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REVIEW ARTICLE

Naturally occurring didemnaketals: Structural elucidation, features, and pharmacological activities

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Didemnaketals;
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Abstract Didemnaketals are rare terpenoid class reported only in the marine ascidian *Didemnum* species. They possess important biological activities like HIV-1 protease inhibitor, protein kinase inhibition, antimicrobial, antiproliferative, and cytotoxic. A compilation of new naturally occurring didemnaketals reported during 1991–2014 is provided with available physical and spectral data: mp, $[\alpha]_D$, UV, IR, ^1H and ^{13}C NMR as well as biological activities and references.

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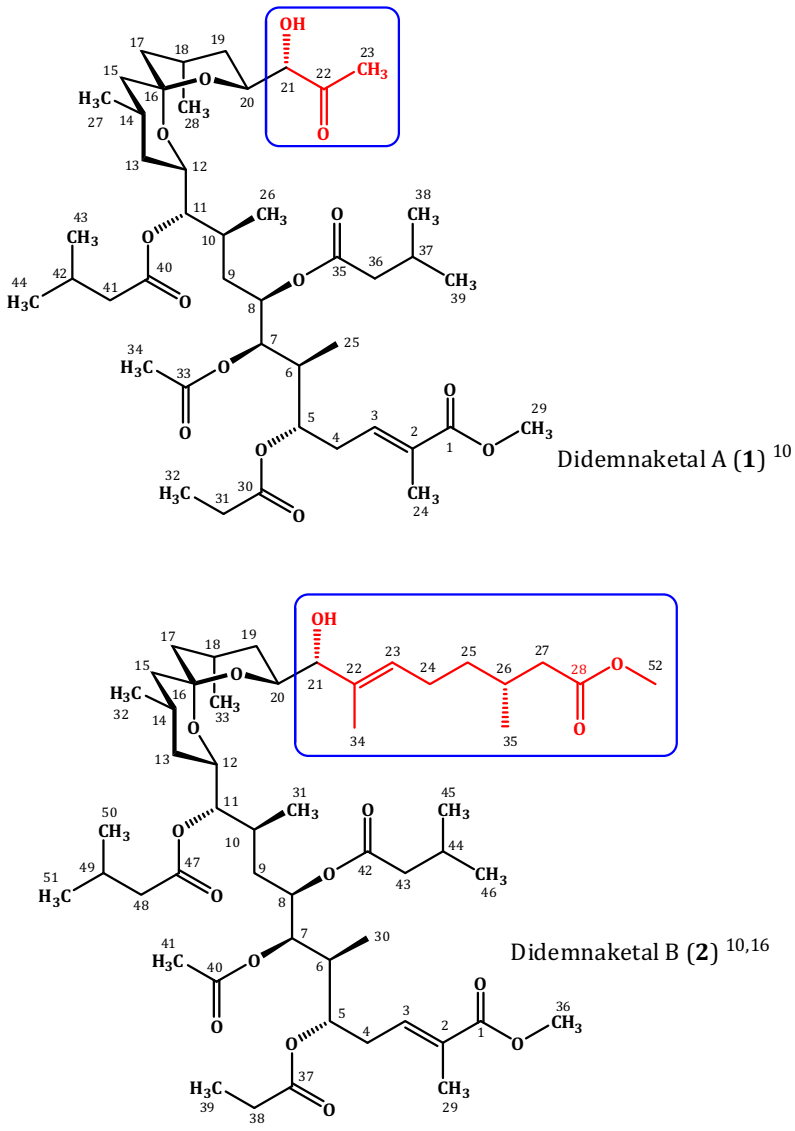
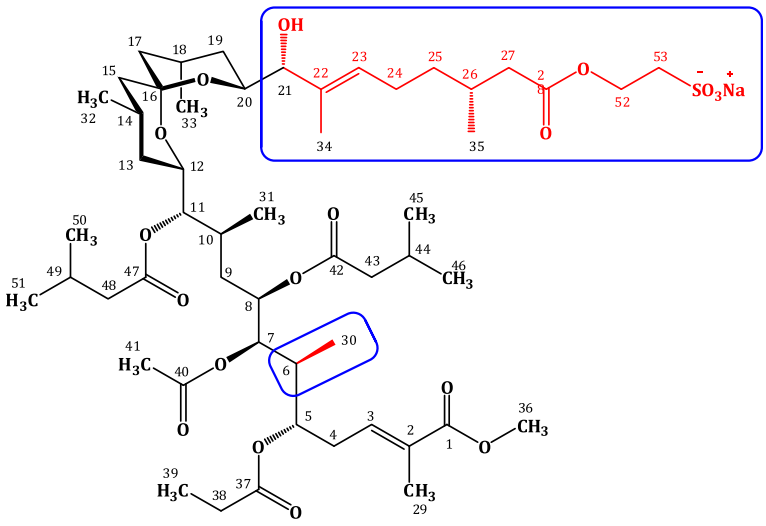


