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Synthesis and biological evaluation of new jasplakinolide (jaspamide) analogs

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ABSTRACT

Synthesis and biological evaluation of jasplakinolide analogs are described. The synthesis of analogs utilized a diastereoselective *syn*-aldol reaction and an orthoester Claisen rearrangement as key steps. All synthetic analogs were evaluated for their ability to disrupt the actin cytoskeleton. Compounds **2**, **3**, and **4** essentially displayed similar activity to jasplakinolide.

Natural products will continue to be a great source of life-improving drugs. Jasplakinolide, a 19-membered depsipeptide, first isolated from the marine sponge *Jaspis splendens* in 1986,[1] and since found in other sea sponges,[2] has shown aggressive antitumor activity, as well as antifungal, insecticidal, and anthelmentic properties.[3,4] Its observed potent antiproliferative activity results from its ability to interact and stabilize actin filaments by binding to F-actin.[5] The impressive anticancer activity and drug potential of jasplakinolide was probed by the National Cancer Institute (NCI) during preclinical trials. The trials were terminated due to toxicity.[6a] Detailed biological studies revealed jasplakinolide's ability to promote actin filament assembly in vitro, as well as its ability to permeate cells and alter the actin skeleton organization in cells. Modified jasplakinolide analogs continue to hold promise for cancer chemotherapy, as well as tools for biological probes.[6]

We previously reported an enantioselective synthesis of the antitumor depsipeptide doliculide.[7] Using synthetic doliculide, we determined its biological mechanism of action.[8] Doliculide, like jasplakinolide,[6] arrests cells at the G2/M phase of the cell cycle by impeding normal actin assembly. In addition, both molecules, along with other natural products, such as the chondramides,[9] and phalloidin,[10] cause a hyperassembly of purified actin into F-actin aggregates. These cytotoxic natural products appear to have the same binding site, as all inhibit the binding of FITC (fluorescein isothiocyanate)-labeled phalloidin to actin polymer.[8] Through our modeling studies, which are in agreement with previous SAR studies,[11] it was predicted that analogs of doliculide would not yield rewarding increases in biological activity.[8] However, it seems that doliculide provides a 'core' pharmacophore for the F-actin site. Jasplakinolide superimposed on doliculide reveals that several key groups (benzyl moiety with the indole group, and the halide substituents I and Br) overlap very well. It was shown that a larger macrocyclic core presented a better starting point for derivative studies.

The unique and complex structure, as well as elevated natural bioactivity, has inspired several groups to synthesize jasplakinolide.[12] In addition, many analog studies have been carried out.[13] We have published an efficient total synthesis of jasplakinolide, featuring a *syn*-aldol and an orthoester Claisen rearrangement as key steps.[12f] Minor changes to this synthetic route have allowed us to conveniently and systematically study structural variants of jasplakinolide. Our proposed analogs have permitted us to probe the importance of various substituents, reduce molecular complexity, and, in some cases, simplify the synthetic route. The synthesis and biological results for our jasplakinolide derivatives are reported below.

Figure 1 shows natural jasplakinolide **1** and related analogs that have been synthesized in our laboratory. We chose analogs that could be made through simple amendments to our preexisting synthetic route. By changing the phenolic hydroxyl group to methoxy in **2**, we were able to start the synthesis of the key β-hydroxy tyrosine intermediate from commercial *p*-anisaldehyde and eliminate the need for future deprotection reactions. Additionally, analog **5** was synthesized to address the importance of a phenolic substituent. Compounds **3** and **4** were made to investigate the

