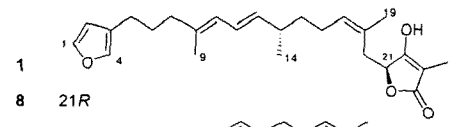
Cytotoxic Pyrrolo- and Furanoterpenoids from a Sponge *Sarcotragus* Species

Yonghong Liu and Jee H. Jung*
College of Pharmacy, Pusan National University, Busan 609-735, Korea

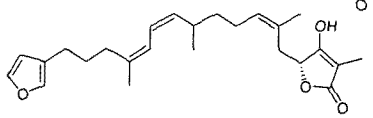
Marine sponges of the order Dictyoceratida have frequently afforded a wide variety of linear sesterterpenes, many of which contain furanyl and tetronic acid termini. In our study on the cytotoxic compounds of a sponge *Sarcotragus* sp. (family Thorectidae, order Dictyoceratida), ten new furanosesterterpenes (**1-3, 5, 7, 8, 16-18, 23**), seven pyrrolosesterterpenes (**9-15**), five norsesterterpenes (**19, 20, 24-26**), and two furanoditerpenes (**21, 22**) were isolated. The pyrrolosesterterpenes were chemically unique incorporating a pyrrole ring in place of the furan ring. They might be biosynthesized by condensation of furanosesterterpene and amino acid derived unit. Unlike other common furanosesterterpenes, compounds **16-18, 24**, and **25** were carrying an oxidized furan ring similar to that found in manoalide. The gross structures of the compounds were elucidated by the aid of COSY, HMQC, and HMBC experiments while the absolute configuration of the tetronic acid moiety was proposed by comparison of the NMR and CD data of each diastereomeric pair.

The isolated compounds were evaluated for cytotoxicity and showed a marginal to significant activity against a small panel of five human tumor cell lines (Table 1). Of the compounds tested, some of the derivatives with the tetronic acid function (**3-9, 13, 17, 18, 23**) exhibited higher potencies than the trinorsesterterpenes (**19, 20**) and diterpenes (**21, 22**), though the presence or absence of this moiety may not be the only determining factor as other tetronic acid containing compounds (**1, 3, 14,-16**) also had lower potencies, being comparable to **19-22** in activity. Of the compounds, bisfuranosesterterpenes with conjugated tetronic acid function (**4-7**) showed the highest potency. Compound **5**(ircinin-1) was subjected to further evaluation of activity on cell cycle modulation. Ircinin-1 was shown to arrest G1 phase and to induce apoptosis by modulation of P53 and P21 expression.

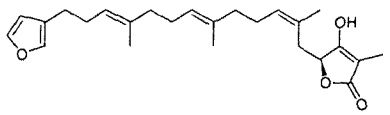


1

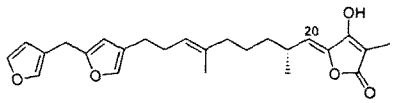
8 21*R*



2

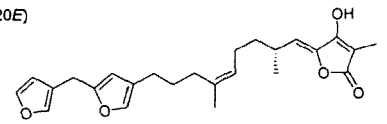


3



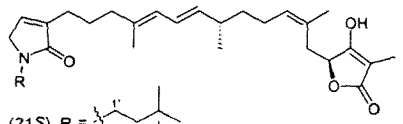
4

5 (20*E*)



6

7 (20*E*)



9 (21*S*), R =

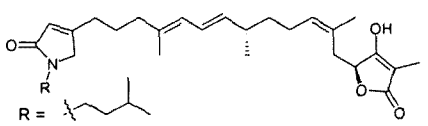
10 (21*R*), R =

11 (21*S*), R =

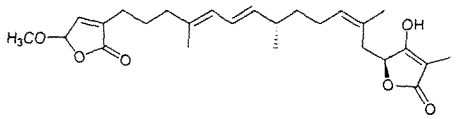
12 (21*R*), R =

13 (21*S*), R =

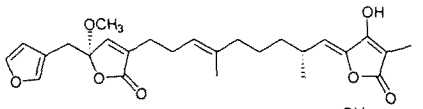
14 (21*R*), R =



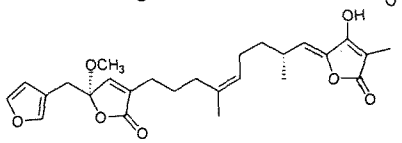
15 R =



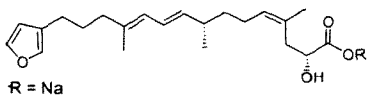
16



17

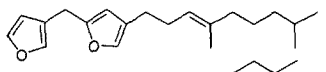


18

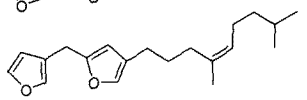


19 R = Na

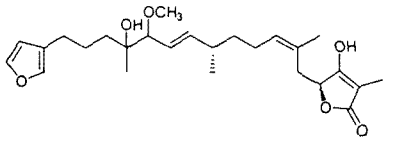
20 R = CH_3



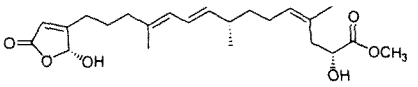
21



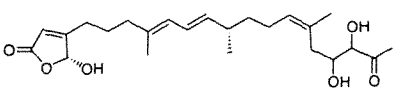
22



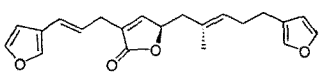
23



24



25



26

Table 1. Cytotoxicity of Compounds 1-23 against Human Solid Tumor Cell Lines[a]

compd	A549	SK-OV-3	SK-MEL-2	XF498	HCT15
1	29.7	22.1	>30	24.8	27.2
2	10.1	11.3	7.8	8.9	9.0
3	16.9	26.8	16.3	20.4	27.5
4	3.7	6.6	9.0	5.4	6.9
5	5.0	9.4	10.2	6.5	9.8
6	3.8	5.9	5.8	3.7	4.7
7	3.8	6.2	8.3	5.0	7.3
8	12.3	9.6	5.6	9.8	6.5
9	15.1	5.3	4.1	5.5	5.0
10	4.3	4.0	3.4	3.9	3.8
11	6.3	6.7	4.3	5.2	4.9
12	16.8	13.1	4.8	10.5	5.4
13	19.0	6.9	3.8	5.4	5.3
14	27.1	26.8	15.9	25.2	22.3
15	>30	25.9	13.2	>30	21.6
16	24.1	15.2	7.6	20.1	10.5
17	9.1	10.0	5.1	7.6	7.3
18	6.7	6.8	5.9	6.3	6.1
19	24.8	23.3	25.7	25.9	23.7
20	18.1	10.0	7.8	24.3	8.7
21,22[c]	>30	26.8	6.2	29.6	23.9
23	9.0	8.4	9.9	11.3	10.1
cisplatin	0.72	1.23	2.26	1.03	1.10
doxorubicin	0.02	0.16	0.02	0.13	0.06

[a]Data expressed in ED_{50} values (μg/mL). A549, human lung cancer; SK-OV-3, human ovarian cancer; SK-MEL-2, human skin cancer; XF498, human CNS cancer; HCT 15, human colon cancer. [b]Compounds were assayed in several separate batches. [c]Obtained as an inseparable mixture.