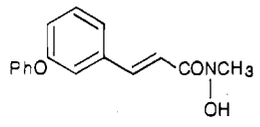
monoalkylated hydroxylamine **3** together with about 10% bisalkylated product. Hydrolysis of the crude reaction mixture with concentrated HCl in MeOH gave the deprotected hydroxylamine hydrochloride, which was purified by crystallization (EtOAc). Acetylation followed by O-deacetylation, as above, gave **2** in good overall yield. Acetylation of **3** followed by deprotection (PPTS, MeOH) gave less pure product.

Both **1** and **2** have so far been found to be devoid of toxicity problems and to be nonmutagenic[11] in the Ames Salmonella test. Furthermore, **1** and **2** selectively inhibit the ex vivo Ca^{2+} ionophore stimulated production of LTB_4 in whole rat blood for well over 6 h after a single oral dose of 50 mg/kg; compound **2**, in fact, has an ED_{50} at 6 h of 9 mg/kg. In contrast, compound **4**, which is structurally



4

similar to and in vitro is equipotent with **2** shows no ex vivo activity at 6 h after 50 mg/kg orally in rats. It should be noted that **4** is structurally related to the hydroxamic acid based inhibitors recently disclosed by several other groups.[12]

Compound **2** has also demonstrated its ability to block the "leukotriene-dependent" anaphylactic bronchospasm[13] in anesthetized guinea pigs in a dose-related manner. In the 6-h carrageenin sponge implant model of inflammation,[14] **2** selectively inhibits the formation of LTB_4 over PGE_2 in the sponge exudates with an ED_{50} of 2.6 mg/kg. This inhibition was accompanied by a decrease in the number of leukocytes in the sponge exudate, but there was no *direct* correlation between the two values. Further extensive biological observations with compounds **1** and **2** will appear in due course.[15]

Thus, with the development of potent, selective, orally active inhibitors of 5-LO, it should be possible to determine the relevance of lipoxygenase products in human disease states.

Acknowledgment. We thank our biological collaborators for their dedicated support in this project.

Registry No. **1**, 106328-28-3; **1** (*O*-acetyl deriv), 106328-89-6; **2**, 106328-57-8; **2** (*O*-acetyl deriv), 112270-90-3; **3**, 112270-88-9; 5-LO, 80619-02-9; 4-(benzyloxy)benzaldehyde oxime, 76193-67-4; 3-phenoxybenzaldehyde, 39515-51-0; malonic acid, 141-82-2; methyl 3-[(4-phenoxy)phenyl]propenoate, 87087-33-0; 3-bromo-1-[(4-phenoxy)phenyl]propene, 112270-87-8; *N*-hydroxy-3-(4-phenoxyphenyl)-2-propenamine hydrochloride, 112270-89-0.

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9-(*trans*-2′,*trans*-3′-Dihydroxycyclopent-4′-enyl) Derivatives of Adenine and 3-Deazaadenine: Potent Inhibitors of Bovine Liver *S*-Adenosylhomocysteine Hydrolase

Sir:

Neplanocin A (NpcA, Chart I), a cytotoxic, cyclopentenyl analogue of adenosine, is a naturally occurring antitumor antibiotic, which was isolated from the bacterium *Ampullariella regularis*.[1-4] NpcA possesses antitumor activity in vivo against murine L1210 leukemia in mice[2,5] and antiviral activity in cell culture against vaccinia virus,[6] herpes simplex-1,[7] herpes simplex-2,[7] and vesicular stomatitis virus.[7] Our laboratory has shown that NpcA is a potent, irreversible inhibitor of *S*-adenosylhomocysteine (AdoHcy) hydrolase (E.C. 3.3.1.1) isolated from bovine liver[6] and *Alcaleigenes faecalis*.[8] This enzyme, which catalyzes the reversible hydrolysis of AdoHcy to adenosine and homocysteine, is the only metabolic route for the removal of AdoHcy in eukaryotic cells.[9] Subsequently, inhibition of AdoHcy hydrolase by NpcA in eukaryotic cells (e.g., mouse L929 and neuroblastoma N2a cells) leads to elevation of cellular levels of AdoHcy and inhibition of *S*-adenosylmethionine (AdoMet) dependent methylations.[10,11] The inhibition of AdoHcy hydrolase has been correlated with the antiviral activity of NpcA,[12] and