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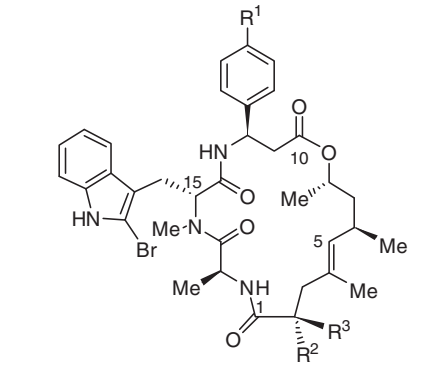
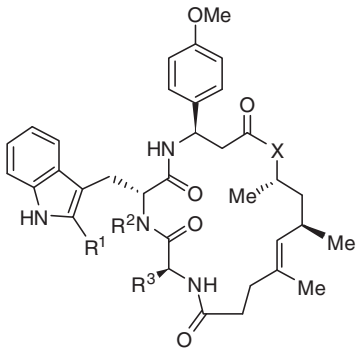
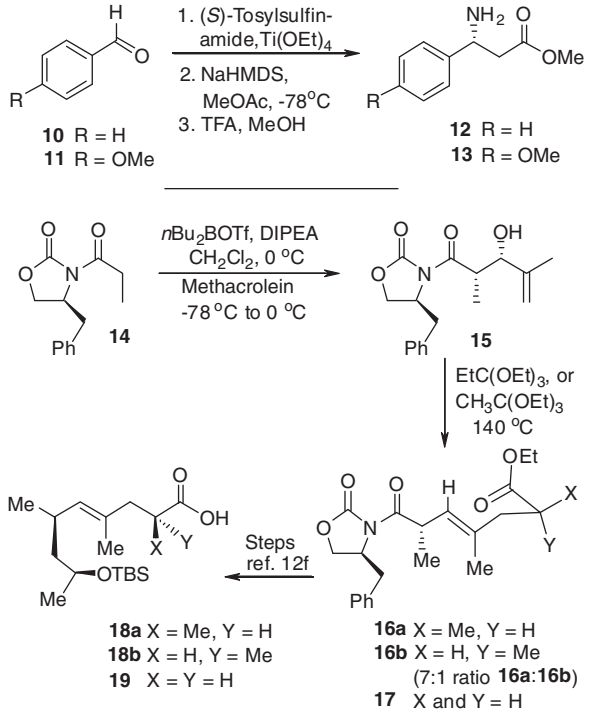


1 Jasplakinolide $R^1 = OH, R^2 = Me, R^3 = H$
2 $R^1 = OMe, R^2 = Me, R^3 = H$
3 $R^1 = OMe, R^2 = H, R^3 = Me$
4 $R^1 = OMe, R^2 = H, R^3 = H$
5 $R^1 = H, R^2 = H, R^3 = H$

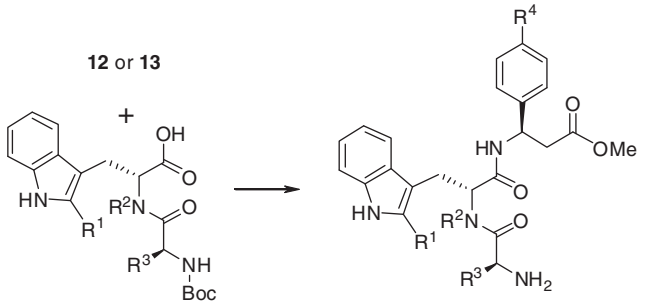


6 $R^1 = Br, R^2 = H, R^3 = Me, X = O$
7 $R^1 = H, R^2 = Me, R^3 = Me, X = O$
8 $R^1 = Br, R^2 = Me, R^3 = H, X = O$
9 $R^1 = Br, R^2 = Me, R^3 = Me, X = NH$

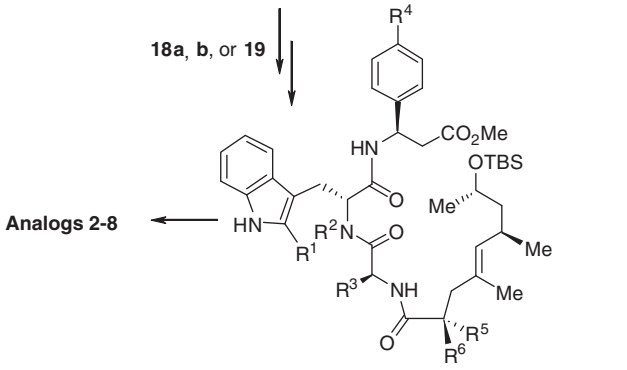
Figure 1. Jasplakinolide and its analogs.



