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Synthesis and cytotoxicity of (−)-renieramycin G analogs

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ABSTRACT

(−)-Renieramycin G and fifteen C-22 analogs were prepared employing L-tyrosine as the chiral starting material. These analogs, along with (−)-renieramycin G itself, were evaluated in vitro for cytotoxicity against HCT-8, BEL-7402, A2780, MCF-7, A549, BGC-823, Ketr3, KB, Hela cells. The IC_{50} values of most of these analogs were at the level of μM. Among these analogs, 2-thiophenecarboxylate ester derivative **17** exhibited potent cytotoxic activity against KB cell line with the IC_{50} of 20 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 (−)-renieramycin G derivatives.

The tetrahydroisoquinoline family[1] of alkaloids includes a number of natural compounds that display a range of biological properties such as antitumor and antimicrobial activities. Ecteinascidin 743 (Et 743) is the most potent one of this family. The structure–activity relationship of Et 743[2] and saframycin[3–5] had been studied. So far, the research in this field has resulted in the discovery of a few promising antitumor analogs,[6] such as phthalascidin (Pt 650)[2,7] and Zalypsis®[8–10] (Fig. 1).

(−)-Renieramycin G was isolated from the marine sponge *Xestospongia caycedoi* by Davidson in 1992.[11] Despite having an amide carbonyl residue at C-21, which was unique in this family, it was reported to retain cytotoxicity against KB and LoVo cell lines with MIC values of 0.5 and 1.0 μg/mL,[12] respectively. This result is surprising because virtually all other members of the tetrahydroisoquinoline alkaloids with cytotoxic activity possess a carbinolamine or cyano function at C-21, which permits the formation of a potent, electrophilic iminium ion species involving in the formation of covalent bonds to DNA and possibly, other biomacromolecules at this position.

There have been several reports on the total synthesis of (−)-renieramycin G.[13–15] A few studies on the structure–activity relationship of the related tetrahydoisoquinoline alkaloids have also been reported.[16–20] However, the structure–activity relationship of (−)-renieramycin G has not been studied so far. In this paper, we reported the total synthesis and the cytotoxic activities of (−)-renieramycin G and its C-22 derivatives.

Our synthesis of (−)-renieramycin G via a new method employing L-tyrosine as the chiral starting material has been reported previously.[15] In this report, we tried a more efficient total synthetic route for the synthesis of (−)-renieramycin G and its C-22 analogs, which avoided the use of the Br protection group on the left benzene ring (Scheme 1).

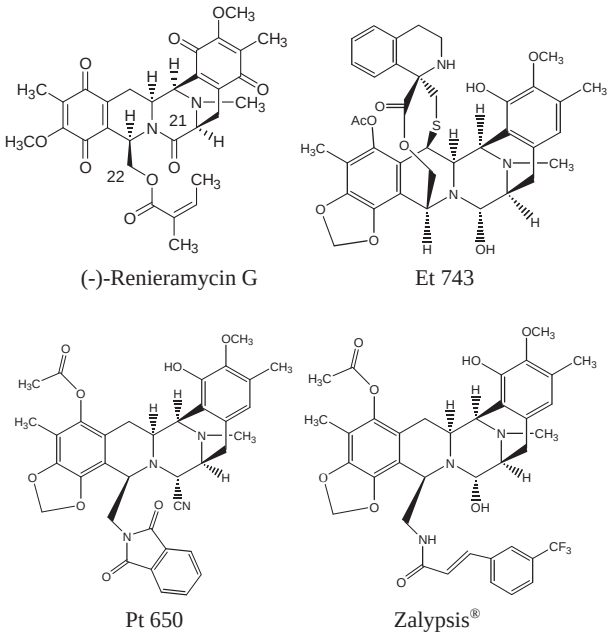

Figure 1. Structures of tetrahydroisoquinoline compounds.

