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Total Synthesis of Novel 6-Substituted Lavendamycin Antitumor Agents

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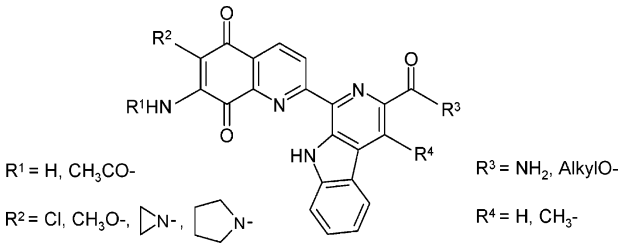
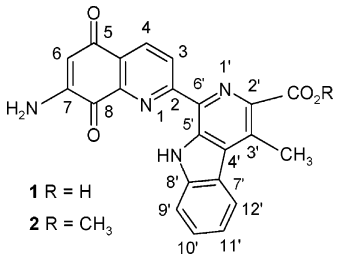
ABSTRACT



Novel 6-substituted lavendamycins have been synthesized for the first time. The key step in these syntheses is a Pictet–Spengler condensation (Scheme 1). Efficient methods for the synthesis of each compound, including a novel reaction for the facile introduction of alkylamino groups at the C-6 position of the lavendamycin system, are discussed. Possible mechanisms for these reactions are also presented.

Lavendamycin (**1**), an antitumor antibiotic, was isolated from the fermentation broth of *Streptomyces lavendulae* in 1981.[1] Total syntheses of lavendamycin methyl ester (**2**) have been reported by Kende,[2a] Boger,[2b] and our group.[3a,b] In 1993 and 1996, we introduced two short and efficient methods for the synthesis of **2**.[3a,b] Formal syntheses of **2** have also been reported.[2c]



As part of our long-term research on the synthesis and biological activity studies of lavendamycin antitumor agents,[3] we were in need of analogues with various substituents at the C-6 position. In this letter, we report for the first time the synthesis of a number of these novel analogues (Table 1) via new and efficient methods. These compounds are the first examples of C-6-substituted lavendamycins and are part of a much larger series of derivatives with a wide range of molecular reduction potentials and lipophilicity. Our analogues will be the subject of future antitumor studies in general and, in particular, an evaluation of a possible correlation of reduction potential with antitumor activity.[4] Analogues **6**−**18** in Table 1 are the 6-substituted derivatives of our previously synthesized lavendamycins **2**−**5**.[3a−e] Our

(1) (a) Doyle, T. W.; Balitz, D. M.; Grulich, R. E.; Nettleton, D. E.; Gould, S. J.; Tann, C.-H.; Mews, A. E. *Tetrahedron Lett.* **1981**, *22*, 4595. (b) Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiot.* **1982**, *35*, 259.

(2) (a) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *21*, 91. (b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. (c) Rama Rao, A. V. *Recent Prog. Chem. Synth. Antibiot.*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; p 497 and references therein.

(3) (a) Behforouz, M.; Gu, Z.; Cai, W.; Horn, M. A.; Ahmadian, M. *J. Org. Chem.* **1993**, *58*, 7089. (b) Behforouz, M.; Haddad, J.; Cai, W.; Arnold, M. B.; Mohammadi, F.; Sousa, A. C.; Horn, M. A. *J. Org. Chem.* **1996**, *61*, 6552. (c) Behforouz, M.; Haddad, J.; Cai, W.; Gu, Z. *J. Org. Chem.* **1998**, *63*, 343. (d) Fang, Y.; Linardic, C. M.; Richardson, D. A.; Cai, W.; Behforouz, M.; Abraham, R. T. *Mol. Cancer Ther.* **2003**, 517. (e) Behforouz, M.; Merriman, R. L. U.S. Patent 5 525 611, June 11, 1996. (f) Behforouz, M.; Cai, W.; Stocksdale, M. G.; Jung, J. Y. *J. Med. Chem.*, accepted for publication.

(4) (a) Hodnett, E. M.; Wongwiechintana, C.; Dunn, W. J., III; Marrs, P. *J. Med. Chem.* **1983**, *26*, 570. (b) Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329.