Scheme 1. Synthesis of key fragments.



20 $R^1 = Br, R^2 = Me, R^3 = Me$
21 $R^1 = Br, R^2 = H, R^3 = Me$
22 $R^1 = H, R^2 = Me, R^3 = Me$
23 $R^1 = Br, R^2 = Me, R^3 = H$
24a $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = H$
24b $R^1 = Br, R^2 = H, R^3 = Me, R^4 = OMe$
24c $R^1 = H, R^2 = Me, R^3 = Me, R^4 = OMe$
24d $R^1 = Br, R^2 = Me, R^3 = H, R^4 = OMe$
24e $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = OMe$



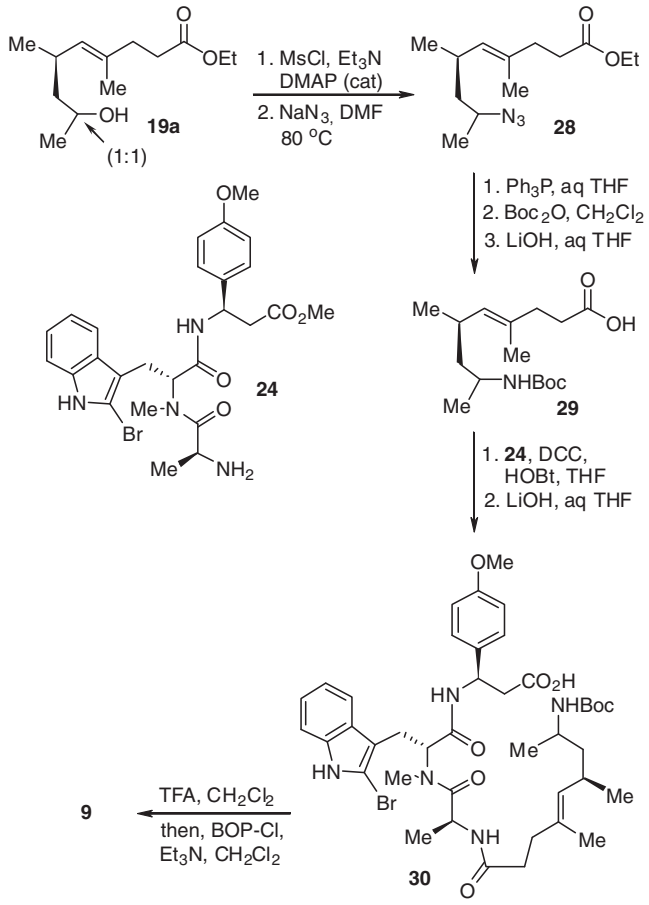
25 $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = OMe, R^5 = Me, R^6 = H$
26 $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = OMe, R^5 = H, R^6 = Me$
27a $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = H, R^5 = H, R^6 = H$
27b $R^1 = Br, R^2 = H, R^3 = Me, R^4 = OMe, R^5 = H, R^6 = H$
27c $R^1 = H, R^2 = Me, R^3 = Me, R^4 = OMe, R^5 = H, R^6 = H$
27d $R^1 = Br, R^2 = Me, R^3 = H, R^4 = OMe, R^5 = H, R^6 = H$
27e $R^1 = Br, R^2 = Me, R^3 = Me, R^4 = OMe, R^5 = H, R^6 = H$

Scheme 2. Synthetic approach to analogs **2**–**8**.

stereochemistry and importance of the methyl group at C2. A non-*N*-methylated derivative **6** was also investigated, to allow for a highly simplified reaction scheme, eliminating four steps from our original synthetic strategy. The effect on activity of the indole bromine residue and the C18 methyl group were also probed (compounds **7** and **8**). Replacing alanine with glycine reduces the chiral complexity of the molecule and may allow for alternative molecular conformations. In an effort to address toxicity, we also synthesized the cycloamide derivative **9**.

