

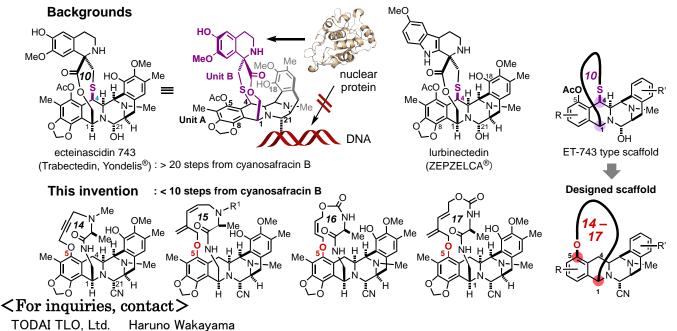
## ≪ TETRAHYDROISOQUINOLINE ALKALOIDAL COMPOUNDS WITH MACROCYCLIC SCAFFOLD EXHIBITING ANTI-TUMOR ACTIVITIES≫

#### <Invention Overview>

#### Tetrahydroisoquinoline Alkaloids

Ecteinascidin743 (ET-743), a natural product isolated from a marine sponge, has been clinically applied as an antitumor agent (Trabectedin, the trade name "Yondelis"). Structurally, ET-743 can be divided into 2 parts, a core scaffold (unit A) consisting of two tetrahydroisoquinoline (THIQ) rings, and a 10-membered macrolactone ring with an additional THIQ moiety (unit B). Unit A recognizes DNA duplexes through hydrogen bonds and alkylates at minor groove of DNA sequence-selectively. Unit B, meanwhile, is thought to inhibit the approach of nucleic proteins (e.g., transcription factor, DNA-repair proteins) to DNA, and thereby inducing DNA double-strand break and cell death. A synthetic derivative, lurbinectedin (ZEPZELCA), bearing a tetrahydro-6-carboline ring in place of the THIQ ring on unit B, has also been approved as a chemotherapeutic agent for small cell lung cancer. Based on the structural and mechanistic insights into the potent and unique anti-cancer agent ET-743, diversification of unit B is a promising approach to generate novel antitumor agents targeting DNA-protein interactions. However, the commercialized semisynthetic process of ET-743 requires more than 20-step chemical conversions starting from cyanosafracin B obtained from microbial cultures, which makes it difficult to modify the structure of unit B.

Exploiting our experimental findings, we designed an unnatural, novel macrocyclic scaffold connecting C1 and C5 hydroxyl group of unit A, instead of C4 position in ET-743. This design enabled rapid synthesis of a series of drug lead candidates ranging from 14 to 17 membered macrocycles exhibiting comparable antitumor activity with ET-743. This versatile synthetic platform with significantly fewer number of steps also allowed flexible modification of unit B by just a single step appendage reaction (such as [4+2] cycloaddition).



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#### Evaluation of anti-cancer activity

These structurally simplified macrocyclic compounds can be synthesized within 10 steps in a time- and cost-efficient manner. Antitumor activities (GI<sub>50</sub> values) of the synthetic compounds were evaluated against 39 cancer cell lines (JFCR39). Most of the macrocyclic compounds generated in this invention exhibit superior antitumor activities compared to the natural product, cyanosafracin B and synthetic intermediates without the macrocyclic scaffold. Notably, several synthetic compounds (e. g. TFR5) exhibited very potent antitumor activity comparable to approved drugs, ET-743 and lurbinectedin.

						MeO
	More potent ac rather tha approved dr	n			HO MeO O HO HO HO HO HO HO Me Me S H H N Me Me Me Me Me Me Me Me	HN = HO =
			inver	nted compound (TFR5)	ecteinascidin 743 (Yondelis®)	lurbinectedin (ZEPZELCA <sup>®</sup> )
	<b>GI<sub>50</sub>:</b> 50% gro inhibitory concer			GI <sub>50</sub>	GI <sub>50</sub>	GI <sub>50</sub>
I	Breast	MCF-7		0.67 nM	2.6 nM	1.7 nM
(	cancer cell lines	MDA-M	B-231	2.3 nM	3.9 nM	3.4 nM
(	Colorectal	HT-29		2.0 nM	9.8 nM	2.4 nM
(	cancer cell lines	HCT-11	6	2.4 nM	4.9 nM	6.4 nM
	Lung cancer cell lines	NCI-H2 NCI-H4		2.6 nM 2.8 nM	2.1 nM 1.8 nM	5.3 nM 1.5 nM

