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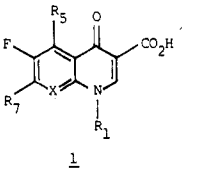
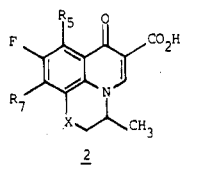
7-Substituted 5-Amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids: Synthesis and Biological Activity of a New Class of Quinolone Antibacterials

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



1

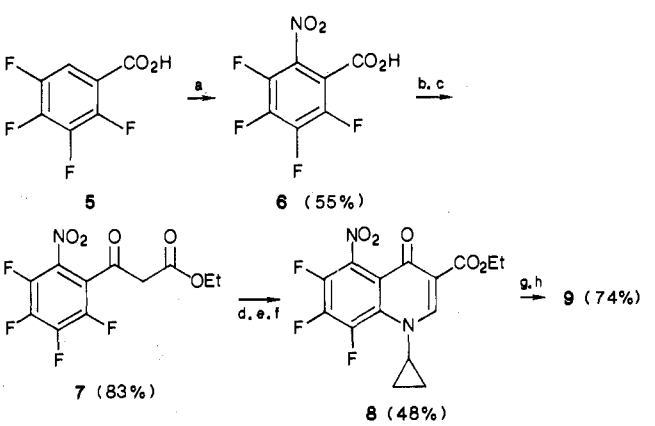


2

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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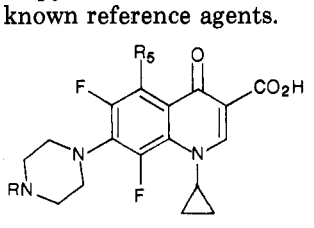
Table I. Physical Properties of the 5,7-Substituted 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic Acids **3** and **4**

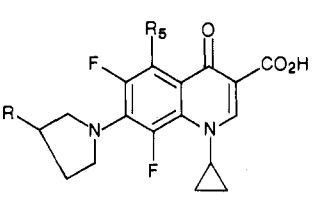
no.	R	R^5	starting quinolone	yield,[a] %	mp, °C	elem formula analy.[b]	method of purification
3a	H	NH_2	9	75	257–259	$C_{17}H_{18}F_2N_4O_3 \cdot 1.3H_2O$ C, H, N	CH_3CN wash
3b	CH_3	NH_2	9	62	247–248	$C_{18}H_{20}F_2N_4O_3 \cdot 0.2H_2O$ C, H, N	CH_3CN wash
3c	H	MeNH	11	76	210–215	$C_{18}H_{20}F_2N_4O_3 \cdot 2.4H_2O$ C, H, N	dissolve in H_2O, pH 11.0; prec at pH 6.2
3d	H	AcNH	12	91	256–258	$C_{19}H_{20}F_2N_4O_4 \cdot 0.5H_2O$ C, H, N	CH_3CN wash, EtOH wash
3e	CH_3	Me_2N	**3a**[c]	38	185–205	$C_{20}H_{24}F_2N_4O_3 \cdot 0.8HCl \cdot 1.75H_2O$ C, H, N, Cl	HCl conc, HCl wash
4a	NH_2[d]	NH_2	9	56[d]	233–234	$C_{17}H_{18}F_2N_4O_3 \cdot 0.5H_2O$ C, H, N	dissolve in H_2O, pH 11.0; prec at pH 7.5
4b	NH_2CH_2	NH_2	9	77	196–200	$C_{18}H_{20}F_2N_4O_3 \cdot 0.3H_2O$ C, H, N	CH_3CN wash
4c	$MeNHCH_2$	NH_2	9	87	184–188	$C_{19}H_{22}F_2N_4O_3$ C, H, N	dissolve in H_2O, pH 11.0, prec at pH 7.2, dried 100 °C vacuum
4d	$EtNHCH_2$	NH_2	9	95[e]	256–258	$C_{20}H_{24}F_2N_4O_4 \cdot HCl$	dissolve in conc HCl, filter conc
4e	$EtNHCH_2$	MeNH	11	82	202–204	$C_{21}H_{26}F_2N_4O_3 \cdot 0.5H_2O$ C, H, N	CH_3CN wash, EtOH wash
4f	$EtNHCH_2$	AcNH	12	91	256–258	$C_{19}H_{20}F_2N_4O_4 \cdot 0.5H_2O$ C, H, N	CH_3CN wash, EtOH wash

