Phylogenetic distribution of bromophenols in marine algae and the generation of a comprehensive bromophenol database

Joshua Jacobtorweihen · Verena Spiegler

Abstract Marine algae are the source of a plethora of halogenated compounds, in particular brominated phenols, possessing various bioactivities. Since these natural products are typically unavailable commercially, isolation is usually indispensable for biological activity testing. However, targeted isolation may be challenging due to difficulties in identifying desired compounds via high-resolution LC–MS in crude extracts or fractions. While bromophenols have been extensively reviewed regarding their bioactivities, less attention has been given to their distribution and chemotaxonomic relevance among marine algae. Knowledge of the distribution of bromophenols may aid species identification and also point to species containing potentially novel compounds. To facilitate targeted and untargeted isolation of bromophenols from marine algae, an overview of the distribution and chemotaxonomic relevance of algal bromophenols considering recent phylogenetic findings is presented along with key analytical features of bromophenols relevant for mass spectrometric identification. Additionally, a comprehensive database listing brominated phenols from marine algae and their key analytical properties has been constructed.

Keywords Macroalgae · Bromophenol · Haloaryl · Chemotaxonomy · Algal metabolite · Database

Abbreviations
MS	Mass spectrometry
ESI	Electro spray ionization
EI	Electron impact ionization
FAB	Fast atom bombardment
FD	Field desorption
DART	Direct analysis in real time

Introduction

Marine algae are well known to be a rich source of halogenated and particularly brominated compounds and in recent years a number of reviews focusing on the bioactivities and potential therapeutic applications have been published (Liu et al. 2011; Jesus et al. 2019; Dong et al. 2020; Carpena et al. 2022). In contrast, chemotaxonomic considerations and analytical properties of bromophenols have only been discussed sparingly (Wang et al. 2013). This is of particular interest as the taxonomy and species assignments of a substantial number of the phytochemically investigated algae have changed considerably over the roughly 60 years since the first reports of

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bromophenols from algae (Hodgkin et al. 1966; Díaz-Tapia et al. 2017a; Cabrera et al. 2021). While the respective algae themselves and their secondary metabolites did not change, chemotaxonomic classifications have to be adapted to recent phylogenetic discoveries.

This review aims at presenting the phylogenetic distribution of bromophenols and at discussing their chemotaxonomic significance in marine algae. A special focus in addition to phylogeny and chemotaxonomy will be given to common analytical features of marine bromophenols, helpful in identifying these natural products via LC–MS in crude extracts or fractions. This is especially relevant since very few of these natural products are commercially available and isolation is almost always necessary for biological activity testing. To aid the identification of bromophenols by mass spectrometry we additionally assembled a comprehensive database (Table S1) comprising all bromophenols detected in marine algae until now. Regarding taxonomic classifications, we verified the current taxonomic status and name of each species and—if needed—updated the names used in the original publication to comply with the currently accepted denotation.

Data acquisition and generation of a comprehensive bromophenol database

The aim of the database generation was to cover every known bromophenolic compound produced by marine algae in Table S1. In order to identify relevant substances from literature, the databases Reaxys® and SciFinder^n were searched by structural features. Additionally, certain genera were entered in Google Scholar together with the term "metabolite" or "bromophenol". Inclusion criteria for compounds were either isolation or unambiguous identification via MS and authentic reference compounds from a marine alga. The molecular feature for inclusion into the database was the presence of a hydroxylated and brominated benzene ring and molecular structures were depicted as reported in the original publications if the structural elucidation was convincing. Here, special attention was paid to the methods used for elucidation of stereochemistry. In case substance properties (state, color, absorption maxima,

fragmentation or adduct formation in MS) had been reported, they were included in the database.

Structures, exact masses, molecular weight, sum formulae and SMILES were generated using Chem-Draw Ver. 21.0, PerkinElmer Informatics Inc. 2022 (Waltham, MA, USA). Since ESI–MS is one of the most common ionization methods today (Kind et al. 2018) and many bromophenols form salt adducts (see also *4.2 Key identifiers and common fragmentation reactions of bromophenols*), the theoretical masses of the most common salt adducts ($[M + NH_4]^+$, $[M + Na]^+$ and $[M + K]^+$) were included (Keller et al. 2008). Exact masses of the adduct ions were calculated using the exact adduct masses given by Keller et al. (2008) and the exact mass of each molecule. Sulfates are listed in protonated form.

The current names, families and information on the higher taxonomy of algae were taken from Algaebase (Guiry and Guiry 2022) if not indicated differently. To ensure traceability, those species for which name changes have occurred since the time of publication are given with the name mentioned in the original publication in brackets. The family was also added if the investigated alga is not a member of the Rhodomelaceae family. An overview of the changed species names is given in Table S2.

Certain compounds have originally been isolated from sponges or corals and later been found in algae, e.g. 3-bromo-4-hydroxybenzaldehyde (**1**), *Pseudoceratina purpurea*, syn. *Psammaplysilla purpurea*; 3-bromo-4-hydroxybenzoic acid (**2**), *Aplysinella rhax*; cupalaurenol (**3**), *Clavularia viridis*, *Aplysia dactylomela*; filiformin (**4**), *Plakortis* sp.), and thus their compound data were extracted from the respective original publications (Ichiba and Higa 1986; Jiménez and Crews 1991; Gochfeld and Hamann 2001; Piña et al. 2003; Wu et al. 2019; Oluwabusola et al. 2020).

Phylogenetical distribution of bromophenols and their chemotaxonomic significance

Bromophenols are common metabolites in marine organisms and especially the most elementary brominated phenols (2-bromophenol, 4-bromophenol, 2,4-dibromophenol, 2,6-dibromophenol and 2,4,6-tribromophenol; Fig. 1, type **O**) are found throughout green, brown and red algae (Whitfield et al. 1999). Due to the widespread distribution of these compounds, they
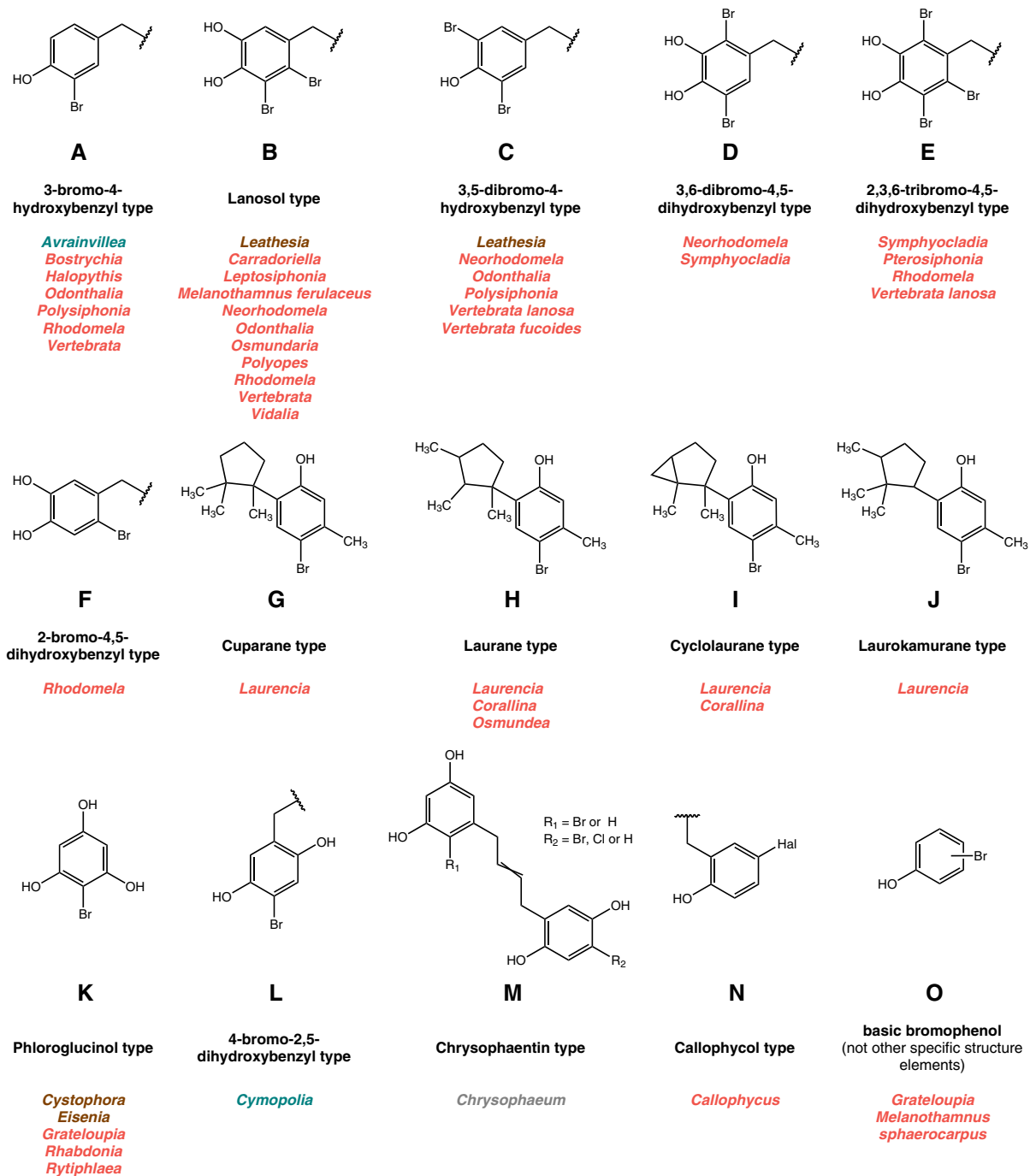
Fig. 1 Basic scaffolds of bromophenols found in algae. The respective genera are given in italics. Red: red algae. Green: Green algae. Brown: Brown algae. Grey: Miscellaneous marine algae

represent no suitable phylogenetical identifiers for these clades. We summarized their distribution as reported in literature in Table S3 (Flodin et al. 1999; Whitfield et al. 1999; Flodin and Whitfield 2000; Chung et al. 2003; Kim et al. 2008) and their reported molecular characteristics are outlined in an extra spreadsheet in Table S1 ("Widespread Basic Bromophenols").

In contrast to these simple molecules, more complex bromophenols show intricate distribution patterns in regard of the species they have been isolated from. Intriguingly, certain compounds are found in almost all species of a genus (e.g., laurinterol, **5**), some are found in different genera (lanosol, **6**) but most compounds (233 of 279) have only been reported to be present in distinct species. The latter might to some extent also be attributed to the varying chemical composition of the seaweeds depending on the time of the year and collection site which has been reported for several algae (Flodin et al. 1999; Chung et al. 2003; Shoeib et al. 2006; Hofer et al. 2019). Another potential explanation for reports on varying contents of secondary metabolites was formulated by Howard et al. (1980) as they found samples of morphological identical *Laurencia* species from different collection sites to differ in their phytochemical composition. As these species were unable to reproduce, they suggested them to be sister species.

The bromophenols found in marine algae can be grouped in 15 basic scaffolds (Fig. 1) and one miscellaneous category as follows: 3-bromo-4-hydroxybenzyl type (**A**), lanosol type (**B**), 3,5-dibromo-4-hydroxybenzyl type (**C**), 3,6-dibromo-4,5-dihydroxybenzyl type (**D**), 2,3,6-tribromo-4,5-dihydroxybenzyl type (**E**), 2-bromo-4,5-dihydroxybenzyl type (**F**), cuparane type (**G**), laurane type (**H**, with subtypes $\mathbf{H^c}$ and $\mathbf{H^b}$), cyclolaurane type (**I**), laurokamurane type (**J**), phloroglucinol type (**K**), 4-bromo-2,5-dihydroxybenzyl type (**L**), chrysophaentin type (**M**) and callophycol type bromophenols (**N**). Compounds not included in this classification comprise basic and widespread bromophenols containing no other specific structure elements (**O**, Table S1 and S3). Only four compounds did not match any of the presented categories and are therefore grouped as "miscellaneous". Moreover, the laurane scaffold (**H**) shows an additional cyclisation in certain *Laurencia* species, justifying the subtypes $\mathbf{H^c}$ (chromane type) and $\mathbf{H^b}$ (dihydrobenzofuran type). This classification is not per se biogenetical as the structural frames of **A**—**F** probably all originate from tyrosine (Manley and Chapman 1978) and those of **G**—**J** are formed from a sesquiterpene precursor (Yu et al. 2014), but rather a phenomenological way to establish species or taxon-specific substitution patterns.

Red algae (Rhodophyta)—Rhodomelaceae

Red algae (Rhodophyta) produce the largest diversity of brominated compounds comprising a great variety of scaffolds, as all structural skeletons shown in Fig. 1 except for the 4-bromo-2,5-dihydroxybenzyl (**L**) and the chrysophaentin type (**M**) can be found. Notably, every red alga reported to contain bromophenols belongs to the class Florideophyceae, one of the largest classes within the Rhodophyta (Guiry and Guiry 2022). However, it should be taken into account that other classes might be phytochemically understudied due to different availabilities. Since the Rhodomelaceae family is the largest family of red algae (Díaz-Tapia et al. 2017a) and it is reported to contain most bromophenols, we will discuss the bromophenols of its members with special attention. Furthermore, the phylogeny of several taxa within this family has been overridden in recent years (Díaz-Tapia et al. 2017a, b; Cabrera et al. 2021; Popolizio et al. 2022), revealing previously unanticipated relationships of chemotaxonomic relevance. The currently accepted tribes within the Rhodomelaceae and their subordinated species for which bromophenols have been reported are summarized in Table 1 together with the respective basic scaffolds (Díaz-Tapia et al. 2017a; Cabrera et al. 2021; Guiry and Guiry 2022).

Bostrychieae

Bostrychia calliptera   For the genus *Bostrychia*, only three compounds from one study have been reported. All of the bromophenols isolated represented the 3-bromo-4-hydroxybenzyl type (**A**) with sulfated phenolic functions (Orfanoudaki et al. 2020) and have only been reported for *B. calliptera*. The simplest derivative is 2-bromo-4-(hydroxymethyl)phenyl hydrogen sulfate (**7**, Fig. 2) and the other two compounds contain a 2,3-dihydroxycyclopent-2-en-1-one side chain (**8**, **9**). Interestingly, the three investigated lineages of *B. calliptera* contained different mycosporine-like amino acid (MAA) and bromophenol patterns, with one lineage even completely lacking bromophenols (Orfanoudaki et al. 2020). Since the lineages were determined to be genetically different (Orfanoudaki et al. 2020), they could potentially be regarded as sibling species differentiated by their phytochemistry.