Modification of macrocyclic structure (unit B) of ET-743 allowed development of the systematic collections of novel anti-tumor drug candidates. This synthetic platform rapidly generates more than 10 kinds of skeletally diverse macrocyclic compounds capable of further structural modifications exploiting the preinstalled functional groups (secondary amine, conjugated diene, and alkyne). The versatile and flexible synthetic platform enables rational structural diversification of the complex macrocyclic structures, while maintaining potent antitumor activities with inhibition of DNA–nuclear protein interactions.

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### <Public Information>

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#### Supplemental Data

Table1 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

1				MeO	
		_0_0	HONO		OMe HO Me
4		NH OMe	Meo NH OMe		Ω HHLI
		OT Me Me	O HO Me	A CMe	Me NJ-Me
		Ma SINH H		AcO S H	MeO
		T T N-Me	N-Me	Mo N-J-Me	O L CN NH
	and the second	Q Y H		OR AN H	O Me
Example 1     A second		V–Ò Ĥ ĈN	ecteinascidin 743	V-0 R OH	NH <sub>2</sub>
í i i i i i i i i i i i i i i i i i i i	HBC-4	, 28	Cocomusoidan 140	idi bii loocodii i	cyanosafracin B(1) <b>59</b>
breast	BSY-1	19			34
cancer cells	HBC-5	79			62
	MCF-7	17	2.6	1.7	52
	MDA-MB-231	32	3.9	3.4	130
central	U251	39			370
nervous	SF-268	89			370
	SF-295	240			500
system	SF-539	35			180
cancer cells	SNB-75	61			150
	SNB-78	45			63
	HCC2998	69	the second second	. · ·	350
1	KM-12	58			530
colorectal	HT-29	58	9.8	2.4	190
cancer cells	HCT-15	310			390
	HCT-116	51	4.9	6.4	290
	NCI-H23	140	2.1	5.3	290
	NCI-H226	260	£1	. 0.0	310
	NCI-H522	21			43
lung	NCI-H460	270	1.8	1.5	400
cancer cells	A549	480	1.0	1.3	1600
( ,	DMS273	480	10.4	د.۱	270
· · · · · · · · · · · · · · · · · · ·	DMS114	14			35
melanoma cells		19			61
	OVCAR-3	41			130
cervical	OVCAR-4	390			290
cancer cells	OVCAR-5	240			390
	OVCAR-8	200			290
	SK-OV-3	420			540
kidney cancer cells	RXF-631L	240			400
mulley cancel cells	ACHN	300			320
	St-4	300			430
	MKN1	36			52
gastric	MKN-B	280			170
cancer cells	MKN-A	260			250
	MKN45	47			300
1	MKN74	370	· · · · · · · · · · · · · · · · · · ·		310
prostate	DU-145	430			490
cancer cells	PC-3	240			290
cancer cens	<u> </u>	240			250



