A review of secondary metabolites isolated from *Plocamium* species worldwide

Michael G. Knott[1,2*]

[1]School of Pharmacy, University of Namibia, Private Bag 13301, Windhoek, Namibia

[2]Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa

Received: 27th September, 2014. Accepted: 24th November, 2014. Published: 23rd February, 2015.

Abstract

A review of halogenated monoterpenes isolated from various *Plocamium* species worldwide is presented here for the first time. It is anticipated that this review will be of great valuable to the natural product chemist working in the field of drug discovery with reference to the characterisation of halogenated monoterpene secondary metabolites from various *Plocamium* species. In addition, the *in vitro* cytotoxic bioactivity of these compounds is also reviewed.

Keywords: halogenated monoterpenes; *Plocamium* species; *in vitro* cytotoxicity

ISTJN 2015; 6:75-93.

1 Introduction

Red algae or red seaweed (Rhodophyta) of the family Plocamiaceae and Rhizophyllidaceae produce a number of different biologically active linear and cyclic polyhalogenated monoterpenes (Kladi *et al.*, 2004). These metabolites exhibit a range of biological activities including antifeedant effects on reef herbivores, antimicrobial, insecticidal, antitubercular and anticancer (Knott *et al.*, 2005). Of the 47 different species of *Plocamium* that occur around the world, at least 7 species occur off Namibia's coast (Bolton, 2014). Namibian *Plocamium*

*Corresponding author. Telephone: +264 61 206 5050; Fax: +264 61 886526605 E-mail: mknott@unam.na (M.G. Knott)

species include; *Plocamium cartilagineum*, *Plocamium corallorhiza*, *Plocamium cornutum*, *Plocamium glomeratum*, *Plocamium maxillosum*, *Plocamium rigidum* and *Plocamium suhrii.*

2 Findings

Halogenated monoterpenes that where isolated from various *Plocamium* species worldwide and described for the first time, are tabulated below in Tables 1-3. Structural re-assignments have substituted the original suggestions for some of the references, however some re-assignments may still be present (Knott, 2003; Knott, 2012).

The following secondary metabolites (**1-101**) below correspond to those listed in Tables 1-3 below. Note, the stereochemistry for some of the compounds is incomplete as this is not a trivial task. X-ray diffraction is the best method to unambiguously determine the stereochemistry of these compounds.

2.1 Review of cytotoxic compounds isolated from *Plocamium* species (Knott, 2012)

A literature review of marine algae belonging to Chlorophyta (green algae), Phaeophyta (brown algae) and Rhodophyta (red algae) soon revealed that Rhodophyta is far more prolific in producing cytotoxic secondary metabolites than both Chlorophyta and Phaeophyta. Red algae are generally more pharmacologically active against a wide variety of different *in vitro* cell lines when compared to a variety of other algal classes. The reason for this is that Rhodophyta possess the highest abundance of unique biosynthetic pathways necessary for organohalogen production (Kladi *et al.*, 2004). Further to this, halogenated low molecular weight metabolites have exhibited an impressive range of biological properties; from antimicrobial to insecticidal activity. It is believed that these halogenated compounds are produced by seaweeds as part of a defence system against micro-organism infections and herbivore grazing (Goodwin *et al.*, 1997). In addition to this, it has been postulated that halogenated compounds are also used to assist in anti-fouling and reduce space competition amongst competing marine algae (Dworjanyn *et al.*, 1999).

Plocamium cartilagineum yielded two compounds **32** and **54** which showed potent toxicity against both *Biomphalaria glabrata* and *Artemia salina* (König *et al.*, 1999). No IC_{50} data was published. Compounds isolated from *P. cartilagineum* showed selective cytotoxic activity against a number of different human tumour cell lines (de Inés *et al.*, 2004) (Table 4).

Table 1: Halogenated monoterpenes isolated from various *Plocamium* species worldwide (Knott, 2003, Knott, 2012).

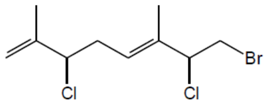
Metabolites isolated from:	Isolated Compounds	Location	Reference
Plocamium angustum **1-2**	2,6-Dimethyloctadienes	Cape Northumberland (W. Australia)	(Dunlop *et al.*,1979)
Plocamium brasiliense **3**	2,6-Dimethyloctatrienes	 Brazil	(Vasconcelos *et al.*, 2010)
Plocamium cartilagineum **4** **5**	2,6-Dimethyloctenes	 Kaikoura (N. Zealand) Figueira de Foz (Portugal)	 (Blunt *et al.*, 1985) (Abreu *et al.*, 1996)
 6	2,6-Dimethyloctadienes	 Kaikoura (N. Zealand)	 (Blunt *et al.*, 1985)
 7 **8-18** **19** **20** **21-22**	2,6-Dimethyloctatrienes Cartilagineal	 California (USA) La Jolla (USA) L' Estartit (Spain) Figueria da Foz (Portugal) Schouten (Tasmania)	 (Crews and Kho-Wiseman, 1974) (Mynderse and Faulkner, 1975) (König *et al.*, 1990) (Abreu *et al.*, 1996) (Jongaramruong and Blackman, 2000)
  23 **24-26** **27-30**	1-Ethyl-1,3-dimethylcyclohexanes	 Antarctica USA Chile	 (Stierle *et al.*, 1979) (Higgs *et al.*, 1977) (San-Martin *et al.*, 1991)
  31-33	1-Ethyl-2,4-dimethylcyclohexanes	 USA	 (Higgs *et al.*, 1977)
  34-39	Hydroxy-bisnor monoterpenes	 Kaikoura (N. Zealand)	 (Blunt *et al.*, 1985)
  40-42 **43-45**	Polyhalodroxylated monoterpenes Furanoid monoterpenes	 Chile Chile	 (Diaz-Marrero *et al.*, 2002) (Darias *et al.*, 2001)
  46-47	Tetrahydropyran monoterpenes	 Chile	 (Cueto *et al.*, 1998)
  48-51	Homosesquiterpenic fatty acids	 Maltese Islands and Corsica	 (Řezanka and Dembitsky, 2001)
	Non-Terpenoid compounds Floridoside and Poly-β-hydroxybutyrate	 Figueira da Foz (Portugal)	 (Abreu *et al.*, 1997)