Table 1 Scaffolds reported for the bromophenol-containing members of Rhodomelaceae. Letters A—K and O refer to structures given in Fig. 1

Tribe	Species	Bromophenol scaffolds
Bostrychieae	*Bostrychia calliptera*	A
Amansieae	*Halopithys incurva*	A, C
	Osmundaria obtusiloba	B, K
	Rytiphlaea tinctoria	B, K
	Vidalia colensoi	B
Laurencieae	*Laurencia caraibica*	H[c]
	Laurencia filiformis	H[c]
	Laurencia glandulifera	H[c], I
	Laurencia johnstonii	H[b], I
	Laurencia microcladia	G, H[c], I, J
	Laurencia nidifica	H, I
	Laurencia nipponica	C
	Laurencia obtusa	G, H
	Laurencia okamurai	G, H[b, c], I, J
	Laurencia pacifica	H[b]
	Laurencia similis	E, P
	Laurencia tristicha	H[b, c], J
	Laurencia sp.[a]	G, H[c]
	Osmundea pinnatifida	H[c]
Rhodomeleae	*Odonthalia corymbifera*	A, B, C, D
	Neorhodomela aculeata	A, B, C, D
	Neorhodomela larix	A, B, C
	Rhodomela confervoides	A, B, E, F
Pterosiphonieae	*Symphyocladia latuscula*	D, E
Polysiphonieae	*Polysiphonia stricta*	A, C
	Polysiphonia morrowii	A
Streblocladieae	*Carradoriella elongata*	A, B
	Leptosiphonia brodiei	A, B, C
	Melanothamnus ferulaceus	A, B
	Melanothamnus sphaerocarpus	O
	Vertebrata lanosa	A, B, C, (E)
	Vertebrata decipiens	B
	Vertebrata thuyoides	B
	Vertebrata fruticulosa	A, B
	Vertebrata fucoides	B, C
	Vertebrata nigra	A, B

[a]Species not further specified

[b]Dihydrobenzofuran type lauranes

[c]Chromane type lauranes

Amansieae

Halopithys incurva *Halopithys incurva* was shown to produce 3-bromo-4-hydroxybenzyl type (**A**) bromophenols (Glombitza et al. 1974; Wagner et al. 1981) by means of MS and isolation. While Glombitza et al. (1974) identified 2-bromo-4-

(hydroxymethyl)phenol (**10**, Fig. 2) and 3-bromo-5-(hydroxymethyl)benzene-1,2-diol (**11**) via GC–MS, Wagner et al. (1981) could isolate 5-bromoprotocatechualdehyde (**12**) from an extract of *H. incurva*. In addition to these compounds, a substance showing an unusual substitution pattern (2-(2,6-dibromo-3,5-dihydroxyphenyl)acetic acid, **13**)
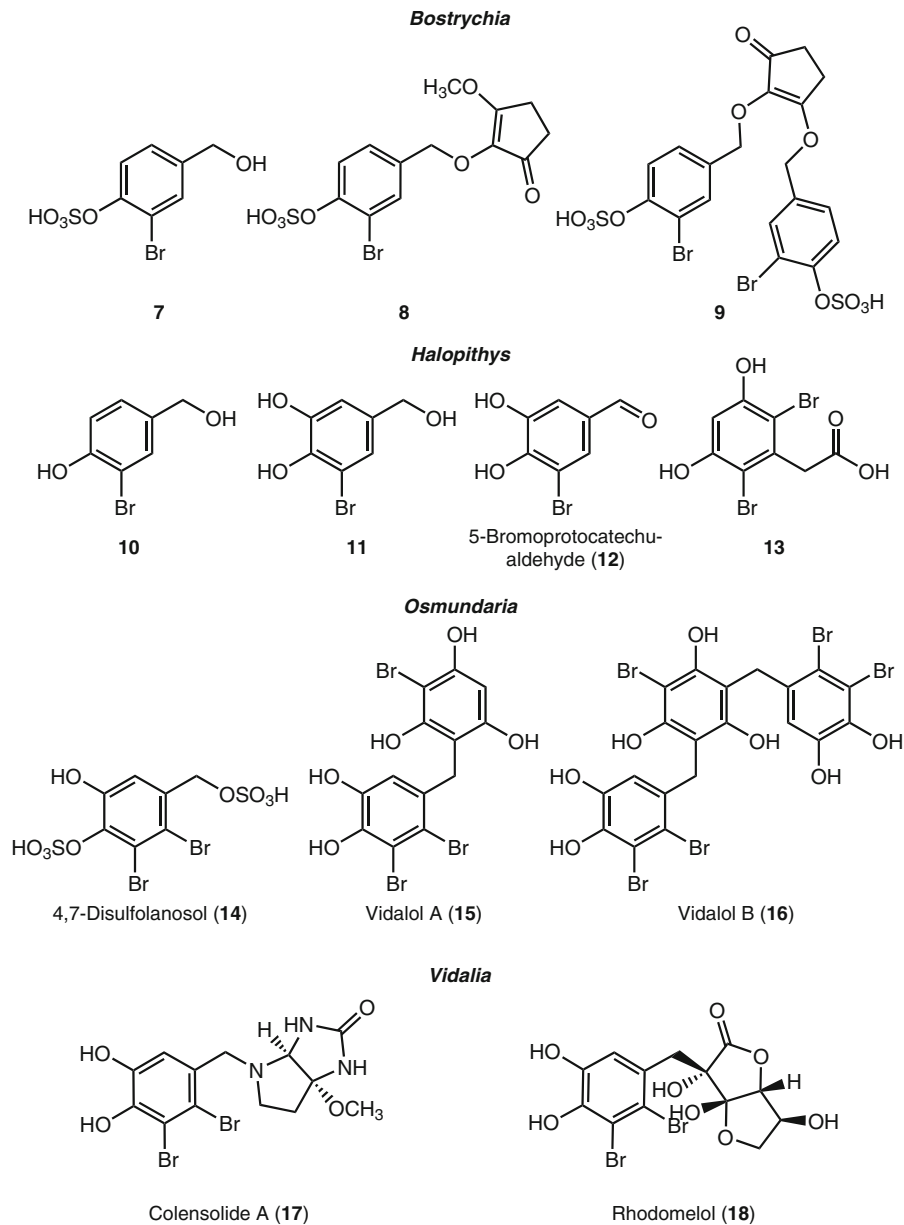
Fig. 2 Structures of selected characteristic bromophenols from the tribes Bostrychieae and Amansieae within the family Rhodomelaceae. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

was reported to occur in *H. incurva.* The authors additionally found hints on the presence of the corresponding sulfate (de Nanteuil and Mastagli 1981). Recent investigations of *H. incurva* extracts also indicated the presence of a 3-bromo-4,5-dihydroxyphenylethanol sulfate, although this compound was only detected by means of mass

spectrometry (Álvarez-Gómez et al. 2019). Finally, another study presented the isolation of two 3,5-dibrominated bromophenols, however these compounds were not included in the database since the authors methylated the phenolic fraction and thus the genuine state of methylation cannot be inferred from the isolated compounds (Chantraine et al. 1973).

As there are only a few reports of single substances found in *H. incurva*, further studies on this alga are needed to corroborate these findings, especially regarding the irregularly substituted **13**.

Rytiphlaea tinctoria Another member of the Amansieae, *Rytiphlaea tinctoria*, produces lanosol (**B**) and phloroglucinol type (**K**) bromophenols, however the isolated compounds were not included into the database since they were methylated before isolation (Chevolot-Magueur et al. 1976). As methylation also commonly occurs naturally in red algae (e.g., in *Rhodomela converfoides*, Li et al. 2011, 2012), permethylation does not allow to detect the genuine methylation pattern of the natural product anymore. In case the compounds are easily degraded, acetylation might be a more feasible alternative (Glombitza and Gerstberger 1985). Interestingly, the lanosol type compounds in this study were isolated from mediterranean algae and the bromophloroglucinols were found in a specimen of the same species collected on the Breton coast (Chevolot-Magueur et al. 1976) which might either be an example for the dependency of the phytochemical composition on the collection site or for the aforementioned concept of sibling species (Howard et al. 1980).

Osmundaria obtusiloba *Osmundaria obtusiloba* (syn. *Vidalia obtusiloba*) produces lanosol type (**B**) bromophenols, and in total seven bromophenols have been isolated from this red alga (Table S1) (Wiemer et al. 1991; de Carvalho et al. 2006). Among those, a number of sulfated phenols including 4,7-disulfolanosol (**14,** Fig. 2), two sulfated dimers (de Carvalho et al. 2006) and Vidalols A and B (**15, 16**) comprised of a lanosol (**B**) and a bromophloroglucinol (**K**) moiety have been reported (Wiemer et al. 1991). The presence of the latter might be a potential chemotaxonomic marker to distinguish *Osmundaria* and *Vidalia* species as *Vidalia* does not seem to contain bromophloroglucinols, although a systematic phytochemical evaluation of a larger subset of species from these genera would be needed to answer this question.
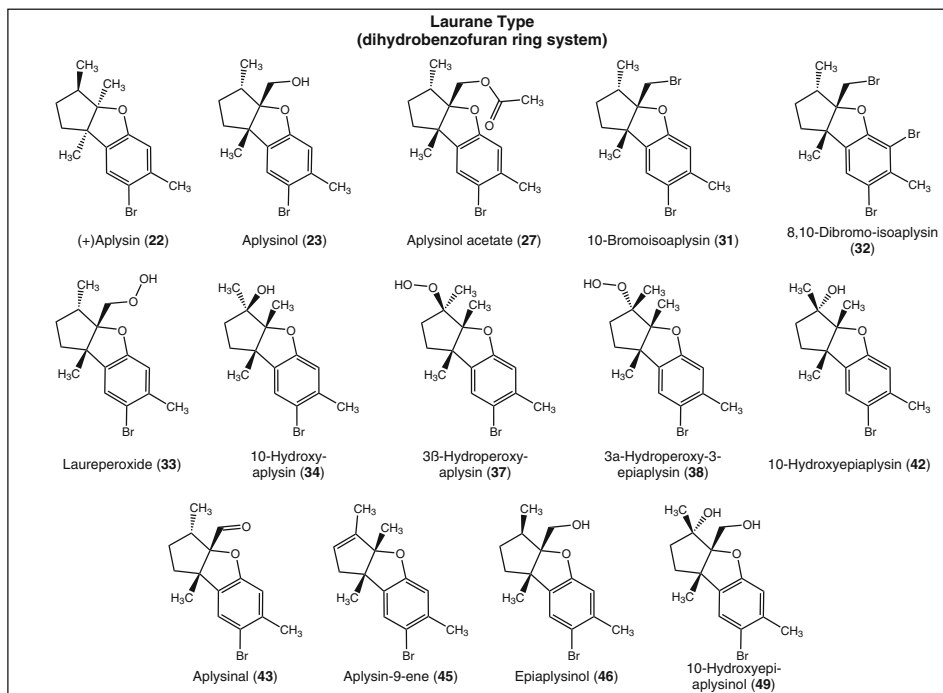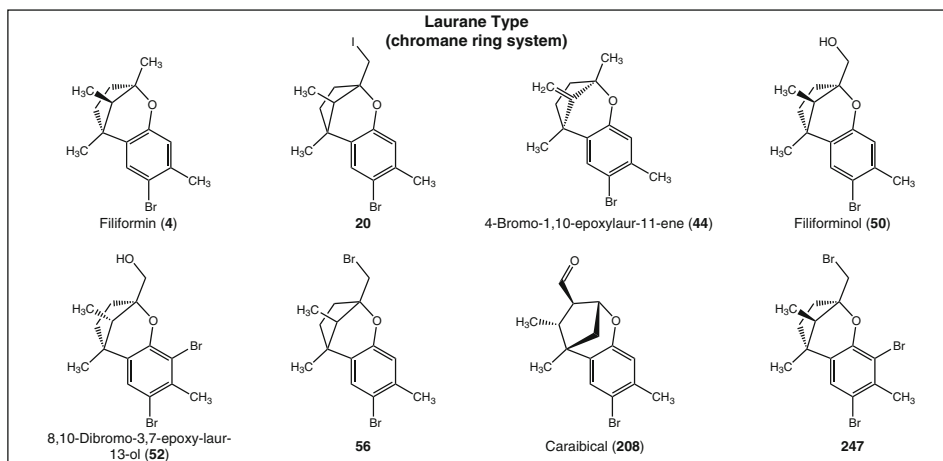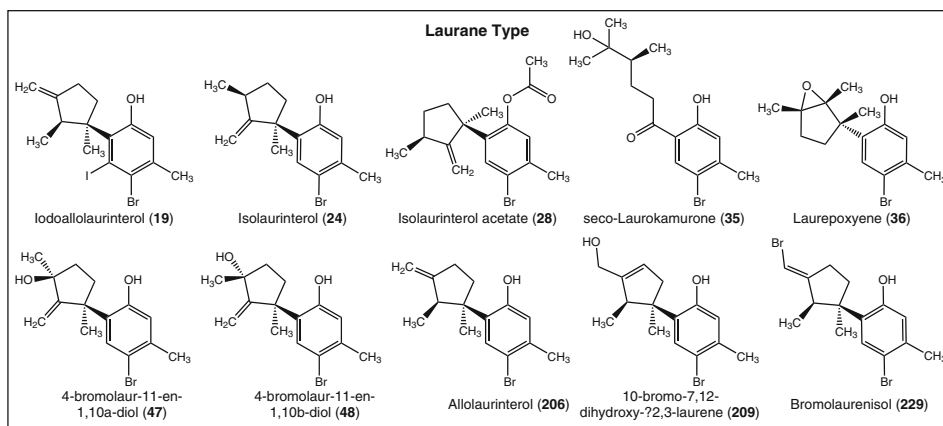
Vidalia colensoi As the genera *Osmundaria* and *Vidalia* are close relatives, it is not surprising that they contain very similar bromophenolic metabolites, for instance lanosol type (**B**) compounds that are otherwise uncommon in other Amansieae. In fact, the two bromophenol-containing species have both once been assigned to the respective other genus (Guiry and Guiry 2022). Six lanosol derivatives have been isolated from *Vidalia colensoi* (syn. *Osmundaria colensoi*) among them Colensolide A (**17,** Fig. 2) which bears a nitrogen-containing aliphatic cycle in its side chain. The authors proposed this side chain to be originating from an oxygenated histidine (Popplewell and Northcote 2009). Additionally, rhodomelol (**18**), another alicyclic compound with a highly oxidized hexahydrofuro[3,2-*b*]furan moiety was found in *V. colensoi* and also had been isolated from other Rhodomelaceae (Glombitza et al. 1985; Lever et al. 2019) before. Since these uncommon side chains do not occur in *Osmundaria* they might also be potential chemotaxonomic markers to distinguish *Vidalia* and *Osmundaria* species.

Laurencieae

Laurencia sp. In recent years the tribe Laurencieae has undergone some regrouping due to molecular genetic evidence, resulting in the genera *Palisada*, *Laurencia*, *Laurenciella*, *Yuzurua*, *Corynecladia*, *Chondrophycus*, *Osmundea* and *Ohelopapa* (Cabrera et al. 2021; Popolizio et al. 2022). Of these, *Laurencia*, *Chondrophycus* and *Osmundea* species have been reported to contain bromophenols. While this has not turned out to be true for *Chondrophycus* (see the paragraph focusing on this genus), the genus *Laurencia* produces a high variety of bromophenols and other secondary metabolites, mostly of sesquiterpene origin (Fujii et al. 2011). In total, 50 bromophenols have been isolated from 12 defined species of *Laurencia*. Additionally, three bromophenolic compounds have been reported for undefined species (Vairappan et al. 2010; Su et al. 2010; Wang et al. 2022). As this review focusses on bromophenols, we will not discuss other metabolites e.g., bromoindoles present in *L. similis* (Sun et al. 2013). A comprehensive overview of all metabolites from *Laurencia* isolated until 2016 is given by Harizani et al. (2016). For an overview of all reported bromophenols from *Laurencia* species see Figs. 3 and 4.