### Table2 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

<ul> <li>A mention of the second respective second sec</li></ul>	and the second sec	<u>^</u>		MeÓ	
		NH HO OME			
		Me N-I-Me	Me N-Me	Ma N-Me	Ğ L ČN " NH
		O H CN	<u>-</u> о н он н		o <sup>™</sup> ), <sup>,Me</sup> NH₂
		13	ecteinascidin 743	lurbinectedin	cyanosafracin B(1)
	HBC-4	120			59
breast	BSY-1	32			34
cancer cells	HBC-5 MCF-7	<u>92</u> 50	2.6	1.7	<u>62</u> 52
	MDA-MB-231	95	2.0	3.4	130
·	U251	220		J.+	370
central	SF-268	350			370
nervous	SF-295	490			500
system	SF-539	120			180
cancer cells	SNB-75	120			150
cancer cens	SNB-78	100			63
	HCC2998	250			350
	KM-12	290			530
colorectal	HT-29	200	9.8	2.4	190
cancer cells	HCT-15	1500			390
	HCT-116	220	4.9	6.4	290
	NCI-H23	350	2.1	5.3	290
	NCI-H226	530			310
lung	NCI-H522	40			43
	NCI-H460	620	1.8	1.5	400
cancer cells	A549	3400	10.4	1.3	1600
	DMS273	320	· · · · · · · · · · · · · · · · · · ·		270
	DMS114	37			35
melanoma cells		57 290			61
	OVCAR-3 OVCAR-4	1400			130 290
· cervical	OVCAR-4	580		·····	390
cancer cells	OVCAR-8	310		· · · · · · · · · · · · · · · · · · ·	290
	SK-OV-3	440			540
	RXF-631L	460			400
kidney cancer cells	ACHN	520	in the estimation of the second se		320
	St-4	420	····	· · · · · · · · · · · · · · · · · · ·	430
	MKN1	220			52
gastric	MKN-B	360			170
cancer cells	MKN-A	540			250
	MKN45	250			300
	MKN74	280			310
prostate	DU-145	830			490
cancer cells	PC-3	450			290

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## Table3 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

2 - 6 - 6 - 6 - 6 - 6 - 6 - 6 - 6 - 6 -	alinan ang ang ng mina ng sing T	O H	HQ	MeO	<b>О</b> Ме
			LI.NH		
			MeD 0= HO Me	N Me	Mo N-Me
		Me NH H	Avo S H	ADO S H H	MeD T N H
		N. N. N.		Ma N-Ma	NH A Me
		V-O Ĥ ĈN	"–о́й о́н"		O" )"""" NH <sub>2</sub>
-		14	ecteinascidin 743	lurbinectedin	cyanosafracin B(1)
	HBC-4	19			59
breast	BSY-1 HBC-5	10 15			34
cancer cells	MCF-7	10	<u></u> 	4 7	<u>62</u> 52
		10	2.6	1.7	130
	MDA-MB-231 U251	27	3.9	3,4	370
central	SF-268	39			370
nervous	SF-295	49			500
system	SF-539	17			180
1 · · · · · · · · · · · · · · · · · · ·	SNB-75	14			150
cancer cells	SNB-78	34			63
	HCC2998	34	<u> </u>		350
colorectal	KM-12	30			530
	HT-29	22	9.8	2.4	190
cancer cells	HCT-15	98			390
	HCT-116	23	4.9	6.4	290
	NCI-H23	34	2.1	5.3	290
	NCI-H226	38			310
lung	NCI-H522	10			43
cancer cells	NCI-H460	57	1.8	1.5	400
Cancer Cens	A549	280	10.4	1.3	1600
	DMS273	29			270
	DMS114	10			35
melanoma cells		12			61
	OVCAR-3	25 38			130
cervical	OVCAR-4 OVCAR-5				<u> </u>
cancer cells	OVCAR-8	34	· · · · · · · · · · · · · · · · · · ·	· · ·	290
	SK-OV-3	59			540
<u> </u>	RXF-631L	48			400
kidney cancer cells	ACHN	38			320
	St-4	36			430
*	MKN1	26			52
gastric	MKN-B	34			170
cancer cells	MKN-A	54			250
]	MKN45	21			300
La serie de la	MKN74	41			310
prostate	DU-145	52			490
cancer cells	PC-3	47			290