Table 2: **Continued**: Halogenated monoterpenes isolated from various *Plocamium* species worldwide (Knott, 2003, Knott, 2012).

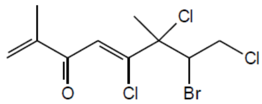
Metabolites isolated from:	Isolated Compounds	Location	Reference
Plocamium coccineum	1-Ethyl-1,3-dimethylcyclohexanes		
52		Bastiagueiro (N.W. Spain)	(Castedo *et al.*, 1984)
53-54		Bastiagueiro (N.W. Spain)	(Sardina *et al.*, 1985)
Plocamium corallorhiza	2,6-Dimethyloctadienes		
55-57	Plocoralides A-C	Kalk Bay (South Africa)	(Knott *et al.*, 2005)
	2,6-Dimethyloctadienes and 2,6-Dimethyloctatriene aldehydes		
58-61		Kenton-On-Sea (South Africa)	(Mann *et al.*, 2007)
Plocamium cornutum	2,6-Dimethyloctatriene		
62-63		Kalk Bay (South Africa)	(Afolayan *et al.*, 2009)
Plocamium costatum	2,6-Dimethyloctene		
64		Eaglehawk Neck (Tasmania)	(König *et al.*, 1999)
	2, 6-Dimethyloctadienes		
65-66	Costatol, Costatone	Port MacDononnell (S. Australia)	(Kazlauskas *et al.*, 1976)
67		Robe (S. Australia)	(Stierle *et al.*, 1976)
	Polysaccharides	Tauranga (New Zealand)	(Falshaw *et al.*, 1999)
Plocamium cruciferum	2,6-Dimethyloctene		
68		Rosy Morn (N. Zealand)	(Bates *et al.*, 1979)
69	Degraded or mixed	Kaikoura (N. Zealand)	(Blunt *et al.*, 1978)
70	biogenesis monoterpene	Rosy Morn (N. Zealand)	(Bates *et al.*, 1979)
Plocamium hamatum	2,6-Dimethyloctene		
71		Palm Is. (W. Australia)	(Coll *et al.*, 1988)
	2,6-Dimethyloctadiene		
72		Palm Is. (W. Australia)	(König *et al.*, 1999)
	1-Ethyl-1,3-dimethylcyclohexane		
73		Palm Is. (W. Australia)	(Coll *et al.*, 1988)
Plocamium maxillosum	Harrietone A OR 6-methylene-4-vinyl-4-methylcyclohex-2-enone		
74		W. Cape (South Africa)	(Knott, 2012)
	Harrietone B OR 6-methylene-4-vinyl-4-methylcyclohex-2-enone		
75		W. Cape (South Africa)	(Knott, 2012)

Table 3: **Continued**: Halogenated monoterpenes isolated from various *Plocamium* species worldwide (Knott, 2003, Knott, 2012).

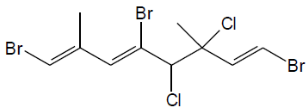
Metabolites isolated from:	Isolated Compounds	Location	Reference
Plocamium mertensii **76** **77**	1-Ethyl-1,3-dimethylcyclohexane Mertensene	 Australia Carnac Is. (W. Australia)	 (Norton *et al.*, 1977) (Capon *et al.*, 1984)
  78-79 **80**	1-Ethyl-2,4-dimethylcyclohexanes	 Australia Carnac Is. (W. Australia)	 (Norton *et al.*, 1977) (Capon *et al.*, 1984)
Plocamium oregonum **81-82**	2,6-Dimethyloctadienes Oregonene A (82)	 California (USA)	 (Crews, 1977)
Plocamium rigidum **83**	Octatrienal	 W. Cape (South Africa)	 (Fakee, 2013)
Plocamium robertiae **84**	1-Ethyl-1,3-dimethylcyclohexane	 E. Cape (South Africa)	 (Knott, 2012)
Plocamium suhrii **85**	2,6-Dimethyloctene	 Noordhoek (South Africa)	 (Antunes *et al.*, 2011)
 86	Octatrienes	 Noordhoek (South Africa)	 (Antunes *et al.*, 2011)
Plocamium telfairae **87**	1-Ethyl-1,3-dimethylcyclohexane Telfairine	 Fakui (Japan)	 (Watanabe *et al.*, 1989)
Plocamium violaceum **88-90**	2,6-Dimethyloctadienes Preplocamene A, B and C	 California (USA)	 (Crews and Kho-Wiseman, 1977)
 91	2,6-Dimethyloctatriene	 California (USA)	 (Crews *et al.*, 1984)
  92 **93-95**	1-Ethyl-1,3-dimethylcyclohexanes Violacene Plocamene D and E	 California (USA) California (USA)	 (Mynderse and Faulkner, 1974) (Crews *et al.*, 1978)
  96 **97**	1-Ethyl-2,4-dimethylcyclohexanes Plocamene-C;Violacene-2 Plocamene B	 California (USA) California (USA)	 (Mynderse et al.,1975) (Crews and Kho-Wiseman, 1975)
Plocamium species **98-101**	2,6-Dimethyloctatrienes	 Antarctica	 (Stierle *et al.*, 1979)



