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Ascidians and Sea Hares: Rich Sources of Bioactive Natural Products

by

David Ross Appleton

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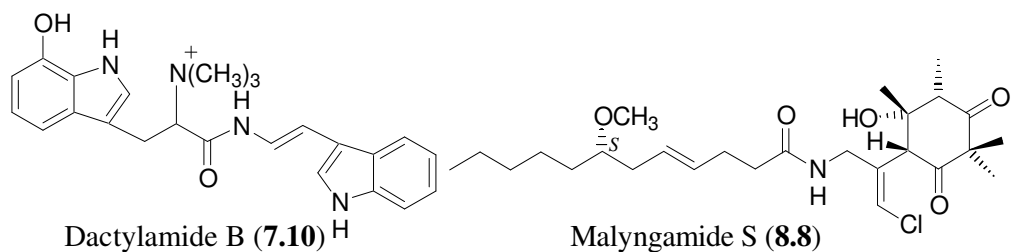
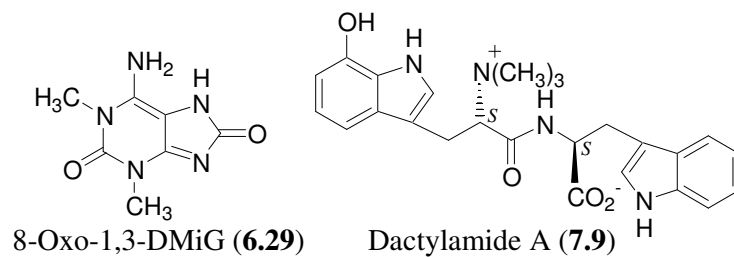
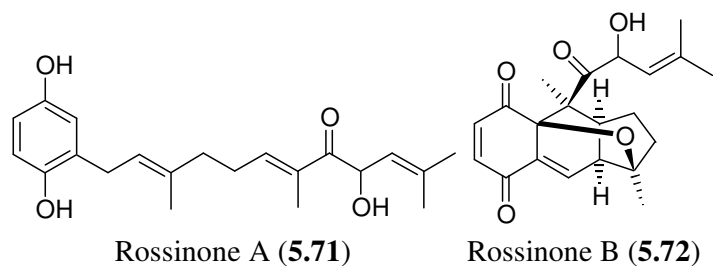
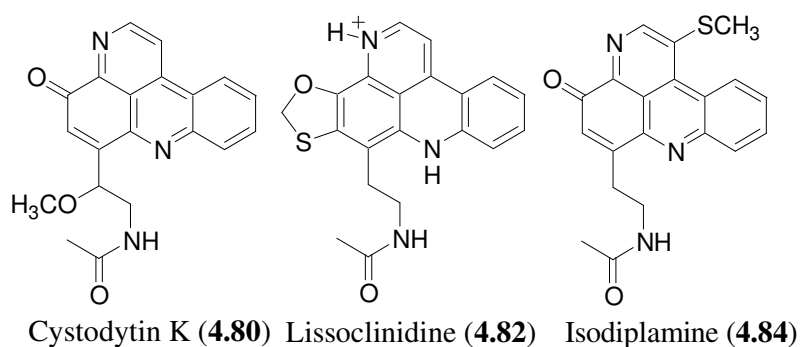
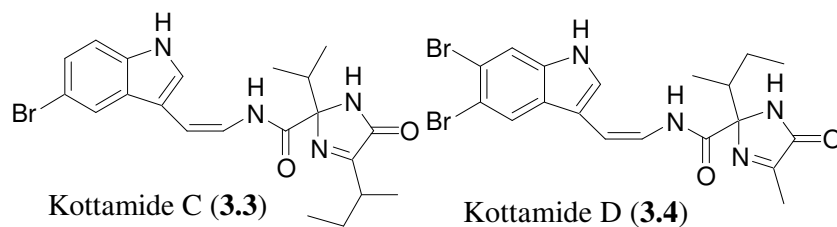
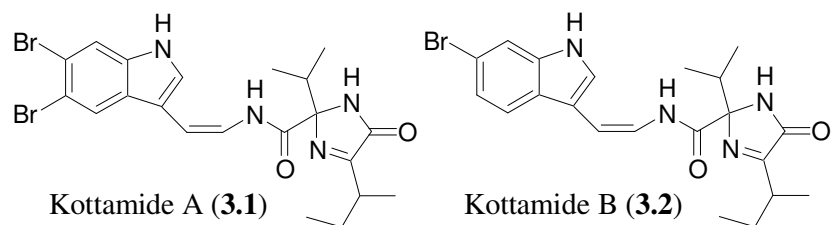


Abstract

A survey of the metabolite content of fifty-two ascidians collected from New Zealand and Antarctica is presented. Using biological assays and reversed phase analytical C₁₈ HPLC techniques, twenty-three specimens were selected for further work. Work on ten of the selected ascidians is presented in this study. Using standard chromatographic techniques combined with analytical C₁₈ HPLC, eighteen metabolites were isolated of which sixteen exhibited biological activity. Ten of the eighteen metabolites were novel, with nine exhibiting biological activity. The New Zealand endemic ascidian *Pycnoclavella kottae*, collected from the Three Kings Islands yielded the novel 2,2,5-trisubstituted imidazol-4-ones, kottamides A - D (**3.1** - **3.4**). Three new pyridoacridines (**4.80**, **4.82**, **4.84**), along with two known pyridoacridines and the known benzopentathiepin, varacin were isolated from the New Zealand endemic ascidian *Lissoclinum notti*. Varacin was investigated for its use in ADEPT and a possible prodrug derivative was prepared. In addition, a novel biologically inactive purine, 8-oxo-1,3-dimethylisoguanine (**6.29**) was isolated from the New Zealand endemic ascidian *Pseudodistoma cereum*. The study of an ascidian of the genus *Aplidium*, collected from the Ross Sea, Antarctica resulted in the isolation of two novel quinone derivatives, rossinones A (**5.71**) and B (**5.72**), which exhibited potent cytotoxicity and antiviral activity. Rossinones A (**5.71**) and B (**5.72**) provide insights into the biosyntheses of several terrestrial plant natural products.

