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Asymmetric synthesis and cytotoxicity of (−)-saframycin A analogues

Wenfang Dong [a], Wei Liu [a], Zheng Yan [a], Xiangwei Liao [b], Baohe Guan [b], Nan Wang [b], Zhanzhu Liu [a,b,*]

[a] State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, PR China
[b] Beijing Key Laboratory of Active Substance Discovery and Druggability Evaluation, Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, PR China

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ABSTRACT

(−)-Saframycin A and its nineteen analogues were prepared from L-tyrosine in 24 steps, and their structures were confirmed through NMR and HRMS. The cytotoxicities of these compounds were tested against HCT-8, BEL-7402, Ketr3, A2780, MCF-7, A549, BGC-803, Hela, HELF and KB cell lines. The IC_{50} values of the cytotoxicity of most compounds were at the level of nM. Compound **7d** with 2-furan amide side chain showed the most potent cytotoxicity of all these compounds with an average IC_{50} value of 6.06 nM.

1. Introduction

The tetrahydroisoquinoline family includes a number of natural products that display a range of biological properties such as antitumour and antimicrobial activities [1]. As the typical member of this family, Et-743 has a unique antitumour mechanism of action and has been launched in Europe for treating soft tissue sarcoma [2–6]. The remarkable clinical results of Et-743 have stimulated further research and resulted in the discovery of several simplified analogues of this family, such as Zalypsis [7,8] and QAD [9].

(−)-Saframycin A, a member of the tetrahydroisoquinoline antibiotics with very potent antitumour activity, was isolated from *Streptomyces lavendulae* in 1977 by Arai et al [10,11] (Fig. 1). There have been several reports on the investigation of the mechanism of action of (−)-saframycin A [12–14]. Generally, it is believed that the guanine residues of double–stranded DNA in the minor groove of the tumour cell are alkylated by an iminium ion generated from the amino nitrile function of (−)-saframycin A in the presence of reducing cofactors [12]. Myers et al reported the study on the structure–activity relationship of a series of the bishydroquinone analogues of (−)-saframycin A [15]. Other studies on the structure–activity relationship of the related tetrahydoisoquinoline alkaloids have also been reported [16–22]. However, the structure–activity relationship of the bisquinone analogues of (−)-saframycin A has not been studied so far.

In this paper, nineteen C-22 amide analogues of (−)-saframycin A were synthesized in 24 steps employing the synthetic route we established before, which featured the use of L-tyrosine as the starting material [23]. All analogues were evaluated in contrast to (−)-saframycin A for their *in vitro* cytotoxicity against a panel of human tumour cell lines, including HCT-8, BEL-7402, Ketr3, A2780, MCF-7, A549, BGC-803, Hela, HELF and KB cells.

2. Chemistry

The preparation of compound **2** basically followed the synthetic route we had built previously [23]. Compound **3** was prepared by acylation of compound **2** with different acids using EDC as the condensation agent. Synthesis of the amide analogues at C-22 of (−)-saframycin A was accomplished by oxidation of compound **3** with air in the presence of salcomine at room temperature in 60–80% yield. Totally twenty compounds were synthesized, including cinnamic acid analogues **4a**–**f**, hippuric acid analogue **5a**, tert-butyl carbamate analogue **5b**, substituted aromatic acid analogues **6a**–**d**, heterocyclic aromatic acid analogues **7a**–**g**, as well as (−)-saframycin A. All these compounds were characterized by their HRMS, ^{1}H NMR and ^{13}C NMR (Scheme 1).

* Corresponding author. Peking Union Medical College and Chinese Academy of Medical Sciences, Institute of Materia Medica, State Key Laboratory of Bioactive Substances and Functions of Natural Medicines, 1 Xian Nong Tan Street, Beijing 100050, PR China. Tel.: +86 10 63165253; fax: +86 10 63017757.
E-mail address: liuzhanzhu@imm.ac.cn (Z. Liu).

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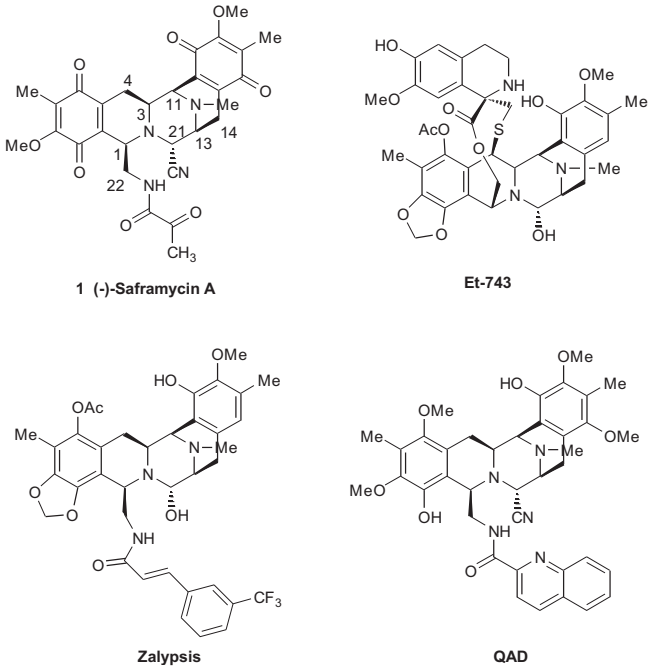


Fig. 1. Structures of tetrahydroisoquinoline compounds.

3. Cytotoxicity

Cytotoxicity of (−)-saframycin A analogues was evaluated against ten human cell lines: HCT-8 (human colon cancer cell line), BEL-7402 (human hepatic carcinoma cell line), Ketr3 (human renal cell carcinoma cell line), A2780 (human ovarian cancer cell line), MCF-7 (human breast cancer cell line), A549 (human lung cancer cell line), BGC-803 (human gastric adenocarcinoma cell line), Hela (human cervical cancer cell line), HELF (human embryonic lung fibroblast cell line) and KB (human oral epidermoid carcinoma cell line) by the standard MTT assay. The results are shown in Table 1.

