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# Absolute configuration assignment of marine natural products in Brazil

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Brazil is one of the most biodiverse countries in the world, with a coastline that stretches over 7,000 km including various marine ecosystems, such as coral reefs, mangroves, and seagrass beds, among other habitats. These diverse environments provide a rich source of compounds, derived from primary or secondary metabolism, which may have countless biological activities. Research on marine natural products (MNP) in Brazil has been ongoing for several decades and led to the discovery of numerous bioactive compounds with potential applications in medicine, agriculture, and cosmetics. These MNP are structurally complex, both from an architectural and stereochemical point of view. However, even with all the well-established techniques for the absolute configuration (AC) assignment, this stage of structural characterization of natural products is still under-explored and remains a challenge. This review presents an overview of natural product chemistry in Brazil, focusing on the stereochemical assignment of marine chiral compounds. The main goals are to describe the techniques employed in the assignments as well as to highlight the importance of choosing the appropriate methods for chiral natural products AC determinations.

## KEYWORDS

biodiversity, Brazilian, secondary metabolites, stereochemical determination, chiral compounds

## 1 Introduction

Brazil is known for its rich biodiversity, which includes a vast array of plant, animal, and microbial species. Many of these organisms are known to produce a variety of compounds with potent biological activity (Valli et al., 2018). Despite plants being one of the most explored sources of natural products, Brazil's marine environment is another rich source of secondary metabolites, with a diverse array of organisms that produce bioactive compounds (Berlinck et al., 2004).

For several decades, Brazil has been actively researching marine natural products (MNP) (Berlinck et al., 2004; Ióca et al., 2018). This research field has focused on exploring the diverse marine fauna and flora of Brazil's extensive coastline, including its coral reefs, mangroves, and seagrass beds, among other habitats. Some of the most promising areas of this research include the discovery of new bioactive compounds with potential pharmaceutical and biomedical applications, as well as the identification of novel structures (Berlinck et al., 2004; Ióca et al., 2018). Up to this point, many bioactive MNPs from both primary and secondary metabolism have been discovered in the

marine environment, highlighting the importance of this region for studying natural products and their potential applications in medicine and other fields (Lorente et al., 2014).

Significant taxonomic differences between terrestrial and marine organisms, whose secondary metabolisms are substantially distinct, allowed the isolation of structurally different compounds from those obtained from traditional sources (Stonik, 2009). Another interesting fact about compounds of marine origin is that they are structurally complex, both from an architectural and stereochemical point of view. These data can be observed in a review of the literature on marine compounds, which reveals that the vast majority of the 1,490 substances reported are chiral compounds with complex structures (Carrol et al., 2021). Since the AC of a compound is often closely related to its biological activity, the determination of absolute stereochemistry is an important step in the characterization of bioactive compounds (Batista et al., 2021).

The determination of the AC of secondary metabolites can be achieved using techniques such as X-ray crystallography, chemical synthesis, Nuclear Magnetic Resonance (NMR) spectroscopy, and chiroptical methods (Batista et al., 2018). X-ray crystallography was used in the first AC assignment of a chiral compound (Bijvoet et al., 1951) and is still considered one of the most reliable techniques (Flack and Bernardinelli, 2008; Harada, 2008; Parsons, 2017). Nevertheless, the requirement of a well-defined single crystal can be prohibitive of a direct AC assignment of natural products, which are usually available in non-crystalline form (Mándi and Kurtan, 2019). Another powerful technique for the AC determination is NMR spectroscopy. However, for being intrinsically insensitive to chirality in the normally used isotropic media, this technique requires the use of chiral derivatizing agents or chiral solvating agents for the AC determination of a target compound (Wenzel and Chisholm, 2011; Seco et al., 2012; Zanardi et al., 2018). Chemical synthesis is also widely used to determine the AC of natural products. By synthesizing the natural product or related compounds using chiral starting materials or chiral catalysts, the AC can be assigned by comparing the physical and spectroscopic properties of the synthesized compounds with those of the natural product. This approach is challenging, since it is necessary to identify viable synthetic routes to obtain the molecules of interest (Sun and Sahinidis, 2022). Furthermore, stereocontrolled organic synthesis is highly dependent on the unequivocal AC of starting materials and products, in addition to being usually laborious, time-consuming, and expensive (Sadlej et al., 2010). Chiroptical methods rely on the differential interaction of a non-racemic chiral sample with left and right circularly polarized radiation and represent an important tool for AC determination of natural products (Grauso et al., 2019). These techniques, which include optical rotation (OR), optical rotational dispersion (ORD), electronic circular dichroism (ECD), vibrational circular dichroism (VCD) and Raman optical activity (ROA), are non-destructive and their measurements are obtained directly in solution (Batista et al., 2018). Despite these well-established techniques, it is worth noting that determining the AC of secondary metabolites can be challenging and often requires the use of associated techniques for confirmation (Batista et al., 2021). Difficulties associated with AC determination are probably because there is no universal technique since each of these methods has advantages and some limitations for complex molecules such as natural products.

## 2 Marine natural products from the Brazilian coast

To contribute to the special issue “Celebrating Natural Products Science in Brazil: 45 Years of Sociedade Brasileira de Química,” this review aims to give an overview regarding the chemistry of MNPs isolated from organisms collected on the Brazilian coast until 2021. The evolution of the research involving Brazilian marine biodiversity will be briefly discussed, paying attention to the organisms and classes of metabolites studied. In addition, the emphasis of the work will be directed to the determination of the AC of chiral compounds.

“Brazil” or “Brazilian” associated with “marine natural products” were used as keywords to perform the search in the following databases: ACS, PubMed, RSC, Science Direct, SciFinder, Scielo, Scopus, Web of Science, and Wiley. Despite trying to address all articles on Brazilian marine biodiversity, some works may not have been mentioned due to the chosen search criteria.

About 4,000 articles were found. After eliminating duplicates, the articles were individually analyzed and only those that described extracts or natural products obtained from organisms collected on the Brazilian coast were selected (more than 400). Approximately 58% of these articles reported isolation of secondary metabolites, 22% of primary metabolites and 20% of crude extracts. A more detailed analysis was carried out considering the marine organism and the classes of metabolites studied (Figure 1). Regarding the types of marine organisms evaluated, the majority were algae and seaweeds, followed by sponges and corals. It was also found articles reporting studies on fungi and bacteria, as well as bryozoans and crustaceans among others. In relation to the classes of metabolites analyzed (Figure 2), the most common were terpenes (41%), followed by alkaloids (20%), carotenoids and sterols (7%), polyketides (5%), peptides (5%) among others.