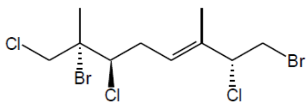
1



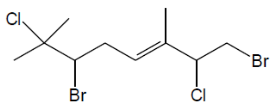
2



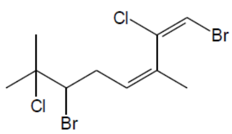
3



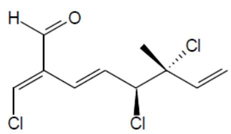
4



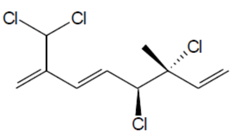
5



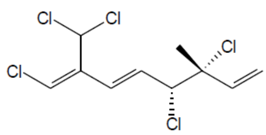
6



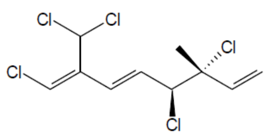
7



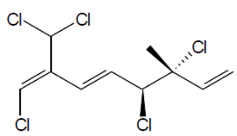
8



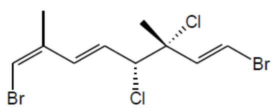
9



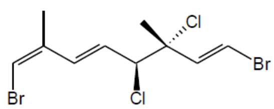
10



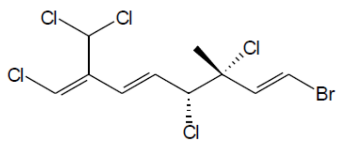
11



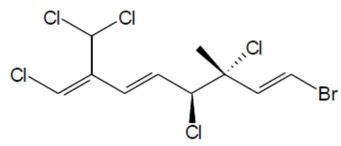
12



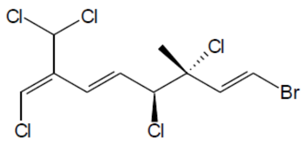
13



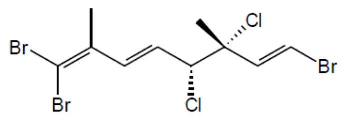
14



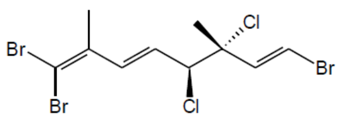
15



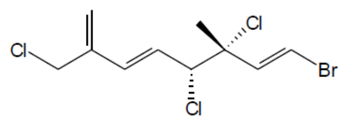
16



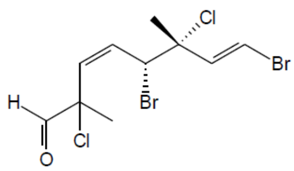
17



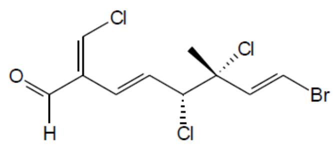
18



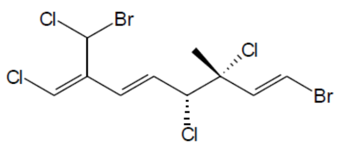
19



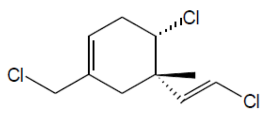
20



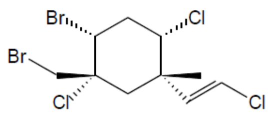
21



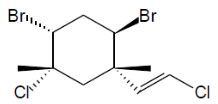
22



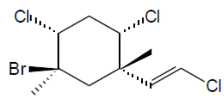
23



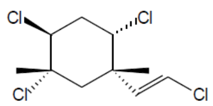
24



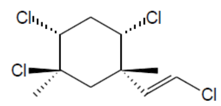
25



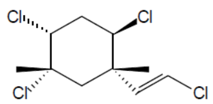
26



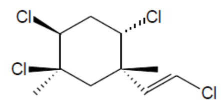
27



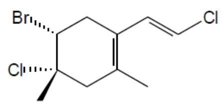
28



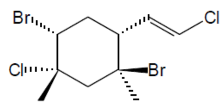
29



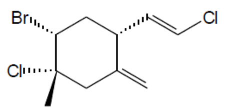
30



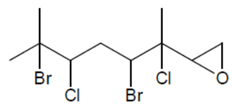
31



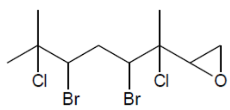
32



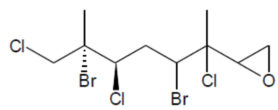
33



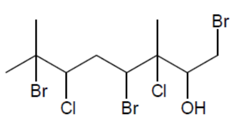
34



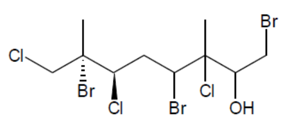
35



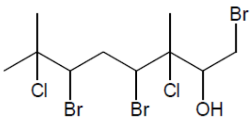
36



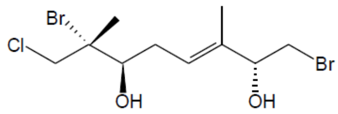
37



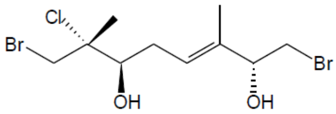
38



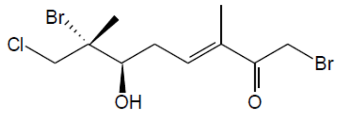
39



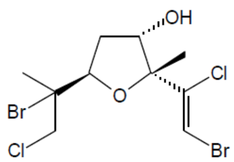
40



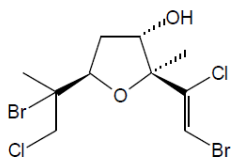
41



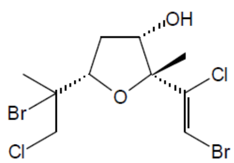
42



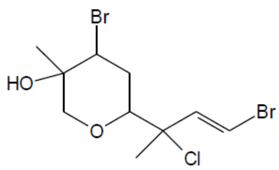
