Derivatives of Methyl 5-Methyl-4-oxo-1,2,4,5,8,8a-hexahydrocyclopropa[*c*]-pyrrolo[3,2-*e*]indole-7-carboxylate: A Case of Inverse Electronic Effects on the Reactivity of CC-1065 Derivatives

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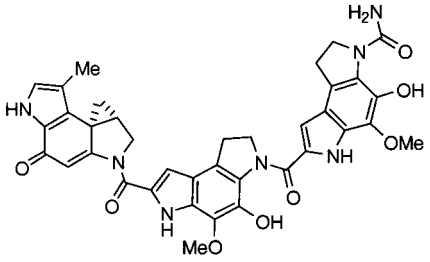
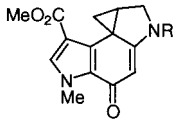
The isolation of the antitumor agent CC-1065 (**1**)[1] at the Upjohn Company in 1978 marked the beginning of a series of discoveries of natural and synthetic derivatives of cyclopropaindolones with promising therapeutic properties.[2] These agents retard cancer cell growth by alkylation of the DNA in a highly selective manner. The cyclopropane is attacked by the N-3 nitrogen of an adenine, leading to the opening of the cyclopropane and the transformation of the cyclohexadienone in an aromatic ring.[3]



CC-1065 (**1**)

An important aspect of the development of new cyclopropaindolone (CPI) derivatives with increased biological activity is the possibility of predicting their potency by solvolytic studies. From the study of many of these derivatives, it has been shown, mainly by the notable and detailed work of D. Boger's group, that the introduction of electron-withdrawing groups causes a linear decrease in speed of the acidic solvolysis. This, in turn, enhances the stability of cyclopropaindolones in plasma and causes an increase in *in vivo* cytotoxic potency.[3,4]

These findings suggest that the best candidates for drug development are those derivatives with greater electron-deficiency. This study shows that this is not always the case, as 5-methyl-CPI derivatives **2a**−**e** were found to exhibit a nonlinear solvolytic



2a: R = H
2b: R = $CONH_2$
2c: R = $CO_2C(Me)_3$
2d: R = COMe
2e: R = SO_2Me

behavior, with a region of increased reactivity (log *k*) correlating with decreased electron-deficiency as reflected by the σ_p Hammett constant of their R substituents (Figure 1).

Compounds **2a**−**e** were prepared according to Scheme 1. A key reaction was the photochemical oxidative cyclization of bis-pyrrylethene **6**, previously developed by us.[5] Condensation of sulfone **4**[6] with pyrrolecarbaldehyde **5**, both easily obtained from aldehyde **3**,[7] followed by oxidation with DDQ and acetylation, leads to bis-pyrrylethene **6**. This compound was obtained as a single isomer about the central double bond, with an unknown, but irrelevant, stereochemistry. The tosyl substituent in compound **6** stabilizes the structure against unwanted oxidation by singlet oxygen and allows a very good yield in a photochemical oxidative cyclization of such a densely functionalized compound, providing pyrroloindole **7** in 90%. Protecting-group manipulations and regioselective reductions of an indole and an ester, yield alcohol **12**. Compound **8** was deacetylated to obtain a greater yield in the regioselective reduction of the upper pyrrole ring. Cyclization of phenolic alcohol **12** under Mitsunobu conditions, followed by changing the substituents on the indoline nitrogen, leads to the desired derivatives **2a**−**e**, in which groups with different electron-withdrawing properties are introduced.

The solvolysis of cyclopropapyrroloindolones **2a**−**e** at pH 1.4 in a MeOH−H_2O (1:1) solution was studied by following the disappearance of the characteristic long-wavelength UV-absorption of the cyclohexadienone chromophore. All of the compounds studied, with the exception of **2e**, show a linear increase in solvolysis speed with increasing electron-deficiency (Table 1 and Figure 1). Thus, contrary to expectation, the simple unsubstituted derivative **2a** shows greater stability, while the *N*-acetylated, electron-deficient compound **2d** shows greater reactivity. Compounds **2b** and **2c** show intermediate behavior. Surprisingly, no solvolysis was detected after more than one week in the very electron-deficient **2e**. We estimate that it possesses a *k* of less than 4×10^{-7} s^{-1}, the corresponding point in Figure 1 displaying this value. While the solvolytic behavior of sulfamide **2e** is abnormal in comparison with the structurally similar derivatives **2a**−**d**, the decreased reactivity in a more electron-deficient compound has ample literature precedent.[3,4]