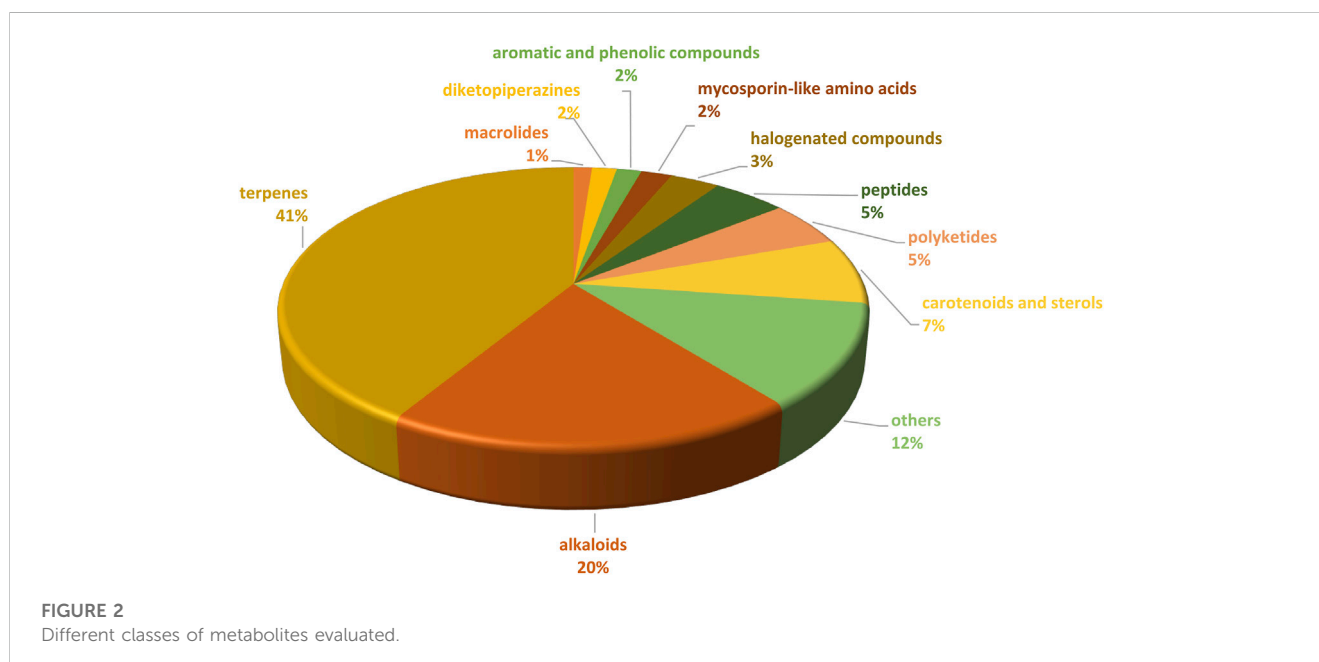
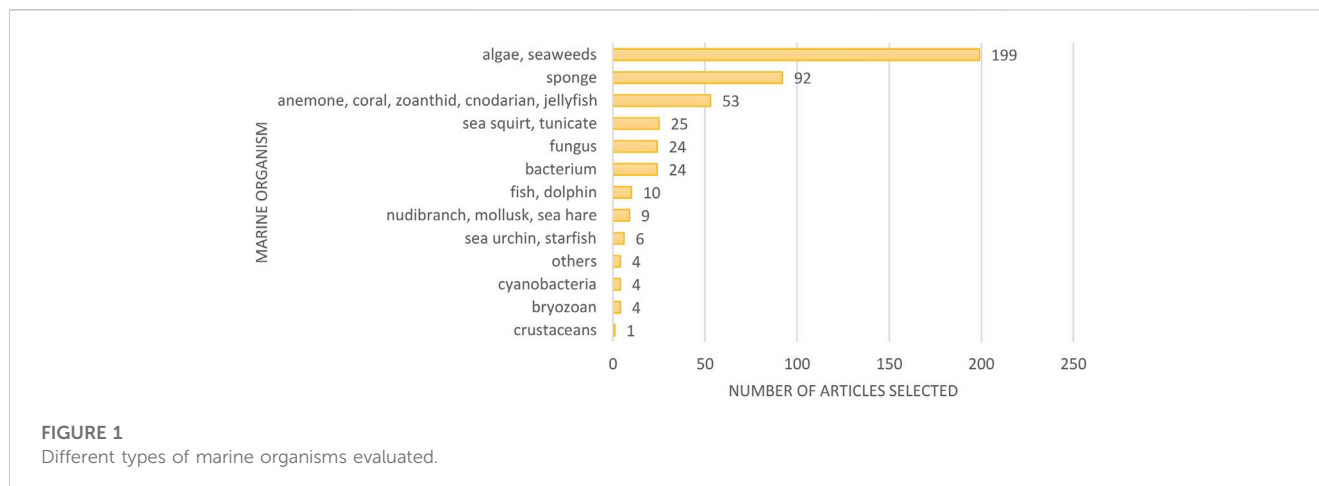
## 3 Absolute configuration

This section presents a list of natural compounds isolated from the Brazilian coast that had their AC mentioned. The method used in the assignment will also be specified.

After a careful evaluation of about 250 articles that deal with marine secondary metabolites, it was found that more than half of them describe the isolation of chiral compounds. The rest of the articles mainly leads with identifying compounds in the extract, isolation of non-chiral compounds, or just the biological activity of previously isolated metabolites. Worth mentioning that about 70% of these articles that describe the isolation of chiral compounds do not name any data about their AC and that many works discriminate the AC of only some of the reported metabolites. In addition, several works only mention the AC of the isolated compound but do not describe the method used for this assignment. It is noteworthy that all structures were drawn and the ACs were specified as in the original publication.

### 3.1 Terpenoids

The class of secondary metabolites with more reports of stereochemical description is terpenes. Chamigrane is an abundant subclass of sesquiterpenes isolated from a variety of sources from terrestrial and marine environments. These compounds have



displayed a diverse array of biological activities (White et al., 2010) and most of them are generally produced by the red alga of the genus *Laurencia* (Family Rhodomelaceae) and endophytic fungi (Zhao et al., 2021). Eleven chamigranes, of which four were reported for the first time, have been isolated from a Brazilian specimen of the red alga *Laurencia scoparia* (Davyt et al., 2001). The chamigranes (–)-isorigidol (1) and ma'ílione (2) were submitted to X-ray diffraction analysis, which allowed to determine the AC of 1 and 2 as 3*R*,6*S*,9*S*,10*S* and 6*S*,9*R*,10*S*, respectively (Davyt et al., 2001). The (–)-dendroidiol (3), another chamigrane sesquiterpene, was isolated from the red alga *Laurencia dendroidea* collected from the southeastern Brazilian coast. The AC of 3 was also assigned by X-ray analysis as 3*R*,4*S*,6*S*,9*R*,10*S* (Machado et al., 2014). The phytochemical study of a Brazilian specimen of *Ophionereis reticulata*, a brittle starfish widespread along South America's northeastern coast, led to the isolation of the chamigrane sesquiterpenes (–)-isobtusadiene (4), (–)-acetyl isobtusadiene (5), and (+)-elatalol (6) (Nuzzo et al., 2017). The AC assignment of

the isobtusadiene skeleton was determined as 6*S*,9*R*,10*S* based on modified Mosher's method analysis of 4. The comparison of the experimental and calculated ECD spectra of 5 has supported this assignment. The full characterization of elatalol (6) was based on NMR data and the comparison of the measured OR value with those previously reported (Nuzzo et al., 2017). Elatalol is a typical chamigrane sesquiterpene normally isolated from algae (Nuzzo et al., 2017). A handful of articles surveyed during this bibliographical research reported the occurrence of elatalol in organisms collected from the Brazilian coast but did not mention any data related to its stereochemistry.

Algae of the genus *Laurencia* is known to produce halogenated sesquiterpenes in a wide and variety of skeleton types (Cikos et al., 2021). In addition to the chamigrane, the bisabolane skeleton is also reported in this kind of organism. A halogenated bisabolane sesquiterpene (7) was isolated from *Laurencia scoparia*, a red alga collected at the coast of Ubatuba (SP, Brazil). The AC of (+)-7 was determined by X-ray crystallography as 2*S*,3*S*,6*R*,9*S* (Davyt et al., 2006).

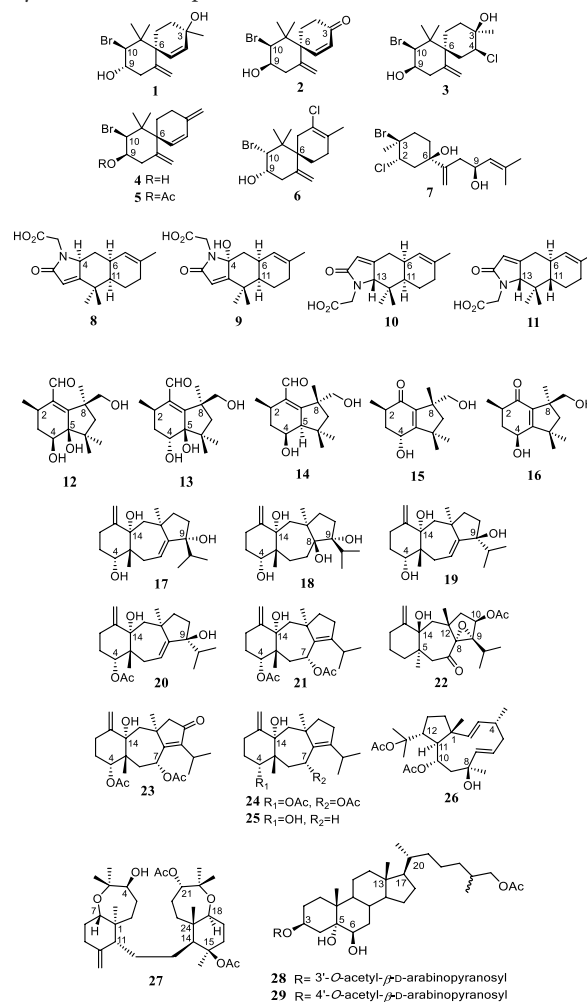
Four nitrogen-containing sesquiterpenes (**8-11**) isolated from the Brazilian endemic sponge *Dysidea robusta* had their AC determined (Williams et al., 2009). The compounds (+)-isopyrodysinoic acid (**8**) and (+)-13-hydroxyisopyrodysinoic acid (**9**) had their AC assigned as 4*S*,6*S*,11*R* and 4*R*,6*S*,11*R*, respectively, by comparison of the sign of the OR with related compounds. The AC of (+)-pyrodysinoic acid (**10**) has been suggested as 6*S*,11*R*,13*S* based on the common biogenetic origin for the skeletons of pyrodysinoic and isopyrodysinoic acids. Furthermore, the NMR analysis of (+)-pyrodysinoic acid B (**11**) established that this compound is an epimer of **10**.