4. Results and discussion

Among the six cinnamic acid derivatives (**4a**–**f**), **4a**, **4b**, **4c** and **4e** showed potent cytotoxicity similar to (−)-saframycin A against MCF-7 (IC_{50} value 2.23–5.44 nM) and Hela (3.85–8.33 nM). In contrast, the IC_{50} values of these compounds against other cell lines were at the level of 10^{-8} M, which implied that cinnamamide side chain derivatives appeared to have better selectivity towards MCF-7 and Hela. Compound **5a**, the hippuric acid derivative with the IC_{50} values at the level of 10^{-8} M against most cell lines, showed decreased cytotoxicity. The tert-butyl carbamate side chain derivative **5b** exhibited potent inhibitory activity against MCF-7 and Hela with the IC_{50} values of 8.89 nM and 7.41 nM. Among the four substituted aromatic acid derivatives (**6a**–**d**), compound **6a**, which had three electron–donating methoxy groups on the benzene ring, showed similar cytotoxicity to (−)-saframycin A against most cell lines, and even higher cytotoxicity against BGC-803 than (−)-saframycin A. Compound **6d** with two electron–withdrawing groups showed the least cytotoxic activity with the IC_{50} values greater than 100 nM against most cell lines. Among the seven heterocyclic aromatic acid derivatives (**7a**–**g**), compound **7d** with 2-furan amide side chain showed the most potent inhibitory activity among all the twenty analogues with the average IC_{50} value of 6.06 nM. 2-Pyrazinamide derivative **7c** also exhibited 20-fold increase cytotoxic activity in comparison with (−)-saframycin A against A549. Four compounds (**4c**, **4e**, **6a**, and **7f**), all of which had electron–rich aromatic rings, showed higher antitumour activity than (−)-saframycin A against BGC-803. Compound **1**, the reductive form of **5b**, showed decreased antitumour activity against most cell lines in comparison with **5b**. Although a general structure–activity relationship of the amide analogues at C-22 of (−)-saframycin A could not be summarized from these data, these data showed that the side chain of the amide group appeared to be closely related to the antitumour activity.

5. Conclusions

(−)-saframycin A and its nineteen analogues were prepared from L-tyrosine employing the synthetic route we had established previously. The cytotoxicity of these compounds was tested against HCT-8, BEL-7402, Ketr3, A2780, MCF-7, A549, BGC-803, Hela, HELF and KB cell lines by MTT assay. Most of the compounds showed potent antitumour activity with the IC_{50} values at the nM level. Some compounds showed better antitumour activity than (−)-saframycin A against A549 and BGC-803. Compound **7d** with 2-furan amide side chain showed the most potent cytotoxicity of all these compounds with an average IC_{50} value of 6.06 nM. This study shows that the side chain of the amide group plays an important role for the antitumour activity of these analogues.

6. Experimental protocols

6.1. General

Melting points were obtained on Yanaco MP-500D melting point apparatus and were uncorrected. Optical rotations were measured on a PerkinElmer Polarimeter 341LC using 10 cm cells and the sodium D line (589 nm) at 20 °C and concentration indicated. HRMS were carried out by Agilent LC/MSD TOF. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 spectrometer (400 MHz, ^1H; 100 MHz, ^{13}C) or a Bruker AV 500 spectrometer (500 MHz, ^1H; 125 MHz, ^{13}C) or a Varian INOVA 600 spectrometer (600 MHz, ^1H; 150 MHz, ^{13}C) in $CDCl_3$, using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are expressed in parts per million (ppm), and the following abbreviations are used: singlet (s), doublet (d), triplet (t), doubled doublet (dd), multiplet (m), etc. All common reagents and solvents were purchased from commercial suppliers and purified before use.

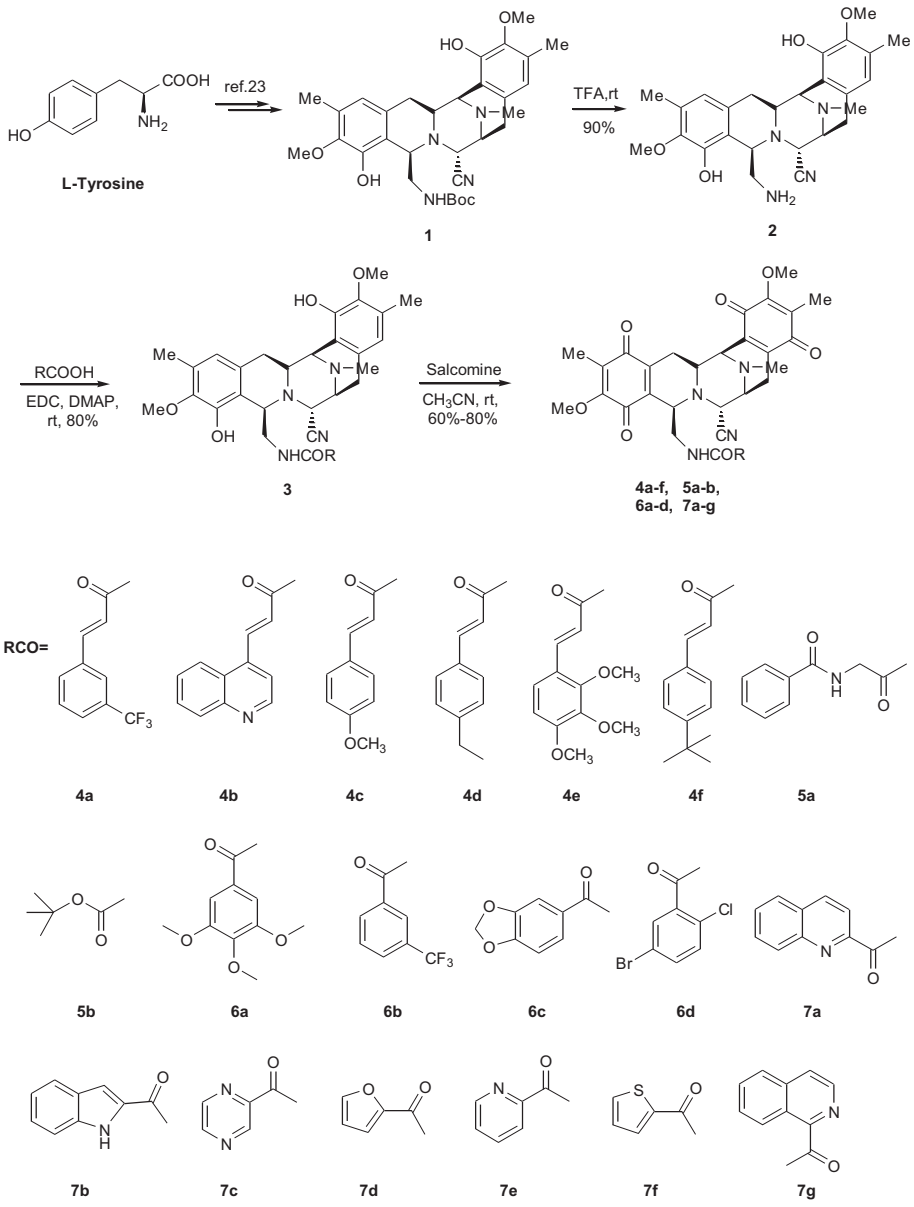
6.2. General procedure for the synthesis of compounds *4a*–*7g*

To a solution of compound **2** (1.0 eq) in CH_2Cl_2 was added the corresponding carboxylic acid (1.5 eq), DMAP (1.0 eq) and EDC (1.5 eq), then the mixture was stirred at room temperature for 10 h. The mixture was diluted with CH_2Cl_2, washed with saturated aq. $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give the crude product. Purification by column chromatography (PE/EtOAc = 1:1) afforded the amide **3** as a white solid (yield 75–85%).