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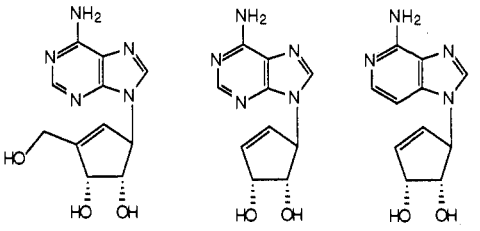
Chart I



this drug is believed to inhibit critical viral mRNA methylations, which adversely affect translational efficiency by perturbing the binding of viral mRNA to ribosomes.[10,13-15]

Wolfson et al.[16] recently reported that NpcA acts as a $K_{cat.}$ inhibitor of AdoHcy hydrolase, having a mechanism similar to that reported for 2'-deoxyadenosine[17] and araA.[18] The mechanism proposed by Wolfson et al.[16] involves the reduction of enzyme-bound NAD^+ to NADH and consequent oxidation of the 3'-hydroxyl group of NpcA to form the 3'-ketocyclopentenyl derivative, which has been proposed to eliminate adenine and generate a reactive electrophile. This proposed mechanism, however, has been questioned since AdoHcy hydrolase, which was inactivated by NpcA, can be reactivated by incubation with NAD^+, suggesting that NcpA acts simply as a $K_{cat.}$ inhibitor reducing NAD^+ to NADH.[19]

In addition of NpcA's inhibitory effects on AdoHcy hydrolase, it also serves as a substrate for adenosine deaminase and consequently can be rapidly deaminated in cells to the biologically inactive neplanocin D (NpcD).[5] NpcA also serves as a substrate for adenosine kinase, being converted to the triphosphate derivative (NpcATP), which subsequently serves as a substrate for AdoMet synthetase, generating the corresponding AdoMet derivative *S*-neplanocylmethionine (NpcMet).[20] Metabolism of NpcA by this phosphorylation pathway has been proposed as the mechanism by which this agent produces cytotoxicity.[21]

Thus, cellular AdoHcy hydrolase may represent the molecular target mediating the antiviral effects of NpcA, while cellular adenosine kinase may represent the molecular target mediating its cytotoxic effects. Therefore, we hypothesized that if the 5'-hydroxymethyl group was removed from NpcA it would give analogue 1 (Chart I),[22] which might retain inhibitory effects toward AdoHcy hydrolase and thus its antiviral effects. At the same time, the absence of a 5'-hydroxymethyl group on analogue 1 should render the analogue less cytotoxic, since it cannot be converted to the corresponding NpcATP and NpcMet

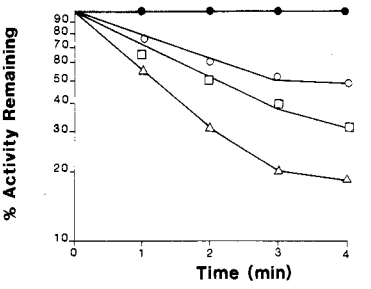


Figure 1. Time course for the inactivation of AdoHcy hydrolase by compound 1. Different concentrations of compound 1, (●, no drug; ○, 20 nM; □, 30 nM; △, 40 nM) were incubated with purified bovine liver *S*-adenosylhomocysteine hydrolase[29] (20 nM) for the indicated times, after which the reaction was stopped with 0.1 N formic acid. The AdoHcy hydrolase activity remaining was determined by using the procedure of Richards et al.,[33] which involves measuring the hydrolysis of [2,8-^{3}H]AdoHcy[34] to [2,8-^{3}H]adenosine and homocysteine. The coupled assay includes adenosine deaminase, which rapidly converts [2,8-^{3}H]adenosine to [2,8-^{3}H]inosine, and the [2,8-^{3}H]inosine is measured by scintillation spectrometry after separation on SP Sephadex-C-25.