[a] Reactions were carried out in refluxing CH_3CN, using a slight excess of side chain and 1.0 equiv of tertiary amine (triethylamine or DBU). [b] All analyses were correct to ±0.4% for the elements shown. [c] **3e** was prepared from **3a** with H_2CO and HCO_2H. [d] Side chain employed was protected at the 3-amino with BOC which was deprotected with HCl, H_2O. Yield is for the combined steps (see ref 15). [e] Crude yield, final yield from HCl dissolution was 18%.

ofloxacin[10] have been reported, no systematic structure–activity relationship has been developed. Some reports have even suggested that substitution at the 5-position was deleterious to antibacterial activity.[1a,11] As part of our continuing efforts in utilizing the optimized fragments described above, we have discovered that, contrary to previous reports,[1a,11] an amino function at the 5-position of the 6,8-difluoro-1-cyclopropylquinolone significantly enhances antibacterial potency while displaying some intriguing physical characteristics. In this communication we describe the synthesis and biological activity of a series of 5-amino-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids appended with piperazine (**3**) or pyrrolidine (**4**) side chains and their comparison to known reference agents.

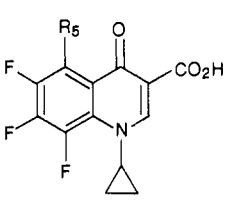


3



4

Chemistry. The crucial intermediate in the synthesis of the 5-amino-6,7,8-trifluoroquinolone precursors was the 6-nitro-2,3,4,5-tetrafluorobenzoic acid[12] (**6**, Scheme I). The nitro acid **6** was converted to the keto ester **7** with the dianion of malonic half-ester[13] and finally to 5-amino-1-cyclopropyl-6,7,8-trifluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**9**) by the general route reported by Chu.[14] This material was reacted with trifluoroacetic anhydride to give **10**, which was alkylated at nitrogen with sodium hydride and methyl iodide, producing the 5-(methylamino)quinolone **11** after aqueous workup. Similarly, acetylation of **9** with acetic anhydride gave **12**. Dimethylation of the amine in **9** gave poor results with Eshweiler–Clark conditions, and so the same reaction was attempted on the piperazinyl adduct **3a**. Treatment of **3a** with formic acid/formaldehyde yielded **3e**, which was methylated at the 5-amino group and the piperazine as well. The pyrrolidines were prepared according to literature methods.[15] Selective nucleophilic displacement of the 7-fluorine with the pyrrolidines and piperazines under standard conditions[6,8] afforded the target quinolones **3** and



9, R = NH_2
10, R = CF_3CONH
11, R = MeNH
12, R = AcNH

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Table II. Biological Testing Results for the 5,7-Substituted 1-Cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolonecarboxylic Acids 3 and 4 and Reference Agents

					antibacterial activity (MICs),[b] μg/mL											in vivo PD_{50},[c] mg/kg: *E. coli*	
			gyrase cleavage,[b]	gyrase 50% inhibn,	*E. coli*		*K. pneum.*	*P. rettg.*	*E. cloac.*	*P. aerug.*	*Staphylococcus aureus*		*Streptococcus faecalis*	*Streptococcus pneum.*	*Streptococcus pyog.*		
no.	R	R_5	μg/mL	μg/mL	H560	Vogel	MGH-2	M1771	MA2646	UI-18	H-228	UC76	MGH-2	SV-1	C203	po	sc
3a	H	NH_2	0.5	2.8	0.003	0.013	0.025	0.05	0.013	0.025	0.05	0.013	0.05	0.05	0.2	0.8	0.2
3b	CH_3	NH_2	0.5	2.8	0.003	0.013	0.013	0.05	0.013	0.1	0.05	0.025	0.1	0.2	0.4	2.2	1.1
3c	H	NHMe	2.5	13.8	0.025	0.1	0.1	0.8	0.1	1.6	0.8	0.2	1.6	0.8	3.1	1.5	0.8
3d	H	NHAc	>100	>100	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25		
3e	CH_3	NMe_2	>200	>200	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25	>25		
4a	NH_2	NH_2	0.25	2.6	0.003	0.006	0.006	0.025	0.006	0.05	0.013	0.006	0.025	0.006	0.025	1.6	0.4
4b	NH_2CH_2	NH_2	0.75	2.9	0.003	0.013	0.025	0.05	0.025	0.1	0.006	0.003	0.013	0.003	0.003	12	0.8
4c	MeNH-CH_2	NH_2	1.0	3.0	0.003	0.025	0.05	0.2	0.05	0.4	0.013	0.006	0.025	0.003	0.003	7.5	0.8
4d	$EtNHCH_2$	NH_2	0.5	2.7	0.013	0.05	0.05	0.05	0.05	0.4	0.013	0.003	0.025	0.003	0.013	16	2.4
4e	$EtNHCH_2$	NHMe	25	13.8	0.05	0.2	0.4	1.6	0.4	3.1	0.025	0.025	0.1	0.025	0.1	11	5
4f	$EtNHCH_2$	NHAc	>100	>100	12.5	>25	>25	>25	>25	>25	12.5	3.1	12.5	6.3	12.5		
1e			0.5	5.3	0.025	0.05	0.1	0.1	0.05	0.4	3.1	0.2	0.8	1.6	0.8	1.2	0.3
1h			0.5	2.8	0.025	0.1	0.05	0.1	0.05	0.2	0.4	0.1	0.4	0.8	0.8	0.45	0.3
1g			0.025	1.4	0.025	0.05	0.1	0.2	0.2	0.4	0.05	0.006	0.025	0.025	0.025	4.2	1.0
2a		H	5.0	7.5	0.1	0.1	0.1	0.1	0.1	0.4	0.4	0.1	0.8	0.8	0.8	2.0	0.8
2b		NH_2	2.5	26	0.1	0.2	0.4	1.6	0.8	0.8	0.8	0.2	1.6	3.1	3.1	7.5	4.6