Chemical investigation of the endophytic fungus *Nemania bipapillata* (AT-05) isolated from the Brazilian alga *Asparagopsis taxiformis* led to the isolation of the botryane sesquiterpenes (+)-(2*R*,4*S*,5*R*,8*S*)-4-deacetyl-5-hydroxy-botryenalol (**12**), (+)-(2*R*,4*R*,5*R*,8*S*)-4-deacetyl-5-hydroxy-botryenalol (**13**), (+)-(2*R*,4*S*,5*R*,8*R*)-4-deacetyl-botryenalol (**14**), (+)-(2*R*,4*R*,8*R*)-nemenonediol A (**15**), and (+)-(2*R*,4*S*,8*S*)-nemenonediol B (**16**). The ACs of **13**, **14**, and **15** were assigned by ECD, and the ACs of **12** and **16** by VCD, both associated with quantum chemical calculations (Medina et al., 2019).

In 1988, Kelecom and Teixeira described the isolation of two new dolastane diterpenes (**17** and **18**) from the brown alga *Dictyota ceriocornishave* (Kelecom and Teixeira, 1988). The species in question was collected in Angra dos Reis, State of Rio de Janeiro, Brazil. In fact, most of the Dictyotacean diterpenes are dolastanes and secodolastanes types in the Tropical Atlantic American coastal region (Valim et al., 2005). The AC of (–)-**17** and (–)-**18** were established from spectral data and chemical correlation with known compounds as 4*R*,9*R*,14*S*, and 4*R*,8*S*,9*R*,14*S*, respectively (Kelecom and Teixeira, 1988). An epimer of **17** (**19**) was isolated from the brown alga *Padina sanctae-crucis* collected in the coastal region of João Pessoa, Paraíba, Brazil (Nogueira et al., 2017). The work suggests that the AC of **19** is 4*R*,9*S*,14*S* however there is no mention of how this configuration was assigned. Moreover, in the original publication there is a discrepancy between the AC reported and one represented in the drawn structure. Herein, the stereochemical descriptors in the text were adjusted to ensure consistency with the drawn structure. The dolastanes **20** and **21** were isolated from the Brazilian brown alga *Canistrocarpus cervicornis* (Bianco et al., 2009; Santos et al., 2011; Figueiredo et al., 2019; Cirne-Santos et al., 2020). The AC of **20** and **21** were mentioned as 4*R*,9*S*,14*S* and 4*R*,7*R*,14*S*, respectively. Again, there is no report on how this assignment was accomplished. A new dolastane diterpene **22** and four known seco-dolastane diterpenes were isolated from the same Brazilian brown alga *Canistrocarpus cervicornis* (Bianco et al., 2015). X-ray analysis of **22** determined its AC as 5*R*,8*R*,9*S*,10*R*,12*S*,14*S*. The dolastane diterpenes (4*R*,7*R*,14*S*)-**23**, (4*R*,7*R*,14*S*)-**24**, and (4*R*,14*S*)-**25**, also isolated from *Canistrocarpus cervicornis* collected in Brazil, had their AC discriminated but apparently, no method was used for this purpose (Figueiredo et al., 2019). The AC of the dolabellane diterpene (–)-10,18-diacetoxy-8-hydroxy-2,6-dolabelladiene (**26**), isolated from the marine brown alga *Dictyota pfaffii*, collected in Atol das Rocas, Brazil, was assigned by X-ray analysis as 1*R*,2*E*,4*R*,6*E*,8*S*,10*S*,11*S*,12*R* (Pardo-Vargas et al., 2014).

The unusual triterpenoid raspacionin (**27**) was isolated from the red sponge *Raspaciona aculeata* and had its AC determined by the Mosher method leading to the assignment of the stereochemistry at C-4 as *S* (Cimino et al., 1993). Finally, as steroids are chemically

related to terpenes, the two examples involving this class of compounds will be included in this section. The steroidal glycoside (–)-riisein A (**28**) and (–)-riisein B (**29**) were isolated from the Brazilian octocoral *Carijoa* (Telesto) *riisei*. The arabinose sugar in these compounds was determined as D series by chiral GC analysis and OR comparisons (Maia et al., 2000).

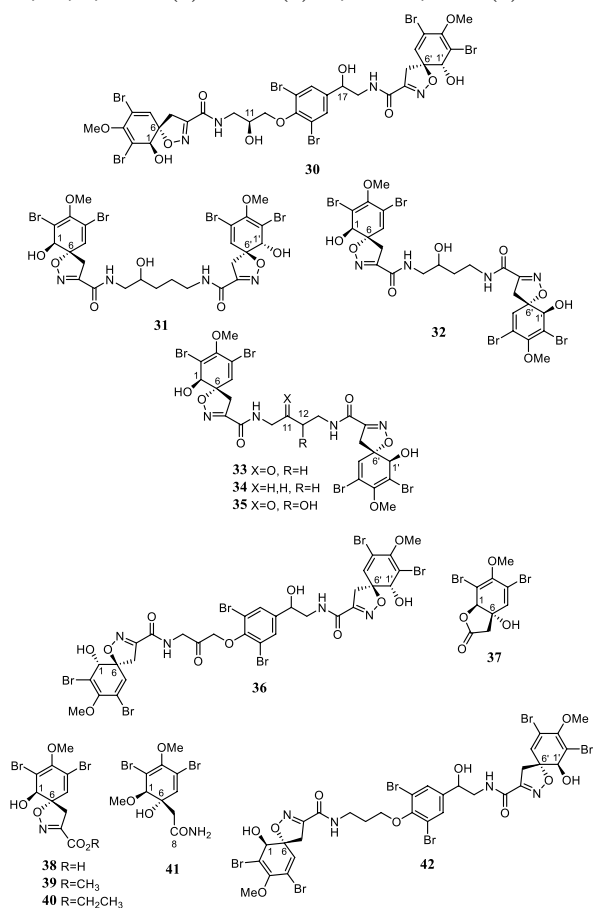


## 3.2 Alkaloids

The second major class of secondary metabolites with reported absolute stereochemistry are alkaloids, including bromotyrosine derivatives. Bromotyrosines metabolites are normally considered chemical markers of sponges from the Verongiida order (Moriou et al., 2021). The dibromotyrosine derivative (+)-fistularin-3 (**30**), isolated from the Brazilian sponges *Aplysina cauliformis* and *A. caissara*, had its AC assigned as 1*R*,1'*R*,6*S*,6'*S*,11*S* by a combination of Marfey's analysis for C-11 and ECD for the spiroxazolidine moieties (Rogers et al., 2005; Lira T. O. et al., 2006).