Most *Laurencia* species contain cuparane (**G**), laurane (**H**), cyclolaurane (**I**) or laurokamurane

Laurane Type

Iodoallolaurinterol (**19**) Isolaurinterol (**24**) Isolaurinterol acetate (**28**) seco-Laurokamurone (**35**) Laurepoxyene (**36**)

4-bromolaur-11-en-1,10a-diol (**47**) 4-bromolaur-11-en-1,10b-diol (**48**) Allolaurinterol (**206**) 10-bromo-7,12-dihydroxy-?2,3-laurene (**209**) Bromolaurenisol (**229**)

Laurane Type
(chromane ring system)

Filiformin (**4**) **20** 4-Bromo-1,10-epoxylaur-11-ene (**44**) Filiforminol (**50**)

8,10-Dibromo-3,7-epoxy-laur-13-ol (**52**) **56** Caraibical (**208**) **247**

Laurane Type
(dihydrobenzofuran ring system)

(+)Aplysin (**22**) Aplysinol (**23**) Aplysinol acetate (**27**) 10-Bromoisoaplysin (**31**) 8,10-Dibromo-isoaplysin (**32**)

Laureperoxide (**33**) 10-Hydroxy-aplysin (**34**) 3ß-Hydroperoxy-aplysin (**37**) 3a-Hydroperoxy-3-epiaplysin (**38**) 10-Hydroxyepiaplysin (**42**)

Aplysinal (**43**) Aplysin-9-ene (**45**) Epiaplysinol (**46**) 10-Hydroxyepi-aplysinol (**49**)

(**J**) type bromophenols and the majority produces one or two of these scaffolds (see Fig. 1 and Table 1). Certain species like *L. okamurai* and *L. microcladia*, however, were found to contain bromophenolic metabolites of all four skeletons. All of the scaffolds represent sesquiterpenes putatively derived from a bisabolyl cation undergoing cyclisation and C_1-

migration (Yu et al. 2014). The laurane (**H**) scaffold may probably secondarily form another ring via incorporation of the phenolic function, resulting in chromane (**H^c**) or dihydrobenzofuran (**H^b**) ring systems (Zhang et al. 2015). Some species exclusively produce chromane type lauranes (*L. caraibica*, *L. filiformis*, *L. glandulifera*, *L. microcladia*) or those of the dibenzofuran type (*L. johnstonii*, *L. pacifica*), while others produce both (*L. okamurai*, *L. tristicha*) or none of them (*L. nidifica*, *L. nipponica*, *L. obtusa*, *L. similis*). Certain clades within the *Laurencia* complex seem to preferably produce chromane type lauranes, e.g. the clade comprising *L. caraibica* and *L. filiformis* (Kazlauskas et al. 1976; Izac and Sims 1979; Izac et al. 1981). However, it does not seem reasonable to
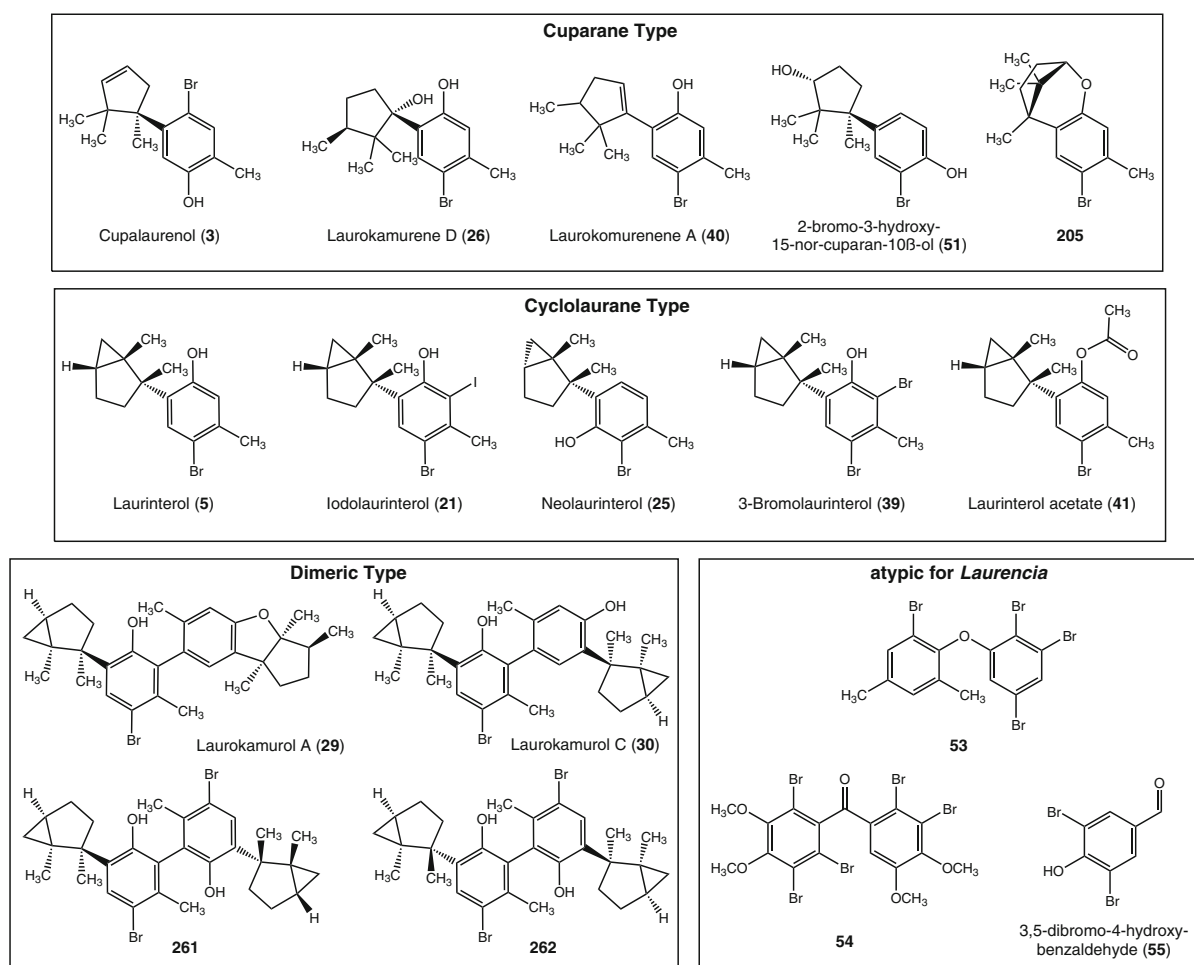
Fig. 4 Cuparane type, cyclolaurane type, dimeric bromophenols and compounds atypic for *Laurencia* isolated from Laurencia species. Structures are grouped by structural similarity with numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

deduce general chemotaxonomic rules from such accumulations of certain compounds, seeing that bromophenols of the same type also occur in other clades of the *Laurencia* complex and not every single *Laurencia* species has been assigned an unequivocal position in the taxonomy of the genus (Cabrera et al. 2021; Popolizio et al. 2022). On the other hand, particular metabolites only occur in one species and their presence might therefore be used as species-specific markers. For instance, *L. caraibica* is the only species producing iodoallolaurinterol (**19**) and an iodinated filiformin derivative (**20**) (Izac and Sims 1979) (Fig. 3). Similarly, iodolaurinterol (**21**) has exclusively been reported for *L. microcladia* (Kladi et al. 2007). In addition, *L. microcladia* also contains cuparane (**G**), cyclolaurane (**I**) and laurokamurane (**J**) skeletons, making it one of the *Laurencia* species with the highest structural diversity in its bromophenols (Kladi et al. 2005, 2006, 2007).

Another species generating a large amount of structurally diverse bromophenols is *L. okamurai* as it produces scaffolds **G—J** including both laurane subtypes (Irie et al. 1969; Suzuki and Kurosawa 1978, 1979a; Mao and Guo 2005, 2006, 2010; Yu et al. 2014; Li et al. 2015, 2017). *L. okamurai* has been the subject of various phytochemical studies and produces some compounds common in several *Laurencia* species (aplysin, aplysinol, laurinterol, isolaurinterol **5, 22—24**) as well as unique compounds. For instance, it is the only known natural source of neolaurinterol, laurokamurene D, the acetates of aplysinol and isolaurinterol**, 25—28**) and the dimeric sesquiterpenoid bromophenols laurokamurols A and C (**29, 30**) (Suzuki and Kurosawa 1978; Mao and Guo 2005, 2010; Li et al. 2017). Laurokamurol A represents a heterodimer comprised of laurinterol and aplysin, while laurokamurol C is a homodimer of two laurinterol molecules (Li et al. 2017). Further unique (**31—38**) along with non-species-specific compounds (**39—43**) were included in the database. Additionally, halogenated non-aromatic chamigranes have been isolated from *L. okamurai* (Ojika et al. 1982).

Just shortly behind *L. okamurai* and with a total of 18 isolated bromophenols, *L. tristicha* is the *Laurencia* species for which second most bromophenols have been reported. Among them, all four bromophenol types (**G—J**, Fig. 1) typical for *Laurencia* are present, though the cuparane type has only been isolated in form of the precursor α-bromocuparane (Zhang et al.

2015). Unique bromophenols from *L. tristicha* are 4-bromo-1,10-epoxylaur-11-ene (**44**), aplysin-9-ene (**45**), epiaplysinol (**46**), 4-bromolaur-11-en-1,10α-diol (**47**), 4-bromolaur-11-en-1,10β-diol (**48**) and 10-hydroxyepiaplysinol (**49**) (Sun et al. 2005, 2007; Ji et al. 2008; Zhang et al. 2021) (Fig. 3).

Apart from these three major bromophenol producers, several other *Laurencia* species have been reported to contain bromophenolic metabolites. *L. filiformis* has been found to produce lauranes (**H**), among them the chromane type compound filiforminol (**50**) (Kazlauskas et al. 1976). Similarly, *L. glandulifera* also produces chromane type lauranes (**H^c**) in addition to cyclolauranes (Suzuki and Kurosawa 1979b), however no unique bromophenolic metabolite has been reported for this species. This is also the case for *L. pacifica*, *L. johnstonii* and *L. nidifica* that only produce dihydrobenzofuran type lauranes (**H^b**), dihydrobenzofuran type lauranes and cyclolauranes (**H^b**, **I**) or regular lauranes and cyclolauranes (**H**, **I**) respectively (Crews and Selover 1986; Vairappan et al. 2001; García-Davis et al. 2018). Further halogenated aliphatic compounds have been isolated from *L. pacifica* (Selover and Crews 1980) but these were not covered by the inclusion criteria (aromatic brominated phenols) of this review. Comparable compounds to those occurring in *L. pacifica* have been found in *L. obtusa* which is also the only algal source of 2-bromo-3-hydroxy-15-nor-cuparan-10β-ol (**51**, Fig. 4) (König and Wright 1997; Kladi et al. 2006; Bawakid et al. 2017).

Finally, two reports on unidentified species of *Laurencia* have described the isolation of cuparane type (cupalaurenol, **3**, Fig. 4), chromane type laurane (8,10-dibromo-3,7-epoxy-laur-13-ol, **52**, Fig. 3) and further halogenated compounds which were not covered by the inclusion criteria (aromatic brominated phenols) of this review (Vairappan et al. 2010; Su et al. 2010).

Despite the apparent diversity of sesquiterpenoid metabolites in the *Laurencia* genus, two species were reported to contain untypical bromophenol scaffolds: Tribrominated phenols (1,2,5-tribromo-3-(2-bromo-4,6-dimethylphenoxy)benzene and 2,3-dibromo-4,5-dimethoxyphenyl)(2,3,6-tribromo-4,5-dimethoxyphenyl)methanone, **53, 54**, Fig. 4) were found in *L. similis* together with highly brominated indoles (Qin et al. 2010; Sun et al. 2013). A possible explanation for the remarkable disparity between the occurrence of these

scaffolds in *L. similis* and the more common scaffolds **G—J** in other *Laurencia* species might be a changed bromoperoxidase selectivity in this species with preference to indoles and polyphenols instead of sesquiterpene scaffolds. Sun et al. (2013) pointed out that a brominated tryptamine derivative might be a plausible precursor of the indole derivatives. However, as this is mere conjecture, further research on the precise biosynthetic pathways leading to the bromophenols found in *L. similis* is needed.

Additionally, Mikami and colleagues (2013) reported the isolation of another *Laurencia*-atypic bromophenol (3,5-dibromo-4-hydroxybenzaldehyde, **55**, Fig. 4) from *L. nipponica*. But as this is the only report on this substance from *L. nipponica* and this alga has been reported to otherwise contain completely different non-bromophenolic metabolites of terpenoid origin (Abe et al. 1999), it remains uncertain whether **55** is a genuine metabolite of *L. nipponica*. An explanation for its occurrence could also be a carryover from *Polysiphonia stricta*, as this alga was investigated within the same study (Mikami et al. 2013) and it commonly contains **55** (Li et al. 2008b).

It seems worth mentioning that other *Laurencia* species have also been phytochemically evaluated, but as they do not contain any bromophenols as defined (molecules including a brominated phenol), they were not included in this review. Examples for such species are *L. distichophylla* (cuparane and laurane-like derivatives, halogenated in the side chain), *L. mariannensis* (halogenated aliphatic heterocycles) and *L. dendroidea* (syn. *L. majuscula*; non-aromatic chamigrane derivatives) (Blunt et al. 1984; Vairappan et al. 2001). As these three species do not belong to a common clade of non-bromophenol-producing species and considering the above-mentioned taxonomic uncertainty concerning the exact placement of each *Laurencia* species in the *Laurencia* complex (Cabrera et al. 2021; Popolizio et al. 2022), it does not seem appropriate to infer chemotaxonomic principles from these phenomenological findings.

Chondrophycus sp. Some of the species originally classified as *Laurencia* have today been reevaluated to be part of independent genera (Cabrera et al. 2021; Popolizio et al. 2022). One example is *Chondrophycus intermedius* (syn. *Laurencia intermedia*) which was reported to contain some laurane (**H**) and cyclolaurane (**I**) type bromophenols (Irie et al. 1970) (Fig. 1).

However, these findings were later corrected by the same group as they reinvestigated the used algal material and found that it actually was a mixture of *Laurencia okamurai*, *Chondrophycus intermedius* (syn. *L. intermedia*) and *Palisada capituliformis* (syn. *L. capituliformis*) (Suzuki and Kurosawa 1979a). Only the thalli of *L. okamurai* contained bromophenols, which is in line with other reports of *Palisada* and *Chondrophycus* species lacking bromophenols (Vairappan et al. 2001; Fujii et al. 2011; Sun et al. 2011) and emphasizes the unique metabolic abilities of the genus *Laurencia*.

Osmundea pinnatifida The only *Osmundea* species reported to contain bromophenols was previously regarded as a member of the genus *Laurencia* (Guiry and Guiry 2022). *Osmundea pinnatifida* (syn. *Laurencia pinnatifida*) is reported to contain a brominated filiformin (7-bromo-2-(bromomethyl)-5,8,10-trimethyl-2,3,4,5-tetrahydro-2,5-methanobenzo[b]oxepine, **56**, Fig. 3) (Gonzalez et al. 1984), which also occurs in *Laurencia caraibica* and *L. glandulifera* (Izac and Sims 1979; Suzuki and Kurosawa 1979b). As described above, the closely related genus *Chondrophycus* does not contain any similar structures, which poses the interesting question if *Osmundea* developed the capability of synthesizing the laurane scaffold independently or—more likely—*Chondrophycus* lost the ability to synthesize such compounds. On the other hand, this is the only report of such a compound being isolated from an *Osmundea* species, making it difficult to assess the chemotaxonomic significance of this finding. In addition, a number of halogenated aliphatic *O*-heterocycles not covered in this review, have been isolated in the same study (Gonzalez et al. 1984).

Rhodomeleae

Rhodomela confervoides Among the non-parasitic genera of the Rhodomeleae (*Rhodomela*, *Odonthalia*, *Neorhodomela* and *Beringiella*) only the latter one has not been studied phytochemically and for the other three, a plethora of 3-bromo-4-hydroxybenzyl type (**A**) and lanosol (**B**) derivatives have been reported. Certain species also contain the scaffolds **C—E** (see Table 1), however these are usually represented to a lesser extent (Suzuki et al. 1980). Along with the tribes Streblocladieae, Polysiphonieae, Pterosiphonieae,

Dipterosiphonieae, Pleurostichidieae, Herposiphonieae and Thaumatelleae, the Rhodomeleae belong to one of the two major subgroups of the Rhodomelaceae, the other one containing the above covered tribes Bostrychieae, Amansieae and Laurencieae (Díaz-Tapia et al. 2017a). Apart from the occurrence of a limited number of lanosol derivatives in the Amansieae, lanosols are mainly concentrated in the Rhodomeleae and the Streblocladieae.

Rhodomela confervoides is the only species of the genus *Rhodomela* that has been investigated regarding its phytochemistry and a total of 63 bromophenols have been identified, a significant portion of which (43 compounds) are unique. Among them, several structural subclasses exist, such as isovanillin type compounds, nucleoside derivatives, amino acid derivatives, γ-ureido butyric acid derivatives, various dimers and sulfur containing compounds. Additionally, basic 3-bromo-4-hydroxybenzyl (**A**, e.g., 5-bromoprotocatechualdehyde, **12**) and lanosol derivatives (**B**, e.g., lanosolaldehyde, lanosol and its methyl and ethyl ethers **6**, **57—59**, Fig. 5) also found in other Rhodomelaceae have been isolated (Fan et al. 2003; Li et al. 2011). Two compounds (3,4,6-tribromo-5-(hydroxymethyl)benzene-1,2-diol and 4,7-disulfolanosol, **60**, **14**) have only been detected by MS (Glombitza et al. 1974). For an overview of all reported bromophenols from *R. confervoides* see Figs. 5 and 6.