## Table4 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

- A second secon	dan orang series and a source of	Ph O		MeO	
		N-P o	HO		OMe HO、人,Me
		OHN N TOTO	Med		9 .H.I
		Men NH OMe	O= HO Me	A Ma OMa	Me N-Me
		HO Me	Aug S H H	ACO S. H	MeO N H
		Me NH H	We I I N N-Me	Me N-Ma	OLCN NH
		- Alling "		of the ty	O <sup>st</sup> y Me
	1. A.	∿-Ó Ĥ ĆN	ecteinascidin 743	V-O H OH Iurbinectedin	NH <sub>a</sub> cyanosafracin B(1)
<b></b>	HBC-4	15	Ecternascidar 745	I DI DI I OCCOURT	59
	BSY-1	3.1			34
breast	HBC-5	6.9			
cancer cells			0.0		62
	MCF-7	4.4	2.6	1.7	52
	MDA-MB-231	6.7	3.9	3.4	130
central	U251	5.8			370
1	SF-268	13			370
nervous	SF-295	29	the second second second		500
system	SF-539	8.2			180
cancer cells	SNB-75	9.9			150
Cancel Cella	SNB-78	7.5			63
	HCC2998	17			350
	KM-12	14			530
colorectal	HT-29	7.3	9.8	2.4	190
cancer cells	HCT-15	43			390
	HCT-116	9.3	4.9	6.4	290
	NCI-H23	20	2.1	5.3	290
	NCI-H226	25		0.0	310
	NCI-H522	2.4			43
lung	NCI-H460	36	1.8	1.5	400
cancer cells	A549	51	10.4	1.3	1600
			{U.4	<u>c'i</u>	270
and the second second	DMS273	15			
	DMS114	3.8			35
melanoma cells		3.3			61
	OVCAR-3	6.4			130
cervical	OVCAR-4	38			290
	OVCAR-5	31			390
cancer cells	OVCAR-8	21			290
	SK-OV-3	34			540
kidney cancer cells	RXF-631L	35			400
Muney cancer cells	ACHN	25			320
	St-4	37			430
	MKN1	4.8			52
gastric	MKN-B	30			170
cancer cells	MKN-A	29			250
	MKN45	7.1			300
1	MKN74	32		· · ·	310
prostate	DU-145	41			490
cancer cells	PC-3	26			290
	<u> </u>	20			200

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## Table5 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

and a second second of the	and the second second	Ph o		MeO	
Low Section 1997		N-4	HO		OMe HO
		07070	Meo NH OMA		а чну I
		Men NH OMA	0 HO Me	MX OMe	Me N Me
					MeO I N H
		Mo N-Mo	III N N-Me	Me N-Me	NH NH
		OF NA		of the H	O <sup>2</sup> Me
in the second		∿O H CN 18	ecteinascidin 743	∿о́н́о́н'' lurbinectedin	่งั∺₂ cyanosafracin B(1)
· · · · · · · · · · · · · · · · · · ·	HBC-4	30	eucentasolain 740	idi bine decidani	59
	BSY-1	19			34
breast	HBC-5	38			62
cancer cells	MCF-7	22	0.0	4 7	52
	en la signa la conserva-		2.6	1.7	130
<u> </u>	MDA-MB-231	41	3.9	3.4	
central	U251	50			370
4	SF-268	74			370
nervous	SF-295	300			500
system	SF-539	33			180
cancer cells	SNB-75	50			150
canoci ociis	SNB-78	40			63
	HCC2998	95			350
	KM-12	100			530
colorectal	HT-29	72	9.8	2.4	190
cancer cells	HCT-15	630			390
	HCT-116	74	4.9	6.4	290
	NCI-H23	110	2.1	5.3	290
	NCI-H226	280			310
	NCI-H522	20			43
lung	NCI-H460	260	1.8	1.5	400
cancer cells	A549	540	10.4	1.3	1600
	DMS273	100	10.4	1.0	270
	DMS114	12			35
melanoma cells	LOX-IMVI	27			61
	OVCAR-3	43			130
	OVCAR-4	350			290
cervical	OVCAR-5	280		· · · · · · · · · · · · · · · · · · ·	390
cancer cells	OVCAR-3	130		· · · · · · · · · · · · · · · · · · ·	290
				· · ·	
	SK-OV-3	410			540
kidney cancer cells	RXF-631L	310			400
	ACHN	240			320
	St-4	300		· · ·	430
	MKN1	50			52
gastric	MKN-B	160			170
cancer cells	MKN-A	210			250
	MKN45	78			300
	MKN74	120			310
prostate	DU-145	330			490
cancer cells	PC-3	170			290