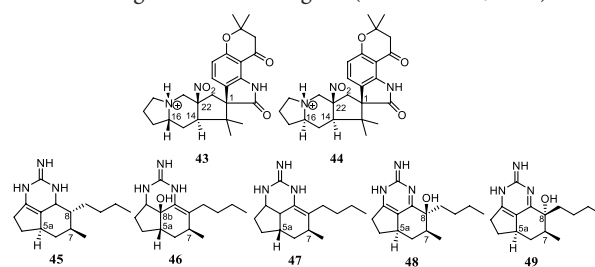
There are reports that fistularin-3 presents stereoisomers with different configurations in the two secondary carbinols C-11 and C-17 and the AC assignment of these stereogenic centers has been challenging (Ji et al., 2021). The relative and absolute configurations of the spiroxazolidine moieties presented in fistularin-3 established by analysis of <sup>1</sup>H NMR and ECD contributed to the AC assignment of

others dibromotyrosine derivatives. Based on these analyses, the same AC of the spiroxazolidine moieties was assigned for all the following metabolites: (+)-caissarine C (31) and (+)-11-hydroxyaerthionin (32) (Lira T. O. et al., 2006); 11-oxoaerthionin (33), aerthionin (34), 11-keto-12-hydroxyaerthionin (35), 11-ketofistularin-3 (36), aeroplysinin-2 (37), verongidoic acid (38) and its methyl ester (39) (Gandolfi et al., 2010; Medeiros et al., 2012), (+)-40 (Kossuga et al., 2007), and (+)-aplysinafulvin (41) (Nuñez et al., 2008). All these compounds were isolated from the Brazilian species of *Aplysina*. The dibromotyrosine derivatives (+)-30 and (+)-11-deoxyfistularin-3 (42) were isolated from *Aplysina cauliformis* and in spite of the mention in the work that the ECD spectra obtained were essentially the same as described in the literature, the authors assigned the ACs of these compounds as 1*S*,1'*S*,6*R*,6'*R*,11*R* (Oliveira et al., 2006). Despite bromotyrosines metabolites being considered chemical markers of sponges from the Verongiida order, the compounds 30, 32 e 38 were isolated from cultures of the bacterium *Pseudovibrio denitrificans* Ab134, isolated from the marine sponge *Arenosclera brasiliensis* collected in Búzios, Brazil (Nicacio et al., 2017). The ACs of the spiroxazolidine moieties were assigned by ECD analysis as 1*R*,1'*R*,6*S*,6'*S* for (+)-30 and (+)-32, and 1*R*,6*S* for (+)-38.



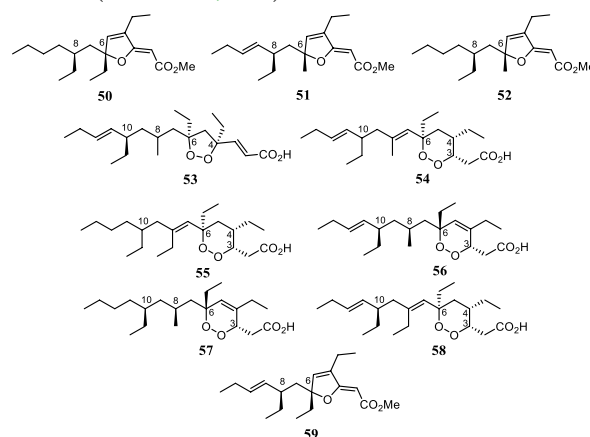
Two new alkaloids citrinalins A (43) and B (44) were isolated from the marine *Penicillium citrinum*, isolated from a seaweed collected in Brazil. The X-ray analysis of 43 enabled the assignment of its AC as 1*S*,14*R*,16*S*,22*S*. The AC of 44 was suggested as 1*S*,14*R*,16*R*,22*S* since both alkaloids presented similar OR values with the same signal (Pimenta et al., 2010). The guanidine alkaloids (5*aR*,7*S*,8*R*)-mirabilin B (45), (5*aS*,7*S*,8*S*)-8*β*-hydroxyptilocaulin (46), (5*aS*,7*S*)-ptilocaulin

(47), (5*aR*,7*S*,8*S*)-8*β*-hydroxymirabilin B (48), (5*aR*,7*S*,8*R*)-8*α*-hydroxymirabilin B (49), isolated from the sponge *Monanchora arbuscula*, had their AC indicated however there is no mention of how these configuration were assigned (Ferreira et al., 2011).



### 3.3 Polyketides

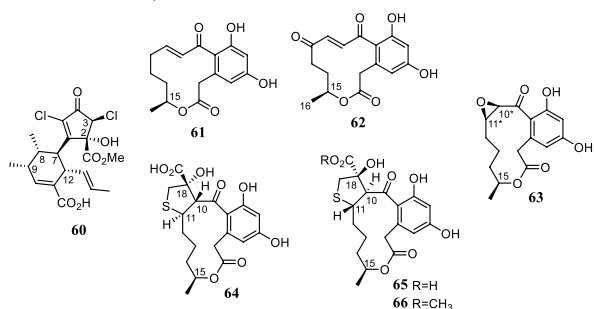
Peroxide and peroxide-derived polyketide are metabolites commonly isolated from marine sponges (Norris and Perkins, 2016). Three peroxide-derived polyketides, the plakilactones 6-desmethyl-6-ethyl-9,10-dihydrospingosoritin A (50), spingosoritin A (51), and 9,10-dihydrospingosoritin A (52), were isolated from the Brazilian sponge *Plakortis angulospiculatus*. The AC of these compounds was deduced based on their negative OR values and comparison with literature data (Epifanio et al., 2005; Santos et al., 2015). The ACs of the plakortides (+)-7,8-dihydroplakortide E (53), (-)-54, (-)-55, (-)-56, (-)-57, and (-)-plakortide P (58), and of the plakilactone (-)-6-desmethyl-6-ethyl-spongisoritin A (59), isolated from the same species, were also assigned based on similarities between OR values with those of structurally related compounds (Santos et al., 2015). The ACs of spingosoritin A (51) and 9,10-dihydrospingosoritin A (52) were confirmed to be (-)-(6*R*,8*R*) and (-)-(6*R*,8*S*), respectively, using VCD, ECD, NMR and OR, all associated with quantum chemical calculations (Batista et al., 2019).



The dichlorinated polyketide roussoellatide (60), isolated from the marine-derived fungus *Roussoella* sp. DLM33, had its AC established by X-ray diffraction analyses as 2*S*,3*S*,7*R*,8*S*,9*R*,12*S* (Ferreira et al., 2015). Finally, the structures and ACs of six macrocyclic curvularin-related polyketides, isolated from a marine-derived *Penicillium* sp. DRF2, were established by spectroscopic data and X-ray diffraction analysis as (15*S*)-10,11-dehydrocurvularin (61), (15*S*)-12-keto-10,11-dehydrocurvularin (62), (15*S*)-*cis*-10,11-epoxycurvularin (63), (10*R*,11*R*,15*S*,18*S*)-

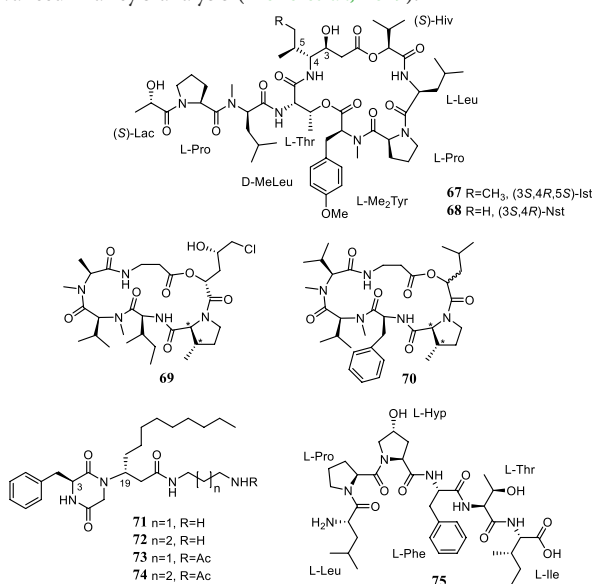


cyclothiocurvularin A (**64**), (10*S*,11*S*,15*S*,18*R*)-cyclothiocurvularin B (**65**), and (10*S*,11*S*,15*S*,18*R*)-cyclothiocurvularin B methyl ester (**66**) (Castro et al., 2016).



