studies reveal that all the caryophyllene-type sesquiterpenes having mostly two rings in the basic class (a four and eight-membered ring/nine-membered) are the inhibitors of elastase with mild potential. However, the conversion of the four-membered into five-membered may enhance the elastase inhibitory potential as shown by the clovan-2,9-dione (**7**; $IC_{50} = 6.73\ \mu g\,mL^{-1}$). The above compounds can be the re-arranged products of the below group of several compounds. *Rumphella antipathies* also produces two 4,5-seco-caryophyllane sesquiterpenoids, rumphellaones B (**11**) and C (**12**) having unprecedented γ-lactone moieties, and could be rearranged and cyclized to form the above compounds and **12** exhibited in vitro anti-inflammatory effects on the release of elastase (inhibition rate = 21.1%) by human neutrophils at a concentration of 10 $\mu g\,mL^{-1}$ (Table 1).[36]

Curcuma longa especially its rhizomes is a rich source of secondary metabolites produces fourteen sesquiterpenoids namely curculonones A–D (**13**–**16**), 6α-hydroxycurcumanolide A (**17**), 1,10-dehydro-10-deoxy-9-oxozedoarondiol (**18**), (*S*)-(+)-*ar*-turmerone (**19**), bisacurone (**20**), curlone (**21**), β-atlantone (**22**), (6*R*)-[(1*R*)-1,5-dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one (**23**), zedoarondiol (**24**), curcumanolide A (**25**) and curcumanolide B (**26**). All the compounds showed elastase inhibition especially the compounds **13**–**15**, **17**, **19**, **23**–**26** (Figure 3) inhibited well the elastase release with IC_{50} values 20.34, 23.52, 21.48, 10.82, 38.98, 36.20, 12.66, 11.70, 12.55 μM, respectively whereas the rest of the compounds have IC_{50} values >50 (Table 1).[37]

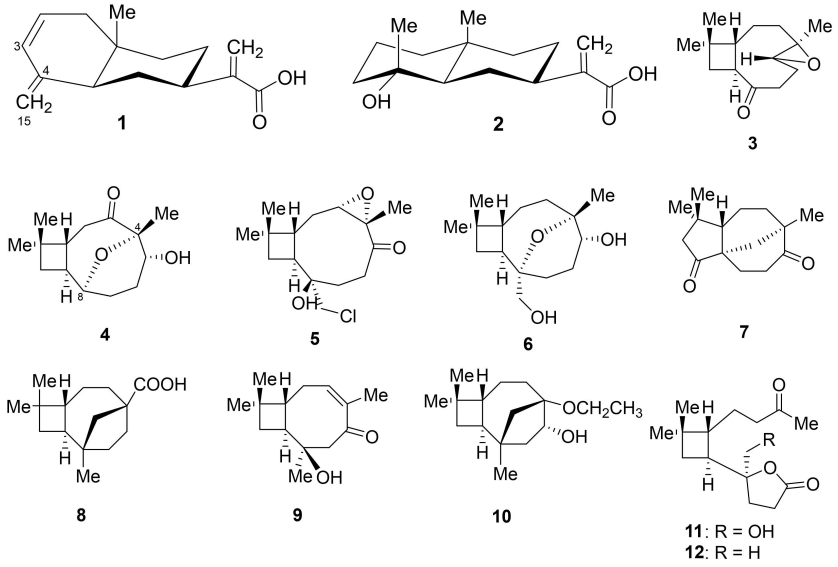


Figure 2. Caryophyllane-type sesquiterpenes (**1**–**12**) isolated from various natural sources.

Table 1. Elastase inhibitory activity of naturally occurring sesquiterpenoids.

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
1	Dehydrocostic acid (**1**)	*Inula viscosa*	43 μM	–	[24]
2	Rumphellolide I (**4**)	*Rumphella antipathies*	32.3%	10 μg mL^{-1}	[29]
3	Rumphellatin D (**5**)		27.2%	10 μg mL^{-1}	[30]
4	Rumphellolide H (**6**)		32.7%	10 μg mL^{-1}	[32]
5	Clovan-2,9-dione (**7**)		6.73 μg mL^{-1}	–	[33]
6	Rumphellaoic acid A (**8**)		29.2%	10 μg mL^{-1}	[34]
7	Rumphellol A (**9**)		31.95%	51.64% (42.4 μM)	[35]
8	Rumphellol B (**10**)		42.22%	42.10% (37.6 μM)	
9	Rumphellaone C (**12**)		–	21.1% (10 μg mL^{-1})	[36]
10	Curculonone A (**13**)	*Curcuma longa*	–	20.34 ± 4.66	[37]
11	Curculonone B (**14**)		–	23.52 ± 3.66	
12	Curculonone C (**15**)		–	21.48 ± 0.89	
13	Curculonone D (**16**)		–	> 50	
14	6α-Hydroxycurcumanolide A (**17**)		–	10.82 ± 1.64	
15	1,10-Dehydro-10-deoxy-9-oxozedoarondiol (**18**)		–	> 50	
16	(*S*)-(+)-*ar*-turmerone (**19**)		–	38.98 ± 18.47	
17	Bisacurone (**20**)		–	> 50	
18	Curlone (**21**)		–	> 50	
19	β-Atlantone (**22**)		–	> 50	
20	(6*R*)-[(1*R*)-1,5-Dimethylhex-4-enyl]-3-methylcyclohex-2-en-1-one (**23**)		–	36.20 ± 3.90	
21	Zedoarondiol (**24**)		–	12.66 ± 3.41	
22	Curcumanolide A (**25**)		–	11.70 ± 2.35	
23	Curcumanolide B (**26**)		–	12.55 ± 2.48	
24	Menelloide C (**27**)	*Menella* sp.	–	–	[38]
25	Menelloide D (**28**)		–	10.5% (10 μg mL^{-1})	
26	(*S*)-(+)-Sydonol (**31**)	*Aspergillus sydowii*	5.23 μM	–	[39]
27	(*E*)-5-(Hydroxymethyl)-2-(60-methylhept-20-en-20-yl)phenol (**32**)		6.11 μM	–	
28	AGI–B4 (**33**)		6.00 μM	–	
29	Phellilin A (**34**)	*Phellinus linteus*	–	between 22.99 to 25.94%	[40]
30	Phellilin B (**35**)		–	between 22.99 to 25.94%	
31	Phellilin C (**36**)		–	between 22.99 to 25.94%	
32	Inulanolide E1 (**37**)	*Inula Britannica*	8.2 (7.2–9.2)		[41]
33	Japonicone B (**39**)		21.9 (20.2–23.8)		
34	Japonicone E (**41**)		42.5 (36.0–49.1)		
35	Inulanolide E (**42**)		10.4 (9.4–11.4)		

Gorgonian coral *Menella* sp. produces two sesquiterpenoids named asmenelloide C (**27**) and D (**28**), only the compound **28** weakly inhibited (10.5%) the release of elastase by human neutrophils at a concentration of 10 μg mL^{-1} which means either the larger ring size, unsaturation or the epoxide may cause this activity.[38] DNA methyl transferase inhibitor, 5-azacytidine induced the synthesis of bisabolane-type sesquiterpenoids in the fungus *Aspergillus sydowii*. The spectroscopic studies helps in the identification of (7*S*)-(+)-7-*O*-methylsydonol (**29**), (7*S*,11*S*)-(+)-12-hydroxysydonic acid (**30**), (*S*)-(+)-sydonol (**31**), (*E*)-5-(hydroxymethyl)-2-(60-methylhept-20-en-20-yl)phenol (**32**) and AGI–B4 (**33**). The compounds **31**–**33** (Figure 4) showed activity against *N*-formyl-methionyl-leucyl-phenylalanine/cytochalasin B (fMLP/CB) induced by human neutrophils with IC_{50} values of 5.23, 6.11 and 6.00 μM, respectively.[39] Novel sesquiterpenes, phellilins A–C (**34**–**36**), isolated from the cultured mycelium of *Phellinus linteus*, were evaluated for their inhibitory potential elastase release by human neutrophils. A weak inhibition of elastase release was found at a concentration of 30 μM, in the range between 22.99 to 25.94% (Table 1).[40] The flowers of *Inula britannica* were investigated which result in isolation of six (**37**–**42**) sesquiterpene lactone dimer japonicone A (**38**), japonicone B (**39**), japonicone D (**40**), japonicone E (**41**), and inulanolide E (**42**). These isolated compounds (**37**–**42**) were

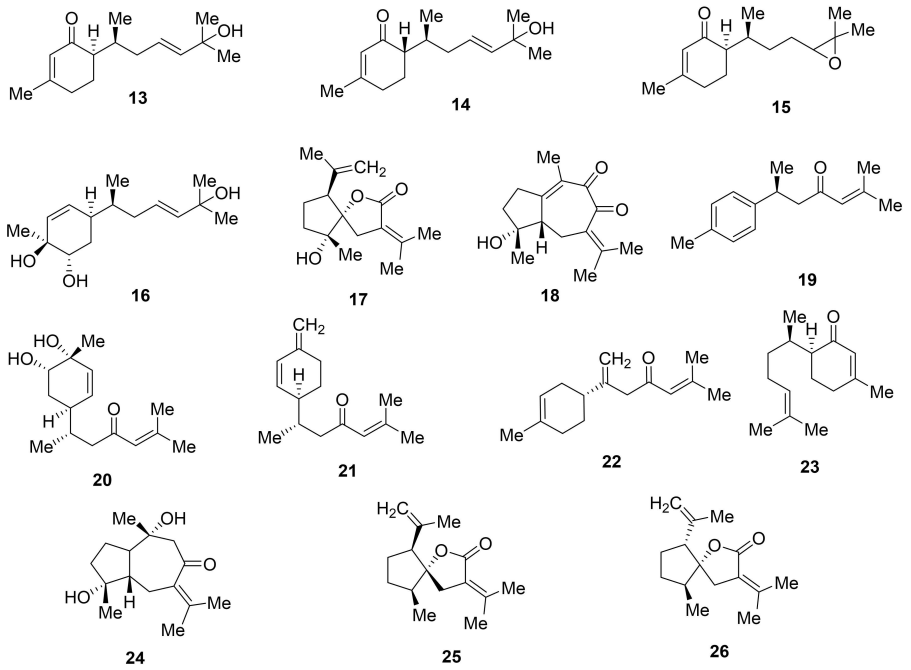


Figure 3. Sesquiterpenoid (**13**–**26**) isolated from various natural sources.

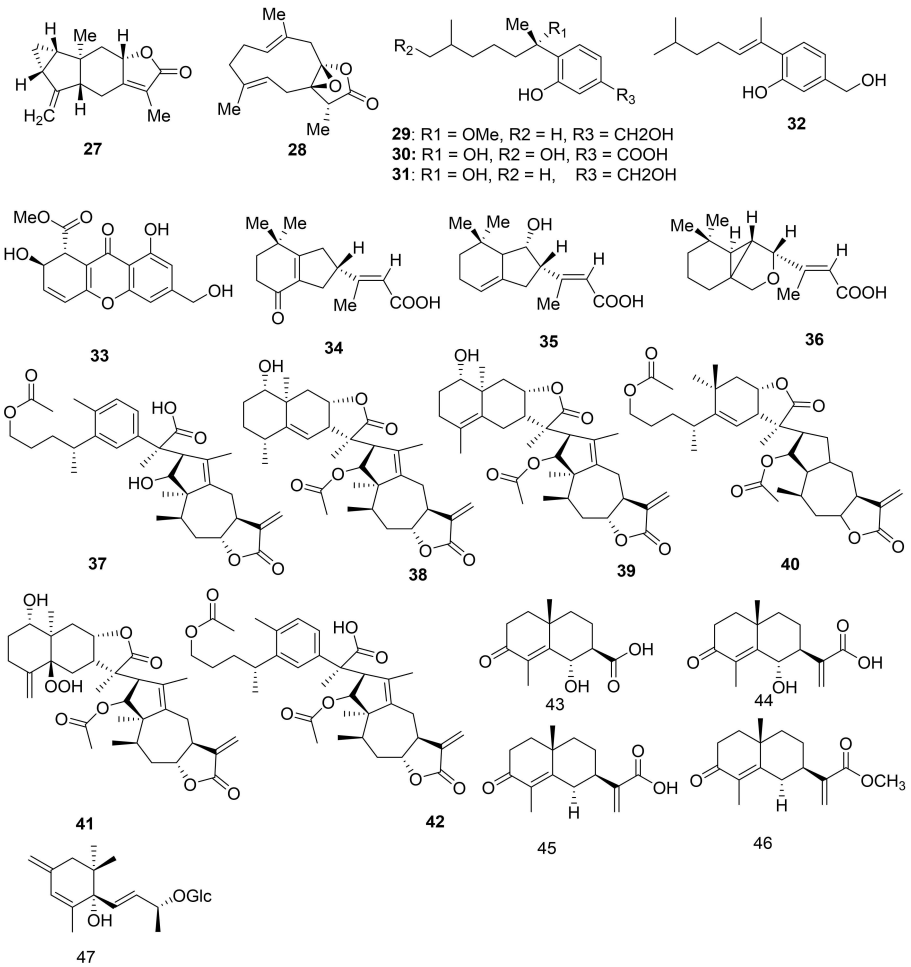


Figure 4. Bisabolane-type sesquiterpenoids and their lactone derivatives (**27**–**47**) isolated from various natural sources.

tested against HNE evaluated in vitro and compounds **37** and **42** showed prominent inhibitory effects against HNE activity, with IC_{50} values of 8.2 and 10.4 μM, respectively, comparable to that of epigallocatechingallate (IC_{50} = 10.9 μM). Additionally, compounds **39** and **41** showed the moderate inhibition had IC_{50} values of 21.9 and 42.5 μM, respectively (Table 1). Compounds **38** and **40** did not display significant activity (IC_{50} > 100 μM). whereas compound **37** and **39** showed the Noncompetitive inhibition, with inhibition constants (K_i) of 8.0 and 22.8 μM, respectively.[41] Eudesmane sesquiterpenes (**43**–**46**) along with (6*S*,9*R*)-roseoside (**47**) were isolated from a medicinal plant of Jordon *Crepis sancta* belonging to family Asteraceae. Compound **43**–**47** (Figure 4) has been tested through Elastase release, and none of compound was found active.[42]

