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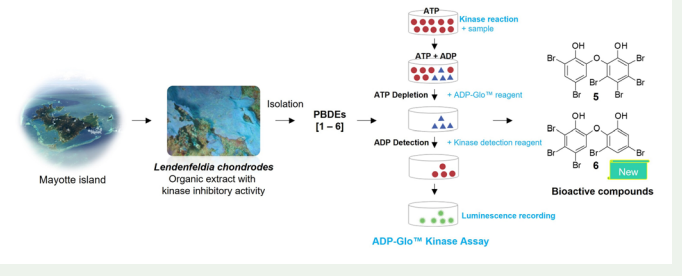
ABSTRACT

CDK7 and FynB protein kinases have been recognized as relevant targets for cancer and brain diseases treatment due to their pivotal regulatory roles in cellular functions such as cell cycle and neural signal transduction. Several studies demonstrated that the inhibition of these proteins could be useful in altering the onset or progression of these diseases. Based on bioassay-guided approach, the extract of the marine sponge *Lendenfeldia chondrodes* (Thorectidae), which exhibited interesting kinase inhibitory activities, was fractionated. The investigation led to the isolation of five known **1**–**5** and one new **6** polybrominated diphenyl ethers (PBDEs). Their structure elucidation was established based on spectroscopic data (NMR and HRMS) and comparison with literature data.



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1. Introduction

Aging is a biological feature marked by a progressive decline of biological functions and stress response capacity (Lopez-Otin et al. 2013). These events promote a variety of age-related disorders such as cancer, neurodegenerative diseases, and skin hyperpigmentation. To date, several natural products have proven to be effective in delaying aging or age-related diseases in model organisms by regulating age-related signaling pathways (Campisi et al. 2019). Marine sponges and their associated microorganisms are well-known for their impressive chemical arsenal as well as the variety of their pharmacological activities. Hence, they represent one of the promising sources for the discovery of anti-aging compounds with potential use as human therapeutic leads. In this context, marine sponges collected in the Mayotte lagoon, located in Western Indian Ocean, and their symbionts were evaluated for their anti-aging activities (Campos et al. 2020; Said Hassane et al. 2020; Saïd Hassane et al. 2022). For this purpose, a set of druggable targets were selected since their inactivation disrupts some key signaling pathways involved in skin-aging and age-related diseases: elastase (Tsuji et al. 2001), tyrosinase (Pillaiyar et al. 2017), CDK7 (Wang et al. 2015; Greenall et al. 2017), Fyn (Schenone et al. 2011; Nygaard et al. 2014) and proteasome (Manasanch and Orlowski 2017). In continuation of our investigation on the search of anti-aging compounds, the fractionation of the marine sponge *Lendenfeldia chondrodes*, identified during our screening of marine sponges, was carried out based on bioassay-guided approach.

Sponges belonging to the genus *Lendenfeldia* (order Dictyoceratida, family Thorectidae, subfamily Phylospongiinae) have been only poorly chemically investigated and yet, have yielded several original and bioactive compounds. A literature review revealed that *Lendenfeldia* species (including the species formerly known as *Phyllospongia dendyi*) have been found to be a rich source of terpenes (Kazlauskas et al. 1980,1982; Rao et al. 1991; Alvi and Crews 1992; Sera et al. 1999; Chill et al. 2004; Dai et al. 2007; Liu et al. 2008), polybrominated diphenyl ethers (PBDEs) (Hattori et al. 2001; Liu et al. 2004; Radwan et al. 2015) and few sterols (Sera et al. 1999; Radwan et al. 2007). Bioactive amino acids and related compounds, betaines along with some osamines were also reported from the aqueous extract of micronesian sponge *L. chondrodes*, formerly identified as *Dysidea herbacea* (Sakai et al. 1997; Sakai et al. 1999; Sakai et al. 2001; Sakai et al. 2004). PBDEs are marine naturally occurring products mainly extracted from marine sponges especially those belonging to the genus *Dysidea* (order Dictyoceratida, family Dysideidae) (Unson et al. 1994). Some authors suggested that they could play a role in the chemical defense of the sponge against potential predators and bacterial invasion. So far, natural PBDEs have been reported to exhibit a wide range of bioactivity including promising anticancer (Mayer et al. 2019; Schmitt et al. 2021) and antibacterial activities (Handayani et al. 1997; Sun et al. 2015).