 Table6 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

 TFR5

	n y				
			есteinascidin 743	Me O H OH lurbinectedin	NH of 1 <sup>.Me</sup> NM <sub>2</sub> cyanosafracin B(1)
	HBC-4	1.5			59
breast	BSY-1	0.60			34
	HBC-5	1.8			62
cancer cells	MCF-7	0.67	2.6	1.7	52
19	MDA-MB-231	2.3	3.9	3.4	130
	U251	1.4			370
central	SF-268	2.8			370
nervous	SF-295	3.4			500
system	SF-539	1.3			180
cancer cells	SNB-75	1.3			150
	SNB-78	3.1			63
	HCC2998	2.8			350
	KM-12	3.1			530
colorectal	HT-29	2.0	9.8	2.4	190
cancer cells	HCT-15	3.9			390
	HCT-116	2.4	4.9	6.4	290
	NCI-H23	2.6	2.1	5.3	290
	NCI-H226	2.5			310
lung	NCI-H522	0.60			43
lung	NCI-H460	2.8	1.8	1.5	400
cancer cells	A549	3.4	10.4	1.3	1600
	DMS273	1.1			270
	DMS114	0.89			35
melanoma cells	LOX-IMVI	0.59			61
	OVCAR-3	2.6			130
cervical	OVCAR-4	3.5			290
	OVCAR-5	3.2			390
cancer cells	OVCAR-8	2.6			290
	SK-OV-3	5.7			540
kidney cancer cells	RXF-631L	3.1			400
Mulley Galloer Cells	ACHN	2.2			320
	St-4	3.8			430
	MKN1	2.3			52
gastric	MKN-B	3.0			170
cancer cells	MKN-A	3.5		a a ser a ser en este	250
	MKN45	1.3	an a s		300
	MKN74	3.7			310
prostate	DU-145	3.5			490
cancer cells	PC-3	3.0			290

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## Table7 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

			10	MeQ	OMe
		Me OMe	HO	$\Delta $	HO Me
		HOLMO		A XNH ONNO	Me H
		Me NH H	ACO OS H		Meo
		N. N-Me	Me N-Me	Me N-Me	Ó CNÍ NH
		CO H CN		of the the	0 <sup></sup> ,Me
en an an Arabana Arabana	entra da cara da seria. Natura da cara da seria da ser	33	ecteinascidin 743	чо н он lurbinectedin	้งห <sub>่อ</sub> cyanosafracin B(1)
	HBC-4	32		10101100000	59
L	BSY-1	18			34
breast	HBC-5	40			62
cancer cells	MCF-7	26	2.6	1.7	52
	MDA-MB-231	52	3.9	3.4	130
	U251	55			370
central	SF-268	110			370
nervous	SF-295	270			500
system	SF-539	46			180
	SNB-75	96			150
cancer cells	SNB-78	83			63
	HCC2998	140			350
	KM-12	110			530
colorectal	HT-29	86	9.8	2.4	190
cancer cells	HCT-15	400			390
	HCT-116	87	4.9	6.4	290
	NCI-H23	93	2.1	5.3	290
	NCI-H226	260		· .	310
· lung	NCI-H522	25			43
lung	NCI-H460	260	1.8	1.5	400
cancer cells	A549	360	10.4	1.3	1600
	DMS273	140			270
and the second second	DMS114	31			35
melanoma cells	EOX-IMVI	31			61
	OVCAR-3	70			130
cervical	OVCAR-4	400			290
	OVCAR-5	310			390
cancer cells	OVCAR-8	180			290
	SK-OV-3	500			540
kidney cancer cells	RXF-631L	300			400
maney current cond	ACHN	260			320
	St-4	270			430
1	MKN1	68			52
gastric	MKN-B	220		1	170
cancer cells	MKN-A	330			250
	MKN45	41			300
	MKN74	260			310
prostate	DU-145	370			490
cancer cells	PC-3	190			290