4.2. Diterpenoids as HNE Inhibitors

Siegesbeckia pubescens belongs to the plant family Compositae is an important part of traditional Chinese medicine with the name as "xi-xian". This plant is rich in terpenoids, and for years, the aerial parts have been used as a traditional medicine to treat inflammatory diseases like rheumatic arthritis, hypertension, malaria, neurasthenia and snakebite.[43] Keeping in view its importance, Wang et al. studied the anti-inflammatory properties of 25 terpenoids (**48**–**72**) which were found inhibitors of elastase release in activated human neutrophils. The first eighteen compounds (**48**–**65**) including the eleven *ent*-pimarane-type diterpenoids (**55**–**65**) showed mild activity (IC_{50} > 10 μg mL^{-1}) whereas the compounds **66**, **69, 70**, and **72** (Figure 5) showed selective inhibitory effects against elastase release. As a part of SAR, it is observed that the inhibitory effects decreased when there is a presence of a C-20 $CH_2OCOiPr$ moiety (**72**, IC_{50} = 6.62 μM) rather than a CH_2OH group (**66**, IC_{50} = 4.34 μM) or the α-$CH_2OCOiPr$ (**69**, IC_{50} = 4.73 μM; **70**, IC_{50} = 3.64 μM; Table 2) rather than a β-CH_2 OH substituent on C-16. While **66** exhibited substantial inhibitory effect through elastase release IC_{50} = 4.34 μM. Similarly, compounds **63** and **66** showed almost equipotent inhibition that means the replacement of hydrogen at C-16 (in **63**) to hydroxyl (in **66**) exhibited no selectivity. Compounds **65**, **68**, and **71** (Figure 5) remained insignificant in present study. However, structurally similar compounds (**69**, **70** and **72**) with an isobutyrate ester rather hydroxy group displayed considerable inhibitory effects. Compound **69** exhibited potent inhibitory effect against elastase release with IC_{50} = 4.73 μM, (Table 2) while **70** and **72** showed selective inhibition against elastase release with IC_{50} values of 3.64 and 6.82 μM, respectively. These observations clarified that the esterification of 17-OH with isobutyric acid improved inhibitory activity. Further it is observed from results that of compound **69** and **70** with acetylation of the 18-OH greatly led to higher inhibition of elastase release in activated human neutrophils. It is therefore, suggested that for the active *ent*-kaurane type diterpenoids, esterification of 17-OH with isobutyric acid and acetylation of 18-OH led to changes in the inhibitory effects on elastase release with a clear difference in selectivity.[44] Although several of terpenoids have been reported to possess anti-inflammatory potential, however, un-

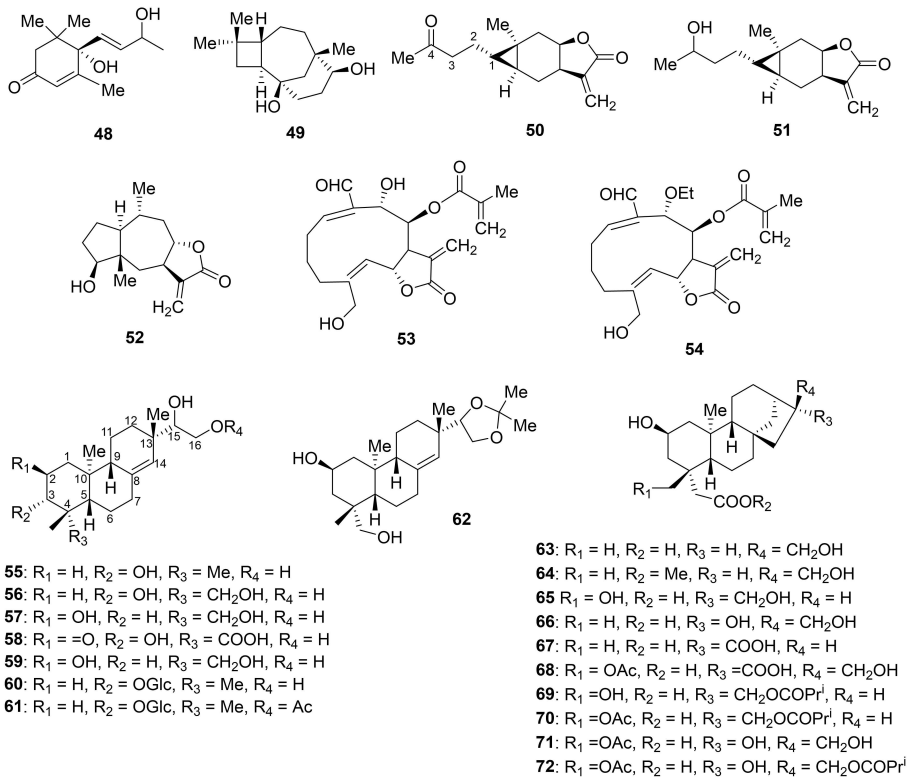


Figure 5. *ent*-Pimarane-type diterpenoids isolated from various natural sources.

Table 2. Elastase inhibitory activity of naturally occurring diterpenoids.

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
1	Compound (**48**)	*Siegesbeckiapubescens*	–	$>10\ \mu g\,mL^{-1}$	[44]
2	Compound (**49**)		–	$>10\ \mu g\,mL^{-1}$	
3	Compound (**50**)		–	$>10\ \mu g\,mL^{-1}$	
4	Compound (**51**)		–	$>10\ \mu g\,mL^{-1}$	
5	Compound (**52**)		–	$>10\ \mu g\,mL^{-1}$	
6	Compound (**53**)		–	$>10\ \mu g\,mL^{-1}$	
7	Compound (**54**)		–	$>10\ \mu g\,mL^{-1}$	
8	Compound (**55**)		–	$>10\ \mu g\,mL^{-1}$	
9	Compound (**56**)		–	$>10\ \mu g\,mL^{-1}$	
10	Compound (**57**)		–	$>10\ \mu g\,mL^{-1}$	
11	Compound (**58**)		–	$>10\ \mu g\,mL^{-1}$	
12	Compound (**59**)		–	$>10\ \mu g\,mL^{-1}$	
13	Compound (**60**)		–	$>10\ \mu g\,mL^{-1}$	
14	Compound (**61**)		–	$>10\ \mu g\,mL^{-1}$	
15	Compound (**62**)		–	$>10\ \mu g\,mL^{-1}$	
16	Compound (**63**)		–	$>10\ \mu g\,mL^{-1}$	
17	Compound (**64**)		–	$>10\ \mu g\,mL^{-1}$	
18	Compound (**65**)		–	$>10\ \mu g\,mL^{-1}$	
19	Compound (**66**)		–	$4.34\pm0.63\ \mu g\,mL^{-1}$	
20	Compound (**67**)		–	$>10\ \mu g\,mL^{-1}$	
21	Compound (**68**)		–	$>10\ \mu g\,mL^{-1}$	
22	Compound (**69**)		–	$4.73\pm0.37\ \mu g\,mL^{-1}$	
23	Compound (**70**)		–	$3.64\pm0.20\ \mu g\,mL^{-1}$	
24	Compound (**71**)		–	$>10\ \mu g\,mL^{-1}$	
25	Compound (**72**)		–	$6.82\pm1.29\ \mu g\,mL^{-1}$	
26	*Ent*-18-acetoxy-7α-hydroxykaur-16-en-15-one (**73**)	*Croton tonkinensis*	–	2.64 ± 0.12	[45]
27	*Ent*-1β-acetoxy-7α,14β-dihydroxykaur-16-en-15-one (**74**)		–	2.48 ± 0.37	
28	*Ent*-7α-hydroxy-14β-acetoxykaur-16-en-15-one (**75**)		–	2.36 ± 0.27	
29	Crotonkinensin A (**76**)		–	1.63 ± 0.18	
30	*Ent*-18-acetoxykaur-16-en-15-one (**77**)		–	0.24 ± 0.04	
31	*Ent*-7β-hydroxy-16-kauren-15-one (**78**)		–	2.23 ± 0.10	
32	*Ent*-11α,18-diacetoxy-7β-hydroxykaur-16-en-15-one (**79**)		–	1.65 ± 0.29	
33	16-Oxo-leoheteronone A (**80**)	*Leonurus japonicus*	–	$26.91\pm6.13\,\%$	[46]
34	15-Methoxyleoheteronin B (**81**)		–	$17.57\pm3.63\,\%$	
35	8,9-Secohispanolone (**82**)		–	$20.54\pm6.67\,\%$	
36	Hispanone (**83**)		–	$IC_{50}=5.42\ \mu M$	
37	Leoheteronin B (**84**)		–	$5.42\pm2.38\ \mu M$ ($70.06\pm12.15\,\%$)	
38	Leoheteronin B (**85**)		–	$15.98\pm7.61\,\%$	
39	Hedychicoronarin (**86**)	*Hedychium coronarium*	–	$>10\ \mu g\,mL^{-1}$ (IC_{50})	[47]
40	Peroxycoronarin D (**87**)		–	$>10\ \mu g\,mL^{-1}$ (IC_{50})	
41	7β-Hydroxycalcaratarin A (**88**)		–	3.86 ± 0.98	
42	(*E*)-7β-Hydroxy-6-oxo-labda-8(17),12-diene-15,16-dial (**89**)-		–	5.36 ± 1.23	
43	Calcaratarin A (**90**),–		–	2.36 ± 0.41	
44	Coronarin A (**91**)		–	2.67 ± 1.68	
45	Coronarin D (**92**)		–	$>10\ \mu g\,mL^{-1}$ (IC_{50})	
46	Coronarin D methyl ether (**93**)		–	$>10\ \mu g\,mL^{-1}$ (IC_{50})	
47	Coronarin D ethyl ether (**94**)		–	$>10\ \mu g\,mL^{-1}$ (IC_{50})	

Table 2. continued

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
48	(*E*)-labda-8(17),12-diene-15,16-dial (**95**)		-	3.70 ± 1.18(IC_{50})	
49	Junceellolides J (**96**)	*Junceella fragilis*	–	5.17 ± 2.71 (% inhibition at 10 μg mL^{-1})	[49]
50	Junceellolides K (**97**)		–	15.04 ± 5.54 (% inhibition at 10 μg mL^{-1})	
51	Junceellolides L (**98**)		–	5.52 ± 4.11 (% inhibition at 10 μg mL^{-1})	
52	(−)-11β,20β-Epoxy-4-deacetoxyjunceellolide D (**99**)		–	15.36 ± 3.34 (% inhibition at 10 μg mL^{-1})	
53	Briaexcavatin E (**100**)	*Briareum excavatum*	–	87% inhibition at concentration 3.0 μM)	[49]
54	Frajunolides A (**101**)	*Junceella fragilis*	–	6.47 ± 3.30% inhibition	[50]
55	Frajunolides A (**102**)		–	15.16 ± 6.18% inhibition	
56	Frajunolides A (**103**)		–	14.47 ± 5.16% inhibition	
57	Frajunolides A (**104**)		–	2.54 ± 2.05% inhibition	
58	Junceellolide E (**105**)		–	29.74 ± 7.12% -inhibition	
59	Umbraculolide A (**106**)		–	-2.37 ± 6.80% inhibition	
60	11α,20α-Epoxy-4-deacetoxyjunceellolide D (**107**)		–	8.91 ± 4.84% inhibition	
61	Juncenolide H (**108**)	*Junceellajuncea*	–	15.12 ± 6.33% inhibition	[51]
62	Juncenolide I (**109**)		–	15.57 ± 5.81% inhibition	
63	Juncenolide J (**110**)		–	2.12 ± 3.38% inhibition	
64	Juncenolide K (**111**)		–	17.48 ± 5.42% inhibition	
65	Frajunolide L (**112**)	*Junceella fragilis*	–	16.2 ± 0.7% inhibition	[52]
66	Frajunolide M (**113**)		–	13.3 ± 3.1% inhibition	
67	Frajunolide N (**114**)		–	22.3 ± 7.7% inhibition	
68	Frajunolide O (**115**)		–	17.2 ± 6.7% inhibition	
69	Frajunolide P (**116**)		–	35.6 ± 503.2% inhibition	[53]
70	Frajunolide Q (**117**)		–	34.1 ± 2.9% inhibition	
71	Frajunolides R (**118**)		–	16.0 ± 5.3% inhibition	
72	Frajunolides S (**119**)		–	− 4.5 ± 3.4% inhibition	
73	Excavatoid E (**120**)	*Briareum excavatum*	–	12.95 ± 6.99% inhibition	[54]
74	Excavatoid F (**121**)			2.57 ± 1.11% inhibition	
75	Excavatoid D (**126**)		–	39.4% inhibition (conc. 10 μg mL^{-1})	[55]
76	Excavatoid L (**127**)		–	31.25 ± 0.07% inhibition (conc. 10 μg mL^{-1})	[56]
77	Excavatoid M (**128**)		–	16.96 ± 2.93% inhibition (conc. 10 μg mL^{-1})	
78	Excavatoid N (**129**)		–	22.21 ± 3.34% inhibition (conc. 10 μg mL^{-1})	
79	Briarenolide E (**130**)	*Briareum* sp.	–	28.3% inhibition (conc. 10 μg mL^{-1})	[57]
80	Briarenolide J (**131**)		–	9.96 μM	[58]
81	Briaviolide A (**132**)	*Briareum violacea*	–	11.04 ± 7.22% inhibition (conc. 10 μg mL^{-1})	[59]
82	Briaviolide B (**133**)		–	13.43 ± 2.66% inhibition (conc. 10 μg mL^{-1})	
83	Briaviolide C (**134**)		–	6.40 ± 4.29% inhibition (conc. 10 μg mL^{-1})	
84	Briaviolide D (**135**)		–	9.31 ± 6.64% inhibition (conc. 10 μg mL^{-1})	
85	Briaviolide E (**136**)		–	26.03 ± 9.51% inhibition (conc. 10 μg mL^{-1})	

