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Synthesis and evaluation of duocarmycin SA analogs incorporating the methyl 1,2,8,8a-tetrahydrocyclopropa[*c*]oxazolo[2,3-*e*]indol-4-one-6-carboxylate (COI) alkylation subunit

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ABSTRACT

The design, synthesis and evaluation of methyl 1,2,8,8a-tetrahydrocyclopropa[*c*]oxazolo[2,3-*e*]indol-4-one-6-carboxylate (COI) derivatives are detailed representing analogs of duocarmycin SA containing an oxazole replacement for the fused pyrrole found in the alkylation subunit.

Duocarmycin SA (**1**)[1] and duocarmycin A (**2**)[2] represent the parent members of a small class of naturally occurring antitumor antibiotics that additionally includes yatakemycin (**3**)[3] and CC-1065 (**4**)[4] and that derive their properties through a sequence-selective alkylation of duplex DNA (Fig. 1).[5–9] Substantial efforts have been devoted to determining the origin of their DNA alkylation properties,[9] including the preparation of derivatives possessing fundamental structural changes used to define relationships between structure, functional reactivity, and biological properties.[10] Most notable of these are the structural features that contribute to the AT-rich non-covalent binding selectivity dominating the minor groove adenine N3 alkylation selectivity,[11] those that are responsible for the source of catalysis for the DNA alkylation reaction,[12,13] and those that subtly impact the unusual and intrinsic stability of the alkylation subunits.[10,13–17]

Herein, we report the synthesis of an analog of duocarmycin SA in which the left-hand subunit pyrrole ring is replaced by an oxazole, providing the methyl 1,2,8,8a-tetrahydrocyclopropa[*c*]oxazolo[2,3-*e*]indol-4-one-6-carboxylate (COI) alkylation subunit (**6** and **7**, Fig. 2). This structural modification changes the hydrogen bond donating pyrrole nitrogen of **1** into a Lewis basic oxazole nitrogen, potentially provides an alkylation subunit heterocyclic system capable of tunable metal cation activation,[18] and changes the electronic nature of the cyclopropylcyclohexadienone alkylation subunit by attaching two inductively withdrawing heteroatoms. The oxazole oxygen potentially represents a cross-conjugated vinylogous ester with the cyclohexadienone carbonyl and is positioned to be deeply imbedded in the minor groove at a site that

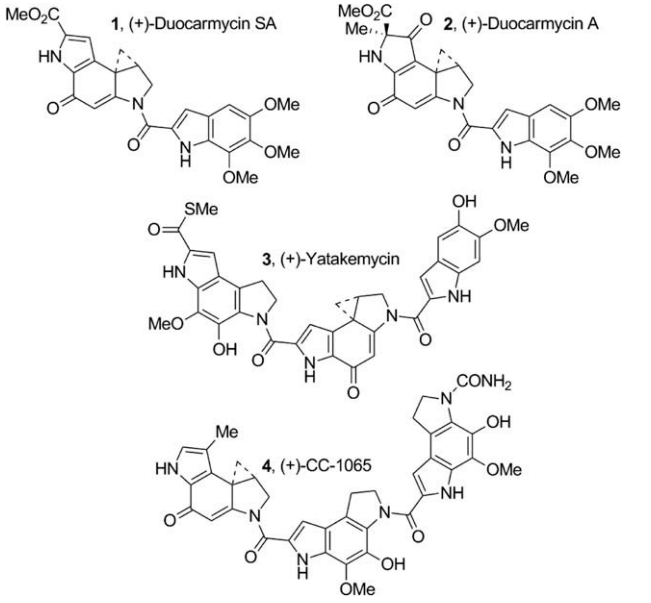

Figure 1. Natural products.