A possible explanation for the considerable amount and diversity of bromophenols in *R. confervoides* might be the secondary modification of adding one or several lanosyl moieties to basic structures like amino acids (e.g. **236**, Fig. 6), nucleosides (e.g. **258**, Fig. 6) (Zhao et al. 2005) or one of the bromophenol scaffolds (e.g. **131**, Fig. 5 (Xu et al. 2003)). However, the exact biosynthetic pathways leading to these compounds still need elucidation. This should especially be emphasized regarding the involved enzymes and mechanisms, as a majority of biosynthetic routes are based on hypothetical propositions made by the original authors despite a lack of experimental data (Wang et al. 2013). One example for an at least partially characterized biosynthetic route is the biogenesis of the 3-bromo-4-hydroxybenzyl type bromophenols starting from tyrosine (Manley and Chapman 1978). Additionally, the authors proposed that this pathway might also be a potential source of lanosol (Manley and Chapman 1978).

Fig. 5: 3-bromo-4-hydroxybenzyl type, basic lanosol type, 2,3,6-tribromo-4,5-dihydroxybenzyl type, 2,6-dibromo-4,5-dibromobenzyl type, isovanillin derived and dimeric bromophenols found in *Rhodomela confervoides* grouped by structural similarity. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature
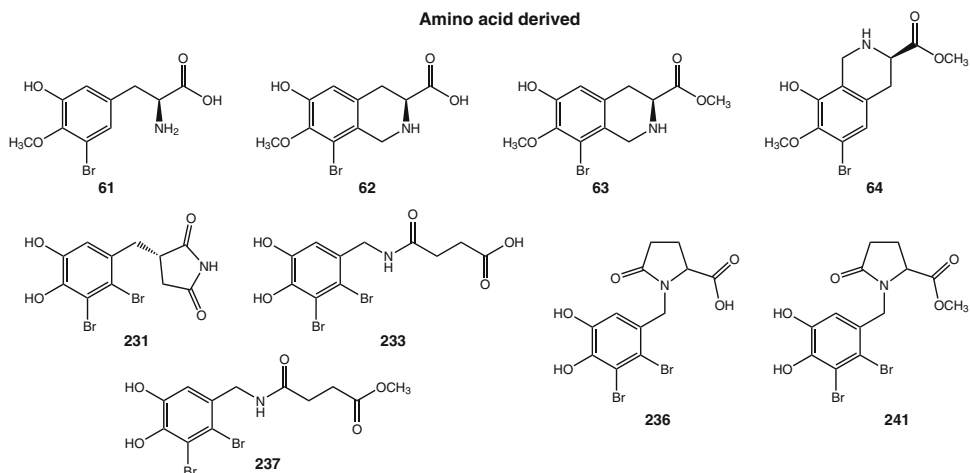
In addition, a number of brominated tyrosine derivatives occurring in *R. confervoides* ((*S*)-2-amino-3-(3-bromo-5-hydroxy-4-methoxyphenyl)propanoic acid, (*S*)-8-bromo-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, methyl (*S*)-8-bromo-6-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate and methyl (*S*)-6-bromo-8-hydroxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate, **61—64**, Fig. 6) corroborate this hypothesis (Ma et al. 2007; Li et al. 2011). Furthermore, the presence of the unique ethylbenzene derivative 3,4-dibromo-5-(2-hydroxyethyl)benzene-1,2-diol (**65**) might be an additional indication that the original amino acid side chain does not necessarily have to be cleaved for bromination to occur (Ma et al. 2006; Li et al. 2011).

Another structural feature found in the bromophenols of *R. confervoides* is the γ-ureido butyric acid side chain which facilitates structural variation via several substitutable sites. For instance, lanosylation of the ureido substructure may occur as in methyl 4-(1,3-bis(2,3-dibromo-4,5-dihydroxybenzyl)ureido)butanoate (**66**) (Ma et al. 2006) or (*R*)-Rhodomelin A (**251**) (Li et al. 2018). Additionally, a compound showing a lanosylated 3-bromo-4,5-dihydroxybenzyl-residue (N′-[3-bromo-2-(2,3-dibromo-4,5-dihydroxybenzyl)-4,5-dihydroxybenzyl]-γ-ureidobutyric acid, **67**, Fig. 6) has recently been reported (Li et al. 2021). Interestingly, similar molecules not showing further lanosylation have been isolated from another member of the Rhodomelaceae family, *Vertebrata lanosa* (Hofer et al. 2019; Jacobtorweihen et al. 2022). In conjunction with the high diversity of dimeric lanosol derivatives in *R. confervoides*, this might be a hint for less specific enzymes involved in lanosylation than those found in *V. lanosa*.
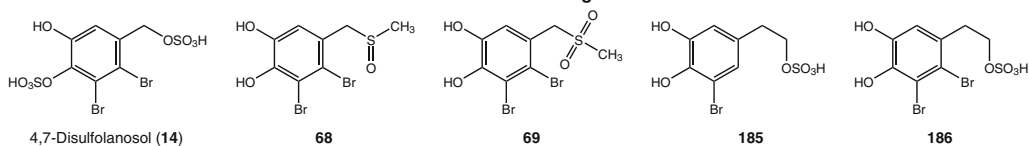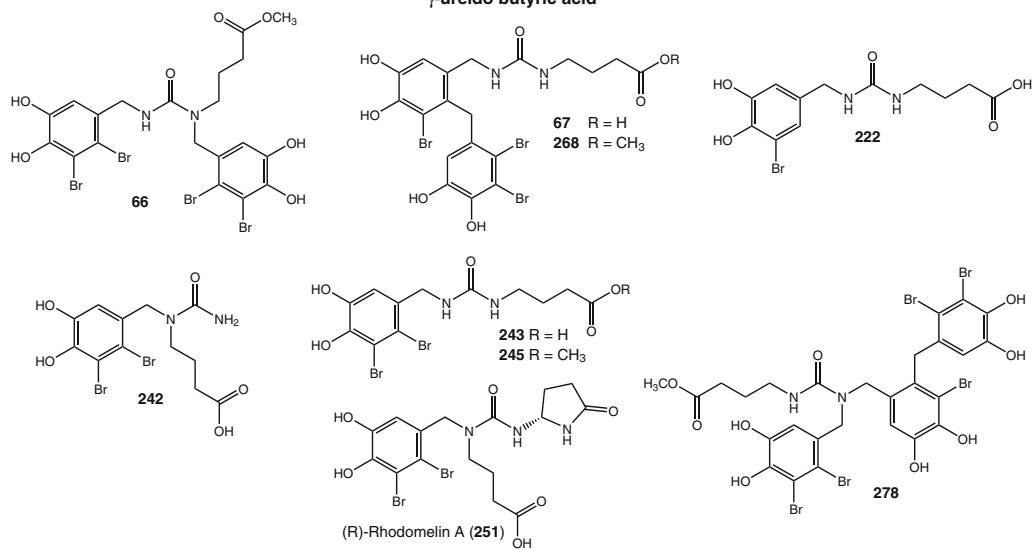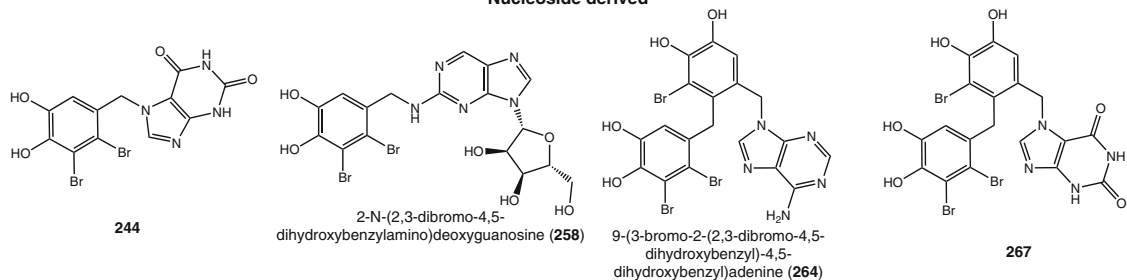
Finally, the occurrence of sulfur in the side chains of 3,4-dibromo-5-((methylsulfinyl)methyl)benzene-1,2-diol (**68**) and 3,4-dibromo-5-((methylsulfonyl)methyl)benzene-1,2-dio**l** (**69**) (Zhao et al. 2004; Li et al. 2011) (Fig. 6) seems rather exceptional for bromophenols. Like other biochemically utilized

3-bromo-4-hydroxy-benzyl type (A)

5-Bromoproto-catechualdehyde (**12**)

196

197

Basic lanosol derivatives (B)

Lanosol (**6**)

Lanosolaldehyde (**57**)

Lanosol methyl ether (**58**)

Lanosol ethyl ether (**59**)

65

163

188

189

190

212

228

232

Isovanillin derived

159

5-Bromoisovanillin (**191**)

193

194

198

199

201

2,3,6-tribromo-4,5-dihydroxybenzyl type (E)

60

2-bromo-4,5-dihydroxybenzyl type (F)

184

Dimers

7,7'-Bis-lanosol ether (**73**)

74

2'-Lanosyl-3'-bromo-5',6'-dihydroxybenzyl alcohol (**131**)

160

187

238

254

255

257

259

266

274

Amino acid derived

61   **62**   **63**   **64**

231   **233**   **236**   **241**

237

Sulfur containing

4,7-Disulfolanosol (**14**)   **68**   **69**   **185**   **186**

γ-ureido butyric acid

66

67 R = H
268 R = CH₃

222

242

243 R = H
245 R = CH₃

(R)-Rhodomelin A (**251**)

278

Nucleoside derived

244

2-N-(2,3-dibromo-4,5-
dihydroxybenzylamino)deoxyguanosine (**258**)

9-(3-bromo-2-(2,3-dibromo-4,5-
dihydroxybenzyl)-4,5-
dihydroxybenzyl)adenine (**264**)

267

◄**Fig. 6** Bromophenols found in *Rhodomela confervoides* grouped by structural features. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

elements, sulfur is incorporated into a marine organosulfur cycle where it can be found in several intermediate metabolites (Thume et al. 2018). Dimethyl sulfoxide (DMSO), one of these metabolites, is very common in sea water and microalgae (Lee and de Mora 1999). Its formation is facilitated by oxidation of zwitterionic organic acids with a cationic sulfonium or sulfoxonium moiety (Lee and de Mora 1999; Thume et al. 2018). Similar to these cationic metabolites, isolation of a dimethylsulfonium lanosol derivative (**70**) from *V. lanosa* was recently reported (Jacobtorweihen et al. 2022) which might be a possible precursor of the sulfoxide derivative (**68**) found in *R. confervoides* (Zhao et al. 2004). To confirm this

hypothesis, the respective sulfonium or sulfoxide derivative along with the enzymatic pathways leading to these molecules had to be identified in *R. confervoides* or in *V. lanosa*, respectively. However, the occurrence of each of the sulfur containing bromophenols is a hint for the existence of pathways attaching sulfur to organic molecules in red algae similar to those reported for microalgae (Thume et al. 2018).

Neorhodomela sp. *Neorhodomela* species are very closely related to the genus *Rhodomela* which is reflected by their morphology, geographical distribution and also by their phytochemical composition (Fan et al. 2003; Park et al. 2012; Díaz-Tapia et al. 2017a). Two species (*N. aculeata* and *N. larix*, formerly *Rhodomela larix*) have been investigated regarding their secondary metabolites (Masuda 1982; Guiry and Guiry 2022). Both contain
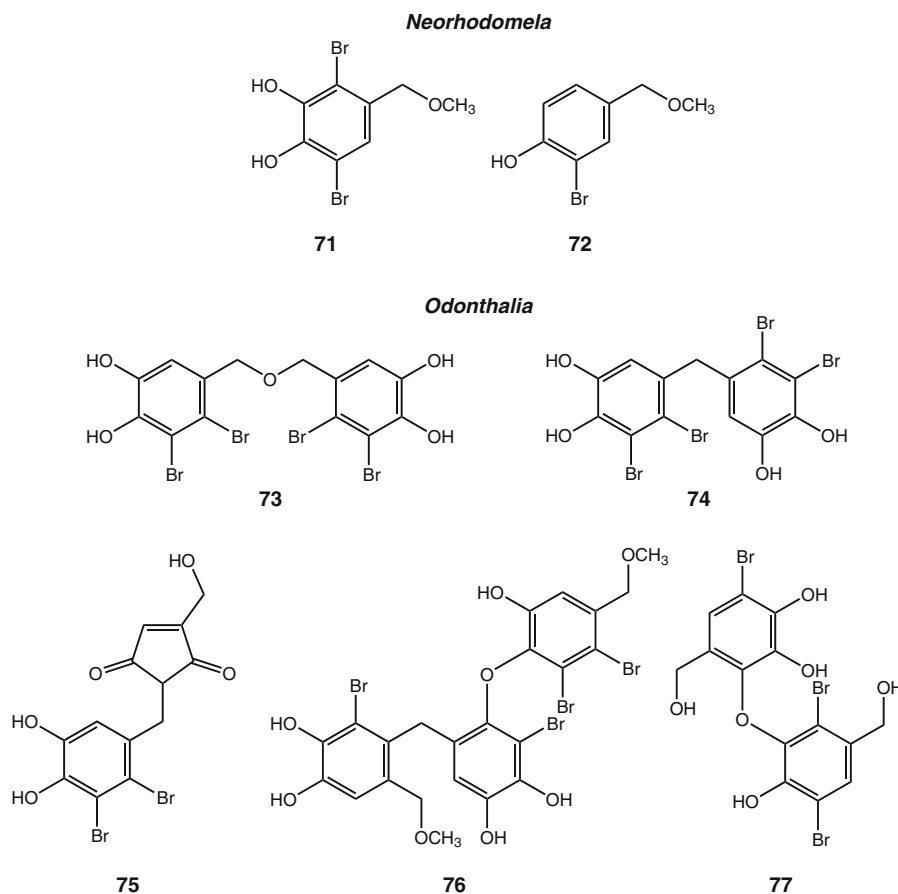
Fig. 7 Selected characteristic bromophenols from *Neorhodomela* and *Odonthalia* species. Compounds are grouped according to the respective genus they occur in, and numbered according to occurrence in Table S1

Basic 2,3,6-tribromo-4,5-dihydroxybenzyl type (E)

60   78   79   80   226

Dimeric 2,3,6-tribromo-4,5-dihydroxybenzyl type

BTDE (81)   82   269

270   271   272
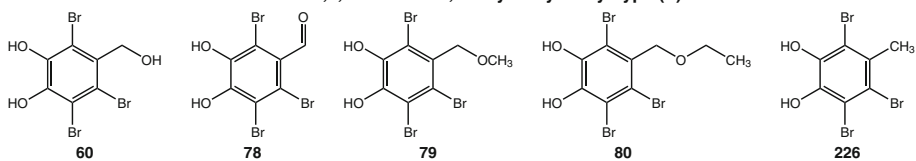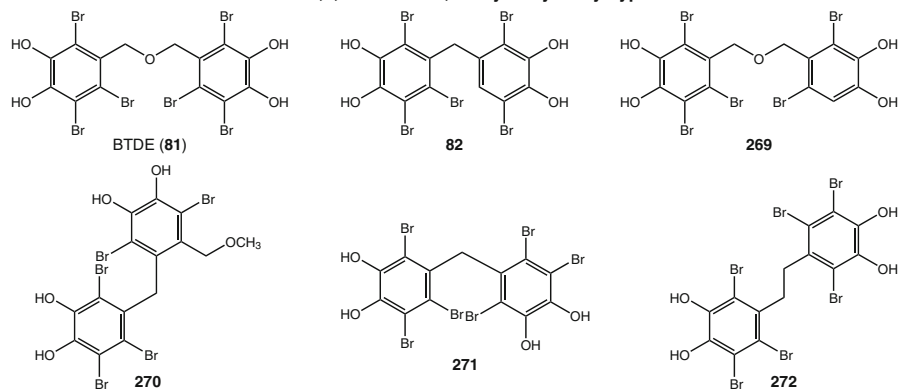
Alicyclic and heterocyclic side chains

