



# Synthesis and evaluation of a series of C5'-substituted duocarmycin SA analogs

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## ABSTRACT

The synthesis and evaluation of a key series of analogs of duocarmycin SA, bearing a single substituent at the C5' position of the DNA binding subunit, are described.

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Duocarmycin SA (**1**,  $IC_{50} = 10 \text{ pM}$ )<sup>1</sup> represents one of the most cytotoxic members of a class of natural products that also include duocarmycin A (**2**),<sup>2</sup> yatakemycin (**3**),<sup>3</sup> and CC-1065 (**4**, Fig. 1).<sup>4</sup> Members of this family of natural products derive their biological properties from a characteristic sequence-selective alkylation of duplex DNA,<sup>5–9</sup> in which a stereoelectronically controlled nucleophilic addition of adenine occurs at the least substituted carbon of the activated cyclopropane within the deeper, narrower minor groove at AT-rich sites in DNA.

Extensive investigations on the natural products in this class as well as their synthetic analogs have defined key and subtle features that contribute to their properties.<sup>9,10</sup> Most notable of these are the structural features that contribute to the AT-rich noncovalent binding selectivity dominating the alkylation selectivity,<sup>11</sup> those that are responsible for the source of catalysis for the DNA alkylation reaction,<sup>12,13</sup> and those that subtly impact the unusual and intrinsic stability of their alkylation subunits.<sup>9,13–17</sup>

Studies have shown that the role of the attached DNA binding subunit goes beyond that of simply providing DNA binding affinity and selectivity,<sup>11</sup> but that it also contributes to and is largely responsible for the DNA alkylation catalysis.<sup>12,18</sup> We have suggested that this catalysis is derived from a DNA binding induced conformational change in the compound that serves to disrupt the vinylogous amide stabilization of the alkylation subunit activating it for nucleophilic attack. Responsible for this conformational change and the resulting activation is the rigid extended and planar structures of both the alkylation subunit and the attached DNA binding subunit. The DNA bound molecule adopts a bent versus planar conformation following the overall curvature and helical pitch of the minor groove with the twist accommodated by the region surrounding the linking amide, the only

flexible portion of the molecule.<sup>12,13,19</sup> Both the C-terminus substituent (C6 methyl ester for **1**) on the alkylation subunit and the minor groove imbedded C5' substituent on the DNA binding subunit contribute to the effective overall rigid length of the compounds. Hence, both can impact the extent of the conformational change or twist in the DNA bound compound, the degree of activation for nucleophilic attack, and the extent of the catalysis of the

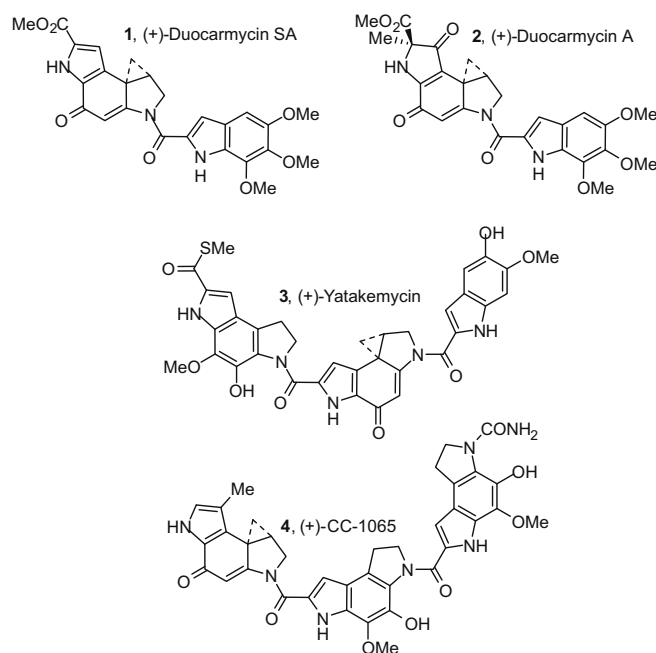


Figure 1. Natural products.