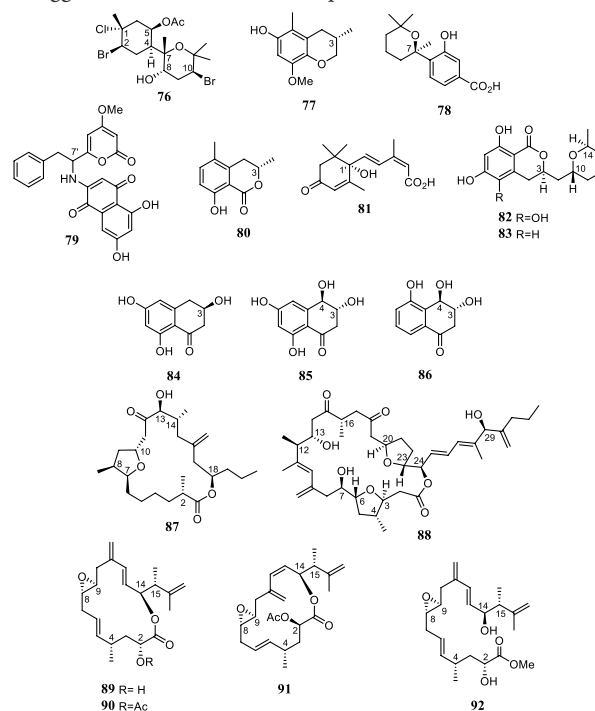
### 3.4 Peptides

Nonribosomal peptides are secondary metabolites with a vast array of biological activities with medical and industrial relevance (Alonzo and Schmeing, 2020). Chemical studies of a Brazilian ascidian of the family Didemnidae led to the isolation of the depsipeptides tamandarins A (**67**) and B (**68**). The ACs of the tamandarins were assigned by Marfey's method and Mosher's analysis (Vervoort et al., 2000). Two new cyclodepsipeptides, [ $\beta$ -MePro] destruxin E chlorohydrin (**69**) and pseudodestruxin C (**70**), isolated from the marine-derived fungus *Beauveria felina*, had their ACs established by Marfey's method and derivatization with *R*-MPA-Cl followed by NMR analysis (Lira S. et al., 2006). The modified diketopiperazine rodriguesines A (**71**) and B (**72**) and *N*-acetyl-rodriguesine A (**73**) and B (**74**) were isolated from two Brazilian ascidians of the genus *Didemnum* and their ACs were assigned by Marfey's analysis and comparison of OR data with reported literature data for related compounds as 3*S*,19*R* (Kossuga et al., 2009). Chemical investigation of the Brazilian endemic marine sponge *Clathria* (*Clathria*) *nicoleae* led to the isolation of a new hexapeptide, clathriamide (**75**), whose AC was determined by advanced Marfey's analysis (Freire et al., 2019).



### 3.5 Others compounds

The halogenated metabolite (+)-5-acetoxycaespitol (**76**) was isolated from the Brazilian red alga *Laurencia catarinensis* and its AC was assigned using the modified Mosher's method as depicted (Lhullier et al., 2010). The structure and AC of 8-methoxy-3,5-dimethylisochroman-6-ol (**77**), isolated from *Penicillium steckii* obtained from a Brazilian alga of the genus *Sargassum*, was established by NMR analysis and by comparison of its OR value with those reported in the literature as *S* (Kossuga et al., 2012). Four compounds (**78**–**81**) were isolated from marine-derived fungal strains obtained from Brazilian marine invertebrates and had their ACs established by comparison of their OR values with literature data (Ióca et al., 2016). Chemical investigation of the deep-sea fungus *Penicillium coralligerum* YK-247 led to the isolation of the new compound (–)-cladomarine (**82**) and the known (–)-cladosporin (**83**). The ACs of these compounds were determined to be 3*R*,10*R*,14*S* by comparison of the OR values and ECD analysis (Takahashi et al., 2017). The compounds (3*R*)-scytalone (**84**), (3*R*,4*R*)-4-hydroxyscytalone (**85**), and (3*R*,4*R*)-3,4,5-trihydroxy-1-tetralone (**86**) were isolated from endophytic fungi isolated from red alga *Asparagopsis taxiformis* and had their ACs established by ECD spectroscopy (Medina et al., 2018). The amphidinolides named amphidinolide T1 (**87**), C4 (**88**), PX1 (**89**), PX2 (**90**), PX3 (**91**), and stragulin A (**92**) were isolated from the Brazilian octocoral *Stragulum bicolor* (Nuzzo et al., 2016; Nuzzo et al., 2019). The AC of **87** was assigned by comparison of OR value with those reported in the literature for the same compound while the ACs of **88** and **92** were suggested based on similarities with analog compounds and modified Mosher's analysis (Nuzzo et al., 2016; Nuzzo et al., 2019). Since compounds **89**–**91** share the same carbon skeleton of the stragulin A (**92**), the same AC of **92** was suggested for these related compounds (Nuzzo et al., 2019).



## 4 Absolute configuration assignment of natural products

As already mentioned, there seems to be no universal methodology for determining the AC of natural products, since each method presented has advantages and limitations. Thus, due to their structural and stereochemical complexity, the best approach for unambiguous AC assignments of chiral secondary metabolites seems to be a combination of methods, taking into account the intrinsic characteristics of each target molecule.

The use of chiroptical methods associated with quantum chemical calculations has proven to be an excellent tool for stereochemical characterization. These techniques have been increasingly used to solve stereochemical problems due to developments in quantum chemical calculations to predict theoretical spectra implemented in commercially available programs (Polavarapu, 2007). The comparison between calculated and observed data greatly helps the correct interpretation of experimental information. Detailed information and good practices for the accurate calculations of chiroptical properties can be found in review articles available in the literature (Batista et al., 2015; Grauso et al., 2019; Mándi and Kurtán, 2019; Polavarapu and Santoro, 2020; Zhu et al., 2023).

## 5 Conclusion

This review covers the state of the art of MNP research in Brazil over the last decades, focusing on the ACs of the isolated secondary metabolites. The AC determination, especially in the case of bioactive compounds, is extremely important. However, from the data presented herein, it was evident that this last step of the structural characterization of chiral compounds is still under-explored by the Brazilian community of natural products. As already mentioned, several methods can be used for the determination of the AC of a given compound. However, a recent review carried out by our research group demonstrated that several misassignments can occur when an inappropriate method is used (Batista et al., 2021). In this context, some highlights regarding the main methods used in the AC assignment of Brazilian MNPs can be made. However, the purpose of the present review is not to question the reliability of the AC assignments reported in the literature but to raise awareness for a more critical analysis when choosing an assignment method.

As can be seen in the data presented herein, a series of compounds were subjected to X-ray analysis. This methodology is very reliable, nevertheless, obtaining crystals is not a trivial task in the case of natural products, which limits its use. The methods that require derivatizations, such as Mosher's method, were also used but they have limitations since their use depends on the presence of specific structural motifs in the compounds under consideration. All described peptides had their ACs established by Marfey's method. This technique has proved to be suitable and the most frequently described for the determination of the AC of amino acid residues of marine peptides (Phyo et al., 2018). The main attention has to be paid to assignments made by comparison

of OR or ECD data with analogous compounds as well as by chemical correlations. Despite the widespread use, AC assignments based on these empirical correlations are not recommended. Although incorrect relative configurations are the main cause for misassignments of the AC of natural compounds in the first place, the practice of determining the AC based on comparisons of experimental OR and/or ECD data with those described for analogous molecules or spectral analyses based on empirical rules do not always generate reliable results (Batista et al., 2021). This is because similar molecules, even from a stereochemical point of view, can present OR values with opposite signs (Freedman et al., 2003; Nakahashi et al., 2011). Furthermore, empirical rules can present exceptions (Batista et al., 2010; Santos et al., 2018). On the other hand, chiroptical methods associated with quantum chemical calculations have proven to be reliable and, especially in the case of vibrational methods (VCD and ROA), can be applied to virtually all types of secondary metabolites (Batista et al., 2015; Mándi and Kurtán, 2019; Polavarapu and Santoro, 2020; Zhu et al., 2023).

Given the fact that Brazil is home to one of the richest biodiversity in the world, it is expected that this crucial step in the structural characterization of MNPs will be more widely considered. This field of research is highly promising and, if well explored, will greatly contribute to the knowledge of the diverse marine natural product chemical space in Brazil.

