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Total synthesis and cytotoxicity of (−)-jorumycin and its analogues

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ABSTRACT

(−)-Jorumycin and its 15 C-22 analogues were prepared employing L-tyrosine as the chiral starting material via 21 steps. These analogues, along with (−)-jorumycin itself, were evaluated in vitro for cytotoxicity against HCT-8, BEL-7402, Ketr3, A2780, MCF-7, A549, BGC-823, Hela, HELF, and KB cells. The IC_{50} values of the cytotoxicity of most of these analogs were at the level of nM, which was similar to that of (−)-jorumycin. Among these analogs including (−)-jorumycin, hippuric acid ester derivative **23** exhibited the most potent and broad-spectrum cytotoxic activity against the ten cell lines with an average IC_{50} of 2.12 nM.

1. Introduction

Isoquinoline marine alkaloids belong to a family of natural products consisting of about sixty members, which have interesting biological activities including cytotoxicity and antimicrobial activity.[1] Among these natural products, Ecteinascidin 743 (Et-743), an exceedingly potent antitumor compound, which was isolated from the marine tunicate *Ecteinascidia turbinate*, has received marketing authorization from the European commission for the treatment of advanced soft-tissue sarcomas[2] (Fig. 1).

(−)-Jorumycin, which is structurally related to the renieramycins, the ecteinascidins and the saframycins, was isolated from the mantle and mucus of the pacific nudibranch *jorunna funebris*.[3] In particular the structure of jorumycin is very similar to that of renieramycin M, which was isolated from the Thai sponge *Xestospongia* sp. Both of them showed very potent cytotoxic activity against a panel of human tumor cell lines.[4] Although there have been several reports on the total synthetic studies of these two natural products, only R. M. Williams' group and Zhu's group have finished the total synthesis of (−)-Jorumycin up to now.[5] Further-

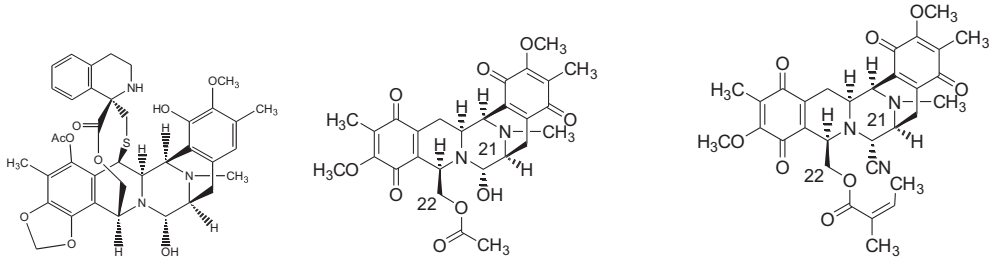

Fig. 1. Structures of Et-743, jorumycin and renieramycin M.

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more, although there were several reports on the structure–activity relationship studies of other isoquinoline alkaloids, none has been reported on that of (−)-jorumycin.[6–11]

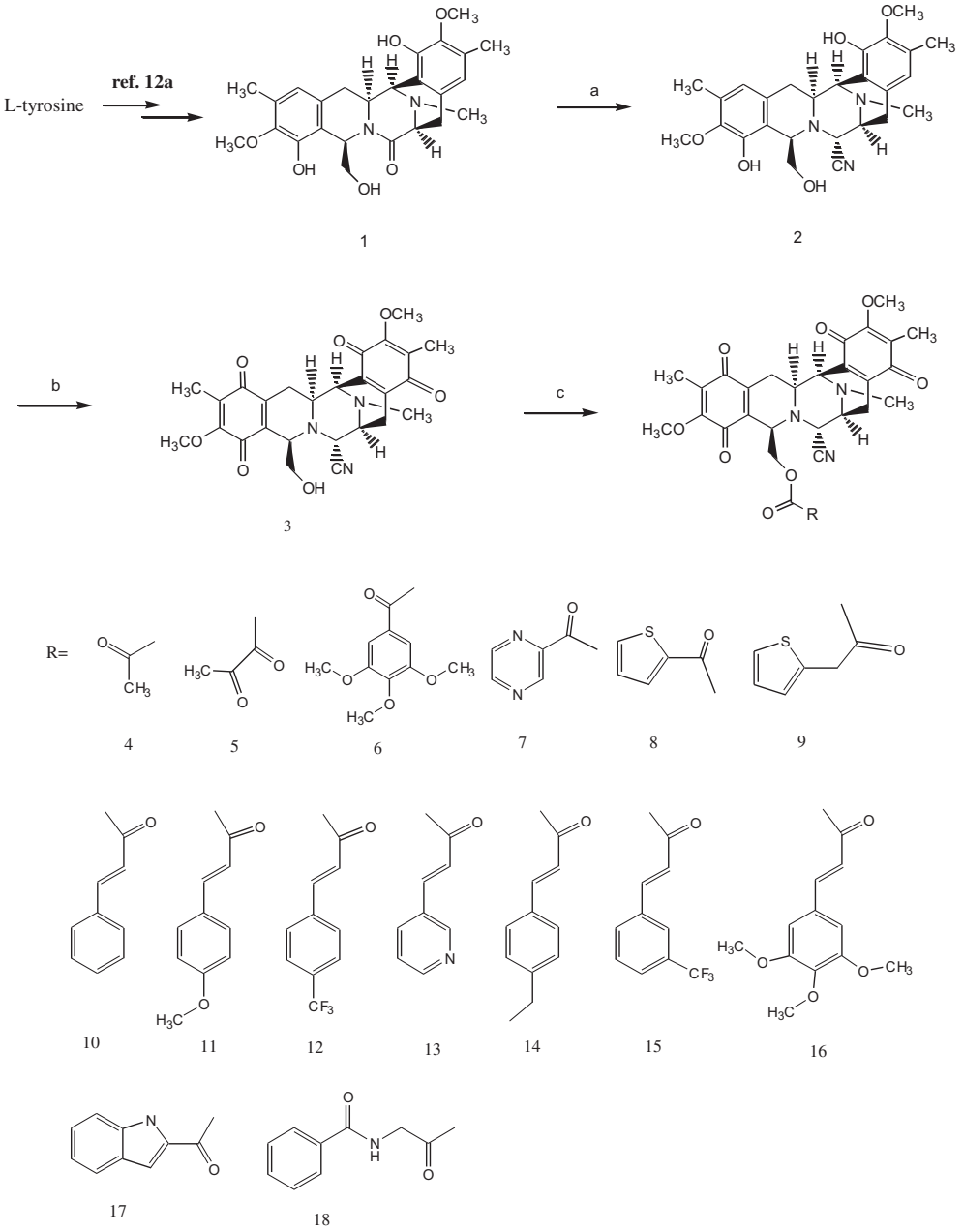
As the continuation of our study on isoquinoline natural products,[12] we now report the total synthesis and the cytotoxic activities of (−)-jorumycin and its analogues.