Table 2. continued

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
86	Briaviolide F (**137**)		–	14.34 ± 5.28 % inhibition (conc. 10 μg mL^{-1})	
87	Briaviolide G (**138**)		–	16.66 ± 3.12 % inhibition (conc. 10 μg mL^{-1})	
88	Briaviolide H (**139**)		–	18.78 ± 2.29 % inhibition (conc. 10 μg mL^{-1})	
89	Briaviolide I (**140**)		–	28.81 ± 6.37 % inhibition (conc. 10 μg mL^{-1})	
90	Briaviolide J (**141**)		–	14.62 ± 4.41 % inhibition (conc. 10 μg mL^{-1})	
91	Benzyl briaviolide A (**142**)		–	28.60 ± 7.54 % inhibition (conc. 10 μg mL^{-1})	
92	Cladieunicellin F (**144**)	*Cladiella* sp.	–	12.91 ± 3.56 % inhibition (conc. 10 μg mL^{-1})	[60]
93	(−)-Solenopodin C (**145**)		–	40.45 ± 5.80 % inhibition (conc. 10 μg mL^{-1})	
94	Lobocrassin A (**145**)	*Lobophytum crassum*	–	0.9 ± 2.5 % inhibition (conc. 10 μg mL^{-1})	[61]
95	Lobocrassin B (**146**)		–	4.9 ± 0.4 % inhibition (conc. 10 μg mL^{-1})	
96	Lobocrassin C (**147**)		–	9.6 ± 9.4 % inhibition (conc. 10 μg mL^{-1})	
98	Lobocrassin D (**148**)		–	11.0 ± 3.9 % inhibition (conc. 10 μg mL^{-1})	
99	Lobocrassin E (**149**)		–	4.4 ± 9.5 % inhibition (conc. 10 μg mL^{-1})	
100	Lobocrassin F (**150**)	*Lobophytumcrassum*	–	6.27 μg mL^{-1}	[62]
101	Flexibilin A (**151**)	*Sinularia flexibilis*	–	22.67 ± 5.32 % inhibition (conc. 10 μg mL^{-1})	[63]
102	Flexibilin B (**152**)		–	45.76 ± 2.92 % inhibition (conc. 10 μg mL^{-1})	
103	Flexibilin C (**153**)		–	10.56 ± 2.75 % inhibition (conc. 10 μg mL^{-1})	
104	(−)-Sandensolide (**154**)		–	8.14 ± 4.03 % inhibition (conc. 10 μg mL^{-1})	
105	Glaucumolides A (155)	*Sarcophyton glaucum*	3.97 ± 0.10	88.94 ± 6.96	[64]
106	Glaucumolides A (156)		3.97 ± 0.10	103.25 ± 1.89	
107	Ximaolide A (157)		> 10	15.13 ± 3.58	
108	Isosarcophytonolide D (158)		> 10	27.12 ± 3.08	
109	Asterolaurin A (**159**)	*Asterospicularialaurae*	–	40 ± 3 % inhibition (conc. 10 μg mL^{-1})	[64]
110	Asterolaurin B (**160**)		–	30 ± 6 % inhibition (conc. 10 μg mL^{-1})	
111	Asterolaurin C (**161**)		–	39 ± 5 % inhibition (conc. 10 μg mL^{-1})	
112	Asterolaurin D (**162**)		–	68 ± 6 % inhibition (conc. 10 μg mL^{-1}) (IC_{50} 18.7 μM)	
113	Asterolaurin E (**163**)		–	36 ± 6 % inhibition (concentration of 10 μg mL^{-1})	
114	Asterolaurin F (**164**)		–	13 ± 6 % inhibition (conc. 10 μg mL^{-1})	
115	Cladielloide A (**165**)	*Cladiella* sp.	–	27.1 ± 4.8 % inhibition concentration of 10 μg mL^{-1} (conc. 10 μg mL^{-1})	[64]
116	Cladielloide B (**166**)		–	6.5 ± 1.9 % inhibition (conc. 10 μg mL^{-1})	

Table 2. continued

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
117	6-*epi*-Cladieunicellin F (**167**)		–	41.08 ± 3.26 % inhibition (conc. 10 μg mL^{-1})	[64]
118	Cladieunicellin F (**168**)		–	12.91 ± 3.56 % inhibition (conc. 10 μg mL^{-1})	
119	Klymollin I (**169**)	*Klyxummolle*	–	6.42 ± 1.37 % inhibition (conc. 10 μg mL^{-1})	[67]
120	Klymollin J (**170**)		–	7.30 ± 3.74 % inhibition (conc. 10 μg mL^{-1})	
121	Klymollin K (**171**)		–	− 1.19 ± 2.49 % inhibition (conc. 10 μg mL^{-1})	
122	Klymollin L (**172**)		–	9.18 ± 3.92 % inhibition (conc. 10 μg mL^{-1})	
123	Klymollin M (**173**)		–	89.16 ± 5.77 (2.92 ± 0.27 μM) % inhibition (conc. 10 μg mL^{-1})	
124	Klymollin N (**174**)		–	6.47 ± 2.06 % inhibition (conc. 10 μg mL^{-1})	
125	Klymollin O (**175**)		–	16.75 ± 2.08 % inhibition (conc. 10 μg mL^{-1})	
126	Klymollin P (**176**)		–	7.35 ± 3.32 % inhibition (conc. 10 μg mL^{-1})	
127	Klymollin Q (**178**)		–	7.33 ± 4.34 % inhibition (conc. 10 μg mL^{-1})	
106	Klymollin R (**179**)		–	11.55 ± 4.14 % inhibition (conc. 10 μg mL^{-1})	
128	Klymollin S (**180**)		–	0.62 ± 2.35 % inhibition (conc. 10 μg mL^{-1})	
129	Krempfielin J (**181**)	*Cladiella krempfi*	–	19.42 ± 7.89 % inhibition (conc. 10 μg mL^{-1})	[68]
130	Krempfielin K (**182**)		–	45.51 ± 2.69 % inhibition (conc. 10 μg mL^{-1})	
131	Krempfielins L (**183**)		–	18.67 ± 5.75 % inhibition (conc. 10 μg mL^{-1})	
132	Krempfielins M (**184**)		–	27.30 ± 5.42 % inhibition (conc. 10 μg mL^{-1})	
133	Krempfielin N (**185**)	*Cladiella krempfi*	–	IC_{50} (4.94 ± 1.68 μM) 73.86 ± 14.18 % inhibition (conc. 10 μg mL^{-1})	[69]
134	Krempfielin O (**186**)		–	13.33 ± 3.56 % inhibition (conc. 10 μg mL^{-1})	
135	Krempfielin P (**187**)		–	35.54 ± 3.17 % inhibition (conc. 10 μg mL^{-1})	
136	Krempfielin Q (**188**)		–	2.99 ± 2.82 % inhibition (conc. 10 μg mL^{-1})	[70]
137	Krempfielin R (**189**)		–	11.09 ± 5.55 % inhibition (conc. 10 μg mL^{-1})	
138	Hirsutalins S (**190**)	*Cladiella hirsuta*	–	46.7 ± 8.0	[71]
139	Hirsutalins P (**191**)		–	19.3 ± 5.6	
140	Hirsutalins V (**192**)		–	4.8 ± 5.6	
141	Briarenones A (**194**)	*Briareum violaceum*	–	–	[72]
142	Briarenones B (**195**)		–	–	
143	Briarenones C (**196**)		–	–	
144	Lobovarol F (**197**)	*Lobophytum varium*	> 20	64.3 ± 3.7	[73]
145	Lobovarol G (**198**)		18.8 ± 1.8	87.3 ± 7.9	
146	Lobovarol H (**199**)		> 20	3.8 ± 2.6	

Table 2. continued

Sr. #	Compound	Biological source	Inhibition (IC_{50})	Release (IC_{50})	Ref.
147	Lobovarol I (**200**)		20.0 ± 3.0	53.2 ± 0.2	
148	Lobovarol J (mixture of **201**a and **201**b)		>20	3.5 ± 1.4	
149	Lobovarol K (**202**)		>20	10.9 ± 5.1	
150	Lobovarol L (**203**)		not tested	not tested	
151	Lobovarol M (**204**)		>20	37.8 ± 6.2	
152	Lobovarol N (**205**)		>20	5.5 ± 0.6	
153	Lobovarol O (**206**)		>20	5.3 ± 1.6	
154	Lobovarol P (**207**)		>20	12.0 ± 4.4	
155	Compound **208**		6.9 ± 2.7	73.7 ± 2.4	
156	Compound **209**		4.4 ± 0.7	117.3 ± 3.2	
157	Callihypolins A (**210**)	*Callicarpa hypoleucophylla*		8.26 ± 3.72	[74]
158	Callihypolins B (**211**)			17.55 ± 2.64	
159	(4a*R*,5*S*,6*R*,8a*R*)-5-[2-(2,5-dihydro-5-methoxy-2-oxofuran-3-yl)ethyl]-3,4,4*a*,5,6,7,8,8a-octahydro-5,6,8atrimethylnaphthalene-1-carboxylic acid (**212**)			12.15 ± 2.38	
160	Patagonic acid (**213**)			13.57 ± 1.48	
161	Limbatolide F (**214**)			7.33 ± 1.56	
162	Limbatolide A (**215**)			10.50 ± 3.23	
163	Methyl (4a*R*,5*S*,6*R*,8*S*,8a*R*)-3,4,4a,5,6,7,8,8a-octahydro-8-hydroxy5,6,8a-trimethyl-5-[2-(2-oxo-2,5-dihydrofuran-3-yl)ethyl]naphthalene-1-carboxylate (**216**)			9.30 ± 2.91	
164	Clerodermic acid (**217**)			11.80 ± 3.55	
165	Visclerodol acid (**218**)			16.30 ± 3.74	
166	Methylfarnesylquinone (**219**)	*Homoeostrichusformosana*	–	$IC_{50} = 0.48\ \mu g\,mL^{-1}$	[75]

fortunately, mechanism of action has not been established in most of cases. This point of investigation should be addressed in future.

The methanolic extract of *Croton tonkinensis* produces *ent*-kaurane-type diterpenoids namely *ent*-18-acetoxy-7α-hydroxykaur-16-en-15-one (**73**), *ent*-1β-acetoxy-7α,14β-dihydroxykaur-16-en-15-one (**74**), *ent*-7α-hydroxy-14β-acetoxykaur-16-en-15-one (**75**), crotonkinensin A (**76**), *ent*-18-acetoxykaur-16-en-15-one (**77**), *ent*-7β-hydroxy-16-kauren-15-one (**78**) and *ent*-11α,18-diacetoxy-7β-hydroxykaur-16-en-15-one (**79**). All these metabolites exhibited significant inhibitory activity against elastase release with IC_{50} values ranging from 1.63 to 2.64 μM. Compound **77** displayed the most significant inhibition and onefold higher activity (IC_{50} of 0.24 and 0.24 μM, respectively; Table 2) of elastase release than the reference compounds. It is suggested that these metabolites or the extracts of *C. tonkinensis* may be developed as new anti-inflammatory drugs or health foods, however, cytotoxicity effects of these compounds is still to be studied.[45] Six labdane type diterpenoids namely, 16-oxoleoheteronone A (**80**) and 15-methoxyleoheteronin B (**81**), 8,9-secohispanolone (**82**), galeopsin (**83**), hispanone (**84**), and leoheteronin B (**85**) were isolated from *Leonurus japonicas*, were evaluated for their inhibitory activity of elastase release. All the compounds **80**–**82**, **84**, **85** (Figure 6) was found mild active release ($IC_{50} = > 10$ μM) whereas hispanone (**83**) with the significant activity with $IC_{50} = 5.42$ μM.[46] Further labdane-type diterpenoids: hedychicoronarin (**86**), peroxycoronarin D (**87**), 7β-hydroxycalcaratarin A (**88**), and (*E*)-7β-hydroxy-6-oxo-labda-8(17),12-diene-15,16-dial (**89**), calcaratarin A (**90**), coronarin A (**91**), coronarin D (**92**), coronarin D methyl ether (**93**), coronarin D ethyl ether (**94**), and (*E*)-labda-8(17),12-diene-15,16-dial (**95**) have been separated from the rhizomes of *Hedychium coronarium*. The detailed anti-inflammatory analysis revealed that the compounds **88**–**91** and **95** (Figure 6) showed the strong inhibition with $IC_{50} \leq 6.17\ \mu g\,mL^{-1}$ of fMLP-induced elastase release (Table 2). The structure–activity analysis substantiated that calcaratarin A (**90**), with 14-dimethoxymethyl group, displayed more potential than its analogue, (*E*)-labda-8(17),12-diene-15,16-dial (**95**) (with 14-formyl group) against elastase release. In addition, the compound **90**, without any substituent at C-7, showed more active inhibition than its analogue **88** (with 7β-hydroxy group) against elastase release. Likewise, the compound **95**, without any substituent at C-6 and C-7, was found to be more potent than its analogue **89** (with 7β-hydroxy-6-oxo group) against elastase release. It is further stated that compound **91** (with a hydroxy group at C-7 and a furan-3-yl group at C-12) displayed more active inhibition than its analogues, **86**, **87**, and **92**–**94** (without any substituent at C-7 and with a 2-oxo-5-substituted-tetrahydrofuran-3-yl group at C-12). These important studies suggest that compounds **88**, **90**, **91** and **95** may further be studied for their mechanism of action, and to develop viable candidates for the prevention of

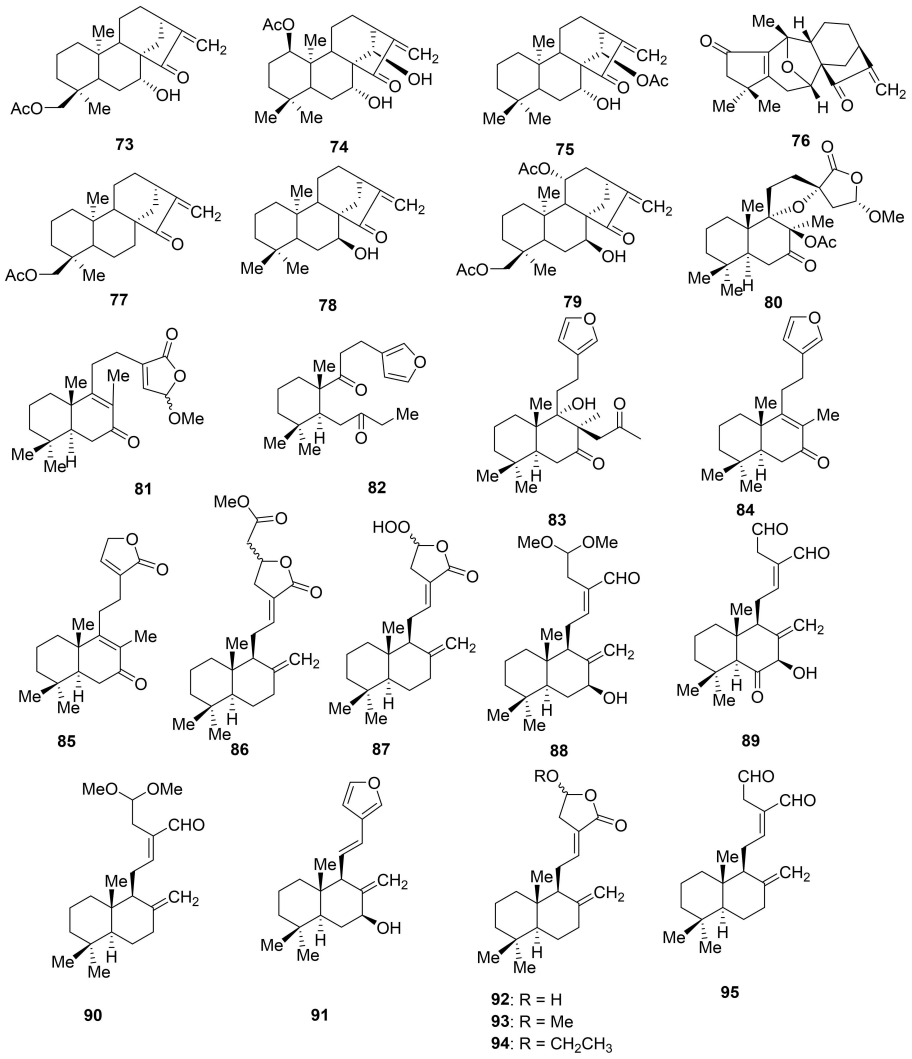


Figure 6. *ent*-kaurane-type and labdane type diterpenoids isolated from various natural sources.