## Author contributions

AB was responsible for conceptualization, investigation, writing: original draft, review, and editing; FS for funding acquisition, conceptualization, writing: original draft, review, and editing; AV for conceptualization, project administration, funding acquisition, supervision, visualization, writing: original draft, review, and editing. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The authors FS and AB declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## References

- Alonso, D. A., and Schmeing, T. M. (2020). Biosynthesis of depsipeptides, or depsis: The peptides with varied generations. *Protein Sci.* 29, 2316–2347. doi:10.1002/pro.3979
- Batista, A. N., Angrisani, B. R., Lima, M. E. D., Silva, S. M., Schettini, V. H., Chagas, H. A., et al. (2021). Absolute configuration reassignment of natural products: An overview of the last decade. *J. Braz. Chem. Soc.* 32, 1499–1518. doi:10.21577/0103-5053.20210079
- Batista, A. N. L., Santos, F. M., Jr, Batista, J. M., Jr, and Cass, Q. B. (2018). Enantiomeric mixtures in natural product chemistry: Separation and absolute configuration assignment. *Molecules* 23, 492. doi:10.3390/molecules23020492
- Batista, A. N. L., Santos, F. M., Jr, Valverde, A. L., and Batista, J. M. (2019). Stereochemistry of spongosoritins: Beyond optical rotation. *Org. Biomol. Chem.* 17, 9772–9777. doi:10.1039/C9OB02010A
- Batista, J. M., Batista, A. N. L., Rinaldo, D., Vilegas, W., Cass, Q. B., Bolzani, V. S., et al. (2010). Absolute configuration reassignment of two chromanes from *Peperomia obtusifolia* (Piperaceae) using VCD and DFT calculations. *Tetrahedron Asymmetry* 21, 2402–2407. doi:10.1016/j.tetasy.2010.09.004
- Batista, J. M., Jr, Blanch, E. W., and Bolzani, V. S. (2015). Recent advances in the use of vibrational chiroptical spectroscopic methods for stereochemical characterization of natural products. *Nat. Prod. Rep.* 32, 1280–1302. doi:10.1039/C5NP00027K
- Berlinck, R. G., Hajdu, E., Rocha, R. M., Oliveira, J. H., Hernández, I. L., Selegim, M. H., et al. (2004). Challenges and rewards of research in marine natural products chemistry in Brazil. *J. Nat. Prod.* 67, 510–522. doi:10.1021/np0304316
- Bianco, É. M., Francisco, T. M., Pinheiro, C. B., Azeredo, R. B. V., Teixeira, V. L., and Pereira, R. C. (2015). 10 $\beta$ -Acetoxy-8 $\alpha$ ,9 $\alpha$ -epoxy-14 $\beta$ -hydroxy-7-oxodolastane – A new diterpene isolated from the Brazilian Brown macroalgae *Canistrocarpus cervicornis*. *Helv. Chim. Acta* 98, 785–794. doi:10.1002/hlca.201400321
- Bianco, É. M., Rogers, R., Teixeira, V. L., and Pereira, R. C. (2009). Antifoulant diterpenes produced by the Brown seaweed *Canistrocarpus cervicornis*. *J. Appl. Phycol.* 21, 341–346. doi:10.1007/s10811-008-9374-9
- Bijvoet, J. M., Peerdeman, A. F., and van Bommel, A. J. (1951). Determination of the absolute configuration of optically active compounds by means of X-Rays. *Nature* 168, 271–272. doi:10.1038/168271a0
- Carroll, A. R., Copp, B. R., Davis, R. A., Keyzers, R. A., and Prinsep, M. R. (2021). Marine natural products. *Nat. Prod. Rep.* 38, 362–413. doi:10.1039/d0np00089b
- Castro, M. V., Ióca, L. P., Williams, D. E., Costa, B. Z., Mizuno, C. M., Santos, M. F., et al. (2016). Condensation of macrocyclic polyketides produced by *Penicillium* sp. DRF2 with mercaptopyruvate represents a new fungal detoxification pathway. *J. Nat. Prod.* 79, 1668–1678. doi:10.1021/acs.jnatprod.6b00295
- Cikoš, A.-M., Jurin, M., Čož-Rakovac, R., Gašo-Sokač, D., Jokić, S., and Jerković, I. (2021). Update on sesquiterpenes from red macroalgae of the *Laurencia* genus and their biological activities (2015–2020). *Algal Res.* 56, 102330. doi:10.1016/j.algal.2021.102330
- Cimino, G., Epifanio, R. A., Madaio, A., Puliti, R., and Trivellone, E. (1993). Absolute stereochemistry of raspacionin, the main triterpenoid from the marine sponge *Raspacionia aculeate*. *J. Nat. Prod.* 56, 1622–1626. doi:10.1021/np50099a028
- Cirne-Santos, C. C., Barros, C. S., Oliveira, M. C., Rabelo, V. W., Azevedo, R. C., Teixeira, V. L., et al. (2020). *In vitro* studies on the inhibition of replication of Zika and Chikungunya viruses by dolastane isolated from seaweed *Canistrocarpus cervicornis*. *Sci. Rep.* 10, 8263. doi:10.1038/s41598-020-65357-7
- Davyt, D., Fernandez, R., Suescun, L., Mombrú, A. W., Saldaña, J., Domínguez, L., et al. (2001). New sesquiterpene derivatives from the red alga *Laurencia scoparia*. Isolation, structure determination, and anthelmintic activity. *J. Nat. Prod.* 64, 1552–1555. doi:10.1021/np0102307
- Davyt, D., Fernandez, R., Suescun, L., Mombrú, A. W., Saldaña, J., Domínguez, L., et al. (2006). Bisabolanes from the red alga *Laurencia scoparia*. *J. Nat. Prod.* 69, 1113–1116. doi:10.1021/np060235+
- Epifanio, R. A., Pinheiro, L. S., and Alves, N. C. (2005). Polyketides from the marine sponge *Plakortis angulospiculatus*. *J. Braz. Chem. Soc.* 16, 1367–1371. doi:10.1590/S0103-50532005000800010
- Ferreira, E. G., Wilke, D. V., Jimenez, P. C., Oliveira, J. R., Pessoa, O. D. L., Silveira, E. R., et al. (2011). Guanidine alkaloids from *Monanchora arbuscula*: Chemistry and antitumor potential. *Chem. Biodivers.* 8, 1433–1445. doi:10.1002/cbdv.201000161
- Ferreira, E. L., Williams, D. E., Ióca, L. P., Morais-Urano, R. P., Santos, M. F., Patrick, B. O., et al. (2015). Structure and biogenesis of roussoellatide, a dichlorinated polyketide from the marine-derived fungus *Roussioella* sp. DLM33. *Org. Lett.* 17, 5152–5155. doi:10.1021/acs.orglett.5b02060
- Figueiredo, C. S., Silva, S. M. P. M., Abreu, L. S., Silva, E. F., Silva, M. S., Miranda, G. E. C., et al. (2019). Dolastane diterpenes from *Canistrocarpus cervicornis* and their effects in modulation of drug resistance in *Staphylococcus aureus*. *Nat. Prod. Res.* 33, 3231–3239. doi:10.1080/14786419.2018.1470512
- Flack, H. D., and Bernardinelli, G. (2008). The use of X-ray crystallography to determine absolute configuration. *Chirality* 20, 681–690. doi:10.1002/chir.20473
- Freedman, T. B., Cao, X., Oliveira, R. V., Cass, Q. B., and Nafie, L. A. (2003). Determination of the absolute configuration and solution conformation of gossypol by vibrational circular dichroism. *Chirality* 15, 196–200. doi:10.1002/chir.10171
- Freire, V. F., Slivinski, J., Bulla, J. I. Q., Moraes, F. C., Paradis, W. C., Salgado, L. T., et al. (2019). Clathriamide, an hexapeptide isolated from the marine sponge *Clathria (Clathria) nicolae*. *Rev. Bras. Farmacogn.* 29, 715–719. doi:10.1016/j.bjp.2019.07.001
- Gandolfi, R. C., Medina, M. B., Berlinck, R. G. S., Lira, S. P., Galetti, F. C. S., Silva, C. L., et al. (2010). Metabólitos secundários das esponjas *Aplysina fistularis* e *Dysidea* sp. e atividade antituberculose da 11-cetofistularina-3. *Quim. Nova* 33, 1853–1858. doi:10.1590/S0100-40422010000900006
- Grauso, L., Teta, R., Esposito, G., Menna, M., and Mangoni, A. (2019). Computational prediction of chiroptical properties in structure elucidation of natural products. *Nat. Prod. Rep.* 36, 1005–1030. doi:10.1039/c9np00018f
- Harada, N. (2008). Determination of absolute configurations by X-ray crystallography and 1H NMR anisotropy. *Chirality* 20, 691–723. doi:10.1002/chir.20478
- Ióca, L. P., Nicacio, K. J., and Berlinck, R. G. S. (2018). Natural products from marine invertebrates and microorganisms in Brazil between 2004 and 2017: Still the challenges, more rewards. *J. Braz. Chem. Soc.* 29, 998–1031. doi:10.21577/0103-5053.20180016
- Ióca, L. P., Romminger, S., Santos, M. F. C., Bandeira, K. F., Rodrigues, F. T., Kossuga, M. H., et al. (2016). A strategy for the rapid identification of fungal metabolites and the discovery of the antiviral activity of pyrenocine A and harzianopyridone. *Quim. Nova* 39, 720–731. doi:10.5935/0100-4042.20160092
- Ji, Y. K., Lee, S. M., Kim, N.-H., Tu, N. V., Kim, Y. N., Heo, J. D., et al. (2021). Stereochemical determination of fistularins isolated from the marine sponge *Ecionemia acervus* and their regulatory effect on intestinal inflammation. *Mar. Drugs* 19, 170. doi:10.3390/md19030170
- Kelecom, A., and Teixeira, V. L. (1988). Dolastane diterpenes from the marine Brown alga *Dityota cervicornis*. *Phytochemistry* 27, 2907–2909. doi:10.1016/0031-9422(88)80686-1
- Kossuga, M. H., Lira, S. P., McHugh, S., Torres, Y. R., Lima, B. A., Gonçalves, R., et al. (2009). Antibacterial modified diketopiperazines from two ascidians of the genus *Didemnum*. *J. Braz. Chem. Soc.* 20, 704–711. doi:10.1590/S0103-50532009000400014
- Kossuga, M. H., Lira, S. P., Nascimento, A. M., Gambardella, M. T. P., Berlinck, R. G. S., Torres, Y. R., et al. (2007). Isolamento e atividades biológicas de produtos naturais das esponjas *Monanchora arbuscula*, *Aplysina* sp. *Petromica ciocalyptoides* e *Topsentia ophiraphidites*, da ascídia *Didemnum ligulum* e do ococtocoral *Carijoa riisei*. *Quim. Nova* 30, 1194–1202. doi:10.1590/S0100-40422007000500027
- Kossuga, M. H., Romminger, S., Xavier, C., Milanetto, M. C., Valle, M. Z., Pimenta, E. F., et al. (2012). Evaluating methods for the isolation of marine-derived fungal strains and production of bioactive secondary metabolites. *Rev. Bras. Farm.* 22, 257–267. doi:10.1590/S0102-695X2011005000222
- Lhullier, C., Falkenberg, M., Ioannou, E., Quesada, A., Papazafiri, P., Horta, P. A., et al. (2010). Cytotoxic halogenated metabolites from the Brazilian red alga *Laurencia catarinensis*. *J. Nat. Prod.* 73, 27–32. doi:10.1021/np900627r
- Lira, S., Vita-marques, A., Selegim, M., Bugni, T. S., Labarbera, D. V., Sette, L. D., et al. (2006). New destruxins from the marine-derived fungus *Beauveria felina*. *J. Antibiot.* 59, 553–563. doi:10.1038/ja.2006.76