110   Symphyoketone (248)   253   273

Sulfur containing

111   112   256

γ-ureido butyric acid

109

108   277
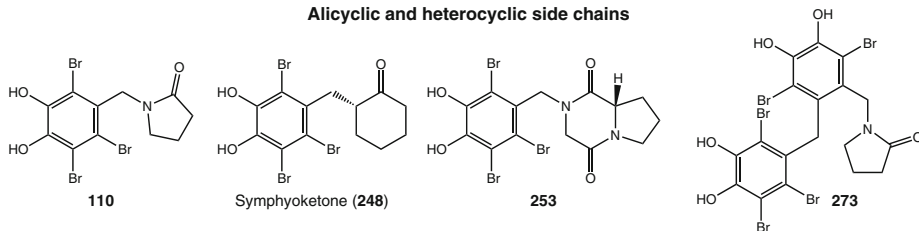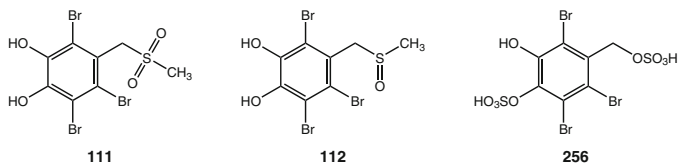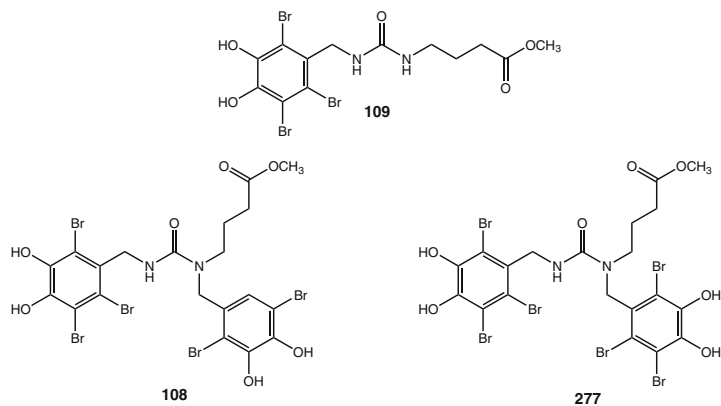
◄**Fig. 8** Basic and dimeric 2,3,6-tribromo-4,5-dihydroxybenzyl type bromophenols as well as compounds containing cyclic side chains or sulfur isolated from *Symphyocladia latiuscula* grouped by structural similarity. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

3-bromo-4-hydroxybenzyl (**A**) and lanosol derivatives (**B**) and occasionally 3,5-dibromo-4-hydroxybenzyl type (**C**) or 3,6-dibromo-4,5-dihydroxybenzyl type (**D**, only *N. aculeata*) bromophenols (Kurata and Amiya 1977; Suzuki et al. 1980; Park et al. 2012; Mikami et al. 2016) (Fig. 1). Potential species-specific markers for *N. aculeata* and *N. larix* are 3,6-dibromo-4-(methoxymethyl)benzene-1,2-diol (**71**) and 2-bromo-4-(methoxymethyl)phenol (**72**), respectively (Suzuki et al. 1980; Park et al. 2012) (Fig. 7). Notably, 4,7-disulfolanosol (**14**, Fig. 2) has only been isolated from *N. larix* and might be considered a potential discriminative marker between the two *Neorhodomela* species. However, for *N. aculeata* only organic solvent partitions of the respective methanol extracts have been examined so far (Park et al. 2012; Mikami et al. 2016), but not the composition of the respective polar phases. In this context, investigations of the more polar constituents in general have the potential to yield novel compounds and might also shed light on the hypothesis formulated by Weinstein et al. (1975) who suggested the bromophenols genuine to the algae to be sulfated, and desulfation occurring only during extraction or isolation. Moreover, the last report on phytochemical investigations of *N. larix* dates back to the 1980s (Carlson et al. 1989) and reinvestigating this alga using state-of-the-art analytical methods could provide further insights to its secondary metabolites. Since the close relative *Rhodomela confervoides* is the source of fourfold as many metabolites, further phytochemical investigations on *N. larix* seem promising.

Odonthalia corymbifera Odonthalia corymbifera is the only species of this genus studied in terms of its phytochemistry and produces a number of lanosol derivatives (**B**) similar to other Rhodomeleae. Some of them are simple lanosol derivatives (lanosol and its methyl and ethyl ethers, **6, 58—59**, Fig. 5), others are common ether- or methylene-linked dimers (**73, 74**, Fig. 7) (Kurata et al. 1997; Kurihara et al. 1999b; Lee et al. 2007). However, *O. corymbifera* also produces a

few unusual bromophenols. One is odonthadione (**75**), a compound containing a cyclopentenedione moiety uncommon in natural products (Islam et al. 2017). Along with **75**, odonthalol (**76**) was purified, which contains an unusual *O*-linkage between the bromophenol subunits (Islam et al. 2017). A structurally related compound consisting of a 3-bromo-4,5-dihydroxybenzylalcohol and a 3,6-dibromo-4,5-dihydroxybenzylalcohol moiety linked via one of the phenolic oxygens (6-bromo-3-(2,5-dibromo-6-hydroxy-3-(hydroxymethyl)phenoxy)-4-(hydroxymethyl)benzene-1,2-diol, **77**) had previously been reported by Kurihara et al. (1999a, b). These compounds could potentially be used as markers to aid species identification.

Pterosiphonieae

Symphyocladia latiuscula Symphyocladia latiuscula produces a staggering number of 46 unique bromophenols which is mainly due to its ability to form tribrominated catechol derivatives of the 2,3,6-tribromo-4,5-dihydroxybenzyl type (**E**). The basic building block of *S. latiuscula*(3,4,6-tribromo-5-(hydroxymethyl)benzene-1,2-diol, **60**) has also been detected in other Rhodomelaceae, such as *V. lanosa* and *R. confervoides* by MS (Glombitza et al. 1974), however it has only been isolated from *S. latiuscula* (Kurihara et al. 1999a; Jae Sue Choi et al. 2000; Paudel et al. 2019). Similar to *R. confervoides*, bromophenols from *S. latiuscula* can in general be divided into monomeric and dimeric molecules, but also more unusual side chains have been found (Xu et al. 2012a, b). An overview of all reported bromophenols from *S. latiuscula* is given in Fig. 8 and 9. Examples for basic 2,3,6-tribromo-4,5-dihydroxybenzyl type bromophenols in *S. latiuscula* are **60,** its aldehyde (**78**), and the respective methyl or ethyl ethers (**79, 80**), while the dimeric compounds may either be symmetrical (e.g., 5,5'-(oxybis(methylene))bis(3,4,6-tribromobenzene-1,2-diol, **81**) or asymmetrical (e.g., 3,4,6-tribromo-5-(2,5-dibromo-3,4-dihydroxybenzyl)benzene-1,2-diol, **82**) (Kurata and Amiya 1980b; Kurihara et al. 1999a; Wang et al. 2005; Xu et al. 2009) (Fig. 8). In addition to this classification, a large number of compounds termed "symphyocladins" with aliphatic side chains mostly comprised of aconitic acid have been isolated (Xu et al. 2012a, 2017, 2019). Symphyocladins are
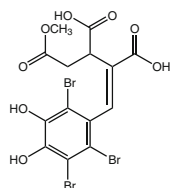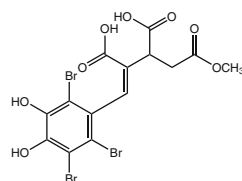
Symphyocladins and related derivatives
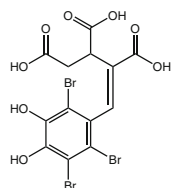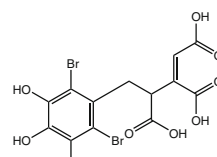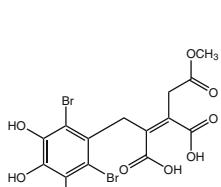
Symphyocladin A (**83**)
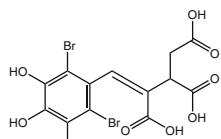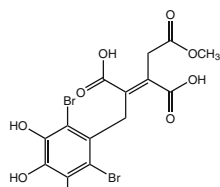
Symphyocladin B (**84**)
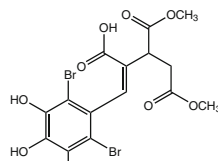
Symphyocladin C (**85**)
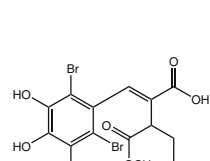
Symphyocladin D (**86**)

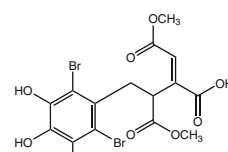Symphyocladin E (**87**)

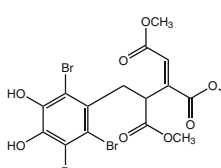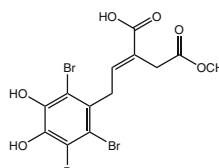Symphyocladin H (**88**)

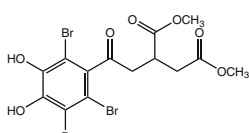Symphyocladin I (**89**)

Symphyocladin J (**90**)
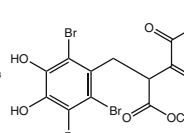
Symphyocladin K (**91**)
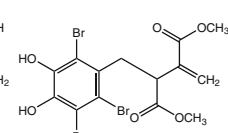
Symphyocladin L (**92**)
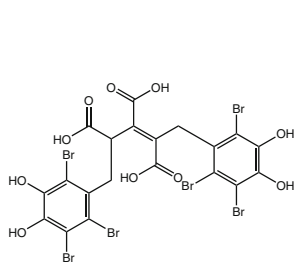
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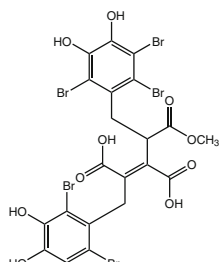
Symphyocladin N (**94**)
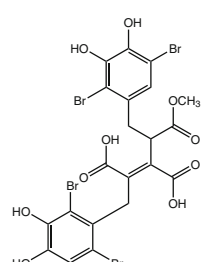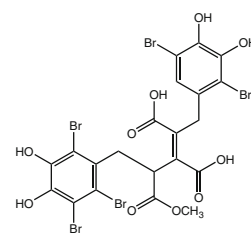
Symphyocladin O (**95**)

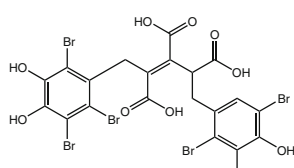Symphyocladin P (**96**)

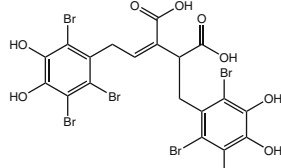Symphyocladin Q (**97**)

Symphyocladin R (**98**)

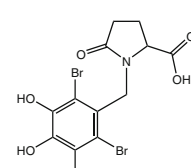Symphyocladin S (**99**)

Symphyocladin T (**100**)
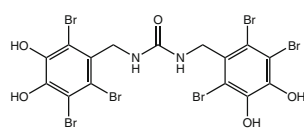
Symphyocladin U (**101**)

Symphyocladin V (**102**)

Symphyocladin W (**103**)
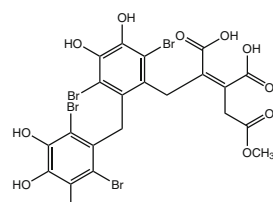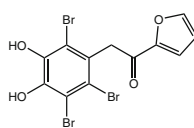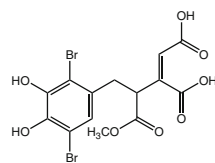
Symphyocladin X (**104**)

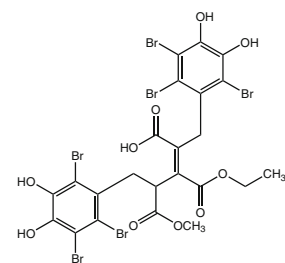Symphyocladin F (**105**)

Symphyocladin G (**106**)

Symphyocladin Y (**107**)

250

279

◀ **Fig. 9** Symphyocladins and other aconitic acid derivatives isolated from *Symphyocladia latiuscula* grouped by structural similarity. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature. 279 may be an artifcact from isolation

found with one (symphyocladins A—E and H—Q, **83—97**) or two brominated 4,5-dihydroxybenzyl moieties (symphyocladins R—X, **98—104**) (Fig. 9). Some symphyocladins possess side chains of other origin than aconitic acid, i.e. pyroglutamic acid in symphyocladin F (**105**), urea in symphyocladin G (**106**) or a furanoyl moiety in symphyocladin Y (**107**). Some of the isomeric symphyocladins (A/B, C/D, H/I, J/K) have not been separated but were isolated as mixtures (Xu et al. 2012a, 2017).

Notably, certain residues occurring in *R. confervoides*, such as γ-ureido butyric acid, are also found in methyl 4-(1-(2,5-dibromo-3,4-dihydroxyben-zyl)-3-(2,3,6-tribromo-4,5-dihydroxybenzyl)ureido) butanoate (**108**) or methyl 4-(3-(2,3,6-tribromo-4,5-dihydroxybenzyl)ureido)butanoate (**109**) from *S. latiuscula* (Xu et al. 2013a, 2014). Also the pyrrolidine moiety (e.g., 1-(2,3,6-tribromo-4,5-dihydroxyben-zyl)pyrrolidin-2-one, **110**) and the oxidized sulfur in benzylic position (as in 3,4,6-tribromo-5-((methylsul-fonyl)methyl)benzene-1,2-diol and 2,3,6-tribromo-4,5-dihydroxybenzyl methyl sulphoxide, **111**, **112**) of the tribrominated phenol (Duan et al. 2007; Xu et al. 2013b) occur in both species.

All of these structural analogies suggest that both species possess similar ways of modifying the basic bromophenol scaffold to generate a variety of secondary metabolites. The effectiveness of these variations is well illustrated by the enormous numbers of bromophenols both species produce (48 bromophenols for *S. latiuscula* and 59 for *R. confervoides*), the majority of which is unique. From a biogenetic point of view, the major factors for variation in bromophenols in these species seem to be either dimerization or linkage to primary metabolites like amino acids, nucleosides or organic acids as suggested for the aconitic acid residue in the symphyocladins (Xu et al. 2017). However, as previously mentioned, the exact biosynthetic routes leading to the plethora of bromophenols from *R. confervoides* and also *S. latiuscula* are unknown and further research is needed to fully understand the function and biosynthesis of these compounds.

Pterosiphonia complanata While *S. latiuscula* is very well studied and a large number of compounds have been isolated from it, only one other member of the Pterosiphonieae has been reported to contain bromophenols. *Pterosiphonia complanata* was also found to produce a 2,3,6-tribrominated compound (3,4,6-tribromo-5-(methoxymethyl)benzene-1,2-diol, **79**, Fig. 8) (Etahiri et al. 2007) which shows that the occurrence of this bromination pattern might be a characteristic of the entire tribe Pterosiphonieae. However, further research on additional species from this particular tribe is needed to verify this hypothesis.

Polysiphonieae

Polysiphonia sp. Similar to the Laurencieae, the clade Polysiphonieae has undergone a massive reclassification in the last two decades due to molecular genetic evidence leading to the placement of several species previously classified as *Polysiphonia* into their own genera and the establishment of the new clade Streblocladieae (Díaz-Tapia et al. 2017a). Today, the only two *Polysiphonia* species studied phytochemically are the closely related *P. stricta* (syn. *P. urceolata*) and *P. morrowii*. Every other *Polysiphonia* species previously reported to possess certain types of bromophenols (e.g., lanosol type compounds for *Vertebrata lanosa*, syn. *Polysiphonia lanosa*) has been reclassified to other genera like *Vertebrata, Carradorriella, Leptosiphonia* or *Melanothamnus* (Díaz-Tapia et al. 2017a; Guiry and Guiry 2022) (see also Table 1).

P. stricta contains 3-bromo-4-hydroxybenzyl type (**A**) and 3,5-dibromo-4-hydroxybenzyl type (**C**) bromophenols as monomers or oligomers (e.g., Urceolatin, **113**) which may sometimes form additional ring systems leading to phenanthrene-like compounds (e.g., 4,7-dibromo-9,10-dihydrophenanthrene-2,3,5,6-te-traol, **114**) (Kurata and Amiya 1980a; Li et al. 2008a, b) (Fig. 10). Notably, for *P. morrowii* only 3-bromo-4-hydroxybenzyl type (**A**) derivatives have been reported (Choi et al. 2018; Mikami et al. 2016; Kim et al. 2011; Kurihara et al. 1999a). However, as the type species for the genus *Polysiphonia*, *P. stricta* has been studied much more extensively and *P. morrowii* might still contain 3,5-brominated compounds that merely have not been found until today.