To a solution of compound **3** (1.0 eq) in CH_3CN was added salcomine (1.0 eq) at room temperature, and the dark suspension was stirred in air for 2 h. The mixture was purified by column chromatography (PE/EtOAc = 1:1) and pTLC (PE/EtOAc = 1:1) to afford compounds **4a**–**f, 5a**–**b, 6a**–**d**, and **7a**–**g**. The preparation and data of compound **1** and (−)-saframycin A were the same as reported before [23].

6.2.1. Data of compound *4a*

Yellow solid, yield 80%, mp: 117–119 °C $[\alpha_D^{20}]$: −208 (*c* 0.10, CH_2Cl_2). HRMS calcd for $C_{36}H_{34}F_3N_4O_7$ $[M + H]^+$ 691.2374, found



Scheme 1. Synthesis of (−)-saframycin A analogues.

691.2351. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.62 (d, 1H, J = 8.4 Hz), 7.60 (d, 1H, J = 9.0 Hz), 7.50 (t, 1H, J = 7.8 Hz), 7.45 (d, 1H, J = 15.6 Hz), 6.15 (d, 1H, J = 15.6 Hz), 5.60 (t, 1H, J = 6.6 Hz), 4.29 (s, 1H), 4.04 (s, 3H), 4.03 (s, 1H), 3.91 (s, 3H), 3.89 (s, 1H), 3.66–3.58 (m, 2H), 3.43 (d, 1H, J = 7.2 Hz), 3.11 (dt, 1H, J = 10.8, 2.4 Hz), 2.89 (dd, 1H, J = 17.4, 2.4 Hz), 2.78 (dd, 1H, J = 21.0, 7.2 Hz), 2.50 (d, 1H, J = 21.0 Hz), 2.29 (s, 3H), 1.96 (s, 3H), 1.71 (s, 3H), 1.37 (ddd, 1H, J = 17.4, 11.4, 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.2, 185.6, 182.4, 181.4, 165.1, 155.9, 155.2, 142.2, 141.2, 140.6, 136.6, 135.2, 135.1, 131.4, 129.4, 128.6, 128.4, 126.4, 124.0, 121.1, 116.9, 61.2, 61.0, 58.1, 57.7, 54.5, 54.2, 53.9, 41.5, 41.4, 25.7, 21.1, 8.8, 8.4.

6.2.2. Data of compound **4b**

Yellow solid, yield 75%, mp: 123–125 °C [α_D^{20}]: −115 (c 0.50, CH_2Cl_2). HRMS calcd for $C_{38}H_{36}N_5O_7$ [M + H]$^+$ 674.2609, found 674.2606. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, 1H, J = 4.4 Hz), 8.15 (d, 1H, J = 15.6 Hz), 7.75 (t, 1H, J = 8.0 Hz), 7.70 (dd, 1H, J = 5.6, 3.6 Hz), 7.63 (t, 1H, J = 8.0 Hz), 7.51 (dd, 1H, J = 5.6, 3.6 Hz), 7.35 (d, 1H, J = 4.8 Hz), 6.32 (d, 1H, J = 15.6 Hz), 6.05 (s, 1H), 4.02 (s, 1H), 4.02 (s, 3H), 3.92 (s, 1H), 3.87 (s, 3H), 3.66 (s, 1H), 3.64 (s, 1H), 3.43 (d, J = 7.2 Hz, 1H), 3.13–3.10 (m, 1H), 2.90 (d, J = 15.6 Hz, 1H), 2.78 (dd, J = 20.8, 7.6 Hz, 1H), 2.48 (d, J = 21.2 Hz, 1H), 2.28 (s, 3H), 1.92 (s, 3H), 1.72–1.69 (m, 1H), 1.61 (s, 3H), 1.43–1.40 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 185.6, 182.4, 181.4, 167.7, 164.7, 155.8, 155.1, 149.8, 148.6, 142.3, 141.2, 140.2, 136.6, 135.1, 132.3, 130.0, 129.9, 128.5, 128.4, 127.4, 126.0, 125.9, 123.5, 117.7, 117.0, 61.1, 61.0, 58.3, 57.6, 54.5, 54.2, 54.1, 41.9, 25.6, 21.2, 8.8, 8.5.

6.2.3. Data of compound **4c**

Yellow solid, yield 78%, mp: 140–142 °C [α_D^{20}]: −175 (c 0.20, CH_2Cl_2). HRMS calcd for $C_{36}H_{37}N_4O_8$ [M + H]$^+$ 653.2606, found 653.2596. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 2H, J = 8.0 Hz), 7.32 (d, 1H, J = 14.8 Hz), 6.86 (d, 2H, J = 8.4 Hz), 5.93 (d, 1H, J = 15.6 Hz), 5.53 (t, 1H, J = 6.0 Hz), 4.26 (s, 1H), 4.03 (s, 3H), 4.02 (s, 1H), 3.89 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.62–3.58 (m, 2H), 3.41 (d, 1H, J = 7.2 Hz), 3.09 (d, 1H, J = 11.6 Hz), 2.87 (d, 1H, J = 17.2 Hz), 2.78 (dd, 1H, J = 21.2, 7.6 Hz), 2.49 (d, 1H, J = 21.2 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H), 1.39–1.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2,

Table 1
Cytotoxicity of (−)-saframycin A analogues against ten cell lines.