various inflammatory disorders by providing future lead compounds.[47]

Four 11,20-epoxybriarane diterpenoids, junceellolides J–L (**96**–**98**) and (−)-11β,20β-epoxy-4-deacetoxyjunceellolide D (**99**) have been purified from the extract of a gorgonian coral *Junceella fragilis* were evaluated for their anti-inflammatory potential, out of which the compounds **97** and **99** exhibited moderate activity on HNE release at 10 μg mL^{-1}.[48] A briarane-related diterpenoid, briaexcavatin E (**100**), was isolated from the Formosan octocoral *Briareum excavatum*, collected off southern Taiwan coast exhibited more than 87 % inhibition of HNE release at a concentration of 3.0 μM (Table 2).[49] The briarane-type diterpenoids, frajunolides A–D (**101**–**104**), junceellolide E (**105**), umbraculolide A (**106**) and 11α,20α-epoxy-4-deacetoxy-junceellolide D (**107**) have been isolated from the extract of a gorgonian coral *J. fragilis*. In vitro anti-inflammatory evaluation of these isolates revealed that compounds **103**, **105**, and **107** (Figure 7) exhibited mild anti-inflammatory activities at a concentration of 10 μg mL^{-1} against elastase release by human neutrophils.[50] Taiwanese gorgonian coral *Junceella juncea* produces briarane-type diterpenoids, juncenolides H–K (**108**–**111**). The juncenolide H (**108**) displayed a moderate inhibitory effect on elastase release by human neutrophils to an extent of 15.12 %, whereas, compound **109** and **111** showed weak inhibition against elastase release only with an extent of 15.5 and 17.5 %, respectively (Table 2).[51] *J. fragilis* also produces further 8-hydroxybriarane diterpenoids, frajunolides L–O (**112**–**115**). At a concentration of 10 μg mL^{-1}, compounds **112**–**115** (Figure 7) showed weak inhibitory activity against elastase release by human neutrophil.[52]

Further searching on *J. fragilis* resulted the production of 8-hydroxybriarane diterpenoids; frajunolides P–S (**116**–**119**). The compound **116** contains an unusual pivaloyloxy group at C-2, while **117** has a chlorine atom on C-6. Testing the anti-inflammatory activities of briaranes **116**–**119** (Figure 8) revealed that compounds **116** and **117** showed moderate inhibitory activities on elastase release at 10 μg mL^{-1}.[53] Briarane-related diterpenoids, excavatoids E (**120**) and F (**121**) are known as the anti-inflammatory metabolites of octocoral *B. excavatum* and displayed moderate inhibitory effects (26.2 and 30.63 %,

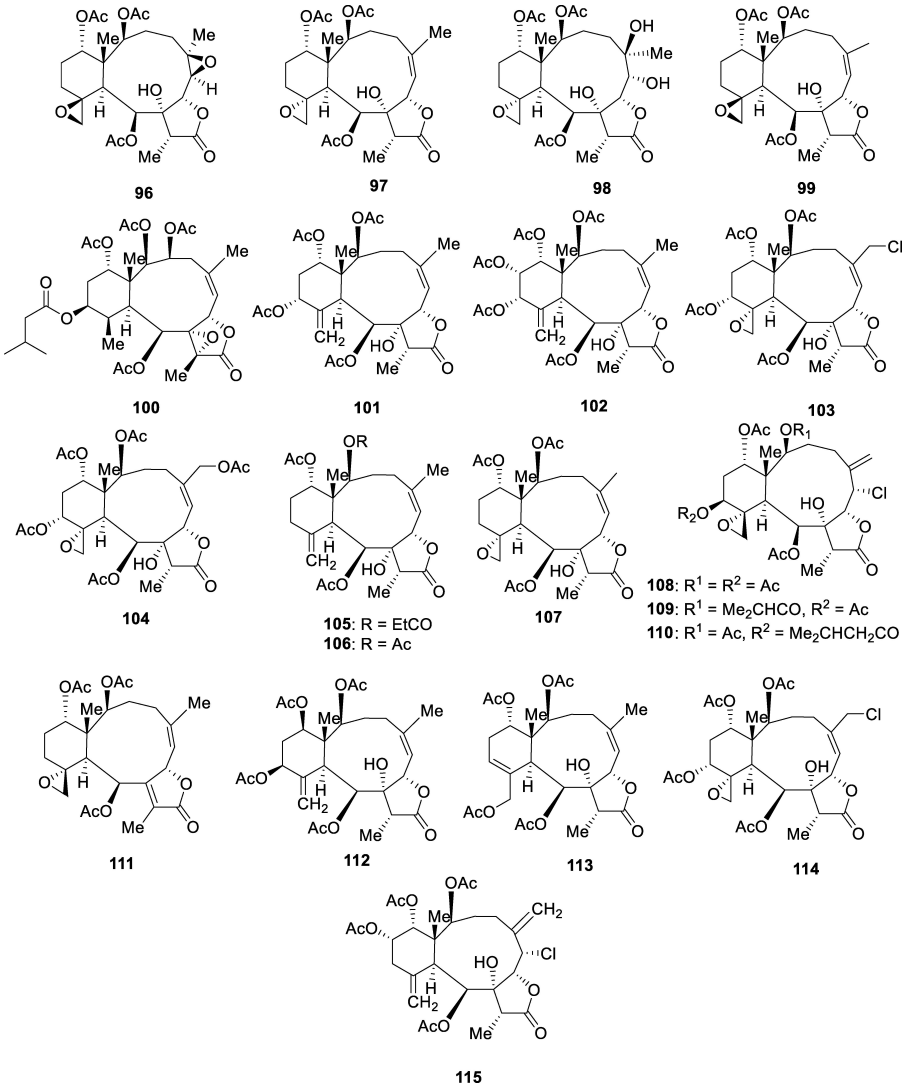


Figure 7. Briarane-type diterpenoids isolated from various natural sources.

respectively) on elastase release by neutrophils.[54] *B. excavatum* yielded more polyoxygenated briaranes, excavatoids A (**122**) and B (**123**) and briaexcavatin I (**124**), while, a wild-type *B. excavatum* produced 5,6-epoxy-briaranes, excavatoids C (**125**) and D (**126**). In most of these type of metabolites, the hydroxyl groups are usually protected by acylation, but excavatoid A (**122**) is the first briarane which possesses six unprotected hydroxy groups and a methoxy group at C-17. On the other hand, excavatoid C (**125**) is the first 12,13-secobriarane, possessing a novel pentacyclic skeleton with an ε-lactone functionality. All these metabolites were tested for their anti-inflammatory potential, however, only excavatoid D (**126**) exhibited 23.8% inhibition of the elastase release by human neutrophils at a concentration of 10 $\mu g\,mL^{-1}$ (Table 2).[55] *B. excavatum* produces macrocyclic diterpenoids, excavatoids L–N (**127**–**129**). Interesting aspect of the structure of these compounds is that the double bonds attached at C-4/5 as presented in briaranes **128** and **129** (Figure 8) are rarely found in briarane-type metabolites. It was found that excavatoid L (**127**) showed modest inhibitory effects on elastase release by human neutrophils.[56] Another *Briareum* sp. produces a 2-ketobriarane diterpenoid, briarenolide E (**130**), which, in an in vitro anti-inflammatory test, displayed modestly inhibitory effects on the release of elastase (inhibition rate 28.3%) by human neutrophils at a concentration of 10 $\mu g\,mL^{-1}$.[57] Briarenolide J (**131**), a novel 6,12-dichlorobriarane diterpenoids was isolated from another octocoral *Briareum* sp. The NMR-based structure elucidation of **131** revealed that it is the first metabolite of a briarane-related natural product bearing a chlorine atom at C-12. This compound displayed inhibitory effects on the release of elastase by human neutrophils with IC_{50} value 9.96 μM.[58] Taiwanese soft corals continued to furnish briarane diterpenoids, as *Briareum violacea* also produced briarane diterpenoids, briaviolides A–J (**132**–**141**). A derivative (**142**) of compound **132** was also prepared to evaluate along with compounds **132**–**141** (Figure 8) for their anti-inflammatory activities on fMLP/CB-induced elastase release by human neutrophils in response. At a concentration of 10 $\mu g\,mL^{-1}$,

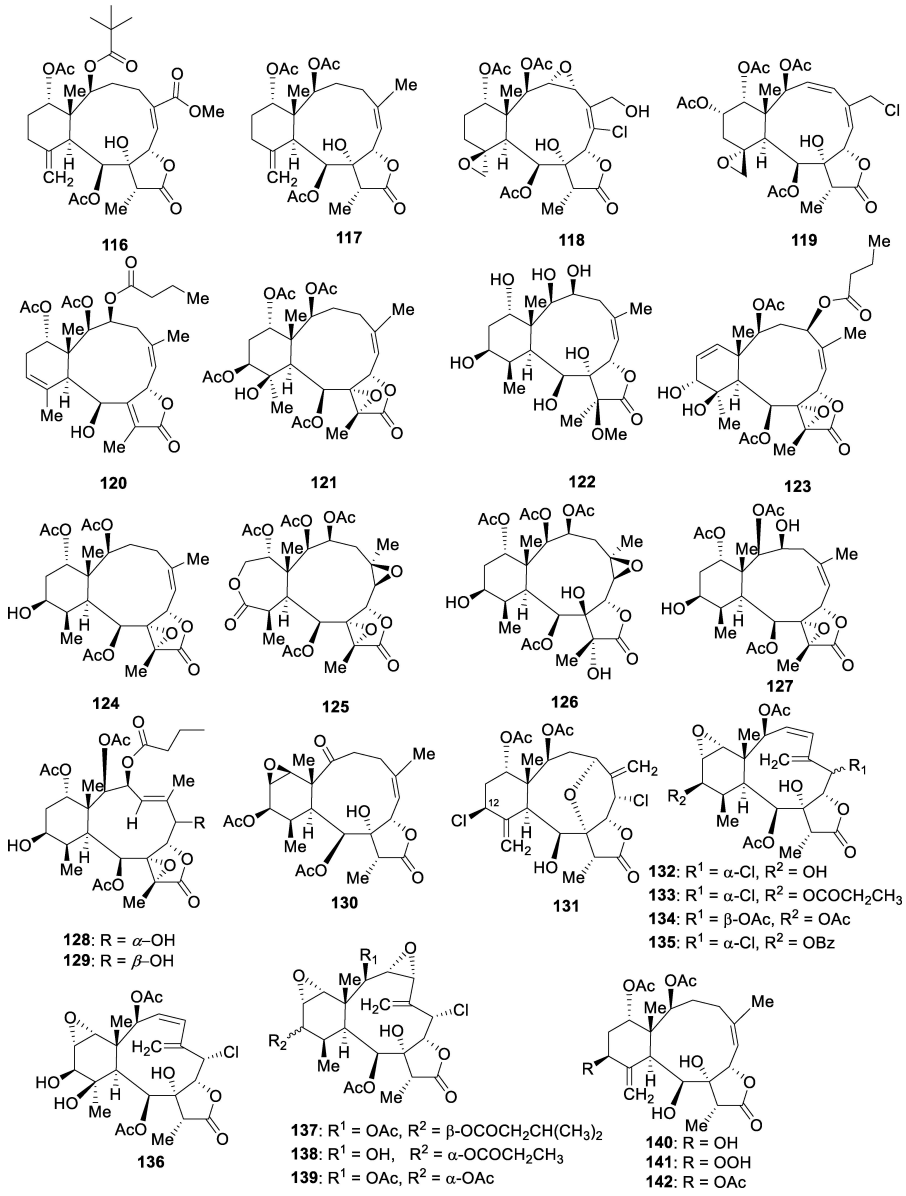


Figure 8. Briarane-type diterpenoids isolated from various natural sources.

compounds **136** and **140** displayed moderate activities (up to 34% inhibition) on elastase release, while Compound **142** has selective activity on the inhibition (28 % inhibition) of elastase release.[59]

Macrocyclic diterpenoids, cladieunicellin F (**143**) and (−)-solenopodin C (**144**), were isolated from an Indonesian octocoral *Cladiella* sp. The in vitro anti-inflammatory studies of these compounds revealed that only compound **144** (Figure 9) exhibit significant inhibitory effects on the release of elastase by human neutrophils at a concentration of 10 $\mu g\,mL^{-1}$.[60]

Five cembrane-type diterpenoids, lobocrassins A–E (**145**–**149**), have been isolated from the extract of another soft coral *Lobophytum crassum*. Spectroscopic based characterized and chemical modification substantiated an interesting feature of compound **145**, that it possesses an α-chloromethyl-α-hydroxy-γ-lactone functionality. The in vitro anti-inflammatory studies of

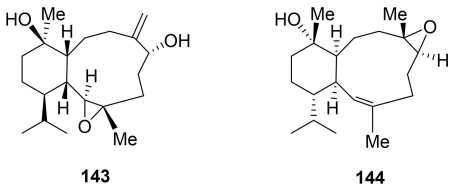


Figure 9. Macrocyclic diterpenoids isolated from various natural sources.