- Lira, T. O., Berlinck, R. G. S., Nascimento, G. G. F., and Hajdu, E. (2006). Further dibromotyrosine-derived metabolites from the marine sponge *Aplysina caissara*. *J. Braz. Chem. Soc.* 17, 1233–1240. doi:10.1590/S0103-50532006000700007
- Lorente, A., Makowski, K., Albericio, F., and Álvarez, M. (2014). Bioactive marine polyketides as potential and promising drugs. *Ann. Mar. Biol. Res.* 1, 1003.
- Machado, F. L. S., Ventura, T. L., Gustinari, L. M., Cassano, V., Resende, J. A., Kaiser, C. R., et al. (2014). Sesquiterpenes from the Brazilian red alga *Laurencia dendroidea*. *J. Agardh. Mol.* 19, 3181–3192. doi:10.3390/molecules19033181
- Maia, L. F., Epifanio, R. A., and Fenical, W. (2000). New cytotoxic sterol glycosides from the octocoral *Carijoa* (Telesto) *riisei*. *J. Nat. Prod.* 63, 1427–1430. doi:10.1021/np9906323
- Mándi, A., and Kurtán, T. (2019). Applications of OR/ECD/VCD to the structure elucidation of natural products. *Nat. Prod. Rep.* 36, 889–918. doi:10.1039/C9NP00002J
- Medeiros, A. I., Gandolfi, R. C., Secatto, A., Falcucci, R. M., Faccioli, L. H., Hajdu, E., et al. (2012). 11-Oxo-aerthionin isolated from the marine sponge *Aplysina fistularis* shows anti-inflammatory activity in LPS-stimulated macrophages. *Immunopharmacol. Immunotoxicol.* 34, 919–924. doi:10.3109/08923973.2012.679984
- Medina, R. P., Araujo, A. R., Andersen, R. J., Soares, M. A., Silva, F. A., and Silva, D. H. S. (2018). Botryane terpenoids produced by endophytic fungi isolated from red alga *Asparagopsis taxiformis* - falkenbergia stage. *Nat. Prod. Res.* 33, 443–446. doi:10.1080/14786419.2018.1455037
- Medina, R. P., Araujo, A. R., Batista, J. M., Jr, Cardoso, C. L., Seidl, C., Vilela, A. F. L., et al. (2019). Botryane terpenoids produced by *Nemania bipapillata*, an endophytic fungus isolated from red alga *Asparagopsis taxiformis* - falkenbergia stage. *Sci. Rep.* 9, 12318. doi:10.1038/s41598-019-48655-7
- Moriou, C., Lacroix, D., Petek, S., El-Demerdash, A., Trepos, R., Leu, T. M., et al. (2021). Bioactive bromotyrosine derivatives from the pacific marine sponge *suberea clavata* (Pulitzer-Finali, 1982). *Mar. Drugs* 19, 143. doi:10.3390/md19030143
- Nakahashi, A., Yaguchi, Y., Miura, N., Emura, M., and Monde, K. (2011). A vibrational circular dichroism approach to the determination of the absolute configurations of flavonoid 5-substituted-2(5H)-furanones. *J. Nat. Prod.* 74, 707–711. doi:10.1021/np1007763
- Nicacio, K. J., Lóca, L. P., Fróes, A. M., Leomil, L., Appolinario, L. R., Thompson, C. C., et al. (2017). Cultures of the marine bacterium *Pseudovibrio denitrificans* Ab134 produce bromotyrosine-derived alkaloids previously only isolated from marine sponges. *J. Nat. Prod.* 80, 235–240. doi:10.1021/acs.jnatprod.6b00838
- Nogueira, R. B. S. S., Tomaz, A. C. A., Pessoa, D. R., Xavier, A. L., Pita, J. C. L. R., Sobral, M. V., et al. (2017). Brown algae *Padina sanctae-crucis* borgesens: A potential nutraceutical. *Mar. Drugs* 26, 251. doi:10.3390/md15100251
- Norris, M. D., and Perkins, M. V. (2016). Structural diversity and chemical synthesis of peroxide and peroxide-derived polyketide metabolites from marine sponges. *Nat. Prod. Rep.* 33, 861–880. doi:10.1039/C5NP00142K
- Núñez, C. V., Almeida, E. V. R., Granato, A. C., Marques, S. O., Santos, K. O., Pereira, F. R., et al. (2008). Chemical variability within the marine sponge *Aplysina fulva*. *Biochem. Syst. Ecol.* 36, 283–296. doi:10.1016/j.bse.2007.09.008
- Nuzzo, G., Gomes, B. A., Amodeo, P., Matthews-Cascon, H., Cutignano, A., Costa-Lotufo, L. V., et al. (2017). Isolation of chamigrene sesquiterpenes and absolute configuration of isoobtusadiene from the brittle star *Ophioneis reticulata*. *J. Nat. Prod.* 80, 3049–3053. doi:10.1021/acs.jnatprod.7b00510
- Nuzzo, G., Gomes, B. A., Gallo, C., Amodeo, P., Sansone, C., Pessoa, O. D. L., et al. (2019). Potent cytotoxic analogs of amphidinolides from the Atlantic octocoral *Stragulum bicolor*. *Mar. Drugs* 17, 58. doi:10.3390/md17010058
- Nuzzo, G., Gomes, B. A., Luongo, E., Torres, M. C., Santos, E. A., Cutignano, A., et al. (2016). Dinoflagellate-related amphidinolides from the Brazilian octocoral *Stragulum bicolor*. *J. Nat. Prod.* 79, 1881–1885. doi:10.1021/acs.jnatprod.6b00259
- Oliveira, M. F., Oliveira, J. H., Galetti, F. C., Souza, A. O., Silva, C. L., Hajdu, E., et al. (2006). Antimycobacterial brominated metabolites from two species of marine sponges. *Planta Med.* 72, 437–441. doi:10.1055/s-2005-916239
- Pardo-Vargas, A., Oliveira, I. B., Stephens, P. R., Cirne-Santos, C. C., Paixão, I. C. P., Ramos, F. A., et al. (2014). Dolabelladienols A-C, new diterpenes isolated from Brazilian Brown alga *Dictyota paffii*. *Mar. Drugs* 12, 4247–4259. doi:10.3390/md12074247
- Parsons, S. (2017). Determination of absolute configuration using X-ray diffraction. *Tetrahedron Asymmetry* 28, 1304–1313. doi:10.1016/j.tetasy.2017.08.018
