mentioned above have rigid planar structures whereas molecular models suggest that steric factors in our 3-phenylpiperidine derivatives may cause the plane of the aromatic ring to lie nearly perpendicular to the plane of the piperidine ring.

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Irreversible Enzyme Inhibitors. 200.[1] Active-Site-Directed Inhibitors of Deoxycytidine Kinase

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Forty-three pyrimidine derivatives, mainly containing the 4-aminopyrimidine system, have been prepared and evaluated as inhibitors of deoxycytidine kinase. The most effective inhibitors were 2-alkylthio-4-aminopyrimidines and 1-alkylcytosines. The best inhibitors in both groups were those with large alkyl substituents, which indicate that hydrophobic bonding is occurring, possibly in the same area adjacent to the active site.

Deoxycytidine kinase is an enzyme which phosphorylates deoxycytidine and, less readily, deoxyguanosine. The enzyme also phosphorylates the synthetic antileukemic drug *ara*-C (1-β-D-arabinofuranosylcytosine), and the development of resistance to this drug is associated with a decreased concentration of the enzyme in resistant cells.[3] It has also been suggested that the deoxycytidine kinase from resistant cells could be due to structural modification of the enzyme in the resistant cells.[3a]

It is known that the affinity of substrates for deoxycytidine kinase decreases in the order deoxycytidine > *ara*-C > deoxyguanosine and it has been shown that deoxycytidine inhibits the phosphorylation of *ara*-C by over 90%.[3a] However, there is a paucity of data on inhibitors of this enzyme. As part of a program investigating active-site-directed irreversible enzyme inhibitors[4a] as possible chemotherapeutic agents, an investigation of inhibitors of deoxycytidine was commenced[4b] and our results obtained from an initial survey of this area form the subject of this paper.

Enzyme Results. Of the 43 compounds tested the ones which caused an inhibition of the enzyme of greater than 20% ($V_0/V_I > 1.25$) are listed in Table I. These compounds can be further divided into several groups. 1-Substituted derivatives of cytosine (**1–8**) show some inhibition of the enzyme with the activity increasing as the length of the side chain attached to N-1 is increased. This inhibition, and the nature of the side chain in these compounds, suggests that hydrophobic bonding of the side chain to the enzyme is occurring. In contrast, the 5- and 6-substituted cytosines, **14–17** and **38–43**, and the related compounds **34–36** showed no significant inhibition of the enzyme when tested at comparable concentrations. Compounds **40–43** all contain a side chain at N-1 which, in the absence of the 5-substituent, can give rise to inhibition of the enzyme. This suggests that the active site of the enzyme cannot tolerate bulky groups at the 5 position of the substrate but that there is a hydrophobic bonding area capable of interaction with a 1-substituent.

The N-4 substituted cytosines were all inactive. This is not surprising in the case of the acyl derivatives **9** and **10** since the ability of the amine group to coordinate to an active site on the enzyme could well be substantially reduced when it is converted to an amide system. The *N*-alkyl derivatives **11–13** are also inactive suggesting that there is little bulk tolerance for an N-4 group. Neither

Table I. Inhibition of Deoxycytidine Kinase[a]

Compd	I, mM	V_0/V_I	I_{50}, mM
1	10	1	
2	5	1.4	12[c]
3	5	2.0	5
4	2.5[b]	1.4	12[c]
5	5	1.8	6
6	2.5	2.0	2.5
7	1[b]	2.0	1
8	0.5[b]	1.4	1.5[c]
22	5	2.0	5
23	10	3.6	7
24	5	1	
25	5	1	
26	7.5	2.4	6
27	0.25[b]	1.5	1[c]
28	2.6	2.0	2.6
29	4	2.8	2.8
30	1.0[b]	2.0	1
31	0.5[b]	1.5	1[c]
32	1[b]	1.5	2[c]
33	0.5[b]	2.0	0.5

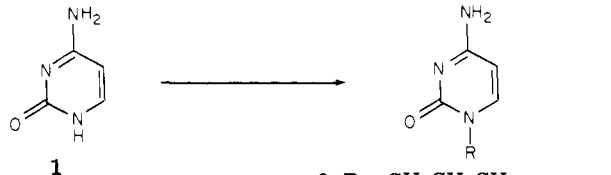
[a] The technical assistance of Julie Beardslee and Nancy Middleton with these assays is acknowledged. [b] Maximum solubility. [c] Estimated.