2. Result and discussion

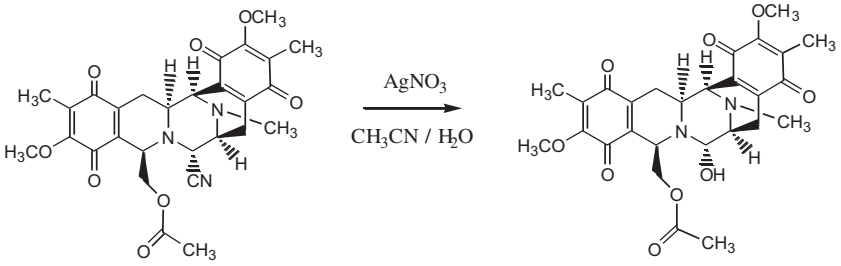
The synthesis of (−)-jorumycin and its analogs basically follows the synthetic route we employed in our total synthesis of (−)-renieramycin G and its analogs, which used L-tyrosine as the chiral starting material.[12a] Intermediate compound **1** was obtained after a multi-step transformation from L-tyrosine as done before. Reduction of compound **1** with $LiAlH_4$ in THF, followed by cyanation with KCN or TMSCN afforded amino nitrile **2** in a yield of 86% after chromatography. The subsequent oxidation of **2** with air in the presence of salcomine gave bisquinone **3**. Finally, 15 analogues with a variety of side chains at C-22 were prepared in 70–85% yields through the condensation of **3** with a series of carboxylic acids. All the compounds were characterized by their HRMS, ^1H and ^{13}C NMR (Scheme 1).

With compound **4** in hand, (−)-jorumycin was easily prepared according to the literature method.[5] The spectral data of the synthesized product was fully consistent with that of the natural product (Scheme 2).

All of the compounds including (−)-jorumycin were tested against 10 human tumor cell lines including HCT-8, BEL-7402, Ketr3, A2780, MCF-7, A549, BGC-823, Hela, HELF, and KB. The results are summarized in Table 1. It can be seen from the screening



Scheme 1. Reagents and conditions (a) $LiAlH_4$, THF; KCN, AcOH, 88%; (b) air, salcomine, CH_3CN, 86%; (c) carboxylic acid, DMAP, EDC, CH_2Cl_2, 74% salcomine=*N*,*N*′-bis(salicylidene) ethylenediaminocobalt(II) hydrate.



Scheme 2. Transformation of compound **4** into (−)-jorumycin.

Table 1
Cytotoxic activity of jorumycin and analogues against 10 cancer cell lines

Compound	Cytotoxicity IC_{50} (nM)									
	HCT-8	BEL-7402	Ketr3	A2780	MCF-7	A549	BGC-823	Hela	HELF	KB
4	**7.56**[a]	2.10	7.73	7.73	**3.44**	7.14	**0.91**	**0.82**	**1.37**	**1.53**
5	NT	NT	NT	NT	NT	NT	NT	43.40	95.68	88.58
6	25.86	NT	**4.51**	31.46	**0.27**	3.29	**1.48**	**0.30**	5.30	**2.02**
7	**9.59**	28.15	**1.00**	7.36	**1.65**	1.17	3.37	**0.82**	**1.79**	7.03
8	17.98	1.82	11.79	8.87	**2.81**	1.58	3.51	2.45	**3.04**	7.97
9	26.53	46.23	23.11	8.95	**16.05**	30.65	20.11	3.52	8.99	6.58
10	81.99	28.15	17.84	45.39	**11.62**	16.06	33.68	**1.77**	18.70	10.85
11	82.46	46.23	27.56	88.54	**9.54**	9.41	4.60	2.89	37.70	4.43
12	NT	NT	79.89	86.30	19.53	15.18	51.07	77.88	NT	41.32
13	NT	20.06	52.26	50.11	42.68	21.48	13.84	3.24	20.25	22.40
14	NT	NT	85.88	100	NT	23.20	32.18	12.17	NT	5.94
15	NT	NT	89.19	NT	NT	NT	22.74	51.99	NT	7.68
16	28.20	1.82	26.07	74.98	**1.02**	2.17	3.47	**0.31**	11.95	**2.22**
17	20.52	NT	7.59	7.16	**5.56**	2.14	**1.31**	**0.89**	**3.26**	3.25
18	**8.57**	2.10	**1.89**	**1.58**	**1.70**	1.53	**0.65**	**0.19**	**1.65**	**1.36**
19 (−)-Jorumycin	12.75	1.22	5.72	3.75	18.62	1.10	3.25	2.11	3.64	2.56

HTC-8: Human colon cancer; BEL-7402: Human hepatic carcinoma; A2780: Human ovarian cancer; MCF-7: Human breast cancer; A549: Human lung cancer; BGC-823: Human gastric adenocarcinoma; Ketr3: Human renal cell carcinoma; KB: Human oral epidermoid carcinoma; HELF human embryonic lung fibroblast carcinoma; Hela: Human cervical cancer.