The synthesis of amino acid **1** and the key 1,2,3,4-tetrahydroisoquinoline precursor **2** basically followed our published procedures.[15,21] The difference was that the use of the bromine

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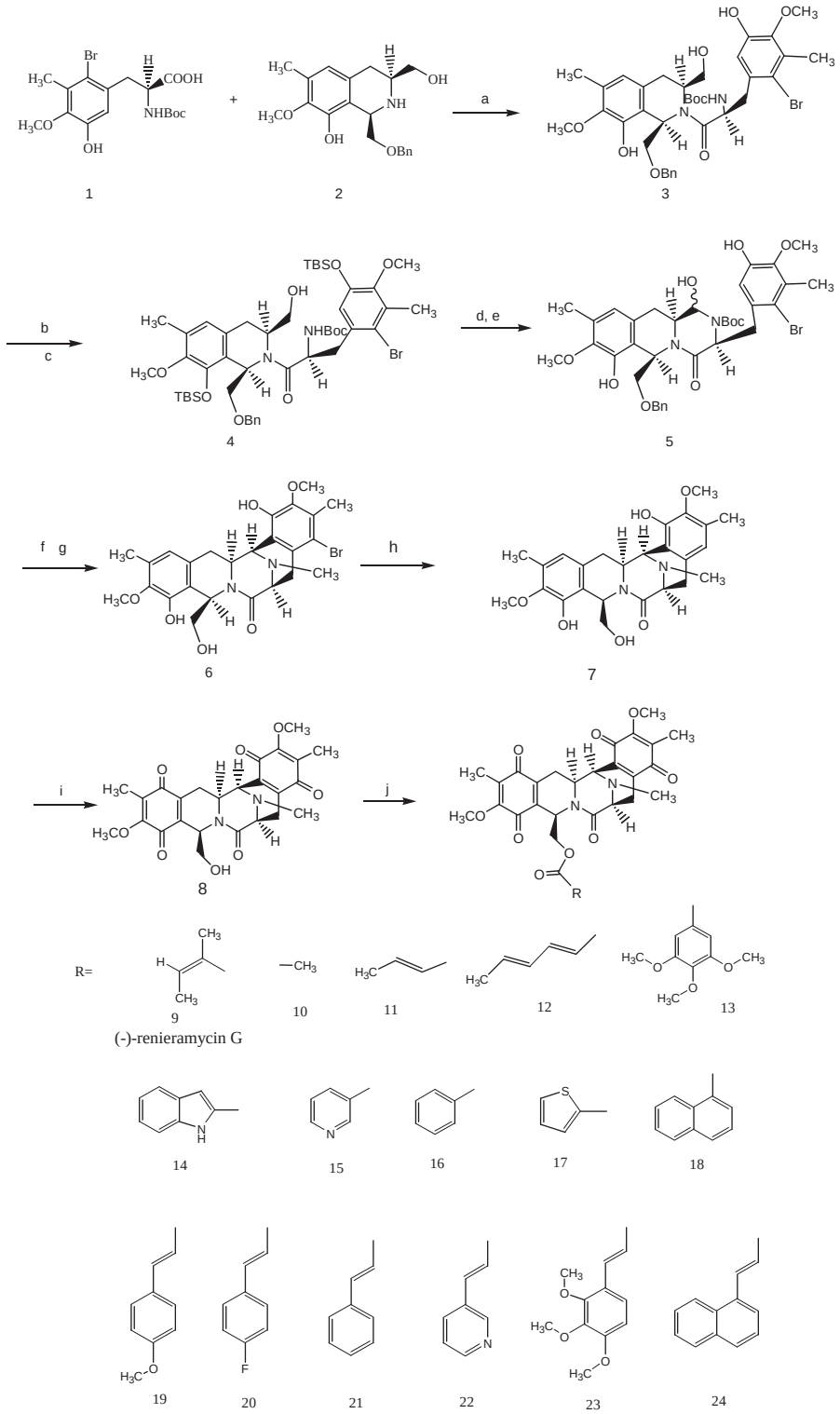

Scheme 1. Reagents and conditions: (a) BOPCl, Et_3N, CH_2Cl_2, 88%; (b) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 88%; (c) HCOOH, THF, H_2O, 92%; (d) Dess–Martin periodinane, CH_2Cl_2, 94%; (e) TBAF, THF, 2 h, 90% (f) CF_3SO_3H, 82%; (g) HCHO, $NaBH_3CN$, HOAc, CH_3OH, 83%; (h) H_2 (50 psi), $Pd(OH)_2$, CH_3OH, 12 h, 87%; (i) air, salcomine, CH_3CN, 86%; (j) DMAP, EDC, CH_2Cl_2, 74%. Salcomine = *N*,*N*′-bis(salicylidene) ethylenediaminocobalt (II) hydrate.