The synthesis of key analog intermediates is shown in Scheme 1. β-Tyrosine derivatives **12** and **13** were accessed according to an asymmetric protocol published by Davis et al., which we had previously utilized during our total synthesis.[14] To produce the key polypropionic acid segments, we first utilized Evans' *syn*-aldol reaction to give aldol condensation product **15**.[15] By heating alcohol **15** in triethyl orthopropionate or triethyl orthoacetate and a catalytic amount of propionic acid, we were able to generate the Claisen rearrangement esters **16a**, **16b**, and **17**.[16] Compound **16b** was the minor (unfavored) product formed during the reaction of **15** with triethyl orthopropionate. Additional steps gave acid products **18a**, **18b** and **19**.

The general connection strategy for the reported jasplakinolide analogs is shown in Scheme 2. Dipeptides **20**–**23** were constructed according to a known D-2-bromotryptophan synthesis and simple coupling reactions between the resulting tryptophan derivatives and Boc-Ala or Boc-Gly.[12b] The Boc-protected acids were coupled



Scheme 3. Synthesis of analog **9**.

to amines **12** or **13** and Boc-deprotected, which yielded tripeptides **24**. Linking the tripeptides with protected 8-hydroxynonenoic acids **18**–**19** gave esters **25**–**27**. TBS-deprotection, ester hydrolysis, and macrolactonization using Yamaguchi's conditions furnished derivatives **2**–**8**.[17]

The synthetic route for macrolactam derivative **9**, which represents the most divergence from our total synthesis path, is described in Scheme 3. Accordingly, starting with alcohol **19a** (1:1 mixture of diastereomers), mesylation and azide substitution gave azide **28** in good yield over two steps. Interestingly, direct azide conversion methods, DPPA and HN_3/Ph_3P/DIAD, were unsuccessful. Staudinger reduction of the azide, Boc-protection of the resulting amine, and subsequent ester hydrolysis gave acid **29**. Acid **29** was coupled to tripeptide amine **24**, which gave the resulting Boc-amino ester that was hydrolyzed yielding the Boc-protected amino acid **30**. Treatment of **30** with TFA, followed by solvent removal, gave the amino TFA salt, which was combined with BOP-Cl and triethylamine to yield the cyclized product, analog **9**.[18]

Analogs were evaluated for their effects on the growth of the human Burkitt lymphoma cell line CA46 (Table 1) and for their ability to induce enhanced actin assembly (data not shown), with the latter activity being concordant with the cytotoxicity data. In general, biological activity was less affected by changes to the non-peptidic 8-hydroxynonenoic acid portion of the molecule, as exemplified by analogs **3** and **4**, which indicate that the C2 methyl group or its stereochemistry is not critical to its hydrophobic interactions in the F-actin binding site. It appears that even minor alterations of the tripeptide part of the molecule (analogs **5** and **6**–**8**) are detrimental to biological activity. Compounds **6** and **8** most likely induce conformational changes which have less favorable interactions in the binding site. The debromo analog **7** demonstrates the importance of a halogen atom on activity. It should also be noted that previous SAR studies on doliculide revealed that the analog lacking an aryl iodine substituent, was significantly less active.[11] In addition, the IC_{50} values of jasplakinolide and analogs **2**, **4**, and **5** indicated that the hydroxy group or the methoxy group appeared to play an important role. Replacing the hydroxy group with methoxy only decreases activity slightly, but replacing the OH with H gave a 10-fold decrease in activity (analog **5**). Also, the macrolactone scaffold seems important for maintaining biological activity, as both diastereomers of the cycloamide, derivative **9**, had high IC_{50} values.