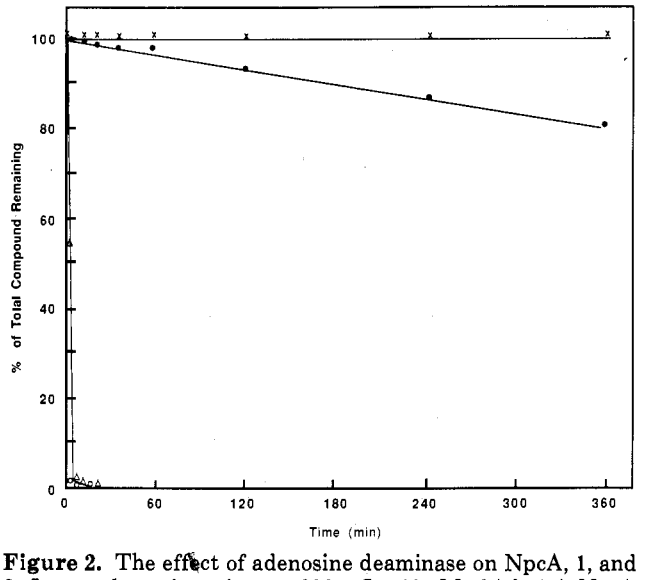


Figure 2. The effect of adenosine deaminase on NpcA, 1, and 2. In a total reaction mixture of 500 μL, 500 μM of Ado (○), NpcA (△), 1 (●), or 2 (x) were incubated with 16 units of calf intestinal adenosine deaminase in phosphate buffer (pH 7.5). At the indicated times, 50-μL aliquots were removed, and the reaction was stopped with 0.4 N $HClO_4$, centrifuged, and analyzed by reverse-phase HPLC as previously described.[6]

analogues. It is also known that adenine nucleosides that do not contain a free 5'-hydroxymethyl group are poor substrates for adenosine deaminase.[23] Thus, the absence of this group in analogue 1 should reduce its interaction with adenosine deaminase and prolong its duration of action in vivo. The 3-deazaadenine analogue 2 (Chart I)[22] was also synthesized to further reduce the interactions with adenosine kinase and adenosine deaminase on the basis of the work done with 3-deazaaristeromycin[24,25] and 3-deazaneplanocin A.[26,27] In this paper, we report the in-

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Table I. NAD^+ Content of Native and Inactivated AdoHcy Hydrolase

inhibitor	residual enzyme activity,[a] %	NAD^+, mol/mol of enzyme tetramer[b]
none	100	1.48[c]
NpcA	0	0
1	20	0.19
2	5	0.16

[a] AdoHcy activity was determined using the coupled assay described by Richards et al.[33] [b] Lypholized bovine liver AdoHcy hydrolase (220 pmol) was dissolved in 0.1 M potassium buffer, pH 7.0, and treated with inhibitor (1.4 equiv 300 pmol) for 20 min at 37 C. Then, 50 μL of the reaction mixture was treated with 50 μL of 5% SDS for 10 min at 4 °C to release bound nucleotides. The mixture was filtered through an Amicon micro partition system at 4 °C. A sample of the filtrate was analyzed for the presence of NAD^+ and NADH by HPLC on a C 18 reverse-phase column (ODS hypersil, 150 × 4.6mm), eluted with 0.1 M phosphate buffer, pH 7.0, containing 2.5% methanol at a flow rate of 1 mL/min. The chromatograms were monitored at 254 and 340 nm with a Spectroflow 783 programmable detector. Assays were done in quadruplicate. [c] The NADH content was 0.43 mol/mol of enzyme tetramer.

hibitory effects of 1 and 2 on bovine liver AdoHcy hydrolase and their substrate activity with purified adenosine deaminase.

Figure 1 illustrates the time course of inactivation of bovine liver AdoHcy hydrolase by increasing concentrations of 1. The inhibition of AdoHcy hydrolase by 1 is both time- and concentration-dependent. Similar results were obtained when AdoHcy hydrolase was inactivated with 2 and NpcA (data not shown). The apparent K_i values for NpcA, 1, and 2 were determined by use of a double-reciprocal plot of the observed rate constants (obtained from the initial linear time points in the time- and concentration-dependent inactivation studies) and inhibitor concentration. NpcA had a K_i value of 3.8 nM; in contrast, compounds 1 and 2 had K_i values of 41 and 35 nM, respectively. The $K_{cat.}$ values determined for NpcA, 1, and 2 from these plots were 1.98, 0.5, and 0.5 min^{-1}, respectively.

Since NpcA pharmacological properties are believed to be partially limited by adenosine deaminase, which converts NpcA quite rapidly to its less biologically active form neplanocin D (see data below), it was determined if compounds 1 and 2 were substrates for this enzyme. Shown in Figure 2 is the effect of calf intestinal adenosine deaminase on NpcA, 1, and 2 in vitro. NpcA is rapidly converted to NpcD by adenosine deaminase, having a $t_{1/2}$ of less than 1 min under the conditions used here. In contrast, compound 1 exhibited a $t_{1/2}$ of 15 h, and compound 2 did not show any detectable deamination after 6 h. In addition, when compounds 1 and 2 were co-incubated with adenosine at equimolar concentrations, neither compound showed any inhibitory effects toward adenosine deaminase (data not shown). In a separate study in our laboratory, we have found compounds 1 and 2 to be potent inhibitors of L929 cell AdoHcy hydrolase and to lack substrate activity for adenosine deaminase and adenosine kinase in cell lysates.[28] The lack of interaction of 1 and 2 with adenosine deaminase and adenosine kinase results in inhibitory effects on cellular AdoHcy hydrolase that are more sustained than those observed with NpcA.[28]