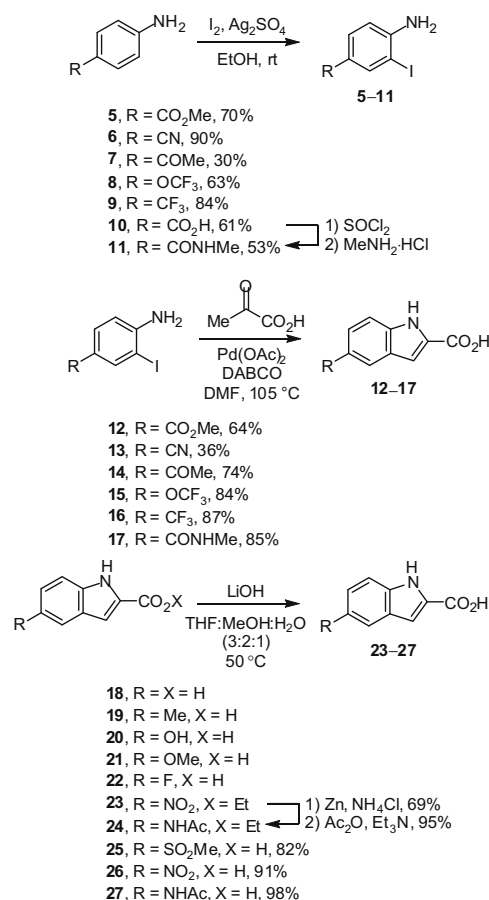
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DNA alkylation reaction. As a result, minor groove bound substituents on both the DNA binding subunit and the alkylation subunit each have been shown to have a pronounced effect on the rate and efficiency of DNA alkylation and the resulting biological potency of the compounds. It has been shown that the substituent at the C5' position of the indole DNA binding subunit of duocarmycin SA is of predominant importance, and that it can alone provide a fully active agent with little or no contribution derived from the C6' and C7' substituents found in duocarmycin A and duocarmycin SA (Fig. 2).<sup>12</sup> Similarly, the removal of the C6 methyl ester from the alkylation subunit of duocarmycin SA was shown to reduce the rate (12–13-fold) and efficiency (10-fold) of DNA alkylation illustrating an important role for the minor groove imbedded substituent.<sup>15v</sup> Additionally, and as first systematically explored with CBI derivatives, the nature of the C5' substituent proved to have pronounced impact that correlated with its presence, size, rigidity and length, but not electronic properties.<sup>18</sup> Herein, we systematically explore the importance of the C5' substituent within duocarmycin SA analogs additionally bearing the minor groove imbedded C6 methyl ester.

The synthesis of the duocarmycin SA alkylation subunit was carried out by a sequence first developed for the total synthesis of duocarmycin SA,<sup>20</sup> which relied on a late-stage chiral resolution to provide optically active material. In most cases, a synthesis of the C5-substituted indole-2-carboxylic acids was required to obtain the appropriately substituted DNA binding subunit. Their synthesis was initially pursued using a Hemetsberger indole synthesis<sup>21</sup> followed by saponification of the methyl indole-2-carboxylate to provide the desired indole-2-carboxylic acid. However, the Hemetsberger reaction, enlisting 3-substituted benzaldehydes, often produced a near 1:1 mixture (by <sup>1</sup>H NMR) of the C5- and C7-substituted indoles and attempts to separate these regioisomers by chromatography proved challenging. Alternatively, a route employing a palladium-catalyzed indole-forming reaction<sup>22</sup> to regioselectively access the desired C5-substituted indole-2-carboxylic acids was explored and proved to be a synthetically attractive route (Scheme 1).

Starting with the commercially available 4-substituted anilines, electrophilic aromatic iodination (1.0 equiv I<sub>2</sub>, 1.0 equiv Ag<sub>2</sub>SO<sub>4</sub>,



Scheme 1.

EtOH, rt, 30–60 min, 30–90%)<sup>23</sup> cleanly afforded the 4-substituted-2-iodoanilines (**5–11**). Treatment of the iodoanilines **5–11** with pyruvic acid (3.0 equiv), DABCO (3.0 equiv), and Pd(OAc)<sub>2</sub> (0.05 equiv) at 105 °C for 4 h in a thoroughly degassed solution of DMF cleanly provided the desired C5-substituted indole-2-carboxylic acids (**12–17**, 36–86%) as a single regioisomeric product.<sup>22</sup> Most C5-substituted indole-2-carboxylic acids were prepared by this method, with a few purchased from commercially available sources either as the free acid (**18–22**) or obtained by hydrolysis of the corresponding methyl or ethyl esters (**23–27**) (10 equiv LiOH, THF/MeOH/H<sub>2</sub>O 3:2:1, 50 °C, 2 h, 57–91%). Boc deprotection of enantiopure **28**<sup>20</sup> was achieved by treatment with 4 N HCl/EtOAc (18 h, 25 °C) to afford the crude amine hydrochloride salt. Without purification, subsequent coupling with the C5-substituted indole-2-carboxylic acid (1.4 equiv, 4.0 equiv EDCI, 2.0 equiv NaHCO<sub>3</sub>, DMF, rt, 30–45 min, 19–98%) provided the benzyl protected coupled products **29–42** (Scheme 2).