[a] Boldface: $IC_{50} \leq$ (−)-jorumycin.

result that the IC_{50} values of most of the (−)-jorumycin analogs were at the level of nM. It is not surprising that (−)-jorumycin and compound **4**, the sole structural difference of which was the C-21 group of being either OH or CN, exhibited potent cytotoxicity with the similar pattern. However, compound **6**, which had a pyruvic acid side chain that existed in another isoquinoline alkaloid (−)-saframycin A, showed sharply decreased cytotoxicity. Compared with the aryl acyl analogs (compounds **6**, **7**, **8**, **17**), the aryl acrylolyl derivatives (compounds **10**–**16**) showed generally decreased cytotoxicity, which might be due to the two-carbon elongation between the carboxylic group and the aryl group. It could also be seen from this series of analogs that the compounds with the strong electron-donating groups on the aromatic ring (compounds **11**, **16**) exhibited stronger cytotoxicity than those with the electron-withdrawing groups (compounds **12**, **15**). Compound **9** exhibited one order of magnitude less potent cytotoxicity than compound **8**, which implied that the one carbon insertion might be the cause. Noticeably, compound **18**, which had a hippuric acid side chain exhibited the most potent cytotoxicity among all of the compounds including (−)-jorumycin itself with an average IC_{50} of 2.12 nM. The possible reason for the potent activity of compound **18** might be the strong tendency of hydrogen bond formation of the hippuric acid moiety.

Although a clear structure–activity relationship could not be drawn from these data, it could be concluded from this study that the C-22 side chain played an important role in the cytotoxic potency and specificity of the isoquinoline alkaloids.

3. Conclusion

Fifteen analogs of (−)-jorumycin along with itself were prepared via a multi-step route with L-tyrosine as the starting material. All of these compounds were screened in vitro for cytotoxic activities against HCT-8, BEL-7402, A2780, MCF-7, A549, BGC-823, Ketr3, KB, HELF, and Hela cells using the standard MTT method. Most of the analogs exhibited similar cytotoxic potency to (−)-jorumycin. Among these analogs, hippuric acid ester derivative **18** exhibited the most potent cytotoxic activity against all of the cell line with an average IC_{50} value of 2.12 nM. From this study, it could be concluded that the C-22 side chain played an important role in the cytotoxic potency and specificity of this class of (−)-jorumycin derivatives.

4. Experimental

4.1. General

^{1}H NMR spectra were determined at 600 MHz or 300 MHz spectrometer at 24 °C in the indicated solvent and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded at 150 MHz spectrometer at 24 °C in the solvent indicated and are reported in parts per million relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS were carried out by Agilent LC/MSD TOF. Optical rotations were measured on a Perkin–Elmer Polarimeter 341LC using 10 cm

cells and the sodium D line (589 nm) at 20 °C and concentration indicated. All reagents were obtained from commercial suppliers unless otherwise stated.

4.2. Synthesis of compound 2

To a solution of compound **1** (248 mg, 0.545 mmol) in dry THF (4 mL) was added $LiAlH_4$ (77 mg, 2.18 mmol, 4 equiv) under ice-salt bath and argon protection. The mixture was stirred for 30 min at this temperature, then glacial acetic acid (12 mmol) and a 5 M solution of KCN (3.5 mmol) in H_2O were added. After stirring at room temperature for 8 h, the reaction mixture was quenched with 10% aqueous $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layer was washed with H_2O and brine, and dried over anhydrous Na_2SO_4. After concentration in vacuo, the residue was chromatographed on silica gel to give compound **2** (218 mg, 86%) as a white solid.

Mp 121–125 °C. $[\alpha]_D^{20}$ −97.3 (*c* 0.6, $CHCl_3$). HRMS calcd for $C_{26}H_{32}N_3O_5$ ($M+H^+$) 466.2342 Da, found 466.2350 Da. ^1H NMR (300 MHz, CD_3COCD_3): δ 7.90 (s, 1H), 7.71 (s, 1H), 6.46 (s, 1H), 6.38 (s, 1H), 4.45 (d, *J*=2.1 Hz, 1H), 4.11 (br s, 1H), 4.09 (t, *J*=1.5 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.63 (dd, *J*=10.0 Hz, 4.5, 1H), 3.35 (br d, *J*=7.5 Hz, 1H), 3.27 (m, 1H), 3.23 (m, 1H), 3.06 (dd, *J*=18.0, 8.0 Hz, 1H), 2.81 (s, 3H), 2.81 (dd, *J*=15.0, 1.8 Hz, 1H), 2.68 (d, *J*=18.0 Hz, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 148.3, 146.8, 145.1, 144.2, 132.9, 132.0, 129.7, 129.6, 121.1, 121.0, 120.5, 119.2, 118.5, 66.6, 61.7, 60.7, 60.5, 59.6, 58.3, 57.7, 56.3, 41.9, 33.1, 26.2, 15.9, 15.7.

4.3. Synthesis of compound 3

To a solution of compound **2** (35 mg, 0.077 mmol) in MeCN (4 mL) was added salcomine (25 mg, 0.077 mmol) at room temperature, and the dark suspension was stirred in air for 5 h. The mixture was filtered through cellulose powder and the filter cake was carefully washed with AcOEt. The combined filtrate was washed with 0.1% aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. After concentration in vacuo, the residue was chromatographed on silica gel to give compound **3** (32 mg, 86%) as an orange film.