Herein, we report the isolation of the 6 PBDEs from *Lendenfeldia chondrodes* and describe the structure characterization of the new PBDE as well as preliminary result on their kinase inhibitory activities (CDK7, FynB).

2. Results and discussion

The preliminary results from marine sponges screening showed that the DCM/MeOH extract of the sponge *Lendenfeldia chondrodes* inhibited the protein kinases CDK7 at

the concentration of 1.1 µg/mL, 11.1 µg/mL and 111.1 µg/mL and Fyn at the concentration of 11.1 µg/mL and 111.1 µg/mL. CDK7 is an essential enzyme that promotes cell cycle progression and RNA polymerase II based transcription (Nigg 1996). This enzyme is critical for some tumor types that rely heavily on transcription to maintain their oncogenic state like high-grade glioma, which is an incurable brain cancer, providing new approaches to cancer treatment (Greenall et al. 2017; Sava et al. 2020). Regarding Fyn, it is a non-receptor tyrosine kinase supporting initiation and progression of cancer as well as a key player in neurodegenerative diseases pathophysiology (Kaufman et al. 2015; Elias and Ditzel 2015; Angelopoulou et al. 2021). Hence, these interesting biological results prompted us to consider the extract as a potential source of compounds with possible application in cancer and neurodegenerative diseases. Bioassay-guided separation was then carried out, and two active fractions against CDK7 were identified. Chromatographic separation of these active fractions afforded five known **1**–**5** and one new PBDE **6** (Figure 1).

Their structures were identified by analyzing HRMS and NMR spectral data as well as comparison with published data in literature. Molecular formula determination was further confirmed by simulating the isotopic pattern using the web interface enviPat (Loos et al. 2015). The simulated isopotic patterns matched perfectly the experimental spectra meaning that the proposed molecular formulae for the isolated compounds were accurate. It is worth noting that the structure elucidation was greatly facilitated by using the NMR data trends table established by Calcul et al. and based on the ^{1}H and ^{13}C NMR shifts of the aromatic rings from known PBDEs derived from sponge-cyanobacteria association (Calcul et al. 2009). In this paper, atoms numbering and nomenclature were adapted to the classification made by Calcul et al. Synonym names along with spectroscopic data are listed in supplemental material. The known compounds were identified as 3,5-dibromo-2-(3′,5′-dibromo-2′-hydroxyphenoxy)phenol (**1**) (Utkina and Denisenko 2006), 3,4,5-tribromo-2-(3′,5′-dibromo-2′-hydroxyphenoxy) phenol (**2**) (Fu et al. 1995), 3,5-dibromo-2-(3′,5′-dibromo-2′-hydroxyphenoxy)anisole

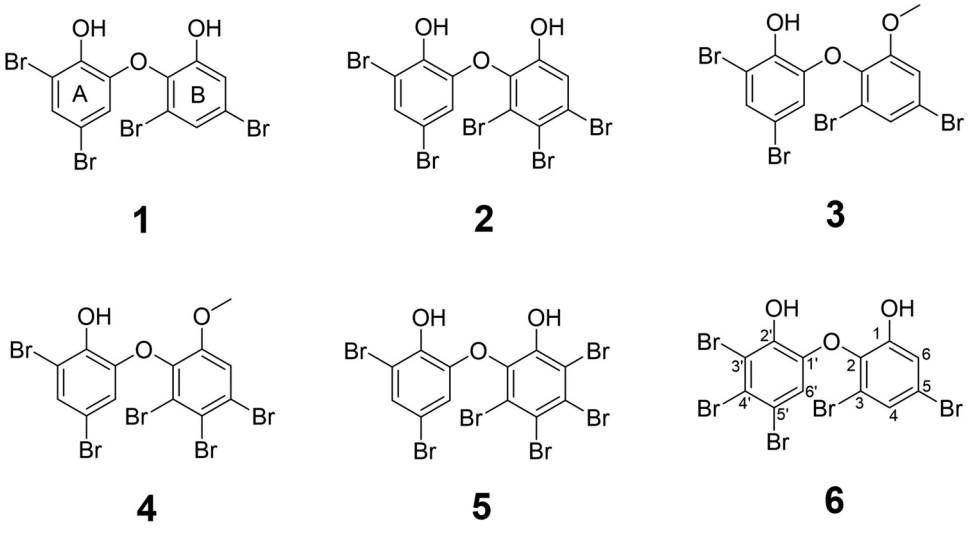

Figure 1. Chemical structures of isolated polybrominated diphenyl ethers **1**–**6**.