43



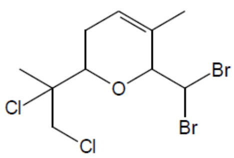
44



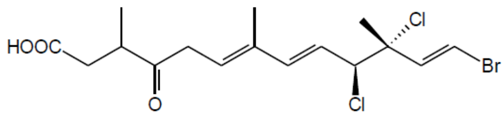
45



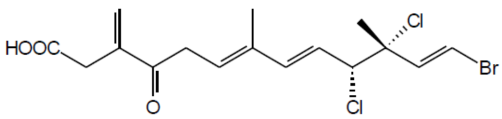
46



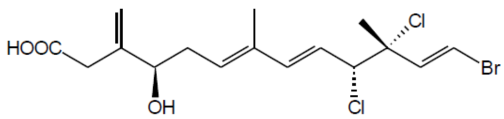
47



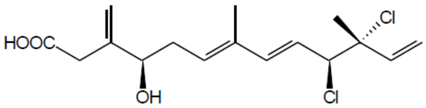
48



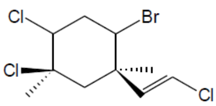
49



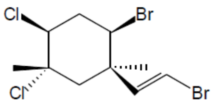
50



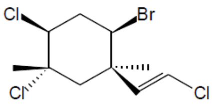
51



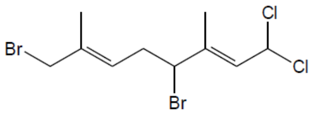
52



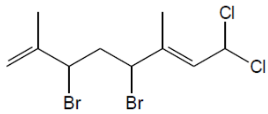
53



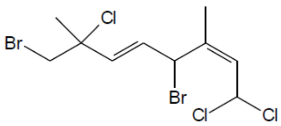
54



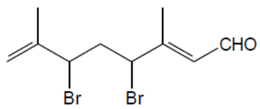
55



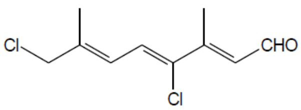
56



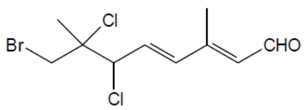
57



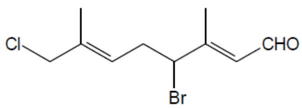
58



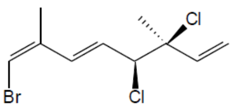
59



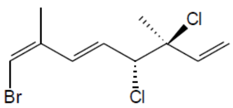
60



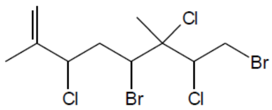
61



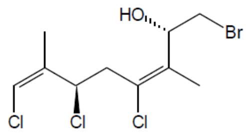
62



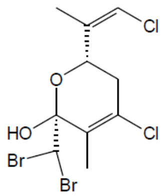
63



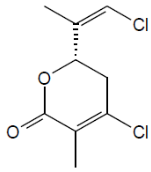
64



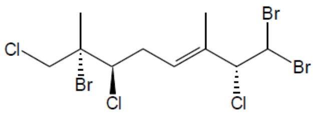
65



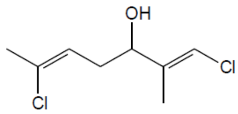
66



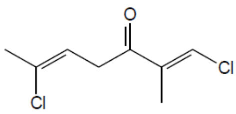
67



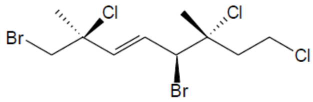
68



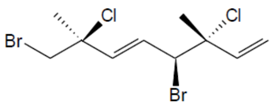
69



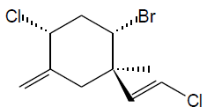
70



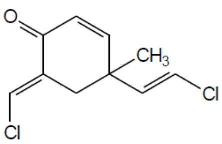
71



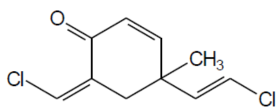
72



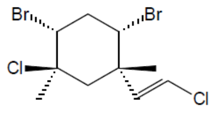
73



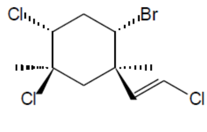
74



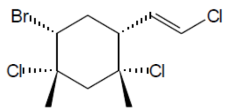
75



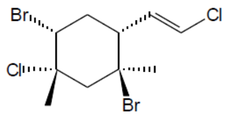
76



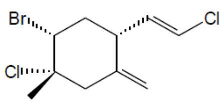
77



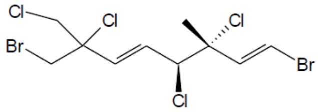
78



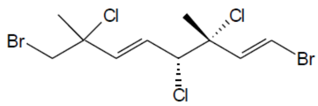
79



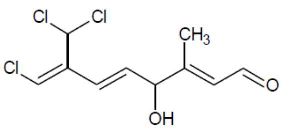
80



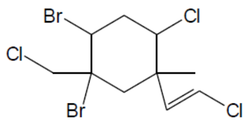
81



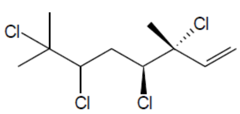
82



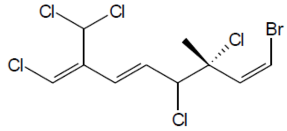
83



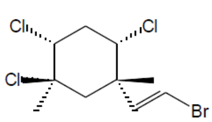
84



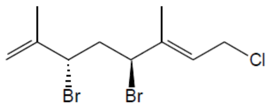
85



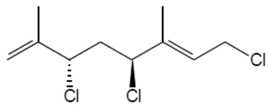