Compound	Cytotoxicity IC_{50} (nM)[a]									
	HCT-8	BEL-7402	Ketr3	A2780	MCF-7	A549	BGC-803	Hela	HELF	KB
Saframycin A	2.49	1.83	9.56	2.75	6.39	40.44	10.98	1.06	2.54	2.23
4a	43.29	29.68	28.88	39.79	**4.20**[b]	77.08	22.34	7.90	>100	11.70
4b	18.21	18.16	11.49	17.46	**2.23**	**35.74**	17.09	8.33	23.42	5.70
4c	46.66	6.23	11.01	14.42	**5.35**	**23.77**	**6.91**	7.77	4.88	9.04
4d	>100	24.34	52.09	25.46	18.51	96.65	21.23	8.68	>100	28.41
4e	27.36	11.43	15.47	33.74	**5.44**	81.82	**6.27**	3.85	>100	9.85
4f	>100	>100	>100		25.57	>100	31.02	31.18	>100	26.28
5a	58.55	22.39	23.60	43.93	39.47	**10.01**	27.68	10.70	16.69	16.91
5b	>100	5.38	12.94	22.69	8.89	**34.27**	66.25	7.41	18.43	29.44
6a	14.94	3.03	**3.63**	3.67	**1.13**	**18.75**	**4.19**	2.52	3.38	**1.27**
6b	>100	21.01	30.56	47.14	26.06	>100	58.53	43.22	25.72	53.88
6c	21.10	2.02	**6.88**	5.11	**4.79**	69.01	20.03	3.34	**2.18**	3.94
6d	>100						66.25	>100		
7a	43.36	23.74	69.90	29.63	14.86	65.26	21.50	9.51	19.84	16.59
7b	90.51	11.49	19.68	11.15	22.85	**34.95**	26.27	5.29	17.48	14.89
7c	10.53	1.87	**1.61**	7.17	**3.06**	**1.89**	12.11	1.89	**1.53**	**1.85**
7d	12.41	**1.22**	**3.01**	3.87	15.31	**0.95**	16.04	2.58	**1.68**	3.55
7e	22.08	3.80	15.07	11.95	15.61	**30.03**	32.08	7.27	6.57	9.17
7f	>100	16.45	37.29	27.36	45.22	>100	**4.19**	17.40	27.22	17.48
7g	>100	84.73	>100	98.05	24.22	88.62	58.53	26.64	85.37	74.95
1	63.80	32.36	23.70	45.03	17.31	**26.82**	32.08	92.71	19.50	31.44

[a] The IC_{50} values represent the inhibitory concentration of 50% of cell growth.
[b] Boldface: $IC_{50} \leq$ (−)-saframycin A.

185.6, 182.4, 181.3, 166.0, 161.1, 155.9, 155.2, 142.2, 141.6, 141.0, 136.7, 135.1, 129.4, 128.6, 128.4, 127.0, 117.0, 116.9, 114.2 (2C), 61.1, 60.9, 58.1, 57.6, 55.4, 54.5, 54.2, 53.9, 41.5, 41.1, 25.6, 21.1, 8.8, 8.6.

*6.2.4. Data of compound **4d***

Yellow solid, yield 80%, mp: 124–126 °C $[\alpha_D^{20}]$: −177 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{37}H_{39}N_4O_7$ $[M + H]^+$ 651.2813, found 651.2800. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, 1H, J = 15.2 Hz), 7.32 (d, 2H, J = 7.6 Hz), 7.17 (d, 2H, J = 8.0 Hz), 6.02 (d, 1H, J = 15.6 Hz), 5.60 (t, 1H, J = 6.4 Hz), 4.26 (s, 1H), 4.04 (s, 3H), 4.02 (s, 1H), 3.89 (s, 1H), 3.86 (s, 3H), 3.61–3.59 (m, 2H), 3.41 (d, 1H, J = 7.6 Hz), 3.09 (d, 1H, J = 11.2 Hz), 2.87 (d, 1H, J = 17.6 Hz), 2.78 (dd, 1H, J = 21.2, 7.6 Hz), 2.66 (q, 2H, J = 7.6 Hz), 2.48 (d, 1H, J = 21.2 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H), 1.36 (ddd, 1H, J = 17.2, 11.6, 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2, 185.6, 182.4, 181.3, 165.9, 155.9, 155.2, 146.7, 142.2, 141.9, 141.0, 136.7, 135.1, 131.8, 128.6, 128.3 (3C), 127.9 (2C), 118.4, 117.0, 61.1, 60.9, 58.1, 57.6, 54.5, 54.2, 53.9, 41.5, 41.2, 28.8, 25.6, 21.1, 15.4, 8.8, 8.5.

*6.2.5. Data of compound **4e***

Yellow solid, yield 76%, mp: 81–83 °C $[\alpha_D^{20}]$: −122 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{38}H_{41}N_4O_{10}$ $[M + H]^+$ 713.2817, found 713.2795. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1H, J = 16.0 Hz), 7.10 (d, 1H, J = 8.8 Hz), 6.65 (d, 1H, J = 8.4 Hz), 6.11 (d, 1H, J = 15.6 Hz), 5.55 (t, 1H, J = 6.4 Hz), 4.32 (s, 1H), 4.26 (s, 1H), 4.04 (s, 3H), 4.02 (s, 1H), 3.89 (s, 6H), 3.86 (s, 6H), 3.59–3.57 (m, 2H), 3.41 (d, 1H, J = 7.2 Hz), 3.10 (d, 1H, J = 11.2 Hz), 2.88 (d, 1H, J = 17.2 Hz), 2.78 (dd, 1H, J = 21.2, 7.6 Hz), 2.48 (d, 1H, J = 21.2 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.76 (s, 3H), 1.38–1.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.1, 185.6, 182.5, 181.4, 166.4, 155.9, 155.2, 153.1, 142.2, 140.9, 136.9, 135.1, 130.9, 128.8, 128.6, 128.4, 123.3, 121.4, 118.8, 117.0, 107.4, 65.6, 61.1, 60.9, 58.2, 57.8, 56.1, 54.5, 54.2, 54.0, 41.5, 30.6, 25.6, 21.2, 19.2, 13.7, 8.8, 8.5.

*6.2.6. Data of compound **4f***

Yellow solid, yield 77%, mp: 115–117 °C $[\alpha_D^{20}]$: −105 (*c* 0.50, CH_2Cl_2). HRMS calcd for $C_{39}H_{43}N_4O_7$ $[M + H]^+$ 679.3126, found 679.3125. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.34 (m, 5H), 6.04 (d, 1H, J = 15.6 Hz), 5.60 (t, 1H, J = 6.4 Hz), 4.26 (s, 1H), 4.04 (s, 3H), 4.03 (s, 1H), 3.90 (s, 1H), 3.85 (s, 3H), 3.61–3.59 (m, 2H), 3.42 (d, 1H, J = 7.2 Hz), 3.10 (d, 1H, J = 11.2 Hz), 2.88 (d, 1H, J = 17.6 Hz), 2.79 (dd, 1H, J = 21.2, 7.2 Hz), 2.48 (d, 1H, J = 21.2 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.74 (s, 3H), 1.39–1.35 (m, 1H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.1, 185.6, 182.4, 181.3, 165.9, 155.9, 155.2, 153.6, 142.2, 141.8, 141.0, 136.7, 135.1, 131.5, 128.6, 128.4, 127.7 (2C), 125.7 (2C), 118.5, 117.0, 61.1, 60.9, 58.1, 57.6, 54.5, 54.2, 53.9, 41.5, 41.3, 34.8, 31.1 (3C), 25.6, 21.2, 8.8, 8.5.