protecting groups on the benzene ring for the synthesis of precursor **2** was obviated. 1,2,3,4-tetrahydroisoquinoline **2** was first coupled with **1** through the action of bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOPCl) to afford amide **3**. Next, complete silylation of compound **3** with *tert*-butyldimethylsilyl chloride (TBSCl), and the subsequent cleavage of the TBS group of the primary alcohol provided compound **4**. Oxidation of **4** with Dess–Martin periodinane provided hemiaminal as a mixture of diastereomers. Cleavage of the aryl TBS ether using TBAF provided compound **5**. Treatment of **5** with CF_3SO_3H at room temperature provided pentacyclic compound in a satisfactory yield with the Boc- and *O*-benzyl groups being removed simultaneously. Without purification, the crude pentacyclic product was reductively methylated with HCHO provided product **6**, which was further converted into

Table 1
Cytotoxicity against nine cell lines of (−)-renieramycin G and its analogs

Compounds	Cytotoxicity IC_{50} (μM)								
	HCT-8	BEL-7402	A2780	MCF-7	A549	BGC-823	Ketr3	KB	Hela
9	8.81	9.07	4.17	3.78	5.00	3.37	3.42	3.30	2.88
10	5.68	3.96	3.26	4.92	4.49	4.27	4.58	2.25	2.68
11	24.66	23.90	25.29	23.78	7.42	10.68	17.24	5.28	12.72
12	3.47	2.13	2.44	2.54	3.20	3.50	3.86	2.03	2.43
13	2.73	2.26	2.16	2.04	2.23	1.18	2.16	1.79	1.28
14	7.85	4.59	3.80	3.88	4.07	2.60	4.42	3.36	2.70
15	19.43	6.47	12.20	17.45	5.94	3.38	4.62	3.16	3.39
16	6.06	3.78	3.07	4.94	3.88	8.35	8.82	2.83	3.10
17	1.48	1.60	1.44	1.86	0.71	0.52	1.67	0.02	0.47
18	27.97	10.92	14.97	14.08	12.46	17.51	13.77	5.41	7.58
19	8.85	7.28	4.16	3.74	8.34	3.84	3.12	3.73	2.81
20	9.15	14.18	15.75	9.67	8.32	7.43	10.44	3.95	9.99
21	5.00	2.30	5.00	3.55	5.00	3.31	7.83	2.96	4.39
22	2.05	2.30	2.24	2.23	2.05	1.26	1.43	0.39	1.18
23	12.44	14.03	16.76	10.62	10.58	9.34	9.29	8.22	5.10
24	9.31	9.81	9.09	3.94	5.00	11.65	7.89	8.67	7.42

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; Hela: human cervical cancer.

compound **7** by removal of the bromine atoms through catalytic hydrogenation. Oxidation of **7** with air in the presence of salcomine gave bisquinone **8**.

With compound **8** in hand, 15 analogs with a variety of side chains at C-22 were prepared besides (−)-renieramycin G (**9**) in 70–85% yields. All the compounds were characterized by HRMS, ^{1}H and ^{13}C NMR measurements.

All of these analogs including (−)-renieramycin G were screened in vitro for cytotoxic activities against HCT-8, BEL-7402, A2780, MCF-7, A549, BGC-823, Ketr3, KB, and Hela cells using the standard MTT method (Table 1). It can be seen from the screening result that the IC_{50} values of the (−)-renieramycin G analogs were at the level of μM. Among the three non-aromatic acid derivatives (compound **10**, **11**, **12**), the crotonic acid derivative **11** was the least cytotoxic with the IC_{50} value at the range of 5–25 μM. It is interesting that both compound **10** with the simple acetyl group, which is the case in another bistetrahydroisoquinoline natural product (−)-jorumycin, and compound **12**, which had an elongated conjugate system, exhibited similar potency to (−)-renieramycin G. Among the six aromatic carboxylic acid ester derivatives (compounds **13**–**18**), compound **18** with a bulky 1-naphthyl group was the least potent with the IC_{50} values of 5–30 μM. Noticeably, compound **17** with a 2-thiophenyl group was the most potent among all of the 16 compounds. It exhibited a very potent inhibitory activity against KB cell line with the IC_{50} value of 20 nM. Among the six aromatic acrylic acid analogs (compounds **19**–**24**), compound **23**, which had three electron-donating methoxy groups on the benzene ring, showed a decrease in the cytotoxic potency in comparison with (−)-renieramycin G. From these results, it could be concluded that the C-22 side chain played an important part in the cytotoxic potency and specificity of this class of (−)-renieramycin G derivatives.