86



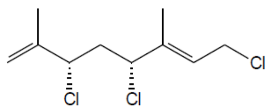
87



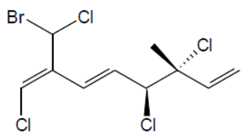
88



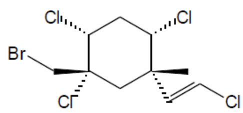
89



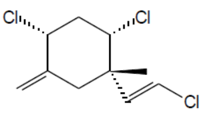
90



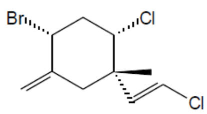
91



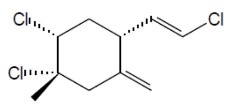
92



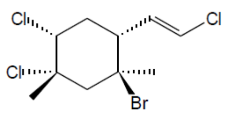
93



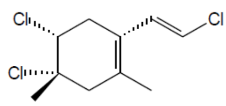
94



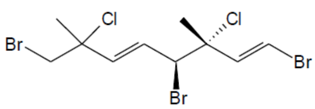
95



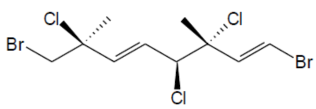
96



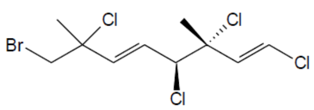
97



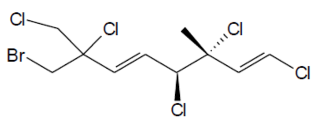
98



99



100



101

Table 4: Minimal inhibitory concentration (MIC) [μM] of test compounds **24, 27, 30, 45, 47, 52, 92** and **93**) on several mammalian cell lines (de Inés *et al.*, 2004).

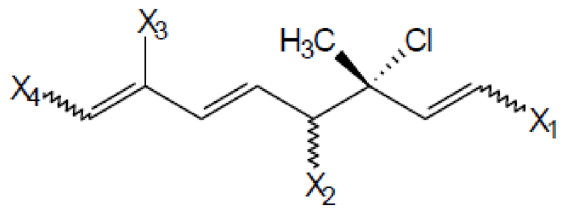
No.	CHO	CT26	SW480	HeLa	SkMe128
45	126	63 (IC$_{50}$ 30 μM)	126	126	126
47	262	262	131 (IC$_{50}$ 73 μM)	262	262
93	3.30	6.52	3.30	13.05	6.52
27	23	181	5.70(IC$_{50}$ 0.08 μM)	5.70(IC$_{50}$ 0.06 μM)	23
30	362	362	362	362	362
52	39	78	78	312	>312
92	141	141	141	282	282
24	63	125	125	125	250
Lindane	>344	>344	>344	>344	>344

P. corallorhiza yielded five compounds which demonstrated moderate to good activity towards oesophageal cancer cells (WHCO1) (Knott *et al.*, 2005). IC$_{50}$ values were 9.3 (**56**), 33.8 (**57**), 17.2 (**100**), 18.1 (**98**) and 34.8 μM (**24**), respectively. For this assay, cisplatin has an IC$_{50}$ value of 13 μM. *P. corallorhiza* also yielded four new halogenated monoterpene aldehydes. Two of these compounds were tested for cytotoxic activity. Compound **58** demonstrated moderate to good activity towards oesophageal cancer cells (WHCO1) with an IC$_{50}$ value of 7.5 μM. Compound **60** was only weakly active and had an IC$_{50}$ value of 64.8 μM (Mann *et al.*, 2007). Compound **24** isolated from *Plocamium hamatum* showed moderate cytotoxic activity IC$_{50}$: Lu1 12.9 μg/ml, KB 13.3 μg/ml and ZR-75-1 7.8 μg/ml) (König *et al.*, 1999).