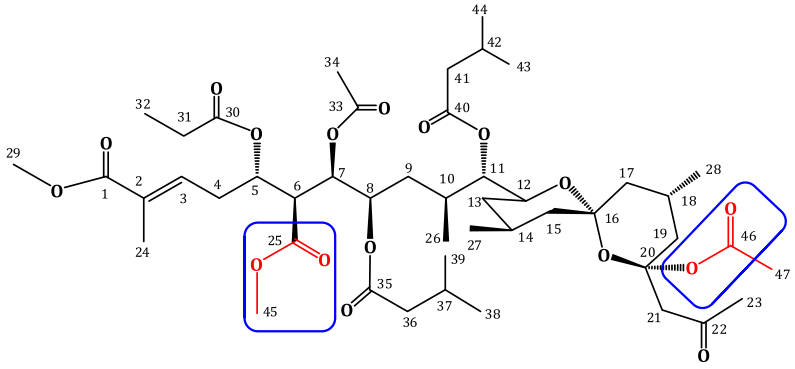
Figure 1

1. Introduction

The number of natural products isolated from marine organisms increases rapidly and many new compounds are discovered every year.[1] A large proportion of natural compounds have been isolated from marine invertebrates such as sponges, ascidians, bryozoans, and molluscs, and some of them are currently in clinical trials.[2] Ascidians or sea-squirts are cosmopolitan, exclusively marine invertebrates, which represent the most highly evolved group of animals commonly investigated by marine natural product chemists.[3] Attention has focused on ascidians because of their biologically active metabolites. The chemistry of ascidians has become one of the most active fields of marine natural products. It has been demonstrated that these sea creatures are prolific producers of unusual structures with significant bioactivities.[4] The compounds isolated from genus *Didemnum* are diverse and possess a wide range of biological activities such as antiplasmodial,[5] antiviral,[6] cytotoxic,[7] and protein kinase inhibitors.[8] Didemnaketals are very rare linear heptaprenoids, isolated from the marine *Didemnum* species. To date, seven spiroketals, didemnaketals **A**–**G** (**1**–**7**) (Fig. 1) were isolated from the marine *Didemnum* species collected from different geographical locations including Auluptagel Island Palau[9,10] and Nabq/Sharm El-Sheikh on the Egyptian Red Sea coast.[8,11] Two of them, didemnaketals **A** (**1**) and **B** (**2**) were reported as a result of oxidation and methanolysis of polar isoethonic ester, didemnaketal **C** (**3**) during long storage of the ascidian sample in MeOH.[9,10,12] While, didemnaketals **C**–**G** (**4**–**7**) were isolated from fresh samples of marine ascidian *Didemnum* species.[8,9,11] Here, we listed the didemnaketals that have appeared in the literature over the past few decades, with their biological activities, physical constants, spectral data, and references. For each compound these data were listed in the following order: name; structure; melting point (°C); optical rotation (concentration, solvent); UV (solvent, λ_{max} nm, log ε); IR (medium, absorption band



Didemnaketal C (**3**) [9]