Table I describes the NAD^+ and NADH content of native bovine liver AdoHcy hydrolase and AdoHcy hydrolase inactivated with NpcA, 1, and 2. A fresh preparation of bovine liver AdoHcy hydrolase isolated by the procedure of Narayanan and Borchardt[29] contained a total of approximately 2 mol of nicotinamide adenine dinucleotides (NAD^+ and NADH) per enzyme tetramer. The NAD^+ content varied from preparation to preparation of the enzyme and was estimated to be between 1.12 and 1.48 mol of NAD^+ per mole of enzyme tetramer. It has recently been reported by our laboratory that inactivation of bovine liver AdoHcy hydrolase by NpcA is accompanied by reduction of the enzyme-bound NAD^+, resulting in a catalytically incompetent form of the enzyme (NADH form).[19] In the present study, when the enzyme was inactivated by compounds 1 and 2, there was a similar decrease in the NAD^+ content followed by a concomitant increase in the NADH content. The decrease in the NAD^+ content, when the enzyme was inactivated by 1 and 2, paralleled the decrease in the catalytic activity of the enzyme (Table I). The enzymatic activity of the AdoHcy hydrolase treated with compounds 1 and 2 could not be recovered by dialysis but was fully recovered by the addition of NAD^+, as was previously observed with NpcA-treated enzyme (data not shown).[19] Thus, the data described here strongly suggest that compounds 1 and 2 inactivate AdoHcy hydrolase by a mechanism similar to that of NpcA.

A number of conflicting reports have been published lately on the release of adenine from nucleosides during the inactivation of AdoHcy hydrolase.[17-19,30] For example, our laboratory showed that adenine is not released when the NpcA-inactivated enzyme is denatured with SDS or by heating.[30] Thus, the critical step in neplanocin A induced inactivation of AdoHcy hydrolase appears to be reduction of NAD^+ to NADH, not the elimination of adenine and the generation of an electrophile. The generation of adenine from the NpcA-inactivated enzyme appears to be simply an artifact of the denaturation process.[31] Accordingly, we have checked for the release of adenine during the inactivation of AdoHcy hydrolase by 1 and 2 using an HPLC system that quantifies the level of NAD^+, NADH, and adenine in microgram quantities of enzyme. It should be noted that traces (0.02–0.05 mol/mol of enzyme tetramer) of adenine were present in the control samples (samples of freshly prepared enzyme preparations not incubated with the inhibitor). However, no increase in adenine above these trace levels was detectable from enzyme inactivated with 1 or 2. Hence, we propose that reduction of the enzyme-bound NAD^+ is the primary mechanism of inhibition of AdoHcy hydrolase by 1 and 2.

By removal of the 4′-hydroxymethyl group (equivalent to the 5′-hydroxymethyl group of adenosine) from NpcA, one can retain the inhibitory effects of compounds 1 and 2 on bovine liver AdoHcy hydrolase and prevent the metabolism of these nucleosides by adenosine deaminase and adenosine kinase.[28] Since removal of the 4′-hydroxymethyl group from NpcA does not alter the mechanism of inhibition of AdoHcy hydrolase, i.e., reduction of enzyme bound NAD^+ to NADH, it appears that the minimal structural requirement for inhibition of AdoHcy hydrolase is a 3′-hydroxyl group in the correct juxtaposition to an appropriate purine base. The 3′-hydroxyl group does need to

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have the proper oxidation potential to reduce the enzyme bound NAD^+ to NADH and, thereby, cause irreversible ($K_{cat.}$) inhibition of AdoHcy hydrolase.

In a separate study, we have reported that compounds **1** and **2** have potent antiviral activity against vaccinia virus, while demonstrating reduced host cell cytotoxicity.[32] The results from this study and others studies[10] conducted in our laboratory strongly suggest that AdoHcy hydrolase is the molecular target for the antiviral effects seen with compounds **1** and **2**, as well as with NpcA. These data also support the hypothesis of Glazer and Knode[21] that the cytotoxicity associated with NpcA, which is reduced in compounds **1** and **2**, is in part a result of the formation of NpcATP by adenosine kinase and its conversion to NpcMet by AdoMet synthetase.