*6.2.7. Data of compound **5a***

Yellow solid, yield 70%, mp: 126–128 °C $[\alpha_D^{20}]$: −94 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{35}H_{36}N_5O_8$ $[M + H]^+$ 654.2558, found 654.2536. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, 2H, J = 7.5 Hz), 7.52 (t, 1H, J = 7.5 Hz), 7.44 (t, 2H, J = 7.5 Hz), 6.97 (t, 1H, J = 5.0 Hz), 6.58 (t, 1H, J = 6.0 Hz), 4.15 (s, 1H), 4.04 (s, 1H), 4.00 (s, 3H), 3.93 (s, 3H), 3.88 (s, 1H), 3.82 (dd, 1H, J = 16.0, 6.0 Hz), 3.65 (dd, 1H, J = 16.0, 5.0 Hz), 3.49–3.47 (m, 2H), 3.41 (d, 1H, J = 7.5 Hz), 3.07 (d, 1H, J = 11.5 Hz), 2.87 (dd, 1H, J = 17.5, 2.0 Hz), 2.77 (dd, 1H, J = 21.0, 7.5 Hz), 2.40 (d, 1H, J = 20.5 Hz), 2.30 (s, 3H), 1.86 (s, 3H), 1.80 (s, 3H), 1.68–1.62 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.8, 185.2, 182.7, 181.2, 169.3, 167.8, 155.6, 155.4, 142.1, 141.9, 135.8, 135.2, 132.7, 132.1, 128.6 (2C), 128.5, 127.2 (2C), 117.1, 61.1, 61.0, 58.4, 56.8, 54.6, 54.3 (2C), 44.0, 41.5, 40.8, 25.3, 21.2, 8.7 (2C).

*6.2.8. Data of compound **5b***

Yellow solid, yield 80%, mp: 116–118 °C $[\alpha_D^{20}]$: −32 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{31}H_{37}N_4O_8$ $[M + H]^+$ 593.2606, found 593.2612. ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.28 (d, 1H, J = 8.4 Hz), 4.08 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.96 (s, 1H), 3.85 (s, 1H), 3.60 (dd, 1H, J = 13.8, 9.6 Hz), 3.43–3.41 (m, 1H), 3.14 (d, 1H, J = 9.0 Hz), 2.93 (d, 1H, J = 14.4 Hz), 2.88 (dd, 1H, J = 17.4, 2.4 Hz), 2.83 (dd, 1H, J = 21.0, 7.2 Hz), 2.32 (s, 3H), 2.19 (d, 1H, J = 21.0 Hz), 1.95 (s, 3H), 1.88 (s, 3H), 1.35–1.30 (m, 1H), 1.18 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.2, 185.6, 182.3, 180.8, 155.8, 155.4, 141.2, 139.8, 136.6, 136.1, 128.2, 127.5, 116.6, 79.6, 61.1, 60.9, 58.1, 57.0, 54.4, 54.2, 53.6, 42.3, 41.6, 28.4, 28.2, 28.0, 27.9, 25.2, 21.5, 8.6, 8.5.

*6.2.9. Data of compound **6a***

Yellow solid, yield 76%, mp: 130–132 °C $[\alpha_D^{20}]$: −143 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{36}H_{39}N_4O_{10}$ $[M + H]^+$ 687.2661, found

687.2678. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.61 (s, 2H), 5.91 (t, 1H, J = 6.6 Hz), 4.20 (s, 1H), 4.05 (s, 3H), 3.97 (s, 1H), 3.95 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.81 (s, 6H), 3.78–3.74 (m, 1H), 3.51 (dd, 1H, J = 12.6, 6.6 Hz), 3.41 (d, 1H, J = 7.2 Hz), 3.10 (d, 1H, J = 11.4 Hz), 2.90 (d, 1H, J = 17.4 Hz), 2.74 (dd, 1H, J = 21.0, 7.8 Hz), 2.48 (d, 1H, J = 21.0 Hz), 2.25 (s, 3H), 2.04 (s, 3H), 1.73 (s, 3H), 1.41 (ddd, 1H, J = 17.4, 11.4, 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.7, 182.5, 181.3, 167.4, 156.0, 154.8, 153.2 (2C), 142.2, 141.4, 136.7, 134.6, 129.5, 128.6, 128.4, 117.1, 103.8 (3C), 61.2, 61.8, 58.3, 57.7, 56.1 (3C), 54.5, 54.1, 54.0, 41.5, 41.3, 26.0, 21.1, 8.8, 8.4.

6.2.10. Data of compound ***6b***

Yellow solid, yield 74%, mp: 117–119 °C [α_D^{20}]: −89 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{34}H_{32}F_3N_4O_7$ [M + H]$^+$ 665.2218, found 665.2232. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84 (s, 1H), 7.74 (d, 1H, J = 7.2 Hz), 7.55 (d, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.8 Hz), 6.22 (t, 1H, J = 6.6 Hz), 4.26 (s, 1H), 4.04 (s, 3H), 4.02 (s, 1H), 3.95 (s, 1H), 3.90 (s, 3H), 3.77 (dd, 1H, J = 14.4, 7.2 Hz), 3.55 (dt, 1H, J = 14.4, 4.8 Hz), 3.44 (d, 1H, J = 7.2 Hz), 3.12 (dt, 1H, J = 10.8, 2.4 Hz), 2.90 (d, 1H, J = 17.4 Hz), 2.79 (dd, 1H, J = 20.4, 7.2 Hz), 2.42 (d, 1H, J = 21.0 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.80 (s, 3H), 1.30 (ddd, 1H, J = 17.4, 11.4, 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.4, 182.3, 181.5, 166.0, 156.0, 155.1, 142.0, 140.9, 136.6, 135.1, 134.6, 129.2 (2C), 128.5, 128.4, 128.3, 124.2, 116.8, 61.1, 60.9, 58.3, 57.7, 54.5, 54.1, 54.0, 42.1, 41.5, 25.6, 21.3, 8.8, 8.6.