Cyclopropaindolones **2a**−**e** also show an abnormal relationship between solvolytic reactivity and in vitro cytotoxic potency (Table 1, Figure 2) relative to other CC-1065 analogues,[3] with those compounds **2a**−**e** with greater potency also having greater

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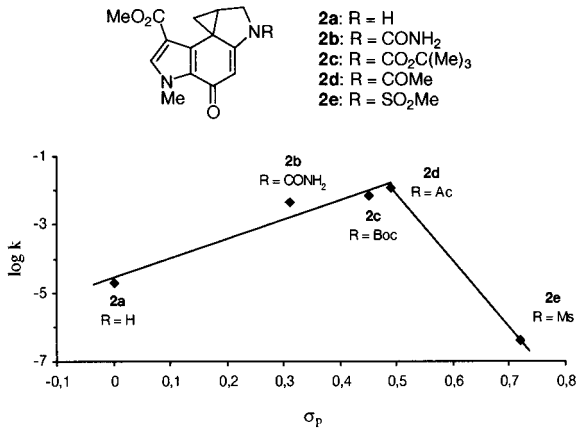
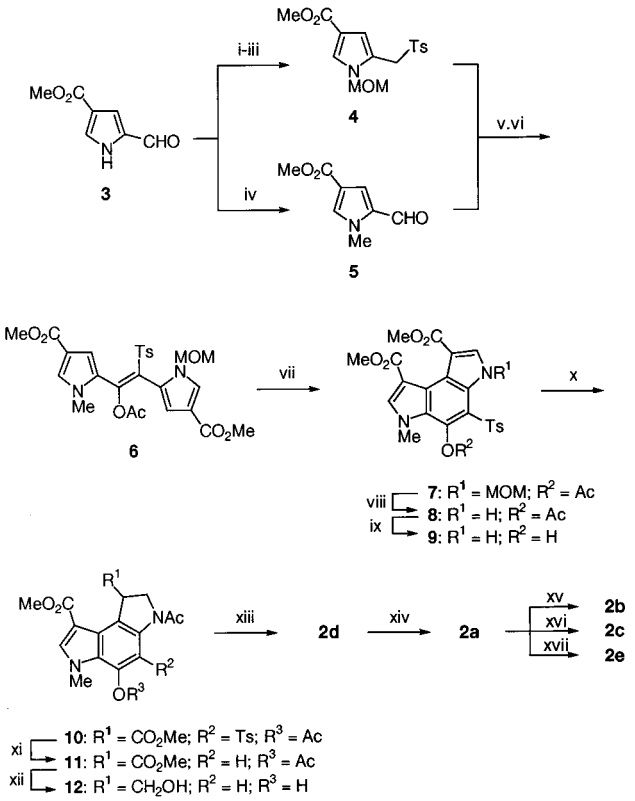


Figure 1.

Scheme 1[a]



[a] (i) KO*t*-Bu, ClMOM, DMF, 88%. (ii) $NaBH_4$, MeOH, 0 °C, 98%. (iii) *p*-Me(C_6H_4)SO_2Na, HCO_2H, 95%. (iv) KO*t*-Bu, MeI, DMF, 95%. (v) LDA, THF, −78 °C to −40 °C, 82%. (vi) DDQ, benzene, reflux; ClAc, Et_3N, CH_2Cl_2, −40 °C; 82%. (vii) hν, cat. I_2, air, EtOH, 90%. (viii) HCOOH, 98%. (ix) NaOMe, MeOH, 95%. (x) Et_3SiH, F_3CCO_2H; Ac_2O, Py; 66%. (xi) Na, naphthalene, THF, −78 °C; Ac_2O, Py; 50%. (xii) $LiAlH_4$, THF, −30 °C, 84%. (xiii) Ph_3P, DEAD, THF, 71%. (xiv) NaOMe, MeOH, 91%. (xv) HCl (g), EtOAc; Et_3N, Me_3SiNCO, THF; $Et_3N/H_2O/CH_3CN$ (1/1/5); 26%. (xvi) Boc_2O, DMAP, CH_2Cl_2, 99%. (xvii) $ClSO_2Me$, Et_3N, CH_2Cl_2, −20 °C, 45%.