In conclusion, 15 analogs of (−)-renieramycin G along with itself were prepared through an improved synthetic route consisted of 19-steps with L-tyrosine as the starting material. Most of the analogs exhibited similar cytotoxic potency to (−)-renieramycin G. Among these analogs, 2-thiophene carboxylic ester derivative **17** exhibited potent cytotoxic activity against KB cell line with the IC_{50} value of 20 nM.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.01.025.

References and notes

1. Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
2. Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496.
3. Myers, A. G.; Plowright, A. T. *J. Am. Chem. Soc.* **2001**, *123*, 5114.
4. Spencer, J. R.; Sendzik, M.; Oeh, J.; Sabbatini, P.; Dalrymple, S. A.; Magill, C.; Kim, H. M.; Zhang, P.; Squires, N.; Moss, K. G.; Sukbuntherng, J.; Graupe, D.; Eksterowicz, J.; Young, P. R.; Myers, A. G.; Green, M. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4884.
5. Ong, C. W.; Chang, Y. A.; Wu, J. Y.; Cheng, C. C. *Tetrahedron* **2003**, *59*, 8245.
6. Martinez, E. J.; Corey, E. J.; Owa, T. *Chem. Biol.* **2001**, *8*, 1151.
7. Plowright, A. T.; Schaus, S. E.; Myers, A. G. *Chem. Biol.* **2002**, *9*, 607.
8. Cuevas, C.; Manzanares, I.; Pérez, M.; Martín, M. J.; Rodríguez, A.; Munt, S. (Pharma Mar, S.A.), ES 2 231 486 T3, 2003.
9. Ocio, E. M.; Maiso, P.; Chen, X.; Garayoa, M.; Álvarez-Fernández, S.; San-Segundo, L.; Vilanova, D.; López-Corral, L.; Montero, J. C.; Hernández-Iglesias, T.; de Alava, E.; Galmarinini, C.; Avilés, P.; Cuevas, C.; San-Miguel, J. F.; Pandiella, A. *Blood* **2009**, *113*, 3781.
10. Leal, J. F. M.; García-Hernández, V.; Moneo, V.; Domingo, A.; Bueren-Calabuig, J. A.; Negri, A.; Gago, F.; Guillén-Navarro, M. J.; Avilés, P.; Cuevas, C.; García-Fernández, L. F.; Galmarini, C. M. *Biochem. Pharmacol.* **2009**, *78*, 162.
11. Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721.
12. (a) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265; (b) He, H.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5822; (c) Parameswaran, P. S.; Naik, C. G.; Kamat, S. Y.; Pramanik, B. N. *Indian J. Chem., Sect B* **1998**, *37*, 1258; (d) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305.
13. Lane, J. W.; Chen, Y.; Williams, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 12684.
14. Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596.
15. Liao, X. W.; Liu, W.; Dong, W. F.; Guan, B. H.; Chen, S. Z.; Liu, Z. Z. *Tetrahedron* **2009**, *65*, 5709.
16. Charupant, K.; Daikuhara, N.; Saito, E.; Amnuoypol, S.; Suwanborirux, K.; Owa, T.; Saito, N. *Bioorg. Med. Chem.* **2009**, *17*, 4548.
17. Lane, J. W.; Estevez, A.; Mortara, K.; Callan, O.; Spencer, J. R.; Williams, R. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3180.
18. Wright, B. J.; Chan, C.; Danishefsky, S. L. *J. Nat. Prod.* **2008**, *71*, 409.
19. Gonzălez, J. F.; de la Cuesta, E.; Avendaño, C. *Bioorg. Med. Chem.* **2007**, *15*, 112.
20. Liu, Z. Z.; Wang, Ye.; Tang, Y. F.; Chen, S. Z.; Chen, X. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1282.
21. Liao, X. W.; Dong, W. F.; Liu, W.; Guan, B. H.; Liu, Z. Z. *J. Heterocycl. Chem.* **2010**, *47*, 50.