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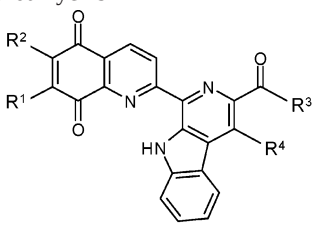
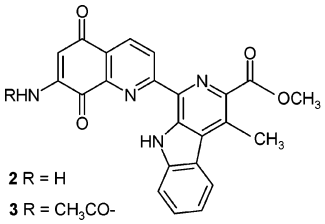
Table 1. 6-Substituted Lavendamycins and Demethyllavendamycins

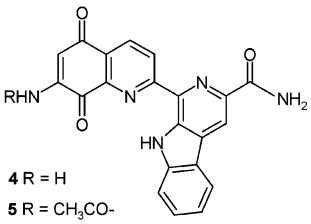


cmpd.	R^1	R^2	R^3	R^4
6	NH_2	OCH_3	OCH_3	H
7	NH_2	OCH_3	OCH_3	CH_3
8	NH_2	OCH_3	NH_2	H
9	NH_2	Cl	OCH_3	CH_3
10	NH_2	Cl	OEt	H
11	NH_2	Cl		H
12	NH_2	Cl	OIsoamyl	H
13	NH_2	Cl	OOctyl	H
14	NH_2	Cl	NH_2	H
15	AcHN		OCH_3	CH_3
16	AcHN		OCH_3	CH_3
17	AcHN		NH_2	H
18	AcHN		NH_2	H

studies have shown **2**−**5** to be highly active antitumor agents.[3d,e]



2 R = H
3 R = CH_3CO-



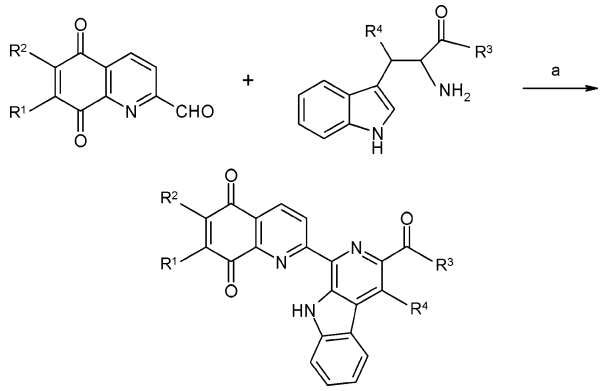
4 R = H
5 R = CH_3CO-

The key step in these syntheses is a Pictet−Spengler condensation of the corresponding aldehydes with the appropriate tryptophans (Scheme 1). Previously, we have reported efficient syntheses of compounds **3**[3a,b] and **5**[3e] via this condensation reaction.

Novel carbaldehyde **25** required for the synthesis of **6**−**8** was prepared according to Scheme 2.

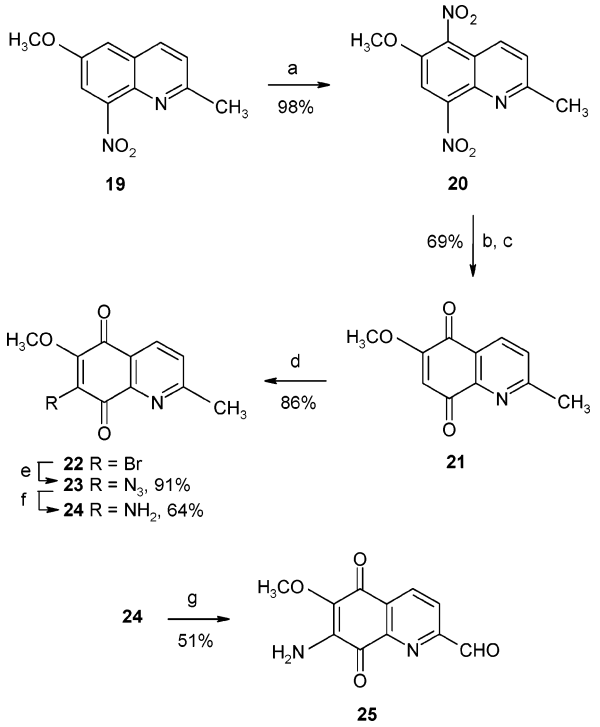
7-Amino-6-methoxy-2-methylquinoline-5,8-dione (**24**) was prepared [5] and then oxidized to the desired aldehyde **25** via a method similar to that previously reported by us for the preparation of **29**.[3a] A controlled amount of bromine must be used in the bromination of **21**.[6]