solvolytic reactivity. This could be due to the general lack of solvolytic reactivity of compounds **2a**−**e**, as suggested by the fact that it is necessary to carry out the kinetic studies at a very acidic pH of 1.4. Thus, while normally the more stable compounds, which remain intact until they reach DNA, show greater cytotoxic potency, in the present series the reverse is true. This can be explained if no degradation occurs in the present series in competition with DNA alkylation, so greater activity is seen for those compounds that react more efficiently with DNA. This

Table 1. Solvolysis Rates[a] and Cytotoxicity

agent (R)	$t_{1/2}$	k_{obs} (s^{-1})	IC_{50} (mg/mL)[c]	σ_p
2a (H)	≥10 h	1.92×10^{-5}	2.5	0.00
2b ($CONH_2$)	145 s	4.75×10^{-3}	0.05	0.31
2c (Boc)	93 s	7.43×10^{-3}	0.5	0.45
2d (Ac)	58 s	1.18×10^{-2}	0.02	0.49
2e (Ms)	very slow[b]	$<4 \times 10^{-7}$	2.5	0.72

[a] Water-MeOH 1:1; [agent] = 10^{-4}; pH = 1.4 ([ClO_4H] = 3.8×10^{-2}). [b] No solvolysis was detected after one week. [c] Values corresponding to *in vitro* cytotoxicity activity against P-338 cell lines. Similar trends were observed in cell lines A549, HT29, and MEL28.

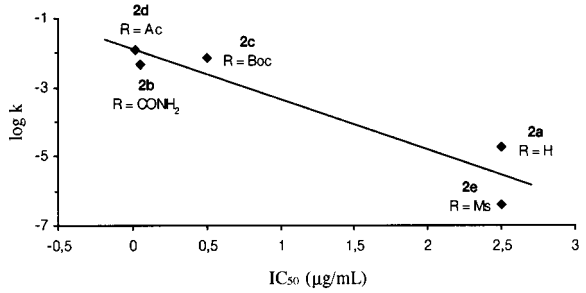


Figure 2.

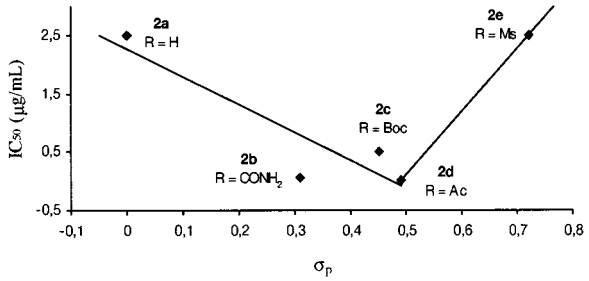


Figure 3.

behavior was also observed in the first studies on CC-1065 derivatives performed at Upjohn.[8] The composite data from previous works and our own show that *there is an optimum of solvolytic reactivity, leading to a maximum cytotoxic potency, in which cyclopropaindolone alkylators are not substantially destroyed before reaching the DNA, but are still able to efficiently alkylate DNA.*

Quite curiously, as a result of a reversal of behavior for both solvolytic reactivity versus electron-deficiency and solvolytic reactivity versus biological activity, in the present series, with the exception of **2e**, a normal relationship of electron-deficiency versus biological activity is found. The most electron-deficient compounds are the most cytotoxic (Figure 3).

This work shows that to infer a linear relationship between a physical constant and a biological activity; compounds with the greatest possible range of the physical constant must be studied.

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Supporting Information Available: Experimental procedures for preparation of derivatives **2a**−**e** (Scheme 1) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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