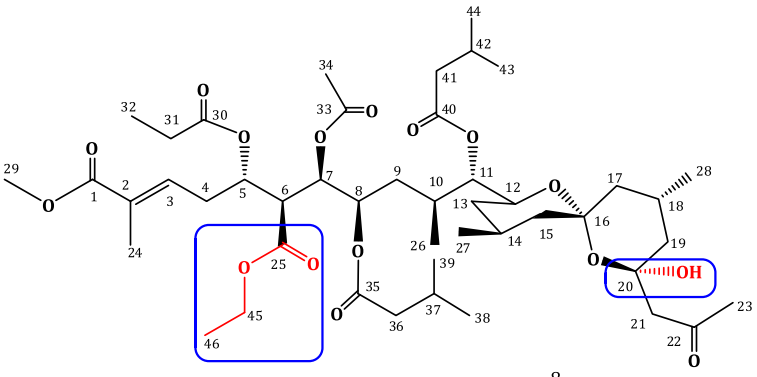
Didemnaketal D (**4**) [8]

Fig. 1 (*continued*)

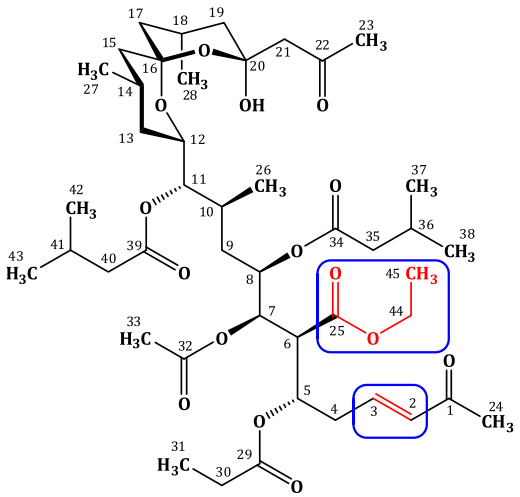
in cm^{-1}); ^{1}H NMR (spectrometer frequency, solvent, chemical shift values in ppm, starting with H-3 and listed in order); ^{13}C NMR (spectrometer frequency, solvent, chemical shift in ppm values starting with C-1 and listed in order); molecular formula; calculated molecular weight; and reference(s) (Tables 1–3). The main aim of this review is for rapid identification of isolated didemnaketals by comparison of spectral data as well as to draw attention of the natural product chemists for evaluation of biological and pharmacological activities of the isolated didemnaketals. The high-light of pharmacological activity may possibly draw the attention of the synthetic chemists for design of new drugs using the known didemnaketals.

2. The structural features of didemnaketals

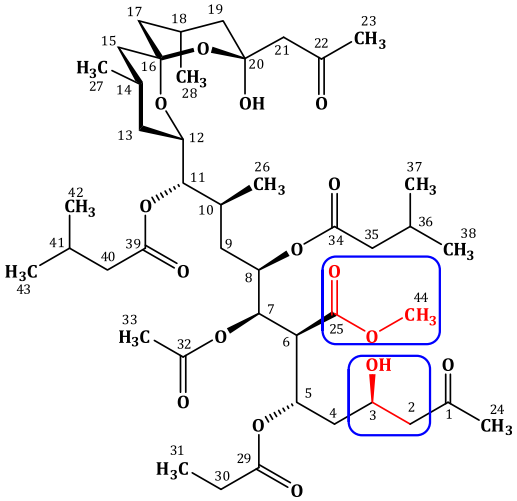
Didemnaketals are a rare class of polyisoprenoids, characterized by the presence of bicyclic ketal region from C-12 to C-20 and *penta*-ester side chain.[13,14] The linear heptaprenoid structure contains a number of intriguing structural features such as a spiroketal moiety and two side chains with eight chiral centers.[13,15] Didemnaketals **D** (**4**) and **E** (**5**) isolated from *Didemnum* sp. collected from Sharm El-sheikh on the Red Sea coast,[8] differ from didemnaketal **A** isolated from the magenta ascidian *Didemnum* sp. collected at Auluptagel island, Palauin,[10] in lacking the methyl at C-6 and the hydroxy at C-21, as well as possessing an additional substituent at C-20. They showed new moieties at C-6 (methyl ester in **D** (**4**) and ethyl ester in **E** (**5**) and an oxygen functionality at C-20 (acetoxy in **D** (**4**) and hydroxy in **E** (**5**)). The new moieties at C-20 represent an unprecedented and complicated spiroketal/ketal (in **4**) and spiroketal/hemiketal (in **5**) moieties, which are not observed in the previously described spiroketal systems.[8] Moreover, didemnaketals **F** (**6**) and **G** (**7**) are characterized by the absence of the methyl functionality at C-2 and terminal methyl ester moiety of the spiroketal skeleton. Instead, they possess a terminal methyl ketone moiety at the left part of the molecule. Additionally, **6** possesses a *di*-substituted double bond at C-2/C-3, while **7** has a secondary alcohol at C-3. Also, they have spiroketal/hemiketal functionality at the right part of the molecule.[8,11]