Scheme 1 [a]



[a] Conditions: (a) Dry *p*-xylene or anisole, 3−19 h, reflux, argon. Yields: **3**, 79%; **5**, 54%; **6**, 45%; **7**, 41%; **8**, 32%; **9**, 59%; **10**, 49%; **11**, 36%; **12**, 56%; **13**, 26%; **14**, 53%.

Scheme 2 [a]



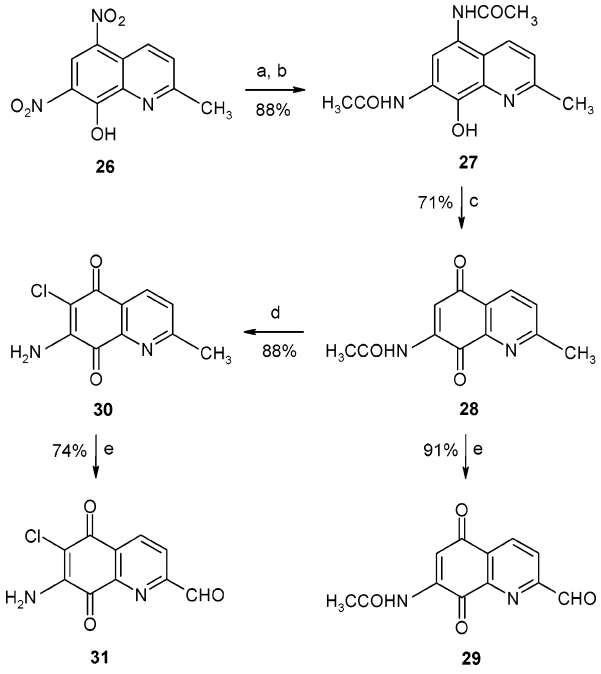
[a] Conditions: (a) HNO_3/H_2SO_4 (70% v/v), 3 h, rt. (b) Pd−C 10%, H_2 (40 psi), HCl, H_2O, 24 h, rt. (c) $FeCl_3$, $CHCl_3$, H_2O, 24 h, rt. (d) Br_2, HOAc, NaOAc, 24 h, rt, argon. (e) NaN_3, H_2O, THF, 4 h, rt, argon. (f) PtO_2, H_2 (50 psi), dry MeOH, 10 h, rt. (g) SeO_2, *p*-dioxane, H_2O, 21 h, reflux, argon.

Carbaldehyde **29** necessary for the synthesis of analogues **15**−**18** was prepared according to Scheme 3,[3a] and the novel

(5) (a) Liao, T. K.; Nyberg, H.; Cheng, C. C. *J. Heterocycl. Chem.* **1976**, *13*, 1063. (b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

(6) Use of more than 1.25 equiv of bromine lowers the yield of **22** and produces undesired side products.

Scheme 3 [a]

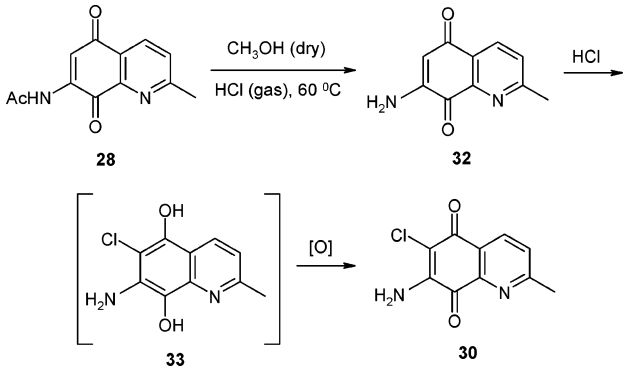


[a] Conditions: (a) Pd−C 5%, H_2 (30 psi), HCl, H_2O, 15 h, rt. (b) Ac_2O, NaOAc, Na_2SO_3, 2.5 h, rt → 0 °C then MeOH, H_2O, reflux, 30 min. (c) $K_2Cr_2O_7$, AcOH, H_2O, 24 h, rt. (d) HCl (gas), dry MeOH, 22 h, 60 °C. (e) SeO_2, *p*-dioxane, H_2O, reflux, 19−23 h.