cytosine nor the related 4-thiomethyl compound **37** inhibited the enzyme. Deoxyguanosine at a concentration 40 times greater than that of deoxycytidine showed no significant inhibition, thus confirming that it has a much weaker affinity for the enzyme.[3a]

The 2-alkoxy- and the 2-alkylthio-4-aminopyrimidines (**22–27** and **28–33**) in general showed considerable inhibition of the enzyme. Where direct comparison can be made the alkylthio compounds showed greater inhibition than their corresponding alkoxy analogues (e.g., **28** and **23**; **29** and **26**). Again the inhibition increased with increasing size of the alkyl side chain. The introduction of polar atoms in the side chain generally decreased the inhibition (e.g., **31** and **32**; **23** and **25**) suggesting that a hydrophobic bonding is occurring with these compounds. Particularly with the alkylthio derivatives, the presence of an aryl group in the side chain sufficiently remote from the pyrimidine ring seems to facilitate inhibition (e.g., **31** and **28**).

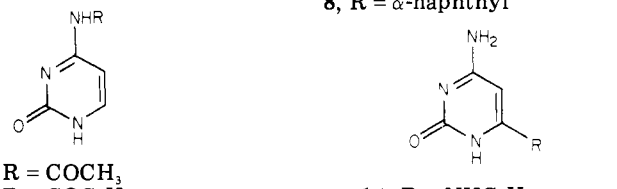
The available evidence does suggest that hydrophobic bonding occurs with groups at either the 1 or the 2 position of the pyrimidine ring, provided that these groups are sufficiently large. It is reasonable to suggest that these derivatives are causing inhibition because the substituents can bind in the *same* hydrophobic area adjacent to the active site. However, at this stage these observations must be regarded as suggesting trends and clearly further work[4b] is necessary before definite conclusions can be drawn regarding the nature of this hydrophobic bonding.

Chemistry. Although some 1-substituted cytosines can be satisfactorily prepared by a base-catalyzed alkylation procedure, this method often suffers from the disadvantage that the ambident nature of the amide system leads to both O- and N-alkylation.[5] These mixtures are generally difficult to separate.[5,6] Conversion of the 4-amino group of cytosine to an amide minimizes any competition by the 4-amino group for the alkylating agent but does not overcome the ambident nature of the cytosine system.[7] It has been found that conversion of cytosine to its silylated derivative[8] followed by alkylation gives the required *N*-alkyl product although only in moderate yields.[7,8] Use of an excess of the alkylating agent leads to complex mixtures.[9] A recent paper describes an improved procedure[10] for the alkylation of the bis(trimethylsilyl) derivative but this method did not prove to be a satisfactory one for the compounds we required. Thallium salts



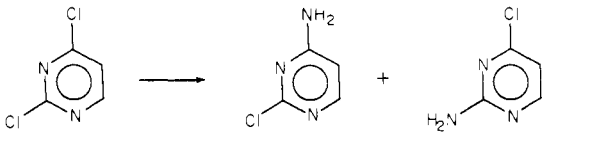
1

2, R = $CH_2CH_2CH_3$
3, R = $CH_2CH_2CH(CH_3)_2$
4, R = $CH_2C_6H_5$
5, R = $CH_2CH_2OC_6H_5$
6, R = $CH_2CH_2CH_2OC_6H_5$
7, R = $(CH_2)_4C_6H_5$
8, R = α-naphthyl