Hydrogenolysis of the benzyl ether to liberate the free phenol (10% Pd/C, 1 atm H<sub>2</sub>, THF/MeOH, rt, 2 h, 11–66%) afforded derivatives **43–55**. In the case of **40**, debenzilation of **28** (10% Pd/C, 25% aqueous HCO<sub>2</sub>NH<sub>4</sub>, THF, rt, 2 h, 28%) prior to Boc deprotection and coupling was employed to avoid competitive reduction of the nitro group under the hydrogenolysis conditions (Scheme 2). Finally, spirocyclization was achieved with relative ease (1 equiv NaHCO<sub>3</sub>, DMF, H<sub>2</sub>O, rt, 30 min, 33–98%) to provide **56–69** (Scheme 2).

The results of the examination of the C5'-substituted (+)-duocarmycin SA analogs in a L1210 cytotoxic assay are summarized in Figure 3.

From these data all analogs, except **65** (R = OMe) and **57** (R = CN), exhibit approximately equal potency (IC<sub>50</sub> = 40–80 pM),

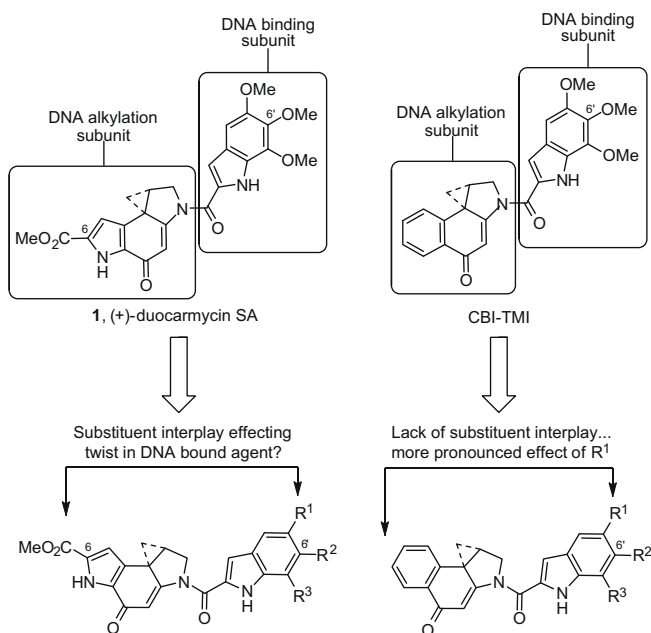
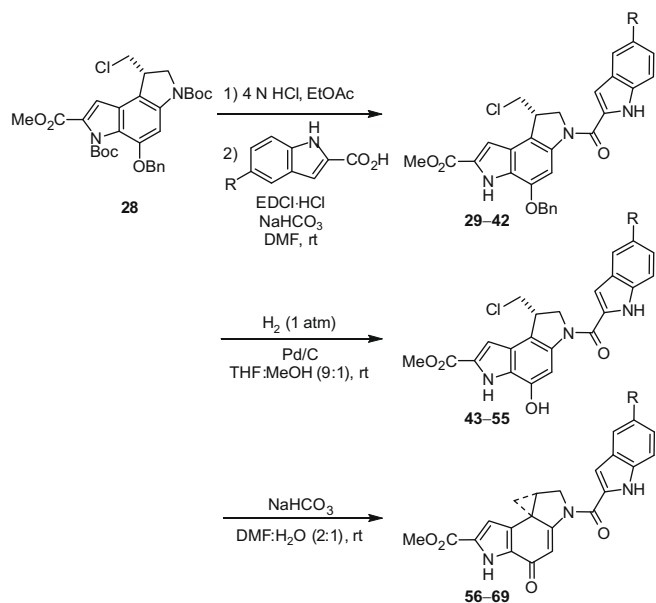


Figure 2. (+)-Duocarmycin SA and CBI analog series.