compounds **145**–**149** (Figure 10) revealed that lobocrassin B (**146**) is a potential inhibitor of the release of elastase by human neutrophils, with IC_{50} value 4.9 $\mu g\,mL^{-1}$ (Table 2).[61] Lobocrassin F (**150**), produced by *L. crassum* is another cembrane-type diterpenoid, which was found to display a significant inhibitory effect on the release of elastase by human neutrophils with IC_{50} value of 6.27 $\mu g\,mL^{-1}$.[62] More cembrane-type diterpenoids,

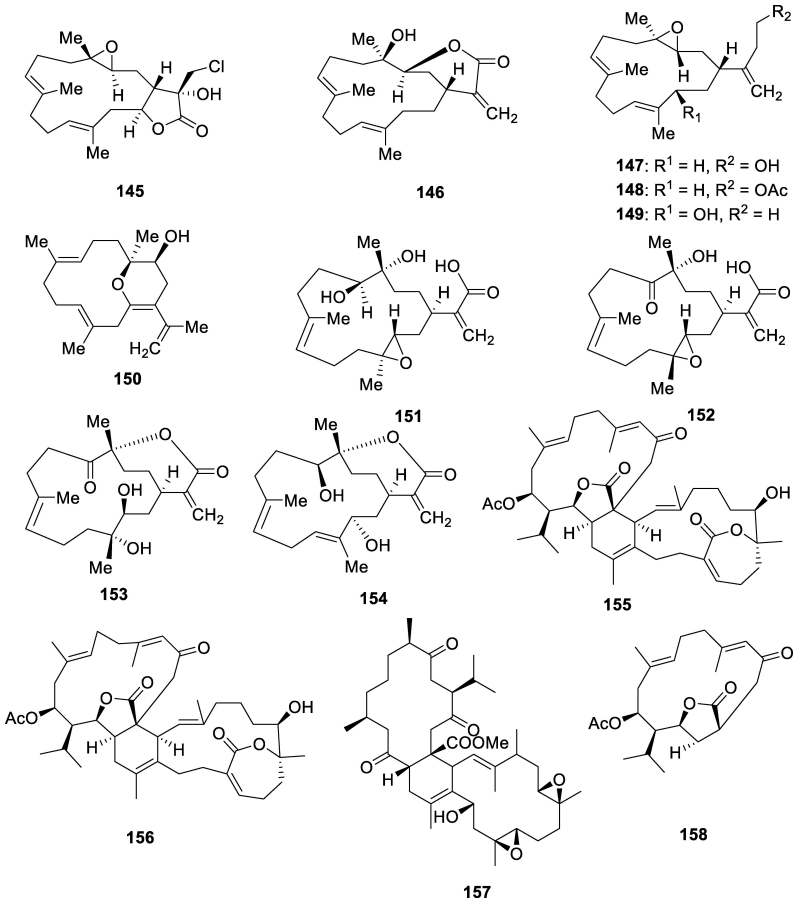


Figure 10. Cembrane-type diterpenoids isolated from various natural sources.

flexibilins A–C (**151**–**153**) and (−)-sandensolide (**154**), were isolated from a soft coral, *Sinularia flexibilis*. At a concentration of 10 μg mL^{-1}, compound **152** displayed a moderate inhibitory effect on the release of elastase by human neutrophils, whereas, others displayed a weak activity (Table 2).[63] cembrane-type diterpenes compounds **155**–**158** (Figure 10) were isolated from the cultured soft coral *Sarcophyton glaucum* and compound **155** and **156** showed exhibited potent inhibitory activity against elastase release, with 88.94 ± 6.96 and 103.25 ± 1.89 % inhibitions in the same fMLP/CB-stimulated cells at the 10 μM concentration.[64]

Six xenicane-type diterpenoids, asterolaurins A–F (**159**–**164**), have been identified as the constituents of the soft coral *Asterospicularialaurae* from southern Taiwan. Spectroscopic identification revealed that compounds **156**–**162** (Figure 11) possess a xenicin skeleton with a 2-oxabicyclo [7.4.0] tridecane ring system, while **163** and **164** are xeniolide A-type compounds. All these isolates **159**–**164** (Figure 11) were tested for their anti-inflammatory effect on elastase release in vitro. Among the isolated xenicanes, compound **162** showed potent inhibition of elastase release than the standard compound genistein. The IC_{50} values observed for compound **162** was 18.7 μM (Table 2). Regarding SAR analysis, it is worth noting that the hemiacetal functionality in compound **162** may play a significant role in the anti-inflammatory activity.[51]

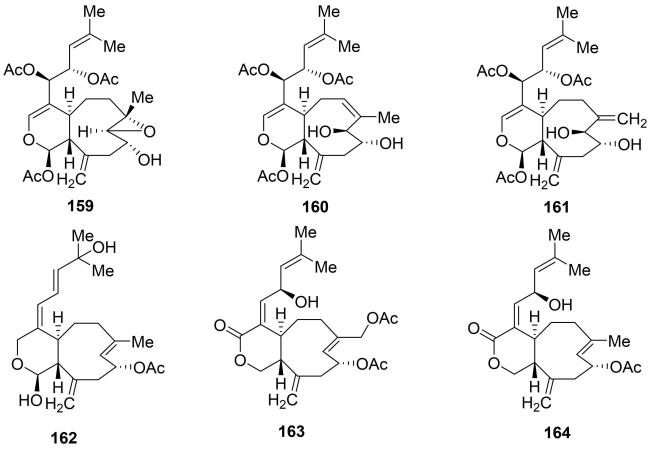


Figure 11. Xenicane-type diterpenoids isolated from various natural sources.

Two eunicellin-type diterpenoids, cladielloides A (**165**) and B (**166**), possessing a 2-hydroxybutyroxy group in their structures, were separated from the extract of an Indonesian octocoral *Cladiella* sp. cladielloide B (**166**) exhibited significant inhibitory effects on elastase release by human neutrophils at a concentration of 10 μg mL^{-1}, while compound **165** only induced weak inhibition of elastase release (Table 2).[65] The same octocoral *Cladiella* sp. also produces 6-*epi*-cladieunicellin F

(**167**), which was characterized by spectroscopic means and was found to be an epimer of cladieunicellin F (**168**). The in vitro anti-inflammatory effects of compound **167** were tested and were compared with its epimers **168**. Eunicellin **167** showed displayed inhibitory effects on the release of elastase by human neutrophils, whereas, eunicellin **168** was found inactive. It was proposed that the stereochemistry of 6-hydroxy group could significantly influence the anti-inflammatory effects.[66] Eleven eunicellin-based diterpenoids, klymollins I–S (**169**–**180**) have been isolated from the EtOAc extract of the soft coral *Klyxummolle* from Taiwan waters. NMR based structure elucidation revealed that these compounds possess a cladiellane skeleton with a C-2, C-9 ether bridge. Compounds **169**–**180** (Figure 12) displayed some potential in elastase release in human neutrophils with compound **173** the most potent in inhibiting the elastase release (IC_{50} = 2.92 μM). The ability of **173** to exhibit such a potent anti-inflammatory activity could be attributed to the presence of the phenylacetate at C-6.[67] Four more eunicellin-based diterpenoids, krempfielins J–M (**181**–**184**) were found in the extract of another Taiwanese soft coral *Cladiella krempfi*. At a concentration of 10 μM, compounds **182** and **184** exhibited significant inhibition of the elastase release (45.51 and 27.30% inhibition, respectively).[68] More eunicellin-type diterpenoids, krempfielins N–P (**185**–**187**), were also isolated from the same soft coral *C. krempfi*. At a concentration of 10 μM, compounds **185** and **187** exhibited significant activity to inhibit elastase release human neutrophils, with compound **185** has been reported to be most active (73.86%, IC_{50} = 4.94 μM).[69] Eunicellin-based diterpenoids krempfielins Q and R (**188** and **189**), separated from the extract of *C. krempfi* inhibited the elastase release (11.09% inhibition).[70] More eunicellin-type hirsutalins S–V (**190**–**192**), along with a known compound (−)-6α-hydroxy polyanthellin A (**193**), were isolated from the soft coral *Cladiella hirsuta*. All compounds were tested for elastase release in fMLP/CB-induced human neutrophils at 10 μg mL^{-1} and compounds **189**, **190**, and **192** (Figure 12) showed the inhabitation at values of 46.7 ± 8.0, 19.3 ± 5.6 and 4.8 ± 5.6 respectively (Table 2).[71]

The briarenones A–C (**194**–**196**; Figure 13), of eunicellin-derived diterpenoids of briarellin type, were isolated from a Formosan gorgonian *Briareum violaceum* and all compounds were tested for elastase release in *N*-formyl-methionyl-leucyl-

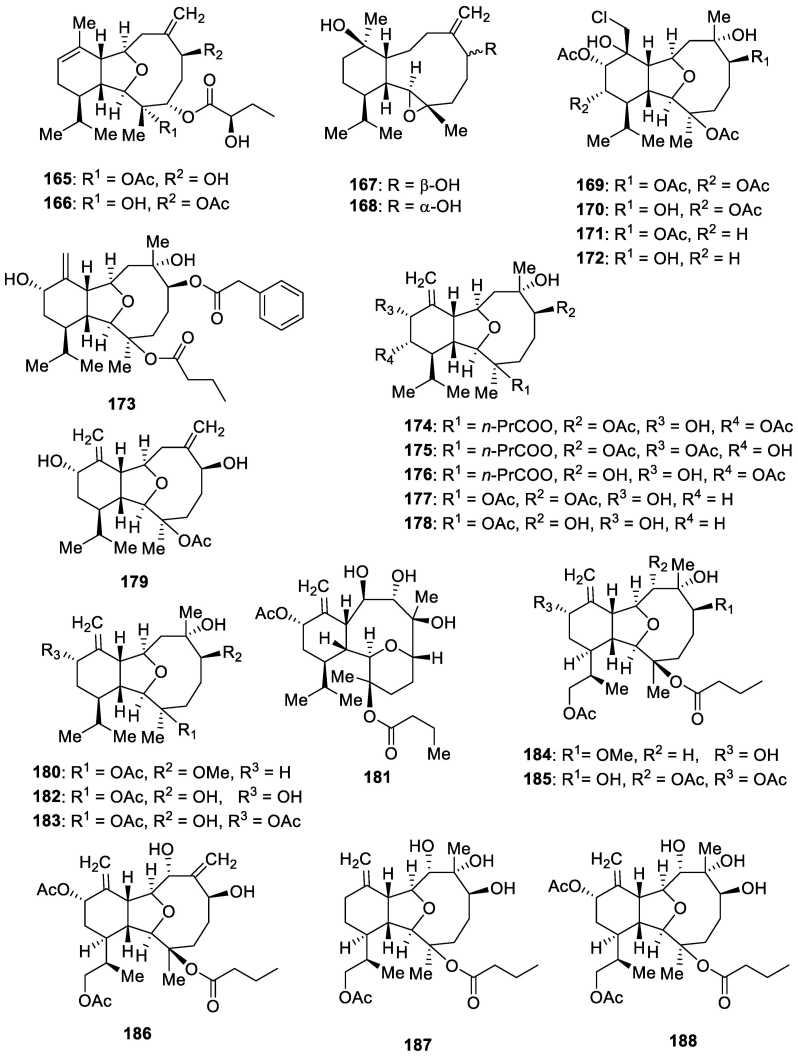


Figure 12. Eunicellin-type diterpenoids isolated from various natural sources.

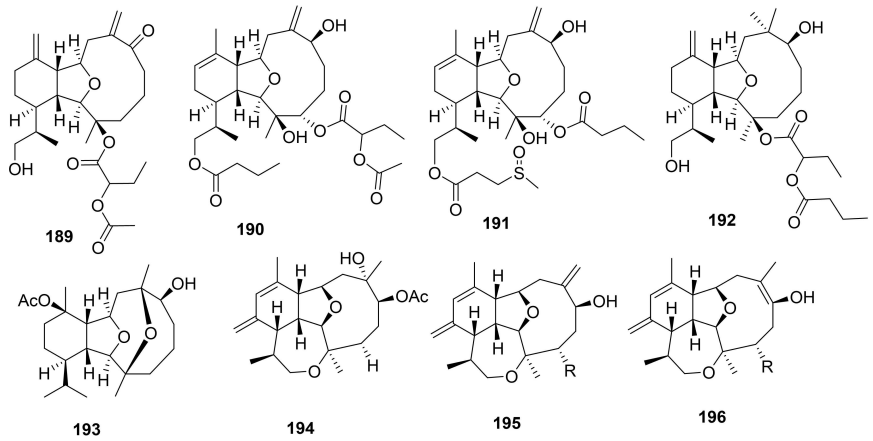


Figure 13. Eunicellin-type diterpenoids isolated from various natural sources.

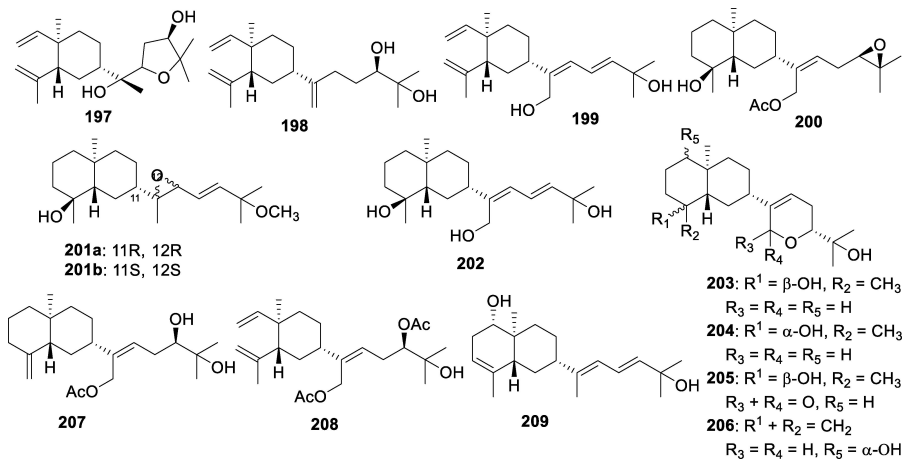


Figure 14. Lobane- and prenyleudesmane-type diterpenoids isolated from various natural sources.