Table 1
Activity of Jasplakinolide and analogs

Compound	IC_{50} (nM)[a]
1 Jasplakinolide	10 ± 5
2	20 ± 1
3	20 ± 10
4	10 ± 10
5	200 ± 70
6	3000
7	200 ± 60
8	300 ± 30
9 (diastereomer 1)	750 ± 70[b]
9 (diastereomer 2)	3000[b]

[a] CA46 Burkitt lymphoma human cell line. Cell growth was measured after 24 h of treatment, as described previously,[8] with cell number the parameter measured.
[b] Racemic synthesis (Scheme 3) resulted in two diastereomers.

In conclusion, we have described a systematic study of jasplakinolide analogs, to further understand how structural changes affect biological activity. The synthesis of these analogs was achieved by taking advantage of an efficient strategy reported by our group. The synthetic route allowed for convenient access to various analogs, most of which reduced the overall complexity of the molecule and/or simplified the synthetic pathway. The best analog, **4** (IC_{50} = 10 ± 10 nM) allowed us to replace the phenolic OH with OMe, which eliminated protection and deprotection steps, and also allowed us to eliminate the C2-chiral center, reducing the overall complexity of the compound.[19]

Acknowledgment

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19. All new compounds were purified by column chromatography and gave satisfactory spectroscopic and analytical results.
Compound **2**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.52 (d, 1H), 7.45 (d, 1H), 7.23 (d, 1H), 7.13–7.06 (m, 4H), 6.80 (d, 2H), 6.58 (d, 1H), 5.80 (m, 1H), 4.71 (d, 1H), 4.66 (m, 1H), 4.58 (m, 1H), 3.77 (s, 3H), 3.27 (dd, 2H), 2.94 (s, 3H), 2.63 (dd, 2H), 2.45 (m, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 1.85 (d, 1H), 1.55 (s, 3H), 1.27 (m, 2H), 1.09 (d, 3H), 1.04 (d, 3H), 0.80 (d, 3H), 0.69 (d, 3H).
Compound **3**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.51 (d, 1H), 7.39–7.37 (m, 1H), 7.22 (d, 1H), 7.12 (m, 2H), 7.06 (d, 2H), 6.78 (d, 2H), 6.51 (d, 1H), 5.64 (m, 1H), 5.22 (m, 1H), 4.96 (d, 1H), 4.62 (m, 2H), 3.76 (s, 3H), 3.34 (dd, 1H), 3.18 (dd, 1H), 2.97 (s, 3H), 2.70 (m, 1H), 2.54 (m, 1H), 2.16 (m, 3H), 1.54 (br s, 3H), 1.32–1.19 (m, 4H), 1.11 (m, 6H), 0.82 (d, 6H).
Compound **4**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.64 (d, 1H), 7.53 (d, 1H), 7.21 (d, 1H), 7.13–7.06 (m, 4H), 6.81 (d, 2H), 6.60 (d, 1H), 5.85 (m, 1H), 5.29–5.26 (m, 1H), 4.70 (m, 1H), 4.57–4.53 (m, 1H), 3.77 (s, 3H), 3.34 (dd, 1H), 3.22 (dd, 1H), 2.92 (s, 3H), 2.63 (d, 2H), 2.50–2.41 (m, 1H), 2.37–2.31 (m, 1H), 2.26 (m, 1H), 2.05–2.0 (m, 1H), 1.57 (s, 3H), 1.26–1.17 (m, 3H), 1.03 (d, 3H), 0.79 (d, 3H), 0.66 (d, 3H).