Didemnaketal E (**5**) [8]



Didemnaketal **F** (**6**) [11]



Didemnaketal **G** (**7**) [11]

Fig. 1 (*continued*)

3. The absolute stereochemistry of didemnaketals

The gross structures of didemnaketals **A**–**G** (**1**–**7**) were determined by extensive 1D and 2D NMR spectroscopic analyses.[8–11]

The absolute stereochemistry at the stereogenic centers of didemnaketals **A**–**C** (**1**–**3**) was determined to be 5*S*,6*S*,7*R*,8*R*,10*S*,11*S*,12*S*,14*S*,16*S*,18*R*,20*S*,21*S* (didemnaketal **A**) and 5*S*,6*S*,7*R*,8*R*,10*S*,11*S*,12*S*,14*S*,16*S*,18*R*,20*S*,21*S*,26*S* (didemnaketals **B** and **C**),[14] using a combination of degradation and derivatization experiments, chiral shift methods, as well as synthesis of the C9–C28 subunit containing the spiroketal moiety through a highly convergent strategy in didemnaketal **B** (**2**).[12,14] The configuration of didemnaketals **D** and **E** was assigned to be 5*S*,6*S*,7*R*,8*R*,10*S*,11*S*,12*R*,14*S*,16*S*,18*R* on the basis of NOESY correlations and comparison of the NMR spectral data with those of previously reported didemnaketals.[8] Fuwa and coworkers revised Faulkner's stereochemical assignment of didemnaketals **B** through its total synthesis.[16] The stereochemical relationship of the C5/C6, C6/C7, and C7/C8 stereogenic centers was correlated by NMR spectroscopic analyses on suitable acetonide derivatives. X-ray crystallographic analysis is used for assignment of the relative configuration of the C10-C20 spiroacetal domain. The absolute configuration of the C5, C8, C11, and C21 stereogenic centers was determined by application of the modified Mosher analysis, while that of the C20 and C26 stereogenic centers was assigned on the basis of the phenyl glycine methyl ester (PGME) method.[16] The geometry of the C2–C3 double bond was confirmed to be *E* by NOE experiment as well as by a large $^{3}J_{H,H}$ value ($^{3}J_{H2,H3}$ = 16.5 Hz).[11,16] The absolute configuration of didemnaketals **F** (**6**) and **G** (**7**) was determined to be 5*S*,6*S*,7*R*,8*R*,10*S*,11*S*,12*S*,14*R*,16*S*,18*R*,[11] based on Fuwa's stereochemical revision of didemnaketals **B** (**2**) as well as extensive spectroscopic studies.[16]

4. Biological activities of didemnaketals

4.1. Potent HIV-1 protease inhibitor activity

Replication of human immunodeficiency virus (HIV) entails expression of several viral polyproteins which require the pres-

Table 1 NMR spectroscopic data of didemnaketals **A** (**1**), **D** (**4**), and **E** (**5**).