aldehyde **31** required for the synthesis of analogues **9**−**14** was obtained by the oxidation of chlorodione **30** [3c] via a method similar to that used for **29**.[3a]

7-Acetamidoquinoline-5,8-dione **28** was converted to chloroquinone **30** in a sequence of reactions shown in Scheme 4.[3c] Acid-catalyzed methanolysis of **28** first gave

Scheme 4

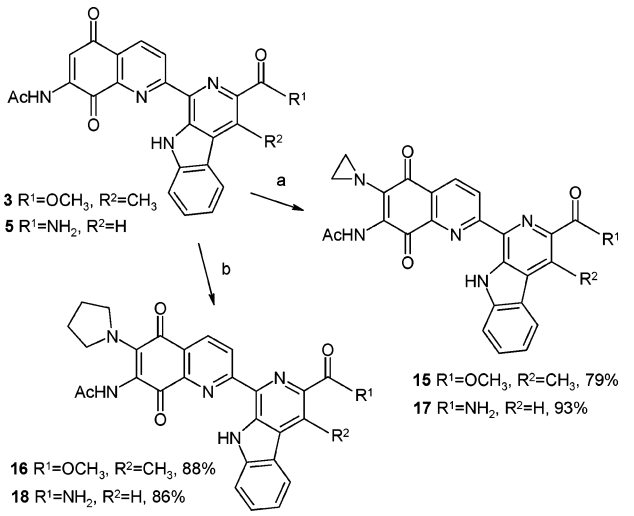


the aminodione derivative **32**. A Michael addition of HCl to aminodione **32** produced the intermediate hydroquinone **33**, which then oxidized to the final 6-chloroquinone **30**. A possible mechanism for the 1,4-addition of HCl to **32** has already been reported.[3c]

Tryptophan pyrrolidine amide (for compound **11**, Scheme 1) was prepared according to the method of Tolstikov et al.[7a] *β*-Methyltryptophan methyl ester (for compounds **7**, **9**, **15**, **16**, and **3**, Scheme 1) was prepared according to our own procedure.[7b] Tryptophan isoamyl ester (for compound **12**, Scheme 1) was prepared in 82% yield by the Fischer esterification reaction in the presence of HCl gas followed by the neutralization of the resulting salt with ammonium hydroxide and EtOAc extraction. The remaining tryptophan derivatives were prepared by the neutralization of the commercially available salts.

7-Acetamido-6-alkylaminolavendamycins (**15**−**18**) were synthesized using a novel and simple method recently developed in our laboratory. Direct addition of aziridine or pyrrolidine to compounds **3** or **5** under very mild reaction conditions resulted in the formation of almost 100% pure products (Scheme 5). No transamination occurs at the C-2′

Scheme 5 [a]



[a] Conditions: (a) Aziridine, $CHCl_3$ or $CHCl_3$/EtOH, 24−48 h, rt. (b) Pyrrolidine, $CHCl_3$ or DMF, 2 h, rt.

amide and ester linkages or even at the vinylogous C-7 amide function during the course of this reaction.

The literature lacks efficient methods for the synthesis of 6,7-diaminoquinolinediones. The use of dihalodiones [8,9] or their methoxy derivatives [9] as the starting materials for the amination of this system gives a mixture of 6- and 7-amino products and not the desired diamino compound. This may be due to the fact that once the replacement of either the C-6 or the C-7 groups occurs by an amine, the resulting quinone system becomes deactivated toward the second Michael addition of another amine molecule as we have observed in compound **32**.