Table8 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

	Second records and the second			MeQ	
			HO		OMe HQ: 人 Me
			Neo NH OMe	YI NH	Ma I HH
		NH HUIT	0= HO Me		TT Me
		Me N-I-Me	Me	ACOQ SH HILT	MeD T TH
		N. K.		Me I I M-Me	NH Ma
		Ň⊶Ó Ĥ ČN	ĩ⊷ó h ỏн″		O" \""" Nita
		35	ecteinascidin 743	lurbinectedin	cyanosafracin B(1)
	HBC-4	2.2			59
breast	BSY-1	1.3			34
	HBC-5	2.7			62
cancer cells	MCF-7	0.87	2.6	1.7	52
	MDA-MB-231	2.7	3.9	3.4	130
· · ·	U251	2.5			370
central	SF-268	3.3			370
nervous	SF-295	3.8			500
system	SF-539	2.2	· · ·		180
cancer cells	SNB-75	1.7			150
cancer cens	<b>SNB-78</b>	3.4			63
	HCC2998	3.6			350
	KM-12	3.8			530
colorectal	HT-29	3.2	9.8	2.4	190
cancer cells	HCT-15	4.5			390
	HCT-116	2.7	4.9	6.4	290
	NCI-H23	3.5	2.1	5.3	290
1	NCI-H226	2.7			310
lung	NCI-H522	1.1			43
	NCI-H460	3.4	1.8	1.5	400
cancer cells	A549	7.2	10.4	1.3	1600
	DMS273	2.5			270
and the second second	DMS114	1.2			35
melanoma cells		1.7			61
	OVCAR-3	3.2			130
cervical	OVCAR-4	3.6	the state of the s	and the second	290
	OVCAR-5	3.3			390
cancer cells	OVCAR-8	3.1			290
1	SK-OV-3	6.5			540
	RXF-631L	2.9			400
kidney cancer cells	ACHN	3.1			320
	St-4	3.8			430
1	MKN1	2.7			52
gastric	MKN-B	3.5			170
cancer cells	MKN-A	3.7			250
1 :	MKN45	2.7	·		300
	MKN74	4.5			310
prostate	DU-145	3.8			490
cancer cells	PC-3	3.3	L		290
		<u> </u>			∠30



### Table9 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

		∬ Me	HO	Meo	QMe
					HO I HA
		O N CO OMe	MED NH OME		9 HIT
		HO	O= HOMO	А Сме	Me N-Me
		Me NH H	Aco S H	Acon S. H	Meo
		L.L.N. P-Me	TIN M-Me	Me A A A A	OL CN NH
		U / I I H -O H CN			or Ma
		36	ecteinascidin 743	∿–о́н́о́н lurbinectedin	NH₂ cyanosafracin B(1)
	HBC-4	3.5		IOI DI LEGCEURI	59
·	BSY-1	3.3			34
breast	HBC-5	7.6			62
cancer cells	MCF-7	2.9	2.6	1.7	52
	and the second s	4.4	3.9	3.4	130
N.	<u>4DA-MB-231</u> U251	4.4	2.8	J.4	370
central	SF-268				
4		6.3		:	370
nervous	SF-295	17			500
system	SF-539	4.3			180
cancer cells	SNB-75	7			150
-	SNB-78	5.7			63
	HCC2998	6.9			350
colorectal	KM-12	9			530
	HT-29	5.7	9.8	2.4	190
cancer cells	HCT-15	29			390
. 1	HCT-116	5.9	4.9	6.4	290
	NCI-H23	13	2.1	5.3	290
	NCI-H226	23			310
lung	NCI-H522	2.4			43
lung	NCI-H460	30	1,8	1.5	400
cancer cells	A549	38	10.4	1.3	1600
	DMS273	6.8			270
	DMS114	3			35
melanoma cells	LOX-IMVI	2.8			61
	OVCAR-3	4.8		· · · ·	130
	OVCAR-4	25			290
0011100	OVCAR-5	20		·····	390
	OVCAR-8	7.9			290
	SK-OV-3	25			540
	RXF-631L	39			400
kidney cancer cells	ACHN	22			320
	ACHN St-4	25			430
	MKN1	4.1	Charles and the second s	<u> </u>	<u>430</u> 52
gastric	the family halfs of a party should need to be	25			<u>52</u> 170
cancer cells	MKN-B			:	
	MKN-A	15			250
	MKN45	4.2		· · · · · · · · · · · · · · · · · · ·	300
	MKN74	20			310
prostate	DU-145	32			490
cancer cells	PC-3	17			290