$[\alpha]_D^{20}$ −131.4 (*c* 1.8, CH_2Cl_2). HRMS calcd for $C_{26}H_{28}N_3O_7$ $(M+H)^+$ 494.1849 Da, found 494.1896 Da. ^1H NMR (300 MHz, $CDCl_3$): δ 4.12 (dd, *J*=9.6, 3.6 Hz, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 3.91 (d, *J*=2.7 Hz, 1H), 3.70 (m, 1H), 3.49 (d, *J*=6.6 Hz, 1H), 3.41 (dd, *J*=10.8, 3.0 Hz, 1H), 3.17 (dd, *J*=16.8, 2.4 Hz, 1H), 2.96 (dd, *J*=20.4, 7.2 Hz, 1H), 2.87 (d, *J*=20.4 Hz, 1H), 2.32 (s, 3H), 2.29 (d, *J*=2.7 Hz, 1H), 1.95 (s, 3H), 1.95 (s, 3H), 1.40 (dd, *J*=16.2, 12.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.3, 185.5, 182.3, 181.4, 155.5, 155.4, 141.6, 141.4, 136.0, 135.6, 129.0, 128.6, 116.8, 64.0, 61.1, 59.0, 58.0, 54.5, 54.3, 54.2, 41.6, 25.4, 21.5, 8.8, 8.7.

4.4. Synthesis of compound 4

To a solution of compound **3** (10 mg, 0.0207 mmol) in CH_2Cl_2 (2 mL) were added DMAP (2.5 mg, 0.0207 mmol) and acetic anhydride (39.3 mg, 0.332 mmol, 16 equiv). The solution was allowed to stand for 2 h at 25 °C in the dark. The mixture was diluted with CH_2Cl_2, washed with 1% aqueous $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, $CHCl_3/CH_3OH$=100:2) to give compound **4** (8 mg, 0.0142 mmol, 81%) as an orange film.

$[\alpha]_D^{20}$ −118.1 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{28}H_{30}N_3O_8$ ($M+H^+$) 536.2027 Da, found 536.2035 Da. ^1H NMR (300 MHz, $CDCl_3$): δ 4.49 (dd, *J*=11.7, 3.3 Hz, 1H), 4.05 (d, *J*=2.4 Hz, 1H), 4.01 (s, 3H), 4.01 (s, 3H), 3.99 (m, 1H), 3.81 (dd, *J*=11.4, 3.6 Hz, 1H), 3.39 (br d, *J*=7.8 Hz, 1H), 3.12 (d, *J*=11.7 Hz, 1H), 2.94 (br d, *J*=16.8 Hz, 1H), 2.77 (dd, *J*=21.0, 7.8 Hz, 1H), 2.36 (d, *J*=21.0 Hz, 1H), 2.30 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.80 (s, 3H), 1.28 (ddd, *J*=17.4, 11.4, 2.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.2, 185.4, 182.5, 181.0, 169.9, 155.5, 155.2, 142.3, 141.9, 135.4, 134.9, 128.8, 117.0, 63.6, 61.1, 61.1, 59.0, 55.8, 54.6, 54.5, 54.3, 41.5, 29.7, 25.3, 21.2, 20.5, 8.8, 8.7.

4.5. Synthesis of compound 5–18

To a solution of compound **3** (10 mg, 0.0207 mmol) in CH_2Cl_2 (2 mL) were added DMAP (2.5 mg, 0.0207 mmol), EDC (5.2 mg, 0.0269 mmol), and pyruvic acid (4.4 mg, 0.05 mmol, 2 equiv). The solution was allowed to stand for 2 h at 25 °C in the dark. The mixture was diluted with CH_2Cl_2, washed with 1% aqueous $NaHCO_3$ and brine successively, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, $CHCl_3/CH_3OH$=100:2) to give compound **5** (9 mg, 0.0162 mmol, 78.7%) as an orange film. Compounds **6**–**18** were prepared in this way using corresponding carboxylic acid in stead.

*4.5.1. Data of compound **5**.* $[\alpha]_D^{20}$ −76.8 (*c* 0.2, $CHCl_3$). HRMS calcd for $C_{29}H_{30}N_3O_9$ ($M+H^+$) 564.1977 Da, found 564.1980. ^1H NMR (600 MHz, $CDCl_3$): δ 4.59 (br d, *J*=11.4 Hz, 1H), 4.08 (m, 2H), 4.05 (s, 3H), 4.02 (m, 1H), 4.00 (s, 3H), 3.88 (m, 1H), 3.42 (br d, *J*=7.2 Hz, 1H), 3.15 (br d, *J*=11.4 Hz, 1H), 2.94 (d, *J*=16.2 Hz, 1H), 2.74 (dd, *J*=21.3, 7.2 Hz, 1H), 2.42 (d, *J*=21.0 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 1.96 (s, 3H), 1.92 (s, 3H), 1.52 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 191.4, 186.4, 185.2, 182.4, 181.1, 160.6, 155.6, 155.4, 142.9, 141.8, 134.8, 134.4, 129.1, 128.2, 116.9, 65.3, 61.1, 59.0, 55.5, 54.6, 54.3, 41.5, 29.7, 26.4, 24.9, 21.1, 20.5, 8.8, 8.7.