9, R = $COCH_3$
10, R = COC_6H_5
11, R = C_6H_5
12, R = $CH_2C_6H_5$
13, R = $(CH_2)_4CH_3$

14, R = NHC_6H_5
15, R = $NHCH_2C_6H_5$
16, R = $NH(CH_2)_3CH_3$
17, R = $OCH_2C_6H_5$



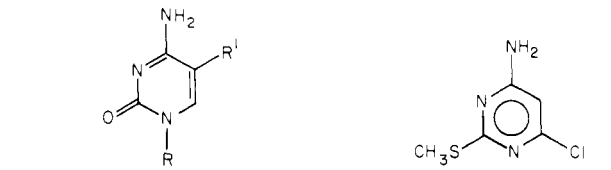
44 **45**

22, R = C_6H_4-*p*-Cl
23, R = $(CH_2)_4CH_3$
24, R = $(CH_2)_5CH_3$
25, R = $(CH_2)_2OCH_3$
26, R = $CH_2C_6H_5$
27, R = $(CH_2)_7CH_3$

28, R = $(CH_2)_4CH_3$
29, R = $CH_2C_6H_5$
30, R = $CH_2C_6H_4$-*p*-Cl
31, R = $(CH_2)_4C_6H_5$
32, R = $(CH_2)_3OC_6H_5$
33, R = β-naphthyl

18, R = SCH_3; R' = $NHCH_2C_6H_5$
19, R = SCH_3; R' = $N(CH_2C_6H_5)_2$
20, R = SCH_3; R' = OH
21, R = $SCH_2CO_2CH_2CH_3$; R' = OH
34, R = H; R' = $OCH_2C_6H_5$
35, R = SCH_3; R' = $OCH_2C_6H_5$
36, R = SO_2CH_3; R' = $OCH_2C_6H_5$

37

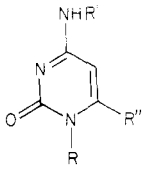


38, R = H; R' = C_6H_4-*p*-OCH_3
39, R = H; R' = C_6H_3-3,4-Cl_2
40, R = $(CH_2)_3C_6H_5$; R' = C_6H_3-3,4-Cl_2
41, R = $(CH_2)_2OC_6H_5$; R' = C_6H_3-3,4-Cl_2
42, R = $(CH_2)_3OC_6H_5$; R' = C_6H_5
43, R = $(CH_2)_3OC_6H_5$; R' = C_6H_4-*p*-Cl

46

of ambident systems have proved effective in achieving specific alkylation[11] but attempts to use the thallium salt of cytosine for this purpose failed, possibly due to solubility

Table II. Physical Constants of



No.	R	R'	R''	Mp, °C	Solvent	Yield, %	Formula[d]
2	$CH_2CH_2CH_3$	H	H	254-256	EtOH	44	*e*
3	$CH_2CH_2CH(CH_3)_2$	H	H	240-242	EtOH-hexane	38	$C_9H_{15}N_3O$
4	$CH_2C_6H_5$	H	H	301-303	DMF-H_2O	30	*f*
5	$CH_2CH_2OC_6H_5$	H	H	237-238	ETOH	35[a]	$C_{12}H_{13}N_3O_2$
6	$(CH_2)_3OC_6H_5$	H	H	254-256	EtOH	21	$C_{13}H_{15}N_3O_2$
7	$(CH_2)_4C_6H_5$	H	H	251-253	DMF	25	$C_{14}H_{17}N_3O$
8	α-Naphthyl	H	H	320-322	DMF	55	$C_{14}H_{13}N_3O$
9	H	$COCH_3$	H	325 dec	AcOH	52	*g*
10	H	COC_6H_5	H	335-339	Me_2SO	66	*h*
11	H	C_6H_5	H	277-280	EtOH	50	*i*
12	H	$CH_2C_6H_5$	H	225-227	EtOH	42	*j*
13	H	$(CH_2)_4CH_3$	H	163-166	EtOH-H_2O	50	$C_9H_{15}N_3O$
14	H	H	NHC_6H_5	~340	DMF-H_2O	*b*	*k*
15	H	H	$NHCH_2C_6H_5$	304-306	DMF	*b*	*l*
16	H	H	$NH(CH_2)_3CH_3$	303-304	DMF	*b*	$C_8H_{14}N_4O$
17	H	H	$OCH_2C_6H_5$	285[c]	DMF-H_2O	38	$C_{11}H_{11}N_3O_2$