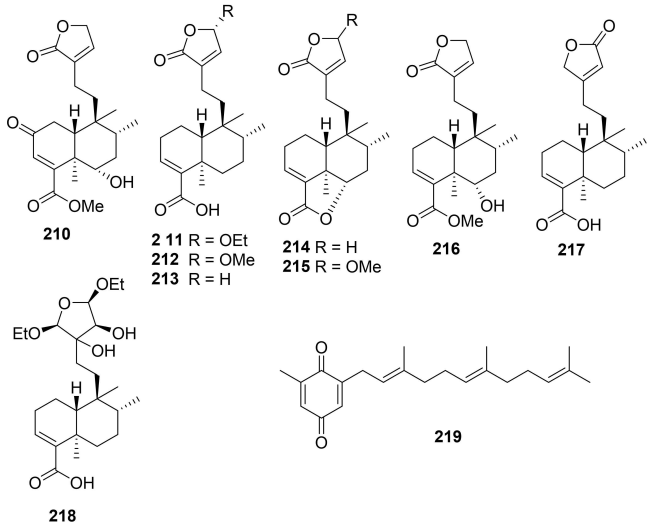


Figure 15. Clerodane-type diterpenoids isolated from various natural sources.

phenylalanine/cytochalasin B (fMLP/CB)-induced human neutrophils assay but found inactive.[72]

Diterpenoids lobovarols F–P (**197**–**207**) are lobane and prenyleudesmane types, and two other compound **208** and **209** were isolated from soft coral *Lobophytum varium*. All compounds were tested for anti-inflammatory activities of diterpenoids **197**–**209** (Figure 14) against the fMLF/CB-induced and results (Table 2) showed that **208** and **209** have potent inhibitory effect against the elastase release with IC_{50} 6.9 ± 2.7 and 4.4 ± 0.7 μM, respectively. Whereas compounds **197** and **198** showed good inhibition with IC_{50} 18.8 ± 1.8 and 20.00 ± 3.0 μM. Thus **197**, **200**, **208**, and **209** have the potential to become anti-inflammatory agents. Compound **197** deserves the attention of additional biological investigation because it was discovered to significantly inhibit elastase release in the absence of fMLF/CB.[73]

Clerodane-type diterpenoids **210**–**218** (Figure 15) were obtained from the leaves of the Taiwan endemic plant

Callicarpa hypoleucophylla. All compounds were tested for anti-inflammatory activity through elastase release and showed moderate to weak activity (Table 2).[74] Methylfarnesylquinone (**219**) is a common phytochemical, has been isolated from the brown alga *Homoeostrichusformosana*. In anti-inflammatory assay, this compound displayed potent in vitro anti-inflammatory activity by inhibiting the elastase release (IC_{50} = 0.48 μg mL^{-1}) in fMLP/CB-induced human neutrophils (Table 2).[75]

4.3. Triterpenoid as an HNE inhibitor

Two nortriterpene lactones (**220** and **221**) have been purified from the fruit extract of *Schisandra arisanensis*. The spectroscopic analysis of these compounds revealed that compound **220** may be categorized as schisanartane-type nortriterpenoid, while compounds **221** as preschisanartane-type nortriterpenoid (Figure 16, Table 3). The inhibitory effects on elastase release by human neutrophils in response to fMLP/CB were tested for compound **220** and **221**, which showed mild anti-inflammatory effects (22.24 ± 4.91 and 18.47 ± 2.20) on elastase release. In this anti-inflammatory assay genistein was used as a standard compound (51.60 ± 5.89 %).[76] Lupeol (**222**), isolated from the ethanolic extract of *Distyliumracemosum* branches, moderately inhibited the elastase release with IC_{50} values of 72.2 μg mL^{-1}. However, this activity was weaker than the positive control, oleanolic acid (IC_{50} = 9.7 μg mL^{-1}).[77] Ursolic acid 3-*O*-acetate (**223**) was isolated from the ethanol extract of *Callistemon lanceolatus* stems showed moderate elastase inhibitory activity with an IC_{50} value of 17.3 μg mL^{-1}, compared to that of oleanolic acid (**224**) as a positive control (IC_{50} 3.0 μg mL^{-1}).[78] The triterpenoids; **225**–**227** (Figure 16), isolated from the leaves and twigs of *Pachycentria formosana*, were evaluated for their inhibitory effect on fMLP/CB-induced elastase release. Among the isolated compounds, Oleanolic acid (**224**), Ursolic acid acetate (**223**), 3-*O*-[(*E*)-feruloyl]ursolic acid (**225**), 3-Epibetulinic acid (**226**), Lawsonic acid (**227**) showed the inhibition fMLP/CB-induced elastase release with IC_{50} values 4.90 ± 0.22, 24.8 ± 3.2, 18.6 ± 3.2, 1.49 ± 0.13 and 16.1 ± 0.6 respectively (Table 3). This analysis revealed that increase in the aromatic character of triterpenoids may lead to a decrease in anti-inflammatory potential.[79] In an in vitro HNE inhibition assay,

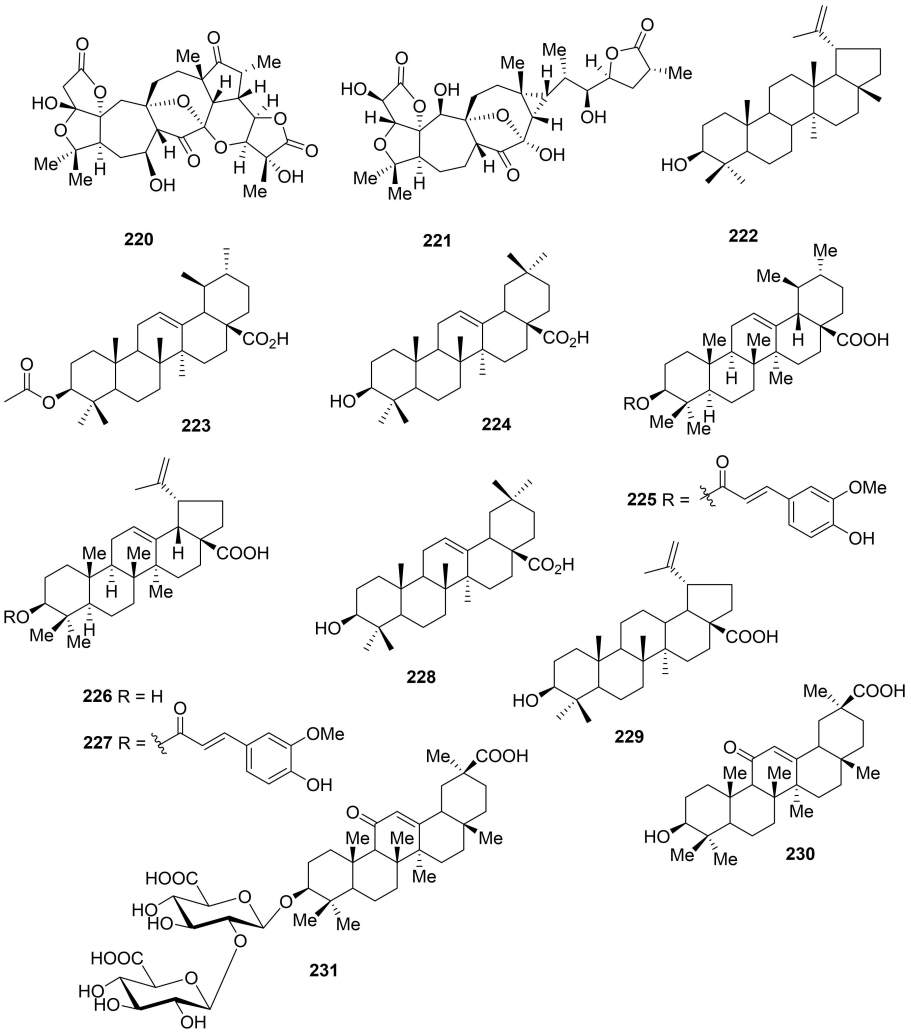


Figure 16. Schisanartane-type nortriterpenoid and other terpenoids isolated from various natural sources.

Table 3. Elastase inhibitory activity of naturally occurring triterpenoids.

Sr. #	Compound	Biological source	Inhibition	Release (IC_{50})	Ref.
1	Arisanlactone B (**220**)	*Schisandra arisanensis*	–	22.24 ± 4.91 %	[76]
2	2β-Hydroxyarisanlactone C (**221**)		–	18.47 ± 2.20 %	
3	Lupeol (**222**)	*Distyliumracemosum*	–	72.2 μg mL^{-1} (IC_{50})	[77]
4	Ursolic acid 3-*O*-acetate (**223**)	*Callistemon lanceolatus*	–	17.3 μg mL^{-1} (IC_{50})	[78]
5	Ursolic acid 3-*O*-acetate (**223**)	*Pachycentria formosana*	–	24.8 ± 3.2	[79]
6	3-*O*-[(*E*)-Feruloyl]ursolic acid (**225**)		–	18.6 ± 3.2	
7	3-Epibetulinic acid (**226**)		–	1.49 ± 0.13	
8	Lawsonic acid (**227**)		–	16.1 ± 0.6	
9	Ursolic acid (**228**)	*Lepidoziachordulifera*	–	5.51 μM	[80]
10	Betulinic acid (**229**)		–	6.83 μM	
11	Glycyrrhetinic acid (**230**),		–	36.90 μM	
12	Glycyrrhizin (**231**)		–	27.58 μM	
13	Oleanolic acid (**224**)		–	8.05 μM	
14	Lupeol (**222**)		–	8.20 μM	
15	ursolic acid (**228**)	*Pseudomonas aeruginosa*	96 %	–	[83]
16	betulinic acid (**229**)		92 %	–	
17	Δ^1-Lupenone (**232**)	*Ganoderma mastoporum*	–	3.26 ± 0.07 μg mL^{-1}	[84]
18	Ganodermanondiol (**233**)		–	5.01 ± 0.82 μg mL^{-1}	
19	Lucidumol B (**234**)		–	3.32 ± 0.14 μg mL^{-1}	
20	Taibaienoside I (**237**)	*Panax japonicas*	–	1.36 ± 0.12	[85]
21	Chikusetsusaponin-IVa (**240**)		–	4.76 ± 1.71	
22	Chikusetsusaponin-IVa methyl ester (**241**)		–	1.97 ± 0.63	
23	Chikusetsusaponin-IVa butyl ester (**242**)		–	7.28 ± 1.48	
24	Chikusetsusaponin-Ib (**245**)		–	1.87 ± 0.27	
25	Pseudoginsenoside RT1 (**246**)		–	44.5 ± 2.53	
26	Pseudoginsenoside RT1 methyl ester (**247**)		–	7.75 ± 1.51	
27	Hederagenin-3-*O*-(3,4-*O*-di-acetyl-α-L-arabinopyranoside)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (SMG-1, **1**)	*Sapindusmukorossi*	–	80 % at a concentration of 3.0 μM inhibition	[86]
28	23-Hydroxy-3-oxoolean-12-en-28-oic acid (**250**)	*Tripterygium hypoglaucum*	–	1.93 μM	[87]
29	3,23-Hydroxy-olean-12-en-28-oic acid (**251**)		–	1.92 μM	

pentacyclic and tetracyclic triterpenoids were evaluated for their anti-inflammatory activity. Among tested compounds, six pentacyclic triterpenes which includes Ursolic acid (**228**), oleanolic acid (**224**), betulinic acid (**229**), glycyrrhetinic acid (**230**), glycyrrhizin (**231**), lupeol (**222**) Significantly inhibited HNE as compare to tetracyclic triterpenes. In this study at 30 μM, the pentacyclic triterpenes ursolic acid, oleanolic acid, betulinic acid, and lupeol inhibited HNE activity by more than 80 % (p,0.01). Among the six pentacyclic triterpenes, ursolic acid (1) had the most potent inhibitory activity, with a minimal inhibition (12.2 %) at 1 μM and a maximal inhibition (80 %) at 10 μM. The IC_{50} values of the six natural pentacyclic triterpenes were consistently around 5.51 μM (ursolic acid), 8.05 μM (oleanolic acid), 36.90 μM (glycyrrhetinic acid), 27.58 μM (glycyrrhizin), 6.83 μM (betulinic acid), and 8.20 μM (lupeol; Table 3). Ursolic acid (228) has the highest inhibitory potency (IC_{50} = 5.51 M) among these pentacyclic triterpenes. Important aspect of this study is that the HNE inhibitory activity of ursolic acid (**228)** was in detail verified using a mouse model of acute smoke-induced lung inflammation, which revealed that the pentacyclic triterpenes competitively and reversibly inhibited HNE. Interestingly, none of the tested tetra cyclic triterpenoids displayed any potential, which lead to the conclusion that pentacyclic nucleus of triterpenoids is the basic nucleus responsible for anti-inflammatory activity. However, molecular docking experiments indicated that in pentacyclic triterpenoids, the molecular scaffold, 28-COOH, and a double bond at an appropriate location contribute to the anti-inflammatory potential of these compounds.[80] Pentacyclic triterpenes, such as ursolic acid and oleanolic acid, are abundant in apples and other fruits and are employed in nutraceuticals to treat a variety of disorders.[81] Furthermore, published studies show that ursolic acid administration reduces trauma-hemorrhagic shock-induced liver and pulmonary damage in rats. In addition, ursolic acid delivery lowers hepatic malondialdehyde levels and increases plasma aspartate aminotransferase and alanine aminotransferase levels following trauma-hemorrhagic shock.[82]

In other studies, ursolic acid (**228**) and betulinic acid (**229**) have been reported to inhibit 96 and 92%, respectively (Table 3), the activity of the elastase release in *Pseudomonas aeruginosa*.[83] The methanolic extracts of the fruiting bodies of *Ganoderma mastoporum* contains triterpenoids; Δ^1-lupenone (**232**), ganodermanondiol (**233**) and lucidumol B (**234**; Figure 17), which displayed inhibitory effects towards elastase release in a concentration-dependent manner with IC_{50} values were in the range between 1.94 and 5.01 $\mu g\,mL^{-1}$ against elastase release, respectively, with lucidumol B (**234**) displayed more significant inhibition of elastase release. Interesting point to note in this study is that tetracyclic triterpenoids also showed anti-inflammatory potential, which otherwise in study by Feng *et al.*[80] was found to be inactive,[84] which revealed that the core structure is not much responsible for the activity, rather 28-COOH, and a double bond at an appropriate location contribute to the anti-inflammatory potential of these compounds.