*4.5.2. Data of compound **6**.* $[\alpha]_D^{20}$ −63.9 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{36}H_{37}N_3O_{11}$ ($M+H^+$) 688.2501 Da, found 688.2510. ^1H NMR (300 MHz, $CDCl_3$): δ 6.86 (s, 2H), 5.16 (br d, *J*=12.3 Hz, 1H), 4.09 (m, 1H), 4.03 (s, 3H), 3.95 (m, 2H), 3.87 (s, 3H), 3.77 (s, 3H), 3.75 (s, 6H), 3.37 (d, *J*=5.1 Hz, 1H), 3.11 (br d, *J*=11.4 Hz, 1H), 2.93 (d, *J*=17.4 Hz, 1H), 2.70 (dd, *J*=21.0, 9.0 Hz, 1H), 2.37 (br d, *J*=21.0 Hz, 1H), 2.19 (s, 3H), 1.95 (s, 3H), 1.61 (s, 3H), 1.44 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.8, 185.7, 182.4, 181.2, 165.1, 155.6, 154.6, 152.8, 142.1, 142.0, 141.9, 135.7, 134.4, 128.6, 128.4, 124.0, 117.0, 106.4, 61.4, 61.3, 60.8, 60.6, 58.1, 56.6, 55.9, 54.6, 54.1, 54.1, 41.4, 29.7, 26.1, 20.8, 8.8, 8.2.

*4.5.3. Data of compound **7**.* $[\alpha]_D^{20}$ −171.4 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{31}H_{30}N_5O_8$ ($M+H^+$) 600.2094 Da, found 600.1951. ^1H NMR (300 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.72 (s, *J*=2.1 Hz, 1H), 8.55 (s, 1H), 4.89 (br d, *J*=8.7 Hz, 1H), 4.19 (br d, *J*=15.9 Hz, 2H), 4.09 (br d, *J*=14 Hz, 1H), 4.02 (s, 3H), 3.94 (m, 1H), 3.88 (s, 3H), 3.38 (d, *J*=8.4 Hz, 1H), 3.11 (br d, *J*=11.4 Hz, 1H), 2.91 (dd, *J*=16.8, 2.4 Hz, 2H), 2.71 (dd, *J*=21.0, 7.8 Hz, 1H), 2.39 (br d, *J*=21.3 Hz, 1H), 2.25 (s, 3H), 1.96 (s, 3H), 1.71 (s, 3H), 1.25 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.9, 185.4, 182.2, 181.2, 163.6, 155.5, 154.9, 147.8, 146.3, 144.3, 143.0, 142.8, 142.1, 134.8, 134.7, 128.9, 128.3, 117.1, 64.8, 61.1, 61.0, 59.0, 56.0, 54.8, 54.6, 54.4, 41.5, 29.7, 25.2, 21.0, 8.9, 8.6.

*4.5.4. Data of compound **8**.* $[\alpha]_D^{20}$ −21.2 (*c* 0.3, $CHCl_3$). HRMS calcd for $C_{31}H_{30}N_3O_8S$ ($M+H^+$) 604.1753 Da, found 604.1672 Da. ^1H NMR (300 MHz, $CDCl_3$): δ 7.51 (dd, *J*=3.6, 1.2 Hz, 1H), 7.45 (dd, *J*=4.8, 0.9 Hz, 1H), 7.03 (dd, *J*=4.8, 0.9 Hz, 1H), 4.96 (dd, *J*=12.0, 3.0 Hz, 1H), 4.07 (m, 1H), 4.04 (s, 3H), 4.02 (m, 1H), 3.96 (m, 1H), 3.80 (s, 3H), 3.40 (d, *J*=7.2 Hz, 1H), 3.11 (br d, *J*=8.4 Hz, 1H), 2.92 (dd, *J*=17.7, 2.1 Hz, 2H), 2.71 (dd, *J*=21.0, 7.5 Hz, 1H), 2.33 (br d, *J*=21.0 Hz, 1H), 2.23 (s, 3H), 1.98 (s, 3H), 1.79 (s, 3H), 1.41 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 185.9, 185.5, 182.2, 181.1, 160.9, 155.6, 154.9, 142.3, 142.1, 135.1, 134.5, 134.3, 132.5, 132.2, 128.7, 128.3, 128.0, 116.9, 61.9, 61.2, 60.8, 58.3, 56.6, 54.6, 54.2, 41.4, 29.7, 25.6, 21.0, 8.9, 8.8.

*4.5.5. Data of compound **9**.* $[\alpha]_D^{20}$ −124.8 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{32}H_{32}N_3O_8S$ ($M+H^+$) 618.1910 Da, found 618.1834 Da. ^1H NMR (300 MHz, $CDCl_3$): δ 7.11 (d, *J*=4.8 Hz, 1H), 6.86 (dd, *J*=5.1,3.3 Hz, 1H),

6.72 (d, *J*=3.3 Hz, 1H), 4.37 (dd, *J*=9.3, 3.0 Hz, 1H), 4.04 (s, 3H), 4.02 (m, 1H), 4.00 (s, 3H), 3.96 (m, 2H), 3.93 (d, *J*=2.1 Hz, 1H), 3.63 (d, *J*=4.8 Hz, 2H), 3.30 (br d, *J*=7.2 Hz, 1H), 3.05 (br d, *J*=11.7 Hz, 1H), 2.82 (dd, *J*=14.7, 0.6 Hz, 1H), 2.75 (dd, *J*=21.0, 7.5 Hz, 1H), 2.30 (s, 3H), 2.23 (d, *J*=21.0 Hz, 1H), 1.96 (s, 3H), 1.94 (s, 3H), 1.25 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.2, 185.2, 182.4, 180.9, 169.3, 155.6, 155.1, 142.0, 141.9, 134.9, 134.7, 134.2, 128.6, 127.0, 126.9, 125.2, 116.8, 64.7, 61.1, 61.0, 58.9, 56.0, 54.5, 54.4, 54.2, 41.5, 35.3, 25.1, 21.2, 8.8, 8.7.

