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Synthesis of 2-substituted *endo*-hymenialdisine derivatives

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Abstract—The first synthesis of 2-substituted *endo*-hymenialdisine derivatives **1**–**4** is described started with 2-substituted pyrroles and 5-substituted pyrrolo-2-carboxylic acids.

The marine natural product hymenialdisine was originally isolated from the sponges *Axinella verrucosa* and *Acantella aurantiaca*.[1] Hymenialdisine has revealed low nanomolar inhibition activities against a panel of kinases such as GSK-3β, members of the CDK family, Erk1, Erk2, CK1, and MEK.[2,3] The chemical structure and kinase inhibition activity of four known hymenialdisine analogues are presented in Figure 1. Comparing the inhibition activities among these analogues, the inhibition activity of hymenialdisine is about 80-fold higher than that of the debromo one against kinase MEK-1. The inhibition activity of diacetyl hymenialdisine is about 4-fold higher against kinase GSK-3β and is about 2-fold higher against kinase CDK5 than that of debromo diacetyl hymenialdisine. In the X-ray structure of hymenialdisine–CDK2 complex,[2] some level of hydrophobic interaction between the bromine atom and the hydrophobic backbone of CDK2 is observed. Therefore, the bulky and lipophilic effects of the bromo atom of hymenialdisine could play a key role in gaining the high inhibition potency.

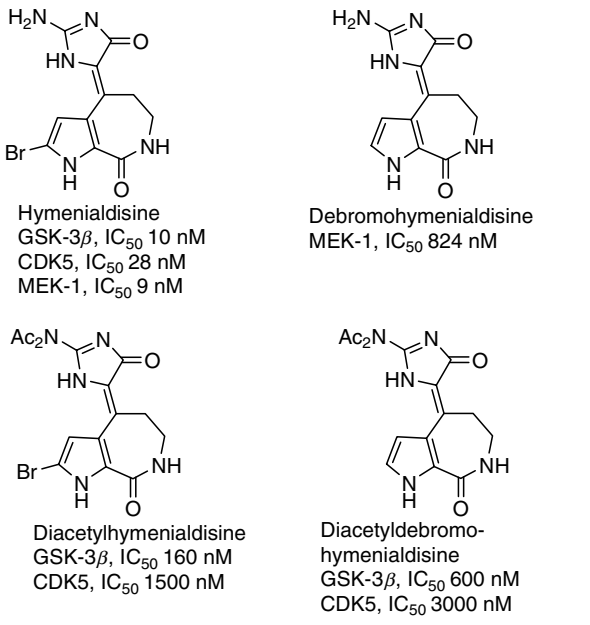

Figure 1. Chemical structure and kinase inhibition activity of hymenialdisine analogues.

The chemical structure modification of natural product possessing superior bioactivity is considered as the most efficient way to find drug candidates, which have high potency and selectivity. Lack of inhibition selectivity is the main characteristics and disadvantage of hymenialdisine. In view of the inhibition potency gained by the bromo substituent, the chemical modification of hymenialdisine is anticipated to be focused on replacing the bromo atom with other lipophilic substituents at the α-position of the pyrrolyl ring. In this Letter, we report the first synthesis of four *endo*-hymenialdisine derivatives **1**–**4** by substituting the bromo atom with methyl, benzyl, phenyl, and *tert*-butyl groups, respectively (Fig. 2).

The synthesis of hymenialdisine derivatives **1**–**4** was commenced with 2-substituted pyrroles[4] and 5-substituted pyrrolo-2-carboxylic acids.[5] As shown in Scheme 1, three methods were used to link 2-substituted pyrrolyl

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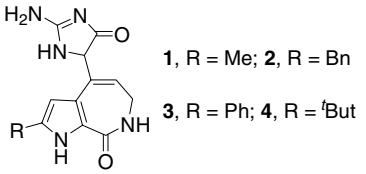
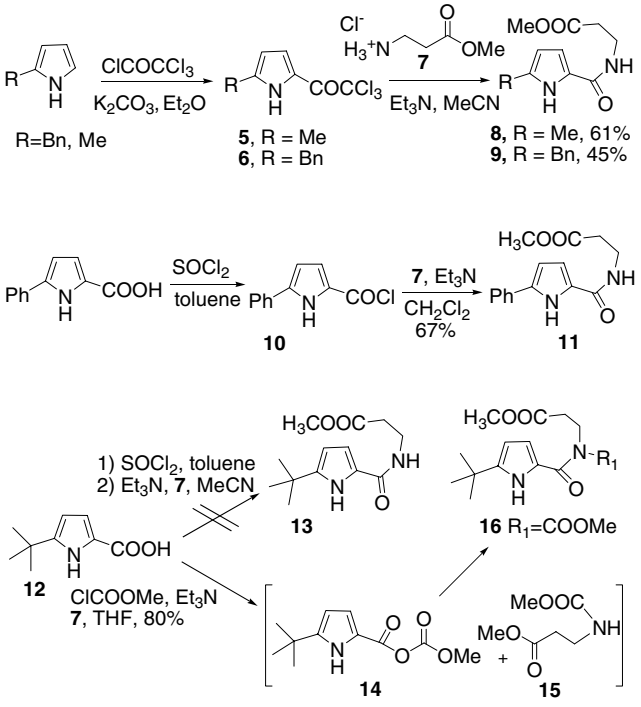