6.2.11. Data of compound ***6c***

Yellow solid, yield 74%, mp: 125–127 °C [α_D^{20}]: −133 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{34}H_{33}N_4O_9$ [M + H]$^+$ 641.2242, found 641.2247. ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.83 (d, 1H, J = 8.4 Hz), 6.68 (d, 1H, J = 8.4 Hz), 6.00 (s, 2H), 5.87 (t, 1H, J = 6.6 Hz), 4.16 (s, 1H), 4.06 (s, 3H), 4.01 (s, 1H), 3.95 (s, 1H), 3.89 (s, 3H), 3.74 (dd, 1H, J = 14.4, 7.2 Hz), 3.53 (dt, 1H, J = 14.4, 4.8 Hz), 3.43 (d, 1H, J = 7.2 Hz), 3.10 (dt, 1H, J = 11.4, 2.4 Hz), 2.86 (dd, 1H, J = 17.4, 2.4 Hz), 2.79 (dd, 1H, J = 20.4, 7.2 Hz), 2.42 (d, 1H, J = 20.4 Hz), 2.28 (s, 3H), 1.94 (s, 3H), 1.80 (s, 3H), 1.28–1.22 (m, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.5, 182.3, 181.1, 166.6, 156.2, 155.1, 150.5, 148.1, 142.0, 140.6, 136.6, 135.2, 128.3, 128.1, 128.0, 120.7, 116.9, 107.9, 107.4, 101.8, 61.1, 60.9, 58.2, 57.6, 54.5, 54.2, 53.9, 41.5, 41.2, 25.5, 21.3, 8.7, 8.6.

6.2.12. Data of compound ***6d***

Yellow solid, yield 60%, mp: 132–134 °C [α_D^{20}]: −25 (*c* 0.10, CH_2Cl_2). HRMS calcd for $C_{33}H_{31}BrClN_4O_7$ [M + H]$^+$ 709.1059, found 709.1058. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (s, 1H), 7.45 (d, 1H, J = 8.4 Hz), 7.14 (d, 1H, J = 8.4 Hz), 6.22 (t, 1H, J = 7.2 Hz), 4.15 (s, 1H), 4.07 (s, 3H), 4.05 (s, 1H), 3.98 (s, 1H), 3.94 (s, 3H), 3.98–3.95 (m, 1H), 3.45 (d, 1H, J = 7.8 Hz), 3.41 (dt, 1H, J = 15.0, 4.2 Hz), 3.14 (dt, 1H, J = 11.4, 3.0 Hz), 2.85 (dd, 1H, J = 17.4, 1.8 Hz), 2.80 (dd, 1H, J = 21.0, 7.8 Hz), 2.32 (d, 1H, J = 21.0 Hz), 2.29 (s, 3H), 1.94 (s, 3H), 1.79 (s, 3H), 1.37 (ddd, 1H, J = 28.8, 13.8, 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.5, 182.2, 181.1, 164.6, 156.3, 155.2, 141.6, 140.6, 136.2, 135.5, 135.0, 134.7, 133.6, 131.5, 128.7, 128.2, 127.9, 121.3, 116.6, 61.1, 61.0, 58.1, 57.4, 54.5, 54.1, 53.9, 41.6, 41.5, 25.5, 21.4, 8.7, 8.6.

6.2.13. Data of compound ***7a***

Yellow solid, yield 75%, mp: 119–121 °C [α_D^{20}]: −121 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{36}H_{34}N_5O_7$ [M + H]$^+$ 648.2453, found 648.2464. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 8.5 Hz), 7.86 (d, 1H, J = 8.0 Hz), 7.84 (s, 1H), 7.79 (d, 1H, J = 8.0 Hz), 7.75 (t, 1H, J = 7.5 Hz), 7.63 (t, 1H, J = 7.5 Hz), 4.16 (s, 1H), 4.10 (s, 1H), 4.09 (s, 3H), 3.93 (s, 1H), 3.44 (d, 1H, J = 14.0 Hz), 3.39 (d, 1H, J = 7.0 Hz), 3.30 (s, 3H), 3.09 (d, 1H, J = 11.0 Hz), 2.88 (d, 1H, J = 17.0 Hz), 2.75 (dd, 1H, J = 21.0, 7.0 Hz), 2.50 (d, 1H, J = 20.5 Hz), 2.20 (s, 3H), 2.04–2.01 (m, 1H), 2.01 (s, 3H), 1.60 (s, 3H), 1.60–1.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 185.6, 182.1, 181.0, 164.6, 155.9, 154.6, 149.3, 146.2, 142.7, 142.1, 137.5, 136.0, 134.5, 130.4, 129.6, 129.2, 128.4, 128.2, 127.7, 127.3, 119.0, 117.2, 61.2, 60.2, 58.4, 57.3, 54.6, 54.2, 54.1, 41.4, 40.1, 25.7, 21.0, 8.8, 8.6.

6.2.14. Data of compound ***7b***

Yellow solid, yield 62%, mp: 127–129 °C [α_D^{20}]: −149 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{35}H_{34}N_5O_7$ [M + H]$^+$ 636.2453, found 636.2468. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.00 (s, 1H), 7.48 (d, 1H, J = 8.0 Hz), 7.40 (d, 1H, J = 8.0 Hz), 7.28 (t, 1H, J = 8.0 Hz), 7.12 (t, 1H, J = 8.0 Hz), 6.31 (s, 1H), 5.93 (t, 1H, J = 6.5 Hz), 4.15 (s, 1H), 4.06 (s, 3H), 4.00 (s, 1H), 3.99 (s, 1H), 3.84–3.80 (m, 1H), 3.64–3.61 (m, 1H), 3.61 (s, 3H), 3.40 (d, 1H, J = 7.5 Hz), 3.09 (d, 1H, J = 11.0 Hz), 2.88 (d, 1H, J = 17.0 Hz), 2.73 (dd, 1H, J = 21.0, 7.5 Hz), 2.50 (d, 1H, J = 21.0 Hz), 2.25 (s, 3H), 1.96 (s, 3H), 1.64 (s, 3H), 1.32 (ddd, 1H, J = 17.5, 11.5, 2.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.3, 185.4, 182.2, 181.1, 161.3, 155.9, 155.2, 142.1, 141.6, 136.2, 136.1, 135.0, 129.8, 128.5, 128.2, 127.3, 124.9, 121.8, 121.0, 117.0, 112.2, 101.4, 61.2, 60.7, 58.2, 57.4, 54.6, 54.1, 54.1, 41.4, 40.1, 25.6, 21.1, 8.8, 8.5.

6.2.15. Data of compound ***7c***

Yellow solid, yield 64%, mp: 120–122 °C [α_D^{20}]: −75 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{31}H_{31}N_6O_7$ [M + H]$^+$ 599.2249, found 599.2238. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.70 (s, 1H), 8.24 (s, 1H), 7.46 (t, 1H, J = 6.5 Hz), 4.08 (s, 1H), 4.07 (s, 3H), 4.05 (s, 1H), 3.99 (s, 1H), 3.94 (s, 3H), 3.86–3.82 (m, 1H), 3.58–3.53 (m, 1H), 3.44 (d, 1H, J = 7.5 Hz), 3.12 (d, 1H, J = 11.5 Hz), 2.87 (d, 1H, J = 17.5 Hz), 2.82 (dd, 1H, J = 21.0, 7.5 Hz), 2.39 (d, 1H, J = 21.0 Hz), 2.32 (s, 3H), 1.91 (s, 3H), 1.90 (s, 3H), 1.35–1.32 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.1, 185.4, 182.3, 180.8, 163.0, 156.0, 155.1, 147.5, 144.6, 143.7, 142.4, 142.1, 141.5, 135.8, 135.2, 128.3, 128.1, 116.8, 61.2, 61.1, 58.5, 57.0, 54.5, 54.3, 54.2, 41.6, 40.6, 25.2, 21.4, 8.8, 8.6.