(**3**) (Fu et al. 1995), 3,4,5-tribromo-2-(3′,5′-dibromo-2′-hydroxyphenoxy)anisole (**4**) (Liu et al. 2004), and 3,4,5,6-tetrabromo-2-(3′,5′-dibromo-2′-hydroxyphenoxy)phenol (**5**) (Norton et al. 1981) (Figure 1, Figures S1–S15, Tables S1–S6).

Compounds **1**–**3** and **5** were previously isolated from *Dysidea* spp. (collection sites: Australia, Micronesia, Fiji), whereas only compounds **4**–**5** were reported from *Lendenfeldia dendyi* (formerly known as *Phyllospongia dendyi*).

2.1. Structure elucidation of the new compound

Compound **6** was isolated as a white crystal. The mass spectrum showed a distribution of negatively charged ions at *m/z* 590.6, 592.6, 594.6, 596.6, 598.6, 600.6 with a relative isotopic abundance of 1:5:10:10:5:1 suggesting the presence of five bromine atoms. The molecular formula was determined to be $C_{12}H_5Br_5O_3$ based on the $[M - H]^-$ peak at *m/z* 594.6042. The ^{13}C NMR spectrum showed the presence of 12 aromatic carbon atoms and the ^1H NMR spectrum (Figures S17–S18, Table S7) showed a pair of *meta*-coupled signals at δ 7.02 (1H, *d*, *J* = 2.2 Hz), 7.46 (1H, *d*, *J* = 2.2 Hz) and singlet at δ 7.15 (1H, *s*) belonging to aromatic ring. These data are consistent with the compound **6** being of a polybrominated diphenyl ether. Carbon atom assignments were made with NMR data trends table (Calcul et al. 2009) and using HSQC NMR spectra with crosspeak correlation between the protons H-4 at δ 7.46 and the signal at δ 132.0 (C-4), H-6 at δ 7.02 and the signal at δ 122.9 (C-6), H-6′ at δ 7.15 and the signal at δ123.0 ppm (C-6′) (Figure S19). HMBC experiment revealed coupling from H-6′ (δ 7.15) to C-1′ (δ 146.2), C-2′ (δ 149.6), C-4′ (δ 123.4), C-5′ (δ 113.1), and a weak correlation to C-3′ (δ 116.7) for the pentasubstitued ring A moiety (Figure S20). The substitution of the ring B was also determined by HMBC correlations from H-4 (δ 7.46) to C-2 (δ 147.9), C-3 (δ 113.3), C-5 (δ 111.1), C-6 (δ 122.9) and from H-6 (δ 7.02) to C-1 (δ 146.9), C-2 (δ 147.9), C-4 (δ 132.0), C-5 (δ 111.1) (Figure S20), these chemical shifts were consistent with the ring subtype B-9. The exploitation of the NMR data trends table indicated that compound **6** was a new combination of known rings subtypes A-5 with an additional bromine at position C-4′ and B-9. Consequently, compound **6** was identified as 3,5-dibromo-2-(3′,4′,5′-tribromo-2′-hydroxyphenoxy)phenol.

2.2. Possible biosynthetic origin for purified compounds

Several studies proposed that halogenated natural products like PBDEs isolated from marine invertebrates are produced by the symbiotic filamentous cyanobacteria *Oscillatoria spongeliae* encountered in the mesohyl of Dictyocerid sponges (Hinde et al. 1994; Ridley et al. 2005). Agarwal and co-workers (2014) released a report establishing marine bacteria as producers of bromophenol monomers, hydroxylated PBDEs as well as their methylated derivatives and describe the genetic and molecular bases of their biosynthesis pathway (Agarwal et al. 2014). They also hypothesized that dihydroxylated PBDEs arise from the heterocoupling of bromophenol to bromocatechol monomers through ether link mediated by cytochrome P450 enzymes (Agarwal and Moore 2014). Thus, we assume that compounds **1**–**5** originate from the combination

of 2,4-dibromophenol (ring A) with different bromocatechol monomers (ring B), while compound **6** arises from the heterocoupling of 2,3,4-tribromophenol to 3,5-dibromocatechol (Figure S21). Both 2,4-dibromophenol and 3,5-dibromocatechol along with methoxylated 3,5-dibromocatechol were detected in marine invertebrate such as *Dysidea* sponges, supporting further our assumption (Agarwal and Moore 2014; Agarwal et al. 2015).