R	Compd	Yield (%)	Compd	Yield (%)	Compd	Yield (%)
CO <sub>2</sub> Me	<b>29</b>	51	<b>43</b>	51	<b>56</b>	72
CN	<b>30</b>	95	<b>44</b>	66	<b>57</b>	59
COMe	<b>31</b>	96	<b>45</b>	31	<b>58</b>	91
OCF <sub>3</sub>	<b>32</b>	67	<b>46</b>	43	<b>59</b>	44
CF <sub>3</sub>	<b>33</b>	57	<b>47</b>	17	<b>60</b>	63
CONHMe	<b>34</b>	68	<b>48</b>	38	<b>61</b>	67
H	<b>35</b>	78	<b>49</b>	11	<b>62</b>	41
Me	<b>36</b>	33	<b>50</b>	33	<b>63</b>	60
OH	<b>37</b>	69	<b>51</b>	19	<b>64</b>	68
OMe	<b>38</b>	75	<b>52</b>	40	<b>65</b>	34
F	<b>39</b>	96	<b>53</b>	33	<b>66</b>	37
NO <sub>2</sub>	<b>40</b>	37*	-	-	<b>67</b>	98
NHAc	<b>41</b>	98	<b>54</b>	22	<b>68</b>	68
SO <sub>2</sub> Me	<b>42</b>	70	<b>55</b>	52	<b>69</b>	67

\* = Debenzylated before coupling

Scheme 2.

all being  $\leq 10$ -fold less potent than (+)-duocarmycin SA, (**1**, IC<sub>50</sub> = 6–10 pM). Additionally and according to expectations, the spiro and seco analogs containing the same C5'-substituent on the DNA binding subunit exhibited equal potency and were essentially indistinguishable. This indicates that the seco analogs, regardless of the C5'-substituent, are able to cyclize in situ to the corresponding cyclopropane, the active DNA alkylating agent. Contrary to initial expectations, all C5'-substituted analogues with the exception of **65** and **57**, were found to exhibit an approximately 10-fold decrease in cytotoxic potency as compared to **1** and to approach the potency of **62** lacking a C5' substituent altogether. This is in contrast to observations<sup>18</sup> made for the series of C5'-substituted analogs containing the CBI alkylation subunit, where the presence of a simple C5' substituent, regardless of that substituent's electronic nature, typically produced analogs that substantially increased the activity (as much as 100-fold) and some that matched or even exceeded the potency of **1** (1000-fold increase). This suggests that within the duocarmycin SA structure that already incorporates a more extended alkylation subunit and its minor groove imbedded C6 methyl ester, the addition of a simple indole C5' substituent typically does little to further enhance its properties. The exceptions to this generalization are **65** and **57**, incorporating a C5' methoxy group or nitrile, respectively. The former incorporates a substituent (OMe) found in the natural products themselves, and it is significantly more potent than even its

	R <sup>1</sup>	R <sup>2</sup>	IC <sub>50</sub> , pM <sup>a</sup>
<b>1</b>	(+)-duocarmycin SA	-	6–10
<b>56</b>	CO <sub>2</sub> Me	H	47 (48)
<b>57</b>	CN	H	7 (9)
<b>58</b>	COMe	H	43 (38)
<b>59</b>	OCF <sub>3</sub>	H	49 (85)
<b>60</b>	CF <sub>3</sub>	H	65 (75)
<b>61</b>	CONHMe	H	70 (61)
<b>62</b>	H	H	68 (72)
<b>63</b>	Me	H	77 (78)
<b>64</b>	OH	H	53 (50)
<b>65</b>	OMe	H	7.5 (21)
<b>66</b>	F	H	54 (79)
<b>67</b>	NO <sub>2</sub>	H	41 (35)
<b>68</b>	NHAc	H	83 (81)
<b>69</b>	SO <sub>2</sub> Me	H	58 (58)
<b>70</b>	OMe	OH	7 (18)
<b>71</b>	OH	OMe	33 (41)

<sup>a</sup> L1210 cytotoxic activity, average of 2–7 determinations run in duplicate. Results of the examination of the seco derivative are in parentheses.

Figure 3. In vitro cytotoxic activity, L1210.

most closely related derivative (OH, OCF<sub>3</sub>). The latter incorporates an electron-withdrawing versus electron-donating substituent, and one that is sterically small, but extended linearly. Because other electron-withdrawing substituents proved noticeably less potent, it does not appear that it is electronic properties of these two substituents that are responsible for their enhanced activity. Additional potential contributing features including hybridization (sp<sup>2</sup> vs sp<sup>3</sup>) or hydrogen bond donor or acceptor properties do not appear to account for the unique properties of **65** and **57**. Although it is easy to rationalize the observations that a C5' substituent does not have such a significant impact with duocarmycin SA (10-fold difference between **1** and **62**), at present it is difficult to rationalize the origin of the observations with the two unique substituents (OMe, CN) that significantly impact the activity.

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## Supplementary data

Supplementary data (full experimental details are provided) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.03.078.

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