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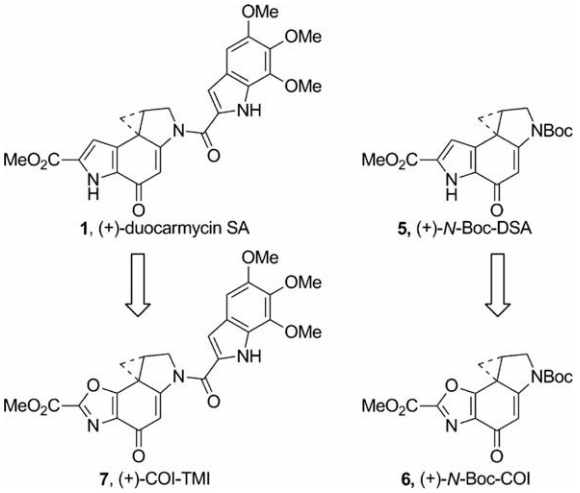
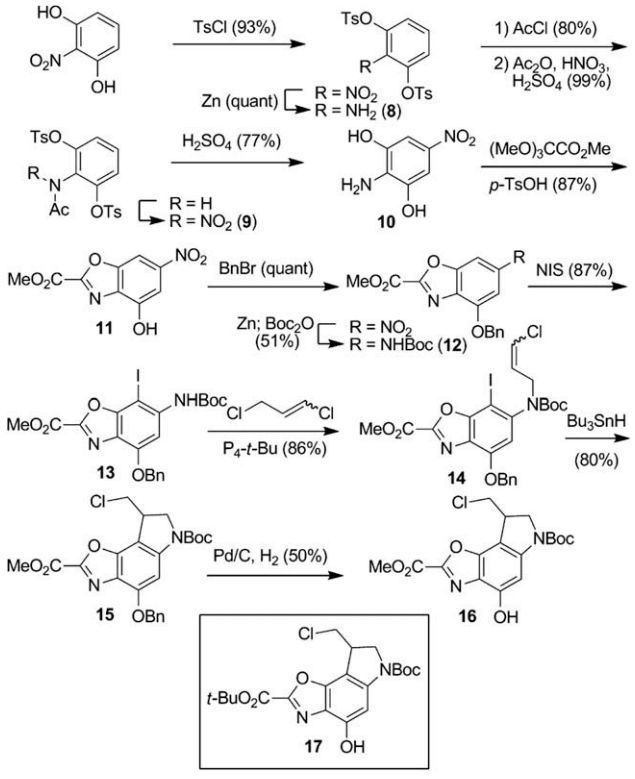


Figure 2. Duocarmycin SA analog.

is sensitive to steric interactions contributing to the differences between the natural and unnatural enantiomers of the natural products.[19] Consequently, the examination of COI and its derivatives was anticipated to additionally probe the effect of replacing this center (CH for **1** and C=O for **2**) with the less sterically demanding lone pair electrons on oxygen that would be directed into the DNA minor groove.[20]

The synthesis[21] of the duocarmycin SA analog **6** commenced with protection of 2-nitroresorcinol as the ditosylate (2.05 equiv TsCl, 3 equiv Et_3N, THF, 23 °C, 5 h, 93%) followed by reduction of the nitro group (10 equiv Zn, 15 equiv NH_4Cl, acetone, H_2O, quantitative) to provide aniline **8** (Scheme 1). Acetylation (1.5 equiv AcCl, 0.2 equiv DMAP, 3.0 equiv pyridine, DMF, 80%) followed by nitration (15 equiv Ac_2O, 1.7 equiv HNO_3, 0.5 equiv H_2SO_4, 99%) of aniline **8** produced **9**, which provided aniline **10** (77%) when exposed to concentrated sulfuric acid resulting from *p*-nitration and *O*-tosylate deprotection.[22] Acid-catalyzed condensation of **10** with methyltrimethoxy acetate (1.8 equiv, 0.05 equiv TsOH, toluene, DME, 80 °C, 87%) produced benzoxazole **11**. Benzylation of the remaining free phenol (1.5 equiv BnBr, 1.8 equiv K_2CO_3, DMF, quantitative), nitro reduction (10 equiv Zn, 15 equiv NH_4Cl, acetone, H_2O) and Boc protection of the resultant aniline (4.0 equiv Boc_2O, 2.2 equiv Et_3N, dioxane, 60 °C, 51%, two steps) gave benzoxazole **12**. Regioselective iodination of **12** using *N*-iodosuccinimide (1.4 equiv, 0.1 equiv TsOH, THF, MeOH, 87%) yielded aryl iodide **13**. Alkylation of aniline **13** using P_4-*t*-Bu phosphazene base and 1,3-dichloropropene (1.4 equiv P_4-base, 1.8 equiv 1,3-dichloropropene, benzene, 86%) produced vinyl chloride **14** as a mixture of alkene isomers.[15m,n] Once installed, the benzoxazole methyl ester proved especially sensitive to hydrolysis and this influenced our choice of reaction conditions, including the use of P_4-base/benzene for the N-alkylation of **13**. Free radical 5-*exo*-*trig* ring closure of **14** using freshly prepared Bu_3SnH (0.3 equiv AIBN, 1.2 equiv Bu_3SnH, benzene, 80%) produced **15**.[23] Debenzylation (10% Pd/C, 1 atm H_2 gas, THF, MeOH, 50%) of **15** resulted in formation of phenol **16**.