[a] Based on reacted cytosine. [b] Yields were difficult to determine accurately due to a pronounced tendency of the products to include solvents but were approximately quantitative. [c] Partially melts at ~235 °C, then recrystallizes, and remelts at ~285 °C. [d] Anal. C, H, N. [e] Lit.[7] mp 256-259 °C. [f] Lit. mp 286 °C [*J. Chem. Soc.*, 811 (1963)]. [g] Lit. mp >320 °C [*Am. Chem. J.*, 29, 429 (1903)]. [h] Lit. mp 325 °C dec [*J. Chem. Soc.*, 2384 (1956)]. [i] Lit.[12] mp 266 °C. [j] Lit.[12] mp 217-218 °C. [k] Lit.[13] mp 344-345 °C. [l] Lit.[13] mp 306-308 °C.

problems. Chromatography indicated that the cytosine was largely unreacted but that, of the small amount of product, the N-alkylated material was the major, if not the only, isomer formed. Of all the methods attempted one using potassium hydroxide in dimethyl sulfoxide was found to be the most convenient although even with this method yields were not good.

The 4-*N*-acylcytosines **9** and **10** were prepared by a standard method although the procedure is complicated by the very low solubility of cytosine in the high boiling solvents generally used. The 4-*N*-alkyl derivatives **11**–**13** were obtained in acceptable yields by modifying a literature procedure[12] in order to give a much more generally applicable reaction (Table II).

Commercially available 4-amino-6-chloro-2-methylthiopyrimidine was used to prepare the 6-substituted systems **18**, **19**, and **35** or by conversion to 6-chlorocytosine[13] provided the means to prepare compounds **14**–**17**. Compounds **20** and **21** were prepared by standard methods from 4-amino-2-mercapto-6-hydroxypyrimidine. The methylthio group at position 2 can be converted to the hydroxyl group (which generally exists in the tautomeric keto form) by heating in acid.[13] An alternative procedure involves similar treatment of the related ethoxycarbonylmethylthio group.[14] A third procedure involves oxidation of the alkylthio group (e.g., **36**) to the corresponding sulfoxide or sulfone followed by base-catalyzed hydrolysis.[15] All three procedures can involve relatively vigorous conditions at some stage and the most convenient method was the first. If necessary (e.g., **34**) the methylmercapto group can be readily hydrogenolyzed with Raney nickel.

2,4-Dichloropyrimidine reacts with ammonia to form a mixture of 2-chloro-4-aminopyrimidine and 2-amino-4-chloropyrimidine in which the former predominates.[16,17] These isomers could be satisfactorily separated by fractional crystallization from dioxane or dimethoxyethane although the separation was complicated by the presence of impurities in the commercially obtained starting material. Conversion of 4-amino-2-chloropyrimidine to the corresponding 2-alkoxy derivative could be satisfactorily achieved using alkoxide if the corresponding alcohol is used as the solvent (i.e., in excess). When for reasons of experimental convenience the reaction was conducted in an inert solvent (e.g., diglyme, dimethoxyethane) using only a slight excess of the alkoxide, a complex mixture of products was obtained which proved difficult to separate. It appears that the 4-aminopyrimidine (**44**) is sufficiently acidic to react with the alkoxide, at least to some extent. Since no difficulty was experienced in the preparation of **22**, the acidity of the starting material is considerably less than that of a phenol but comparable to that of an alcohol. The related compound **46** readily evolves hydrogen when treated with sodium hydride but reacts with alkoxide, in the presence of excess alcohol, to form the corresponding alkoxy derivative (e.g., **35**).

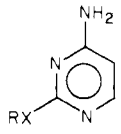
The alkylthio analogues **28**–**33** were prepared from 4-amino-2-mercaptopyrimidine[18] by standard methods and were obtained in good yield (Table III). The preparation of compounds analogous to **37** was not pursued when only low yields of this compound were obtained. Similar difficulties in the preparation of this type of system have been reported.[19] Compounds **38**–**43** were available to us as a result of previous work by this group.[20,21]

Experimental Section

Elemental analyses (C, H, and N), obtained by Galbraith Laboratories, Knoxville, Tenn., were within 0.4% of the theoretical values for all analytical samples. Each analytical sample had an ir spectrum in accord with its assigned structure. Melting points are uncorrected and were taken in capillary tubes on a Mel-Temp block.