6.2.16. Data of compound ***7d***

Yellow solid, yield 65%, mp: 130–132 °C [α_D^{20}]: −75 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{31}H_{31}N_4O_8$ [M + H]$^+$ 587.2136, found 587.2120. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H), 6.89 (s, 1H), 6.42 (s, 1H), 6.09 (t, 1H, J = 6.5 Hz), 4.09 (s, 1H), 4.05 (s, 3H), 4.02 (s, 1H), 3.97 (s, 1H), 3.96 (s, 3H), 3.77 (dd, 1H, J = 13.0, 7.5 Hz), 3.48 (dt, 1H, J = 14.5, 5.0 Hz), 3.44 (d, 1H, J = 7.5 Hz), 3.12 (d, 1H, J = 11.0 Hz), 2.88 (dd, 1H, J = 17.5, 2.5 Hz), 2.82 (dd, 1H, J = 21.0, 7.5 Hz), 2.40 (d, 1H, J = 21.5 Hz), 2.30 (s, 3H), 1.94 (s, 3H), 1.92 (s, 3H), 1.34–1.30 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.1, 185.4, 182.3, 180.9, 158.0, 156.0, 155.1, 147.3, 144.0, 142.0, 141.1, 136.1, 135.3, 128.3, 128.1, 116.8, 114.8, 112.3, 61.1, 60.4, 58.3, 57.2, 54.5, 54.3, 54.0, 41.5, 40.2, 25.2, 21.4, 8.8, 8.7.

6.2.17. Data of compound ***7e***

Yellow solid, yield 65%, mp: 127–129 °C [α_D^{20}]: −93 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{32}H_{32}N_5O_7$ [M + H]$^+$ 598.2296, found 598.2272. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, 1H, J = 4.0 Hz), 7.92 (d, 1H, J = 7.5 Hz), 7.77–7.72 (m, 2H), 7.36 (t, 1H, J = 6.5 Hz), 4.09 (s, 1H), 4.07 (s, 3H), 4.03 (s, 1H), 3.99 (s, 1H), 3.89 (s, 3H), 3.76 (dd, 1H, J = 12.5, 5.5 Hz), 3.61–3.59 (m, 1H), 3.43 (d, 1H, J = 7.5 Hz), 3.10 (d, 1H, J = 11.0 Hz), 2.84 (d, 1H, J = 16.5 Hz), 2.81 (dd, 1H, J = 21.0, 7.5 Hz), 2.42 (d, 1H, J = 21.0 Hz), 2.31 (s, 3H), 1.90 (s, 3H), 1.89 (s, 3H), 1.42–1.36 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 186.1, 185.4, 182.3, 180.8, 164.3, 156.0, 155.1, 149.2, 148.0, 142.0, 141.5, 137.3, 136.1, 135.1, 128.1, 127.9, 126.2, 122.4, 116.9, 61.1, 61.0, 58.4, 57.1, 54.6, 54.3, 54.2, 41.5, 40.5, 25.2, 21.3, 8.9, 8.7.

6.2.18. Data of compound ***7f***

Yellow solid, yield 62%, mp: 125–127 °C [α_D^{20}]: −73 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{31}H_{31}N_4O_7S$ [M + H]$^+$ 603.1908, found 603.1901. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 (d, 1H, J = 4.8 Hz), 7.19

(d, 1H, $J = 4.8$ Hz), 6.98 (t, 1H, $J = 4.8$ Hz), 5.77 (t, 1H, $J = 6.6$ Hz), 4.12 (s, 1H), 4.06 (s, 3H), 4.03 (s, 1H), 3.97 (s, 1H), 3.90 (s, 3H), 3.77 (dd, 1H, $J = 14.4$, 7.8 Hz), 3.50 (dt, 1H, $J = 14.4$, 5.4 Hz), 3.44 (d, 1H, $J = 7.8$ Hz), 3.12 (dt, 1H, $J = 10.8$, 2.4 Hz), 2.87 (dd, 1H, $J = 17.4$, 2.4 Hz), 2.82 (dd, 1H, $J = 21.0$, 7.8 Hz), 2.40 (d, 1H, $J = 21.0$ Hz), 2.28 (s, 3H), 1.93 (s, 3H), 1.90 (s, 3H), 1.30 (ddd, 1H, $J = 17.4$, 11.4, 2.4 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 186.1, 185.4, 182.3, 181.0, 161.6, 156.1, 155.3, 141.9, 140.9, 137.5, 136.2, 135.3, 129.6, 128.8, 128.3, 128.1, 127.9, 116.8, 61.1, 61.0, 58.2, 57.4, 54.5, 54.2, 54.0, 41.5, 40.9, 25.5, 21.3, 8.8, 8.7.

6.2.19. Data of compound ***7g***

Yellow solid, yield 70%, mp: 124–126 °C [α_D^{20}]: −120 (*c* 0.20, CH_2Cl_2). HRMS calcd for $C_{36}H_{34}N_5O_7$ $[M + H]^+$ 648.2453, found 648.2465. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (d, 1H, $J = 8.5$ Hz), 8.00 (d, 1H, $J = 8.5$ Hz), 7.87–7.84 (m, 2H), 7.79 (d, 1H, $J = 8.0$ Hz), 7.75 (t, 1H, $J = 8.0$ Hz), 7.63 (t, 1H, $J = 7.0$ Hz), 4.16 (s, 1H), 4.08 (s, 3H), 4.04 (s, 1H), 3.93 (s, 1H), 3.44 (d, 1H, $J = 14.5$ Hz), 3.39 (d, 1H, $J = 7.5$ Hz), 3.30 (s, 3H), 3.08 (d, 1H, $J = 11.0$ Hz), 2.88 (d, 1H, $J = 16.5$ Hz), 2.75 (dd, 1H, $J = 21.0$, 7.5 Hz), 2.50 (d, 1H, $J = 21.0$ Hz), 2.19 (s, 3H), 2.06–2.03 (m, 1H), 2.01 (s, 3H), 1.60 (s, 3H), 1.60–1.56 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.7, 185.6, 182.1, 181.0, 164.6, 155.9, 154.6, 149.3, 146.2, 142.7, 142.1, 137.5, 136.0, 134.5, 130.4, 129.6, 129.2, 128.4, 128.2, 127.7, 127.3, 119.0, 117.2, 61.2, 60.2, 58.4, 57.3, 54.6, 54.2, 54.1, 41.4, 40.1, 25.7, 21.0, 8.8, 8.6.