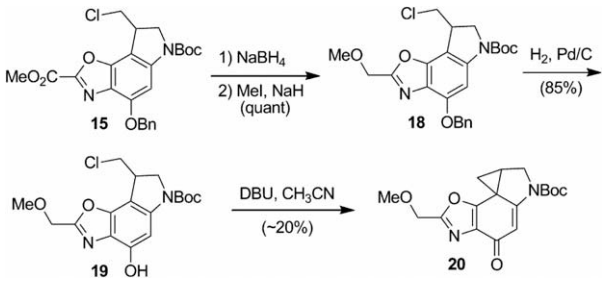


Scheme 1.

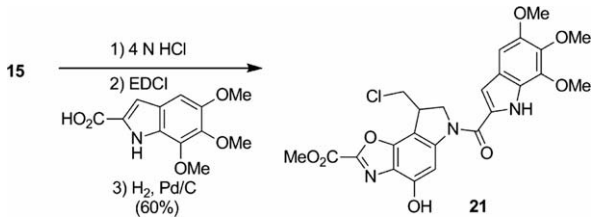
Exposure of phenol **16** to the basic conditions commonly employed to effect spirocyclization in duocarmycin-like systems (NaH, THF; $NaHCO_3$, DMF, H_2O; DBU, CH_3CN) did not provide **6** and instead resulted in rapid hydrolysis of the methyl ester. Replacement of the methyl ester with a *tert*-butyl ester, as in **17**, stabilized the molecule to competitive ester hydrolysis. However, even exposure of **17** to basic spirocyclization conditions did not result in ring closure, and the phenol starting material was recovered. Deprotonation of the phenol precursors to the spirocyclopropane alkylation units typically results in the formation of a yellow reaction mixture, which changes to colorless upon formation of the spirocyclopropane. Exposure of **17** to $NaHCO_3$ in DMF and H_2O resulted in a bright yellow solution, but dissipation of the yellow color and spirocyclization were not observed. This suggests that the phenolate ion forms, but does not react to displace chloride and form the cyclopropane.

Attempts to promote the spirocyclization of phenol **17** using silver salts or Bu_4NI as additives were also unsuccessful. In order to probe the impact of the ester on the problematic spirocyclization, reduction of the methyl ester **15** (5.0 equiv $NaBH_4$, MeOH) and methylation of the resultant alcohol (2.0 equiv NaH, 10 equiv MeI, THF, quantitative) produced methyl ether **18** (Scheme 2). After debenzylation, exposure of phenol **19** to DBU in CH_3CN slowly produced spirocycle **20** in poor yield (~20%) and with decomposition occurring during isolation and purification. Due to this reactivity and despite our expertise in handling even the most reactive alkylation subunits,[24] it was not possible to isolate a pure sample of **20**.

The reactivity of **20** and the inability of **16** to spirocyclize to provide *N*-Boc-COI (**6**) suggest that there is an intrinsic reactivity of this modified alkylation subunit that substantially exceeds that of duocarmycin SA. To date, the spirocyclization precursors to the



Scheme 2.



Scheme 3.

Table 1
In vitro cytotoxic activity, L1210 cell line

Compound	IC_{50} (pM)
(+)-**5**, (+)-*N*-Boc-DSA	6000
16, *seco*-*N*-Boc-COI	550,000
(+)-**1**, (+)-duocarmycin SA	10
21, *seco*-COI–TMI	5400

alkylation subunits containing the cyclopropane have displayed biological properties indistinguishable from the final products. Consequently, we elected to examine the cytotoxic activity of **16**, the seco precursor to *N*-Boc-COI (**6**), as well as **21** (Scheme 3), the seco precursor to COI–TMI (Table 1, TMI = 5,6,7-trimethoxyindole). Consistent with the indirect observations on their intrinsic reactivity and the observation of a direct relationship between chemical stability and cytotoxic potency,[16] **16** and **21** proved to be 100 and 550 times less potent than (+)-*N*-Boc-DSA (**5**) or (+)-duocarmycin SA (**1**), respectively. While this represents a substantial reduction in the activity relative to duocarmycin SA, it is still of a magnitude that is quite active (**21**, IC_{50} = 5.4 nM) and perhaps surpasses the anticipated potency given its inferred reactivity. The origin of the reactivity of the modified COI alkylation subunit and the resulting loss in cytotoxic activity is not well understood, especially when compared to the analogous CPyI,[18] CBI,[24,25] and CTI[17] alkylation subunit analogs.

To further characterize the modified alkylation subunit, the DNA alkylation selectivity and efficiency of compound **21** were examined using an assay previously described and singly ^{32}P end-labeled double-stranded w794 DNA.[26] Figure 3 illustrates the DNA alkylation selectivity of racemic *seco*-COI–TMI alongside (+)- and *ent*-(−)-duocarmycin SA. Within w794 DNA, *seco*-COI–TMI was found to alkylate the same site as (+)-duocarmycin SA, and with an efficiency nearly identical to (+)-duocarmycin SA. In this comparison, it is notable that the natural enantiomer of *seco*-COI–TMI (in the racemic mixture) alkylates DNA much more effectively than the unnatural enantiomer (not detected), and that its natural enantiomer DNA alkylation properties (efficiency and selectivity) are not readily distinguishable from those of (+)-duocarmycin SA (natural enantiomer).