Two new compounds known as Harrietone A (**74**) and Harrietone B (**75**) were isolated from *Plocamium maxillosum* and showed good cytotoxic activity against MDA-MB-231 metastatic breast cancer cell line with IC$_{50}$ = 12 μM for compounds **74** and IC$_{50}$ = 27 μM for compound **75**. Tamoxifen was used as a standard and had an IC$_{50}$ of 0.1 μM on MDA-MB-231 cell lines (Knott, 2012).

Five known halogenated monoterpenes (**14, 15, 10, 12, 13**), together with two new ones (**86**) and (**85**) were isolated from the red macroalga *P. suhrii.* During this study five related compounds from *P. cornutum*, as well as the seven compounds from *P. suhrii* were evaluated for their cytotoxic effects on an oesophageal cancer cell line (WHCO1). During this assay compounds **10, 12, 14, 15, 85** and **86** showed greater cytotoxicity than the known anti-cancer drug cisplatin (Antunes *et al.*, 2011) (Table 5).

Table 5: Selected structural features and cytotoxic effects of compounds (**14, 15, 10, 12, 13, 86** and **85**) on oesophageal cancer cells (Antunes *et al.*, 2011).



Compound	X_1	X_2	X_3	X_4	IC_{50} (μg/ml)	IC_{50} (μM)
15	1*E*-Br	4S* -Cl	$CHCl_2$	7*Z* -Cl	2.5	6.6
14	1*E*-Br	4R* -Cl	$CHCl_2$	7*Z* -Cl	3.8	9.9
86	1*Z*-Br	4S* -Cl	$CHCl_2$	7*Z* -Cl	3.6	9.3
10	H	4S* -Cl	$CHCl_2$	7*Z* -Cl	2.6	8.5
85					2.2	7.9
12	1*E*-Br	4R* -Cl	CH_3	7*Z* -Br	3.1	8.4
13	1*E*-Br	4S* -Cl	CH_3	7*Z* -Br	5.5	15.1

3 Conclusion

Building up summarised databases such as those seen in Tables 4-5 will assist future drug developing researcher's to better understand some of the structure activity relationships (SAR's) that exist between different compounds and selected types of cancer cells. However, it should be noted that there is more to rational drug selection than simply low IC_{50} values. For example, comparing the 'drug-likeness' of marine natural products with all other natural products, as measured by an examination of their Lipinski characteristics can also be very useful. Examining Lipinski's 'rule of five' criteria, Lipinski suggested that to be drug-like and orally-bioavailable, a molecule must have a partition coefficient ($\log P$) < 5, a molecular weight < 500 Da, < 5 hydrogen bond donors (HBD) and < 10 hydrogen acceptors (HBA) (Blunt *et al.*, 2011) (Knott, 2012).

In the search for new or novel halogenated monoterpenes from different *Plocamium* species, it is important to know what compounds have already been characterised or discovered. Furthermore, with the large number of metabolites that have already been isolated from various *Plocamium* species; an effective, reliable and rapid literature review of all these compounds is essential. Being able to provide this information both rapidly and accurately as seen in Tables 1-3, is extremely valuable to the natural product chemist who is researching halogenated monoterpenes.

Note:
This review forms part of my PhD thesis which was completed at Rhodes University, Grahamstown, South Africa (Knott, 2012).

References

[1] Abreu, P.M.; Galindro, J.M. Polyhalogenated monoterpenes from *Plocamium cartilagineum* from the Portuguese coast. J. Nat. Prod. 1996, 59, 1159-1162.

[2] Abreu, P.M.; Galindro, J.M.; Relva, A.M.; Ramos, A.M. Non-terpenoid compounds from *Plocamium cartilagineum*. Phytochemistry 1997, 45, 1601-1603.

[3] Afolayan, A.F.; Mann, M.G.A.; Lategan, C.A.; Smith, P.A.; Bolton, J.J.; Beukes, D.R. Antiplasmodial halogenated monoterpenes from the marine red alga, *Plocamium cornutum*. Phytochemistry 2009, 70, 597-600.

[4] Antunes, E.M.; Afolayan, A.F.; Chiwakata, M.T.; Fakee, J.; Knott, M.G.; Whibley, C.E.; Hendricks, D.T.; Bolton, J.J.; Beukes, D.R. Identification and in vitro anti-esophageal cancer activity of a series of halogenated monoterpenes isolated from the South African seaweeds *Plocamium suhrii* and *Plocamium cornutum*. Phytochemistry 2011, 72, 769-772.

[5] Bates, P.; Blunt, J.W.; Hartshorn, M.P.; Jones, A.J.; Munro, M.H.G; Robertson, S.C. Halogenated metabolites from the red alga *Plocamium cruciferum*. Aust. J. Chem. 1979, 32, 2545-2554.