No.	Didemnaketal **A** (**1**)		Didemnaketal **D** (**4**)		Didemnaketal **E** (**5**)	
	δ_H (J in Hz)[a]	δ_C[a]	δ_H (J in Hz)[b]	δ_C[b]	δ_H (J in Hz)[a]	δ_C[a]
1	-	168.1	-	-	-	176.7
2	-	130.2	-	175.3	-	131.7
3	6.71 ddd (5, 7, 2)	136.1	-	133.1	5.15 t (6.2)	127.2
4	2.49 ddd (16, 5, 5) 2.53 ddd (16, 7, 7)	30.8	5.23 t (6.0)	128.2	2.03 m	33.3
5	4.83 m	72.2	2.24 m, 2.17 m	34.6	3.45 dt (11.6, 7.1)	72.9
6	2.09 m	36.7	3.51 dt (11.5, 7.3)	75.1	2.29 dt (11.6, 6.9)	41.8
7	5.16 dd (9, 2)	72.9	3.00 m	42.2	4.85 t (9.1)	67.9
8	5.22 br t (10)	70.6	4.95 m	69.0	3.95 m	69.3
9	1.24 m, 1.61 m	32.2	4.12 m	70.9	1.64 m, 1.25 m	36.4
10	1.84 m	29.4	1.68 m, 1.23 m	37.9	1.94 m	33.7
11	4.78 dd (6, 6)	78.2	2.26 m	35.5	5.00 m	74.7
12	3.69 m	69.2	5.08 dd (6.5, 6.3)	76.8	3.67 m	73.9
13	0.81 ddd (12, 12, 12) 1.45 br d (13)	34.5	4.08 m	75.5	1.05 m, 0.80 m	36.6
14	1.93 m	24.9	1.27 m, 0.77 m	37.7	1.69 m	25.4
15	0.98 br m 1.67 dd (14, 3)	43.9	1.78 m	27.6	1.62 m, 1.08 m	45.0
16	-	98.4	1.08 m, 1.67 m	46.2	-	98.8
17	1.45 br d (13) 1.59 br d (13)	40	-	100.3	2.10 m, 1.95 m	46.7
18	1.99 m	24.3	2.22 m, 2.07 m	47.6	1.68 m	24.6
19	1.34 br dd (14, 3) 1.71 ddd (14, 11, 5)	31.8	1.75 m	25.8	2.20 m	33.9
20	3.89 ddd (11, 5, 3)	67.5	1.62 m, 1.42 m	37.7	-	99.7
21	4.14 dd (5, 5)	79.1	-	101.5	2.99 d (13.5) 2.80 d (13.5)	41.1
22	-	209.3	3.07 d (14.1) 3.05 d (14.1)	42.3	-	202.6
23	2.32 s	28.1	-	204.4	2.16 s	20.6
24	1.82 s	12.5	2.15 s	21.1	1.63 s	17.0
25	0.98 d	9.8	1.71 s	17.6	-	173.2
26	0.98 d	16.1	-	178.2	0.88 d (6.8)	14.8
27	0.86 d (7)	22.0	0.88 d (6.5)	15.1	0.92 d (6.9)	22.2
28	1.08 m	20.6	0.95 d (7.2)	22.7	0.94 d (6.5)	19.6
29	3.72 s	51.8	0.92 d (6.5)	22.5	3.65 s	51.7
30	-	173.8	3.68 s	55.3	-	170.3
31	2.28 br m	27.5	-	170.4	2.15 m	26.6
32	1.08 m	8.3	2.24 m	26.4	1.05 t (7.5)	7.7
33	-	170.2	1.02 t (6.3)	8.4	-	169.9
34	1.98 s	20.8	-	171.4	2.05 s	21.3
35	-	172.4	2.06 s	21.2	-	173.2
36	2.13 m	43.1	-	178.2	2.15 m	41.8
37	2.04 m	25.2	2.32 m	40.9	2.85 m	33.3
38	0.93 d	22.3	2.90 m	35.4	1.30 d (6.6)	14.3
39	0.93 d	22.4	1.22 d (7.0)	17.5	1.30 d (6.6)	14.3
40	-	172.7	1.22 d (7.0)	17.5	-	168.6
41	2.24 m	43.6	-	172.2	1.98 m	34.2
42	2.08 m	25.5	2.31 m	38.1	1.92 m	30.1
43	0.98 d	22.5	2.03 m	31.1	1.19 d (6.5)	17.2
44	0.98 d	22.5	0.98 (d, 7.0)	20.0	1.19 d (6.5)	17.2
45	-	-	0.98 (d, 7.0)	20.0	4.15 q (6.9)	60.1
46	-	-	3.67 s	51.9	1.25 t (6.9)	14.3
47	-	-	-	172.2	-	-