Table10 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

1	a sa san sa marana na sa				
		HO Me	HO	Meg	OMe HO. J. Me
	1. T	о <sub>н</sub> н∑≬	MeO NH OMe		9 HHLI
		Me N-Me	O= HO Me	HO. A Me	Me NJ Me
		Q N H	Me H	ACO S H H	MeO T H
			N N N	Me N-T-Me	NH
	The Area and	OS WHE	. <u>-o</u> Ĥ ÔH		o∽, Me NHa
		37 Me <sup>-NH</sup>	ecteinascidin 743	lurbinectedin	cyanosafracin B(1)
	HBC-4	42			59
breast	BSY-1	26			34
	HBC-5	100			62
cancer cells	MCF-7	33	2.6	1.7	52
	MDA-MB-231	77	3.9	3.4	130
o o natural	U251	110			370
central	SF-268	250			370
nervous	SF-295	460			500
system	SF-539	69			180
cancer cells	SNB-75	100			150
	SNB-78	92			63
A second second	HCC2998	210			350
colorectal	KM-12	200			530
	HT-29	93	9.8	2.4	190
cancer cells	HCT-15	480			390
	HCT-116	140	4.9	6.4	290
	NCI-H23	270	2.1	5.3	290
	NCI-H226	280			310
lung	NCI-H522	28			43
cancer cells	NCI-H460	410	1.8	1.5	400
	A549	1500	10.4	1.3	1600
	DMS273	270	e de la composición d		270
	DMS114	29			35
melanoma cells		40			61
	OVCAR-3	160			130
cervical	OVCAR-4	450			290
cancer cells	OVCAR-5	440	and the second second		390
	OVCAR-8	230			290
	SK-OV-3	580			<u>540</u> 400
kidney cancer cells	RXF-631L	370 260			320
		400			430
and the second second	St-4 MKN1	220			430 52
gastric	MKN-B	340			<u>52</u> 170
	MKN-A	340			250
cancer cells	MKN45	180			300
	from the second second second	330			310
prostate	MKN74 DU-145	440			490
cancer cells	PC-3	350			290
	<u>: ୮୦-୬</u>	300	1		£30 ]



 $\label{eq:table11} \mbox{Table11}: antitumor activity \ [nM] of \ Compound \ 29 \ (GI_{50} \ value: \ 50\% \ growth \ inhibitory \ concentration)$ 

			есteinascidin 743	Urbinectedin	orr <sup>NH</sup> orr <sup>Ma</sup> NH₂ cyanosafracin B(1)
	HBC-4	4z <10	ecternascium 743	larbinectedin	59
	BSY-1	<10			34
breast	HBC-5	17			62
cancer cells	MCF-7	<10	2.6	1.7	52
	MDA-MB-231	<10	3.9	3.4	130
	U251	13			370
central	SF-268	27			370
nervous	SF-295	38			500
system	SF-539	17			180
	SNB-75	<10			150
cancer cells	SNB-78	11			63
	HCC2998	18			350
م م ام سم م ام م	KM-12	19			530
colorectal	HT-29	13	9.8	2.4	190
cancer cells	HCT-15	47			390
	HCT-116	21	4.9	6.4	290
	NCI-H23	31	2.1	5.3	290
	NCI-H226	30			310
	NCI-H522	<10			43
lung	NCI-H460	22	1.8	1.5	400
cancer cells	A549	110	10.4	1.3	1600
	DMS273	16			270
	DMS114	<10			35
melanoma cells		<10		<b></b>	61
	OVCAR-3	15			130
cervical	OVCAR-4	55	<u> </u>		290
	OVCAR-5	47			390
cancer cells	OVCAR-8	34	······································		290
	SK-OV-3	49	······································		540
111 11	RXF-631L	34			400
kidney cancer cells	ACHN	42			320
	St-4	37	·····		430
	MKN1	18			52
gastric	MKN-B	25			170
cancer cells	MKN-A	36			250
Cancer Cens	MKN45	16			300
	MKN74	35	налогиалыкта алар калдаа родунт котого, старовала парт прарту у адо	л алардого кара токи телено у малекратара. У така то архитекат на алуче	310
prostate	DU-145	58			490
cancer cells	PC-3	40			290