Enzyme Assay. [^{3}H]Deoxycytidine was analyzed by adsorption to DEAE-cellulose filter disks, according to the method of Ives et al.[22] Assay component concentrations were as follows: deoxycytidine, 0.025 mM; ATP, 5 mM; $MgCl_2$, 5 mM; Tris pH 8.0 buffer, 50 mM. The inhibitor was dissolved in dimethyl sulfoxide. The rate of the enzymic reaction is unchanged when either dimethyl sulfoxide or methoxyethanol is used as the organic solvent. For each assay, 50 μl of the above assay mixture, 10 μl of the inhibitor in dimethyl sulfoxide solution, and 40 μl of the enzyme solution were used.

The enzyme was obtained from the 0–45% $(NH_4)_2SO_4$ fraction from Walker 256 rat tumor by treating it with 1 M HOAc to pH

Table III. Physical Constants of 

No.	R	X	Mp, °C	Solvent	Yield, %	Formula[a]
22	C_6H_4-*p*-Cl	O	166–168	EtOH-H_2O	56	$C_{10}H_8ClN_3O$
23	$(CH_2)_4CH_3$	O	49–51	$CHCl_3$-hexane	52	$C_9H_{15}N_3O$
24	$(CH_2)_2CH_3$	O	76–78	$CHCl_3$-hexane	89	*b*
25	$(CH_2)_2OCH_3$	O	87–89	$CHCl_3$-hexane	82	$C_7H_{11}N_3O_2$
26	$CH_2C_6H_5$	O	80–81	$CHCl_3$-hexane	56	$C_{11}H_{11}N_3O$
27	$(CH_2)_7CH_3$	O	46–48	$CHCl_3$-hexane	35	$C_{12}H_{21}N_3O$
28	$(CH_2)_4CH_3$	S	65–66	$CHCl_3$-hexane	72	$C_9H_{15}N_3S$
29	$CH_2C_6H_5$	S	118–119	$CHCl_3$-hexane	73	$C_{11}H_{11}N_3S$
30	$CH_2C_6H_4$-*p*-Cl	S	145–147	$CHCl_3$	76	$C_{11}H_{10}ClN_3S$
31	$(CH_2)_4C_6H_5$	S	62–64	$CHCl_3$-hexane	90	$C_{14}H_{17}N_3S$
32	$(CH_2)_3OC_6H_5$	S	89–90	$CHCl_3$-hexane	90	$C_{13}H_{15}N_3OS$
33	β-Naphthyl	S	117–118	$CHCl_3$-hexane	81	$C_{15}H_{13}N_3S$

[a] Anal. C, H, N. [b] Lit. mp 77–78 °C [*Chem. Pharm. Bull.*, 13, 557 (1965)].

4.5, centrifuging for 10 min at 20000 rpm, and, after discarding the precipitate, returning the pH of the solution to 7.4 with 1 M KOH.

1-Alkylcytosines. Method A.[8] Cytosine (1 mM) was dissolved in hexamethyldisilazane (2 ml), containing a catalytic amount of $(NH_4)_2SO_4$, by refluxing for ca. 10 min. A solution of the alkyl halide (1 mM) in acetonitrile was added to the cooled solution and the mixture was warmed (50–80 °C) until TLC indicated the starting material was no longer present (1–2 days).

Method B. Cytosine (10 mM) was dissolved in Me_2SO (15 ml) and water (15 ml) containing KOH (10 mM). The alkyl halide (10.4 mM) was added to this solution and the mixture was stirred at room temperature for 24 h. The resulting precipitate was filtered and recrystallized from the appropriate solvent.

4-*N*-(1-Pentyl)cytosine (13). Cytosine (510 mg, 4.6 mM) and *n*-pentylamine (530 mg, 6.1 mM) were refluxed in diglyme (5 ml), containing a little NH_4Cl, for 6 h. The solid obtained on cooling the solution was recrystallized from aqueous ethanol.

6-(1-Butylamino)cytosine (16). 6-Chlorocytosine hydrochloride[13] (642 mg, 3.5 mM) and 1-butylamine (600 mg, 8.2 mM) were refluxed in aqueous solution for 1.75 h. The cooled solution was filtered and the precipitate was washed with water and recrystallized from DMF.