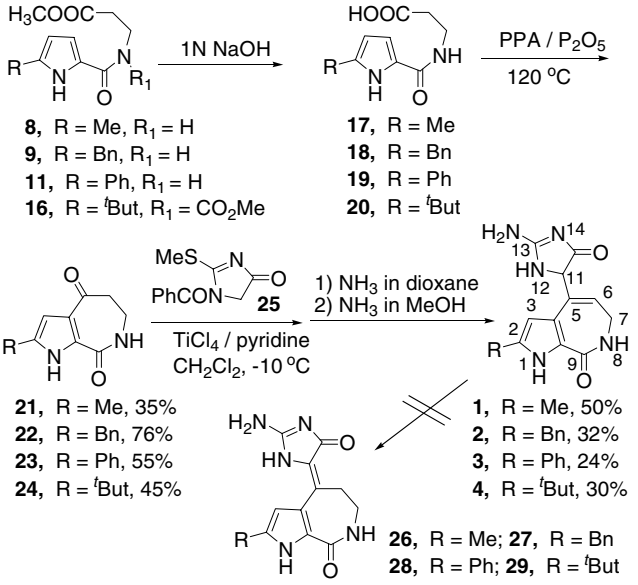
Figure 2. 2-Substituted *endo*-hymenialdisine derivatives.



Scheme 1. Synthesis of 5-subtituted pyrrolo-2-carboxamides.

moiety with β-alanine. When 2-methylpyrrole or 2-benzylpyrrole reacted with trichloroacetyl chloride in the presence of K_2CO_3 in Et_2O, 5-substituted 2-trichloroacetylpyrroles **5** and **6** were obtained in almost quantitative yields. Without purification, the crude compounds **5** and **6** were used directly to condense with β-alanine methyl ester hydrochloride **7** in MeCN by using Et_3N as a base to produce compounds **8** and **9** with yields of 61% and 45%, respectively. Compound **11** was obtained in 67% yield by transferring 5-phenylpyrrolo-2-carboxylic acid into its acyl chloride **10** first, followed by condensation with **7**. However, 5-*tert*-butylpyrrolo-2-carboxylic acid **12** failed to produce compound **13** in the same synthetic approach for the preparation of **11**. As an alternate approach, compound **16** with a methoxycarbonyl protecting group on the amide nitrogen was prepared with 80% yield by treatment of **12** with **7**, methyl chloroformate, and Et_3N in THF at room temperature for 8 h. The conversion of **12** into amide **16** was most likely to proceed through the reaction of anhydride **14** with in situ formed *N*-methoxycarbonyl β-alanine methyl ester **15**.

At this stage, preparation of the 2-substituted pyrrolo[2,3-*c*]azepin-4,8-dione intermediates **21**–**24** from acids **17**–**20** became the main concern (Scheme 2).



Scheme 2. Syntheses of 2-substituted *endo*-hymenialdisine derivatives **1**–**4**.

5-Subtituted pyrrolo-2-carboxamides **8**, **9**, **11**, and **16** were first converted to the corresponding acids **17**–**20** by hydrolysis with 1 N HCl. After intra-molecular cyclization by using PPA and P_2O_5 under nitrogen at 120 °C,[6] the key intermediates **21**–**24** were obtained with yields of 35%, 76%, 55%, and 45%, respectively. The guanidine moiety was then successfully installed on the azepine ring by utilizing the recent reported one-pot three-step methodology.[6b] Thus, condensations of **21**–**24** with 1-benzoyl-2-methylsulfanyl-1,5-dihydroimidaol-4-one **24** in the presence of $TiCl_4$ and pyridine, followed by two-step ammonia hydrolysis (first with diluted ammonia solution in dioxane for 0.5 h, subsequently with saturated ammonia solution in MeOH for 4 h) provided 2-substituted *endo*-hymenialdisine derivatives **1**–**4** in low to moderate yields without isolation of *exo*-isomers **26**–**29**. Attempts of isomerization of *endo*-hymenialdisine derivatives **1**–**4** into the corresponding *exo*-isomers **26**–**29** were unsuccessful by irradiation of compounds **1**–**4** with microwave in aqueous ammonia according to the literature method for the isomerization of *endo*-debromohymenialdisine.[6b] Failure to shift 5,6-double bond to 5,11-double is due to the existence of 2-substituents at the pyrrolyl ring, which precludes the aromatic isomerization of the conjugated system under the same reaction condition. In other words, the aromatic isomerization of *endo*-hymenialdisines **1**–**4** probably requires higher energy compared to that of *endo*-debromohymenialdisine.