[a] Lowest concentration necessary for the gyrase-mediated cleavage of DNA (ref 8). [b] Standard microtitration techniques (ref 16a). [c] Dose to protect 50% of mice from lethal infection (ref 16b) orally (po) and subcutaneously (sc). [d] All values are accurate to ±50% and have been obtained from duplicate or triplicate experiments.

4. The physical properties of **3** and **4** are described in Table I.

Biology. The quinolones **3** and **4** were tested against an assortment of 11 organisms by using standard microtitration techniques,[16a] and their minimum inhibitory concentrations (MICs) were compared to the standard drugs in Figure 1. The compounds were also tested for their inhibition of DNA-gyrase. The first assay employed for this study measured the concentration of drug (micrograms/milliliter) required to produce linear DNA from closed circular DNA by the denaturation of the drug–gyrase–DNA complex (the gyrase cleavage value). The 50% inhibition concentration was also calculated. Both assays are described in detail elsewhere.[8] The in vivo potency, expressed as the median protective dose (PD_{50}, milligrams/kilogram), of these compounds was determined in acute, lethal systemic infections in 18–22-g female Charles River CD-1 mice. Challenges were accomplished by the intraperitoneal injection of an estimated 100 median lethal dose in 0.5-mL volumes of 5% hog gastric mucin. Single doses of compound, in twofold rising incremental series, were administered concurrently with challenge in 0.5-mL volumes—subcutaneously as aqueous solutions and orally by gavage in 5% gum acacia. Survival percentages among groups of eight mice at each dose interval were used to estimate the median protective doses by the log probit method.[16b] The combined results from all assays are given in Table II.

Results and Discussion

Ciprofloxacin (**1e**) is widely accepted as one of the most potent quinolones (in vitro) in clinical development.[5] The piperazinyl substituent at C_7 is known to confer especially good activity against the Gram-negative pathogens (*Escherichia coli*, *Klebsiella pneumoniae*, *P. rettgeri*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*) but is generally weaker against the Gram-positive organisms.[6] The pyrrolidinyl analogues such as **1g** display especially good activity versus *Streptococci* and *Staphylococci*.[7] The 8-fluorociprofloxacin **1h**[18] is included as an important reference agent to test the effect of adding a fluorine at C_8 without an amino group at C_5. Compound **1h** is essentially equivalent to ciprofloxacin in vitro but shows a slight improvement over ciprofloxacin in vivo, which is perfectly consistent with the previously reported effect of an 8-fluoro substituent.[6a] Addition of a 5-amino group to **1h** produces the 5-amino-6,8-difluoro-7-piperazinylquinolone **3a**, which displays 2–16 times increased potency against both Gram-negative and Gram-positive bacteria. The 5-amino group appears to have compensated for the weaker Gram-positive activity associated with the piperazine side chain. In fact, the 5-aminoquinolone **3a** is more potent against *Streptococci* and *Staphylococci* than any of the piperazinyl-containing quinolone reference agents that we have tested.[6,8] The 7-(4-methylpiperazinyl) analogue **3b** is less active than **3a** but still displays considerable improvement over **1h** and ciprofloxacin itself.[17]

In the pyrrolidine series, addition of the 5-amino group to the reference agent **1g** produces the 5-aminoquinolone **4d**, which has a much less dramatic antibacterial improvement, possibly owing to the already balanced antibacterial spectrum possessed by **1g**. The other agents in the 5-amino-7-pyrrolidinyl series, especially the 7-(3-amino-1-pyrrolidinyl) **4a** and 7-[3-(aminomethyl)-1-pyrrolidinyl] **4b**, display excellent broad spectrum in vitro potency.