[a] Recorded in $CDCl_3$ at 400 and 100 MHz.
[b] Recorded in CD_3OD at 500 and 125 MHz.

ence of a virus-specific protease for their maturation. Inhibition of this enzyme results in immature viral particles and inhibition of viral replication *in vitro*. Inhibition of HIV-1 protease is one of the most effective ways to treat AIDS, but the emergence of drug resistant viral strains mandates new approaches.[13] Didemnaketals **A** (**1**) and **B** (**2**) were found to inhibit HIV-1 protease

Table 2 NMR data of didemnaketals **B** (**2**) and **C** (**3**) ($CDCl_3$, 500 and 125 MHz).

No.	Didemnaketal **B** (**2**)		Didemnaketal **C** (**3**)	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1	-	168.0	-	168.0
2	-	130.3	-	130.2
3	6.69 t (7)	135.5	6.66 t (6)	135.9
4	2.47 dt (16, 7) 2.51 dt (16, 5)	30.9	2.41 m, 2.50 m	30.9
5	4.83 m	72.3	4.79 m	72.2
6	1.96 m	37.0	1.93 m	36.9
7	5.12 dd (9, 3)	72.7	5.10 t (9)	72.7
8	5.23 dd (9, 8)	70.6	5.18 m	70.5
9	1.22 m, 1.66 m	32.9	1.14, m, 1.60 m	33.0
10	1.90 m	29.5	1.90 m	29.6
11	4.77 dd (6, 5)	78.6	4.71 t (6)	78.5
12	3.85 m	69.1	3.84 m	69.0
13	0.80 q (14) 1.44 m	35.1	0.78 m, 1.40 m	35.0
14	2.06 m	24.8	2.04 m	24.4
15	1.00 d (7) 1.67 m	44.3	0.96 m	44.3
16	-	98.3	-	98.4
17	1.54 br d (14) 1.64 m	40.7	1.39 m, 1.54 m	40.6
18	1.91 m	24.5	2.05 m	24.7
19	1.12 m 1.58 br d (14)	29.98	1.07 m, 1.56 m	29.6
20	3.87 m	66.6	3.84 m	66.3
21	4.05 d (3)	78.0	4.03 br s	77.6
22	-	133.0	-	133.0
23	5.48 t (7)	126.3	5.41 t (7)	125.9
24	2.08 m, 2.08 m	24.9	1.91 m, 2.04 m	25.1
25	1.25 m, 1.38 m	36.5	1.20 m, 1.39 m	36.2
26	2.00 m,	30.04	1.90 m	29.4
27	2.13 m 2.29 dd (7, 5)	41.5	1.90 m, 2.24 m	41.7
28	-	173.5	-	173.8
29	1.84 s	12.6	1.80 m	12.6
30	0.97 d (7)	9.9	0.94 d (7)	9.9
31	0.98 d (7)	16.2	0.97 d (7)	16.1
32	0.86 d (7)	22.1	0.82 d (6)	22.1
33	1.07 d (6)	20.84	1.04 d (7)	20.8
34	1.62 s	13.3	1.57 br s	13.6
35	0.96 d (7)	19.6	0.91 d (7)	19.5
36	3.73 s	51.8	3.70 s	51.9
37	-	173.7	-	173.3
38	2.35 m, 2.35 m	27.6	2.22 m, 2.28 m	27.6
39	1.09 t (7)	8.9	1.06 t (7)	8.9
40	-	170.1	-	170.3
41	1.98 s	20.77	1.95 s	20.8
42	-	172.3	-	172.4
43	2.13 d (7)	43.2	2.12 m	43.1
44	2.06 m	25.3	2.05 m	25.2
45	0.94 d (6)	22.5	0.90 d (7)	22.5
46	0.94 d (6)	22.5	0.95 d (7)	22.5
47	-	172.7	-	172.8
48	2.25 d (7)	43.7	2.22 m	43.6
49	2.12 m	25.6	2.00 m	25.6
50	0.99 d (6)	22.6	0.90 d (7)	22.5
51	0.99 d (6)	22.6	0.95 d (7)	22.5
52	3.66 s	51.3	4.46 t (7)	59.5
53	-	-	3.17 t (7)	50.0

Table 3 NMR data of didemnaketals **F** (**6**) and **G** (**7**) ($CDCl_3$, 600 and 150 MHz).