4.5.6. Data of compound ***10***. $[\alpha]_D^{20}$ −167.4 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{35}H_{33}N_3O_8$ ($M+H^+$) 624.2340 Da, found 624.2321 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (s, 5H), 7.35 (d, *J*=15.9 Hz, 1H), 6.09 (d, *J*=15.9 Hz, 1H), 4.90 (dd, *J*=9.3, 2.1 Hz, 1H), 4.09 (m, 1H), 4.03 (s, 3H), 4.01 (m, 2H), 3.69 (s, 3H), 3.39 (d, *J*=6.9 Hz, 1H), 3.11 (br d, *J*=11.4 Hz, 1H), 2.94 (d, *J*=17.4 Hz, 1H), 2.77 (dd, *J*=21.0, 7.5 Hz, 1H), 2.45 (br d, *J*=21.0 Hz, 1H), 2.25 (s, 3H), 1.99 (s, 3H), 1.60 (s, 3H), 1.37 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.7, 182.4, 181.2, 165.8, 155.6, 155.0, 145.8, 142.3, 142.1, 135.5, 134.6, 133.8, 130.8, 129.0, 128.7, 128.4, 128.2, 117.0, 116.6, 61.7, 61.2, 60.7, 58.4, 56.6, 54.6, 54.3, 41.4, 30.4, 29.7, 25.6, 20.9, 8.9, 8.5.

4.5.7. Data of compound ***11***. $[\alpha]_D^{20}$ −272.0 (*c* 0.5, $CHCl_3$). HRMS calcd for $C_{36}H_{35}N_3O_9$ ($M+H^+$) 654.2446 Da, found 654.2399 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J*=8.7 Hz, 1H), 7.35 (d, *J*=15.9 Hz, 1H), 6.90 (d, *J*=8.7 Hz, 1H), 5.95 (d, *J*=15.9 Hz, 1H), 4.90 (dd, *J*=11.7, 3.0 Hz, 1H), 4.09 (m, 1H), 4.03 (s, 3H), 4.01 (m, 2H), 3.84 (s, 3H), 3.70 (s, 3H), 3.38 (d, *J*=6.6 Hz, 1H), 3.10 (br d, *J*=11.1 Hz, 1H), 2.93 (d, *J*=17.4 Hz, 1H), 2.76 (dd, *J*=21.0, 7.2 Hz, 1H), 2.45 (br d, *J*=21.0 Hz, 1H), 2.25 (s, 3H), 1.98 (s, 3H), 1.62 (s, 3H), 1.35 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.7, 182.4, 181.2, 166.1, 161.8, 155.6, 155.0, 145.5, 142.3, 142.1, 135.6, 134.6, 130.2, 130.0, 128.7, 128.5, 126.5, 117.0, 114.4, 113.9, 61.5, 61.2, 60.7, 58.4, 56.6, 55.4, 54.6, 54.3, 53.4, 41.4, 29.7, 25.6, 20.9, 8.9, 8.5.

4.5.8. Data of compound ***12***. $[\alpha]_D^{20}$ −111.7 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{28}H_{30}N_3O_8$ ($M+H^+$) 692.2214 Da, found 693.2174 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J*=7.8 Hz, 1H), 7.54 (d, *J*=8.4 Hz, 1H), 7.38 (d, *J*=16.5 Hz, 1H), 6.18 (d, *J*=15.9 Hz, 1H), 4.87 (dd, *J*=11.4, 2.4 Hz, 1H), 4.09 (m, 1H), 4.04 (s, 3H), 3.97 (m, 2H), 3.77 (s, 3H), 3.38 (d, *J*=6.6 Hz, 1H), 3.12 (br d, *J*=10.8 Hz, 1H), 2.93 (d, *J*=17.1 Hz, 1H), 2.71 (dd, *J*=20.7, 7.5 Hz, 1H), 2.42 (br d, *J*=21.3 Hz, 1H), 2.26 (s, 3H), 1.99 (s, 3H), 1.60 (s, 3H), 1.31 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.7, 182.4, 181.1, 165.3, 155.6, 154.9, 144.0, 142.3, 142.2, 135.4, 134.6, 128.8, 128.3, 128.2, 125.9, 125.9, 119.2, 116.9, 62.2, 61.2, 60.8, 58.5, 56.5, 54.6, 54.3, 54.2, 41.5, 29.7, 25.6, 20.9, 8.8, 8.5.

4.5.9. Data of compound ***13***. $[\alpha]_D^{20}$ −81.0 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{34}H_{33}N_4O_8$ ($M+H^+$) 625.2293 Da, found 625.2295 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (d, *J*=3.6 Hz, 1H), 7.72 (m, 1H), 7.41 (d, *J*=15.6 Hz, 1H), 7.29 (m, 2H), 6.09 (d, *J*=15.3 Hz, 1H), 4.91 (dd, *J*=11.7, 3.0 Hz, 1H), 4.10 (d, *J*=2.1 Hz, 1H), 4.03 (s, 3H), 3.99 (m, 1H), 3.95 (m, 1H), 3.73 (s, 3H), 3.39 (d, *J*=7.2 Hz, 1H), 3.11 (br d, *J*=11.4 Hz, 1H), 2.94 (dd, *J*=17.4, 2.1 Hz, 1H), 2.77 (dd, *J*=21.0, 7.2 Hz, 1H), 2.42 (br d, *J*=21.0 Hz, 1H), 2.24 (s, 3H), 1.98 (s, 3H), 1.60 (s, 3H), 1.35 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.6, 182.4, 174.1, 165.7, 155.2, 152.2, 150.1, 144.3, 142.2, 136.8, 135.4, 134.7, 128.6, 125.0, 124.6, 120.8, 117.0, 61.7, 61.2, 60.6, 58.4, 56.5, 54.6, 54.3, 53.4, 41.4, 30.4, 29.7, 25.5, 20.9, 8.9, 8.4.