6.3. Cytotoxicity assay

Each compound was tested *in vitro* against ten different cell lines, including HCT-8 (human colon cancer cell line), BEL-7402 (human hepatic carcinoma cell line), Ketr3 (human renal cell carcinoma cell line), A2780 (human ovarian cancer cell line), MCF-7 (human breast cancer cell line), A549 (human lung cancer cell line), BGC-803 (human gastric adenocarcinoma cell line), Hela (human cervical cancer cell line), HELF (human embryonic lung fibroblast cell line), and KB (human oral epidermoid carcinoma cell line). Each sample was prepared as a 20.0 mM stock solution that was dissolved in DMSO and added to the cells with less than 1% DMSO in the final drug dilution with culture medium. Cell lines were cultured in PRMI1640 or DMEM/F12 supplemented with 10% foetal 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 × 10^4 cells/mL and were allowed to adhere for 24 h before treatment with tested compounds in DMSO solution (10^{-8}, 10^{-9}, 10^{-10} mol/L final concentration). The Cells were incubated for 72 h after treated with different concentrations of all tested compounds, and cell viability was assayed by MTT assay. 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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Appendix. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2012.01.017.

References

[1] J.D. Scott, R.M. Williams, Chem. Rev. 102 (2002) 1669–1730.
[2] K.L. Rinehart, Med. Drug Rev. 20 (2000) 1–27.
[3] D. Friedman, Z. Hu, E.A. Kolb, B. Gorfain, K.W. Scotto, Cancer Res. 62 (2002) 3377–3381.
[4] Y. Takebayashi, P. Pourquier, D.B. Zimonic, K. Nakayama, S. Emmert, T. Ueda, Y. Urasaki, A. Kanzaki, S. Akiyama, N. Popescu, K.H. Kraemer, Y. Pommier, Nat. Med. 7 (2001) 961–966.
[5] G.J. Aune, T. Furuta, Y. Pommier, Anticancer Drug 13 (2002) 545–555.
[6] T.F. Molinski, D.S. Dalisay, S.L. Lievens, J.P. Saludes, Nat. Rev. Drug Discov. 8 (2009) 69–85.
[7] E.M. Ocio, P. Maiso, X. Chen, M. Garayoa, S. Alvarez-Fernandez, L. San-Segundo, D. Vilanova, L. Lopez-Corral, J.C. Montero, T. Hernandez-Iglesias, E. de Alava, C. Galmarinini, P. Aviles, C. Cuevas, J.F. San-Miguel, A. Pandiella, Blood 113 (2009) 3781–3791.
[8] J.F.M. Leal, V. Garcia-Hernandez, V. Moneo, A. Domingo, J.A. Bueren-Calabuig, A. Negri, F. Gago, M.J. Guillen-Navarro, P. Aviles, C. Cuevas, L.F. Garcia-Fernandez, C.M. Galmarini, Biochem. Pharmacol. 78 (2009) 162–170.
[9] A.T. Plowright, S.E. Schaus, A.G. Myers, Chem. Biol. 9 (2002) 607–618.
[10] T. Arai, K. Takahashi, A.J. Kubo, Antibiot. 30 (1977) 1015–1018.
[11] T. Arai, K. Takahashi, S. Nakahara, A. Kubo, Experientia 36 (1980) 1025–1027.
[12] (a) J.W. Lown, A.V. Joshua, H.H. Chen, J. Can. Chem. 59 (1981) 2945–2952;
(b) J.W. Lown, A.V. Joshua, J.S. Lee, Biochemistry 21 (1982) 419–428;
(c) K.E. Rao, J.W. Lown, Chem. Res. Toxicol. 3 (1990) 262–267;
(d) K.E. Rao, J.W. Lown, Biochemistry 31 (1992) 12076–12082.
[13] G.C. Hill, W.A. Remers, J. Med. Chem. 34 (1991) 1990–1998.
[14] (a) Y. Takebayashi, P. Pourquier, A. Yoshida, G. Kohlhagen, Y. Pommier, Proc. Natl. Acad. Sci. U.S.A 96 (1999) 7196–7201;
(b) S. Jin, B. Gorfajn, G. Faircloth, K.W. Scotto, Proc. Natl. Acad. Sci. U.S.A 97 (2000) 6775–6779;
(c) M. Minuzzo, S. Marchini, M. Broggini, G. Faircloth, M. D'Incalci, R. Mantovani, Proc. Natl. Acad. Sci. U.S.A 97 (2000) 6780–6784.
[15] A.G. Myers, A.T. Plowright, J. Am. Chem. Soc. 123 (2001) 5114–5115.
[16] K. Charupant, N. Daikuhara, E. Saito, S. Amnuoypol, K. Suwanborirux, T. Owa, N. Saito, Bioorg. Med. Chem. 17 (2009) 4548–4558.
[17] J.W. Lane, A. Estevez, K. Mortara, O. Callan, J.R. Spencer, R.M. Williams, Bioorg. Med. Chem. Lett. 16 (2006) 3180–3183.
[18] B.J. Wright, C. Chan, S.L. Danishefsky, J. Nat. Prod. 71 (2008) 409–414.
[19] J.F. González, E. de la Cuesta, C. Avendano, Bioorg. Med. Chem. 15 (2007) 112–118.
[20] Z.Z. Liu, Ye. Wang, Y.F. Tang, S.Z. Chen, X.G. Chen, Bioorg. Med. Chem. Lett. 16 (2006) 1282–1285.
[21] W. Liu, W.F. Dong, X.W. Liao, Z. Yan, B.H. Guan, N. Wang, Z.Z. Liu, Bioorg. Med. Chem. Lett. 21 (2011) 1419–1421.
[22] J.R. Spencer, M. Sendzik, J. Oeh, P. Sabbatini, S.A. Dalrymple, C. Magill, H.M. Kim, P.L. Zhang, N. Squires, K.G. Moss, J. Sukbuntherng, D. Graupe, J. Eksterowicz, P.R. Young, A.G. Myers, M.J. Green, Bioorg. Med. Chem. Lett. 16 (2006) 4884–4888.
[23] W.F. Dong, W. Liu, X.W. Liao, B.H. Guan, S.Z. Chen, Z.Z. Liu, J. Org. Chem. 76 (2011) 5363–5368.