No.	Didemnaketal **F** (**6**)		Didemnaketal **G** (**7**)	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1	-	198.5	-	207.2
2	6.11 d (16.5)	133.0	2.61 dd (14.5, 7.3) 2.45 dd (14.5, 7.5)	50.1
3	6.75 dt (16.5, 6.8)	145.8	4.28 quin (7.3)	67.5
4	1.97 m	29.9	1.65 m, 0.87 m	36.1
5	3.45 dt (11.6, 7.3)	72.3	3.45 dt (11.5, 6.9)	72.3
6	2.30 dt (11.6, 6.9)	41.6	2.95 dt (11.6, 6.5)	41.7
7	4.83 t (9.6)	67.9	4.83 t (9.8)	67.9
8	4.30 m	67.5	3.90 m	67.5
9	1.70 m, 1.25 m	36.8	1.75 m, 1.29 m	36.9
10	1.92 m	34.1	1.95 m	33.9
11	5.02 dd (6.8, 6.3)	76.5	5.01 dd (6.5, 6.3)	76.8
12	3.86 m	75.3	3.86 m	75.3
13	1.48 m, 0.88 m	36.1	1.47 m, 0.85 m	36.1
14	1.72 m	25.5	1.70 m	26.6
15	1.62 m, 1.08 m	44.8	1.63 m, 1.08 m	44.7
16	-	98.7	-	98.7
17	1.72 m, 1.56 m	42.0	1.74 m, 1.55 m	41.1
18	1.75 m	24.6	1.75 m	24.6
19	2.15 m, 1.74 m	33.1	2.15 m	32.0
20	-	99.8	-	99.8
21	2.95 m, 2.86 m	41.2	2.85 m, 2.72 m	41.1
22	-	202.5	-	202.5
23	2.19 s	21.3	2.06 s	21.0
24	2.24 s	29.7	2.16 s	31.2
25	-	172.6	-	175.8
26	0.90 d (6.5)	14.8	0.88 d (6.5)	14.8
27	0.91 d (6.8)	22.2	0.92 d (6.8)	22.0
28	0.97 d (6.5)	19.8	0.90 d (6.5)	20.5
29	-	170.5	-	170.2
30	2.16 q (7.3)	26.6	2.18 q (7.3)	26.8
31	1.03 t (7.3)	7.5	1.03 t (6.9)	7.5
32	-	170.2	-	170.5
33	2.05 s	21.0	2.01 s	21.3
34	-	176.6	-	176.6
35	2.13 m	41.8	2.33 m	39.8
36	2.87 m	33.9	2.85 m	33.2
37	1.20 d (6.8)	17.2	1.22 d (6.8)	17.2
38	1.20 d (6.8)	17.2	1.22 d (6.8)	17.2
39	-	168.6	-	168.6
40	2.03 m	33.2	2.05 m	33.1
41	1.97 m	31.2	1.97 m	29.7
42	0.95 d (6.3)	22.0	0.93 d (6.3)	22.2
43	0.95 d (6.3)	22.0	0.93 d (6.3)	22.2
44	4.11 q (6.8)	60.4	3.64 s	51.8
45	1.27 t (6.8)	14.3		

with an IC_{50} of 2 and 10 μM, respectively.[10] So, several synthetic studies of the didemnaketals especially **A** (**1**) have been conducted to determine the structural components necessary for activity; as well as stable analogs that may provide a unique and potent mode of HIV-1 protease inhibition by an unusual mechanism.[13] Unfortunately, didemnaketal **C** (**3**) did not inhibit HIV-1 in a peptidolysis assay.[14,17]

4.2. Protein kinase inhibitory activity

Didemnaketals **D** (**4**) and **E** (**5**) displayed moderate protein kinase inhibitory activity against CDK5, CK1, DyrK1A and, GSK3 at concentration 10 μg/mL. The IC_{50} of both compounds were higher than 10 μg/mL. Such activity is not sufficient to pursue with these compounds into the *in vivo* studies.[8]