Compound **5**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.71 (d, 1H), 7.58 (m, 2H), 7.25–7.11 (m, 6H), 6.61 (d, 1H), 5.89 (m, 1H), 5.35 (m, 2H), 4.73–4.69 (m, 2H), 4.56 (m, 1H), 3.38 (dd, 1H), 3.25 (dd, 1H), 2.97 (s, 3H), 2.68 (d, 2H), 2.49–2.27 (m, 2H), 2.26–2.13 (m, 1H), 2.05–1.94 (m, 1H), 1.56 (s, 3H), 1.25–1.16 (m, 3H), 1.04 (d, 3H), 0.79 (d, 3H), 0.71 (d, 3H).
Compound **6**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.76 (d, 1H), 7.59 (d, 1H), 7.19–7.00 (m, 5H), 6.81 (d, 1H), 6.47 (d, 1H), 6.17 (d, 1H), 5.13 (m, 1H), 4.74 (m, 2H), 4.58 (m, 2H), 3.77 (s, 3H), 3.32 (m, 2H), 2.54–2.41 (m, 2H), 2.38–2.26 (m, 1H), 2.17–2.11 (m, 1H), 2.01 (m, 1H), 1.61 (s, 3H), 1.15–1.04 (m, 3H), 1.03 (d, 3H), 0.85 (d, 3H), 0.80 (d, 3H).
Compound **7**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.62 (m, 1H), 7.37 (d, 1H), 7.21–7.10 (m, 4H), 6.96 (s, 1H), 6.82 (d, 2H), 6.77 (d, 1H), 5.71 (m, 1H), 5.30 (m, 1H), 4.81 (m, 2H), 4.61 (m, 1H), 3.78 (s, 3H), 3.42 (dd, 1H), 3.24 (dd, 1H), 2.92 (s, 3H), 2.65 (m, 2H), 2.49–2.35 (m, 2H), 2.32–2.19 (m, 1H), 2.14–2.02 (m, 1H), 1.61 (s, 3H), 1.20–109 (m, 3H), 1.06 (d, 3H), 0.98 (d, 3H), 0.83 (d, 3H).
Compound **8**: (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.57–7.52 (m, 2H), 7.20–7.10 (m, 5H), 6.82 (d, 2H), 6.64 (br s, 1H), 5.62 (m, 1H), 5.22 (m, 1H), 4.85 (d, 1H), 4.58–4.50 (m, 1H), 4.27–4.18 (m, 1H), 3.78 (s, 3H), 3.41 (dd, 1H), 3.19 (dd, 1H), 2.74 (dd, 1H), 2.59 (dd, 1H), 2.51–2.39 (m, 3H), 2.38–2.34 (m, 2H), 2.10–1.95 (m, 2H), 1.60 (s, 3H), 1.22–1.12 (m, 3H), 1.07 (d, 3H), 0.87 (d, 3H).
Compound **9** (diastereomer 1): (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.65 (d, 1H), 8.06 (s, 1H), 7.55 (m, 1H), 7.19–7.10 (m, 6H), 6.82 (d, 2H), 6.70 (d, 1H), 5.89 (m, 1H), 5.24 (m, 1H), 4.98 (d, 1H), 4.80 (m, 1H), 4.66 (d, 1H), 3.78 (s, 3H), 3.48 (dd, 1H), 3.17 (dd, 1H), 3.02 (s, 3H), 2.59 (dd, 1H), 2.50 (m, 1H), 2.25 (m, 2H), 2.13 (m, 1H), 1.78 (d, 1H), 1.56 (s, 3H), 1.26 (m, 1H), 1.10 (d, 3H), 0.86 (d, 3H), 0.79 (d, 3H), 0.70 (d, 3H).
Compound **9** (diastereomer 2): (^{1}H NMR 400 MHz, $CDCl_3$) δ 8.61 (d, 1H), 7.99 (s, 1H), 7.53 (d, 1H), 7.17–7.08 (m, 6H), 6.84 (d, 2H), 6.60 (m, 1H), 5.91 (m, 1H), 5.29 (m, 1H), 4.93 (d, 1H), 4.71 (d, 1H), 4.62 (m, 1H), 3.77 (s, 3H), 3.33 (dd, 1H), 3.21 (dd, 1H), 2.96 (s, 3H), 2.47 (m, 2H), 2.31–2.21 (m, 2H), 1.89 (m, 1H), 1.57 (s, 3H), 1.30 (m, 1H), 1.10 (d, 3H), 0.83 (d, 3H), 0.78 (d, 3H), 0.75 (d, 3H).