2.3. Biological assay

Compounds **1**–**6** were evaluated in primary screening for their inhibitory activities in CDK7 and Fyn kinase assays at three different concentrations 33 µg/mL, 3.3 µg/mL and 0.33 µg/mL. No kinase inhibitory activities were detected for compounds **1**–**4**. Compounds **5** and **6** showed an inhibitory effect on CDK7 kinase activity as well as on FynB kinase activity at 33 µg/mL; however, IC50 experiment and screening against a large set of kinase were prevented by lack of compound materials. These observations are consistent with studies showing that PBDEs exhibit a wide range of biological activities depending on the bromine substitution patterns, the location of hydroxyl groups and the presence/absence of methoxyl groups (Schmitt et al. 2021). Even though natural PBDEs are known for their anticancer activity since 1995, there is only few studies demonstrating the potential of these compounds for anticancer therapy or reporting kinase inhibitory activity (Fu et al. 1995; Xu et al. 2005; Mayer et al. 2019; Schmitt et al. 2021). It is only recently that a therapeutic window has been identified for a PBDE (P01F08) isolated since 1995, enabling its possible use in the treatment of acute myeloid leukemia (Mayer et al. 2019).

Interestingly, some literature reported that compounds **2** and **5** displayed inhibitory activity to several proteins implicated in tumor development such as 15-lipoxygenase, microtubule proteins and Mcl-1 (Fu et al. 1995; Liu et al. 2004; Calcul et al. 2009). Furthermore, a few kinase inhibitory activity have been reported for some PBDEs obtained from *Dysidea* sponges (Xu et al. 2005; Zhang et al. 2008). Taken together, these data suggest that these metabolites might provide potential new small CDK7 and FynB kinase inhibitors, but they need to be further investigated. For future work, metagenomic and biosynthetic approaches could be considered to overcome the lack of material issue.

3. Experimental section

3.1. General experimental procedures

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III – 600 MHz spectrometer equipped with TCI Cryoprobe in 2.0 mm o.d. capillary tube at 300 K. Chemical shifts (δ) were referenced to trimethylsilane and deuterated methanol signals (δ ^{1}H 3.31 and δ ^{13}C 49.00). High- and low-resolution mass measurement were obtained from Waters SYNAPT G2 HDMS mass spectrometer with an API source and ESI-TOF. Medium pressure liquid chromatography (MPLC) separations were carried out on Buchi Sepacore flash systems C-605/C-615/C-660 and glass column (230 × 15 mm i.d.) packed with Macherey-Nagel MN Kieselgel silica gel (60 – 200 µm). Thin-layer

chromatography (TLC) was performed on precoated TLC sheets of silica gel 60, Alugram SIL G/UV254 and visualized with vanillin – sulfuric acid. High performance liquid chromatography (HPLC) and semi-preparative HPLC separations were performed on a Thermo Scientific Dionex Ultimate 3000 system with photodiode array and Corona detectors. The columns used for HPLC and semi-preparative HPLC were Phenomenex Gemini C18 (150 × 4.6 mm i.d., 3 µm) and Phenomenex Gemini C18 (250 × 10 mm i.d., 5 µm). All solvents were analytical or HPLC grade.

3.2. Marine sponge

The sponge *Lendenfeldia chondrodes* (phylum Porifera, class Demospongiae, order Dictyoceratida, family Thorectidae, subfamily Phylospongiinae) was collected in May 2013 by scuba diving in the lagoon of Mayotte (12°56,388′ S, 45°03,247′ E). Collection depth was from 9 to 18 m. The specimen was identified by Dr Nicole J. de Voogd. For identification, a voucher specimen was preserved in 80% ethanol and is deposited at Naturalis Biodiversity Center, Leiden the Netherlands as RMNH POR.8385. The sponge is bright blue colored and forms thin, firm, almost rubbery encrustations. Oscules are very small and not clearly visible to the naked eye. The skeleton is composed of a loose network of irregularly branching primary and secondary fibers. Some primary fibers are partially cored by foreign debris. The sponge is easily confused with species belonging to the genera *Phyllospongia* and *Dysidae*, but these species are different in consistency, have a clear sand cortex, and the fibers are lightly cored in *Lendenfeldia chondrodes*. The species was originally described by De Laubenfels (1954) from Palau (Western Pacific) (De Laubenfels 1954), but has been reported as a pest species in aquaria (Galitz et al. 2018). Six species belonging to the genus *Lendenfeldia* are currently accepted, (de Voogd et al. 2021) although these descriptions are very difficult to interpret due to the lack of characters and plasticity of the outer morphological characters. *Lendenfeldia chondrodes* was recently re-examined and our specimen suits this description well (Galitz et al. 2018). Sponge samples were frozen immediately and kept at −20 °C until processed.