- Phyo, Y. Z., Ribeiro, J., Fernandes, C., Kijjoo, A., and Pinto, M. M. M. (2018). Marine natural peptides: Determination of absolute configuration using liquid chromatography methods and evaluation of bioactivities. *Molecules* 23, 306. doi:10.3390/molecules23020306
- Pimenta, E. F., Vita-Marques, A. M., Tininis, A., Selegim, M. H., Sette, L. D., Veloso, K., et al. (2010). Use of experimental design for the optimization of the production of new secondary metabolites by two *Penicillium* species. *J. Nat. Prod.* 73, 1821–1832. doi:10.1021/np100470h
- Polavarapu, P. L. (2007). Renaissance in chiroptical spectroscopic methods for molecular structure determination. *Chem. Rec.* 7, 125–136. doi:10.1002/tcr.20117
- Polavarapu, P. L., and Santoro, E. (2020). Vibrational optical activity for structural characterization of natural products. *Nat. Prod. Rep.* 37, 1661–1699. doi:10.1039/D0NP00025F
- Rogers, E. W., Oliveira, M. F., Berlinck, R. G., König, G. M., and Molinski, T. F. (2005). Stereochemical heterogeneity in Verongid sponge metabolites. Absolute stereochemistry of (+)-fistularin-3 and (+)-11-epi-fistularin-3 by microscale LCMS-Marfey's analysis. *J. Nat. Prod.* 68, 891–896. doi:10.1021/np050050n
- Sadlej, J., Dobrowolski, J. C., and Rode, J. E. (2010). VCD spectroscopy as a novel probe for chirality transfer in molecular interactions. *Chem. Soc. Rev.* 39, 1478–1488. doi:10.1039/B915178H
- Santos, A. O., Britta, E. A., Bianco, E. M., Ueda-Nakamura, T., Filho, B. P. D., Pereira, R. C., et al. (2011). 4-Acetoxydolastane diterpene from the Brazilian Brown alga *Canistrocarpus cervicornis* as antileishmanial agent. *Mar. Drugs* 9, 2369–2383. doi:10.3390/md9112369
- Santos, E. A., Quintela, A. L., Ferreira, E. G., Sousa, T. S., Pinto, F., Hajdu, E., et al. (2015). Cytotoxic plakortides from the Brazilian marine sponge *Plakortis angulospiculatus*. *J. Nat. Prod.* 78, 996–1004. doi:10.1021/np5008944
- Santos, F. M., Jr, Bicalho, K. U., Calisto, Í. H., Scatena, G. S., Fernandes, J. B., Cass, Q. B., et al. (2018). Scope of the 2(5H)-furanone helicity rule: A combined ECD, VCD, and DFT investigation. *Org. Biomol. Chem.* 16, 4509–4516. doi:10.1039/C8OB01085D
- Seco, J. M., Quinoa, E., and Riguera, R. (2012). Assignment of the absolute configuration of polyfunctional compounds by NMR using chiral derivatizing agents. *Chem. Rev.* 112, 4603–4641. doi:10.1021/cr2003344
- Stonik, V. A. (2009). Marine natural products: A way to new drugs. *Acta Naturae* 1, 15–25. doi:10.32607/20758251-2009-1-2-15-25
- Sun, Y., and Sahinidis, N. V. (2022). Computer-aided retrosynthetic design: Fundamentals, tools, and outlook. *Curr. Opin. Chem. Eng.* 35, 100721. doi:10.1016/j.coche.2021.100721
- Takahashi, K., Sakai, K., Nagano, Y., Sakaguchi, S. O., Lima, A. O., Pellizari, V. H., et al. (2017). Cladomarine, a new anti-saprolegniasis compound isolated from the deep-sea fungus, *Penicillium coralligerum* YK-247. *J. Antibiot.* 70, 911–914. doi:10.1038/ja.2017.58
- Valli, M., Russo, H. M., and Bolzani, V. S. (2018). The potential contribution of the natural products from Brazilian biodiversity to bioeconomy. *An. Acad. Bras. Ciênc.* 90, 763–778. doi:10.1590/0001-3765201820170653
- Vallim, M. A., Paula, J. C., Pereira, R. C., and Teixeira, V. L. (2005). The diterpenes from Dictyotacean marine Brown algae in the Tropical Atlantic American region. *Biochem. Syst. Ecol.* 33, 1–16. doi:10.1016/j.bse.2004.06.002
- Vervoort, H., Fenical, W., and Epifanio, R. A. (2000). Tamandarins A and B: New cytotoxic depsipeptides from a Brazilian ascidian of the family Didemnidae. *J. Org. Chem.* 65, 782–792. doi:10.1021/jo991425a
- Wenzel, T. J., and Chisholm, C. D. (2011). Assignment of absolute configuration using chiral reagents and NMR spectroscopy. *Chirality* 23, 190–214. doi:10.1002/chir.20889
- White, D. E., Stewart, I. C., Seashore-Ludlow, B. A., Grubbs, R. H., and Stoltz, B. M. (2010). A general enantioselective route to the chamigrene natural product family. *Tetrahedron* 66, 4668–4686. doi:10.1016/j.tet.2010.04.128
- Williams, D. E., Marques, S. O., Hajdu, E., Peixinho, S., Andersen, R. J., and Berlinck, R. G. (2009). Pyrodisynic acid derivatives from the marine sponge *Dysidea robusta*. *J. Nat. Prod.* 72, 1691–1694. doi:10.1021/np900033v
- Zanardi, M. M., Biglione, F. A., Sortino, M. A., and Sarotti, A. M. (2018). General quantum-based NMR method for the assignment of absolute configuration by single or double derivatization: Scope and limitations. *J. Org. Chem.* 83, 11839–11849. doi:10.1021/acs.joc.8b01749
- Zhao, Z.-Z., Zhao, Q.-L., Feng, W.-S., He, H.-R., Li, M., Xue, G.-M., et al. (2021). Structure and absolute configuration assignments of ochracines F-L, chamigrane and cadinane sesquiterpenes from the basidiomycete *Steccherinum ochraceum* HFG119. *RSC Adv.* 11, 18693–18701. doi:10.1039/D1RA03320D
- Zhu, H., Wang, Y., and Nafie, L. A. (2023). Computational methods and points for attention in absolute configuration determination. *Front. Nat. Prod.* 1. doi:10.3389/fntpr.2022.1086897