[6] Blunt, J.W.; Bowman, N.J.; Munro, M.H.G.; Parsons, M.J.; Wright, G.J. Polyhalogenated monoterpenes of the New Zealand marine red alga *Plocamium cartilagineum*. Aust. J. Chem. 1985, 38, 519-525.

[7] Blunt, J.W.; Hartshorn, M.P.; Jones, A.J.; Munro, M.H.G.; Yorke, S.C. A novel C8 dichlorodienol metabolite of the red alga *Plocamium cruciferum*. Tetrahedron Lett. 1978, 45, 4417-4418.

[8] Blunt, J.W.; Copp, B.R.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. Nat. Prod. Rep. 2011, 28(2), 196-268.

[9] Bolton, J. Pers. Comm., University of Cape Town, Cape Town, South Africa. 2014

[10] Capon, R.J.; Engelhardt, L.M.; Ghisalberti, E.L.; Jefferies, P.R.; Patrick, V.A.;White, A.H. Structural studies on polyhalogenated monoterpenes from *Plocamium* species. Aust. J. Chem. 1984, 37, 537-544.

[11] Castedo, L.; Garcia, M.L.; Quinoa, E. Halogenated monoterpenes from *Plocamium coccineum* of northwest Spain. J. Nat. Prod. 1984, 47, 724-726.

[12] Coll, J.C.; Skeleton, B.W.; White, A.H.; Wright, A.D. Tropical marine algae II. The structure determination of new halogenated monoterpenes from *Plocamium hamatum* J. Agardh (Rhodophyta, Gigartinales, Plocamiaceae). Aust. J. Chem. 1988, 41, 1743-1753.

[13] Crews, P. Monoterpene halogenation by the red alga *Plocamium oregonum*. J. Org. Chem. 1977, 42, 2634-2636.

[14] Crews, P.; Kho-Wiseman, E. Acyclic polyhalogenated monoterpenes from the red alga *Plocamium violaceum*. J.Org. Chem. 1977, 42, 2812-2815.

[15] Crews, P.; Kho-Wiseman, E. *Plocamene* B, a new cyclic monoterpene skeleton from a red marine alga. J. Org. Chem. 1975, 40, 2568.

[16] Crews, P.; Kho-Wiseman, E., & Montana, P. Halogenated alicyclic monoterpenes from the red alga *Plocamium*. J. Org. Chem. 1978, 43, 116-120.

[17] Crews, P.; Kho-Wiseman, E.J. Cartilagineal. An unusual monoterpene aldehyde from marine alga. J. Org. Chem. 1974, 39, 3303-3304.

[18] Crews, P.; Naylor, S.; Hanke, F.J.; Hogue, E.R.; Kho-Wiseman, E.; Braslau, R. Halogen regiochemistry and substituent stereochemistry determination in marine monoterpenes by 13C NMR. J. Org. Chem. 1984, 49, 1371-1377.

[19] Cueto, M.; Darias, J.; Rovirosa, J.; San-Martin, A. Tetrahydropyran monoterpenes from *Plocamium cartilagineum* and *Pantoneura plocamioides*. J. Nat. Prod. 1998, 61, 1466.

[20] Darias, J.; Rovirosa, J.; San-Martin, A.; Diaz, A.; Dorta, E.; Ceuto, M. Furoplocamioids A-C, novel polyhalogenated furanoid monoterpenes from *Plocamium cartilagineum* J. Nat. Prod. 2001, 64, 1383-1387.

[21] Diaz-Marrero, A.R.; Rovirosa, J.; Darias, J.; San-Martin, A.; Ceuto, M. Plocamenols A-C, novel linear polyhalohyroxylated monoterpenes from *Plocamium cartilagineum*. J. Nat. Prod. 2002, 65, 585-588.

[22] de Inés, C.; Argandoña, Rovirosa, J.; San-Martin, A.; Diaz-Marrero, A.R.; Cueto, M.; González-Coloma, A. Cytotoxic activity of halogenated monoterpenes from *Plocamium cartilagineum*. Z. Naturforsch 2004, 59c, 339-344.

[23] Dunlop, R.W.; Murphy, P.T.; Wells, R.J. New polyhalogenated monoterpene from the red alga *Plocamium angustum*. Aust.J. Chem. 1979, 32, 2735-2739.

[24] Dworjanyn, S.A.; De Nys, R.; Steinberg, P.D. Localisation and surface quantification of secondary metabolites in the red alga *Delisea pulchra*. Mar. Biol. 1999, 133, 727-736.

[25] Fakee, J. The Isolation and Characterisation of Secondary Metabolites from Selected South African Marine Red Algae (Rhodophyta). MSc thesis, Rhodes University, Grahamstown, South Africa, 2013, 27.

[26] Falshaw, R.; Furneaux, R.H.; Miller, I.J. The backbone structure of the sulfated galactan from *Plocamium costatum* (C. Agardh). Bot. Mar. 1999, 42, 431-435.

[27] Goodwin, K.D.; North, W.J.; Lidstrom, M.E. Production of bromoform and dibromomethane by Giant Kelp: Factors affecting release and comparison to anthropogenic bromine sources. Limnol. Oceanogr. 1997, 42, 1725-1734.