4.5.10. Data of compound ***14***. $[\alpha]_D^{20}$ −177.1 (*c* 0.3, $CHCl_3$). HRMS calcd for $C_{37}H_{37}N_3O_8$ ($M+H^+$) 652.2653 Da, found 652.2651 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, *J*=16.2 Hz, 1H), 7.35 (d, *J*=8.1 Hz, 1H), 7.23 (d, *J*=8.1 Hz, 1H), 6.09 (d, *J*=16.2 Hz, 1H), 4.91 (br d, *J*=10.8 Hz, 1H), 4.09 (m, 1H), 4.04 (s, 3H), 4.01 (m, 1H), 3.97 (d, *J*=11.4 Hz, 1H), 3.66 (s, 3H), 3.39 (d, *J*=6.9 Hz, 1H), 3.11 (br d, *J*=10.8 Hz, 1H), 2.94 (d, *J*=17.4 Hz, 1H), 2.70 (dd, *J*=21.0, 7.2 Hz, 1H), 2.49 (br d, *J*=21.0 Hz, 1H), 2.25 (s, 3H), 1.99 (s, 3H), 1.62 (s, 3H), 1.58 (m, 2H), 1.35 (m, 1H), 1.25 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.7, 182.4, 181.2, 165.9, 155.6, 155.0, 147.7, 145.8, 142.3, 142.1, 135.6, 134.6, 131.3, 128.7, 128.5, 128.3, 117.0, 115.5, 61.6, 61.2, 60.6, 58.4, 56.6, 54.6, 54.3, 54.1, 41.4, 29.7, 28.8, 25.6, 20.9, 15.4, 8.9, 8.5.

4.5.11. Data of compound ***15***. $[\alpha]_D^{20}$ −156.0 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{36}H_{32}N_3O_8F_3$ ($M+H^+$) 692.2100 Da, found 692.2129 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (m, 2H), 7.55 (m, 2H), 7.45 (d, *J*=15.9 Hz, 1H), 6.18 (d, *J*=16.2 Hz, 1H), 4.89 (dd, *J*=11.74, 3.0 Hz, 1H), 4.09 (m, 1H), 4.04 (s, 3H), 3.98 (m, 2H), 3.78 (s, 3H), 3.38 (d, *J*=7.5 Hz, 1H), 3.12 (br d, *J*=11.7 Hz, 1H), 2.96 (d, *J*=15.3 Hz, 1H), 2.75 (dd, *J*=21.0, 7.5 Hz, 1H), 2.44 (br d, *J*=21.0 Hz, 1H), 2.26 (s, 3H), 1.99 (s, 3H), 1.59 (s, 3H), 1.32 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.6, 182.5, 181.2, 165.4, 155.6, 155.0, 144.2, 142.3, 142.2, 134.6, 134.6, 131.5, 129.6, 128.8, 128.3, 127.1, 124.4, 118.5, 116.9, 62.2, 61.2, 60.8, 58.5, 56.5, 54.6, 54.3, 54.2, 41.5, 29.7, 25.6, 20.9, 8.8, 8.4.

4.5.12. Data of compound ***16***. $[\alpha]_D^{20}$ −219.1 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{38}H_{39}N_3O_{11}$ ($M+H^+$) 714.2657 Da, found 714.2670 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J*=15.9 Hz, 1H), 6.62 (s, 2H), 5.96 (d, *J*=15.9 Hz, 1H), 4.94 (dd, *J*=11.7, 3.0 Hz, 1H), 4.09 (m, 1H), 4.04 (s, 3H), 3.97 (m, 2H), 3.91 (s, 6H), 3.89 (s, 3H), 3.75 (s, 3H), 3.37 (d, *J*=7.8 Hz, 1H), 3.12 (br d, *J*=11.4 Hz, 1H), 2.93 (d, *J*=16.2 Hz, 1H), 2.70 (dd, *J*=21.0, 7.2 Hz, 1H), 2.45 (br d, *J*=21.0 Hz, 1H), 2.26 (s, 3H), 1.98 (s, 3H), 1.64 (s, 3H), 1.45 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.0, 185.9, 182.5, 181.2, 165.8, 155.6, 154.9, 153.5, 146.1, 142.3, 142.2, 140.5, 135.6, 134.6, 129.2, 128.6, 128.4, 117.0, 115.6, 105.4, 61.7, 61.2, 61.0, 60.7, 58.4, 56.6, 56.3, 54.6, 54.3, 54.2, 41.5, 29.7, 25.7, 20.9, 8.8, 8.5.

4.5.13. Data of compound ***17***. $[\alpha]_D^{20}$ −229.2 (*c* 0.46, $CHCl_3$). HRMS calcd for $C_{35}H_{32}N_4O_8$ ($M+H^+$) 637.2293 Da, found 637.2243 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (s, 1H), 7.59 (d, *J*=8.1 Hz, 1H), 7.38 (d, *J*=8.1 Hz, 1H), 7.33 (t, *J*=8.1 Hz, 1H), 7.16 (t, *J*=8.1 Hz, 1H), δ 6.74 (s, 1H), δ 5.13 (dd, *J*=9.3, 2.4 Hz, 1H), 4.09 (m, 2H), 4.08 (s, 3H), 4.00 (d, *J*=19.5 Hz, 1H), 3.36 (s, 3H), 3.11 (d, *J*=11.4 Hz, 1H), 2.95 (br d, *J*=18.3 Hz, 2H), 2.72 (dd, *J*=21.0, 7.5 Hz, 1H), 2.43 (br d, *J*=21.3 Hz, 1H), 2.20 (s, 3H), 2.02 (s, 3H), 1.50 (s, 3H), 1.25 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.3, 185.6, 182.1, 181.2, 161.0, 155.6, 155.0, 142.4, 141.9, 136.9, 135.3, 134.6, 128.8, 128.2, 127.1, 126.2, 125.8, 122.7, 121.2, 117.0, 112.2, 108.2, 61.5, 61.2, 60.4, 58.3, 56.6, 54.5, 54.4, 54.1, 41.4, 25.5, 20.9, 8.9, 8.4.