Table12 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

þ	4	MeQ au			
					HO HH HO Me HO HH HO Me HH HHO No HH
		Me N-Me O H CN	Me NMe N H O H OH		
		44	ecteinascidin 743	lurbinectedin	cyanosafracin B(1)
	HBC-4	<10			59
breast cancer cells	BSY-1	<10			34
	HBC-5	<10			62
	MCF-7	<10	2.6	1.7	52
	MDA-MB-231	<10	3.9	3.4	130
central nervous system cancer cells	U251	<10			370
	SF-268	<10			370
	SF-295	<10			500
	SF-539	<10			180
	SNB-75	<10			150
	SNB-78	<10			63
colorectal cancer cells	HCC2998	<10			350
	KM-12	<10			530
	HT-29	<10	9.8	2.4	190
	HCT-15	<10			390
	HCT-116	<10	4.9	6.4	290
	NCI-H23	<10	2.1	5.3	290
	NCI-H226	<10			310
l	NCI-H522	<10			43
lung	NCI-H460	<10	1.8	1.5	400
cancer cells	A549	<10	10.4	1.3	1600
	DMS273	<10			270
	DMS114	<10		······································	35
melanoma cells		<10			61
	OVCAR-3	<10			130
cervica	OVCAR-4	<10			290
	OVCAR-5	<10			390
cancer cells	OVCAR-8	<10		······································	290
	SK-OV-3	<10			540
kidney cancer cells	RXF-631L	<10			400
	ACHN	<10			320
gastric cancer cells	St-4	<10			430
	MKN1	<10			52
	MKN-B	<10			170
	MKN-A	<10			250
	MKN45	<10			300
	MKN74	<10			310
prostate	DU-145	<10	·····	······································	490
cancer cells	PC-3	<10			290
	<u> </u>				290



Table13 :antitumor activity [nM] of Compound 29 (GI<sub>50</sub> value: 50% growth inhibitory concentration)

···· · · · · · · ·		N CH O	HO	MeO	OMe HO
444-11-1 4			MeD OHe OMe		Me H N-j-Me
			Acto o S H H	ACO O S H H	MeO H
		No No Me		Mo NMe	NH Me
		V-0 H CN	V-0 Ĥ ÕH ``	0 7 7 7 7 H 0 H OH	
r	HBC-4	47 200	ecteinascidin 743	lurbinectedin	cyanosafracin B(1) 59
breast cancer cells	BSY-1	150			34
	HBC-5	300			62
	MCF-7	63	2.6	1.7	52
	MDA-MB-231	160	3.9	3.4	130
· · · ·	U251	350			370
central	SF-268	620			370
nervous	SF-295	1800			500
system	SF-539	290			180
cancer cells	SNB-75	330			150
	SNB-78	260			63
	HCC2998	410			350
colorectal	KM-12	450			530
cancer cells	HT-29	490	9.8	2.4	190
	HCT-15	2200			390
	HCT-116	450	4.9	6.4	290
	NCI-H23	850	2.1	5.3	290
	NCI-H226	2300	<u></u>	·····	310
lung	NCI-H522 NCI-H460	29	1.0	4 5	43
cancer cells	A549	630 3900	<u> </u>	1.5	400
	DMS273	450	10.4	[]	270
	DMS273	31			35
melanoma cells	LOX-IMVI	160	·····	<u></u>	61
	OVCAR-3	330			130
	OVCAR-4	3500			290
cervical	OVCAR-5	2800	*****		390
cancer cells	OVCAR-8	1100			290
	SK-OV-3	3900			540
	RXF-631L	2100			400
kidney cancer cells	ACHN	2800			320
gastric cancer cells	St-4	2200			430
	MKN1	290			52
	MKN-B	730			170
	MKN-A	1400			250
	MKN45	470			300
	MKN74	1600			310
prostate	DU-145	3900			490
cancer cells	PC-3	1500			290