In addition, six sea hares of three species collected from the Auckland, New Zealand region were surveyed using the same methodology, with three novel and seven known compounds being isolated. The study of the sea hare *Aplysia dactylomela* resulted in the isolation of two inactive novel tryptophan dipeptides, dactylamides A (**7.9**) and B (**7.10**), the known ink pigment aplysiolysin and four known sesquiterpenes. A new malyngamide, S (**8.8**) along with an algal toxin, lyngbyatoxin A and its acetate were isolated from the sea hare *Bursatella leachii*. A survey of nine algae collected from the same locations as the sea hares resulted in the identification of several of the dietary sources of these sea hares.

Standard spectroscopic techniques were used for structural elucidation, including the use of natural abundance ¹H-¹⁵N 2-D NMR where required. All compounds were assayed for a range of biological activities.



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Abbreviations

Ac	Acetyl
ADEPT	Antibody-directed enzyme prodrug therapy
aq	Aqueous
atm	Atmospheres
b	Broad
BOC	t-Butyloxycarbonyl
BOP	Benzotriazol-1-yloxy tri(dimethylamine)phosphonium hexafluorophosphate
<i>B.s.</i>	<i>Bacillus subtilis</i>
C₁₈	Octadecyl-derivatised silica
<i>C.a.</i>	<i>Candida albicans</i>
Calcd	Calculated
CD	Circular dichroism
CI	Chemical ionisation
COSY	Gradient correlation spectroscopy (¹ H- ¹ H)
d	Doublet
DBU	1,8-Diaza-bicyclo[5.4.0]undec-7-ene
dec	Decomposed
DEPT	Distortionless enhancement by polarisation transfer
DHA	Docosahexaenoic acid
DMG	Dimethylguanine
DMiG	Dimethylisoguanine
DNA	Deoxyribonucleic acid
DPPA	Diphenylphosphorylazide
<i>E.c.</i>	<i>Escherichia coli</i>
ED₅₀	Median effective dose
EI	Electron impact
EPA	Eicosapentaenoic acid
ETA	Eicosatetraenoic acid
Et	Ethyl
et al.	et alii
FAB	Fast atom bombardment
fMLP	<i>N</i> -Formyl-methionyl-leucyl-phenylalanine
GC-MS	Gas chromatography-mass spectrometry
GI₅₀	50% Growth inhibition
HMBC	Gradient heteronuclear multiple-bond correlation
HPLC	High performance liquid chromatography
HR	High resolution

HSQC	Gradient heteronuclear single-quantum correlation
HSV	Herpes simplex virus
IC₅₀	50% Inhibitory concentration
IR	Infrared
LC₅₀	50% Lethal dose concentration
m	Multiplet
M	mol/L
Me	Methyl
MIC	Minimum inhibitory concentration
mp	Melting point
MS	Mass spectrometry
<i>M.t.</i>	<i>Mycobacterium tuberculosis</i> H ₃₇ Rv
mult	Multiplicity
<i>m/z</i>	Mass to charge ratio
N	Normal
NCI	National Cancer Institute of America
NMR	Nuclear magnetic resonance
No.	Number
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
Obsc	Obscured
p	Pentet
PMA	Phorbol myristate acetate
PMS	1-Methoxy phenazinemethosulfate
PNBnzOC	<i>para</i> -Nitrobenzyloxycarbonyl
ppm	Parts per million
PV1	Polio virus, Type 1
q	Quartet
Rel int%	Relative intensity (%)
resp	Respectively
RNA	Ribonucleic acid
ROESY	Rotating frame Overhauser enhancement spectroscopy
s	Singlet
sat	Saturated
SCUBA	Self contained underwater breathing apparatus
sep	Septet
sp.	Species
spp.	Species (plural)
t	Triplet
TFA	Trifluoroacetic Acid
TGI	Total growth inhibition

TLC	Thin layer chromatography
<i>T.m.</i>	<i>Trichophyton mentagrophytes</i>
TMG	Trimethylguanine
TMiG	Trimethylisoguanine
TOCSY	Gradient total correlation spectroscopy
UV	Ultraviolet
Vis	Visible
v/v	Volume/volume
WST-1	2-(4-Iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt
¹H NMR	Proton nuclear magnetic resonance
¹³C NMR	Carbon-13 nuclear magnetic resonance
¹⁵N NMR	Nitrogen-15 nuclear magnetic resonance
2-D	Two-dimensional
δ_A	Chemical shift (ppm) for nucleus A
[α]_x²⁰	Optical rotation at 20 °C at 'x' nm; D = sodium D-line (489 nm)
ⁿJ_{AB}	Coupling constant between atoms A and B, 'n' bonds apart