4.5.14. Data of compound ***18***. $[\alpha]_D^{20}$ −127.9 (*c* 0.4, $CHCl_3$). HRMS calcd for $C_{35}H_{34}N_4O_9$ ($M+H^+$) 637.2293 Da, found 655.2316 Da. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, *J*=6.9 Hz, 2H), 7.54 (m, 1H), 7.46 (d, *J*=6.9 Hz, 1H), 6.60 (m, 1H), 4.69 (dd, *J*=9.0, 3.0 Hz, 1H), 4.23 (dd, *J*=18.0, 6.0 Hz, 1H), 4.10 (d, *J*=2.1 Hz, 1H), 4.05 (s, 3H), 4.03 (m, 1H), 4.00 (s, 1H), 3.97 (s, 3H), 3.81 (m, 2H), 3.39 (d, *J*=7.5 Hz, 1H), 3.11 (d, *J*=11.7 Hz, 1H), 2.94 (br d, *J*=18.0 Hz, 1H), 2.68 (dd, *J*=21.0, 7.5 Hz, 1H), 2.40 (d, *J*=21.0 Hz, 1H), 2.34 (s, 3H), 1.89 (s, 3H), 1.82 (s, 3H), 1.45 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ186.9, 185.1, 182.4, 181.1, 169.5, 167.0, 155.6, 155.4, 142.2, 141.8, 135.3, 134.7, 133.1, 131.9, 129.0, 128.6, 127.9, 127.1, 116.8, 63.2, 61.2, 61.0, 58.6, 56.0, 54.5, 54.4, 54.1, 41.5, 30.9, 25.2, 21.0, 8.8, 8.5.

4.6. Synthesis of (−)-jorumycin (compound 19)

To a solution of compound **4** (26 mg, 0.048 mmol) in a mixture of CH_3CN (3 mL) and water (2 mL) was added silver nitrate (203 mg, 1.2 mmol, 25 equiv), and the suspension was stirred at 50 °C for 17 h. The reaction mixture was partitioned between EtOAc (10 mL×3) and water (5 mL), and the combined organic layer was washed with saturated brine, dried with Na_2SO_4. After

concentration in vacuo, the residue was chromatographed on silica gel to afford (−)-jorumycin (21 mg, 86%) as a yellow film.

$[\alpha]_D^{20}$ −65.7 (*c* 0.8, $CHCl_3$). HRMS calcd for $C_{27}H_{29}N_2O_8$ ($M+H^+$) 509.1923 Da, found 509.1903 Da. ^1H NMR (600 MHz, $CDCl_3$): δ 4.43 (dd, *J*=10.8, 3.0 Hz, 1H), 4.42 (d, *J*=11.4 Hz, 1H), 4.36 (br d, *J*=2.4 Hz, 1H), 4.00 (s, 3H), 3.98 (s, 3H), 3.91 (br s, 1H), 3.82 (dd, *J*=11.4, 3.6 Hz, 1H), 3.18 (br s, 1H), 3.17 (br d, *J*=19.8 Hz, 1H), 2.83 (dd, *J*=16.8, 2.1 Hz, 1H), 2.65 (dd, *J*=21.0, 7.8 Hz, 1H), 2.26 (s, 3H), 2.24 (d, *J*=21.6 Hz, 1H), 1.95 (s, 3H), 1.93 (s, 3H), 1.75 (s, 3H), 1.26 (ddd, *J*=16.8, 9.4, 2.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.5, 185.8, 182.5, 181.3, 170.0, 155.6, 155.2, 141.9, 141.8, 137.3, 134.2, 128.7, 128.3, 83.0, 64.2, 61.0 (2), 57.4, 54.2, 52.7, 51.0, 41.4, 25.6, 20.6, 20.5, 8.7, 8.6.

4.7. Cell lines

The tumor cell lines panel consisted of HTC-8 (human colon cancer), BEL-7402 (human hepatic carcinoma), A2780 (human ovarian cancer), MCF-7 (human breast cancer), A549 (human lung cancer), BGC-823 (human gastric adenocarcinoma), Ketr3 (human renal cell carcinoma), KB (human oral epidermoid carcinoma), HELF (human embryonic lung fibroblast carcinoma), and Hela (human cervical cancer cell lines).

4.8. Cytotoxicity evaluation

Human cancer cells were cultured in PRMI1640 or DMEM/F12 supplemented with 10% fetal bovine serum, containing penicillin streptomycin at 37 °C and humidified at 5% CO_2. Briefly, cells were placed in the appropriate media on 96-well plates in a 100 μL total volume at a density of $1–2.5\times10^4$ cells/mL and were allowed to adhere for 24 h before treatment with tested drugs in DMSO solution (10^{-5}, 10^{-6}, 10^{-7} mol/L final concentration). Triplicate wells were treated with media and agents. Cell viability was assayed after 96 h of continuous drug exposure with a tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium salt; MTT (0.5 mg/mL, 100 μL), Ameresco Corp] in fresh medium. After the medium was removed, 150 μL of DMSO was added to each well. The plates were gently agitated until the color reaction was uniform and the OD_{570} was determined using microplate reader (Wellscan MK3, Labsystems Dragon). Microsoft Excel 2003 was used for data analysis. Media-only treated cells served as the indicator of 100% cell viability. The 50% inhibitory concentration (IC_{50}) was defined as the concentration that reduced the absorbance of the untreated wells by 50% of vehicle in the MTT assay. Assays were performed in triplicate on three independent experiments.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.016.

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