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Registry No. 1, 111005-70-0; 2, 111005-71-1; AdoHcy hydrolase, 9025-54-1; NAD, 53-84-9; neplanocin A, 72877-50-0; adenosine deaminase, 9026-93-1.

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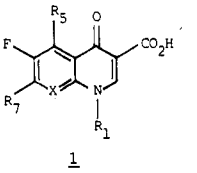
7-Substituted 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids: Synthesis and Biological Activity of a New Class of Quinolone Antibacterials

Sir:

The orally active fluoroquinolone antiinfectives, represented generically by **1** and **2** in Figure 1, have generated much excitement in laboratories and clinics around the world.[1] The earliest entries into this class of agents were enoxacin[2] (**1a**), norfloxacin[3] (**1b**), pefloxacin[3] (**1c**), and ofloxacin[4] (**2a**), all of which contain a piperazinyl moiety for R_7 and a two-atom fragment for R_1.[5] Many new R_1 substituents have been reported[5] with the halophenyl (difloxacin, **1d**) and cyclopropyl (ciprofloxacin, **1e**) among the most successful modifications. Structure–activity studies in these laboratories[6] involving the 7- and 8-positions of the 4-quinolone (R_7 and X) have demonstrated that amino-substituted pyrrolidines were efficient mimics of the piperazine side chain, and they conferred remarkable improvements in the Gram-positive (*Staphylococci* and *Streptococci*) antibacterial potency in vitro. A fluorine atom was desirable at C_8 (X = CF) for optimal in vivo efficacy (CI-934, **1f**, and PD 117,558,[7] **1g**). All of these agents and several of the earliest quinolones have been evaluated side by side for their antibacterial activity and their inhibition of the target enzyme, DNA-gyrase.[8] Although a few examples of 5-substituted quinolones, such as 5-halo,[9] 5-alkyl,[9a] and an 8-amino version (**2b**) of



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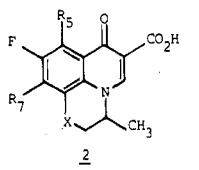
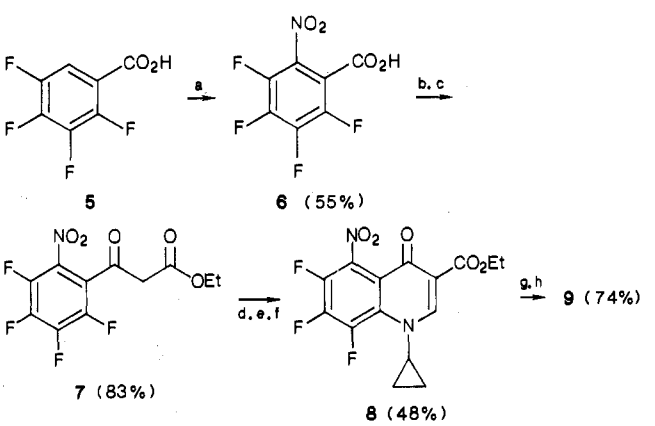


2

Name		R_1	X	R_5	R_7
enoxacin	1a	Et	N	H	piperazinyl-
norfloxacin	1b	Et	CH	H	piperazinyl-
pefloxacin	1c	Et	CH	H	4-Me-piperazinyl-
ofloxacin	2a	-	O	H	4-Me-piperazinyl-
difloxacin	1d	4-F-Ph	CH	H	4-Me-piperazinyl-
ciprofloxacin	1e	c-C_3H_5	CH	H	piperazinyl-
CI-934	1f	Et	CF	H	3-EtNHCH$_2$-pyrrolidinyl-
PD 117,558	1g	c-C_3H_5	CF	H	3-EtNHCH$_2$-pyrrolidinyl-
	1h	c-C_3H_5	CF	H	piperazinyl-
	2b	-	O	NH_2	4-Me-piperazinyl-

Figure 1. Some of the known quinolone antiinfectives in clinical or laboratory study.

Scheme I[a]



[a] a, H_2SO_4, 90% HNO_3, room temperature. b, $(COCl)_2$, H_2CCl_2, DMF. c, malonic monoester dianion. d, $HC(OEt)_3$, Ac_2O. e, c-C_3H_5-NH_2. f, *t*-BuOK, *t*-BuOH. g, RaNi. h, HCl.

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