3.3. Extraction and isolation

The frozen sponge (12.4 g, dry weight) was chopped into small pieces, lyophilized and extracted three times using MeOH/CH_2Cl_2 (1:1, v:v) (× 2). The filtrate was evaporated under reduced pressure and the resulting residue (2.9 g) was subject to a process of bioassay-guided fractionation. The active extract (874 mg) was fractionated using MPLC over silica gel in a glass column (230 × 15 mm i.d.), eluting with a combination of cyclohexane, ethyl acetate (EtOAc), dichloromethane (CH_2Cl_2), and methanol (MeOH) of increasing polarity (15 mL.min^{-1}) affording eleven fractions. An aliquot (20 mg) of the active fraction (F3) that eluted with 25% EtOAc in cyclohexane (118 mg) was further separated by semipreparative reverse-phase HPLC (Phenomenex Gemini C18 column, 250 × 10 mm i.d., 5 µm., 2.7 mL.min^{-1}, UV 230 nm). Step gradient elution was employed with acetonitrile (CH_3CN) and water, each containing 0.1% formic acid: 70% to 80% CH_3CN (5 min), 80% CH_3CN (15 min), 80% to 100% CH_3CN (10 min), 100% CH_3CN (10 min),

100% to 70% CH_3CN (5 min). This provided compounds **1** (0.6 mg), **2** (10.4 mg), **3** (0.9 mg) and **4** (0.6 mg). The active fraction (F4) that eluted with 50% EtOAc in cyclohexane (80 mg) was also purified by semipreparative reverse-phase HPLC (Phenomenex Gemini C18 column, 250 × 10 mm i.d., 5 µm., 4.5 mL.min^{-1}, UV 230 nm). Step gradient conditions were employed with acetonitrile (CH_3CN) and water, each containing 0.1% formic acid: 65% CH_3CN (30 min), 65% to 100% CH_3CN (5 min), 100% CH_3CN (15 min) to give compounds **1** (1.3 mg), **2** (44 mg), **5** (2.5 mg) and **6** (3.5 mg).

3,5-dibromo-2-(3′,4′,5′-tribromo-2′-hydroxyphenoxy)phenol (**6**). White cristal. ^{1}H and ^{13}C-NMR: see Table S7. HRMS *m/z* 594.6042 $[M-H]^-$ ($C_{12}H_4O_3Br_5$ calcd. for 594,6042).

3.4. CDK7 and Fyn kinase assays

CDK7 activity was evaluated using CDK7 (Crelux construct CTX4CZY3, PC11452). The inhibitory potency of the compounds against CDK7 was determined by using the ADP-Glo Kinase Assay (Promega, Madison, WI, USA). Fyn activity was evaluated using FynB wt (Crelux construct CTX4, PC09815-1). The inhibitory potency of the compounds against FynB was determined by using the ADP-Glo Kinase Assay (Promega) and Fyn kinase substrate (Enzo Life Sciences, P215). The assays were performed according to previously described methods (Said Hassane et al. 2020).

4. Conclusion

Six PBDEs were isolated from the active fractions of the marine sponge *Lendenfeldia chondrodes*. Except of compound **6** described herein for the first time, all known compounds (**1**–**5**) were previously reported from marine sponges *Lendenfeldia dendyi* and related species (*Dysidea* spp.). The kinase inhibitory activity of the organic extract and fractions from the marine sponge *Lendenfeldia chondrodes* suggest the presence of potential kinase inhibitors. Preliminary screening revealed compounds **5** and **6** as bioactive but lack of compound materials prevented further investigation.

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Authors' contribution

Conceptualization, A.G.-B., J.O.; supervision, A.G.-B, M.F., L.D.; chemical investigations (extraction, isolation, and structural identification of the compounds), F.T., P.-E.C. and G.H; bioassays methodology and validation, Crelux; sponge identification, N.J.d.V.; writing—original draft preparation, C.S.H.; writing—review and editing, C.S.H, A.G.-B, P.-E.C, L.D, G.H, N.dV. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

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