Triterpenoid saponins **235**–**247** (Figure 18), and oleanolic acid (**222**) were separated from the roots of *Panax japonicus* var. *major*. All these compounds were tested in elastase release by human neutrophils inhibitory assay, and were showed varying potential as anti-inflammatory agents. However, among all these isolates, compounds **222**, **242**, **244** and **246** exhibited strong inhibition with IC_{50} values ranging from 0.78 to 43.6 μM (Table 3). Compounds **237** and **238**, with carboxylic acid and methyl ester functionalities, respectively, at the sugar C-6′ position, inhibited elastase release, and the potency increased significantly when carboxylic acid group was esterified with a butyl group in **2** (IC_{50} = 1.36 μM for elastase). Compounds **239**, **240**, and **241** have a carboxylic acid, a methyl ester, and a butyl ester group, respectively, at the C-6′-position. Further **240** was more potent than **239** and **241** against elastase release.[85] Hederagenin-3-*O*-(3,4-*O*-di-acetyl-α-L-arabinopyranoside)-(1→3)-α-L-rhamnopyranosyl-(1→2)-α-L-arabinopyranoside (SMG-1, **248**), isolated from *Sapindusmukorossi*, potently inhibited exhibited 80% inhibition of elastase release at a concentration of 3.0 μM and reduced membrane-associated p47 phox expression in fMLP-induced intact neutrophils. According to the findings, SMG-1 (248) inhibited fMLP binding to its receptor in a concentration-dependent manner, demonstrating that saponin 248 is a natural fMLP receptor inhibitor with the potential to be developed into a useful new therapeutic agent for treating neutrophilic inflammatory diseases.[86] Triterpenes **249**–**258** (Figure 18) were obtained from the aerial parts of *Tripterygium hypoglaucum*, among all the isolated compounds 23-hydroxy-3-oxoolean-12-en-28-oic acid (**250**) and 3,23-hydroxy-olean-12-en-28-oic acid (**251**) were found active against elastase release with IC_{50} = 1.93 and 1.92 μM, respectively. Interestingly other isolated compound which includes 19-*O*-D-glucopyranosyl-labda-8(17),14-dien-13-ol (**249**) α-boswellic acid (**252**), wilforlide B (**253**), wilforlide A (**254**), olean-12-en-28-oic acid (**255**) 3,28-dihydroxy-olean-12-en-29-oic acid (**256**), 3-oxo-21- hydroxy-olean-12-ene (**257**) and oleanolic acid (**222**) were found inactive.[87]

5. Conclusions

HNE inhibitors have great potential as therapeutic agents for various inflammatory conditions, including COPD and emphysema. The discovery of natural sources of HNE inhibitors, such as endophytic fungi, offers an exciting avenue for the development of new drugs

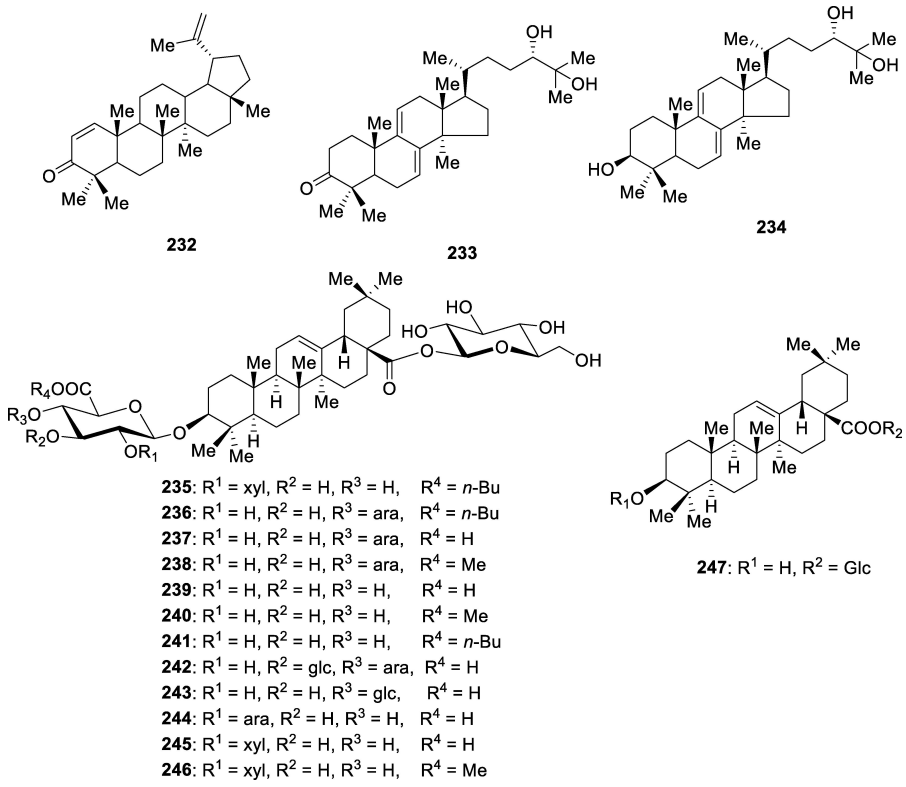
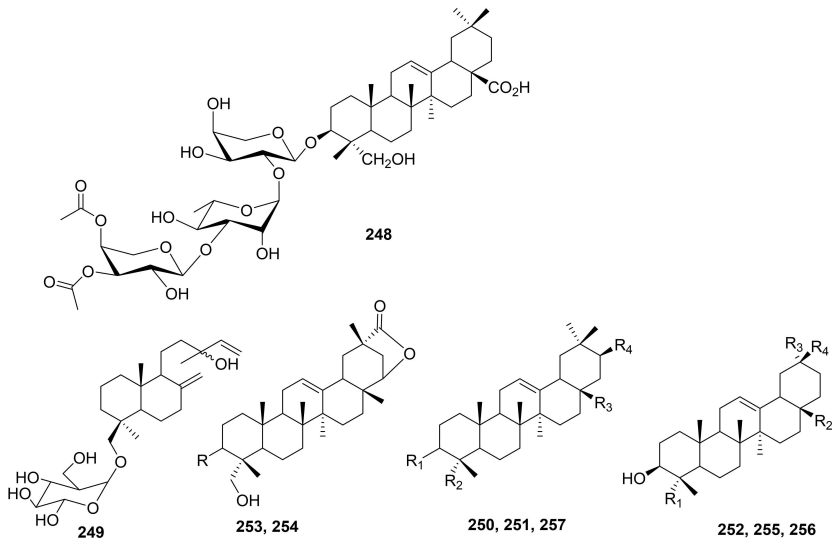


Figure 17. Triterpenoids isolated from various natural sources.



2: R_1H =O, R_2 = CH_2OH, R_3 = COOH, R_4 = H; 3: R_1 = OH, R_2 = CH_2OH, R_3 = COOH, R_4 = H
4: R_1 = COOH, R_2 = R_3 = R_4 = CH_3; 5: RH = O; 6: R = OH; 7: R_1 = CH_3, R_2 = COOH, R_3 = CH_2OH, R_4 = CH_3
8: R_1 = CH_3, R_2 = CH_2OH, R_3 = CH_3, R_4 = COOH; 9: R_1H =O, R_2 = R_3 = CH_3, R_4 = OH

Figure 18. Triterpenoids isolated from various natural sources.

with reduced side effects. On the basis of the above data, it can be deduced that natural sources provided a variety of terpenoids with stronger inhibition than those in standard use. By continuing to study the structure-activity relationships and mechanisms of action of terpenoids, researchers might be able to design new drugs with improved potency, specificity, and safety profiles. Further research in this area could lead to the development of safe and effective treatments for inflammatory diseases. Further in vivo tests and clinical trials are necessary to fully understand the efficacy of terpenoids as HNE inhibitors in treating various diseases. It is hoped that the information presented on the potential therapeutic effects of terpenoids will guide researchers in the development of safer and more effective drugs derived from natural terpenoids for managing these diseases and their associated complications.

Conflict of Interests

The authors declare no conflict of interest.

Keywords: anti-inflammatory agents · cystic fibrosis · human neutrophil elastase inhibitors · natural products · terpenoids

[1] B. Korkmaz, M. S. Horwitz, D. E. Jenne, F. Gauthier, *Pharmacol. Rev.* **2010**, *62*, 726–759.
[2] A. Masic, J. S. Booth, G. K. Mutwiri, L. A. Babiuk, Y. Zhou, *J. Virol.* **2009**, *83*, 10198–10210.
[3] H. Darani, M. Doenhoff, *Scand. J. Immunol.* **2009**, *70*, 384–388.
[4] A. Santillo, A. Kelly, C. Palermo, A. Sevi, M. Albenzio, *Int. Dairy J.* **2009**, *19*, 655–660.
[5] T. Tamada, T. Kinoshita, K. Kurihara, M. Adachi, T. Ohhara, K. Imai, R. Kuroki, T. Tada, *J. Am. Chem. Soc.* **2009**, *131*, 11033–11040.
[6] L. D. Black, K. K. Brewer, S. M. Morris, B. M. Schreiber, P. Toselli, M. A. Nugent, B. Suki, P. J. Stone, *J. Appl. Physiol.* **2005**, *98*, 1434–1441.
[7] A. Roghanian, J.-M. Sallenave, *Journal of Aerosol Medicine And Pulmonary Drug Delivery* **2008**, *21*, 125–144.
[8] J. L. Wright, M. Cosio, A. Churg, *American Journal Of Physiology-Lung Cellular And Molecular Physiology* **2008**, *295*, L1-L15.
[9] a) H. L. Malech, J. I. Gallin, *N. Engl. J. Med.* **1987**, *317*, 687–694; b) V. Witko-Sarsat, P. Rieu, B. Descamps-Latscha, P. Lesavre, L. Halbwachs-Mecarelli, *Lab. Invest.* **2000**, *80*, 617–653; c) K. Okajima, N. Harada, M. Uchiba, *J. Pharmacol. Exp. Ther.* **2002**, *301*, 1157–1165; d) M. Ennis, *Current Allergy and Asthma Reports* **2003**, *3*, 159–165; e) J. Vinten-Johansen, *Cardiovasc. Res.* **2004**, *61*, 481–497.
[10] a) N. Borregaard, *Eur. J. Haematol.* **1988**, *41*, 401–413; b) M. Faurschou, N. Borregaard, *Microbes Infect.* **2003**, *5*, 1317–1327; c) A. Mollica, M. P. Paradisi, K. Varani, S. Spisani, G. Lucente, *Bioorg. Med. Chem.* **2006**, *14*, 2253–2265.
[11] L. Marinaccio, A. Stefanucci, G. Scioli, A. Della Valle, G. Zengin, A. Cichelli, A. Mollica, *Int. J. Mol. Sci.* **2022**, *23*, 2924.
[12] E. Hajjar, T. Broemstrup, C. Kantari, V. Witko-Sarsat, N. Reuter, *The FEBS journal* **2010**, *277(10)*, 2238–2254.
[13] P. J. Barnes, R. Stockley, *Eur. Respir. J.* **2005**, *25*, 1084–1106.
[14] K. Imaki, T. Okada, Y. Nakayama, Y. Nagao, K. Kobayashi, Y. Sakai, T. Mohri, T. Amino, H. Nakai, M. Kawamura, *Bioorg. Med. Chem.* **1996**, *4*, 2115–2134.
[15] a) R. A. Pauwels, A. S. Buist, P. M. Calverley, C. R. Jenkins, S. S. Hurd, *Am. J. Respir. Crit. Care Med.* **2001**, *163*, 1256–1276; b) B. Patel, R. Priefer, *Life Sci.* **2022**, 120374.
[16] a) W. C. Groutas, D. Dou, K. R. Alliston, *Expert Opin. Ther. Pat.* **2011**, *21(3)*, 339–354; b) Z. Sun, P. Yang, *Lancet Oncol.* **2004**, *5(3)*, 182–190.
[17] B. Korkmaz, T. Moreau, F. J. B. Gauthier, *Biochimie* **2008**, *90*, 227–242.
[18] A. Masyita, R. M. Sari, A. D. Astuti, B. Yasir, N. R. Rumata, T. B. Emran, F. Nainu, J. Simal-Gandara, *Food Chem.* **2022**, *10*, 100217.
[19] a) A. K. Surowiak, L. Balcerzak, S. Lochyński, D. J. Strub, *Int. J. Mol. Sci.* **2021**, *22*, 5036; b) E. Proshkina, S. Plyusnin, T. Babak, E. Lashmanova, F. Maganova, L. Koval, E. Platonova, M. Shaposhnikov, A. Moskalev, *Antioxidants* **2020**, *9*, 529.
[20] R. de Cássia da Silveira e Sá, L. N. Andrade, D. P. de Sousa, *Molecules* **2013**, *18*, 1227–1254.
[21] a) H. N. Nguyen, S. L. Ullevig, J. D. Short, L. Wang, Y. J. Ahn, R. Asmis, *Antioxidants* **2021**, *10*, 1161; b) E. S. Mengoni, G. Vichera, L. A. Rigano, M. L. Rodriguez-Puebla, S. R. Galliano, E. E. Cafferata, O. H. Pivetta, S. Moreno, A. A. Vojnov, *Fitoterapia* **2011**, *82*, 414–421.
[22] M. Passi, S. Shahid, S. Chockalingam, I. K. Sundar, G. Packirisamy, *Int. J. Nanomed.* **2020**, 3803–3826.
[23] S. K. Mishra, P. M. Ishfaq, S. Tripathi, N. Gupta in *Fruits as Boosters of the Immune System* (Eds.: 01), Springer, **2022**, pp. 391–411.
[24] V. Hernandez, S. Manez, M. Recio, R. Giner, J. Rios, *Eur. J. Pharm. Sci.* **2005**, *26*, 162–169.