Examples for further polycyclic compounds from *P. stricta* are urceolatol (**115**), (5*S*,10*S*)-2,7-dibromo-

Polysiphonia

Urceolatin (**113**)

114

Urceolatol (**115**)

116

117

118

119

120

Leptosiphonia

121

Melanothamnus

Polysiphenol (**122**)

Vertebrata

70

Vertebratol (**123**) R = H
124 R = SO$_3$H

125

126

Rhodomelol (**18**) R = H
Methylrhodomelol (**127**) R = CH$_3$

Polysiphonol (**128**)

129

130

132

133

◄ **Fig. 10** Selected characteristic bromophenols found in the Polysiphonieae and the Streblocladieae. Compounds are grouped according to the respective genus they occur in. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

5,10-dimethoxy-5,10-dihydrochromeno[5,4,3-cde]chromene-3,8-diol (**116**), 1,8-dibromo-5,7-dihydrodibenzo[c,e]oxepine-2,3,9,10-tetraol (**117**) and urceolatin (**113**) (Liu et al. 2006, 2009; Li et al. 2008a, b) (Fig. 10). The 3,5-dibromo-4-hydroxybenzyl type (**C**) bromophenols are also found to be incorporated into dimers, but unlike type **A**, these do not form additional ring systems, as exemplified by 3-(3-bromo-4,5-dihydroxyphenyl)-2-(3,5-dibromo-4-hydroxyphenyl)propanoic acid (**118**) and 4,4'-(ethane-1,2-diyl)bis(2,6-dibromophenol) (**119**) (Kurata et al. 1976; Li et al. 2007) (Fig. 10). The only bromophenol reported to be unique to *P. morrowii* is 5,5'-(oxybis(methylene))bis(3-bromobenzene-1,2-diol) (**120**) (Choi et al. 2018).

One of the most striking features in the phytochemistry of *Polysiphonia* species is the complete absence of 2,3-dibrominated lanosol derivatives. This is especially surprising as most of the closer related tribes (Streblocladieae, Rhodomeleae and Pterosiphonieae) produce 2,3-dibrominated (**B**) or 2,3,6-tribrominated 3,4-dihydroxybenzyl (**E**) type compounds (Fan et al. 2003; Li et al. 2012; Xu et al. 2017; Hofer et al. 2019). However upon closer inspection, the lack of lanosol derivatives supports the recent regrouping of this section of the Rhodomelaceae quite well (Díaz-Tapia et al. 2017a; Savoie and Saunders 2019) and it might—in addition to other identifying features (Savoie and Saunders 2019)—serve as a characteristic for *P. stricta* and *P. morrowii*. On the other hand, only a small portion of *Polysiphonia* species has been studied regarding their phytochemistry and it might therefore be too early to infer universal chemotaxonomic rules from the phytochemistry of just two species.

Streblocladieae

Carradoriella elongata One more of the species formerly classified as *Polysiphonia* is *Carradoriella elongata* (syn. *Polysiphonia elongata*) (Díaz-Tapia et al. 2017a; Savoie and Saunders 2019; Guiry and Guiry 2022) which was found to contain 3-bromo-4-hydroxybenzyl type (**A**) and lanosol (**B**) type bromophenols (Glombitza et al. 1974). The compounds that have been reported are lanosol (**6**), lanosolaldehyde (**57**, Fig. 5), 4,7-disulfolanosol (**14**, Fig. 2), 5-bromoprotocatechualdehyde (**12**, Fig. 2). As this is the only report on the phytochemistry of *Carradoriella* species, further investigations on these algae are needed to dereplicate the results and explore the potential chemodiversity of this genus.

Leptosiphonia brodiei Similar to *C. elongata*, the only report on the bromophenol composition of *Leptosiphonia brodiei* (syn. *Polysiphonia brodiei*) is the MS analysis of Glombitza et al. (1974). They identified 3-bromo-4-hydroxybenzyl type (**A**), lanosol type (**B**) and 3,5-dibromo-4-hydroxybenzyl type (**C**) bromophenols, namely lanosol (**6**, Fig. 5), 4,7-disulfolanosol (**14**, Fig. 2), 2,6-dibromo-4-(hydroxymethyl)phenol (**121**, Fig. 10) and 2-bromo-4-(hydroxymethyl)phenol (**10**, Fig. 2). Once again, this is the only study concerning the phytochemistry of a *Leptosiphonia* species and further investigations on these algae are needed.

Melanothamnus sp. As with *Carradoriella* and *Leptosiphonia*, both phytochemically investigated *Melanothamnus* species had been classified as *Polysiphonia* species until recently (Díaz-Tapia et al. 2017b). For *Melanothamnus ferulaceus* (syn. *Polysiphonia ferulacea*), lanosol-type bromophenols (**B**) are described, whereas *M. sphaerocarpus* (syn. *Polysiphonia sphaerocarpa*) was found to contain simple brominated phenols (**O**). For members of the Streblocladieae, the presence of the lanosol-type bromophenols is not surprising as these are also present in other members of this tribe (e.g., *Vertebrata*, *Leptosiphonia*). The compounds described for *M. ferulaceus* are lanosol (**6**), its methyl ether (**58**) and a unique 3-bromo-4-hydroxybenzyl type (**A**) compound (polysiphenol, **122**, Fig. 10) (Aknin et al. 1992). Interestingly, polysiphenol represents a regioisomer of 4,7-dibromo-9,10-dihydrophenanthrene-2,3,5,6-tetraol (**114**, Fig. 10) found in *Polysiphonia stricta* (Li et al. 2008b). As both molecules are probably formed via linkage of the benzylic carbons of two 3-bromo-4-hydroxybenzyl alcohol derivatives with an additional

C–C bond formed between the two arenes, it seems likely that they share the same biogenetic origin and only differ in the rotation of one of the benzene rings. Since this is the only study focusing on the phytochemistry of *M. ferulaceus*, further investigations are needed to elucidate the phylogenetical implications of the occurrence of these metabolites.

Another peculiar phenomenon in this genus is the occurrence of brominated basic phenols, cresols and anisoles in *M. sphaerocarpus* (Flodin and Whitfield 2000) as these types of structures are very different from the bromophenols found in other members of the Rhodomelaceae. Since these compounds were however only detected in smaller amounts compared to other species, they could also be a sign of contamination with bacteria or fungi, as the authors of the original publication already pointed out in regard of the *O*-methylated anisoles (Flodin and Whitfield 2000).

As the term *cresol* is ambiguous and the original publication does not include any structural formulas, the reported cresols were not included in the database. Additionally, their assignment of 3-bromo-4-hydroxybenzaldehyde (**1**) and 3,5-dibromo-4-hydroxybenzaldehyde (**55**) in the extract solely based on MS data is tentative and the detected compounds might represent isomers of the assigned compounds (e.g. a 2,3-dibrominated derivative for **55**). A biogenetic assignment of the substitution pattern of these compounds does not seem to fit either as *M. sphaerocarpus* is not classified as a member of the *Polysiphonia* genus any longer and the members of the Streblocladieae produce both 3,5-dibrominated and 2,3-dibrominated phenols (Suzuki et al. 1980; Jacobtorweihen et al. 2022). The anisole derivatives however were included since they were identified by GC–MS and comparison to authentic reference compounds (Flodin and Whitfield 2000). Once again, further studies on this species are needed to corroborate the findings reported by Flodin and Whitfield (2000), especially regarding the bromination pattern of the aldehydes.

Vertebrata sp. Just as the other members of the Streblocladieae discussed before, most *Vertebrata* species were previously classified as *Polysiphonia* sp. until recent molecular genetic findings defined them to be members of a separate clade within the Rhodomelaceae (Díaz-Tapia et al. 2017a, b). In total, six *Vertebrata* species have been investigated regarding their bromophenols with *V. lanosa* being the most extensively studied species. For the remaining species, only single reports on their phytochemistry exist (*V. decipiens*) and some were even only screened by GC–MS (*V. thuyoides*, *V. fruticulosa*, *V. fucoides* and *V. nigra*) (Glombitza et al. 1974; Lever et al. 2019). Most compounds found in *Vertebrata* species are lanosol-derived (**B**) with varying side chains (Stoffelen et al. 1972; Hofer et al. 2019; Jacobtorweihen et al. 2022). Some side chains are of bromophenolic origin (dimers **72** and **73**), some amino acid derived (e.g., vertebratol, **123**, Fig. 10) and other ones comprise unusual heterocycles (e.g., rhodomelol, **18**) (Glombitza et al. 1985; Hofer et al. 2019). Additionally, a number of sulfated derivatives has been reported (**14**, **70**, **124** and **125**) (Jacobtorweihen et al. 2022) (Fig. 10). Only certain compounds deviate from this general bromination pattern (2,6-dibromo-4-(hydroxymethyl)phenol and 3,5-dibromotyrosine, **121**, **126**, Fig. 10) and they are only found in *V. lanosa* and *V. fucoides* (Glombitza et al. 1974; Jacobtorweihen et al. 2022). However, as none of the species has been investigated to the same extent as *V. lanosa* it is likely that closer analysis of their brominated metabolites might lead to the discovery of further 3,5-dibrominated compounds.

V. lanosa itself contains a variety of unique compounds of which rhodomelol (**18**) and methylrhodomelol (**127**) have been known longest (Glombitza et al. 1985) (Fig. 10). Both of these substances comprise a lanosyl moiety linked to a cyclic ascorbyl residue and only differ in the methylation of a single hydroxyl function. A similar non-brominated scaffold, delesserine, has been isolated from another red alga, *Delesseria sanguinea* (Yvin et al. 1982) and rhodomelol and its lanosylated derivative polysiphonol (**128**) have been found in *V. decipiens* (Lever et al. 2019). It should be noted that methylrhodomelol does not represent an artifact from methanolic extraction as it was also detected in non-methanolic extracts (Glombitza et al. 1985).

More recently, the isolation of several sulfated bromophenols from the aqueous phase of a methanolic *V. lanosa* extract has been described (Jacobtorweihen et al. 2022). Some of these represent sulfated forms of previously reported molecules (5-sulfovertebratol, **124**), some might be precursors in the biosynthesis of the lanosol or 3-bromo-3,4-dihydroxybenzyl

Table 2 Scaffolds reported for bromophenol-containing red algae other than Rhodomelaceae. Letters B, H, I, K, N, O refer to structures given in Fig. 1

Order	Family	Species	Bromophenol skeleton
Gigartinales	Areschougiaceae	*Rhabdonia verticillata*	K
	Placentophoraceae	*Callophycus serratus*	N
		Callophycus sp.	N
Gracilariales	Gracilariaceae	*Gracilaria coronopifolia*	–
Halymeniales	Grateloupiaceae	*Grateloupia elliptica*	B, K, O
	Halymeniaceae	*Polyopes lancifolius*	B
Corallinales	Mesophyllumaceae	*Mesophyllum fragilissimum*	–
	Corallinaceae	*Corallina aberrans*	H, I

alcohol derivatives (3-bromo-5-sulfo-L-dihydrox-yphenylalanine, **125**) and others contain the afore-mentioned sulfonium moiety (4-sulfo-7-dimethylsulfonium lanosol, **70**; see paragraphs on *Rhodomela confervoides* and *Symphyocladia latiuscula*) (Fig. 10). As mentioned in the section about *Neorhodomela*, the investigation of the polar compounds of algal extracts might corroborate the "genuine-sulfate-hypothesis" by Weinstein et al. (1975) as suggested by the presence of the sulfated vertebratol. On the other hand, sulfation or desulfation could potentially be influenced by other factors like seasonal variation or the site of collection. Notably, sulfur-containing and ureido side chains are solely occurring in the tribes Rhodomeleae, Pterosiphonieae and Streblocladieae which all belong to a well-defined clade within the Rhodomelaceae.

Similar to other lanosol-containing species (e.g. *R. confervoides* and *S. latiuscula*), *V. lanosa* also modifies primary metabolites via lanosylation (3-bromo-6-lanosyl dihydroxyphenylalanine and 3-(6′-lanosyl-lanosyl)-tyrosine, **129, 130**, Fig. 10) (Jacobtorweihen et al. 2022). Similarly, dimeric compounds like 2'-lanosyl-3'-bromo-5',6'-dihydroxybenzyl alcohol (**131**) or the more complex 5,5'-(oxy-bis(methylene))bis(3-bromo-4-(2,3-dibromo-4,5-di-hydroxybenzyl)benzene-1,2-diol) (**132**) (Olsen et al. 2013; Hofer et al. 2019) could be regarded as lanosylated lanosol derivatives.

As a final remark on *V. lanosa*, Glombitza et al. (1974) detected 3,4,6-tribromo-5-(hydrox-ymethyl)benzene-1,2-diol (**60**, Fig. 5) by GC–MS in an extract from *V. lanosa*. However, this compound has not been isolated within any of the more recent studies (Olsen et al. 2013; Hofer et al. 2019; Jacobtorweihen et al. 2022).

As already mentioned, Glombitza et al. (1974) also investigated several other "*Polysiphonia*" species later reclassified as *Vertebrata*. In summary, *V. thuyoides*, *V. fruticulosa*, *V. fucoides* and *V. nigra* all contain lanosol (**6**), lanosolaldehyde (**57**) and 4,7-disulfolanosol (**14**) (Fig. 5 and 6), while *V. fruticulosa* and *V. nigra* both additionally contain 2-bromo-4-(hydroxymethyl)phenol (**10**, Fig. 2). Furthermore, *V. fruticulosa* was found to produce 3-bromo-5-(hydrox-ymethyl)benzene-1,2-diol (**11**, Fig. 2), 3,4-dibromo-5-(propoxymethyl)benzene-1,2-diol (**133**) and 2,6-dibromo-4-(hydroxymethyl)phenol (**121**) (Fig. 10).

Red algae other than Rhodomelaceae

In contrast to the bromophenol-rich Rhodomelaceae, other families of red algae have only rarely been reported to contain more complex bromophenolic compounds. Just like the Rhodomelaceae, all of them (except the Corallinales) belong to the subclass Rhodymeniophycidae in the class Florideophyceae (Yang et al. 2015; Guiry and Guiry 2022). However, no chemotaxonomic principles can be inferred from the available data as most species only produce few characteristic compounds (*Callophycus*), investigations are scarce (*Rhabdonia, Grateloupia and Polyopes*) and certain species might not even be the actual producers of the bromophenols (*Gracilaria coronopifolia, Ceramium tenuicorne*) (Nagai et al. 1997). An overview of the reported skeletons is provided in Table 2 and selected characteristic compounds are shown in Fig. 11.
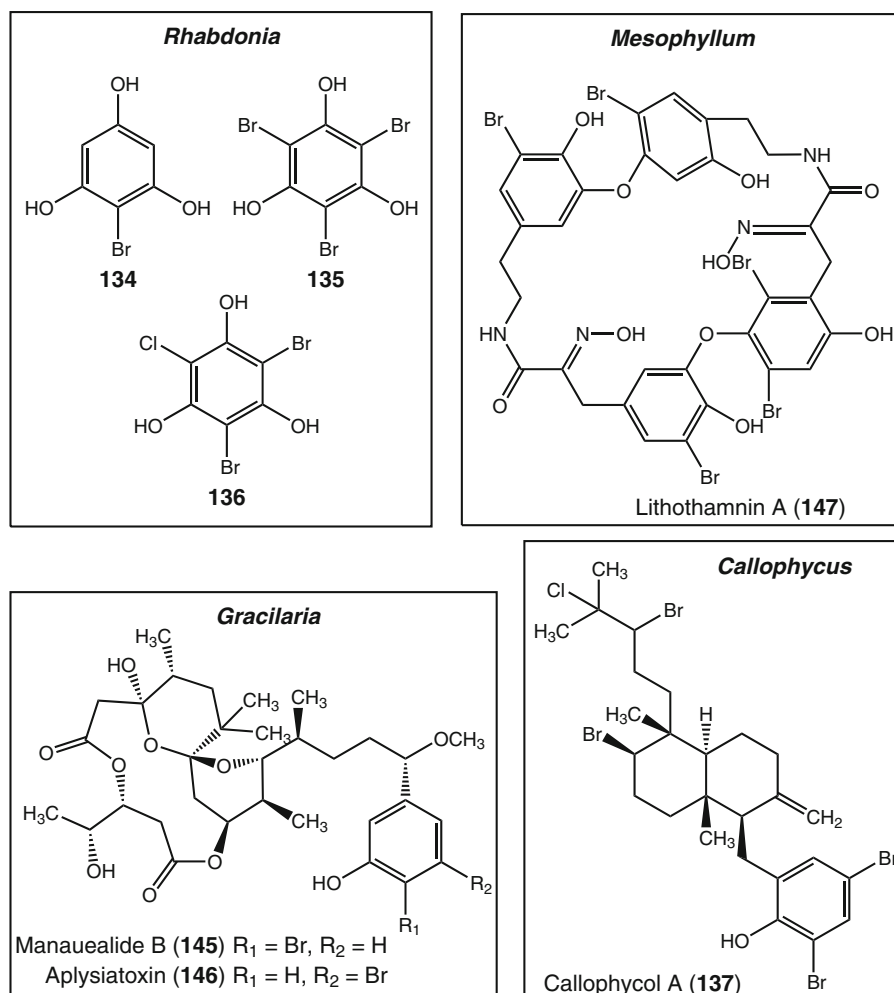
Fig. 11 Selected characteristic bromophenols found in red algae other than the Rhodomelaceae family. Compounds are grouped according to the respective genus they occur in.

Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

Gigartinales

Rhabdonia verticillata and Callophycus sp. The order Gigartinales houses two genera reported to possess bromophenols, *Rhabdonia* (Areschougiaceae) and *Callophycus* (Placentophoraceae). *Rhabdonia verticillata* is the only phytochemically investigated species of its genus as of today and it produces halogenated phloroglucinol derivatives (**K**) (Blackman and Matthews 1982). The isolated bromophenols range from monobrominated (2-bromobenzene-1,3,5-triol, **134**) to tribrominated phloroglucinols (2,4,6-tribromobenzene-1,3,5-triol, **135**) and some even show additional chlorination (2,4-dibromo-6-chlorobenzene-1,3,5-triol, **136**)

(Blackman and Matthews 1982) (Fig. 11). In total, five bromophenols have been reported (Fig. 11 and Table S1).

The genus *Callophycus* contains nine unique bromophenols termed callophycols (**137—144** Fig. 11 and Table S1). These consist of a *p*-halogenated phenol with a highly modified geranyl side chain in *ortho* position and their biosynthesis presumably starts from a *p*-hydroxy benzoic acid followed by ring formation in the side chain and subsequent halogenation (Lane et al. 2007). The halogens in the phenolic residue have either been found to be bromine or iodine, while the aliphatic side chain may also be chlorinated (Lane et al. 2007; Lavoie et al. 2017; Woolner et al. 2018). Finally, it should be noted that

iodocallophycols A—C (**140—142**) were isolated from a non-identified species of the genus *Callophycus* (Lavoie et al. 2017), while all other compounds were reported from *C. serratus* (Lane et al. 2007; Woolner et al. 2018).

Ceramiales

Ceramium tenuicorne Malmvärn et al. (2005, 2008) reported the occurrence of polybrominated diphenyl ethers in the red alga C*eramium tenuicorne* (Ceramiaceae). As they methylated the phenolic fraction before analysis via MS and thus the genuine methylation state could not be inferred from the available data, these compounds were not included in the database. Additionally, in a subsequent mass spectrometric study, the respective substances were eventually detected in cyanobacteria, supporting their initial hypothesis that these compounds did not originate from algae (Malmvärn et al. 2008).

Gracilariales

Gracilaria coronopifolia The edible red alga *Gracilaria coronopifolia* (Gracilariaceae) has been reported to cause cases of food poisoning in Hawaii which has been attributed to manauealides A, B and aplysiatoxin (Nagai et al. 1997). These compounds are macrolides and the bromophenols manauealide B (**145**, Fig. 11) and aplysiatoxin (**146**) were included in the database. However, it should be obvious that the bromophenol moiety in these molecules is not their most striking feature. Additionally, Nagai and colleagues (1997) suggested the isolated compounds to be of epiphytic origin, which could explain why they show only little structural resemblance to secondary metabolites from other algae.

Halymeniales

Grateloupia elliptica and Polyopes lancifolius Kim and colleagues (2008, 2010) investigated a single species from each of the two largest families from the order Halymeniales (Grateloupiaceae and Halymeniaceae) (Guiry and Guiry 2022) regarding their bioactive bromophenols. *Grateloupia elliptica* (Grateloupiaceae) was found to contain a brominated phloroglucinol (**K**), namely 2-bromobenzene-1,3,5-triol (**134**, Fig. 11), and a basic bromophenol (**O**, 2,4-dibromophenol) (Kim et al. 2008). In contrast, *Polyopes lancifolius* (Halymeniaceae) was only reported to produce the lanosol type (**B**) compound 7,7'-bis-lanosol ether (**73**, Fig. 7) (Kim et al. 2010) which was later also isolated from *G. elliptica* (Nguyen et al. 2021). As these are the only reports of a lanosol-like compound isolated from red algae outside the family Rhodomelaceae, further research is needed to identify the precursors of the lanosol dimer and to clarify the chemotaxonomic significance of this finding.

Corallinales

Mesophyllum fragilissimum and Corallina aberrans Mesophyllum fragilissimum (syn. *Lithothamnion fragilissimum*, Mesophyllumaceae) and *Corallina aberrans* (syn. *Marginisporum abberans*, Corallinaceae) are the only two species from the order Corallinales that have been reported to contain bromophenols (Ohta and Takagi 1977; van Wyk et al. 2011). The complex bastadin-like compound lithothamnin A (**147**, Fig. 11) has been isolated from *M. fragilissimum* and comprises four brominated tyrosine moieties. Until now, this is the first and only bastadin-like compound isolated from red algae (van Wyk et al. 2011).

C. aberrans on the other hand has been reported to contain laurane (**H**) and cyclolaurane type (**I**) bromophenols, namely laurinterol, isolaurinterol, aplysin, aplysinol and aplysinal (**5**, **22—24** and **43**) (Ohta and Takagi 1977). As previously discussed, these compound types are typical for *Laurencia* species and the authors of the original publication pointed out that several *Laurencia* species grew in close vicinity to the collection site of their algal material and the isolated compounds might therefore be "derived" from them (Ohta and Takagi 1977).

Brown algae (Phaeophyceae)

Despite the major occurrence of bromophenols in red algae, many brown algae also contain simple bromophenols (**O**, see Tables S1 and S3). Some are reported to possess phloroglucinol derivatives (**K**, *Cystophora retroflexa* and *Eisenia arborea*) and one species (*Leathesia marina*) has even been reported to contain 3-bromo-4-hydroxybenzyl (**A**), lanosol (**B**) and 3,5-dibromo-4-hydroxybenzyl derivatives
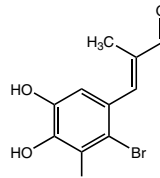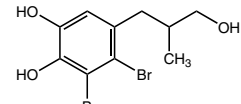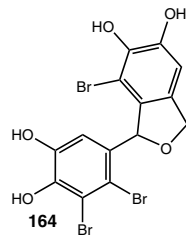
Cystophora
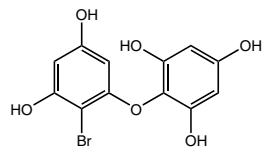
148

Eisenia
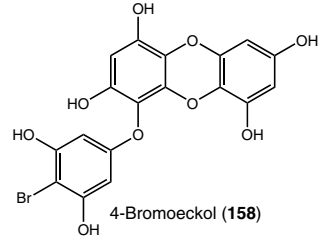
4-Bromoeckol (**158**)

Leathesia
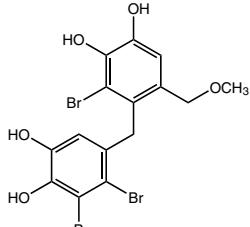
160

161

162

164
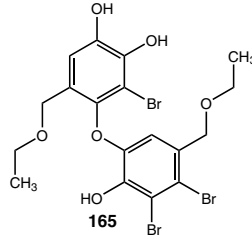
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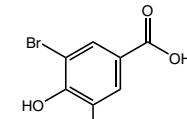
166

Cymopolia
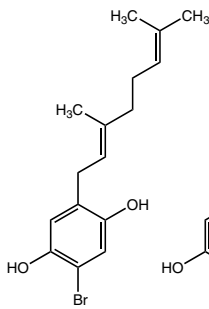
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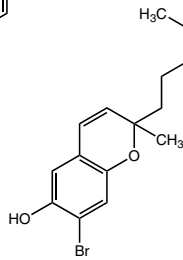
172
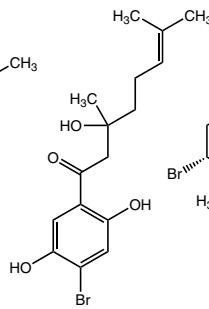
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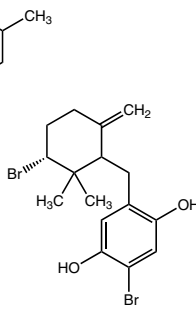
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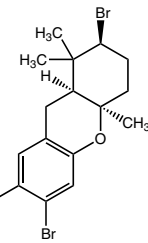
175

Avrainvillea
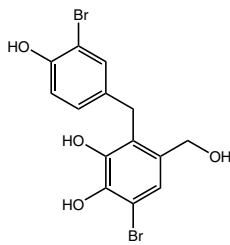
167

168

Chrysophaeum

176

179

◄**Fig. 12** Selected characteristic bromophenols found in brown (*Cystophora*, *Leathesia*, *Eisenia*) and green (*Cymopolia*, *Avrainvillea*) algae and in the microalga *Chrysophaeum taylorii*. Compounds are grouped according to the respective genus they occur in and numbered according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature

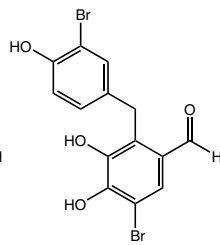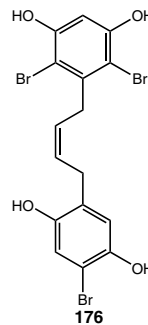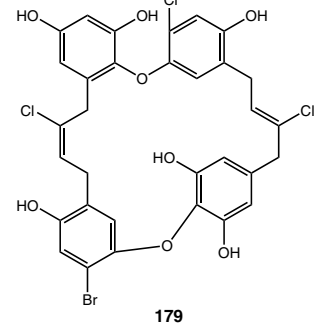(**C**) (Sailler and Glombitza 1999; Xu et al. 2004a, 2018). A potential chemotaxonomic marker for the investigated brown algae might be a C-O linkage between the respective phenolic subunits (see *C. retroflexa* and *L. marina*). For an overview of the structures from brown algae mentioned in the text, see Fig. 12.

Sargassaceae

Cystophora retroflexa *Cystophora retroflexa* (syn. *Cystophora congesta*, Sargassaceae) produces phloroglucinol derived bromophenols (**K**) that are composed of two to four monobrominated, monochlorinated or regular phloroglucinol monomers (**148—157**) (Sailler and Glombitza 1999). The simplest representative (2-(2-bromo-3,5-dihydroxyphenoxy)benzene-1,3,5-triol, **148**, Fig. 12) has first been isolated by Koch and Gregson (1984) and the exact position of the bromine substituent was refined later by Sailler and Glombitza (1999). One remarkable feature of these phloroglucinol oligomers is the linkage between the subunits as the phenolic function of one subunit connects to a previously non-phenolic aromatic carbon of the next subunit, leading to a pyrogallol-like substitution pattern. This structural element is uncommon in other algal bromophenols except for *Odonthalia corymbifera* (**76**, Fig. 7) and might be a potential chemotaxonomic marker for *C. retroflexa*. Moreover, all ten bromophenols isolated from *C. retroflexa* seem to be unique to this alga.

The discussed bromophenols have originally been isolated after acetylation but since acetylation is rather uncommon in algal secondary metabolites, we assume the genuine compounds to be phenolic and included them in the database as the respective non-acetylated phenols. In addition to the included bromophenols, further chlorinated compounds have been isolated (Sailler and Glombitza 1999).

Lessoniaceae

Eisenia arborea Comparable to *C. retroflexa*, *Eisenia arborea* (Lessoniaceae) produces phloroglucinol derivatives (**K**). Apart from the basic bromophloroglucinol (**134**, Fig. 12), a brominated phloroglucinol trimer with a dibenzodioxin substructure (4'-bromoeckol, **158**) has been reported (Glombitza and Gerstberger 1985). The dibenzodioxin substructure is probably formed secondarily via cyclisation of the phenolic phloroglucinol function. As for *C. retroflexa*, also these compounds were isolated after acetylation. Since this is the only report on bromophenols from *E. arborea*, further studies are needed to evaluate the chemotaxonomic relevance of the isolated compounds.

Chordariaceae

Leathesia marina From a chemotaxonomic perspective, the bromophenols of *Leathesia marina* (syn. *L. nana*, Chordariaceae) present an interesting phenomenon as *L. marina* is the only alga outside the Rhodomelaceae to produce lanosol type (**B**, e.g. **6**, **58**, **59**, Fig. 5) and 3,5-dibromo-4-hydroxybenzyl (**C**, **55** and **164**, Fig. 4 and 12) type bromophenols. In total, four 3-bromo-4-hydroxybenzyl type (**A**), 16 lanosol derivatives (**B**) and two 3,5-dibromo-4-hydroxybenzyl type (**C**) bromophenols have been isolated from *L. marina* (Xu et al. 2004a, b, 2018).

It should however be considered that red algae (e.g. *Polysiphonia* spp.) frequently grow as epiphytes on *L. marina* (Poza et al. 2018). As the authors investigating the bromophenols in *L. marina* did not specify whether they checked for epiphytic growth (Xu et al. 2004a, b, 2018), these red algae might potentially be the genuine source of the two 3,5-dibromo-4-hydroxybenzyl type bromophenols (3,5-dibromo-4-hydroxybenzaldehyde and 3,5-dibromo-4-hydroxybenzoic acid, **55**, **166**) found in *L. marina*. Further, 3,5-dibromo-4-hydroxybenzaldehyde is a metabolite also commonly found in *P. stricta* (Li et al. 2008b) and 3,5-dibrominated bromophenols predominantly occur in *Polysiphonia* species, thus, contamination with *Polysiphonia* species cannot be ruled out.

In addition, *p*-methoxylated benzyl derivatives (as in 3-bromo-5-hydroxy-4-methoxybenzoic acid, **157**, isolated from *L. marina*, Fig. 12) are otherwise only found in *Rhodomela converfoides* (Fig. 5) (Li et al.

2011, 2012; Xu et al. 2018) and might be a hint on a potential contamination with this alga. A number of the other metabolites reported for *L. marina* are also found in *R. confervoides* (Figs. 5 and 6), for instance 3,4-dibromo-5-(2-bromo-3,4-dihydroxy-6-(methoxymethyl)benzyl)benzene-1,2-diol (**160**) or lanosol (**6**) and its methyl and ethyl ethers (**58**, **59**, Fig. 5) (Fan et al. 2003). Moreover, more uncommon metabolites like (*E*)-3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylacrylaldehyde (**161**) and 3,4-dibromo-5-(3-hydroxy-2-methylpropyl)benzene-1,2-diol (**162**) found in *L. marina* (Fig. 12) are structurally very closely related to 3-(2,3-dibromo-4,5-dihydroxyphenyl)-2-methylpropanal (**163**, Fig. 5) found in *R. confervoides* (Fan et al. 2003; Xu et al. 2004a) and might originally be formed by *R. confervoides* and in turn secondarily modified by *L. marina*. This could also be true for 7-bromo-1-(2,3-dibromo-4,5-dihydroxyphenyl)-1,3-dihydroisobenzofuran-5,6-diol (**164**) and 3-bromo-4-(3,4-dibromo-5-(ethoxymethyl)-2-hydroxyphenoxy)-5-(ethoxymethyl)benzene-1,2-diol (**165**) which show the same linkage between the phenolic oxygen and an aromatic carbon also occurring in the phloroglucinols from the brown alga *C. retroflexa* (see *3.3.1 Sargassaceae*). Since this type of linkage does not occur in most red algae, it might be a clue for a modification produced by a brown alga. Despite these structural similarities, *R. confervoides* has not been reported to grow epiphytically on other algae (Guiry and Guiry 2022).