The geometric position of 5,6-double bond was unambiguously confirmed by the ^1H NMR spectra.[7] In the ^1H NMR (400 MHz, DMSO-d_6 + D_2O) of the synthesized *endo*-isomers **1**–**14**, the singlet attributed to C11 methyne proton appeared at 4.60 ppm for **1**, 4.65 ppm for **2**, 4.71 ppm for **3**, and 4.66 ppm for **4**. The triplet attributed to C6 olefinic proton appeared at 5.77 ppm for **1**, 5.80 ppm for **2**, 5.87 ppm for **3**, and 5.83 ppm for **4**.

In summary, an efficient synthesis of 2-substituted *endo*-hymenialdisine derivatives **1**–**4** has been achieved, which is the first report of *endo*-hymenialdisine derivatives with a variety of substituents at the α-position of the pyrrolyl ring. The synthesized compounds have stable chemical structures, all of which will be subjected to bioactivity screening as promising kinase inhibitors.

Acknowledgments

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7. Analytic data of 2-substituted *endo*-hymenialdisine derivatives **1**–**4** are listed as below:
   Compound **1**, isolated by chromatography (CH_2Cl_2/MeOH saturated with NH_3 4:1) as a light-yellow solid, mp: 261–262 °C. IR: 3374, 3253, 1703, 1615, 1497 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 5.83 (s, 1H), 5.77 (t, $J = 6.0$ Hz, 1H), 4.60 (s, 1H), 3.28–3.42 (m, 2H), 2.15 (s, 3H) ppm; ^{13}C NMR (200 MHz, DMSO-d_6) δ 188.3, 172.1, 164.4, 135.9, 133.1, 124.7, 124.5, 123.6, 105.7, 65.6, 13.2 ppm. HRMS calcd for $C_{12}H_{13}N_5O_2$ ($M+Na^+$): 282.0969. Found: 282.0959.
   Compound **2**, isolated by chromatography (CH_2Cl_2/MeOH saturated with NH_3 8:1) as a light-yellow solid, mp: 226–228 °C. IR: 3239, 1692, 1630, 1492 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.18–7.56 (m, 5H), 5.88 (s, 1H), 5.80 (t, $J = 6.8$ Hz, 1H), 4.65 (s, 1H), 3.84 (s, 2H), 3.28–3.44 (m, 2H) ppm; ^{13}C NMR (200 MHz, DMSO-d_6) δ 187.2, 172.1, 163.7, 139.9, 136.1, 135.3, 128.7, 128.6, 128.5, 128.4, 126.2, 124.9, 123.7, 122.1, 105.2, 64.9, 37.9, 33.1 ppm. HRMS calcd for $C_{18}H_{18}N_5O_2$ ($M+H^+$): 336.1461. Found: 336.1467.
   Compound **3**, isolated by chromatography (CH_2Cl_2/MeOH saturated with NH_3 6:1) as a light-yellow solid, mp: 253–255 °C. IR: 3346, 1393, 1632, 1481 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.71 (d, $J = 8.0$ Hz, 2H), 7.38 (t, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 8.0$ Hz, 1H), 6.57 (s, 1H), 5.87 (t, $J = 6.8$ Hz, 1H), 4.71 (s, 1H), 3.36–3.49 (m, 2H) ppm; ^{13}C NMR (200 MHz, DMSO-d_6) δ 186.8, 171.7, 163.4, 135.6, 134.7, 131.6, 128.9, 128.7, 127.3, 127.2, 125.4, 125.1, 124.3, 123.1, 104.5, 64.6, 37.6 ppm. HRMS calcd for $C_{17}H_{16}N_5O_2$ ($M+H^+$): 322.1305. Found: 322.1293.
   Compound **4**, isolated by chromatography (CH_2Cl_2/MeOH saturated with NH_3 10:1) as a light-yellow solid, mp: 265–267 °C. IR: ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 5.95 (s, 1H), 5.83 (t, $J = 6.8$ Hz, 1H), 4.66 (s, 1H), 3.34–3.49 (m, 2H), 1.26 (s, 9H) ppm; ^{13}C NMR (200 MHz, DMSO-d_6) δ 187.3, 172.2, 163.6, 145.6, 144.2, 136.1, 125.3, 122.7, 101.6, 65.1, 37.9, 34.9, 30.1 ppm. HRMS calcd for $C_{15}H_{20}N_5O_2$ ($M+H^+$): 302.1618. Found: 302.1605.