What is remarkable is that the DNA alkylation selectivity and efficiency of **21** nearly match those of (+)-duocarmycin SA when conducted with cell free DNA, yet it fails to cyclize to the spirocyclopropane with the ease or facility of duocarmycin SA. Moreover, the cytotoxic potency of **21** does not reflect its DNA alkylation efficiency. Not only is it difficult to rationalize the origin of these observations, but to our knowledge it represents the first instance of such a dramatic lack of correlation between DNA alkylation efficiency and biological activity.

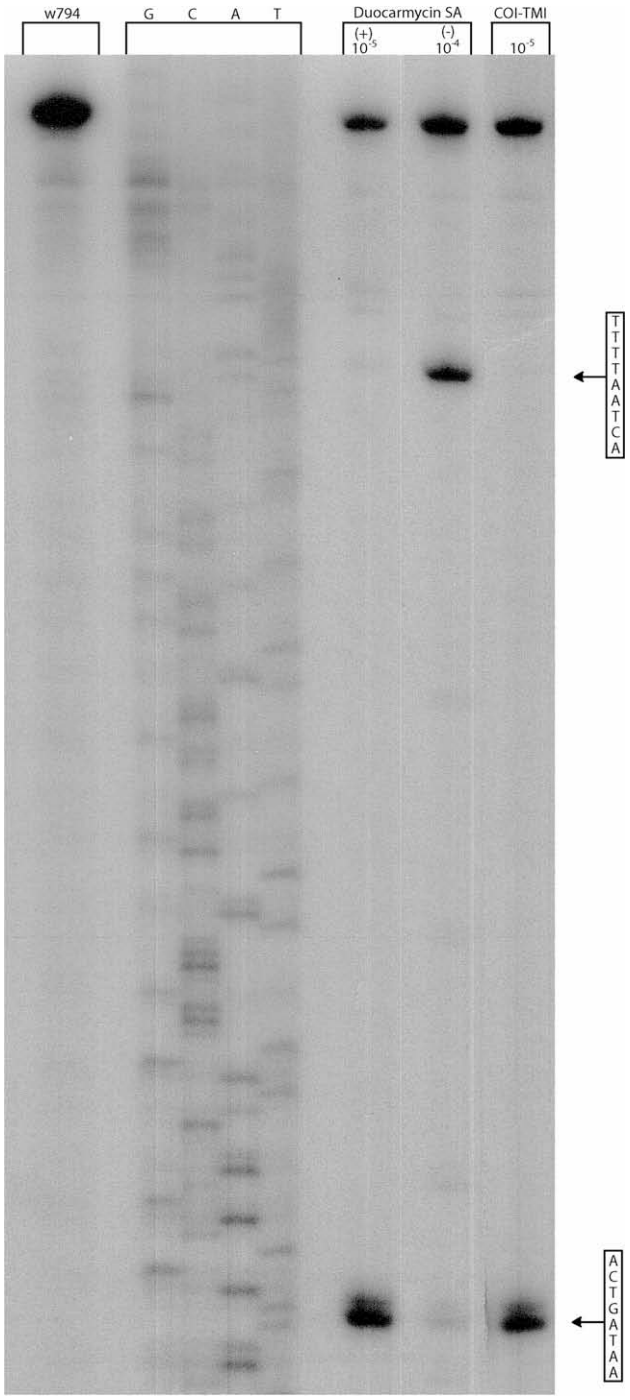


Figure 3. Thermally-induced strand cleavage of w794 DNA (144 bp. nucleotide no. 5238–138) after DNA-agent incubation with (+)- or ent-(−)-duocarmycin SA and COI–TMI (48 h, 23 °C), removal of unbound agent by EtOH precipitation and 30 min thermolysis (100 °C), followed by denaturing 8% PAGE and autoradiography. Lane 1, control DNA; lanes 2–5, Sanger G, C, A, and T sequencing standards; lane 6, (+)-duocarmycin SA (1×10^{-5} M, natural enantiomer); lane 7, (−)-duocarmycin SA (1×10^{-4} M, unnatural enantiomer); lane 8, *seco*-COI–TMI (**21**, 1×10^{-5} M, racemic mixture).

Acknowledgments

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Supplementary data

Supplementary data (synthesis of **16** and **21** and their experimental examination) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.145.

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