To fully clarify the occurrence of lanosol and 3,5-dibromo-4-hydroxybenzyl type bromophenols in *L. marina* further studies on its phytochemistry and the specific epiphyte population of the investigated specimen are needed.

Green algae (Chlorophyta)

Just as the other two classes of algae, a number of green algae have been reported to produce simple bromophenols (**O**) (Flodin et al. 1999; Whitfield et al. 1999), whereas some genera tend to produce more complex bromophenols (*Avrainvillea* and *Cymopolia*). *Avrainvillea* species are the source of a few unique 3-bromo-hydroxybenzyl type (**A**) compounds, while *Cymopolia barbata* produces a variety of unique 4-bromo-2,5-dihydroxybenzyl type (**L**) bromophenols (Carte et al. 1989; Dorta et al. 2002). Since most of the bromophenols from these genera are exclusive to

them, they might serve as potential chemotaxonomic markers. For an overview of the structures from green algae mentioned in the text, see Fig. 12.

Dichotomosiphonaceae

Avrainvillea sp. Four *Avrainvillea* species have been investigated regarding their bromophenols: *A. longicaulis*, *A. nigricans*, *A. rawsonii* and *A. amadelpha*. All of them contain 3-bromo-4-hydroxybenzyl type (**A**) bromophenols and a total of eight different brominated compounds has been isolated from the genus *Avrainvillea*. All of the species either produce avrainvilleol (**167**, *A. longicaulis*, *A. nigricans*, *A. rawsonii*) or the respective aldehyde avrainvilleal (**168**, *A. amadelpha*) (Sun et al. 1983; Colon et al. 1987; Carte et al. 1989; Hawas et al. 2021) (Fig. 12). Avrainvilleol is a dimer comprised of a 3-bromo-4,5-dihydroxybenzyl alcohol subunit substituted with another 3-bromo-4-hydroxybenzyl moiety which may again dimerize (rawsonol and isorawsonol, **169**, **170**) as found in *A. rawsonii* (Carte et al. 1989; Chen et al. 1994). Biogenetically, rawsnonol is probably generated by addition of an avrainvilleol molecule to the 3-bromo-4-hydroxybenzyl moiety of another avrainvilleol via an electrophilic aromatic substitution reaction (Carte et al. 1989). In case of isorawsonol, this substitution takes place in the 3-bromo-4,5-dihydroxybenzyl alcohol moiety (Chen et al. 1994). Since *A. rawsonii* is the only species reported to produce rawsonol and isorawsonol, these compounds might serve as chemotaxonomic markers for this species.

Dasycladaceae

Cymopolia barbata *Cymopolia barbata* (Dasycladaceae) produces a variety of unique 4-bromo-2,5-dihydroxybenzyl type (**L**) bromophenols, which are geranylated in *para*-position of the bromine substituent (Högberg et al. 1976; Takamatsu et al. 2003). This basic scaffold is found in cymopol (**171**, Fig. 12) and all other compounds are derivatives characterized by cyclisation (e.g., cymopochromenol, **172**), hydroxylation (e.g., 3-hydroxycymopolone, **173**) or bromination (e.g., cyclocymopol or cymobarbatol, **174**, **175**) (Estrada et al. 1987; Wall et al. 1989; Park et al. 1992; Dorta et al. 2002). Since no other *Cymopolia*

species have been phytochemically investigated, chemotaxonomic considerations regarding this genus cannot be inferred from the 18 compounds present in *C. barbata*.

Miscellaneous marine algae

Pelagomonadaceae

Chrysophaeum taylorii Related to the large class Phaeophyceae (brown algae) a small clade called Pelagophyceae exists, which contains the microalga *Chrysophaeum taylorii* (Pelagomonadaceae) (Guiry and Guiry 2022). This organism is the source of a number of exceptional halogenated compounds, eight of which represent bromophenols (Plaza et al. 2010; Davison and Bewley 2019). While the hemichrysophaentins B—D (**176—178**, Fig. 12 and Table S1) possess a diaryl butene scaffold, which is hydroxylated and halogenated in several positions (chrysophaentin type, **M**), chrysophaentins B—D, G and H (**179—183**, Fig. 12 and Table S1) represent dimerized hemichrysophaentins. Since all of these compounds are unique to *C. taylorii* and it is the only species of its genus, the phytochemical findings underline the taxonomic position of this alga.

Mass spectrometric analysis of bromophenols

Methods

Over the roughly 60 years of research on halogenated marine secondary metabolites, the means to analyze small molecules have developed tremendously which is also reflected in the methods used in publications reporting bromophenols from algae. While older investigations mainly used EI as the ionization method for the identification of bromophenols (Glombitza et al. 1974, 1985; Blackman and Matthews 1982; Kurata et al. 1997), in more recent reports, the predominant ionization method is ESI (Popplewell and Northcote 2009; Xu et al. 2012a; García-Davis et al. 2018; Hofer et al. 2019). This is especially true for high resolution mass spectrometry (HR-MS) and reflects a general trend in small molecule mass spectrometry (Kind et al. 2018). Based on the methods summarized in the database appended to this review, to this day, both methods have been used to a similar

extent in the analysis of marine bromophenols (EI 116 reports, ESI 123 reports). However, it is probable that the share of publications using ESI in this field will soon surpass the ones using EI.

Key identifiers and common fragmentation reactions of bromophenols

Identification of small molecules via MS generally relies on HR-MS data and subsequent generation of sum formulae (Léon et al. 2019) and for this to be successful, the existence of heteroatoms has to be considered. In case of bromine, its presence can easily be inferred from the isotopic pattern of the compound as the two stable bromine isotopes are approximately distributed evenly (Br^{79}/Br^{81} ca. 50.7/49.3%) (Rosman and Taylor 1998). Several bromine atoms in a molecule lead to more complex isotopic patterns, for instance a molecule containing four bromine atoms will show a cluster of five signals with an intensity ratio of 1:4:6:4:1 (Bright and Chen 1983). The theoretical ratios for any number of bromine atoms can be inferred from Pascal´s triangle (Meija 2005). Additionally, many compounds tend to easily form debrominated fragments, which can be exemplified by (*E*)-4-(2-bromo-4,5-dihydroxyphenyl)but-3-en-2-one (**184**, EI, *m/z* 177 [M—Br]$^+$) and 2'-lanosyl-3'-bromo-5',6'-dihydroxybenzyl alcohol (**131**, (+)ESI, *m/z* 403/401/399 [M—H_2O—HBr]$^+$) (Li et al. 2011; Jacobtorweihen et al. 2022) (Fig. 13a). This phenomenon can also be observed for halogens like iodine (iodoallolaurinterol, **19**, ionization method presumably EI, *m/z* 295/293 [M—I]) (Izac and Sims 1979). To detect the chlorine atoms in chrysophaentins, Plaza et al. (2010) utilized an increased cone voltage in (-)ESI–MS to realize in-source fragmentation of the chlorinated compounds and therefore confirmed the respective number of chlorine atoms. This approach might be helpful in the analysis of compounds substituted with different halogens since the exact number of each halogen may be difficult to assign from the overlapping isotopic patterns.

The presence of other heteroatoms (e.g., sulfur or phosphorus) usually has to be presumed from fragments and may in case of unknown substances prove to be challenging. In bromophenols—apart from a few exceptions (**68—70, 111—112**, Figs. 6, 7 and 10)—sulfur mostly occurs in sulfates and may consequently be detected by the exact mass difference of the [M—
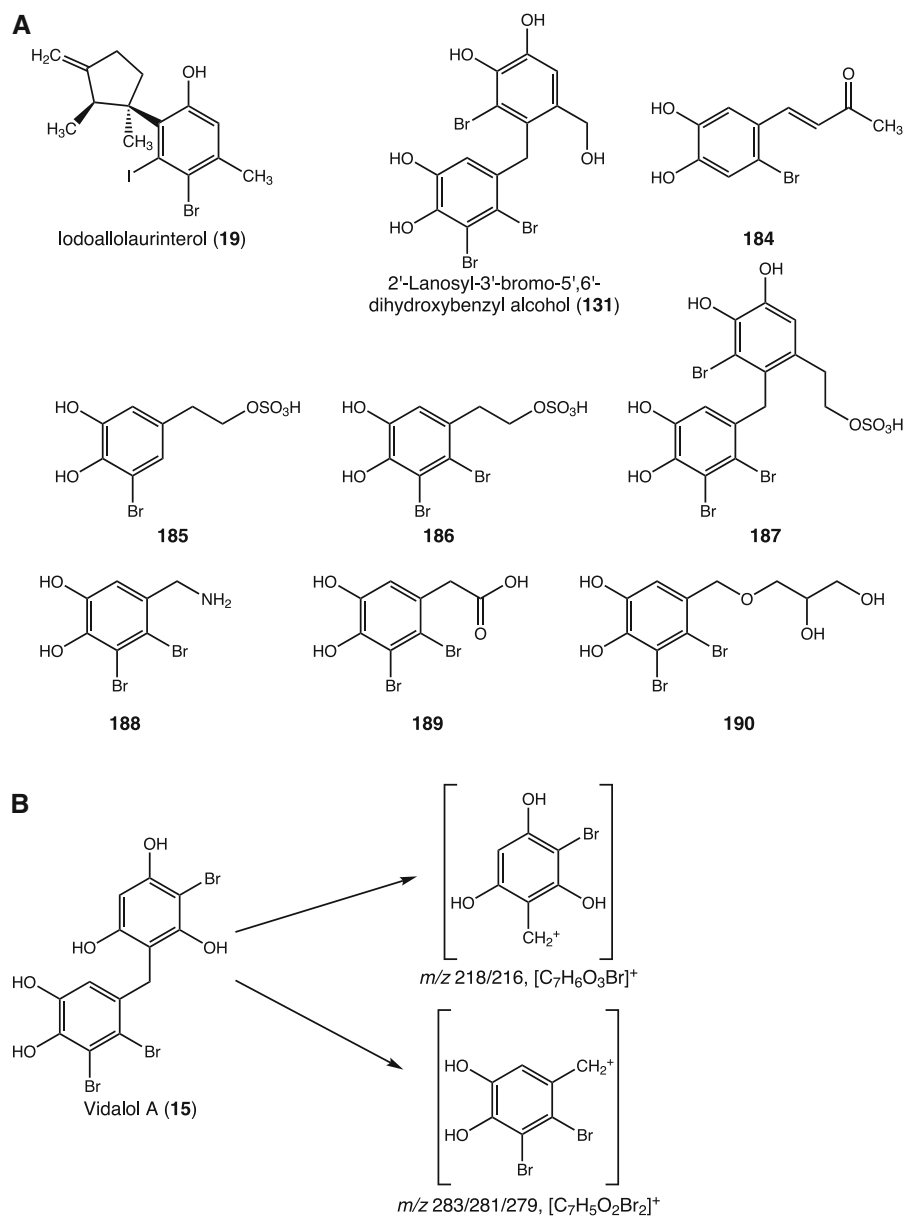
Fig. 13 a Structures of bromophenols discussed regarding their characteristics during mass spectrometric analysis. Numbering according to occurrence in Table S1. Compound names are only displayed if trivial names were reported in literature. **b** Prominent benzylic cation fragments of Vidalol A (**15**) in EI-MS (Wiemer et al. 1991). The dibrominated fragment at the bottom is also commonly formed by other lanosol derivatives

SO$_3$] fragment ($\Delta m/z$ 79.9568) to the parent ion, or the sulfate ion itself (m/z 97.9674) (Ma et al. 2006; Keller et al. 2008). Sulfate ions have been reported for a series of dihydroxyphenethyl hydrogen sulfates (**185**—**187**, Fig. 13a) in negative mode ESI–MS (Ma et al. 2006), while desulfated fragments were found for

4-sulfo-7-dimethylsulfonium lanosol (**70**, m/z 345/343/341, [M—SO$_3$]$^+$, (+)ESI), 3-bromo-5-sulfo-L-dihydroxyphenylalanine (**125**, m/z 276/274 [M—SO$_3$]$^-$, (-)ESI) and 5-sulfovertebratol(**124**, m/z 458/456/454 [M—SO$_3$]$^+$, (+)ESI; Fig. 10) (Jacobtor-weihen et al. 2022). Special attention should be paid to

the respective fragments and neutral losses during analysis of aqueous extracts and fractions since sulfated bromophenols are mainly extracted by polar solvents.

Apart from heteroatom related fragments, the bromophenol scaffold itself may also form certain more or less specific fragments. The most frequent fragmentation reaction is the loss of the benzylic side chain resulting in a benzylic cation. Depending on the complexity of the analyte, a variety of such fragments carrying different structural information may be formed. This is well illustrated by the EI-MS spectrum of vidalol A (**15**) as it forms one fragment corresponding to the benzylic cation of the lanosol subunit (m/z 283/281/279, $C_7H_5O_2Br_2^+$) and another one which comprises the bromophloroglucinol moiety (m/z 218/216, $C_7H_6O_3Br^+$, see Fig. 13b) (Wiemer et al. 1991). For simpler molecules however, usually only one benzylic fragment is formed, which can also be observed in ESI–MS. Especially lanosol derivatives containing easily cleavable side chains such as amino groups (5-(aminomethyl)-3,4-dibromobenzene-1,2-diol, **188**), carboxylic acids (2-(2,3-dibromo-4,5-di-hydroxyphenyl)acetic acid, **189**) or glycerol (3,4-dibromo-5-((2,3-dihydroxypropoxy)methyl)benzene-1,2-diol, **190**) (Fig. 13a) preferentially form the respective benzylic cation (m/z 283/281/279, $C_7H_5Br_2O_2^+$) (Li et al. 2011). Further moieties facilitating easy benzyl cation formation in bromophenols are heterocycles (e.g., in rhodomelol, **18**), amino acid side chains or additional lanosol units found in many dimers (Kurihara et al. 1999b; Xu et al. 2004a; Jacobtorweihen et al. 2022).

In addition to fragments, most organic chemicals form a number of salt adducts and sometimes multimers which can make up the most intensive signals in a mass spectrum, and the analysis of such spectra may even pose a challenge for experienced scientists (Jaeger et al. 2017). For bromophenols, the most frequent reported salt adducts are sodium adducts (32 reports), followed by multimeric adducts comprising two molecules (10 reports). Ammonium and potassium adducts have also been reported occasionally (9 and 3 reports, resp.). As adduct formation also offers structural information, their assignment is critical for the determination of the correct sum formula, especially in unknown metabolites and this may be achieved either manually via the exact mass difference or by using modern software tools (Keller et al. 2008; Jaeger et al. 2017).

Unrelated to mass spectrometry, another shared analytical feature of bromophenols is their UV absorption maximum between 280 and 300 nm.

Conclusion

Aim of this review was to present the distribution of bromophenols among marine algae considering their role as taxonomic markers. Within the phytochemically well-studied family Rhodomelaceae which was subject to recent taxonomic reclassifications, the assignment of new phyla in particular correlates well with an accumulation of specific bromophenol subtypes. For example, the absence of lanosol derivatives (scaffold **B**), but frequent occurrence of 3,5-dibrominated compounds (scaffold **C**) in the genus *Polysiphonia*, in contrast to other tribes such as Rhodomeleae and Streblocladieae, support the phylogenetic classification. Similarly, the predominant occurrence of cuparane, laurane, cyclolaurane and laurokamurane type bromophenols in the genus *Laurencia* further corroborates the distinction of this genus from the other members of the Laurencieae and from other tribes of the Rhodomelaceae. However, for families of red, brown and green algae that are less frequently studied, it remains difficult to make supported statements about their chemotaxonomic relation due to the low number of bromophenol-related reports for the respective species.

In summary, the review is intended to contribute to an improved perception of the chemodiversity in algae while the bromophenol database is provided as a tool to facilitate further phytochemical studies on marine algae, as many genera await further exploration.

Declarations

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