4.3. Antimicrobial activity

Didemnaketals **D** (**4**) and **E** (**5**) were evaluated for their antimicrobial potential against Gram-positive bacteria, Gram-negative bacteria, and yeast using the disk diffusion method. Didemnaketal **D** (**4**) showed moderate activity (11 mm, inhibition zone) toward *Staphylococcus aureus* ATCC 6538, while didemnaketal **E** (**5**) showed moderate activity (11 mm, inhibition zone) against *Bacillus subtilis* ATCC CC33.[8] While, didemnaketal **F** (**6**) showed strong antimicrobial activity against *Escherichia coli* ATCC 25922 and *Candida albicans* ATCC 14053 with inhibition zones of 20 and 24 mm at a concentration of 100 μg/disk. Didemnaketal **G** (**7**) showed moderate activity against *C. albicans* with an inhibition zone of 17 mm at the same concentration.[11]

4.4. Antiproliferative and cytotoxic activities

Didemnaketals **F** (**6**) and **G** (**7**) displayed moderate antiproliferative activity against HeLa cells with IC_{50s} of 49.9 and 14.0 μM, respectively using sulforhodamine B (SRB) assay. In contrast, cytotoxic effects were not observed with didemnaketal **F** (**6**) at concentrations up to 50 μM compared with paclitaxel as a positive control (IC_{50} of 0.0017 μM).[11]

5. Spectral data

Didemnaketal **A** (**1**): Clear oil; $[\alpha]_D$ −11.0° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3490, 1735, 1712 cm^{-1}; HRFABMS *m*/*z* 825.5030 (calcd for $C_{44}H_{73}O_{14}$, $[M + H]^+$, 825.5000).[10]

Didemnaketal **B** (**2**): Clear oil; IR ($CHCl_3$) ν_{max} 3500, 1735, 1710 cm^{-1}; HRFABMS *m*/*z* 933.5951 (calcd for $C_{52}H_{85}O_{14}$, $[M - OH]^+$, 933.59393).[10,16]

Didemnaketal **C** (**3**): Colorless oil; $[\alpha]_D$ + 48 (*c* 0.067, CH_2Cl_2); UV (CH_3CN) λ_{max} 213 nm; IR (film) ν_{max} 3440, 2955, 1740, 1715 cm^{-1}; HRFABMS *m*/*z*: 1067.5522 (calcd for $C_{53}H_{88}O_{18}SNa$, 1067.5589).[9]

Didemnaketal **D** (**4**): Colorless oil, $[\alpha]_D$ −51.9° (*c* 1.5, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 246 (4.08) nm; IR (KBr) ν_{max} 1732, 1715, 1296, 1050 cm^{-1}; HRESIMS *m*/*z* 911.4923 (calcd for $C_{47}H_{75}O_{17}$, $[M + H]^+$, 911.4926).[8]

Didemnaketal **E** (**5**): Colorless oil, $[\alpha]_D$ −46.3° (*c* 1.5, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 234 (4.18) nm; IR (KBr) ν_{max} 3495, 1735, 1710, 1291, 1056 cm^{-1}; HRESIMS *m*/*z* 883.5029 (calcd for $C_{46}H_{75}O_{16}$, $[M + H]^+$, 883.5027).[8]

Didemnaketal **F** (**6**): Colorless oil; $[\alpha]_D$ − 72.8° (*c* 1.5, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 252 (3.93) nm; IR (film) ν_{max} 3460, 1735, 1720, 1675, 1650, 1070 cm^{-1}; HRESIMS *m*/*z* 853.4950 (calcd for $C_{45}H_{73}O_{15}$ $[M + H]^+$, 853.4949).[11]

Didemnaketal **G** (**7**): Colorless oil; $[\alpha]_D$ −85.7° (*c* 1.5, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 258 (3.86) nm; IR (film) ν_{max} 3465, 1731, 1718, 1065 cm^{-1}; HRESIMS *m*/*z* 857.4899 (calcd for $C_{44}H_{73}O_{16}$, $[M + H]^+$, 857.4898).[11]

6. Conflict of interest

None.

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