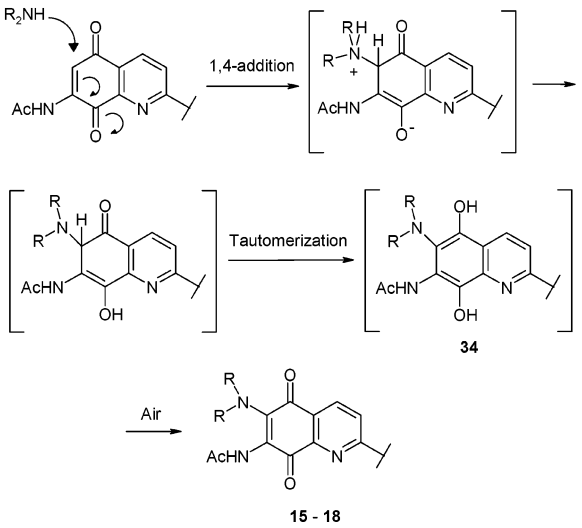
(7) (a) Tolstikov, V. V.; Holpnekozlova, N. V.; Oreshkina, T. D.; Osipova, T. V.; Preobrazhenskaya, M. N.; Sztarisckai, F.; Balzarini, J.; Declercq, E. *J. Antibiot.* **1992**, *45*, 1020. (b) Behforouz, M.; Zarrinmayeh, H.; Ogle, M. E.; Riehle, T. J.; Bell, F. W. *J. Heterocycl. Chem.* **1988**, *25*, 1627.

(8) Choi, H. Y.; Kim, D. W.; Chi, D. Y.; Yoon, E. Y.; Kim, D. J. *J. Org. Chem.* **2002**, *67*, 5390 and references therein.

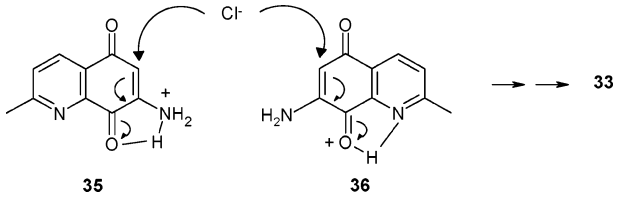
(9) Yoo, K. H.; Yoon, E. Y.; Park, Y. Y.; Park, S. W.; Lee, C.-O.; Lee, W. K.; Chi, D. Y.; Kim, D. J. *Bull. Korean Chem. Soc.* **2001**, *22*, 1067.

This novel and efficient method produces the 6-aminolavendamycins as well as the 6,7-diaminodiones [10] in excellent yields at room temperature. The proposed mechanism for this reaction is presented in Scheme 6. In contrast

Scheme 6



to the unreactivity of aminoquinolinedione **32** toward the amination reaction at the C-6 position, acetylamino compounds **3** and **5** undergo this reaction very efficiently. It appears that placement of an acetyl group on the C-7 nitrogen of the amino function sufficiently decreases its electron-donating ability and thus activates the system at its C-6 position toward a facile Michael addition reaction of the amines with no necessity for the presence of halogen or methoxy activating groups. Although dione **32** resists amination, it should be noted that it undergoes an efficient HCl addition (Scheme 4). The ease of this transformation may be due to the intermediacy of activated species such as **35** and **36**.[3c]



Interestingly, the spontaneous and complete reoxidation of the intermediate **34** to its corresponding quinoline-5,8-dione occurs during the reaction workup. In contrast, the conversion of chlorohydroquinone **33** to its dione **30** results in only partial air oxidation during the reaction workup and ferric chloride is needed to complete the reaction.[3c]

In summary, efficient syntheses of first examples of 6-substituted lavendamycins have been reported, and a novel method for the facile introduction of an amino group at the C-6 position of the lavendamycin system has been introduced.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (**6**−**18**, **25** and **31**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL035381A

(10) Work on the addition of a variety of aliphatic and aromatic amines at the C-6 positions of lavendamycins and aminoquinolinediones is ongoing in our laboratories, and the results will be the subject of future reports.