[28] Higgs, M.D.; Vanderah, D.J.; Faulkner, D.J. Polyhalogenated monoterpenes from Plocamium cartilagineum from the British coast. Tetrahedron 1977, 33, 2775-2780.

[29] Jongaramruong, J.; Blackman, A.J. Polyhalogenated Monoterpenes from a Tasmanian Collection of the Red Seaweed *Plocamium cartilagineum*. J. Nat. Prod. 2000, 63, 1046.

[30] Kazlauskas, R.; Murphy, P.T.; Quinn, R.J.; Wells, R.J. Two polyhalogenated monoterpenes from the red alga *Plocamium costatum*. Tetrahedron Lett. 1976, 49, 4451-4454.

[31] Kladi, M.; Vagias, C.; Roussis, V. Volatile halogenated metabolites from marine red algae. Phytochem. Rev. 2004, 3, 337-366.

[32] Knott, M.G.; Mkwananzi, H.; Arendse, C.E.; Hendricks, D.T.; Bolton, J.J.; Beukes, D.R. Plocoralides A-C, polyhalogenated monoterpenes from the marine alga, *Plocamium corallorhiza*. Phytochemistry 2005, 66, 1108-1112.

[33] Knott, M.G. The natural product chemistry of South African *Plocamium* species. MSc thesis, Rhodes University, Grahamstown, South Africa, 2003, 68.

[34] Knott, M.G. Isolation, structural characterisation and evaluation of cytotoxic activity of natural products from selected South African marine red algae. PhD thesis, Rhodes University, Grahamstown, South Africa, 2012

[35] König, G.M.; Wright, A.D; Linden, A. *Plocamium hamatum* and its monoterpenes: chemical and biological investigations of the tropical marine algae. Phytochemistry 1999, 52, 1047-1053.

[36] König, G.M.; Wright, A.D.; de Nys, R.; Sticher, O. A new polyhalogenated monoterpene from the red alga *Plocamium cartilagineum*. J. Nat. Prod. 1990, 53, 1615-1618.

[37] König, G.M.; Wright, A.D.; de Nys, R.; Sticher, O. Halogenated monoterpenes from *Plocamium costatum* and their biological activity. J. Nat. Prod. 1999, 62, 383-385.

[38] Mann, M.G.A.; Mkwananzi, H.; Antunes, E.M.; Whibley, C.E.; Hendricks, D.T.; Bolton, J.J.; Beukes, D.R. Halogenated monoterpene aldehydes from the South African marine Alga *Plocamium corallorhiza*. J. Nat. Prod. 2007, 70, 596-599.

[39] Mynderse, J.S.; Faulkner, D.J. Violacene; a polyhalogenated monocyclic monoterpene from the red alga *Plocamium violaceum*. J. Am. Chem. Soc. 1974, 96, 6771.

[40] Mynderse, J.S.; Faulkner, D.J. Polyhalogenated monoterpenes from the red alga *Plocamium cartilagineum*. Tetrahedron 1975, 31, 1963-1967.

[41] Mynderse, J.S.; Faulkner, D.J.; Finer, J.; Clardy, J. (1R; 2S; 4S; 5R)-1-Bromo-trans-2-chlorovinyl-4-5-dichloro-1;5-di-methylcyclohexane. A monoterpene skeletal type from the red alga *Plocamium violaceum*. Tetrahedron Lett. 1975, 16, 2175-2178.

[42] Norton, R.S.; Warren, R.G.; Wells, R.J. Three new polyhalogenated monoterpenes from *Plocamium* species. Tetrahedron Lett. 1977, 44, 3905-3908.

[43] Řezanka, T.; Dembitsky, V. Polyhalogenated homosesquiterpenic fatty acids from *Plocamium cartilagineum*. Phytochemistry 2001, 57, 607-611.

[44] San-Martin, A.; Negrete, R.; Rovirosa, J. Insecticide and acaricide activities of polyhalogenated monoterpenes from Chilean *Plocamium cartilagineum*. Phytochemistry 1991, 30, 2165-2169.

[45] Sardina, F.J.; Quinoa, E.; Castedo, L.; Riguera, R. Halogenated monoterpenes from *Plocamium coccineum* of northwest Spain. Chem. Lett. 1985, 10, 697.

[46] Stierle, D.B.; Wing, R.M.; Sims, J.J. Marine natural products XVI. Polyhalogenated acyclic monoterpenes from the red alga *Plocamium* of Antarctica. Tetrahedron 1979, 35, 2855-2859.

[47] Stierle, D.B.; Wing, R.W.; Sims, J.J. Marine natural products costatone and costatolide, new halogenated monoterpenes from the red seaweed, *Plocamium costatum*. Tetrahedron Lett. 1976, 49, 4455-4458.

[48] Vasconcelos, M.A.; Ferreira, W.J.; Pereira, R.C.; Cavalcanti, D.N.; Teixeira, V.L. Chemical constituents from the red alga *Plocamium brasiliense* (Greville) M. Howe and W.R. Taylor. Biochem. Sys. Ecol. 2010, 38, 119-121.

[49] Watanabe, K.; Miyakado, M.; Ohno, N.; Okada, A.; Yanagi, K.; Moriguchi, K.A. A polyhalogenated insecticidal monoterpene from the red alga, *Plocamium telfairiae*. Phytochemistry 1989, 28, 77.