[25] A. J. Hay, M. Hamburger, K. Hostettmann, J. Hoult, *Br. J. Pharmacol.* **1994**, *112*, 9–12.
[26] Y.-C. Chang, C.-C. Chiang, Y.-S. Chang, J.-J. Chen, W.-H. Wang, L.-S. Fang, H.-M. Chung, T.-L. Hwang, P.-J. Sung, *Mar. Drugs* **2020**, *18*, 554.
[27] B. M. Fraga, *Nat. Prod. Rep.* **2006**, *23*, 943–972.
[28] L.-F. Chuang, T.-Y. Fan, J.-J. Li, P.-J. Sung, *Biochem. Syst. Ecol.* **2007**, *7*, 470–471.
[29] P.-J. Sung, Y.-D. Su, T.-L. Hwang, L.-F. Chuang, H.-M. Chung, J.-J. Chen, J.-J. Li, L.-S. Fang, W.-H. Wang, *Chem. Lett.* **2009**, *38*, 282–283.
[30] P.-J. Sung, Y.-D. Su, T.-L. Hwang, L.-F. Chuang, J.-J. Chen, J.-J. Li, L.-S. Fang, W.-H. Wang, *Chem. Lett.* **2008**, *37*, 1244–1245.
[31] a) E. Warnhoff, V. Srinivasan, *Can. J. Chem.* **1966**, *44*, 2259–2267; b) V. Srinivasan, E. Warnhoff, *Can. J. Chem.* **1976**, *54*, 1372–1382.
[32] T.-L. Hwang, Y.-D. Su, W.-P. Hu, L.-F. Chuang, P.-J. Sung, *Heterocycles* **2009**, *78*, 1563–1567.
[33] H.-M. Chung, J.-H. Su, T.-L. Hwang, J.-J. Li, J.-J. Chen, Y.-H. Chen, Y.-C. Chang, Y.-D. Su, Y.-H. Chen, L.-S. Fang, *Tetrahedron* **2013**, *69*, 2740–2744.
[34] H.-M. Chung, W.-H. Wang, T.-L. Hwang, L.-S. Fang, Z.-H. Wen, J.-J. Chen, Y.-C. Wu, P.-J. Sung, *Mar. Drugs* **2014**, *12*, 5856–5863.
[35] H.-M. Chung, W.-H. Wang, T.-L. Hwang, J.-J. Chen, L.-S. Fang, Z.-H. Wen, Y.-B. Wang, Y.-C. Wu, P.-J. Sung, *Int. J. Mol. Sci.* **2014**, *15*, 15679–15688.
[36] H.-M. Chung, W.-H. Wang, T.-L. Hwang, J.-J. Li, L.-S. Fang, Y.-C. Wu, P.-J. Sung, *Molecules* **2014**, *19*, 12320–12327.
[37] J.-J. Chen, C.-S. Tsai, T.-L. Hwang, P.-C. Shieh, J.-F. Chen, P.-J. Sung, *Food Chem.* **2010**, *119*, 974–980.
[38] S.-Y. Kao, J.-H. Su, T.-L. Hwang, J.-H. Sheu, Z.-H. Wen, Y.-C. Wu, P.-J. Sung, *Mar. Drugs* **2011**, *9*, 1534–1542.
[39] Y.-M. Chung, C.-K. Wei, D.-W. Chuang, M. El-Shazly, C.-T. Hsieh, T. Asai, Y. Oshima, T.-J. Hsieh, T.-L. Hwang, Y.-C. Wu, *Bioorg. Med. Chem.* **2013**, *21*, 3866–3872.
[40] S.-C. Huang, P.-C. Kuo, T.-L. Hwang, Y.-Y. Chan, C.-H. Chen, T.-S. Wu, *Tetrahedron Lett.* **2013**, *54*, 3332–3335.
[41] K. C. Kim, D. J. Kim, M. S. Lee, J. Y. Seo, I. D. Yoo, I. S. Lee, *J. Microbiol. Biotechnol.* **2018**, *28*, 1806–1813.
[42] S. S. Ebada, N. A. Al-Jawabri, F. S. Youssef, D. H. El-Kashef, T.-O. Knedel, A. Albohy, M. Korinek, T.-L. Hwang, B.-H. Chen, G.-H. Lin, *RSC Adv.* **2020**, *10*, 38128–38141.
[43] a) J. Xiong, Y. Ma, Y. Xu, *Phytochemistry* **1992**, *31*, 917–921.
[44] R. Wang, Y.-Q. Liu, W. Ha, Y.-P. Shi, T.-L. Hwang, G.-J. Huang, T.-S. Wu, K.-H. Lee, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3944–3947.
[45] P.-C. Kuo, M.-L. Yang, T.-L. Hwang, Y.-Y. Lai, Y.-C. Li, T. D. Thang, T.-S. Wu, *J. Nat. Prod.* **2013**, *76*, 230–236.
[46] J. Qin, H.-M. Li, L.-h. Gao, D. Liu, R.-T. Li, K.-H. Lee, *Phytochem. Lett.* **2014**, *10*, 313–317.
[47] J.-J. Chen, C.-W. Ting, Y.-C. Wu, T.-L. Hwang, M.-J. Cheng, P.-J. Sung, T.-C. Wang, J.-F. Chen, *Int. J. Mol. Sci.* **2013**, *14*, 13063–13077.
[48] J.-H. Sheu, Y.-P. Chen, T.-L. Hwang, M. Y. Chiang, L.-S. Fang, P.-J. Sung, *J. Nat. Prod.* **2006**, *69*, 269–273.
[49] P.-J. Sung, Y.-P. Chen, T.-L. Hwang, W.-P. Hu, L.-S. Fang, Y.-C. Wu, J.-J. Li, J.-H. Sheu, *Tetrahedron* **2006**, *62*, 5686–5691.
[50] Y. C. Shen, Y. H. Chen, T. L. Hwang, J. H. Guh, A. T. Khalil, *Helv. Chim. Acta* **2007**, *90*, 1391–1398.
[51] Y.-C. Lin, M. H. Abd El-Razek, T.-L. Hwang, M. Y. Chiang, Y.-H. Kuo, C.-F. Dai, Y.-C. Shen, *J. Nat. Prod.* **2009**, *72*, 1911–1916.
[52] C.-C. Liaw, Y.-H. Kuo, Y.-S. Lin, T.-L. Hwang, Y.-C. Shen, *Mar. Drugs* **2011**, *9*, 1477–1486.
[53] C.-C. Liaw, Y.-C. Lin, Y.-S. Lin, C.-H. Chen, T.-L. Hwang, Y.-C. Shen, *Mar. Drugs* **2013**, *11*, 2042–2053.
[54] P.-J. Sung, B.-Y. Chen, M.-R. Lin, T.-L. Hwang, W.-H. Wang, J.-H. Sheu, Y.-C. Wu, *Mar. Drugs* **2009**, *7*, 472–482.
[55] P.-J. Sung, Y.-D. Su, G.-Y. Li, M. Y. Chiang, M.-R. Lin, I.-C. Huang, J.-J. Li, L.-S. Fang, W.-H. Wang, *Tetrahedron* **2009**, *65*, 6918–6924.
[56] J.-H. Su, B.-Y. Chen, T.-L. Hwang, Y.-H. Chen, I.-C. Huang, M.-R. Lin, J.-J. Chen, L.-S. Fang, W.-H. Wang, J.-J. Li, *Chem. Pharm. Bull.* **2010**, *58*, 662–665.
[57] P.-H. Hong, Y.-D. Su, N.-C. Lin, Y.-H. Chen, Y.-H. Kuo, T.-L. Hwang, W.-H. Wang, J.-J. Chen, J.-H. Sheu, P.-J. Sung, *Tetrahedron Lett.* **2012**, *53*, 1710–1712.
[58] Y.-D. Su, C.-H. Cheng, W.-F. Chen, Y.-C. Chang, Y.-H. Chen, T.-L. Hwang, Z.-H. Wen, W.-H. Wang, L.-S. Fang, J.-J. Chen, *Tetrahedron Lett.* **2014**, *55*, 6065–6067.
[59] C.-C. Liaw, Y.-B. Cheng, Y.-S. Lin, Y.-H. Kuo, T.-L. Hwang, Y.-C. Shen, *Mar. Drugs* **2014**, *12*, 4677–4692.
[60] Y.-H. Chen, C.-Y. Tai, Y.-D. Su, Y.-C. Chang, M.-C. Lu, C.-F. Weng, J.-H. Su, T.-L. Hwang, Y.-C. Wu, P.-J. Sung, *Mar. Drugs* **2011**, *9*, 934–943.
[61] C.-Y. Kao, J.-H. Su, M.-C. Lu, T.-L. Hwang, W.-H. Wang, J.-J. Chen, J.-H. Sheu, Y.-H. Kuo, C.-F. Weng, L.-S. Fang, *Mar. Drugs* **2011**, *9*, 1319–1331.
[62] C.-H. Lee, C.-Y. Kao, S.-Y. Kao, C.-H. Chang, J.-H. Su, T.-L. Hwang, Y.-H. Kuo, Z.-H. Wen, P.-J. Sung, *Mar. Drugs* **2012**, *10*, 427–438.
[63] L.-C. Hu, J.-H. Su, M. Y.-N. Chiang, M.-C. Lu, T.-L. Hwang, Y.-H. Chen, W.-P. Hu, N.-C. Lin, W.-H. Wang, L.-S. Fang, *Mar. Drugs* **2013**, *11*, 1999–2012.
[64] C.-Y. Huang, P.-J. Sung, C. Uvarani, J.-H. Su, M.-C. Lu, T.-L. Hwang, C.-F. Dai, S.-L. Wu, J.-H. Sheu, *Sci. Rep.* **2015**, *5*, 1–9.
[65] Y.-H. Chen, C.-Y. Tai, T.-L. Hwang, C.-F. Weng, J.-J. Li, L.-S. Fang, W.-H. Wang, Y.-C. Wu, P.-J. Sung, *Mar. Drugs* **2010**, *8*, 2936–2945.
[66] Y.-H. Chen, T.-L. Hwang, Y.-D. Su, Y.-C. Chang, Y.-H. Chen, P.-H. Hong, L.-C. Hu, W.-H. Yen, H.-Y. Hsu, S.-J. Huang, *Chem. Pharm. Bull.* **2012**, *60*, 160–163.
[67] M.-C. Lin, B.-W. Chen, C.-Y. Huang, C.-F. Dai, T.-L. Hwang, J.-H. Sheu, *J. Nat. Prod.* **2013**, *76*, 1661–1667.
[68] Y.-N. Lee, C.-J. Tai, T.-L. Hwang, J.-H. Sheu, *Mar. Drugs* **2013**, *11*, 2741–2750.
[69] Y.-N. Lee, C.-J. Tai, T.-L. Hwang, J.-H. Sheu, *Mar. Drugs* **2014**, *12*, 1148–1156.
[70] C.-J. Tai, U. Chokkalingam, Y. Cheng, S.-P. Shih, M.-C. Lu, J.-H. Su, T.-L. Hwang, J.-H. Sheu, *Int. J. Mol. Sci.* **2014**, *15*, 21865–21874.
[71] T.-Z. Huang, B.-W. Chen, C.-Y. Huang, T.-L. Hwang, C. Uvarani, C.-F. Dai, P.-J. Sung, J.-H. Su, J.-H. Sheu, *Mar. Drugs* **2015**, *13*, 2757–2769.
[72] Y. Cheng, A. F. Ahmed, R. S. Orfali, C.-F. Dai, J.-H. Sheu, *Mar. Drugs* **2019**, *17*, 120.
[73] C.-H. Chang, A. F. Ahmed, T.-S. Yang, Y.-C. Lin, C.-Y. Huang, T.-L. Hwang, J.-H. Sheu, *Mar. Drugs* **2020**, *18*, 223.
[74] Y.-C. Lin, J.-J. Lin, S.-R. Chen, T.-L. Hwang, S.-Y. Fang, M. Korinek, C.-Y. Chen, Y.-S. Lin, T.-Y. Wu, M.-H. Yen, *Molecules* **2020**, *25*, 2288.
[75] H.-Y. Fang, U. Chokkalingam, S.-F. Chiou, T.-L. Hwang, S.-L. Chen, W.-L. Wang, J.-H. Sheu, *Int. J. Mol. Sci.* **2014**, *16*, 736–746.
[76] Y.-B. Cheng, T.-C. Liao, Y.-W. Lo, Y.-C. Chen, Y.-C. Kuo, S.-Y. Chen, C.-T. Chien, T.-L. Hwang, Y.-C. Shen, *J. Nat. Prod.* **2010**, *73*, 1228–1233.
[77] R. K. Ko, G. O. Kim, C. G. Hyun, D. S. Jung, N. H. Lee, *Phytother. Res.* **2011**, *25*, 1451–1456.
[78] J.-H. Kim, J.-E. Kim, H.-J. Bu, N.-H. Lee, *Bull. Korean Chem. Soc.* **2012**, *33*, 344–346.
[79] J. Y. Cho, T. H. Lee, T. L. Hwang, S. Z. Yang, l. S. Chen, T. H. Chou, P. J. Sung, J. J. Chen, *Chem. Biodiversity* **2011**, *8*, 1709–1716.
[80] L. Feng, X. Liu, W. Zhu, F. Guo, R. Wang, K. Chen, C. Huang, Y. Li, *PLoS One* **2013**, *8*, e82794.
[81] S. Jäger, H. Trojan, T. Kopp, M. N. Laszczyk, A. Scheffler, *Molecules* **2009**, *14*, 2016–2031.
[82] T.-L. Hwang, H.-l. Shen, F.-C. Liu, H.-l. Tsai, Y.-C. Wu, F.-R. Chang, H.-P. Yu, *PLoS One* **2014**, *9*, e111365.
[83] M. Gilabert, K. Marcinkevicius, S. Andujar, M. Schiavone, M. Arena, A. Bardón, *Phytomedicine* **2015**, *22*, 77–85.
[84] T. D. Thang, P.-C. Kuo, T.-L. Hwang, M.-L. Yang, N. T. B. Ngoc, T. T. N. Han, C.-W. Lin, T.-S. J. M. Wu, *Molecules* **2013**, *18*, 14285–14292.
[85] H.-H. Chan, T.-L. Hwang, M. V. B. Reddy, D.-T. Li, K. Qian, K. F. Bastow, K.-H. Lee, T.-S. Wu, *J. Nat. Prod.* **2011**, *74*, 796–802.
[86] T.-L. Hwang, C.-C. Wang, Y.-H. Kuo, H.-C. Huang, Y.-C. Wu, L.-M. Kuo, Y.-H. Wu, *Biochem. Pharmacol.* **2010**, *80*, 1190–1200.
[87] Q. Zhao, H.-M. Li, X.-Q. Chen, R.-T. Li, D. Liu, *Chem. Nat. Compd.* **2018**, *54*, 471–474.

Manuscript received: May 8, 2023
Revised manuscript received: August 3, 2023
Accepted manuscript online: August 29, 2023
Version of record online: September 20, 2023