At the enzyme level, addition of the 5-amino group has little effect on the gyrase cleavage value or the IC_{50} concentration when comparing **3a** and **4d** to their 5-hydrogen counterparts. Little variation of gyrase inhibition is seen throughout the primary 5-amino series. In the mouse protection tests, there is a slight but noticeable reduction in oral efficacy in comparing **1h** to **3a** (0.45 mg/kg to 0.80 mg/kg) and **1g** to **4d** (4.1 mg/kg to 16 mg/kg). This difference is magnified more if one considers the fact that the less potent agents in vivo were the more potent in vitro. The small number of direct comparisons available in this data set is too limited to permit generalizations regarding in vivo efficacy of the 5-aminoquinolones as a class.

In an effort to test the structural limitations at R_5, the monomethylamino **3c**, dimethylamino **3e**, and acetylamino **3d** derivatives were prepared and tested. The methyl-

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(17) The 4-methylpiperazinyl adduct **3b** is 4–16 times more potent than its 5-hydrogen analogue. Data not shown.

(18) Grohe, K.; Petersen, U.; Zeiler, H. J.; Metzger, K. G. U.S. Patent 4 556 658, 1985.

amino group in **3c** reduces the in vitro potency 4–16-fold for all strains tested when compared to **3a**. The dimethylamino and acetylamino analogues are inactive—an ~8000-fold reduction in potency! The lost activity of **3e** and **3d** is visible at the enzyme level where methylation or acetylation of the 5-amino group has a devastating effect on enzyme inhibition. The same trends are witnessed in the pyrrolidine series as well (**4e** and **4f**).

While the 5-amino group in the 6,8-difluoro quinolones confers excellent overall spectrum and potency with major improvements over a 5-hydrogen substituent, this phenomena cannot be generalized to other quinolone nuclei. The 8-amino analogue of ofloxacin (**2b**) is substantially less active than ofloxacin (**2a**) in vitro, in vivo, and in the 50% inhibition of the gyrase enzyme.

The 5-amino group in the quinolones **3** and **4** tends to be nonbasic (pK_a for **4a** of 2.7) and nonnucleophilic. Water solubility did not vary much from the corresponding 5-hydrogen analogues.

In summary, we have shown that a 5-amino group in the 6,8-difluoroquinolone series enhances in vitro potency, especially for the piperazinyl side chains and most significantly against the Gram-positive bacterial strains. Several other extremely potent agents were prepared, such as 5-amino-7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (**4a**) and the 7-[3-(aminomethyl)-1-pyrrolidinyl] analog **4b**. Studies are currently under way to further define the structure–activity relationships of R_5 to delineate the interaction between R_5 and the quinolone nucleus itself.

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Articles

Synthesis and Biological Characterization of Pyridohomotropanes. Structure–Activity Relationships of Conformationally Restricted Nicotinoids†

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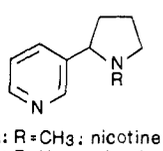
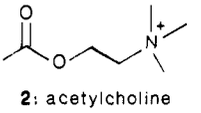
The recently discovered nicotinic agonist pyrido[3,4-*b*]homotropane (PHT) as well as its *N*-methyl and 2′-methyl derivatives (syntheses reported herein) were compared with nicotine, nornicotine, and anatoxin *a* in a series of in vitro and in vivo assays. The results reveal that PHT possesses activity comparable to that of the highly potent agonist, anatoxin *a*. The inactivity observed relative to PHT of *N*-methyl- and 2′-methyl-PHT has helped to further define the structure–activity requirements of conformationally restricted nicotinoids.

There is considerable evidence that nicotine (**1a**) can mimic the actions of acetylcholine (**2**) at the autonomic ganglia, the neuromuscular junction, and some areas of the central nervous system.[1-4] The receptor sites for nicotine in mammalian brain, moreover, appear to exist in multiple forms and are pharmacologically different from those at the neuromuscular junction and electroplax.[4,5] The binding of such nicotinic agonists is believed to be controlled by two factors: (1) an electrostatic interaction involving the alkylammonium group and (2) a hydrogen bond mediated by an unshared pair of electrons on the agonist.[6,7] Efforts to determine the precise structural requirements of the receptor have resulted in the synthesis of conformationally restricted derivatives.[8,9]

We have recently reported the synthesis and biological activity of pyrido[3,4-*b*]homotropane (PHT, **3a**)—the first



1a: R = CH_3; nicotine
b: R = H; nornicotine



2: acetylcholine

derivative of either nicotine or nornicotine to possess both high activity and conformational rigidity.[10] In the present

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