4-Amino-6-benzyloxy-2-methylthiopyrimidine (35). 4-Amino-6-chloro-2-methylthiopyrimidine (2.0 g, 11.4 mM) was dissolved in DME (10 ml) and benzyl alcohol (2.0 g, 1.9 mM) and sodium hydride (500 mg, 57%, 11.8 mM) was added. After the initial reaction had subsided the mixture was refluxed for 4 h. The cooled solution was poured into water and the resulting precipitate (1.48 g, 53%) was recrystallized from aqueous ethanol. The analytical sample, recrystallized from $CHCl_3$–hexane, had mp 123–124 °C. Anal. ($C_{12}H_{13}N_3OS$) C, H, N.

4-Amino-6-benzyloxy-2-methylsulfonylpyrimidine (36). The pyrimidine **35** (1.37 g, 5.5 mM) in chloroform (25 ml) was cooled to 0 °C and a cooled solution of *m*-chloroperbenzoic acid (5 g, 29 mM) in chloroform (75 ml) was added slowly. After 19 h at room temperature the precipitate and the solution were washed with sodium sulfite solution, sodium carbonate solution, and water. Filtration of the solvents and evaporation of the chloroform solution gave material (1.01 g, 53%) which was combined and recrystallized from ethanol. The analytical sample, recrystallized from ethanol, had mp 210–211 °C. Anal. ($C_{12}H_{13}N_3O_3S$) C, H, N.

6-Benzylcytosine (17). The sulfone **36** (500 mg, 1.8 mM) and KOH (450 mg, 8 mM) were dissolved in aqueous ethanol and the solution was refluxed for 7 h. The cooled solution was filtered and the precipitate was recrystallized from aqueous DMF.

4-Amino-6-benzyloxypyrimidine (34). A solution of **35** (485 mg, 2 mM) in ethanol (50 ml) was refluxed with excess Raney nickel for 2 h. The mixture was filtered and the residue washed thoroughly with hot ethanol. Evaporation of the filtrate and crystallization of the residue from chloroform–hexane gave 4-amino-6-benzyloxypyrimidine (240 mg, 61%). The analytical sample, recrystallized from the same solvents, had mp 176–178 °C. Anal. ($C_{11}H_{11}N_3O$) C, H, N.

4-Amino-6-benzylamino-2-methylthiopyrimidine (18). 4-Amino-6-chloro-2-methylthiopyrimidine (710 mg, 4.05 mM) and benzylamine (910 mg, 8.5 mM) were refluxed in diglyme (2 ml) for 5 h. Filtration of the cooled solution removed benzylamine hydrochloride and chromatography of the evaporated filtrate on silica gel, using chloroform as the eluting solvent, gave the 6-benzylamino compound **18** in 43% yield (425 mg). The compound was recrystallized from aqueous ethanol and then from chloroform–hexane for analysis: mp 117–119 °C. Anal. ($C_{12}H_{14}N_4S$) C, H, N.

In a similar manner 4-amino-6-dibenzylamino-2-methylthiopyrimidine (**19**) was prepared: mp 136–138 °C (lit.[23] mp 138 °C).

4-Amino-2-ethoxycarbonylmethylthio-6-hydroxypyrimidine (21). A solution of ethyl bromoacetate (1.72 g, 1 mM) and 4-amino-6-hydroxy-2-mercaptopyrimidine hydrate (1.62 g, 1 mM) in ethanol–Me_2SO (1:1, 50 ml) containing sodium ethoxide (from 250 mg of sodium) was refluxed for 4 h. The cooled solution was poured into water and the precipitate (quantitative yield) was recrystallized from aqueous ethanol and then from ethanol–hexane to give the analytical sample, mp 180–181 °C. Anal. ($C_8H_{11}N_3O_3S$) C, H, N.

In a similar manner 4-amino-6-hydroxy-2-methylthiopyrimidine (**20**) was prepared: mp 277–278 °C (lit.[24] mp 261–262 °C).

2-Alkoxy-4-aminopyrimidines. 2-Chloro-4-aminopyrimidine was added to a solution of excess sodium in the required alcohol and the mixture was heated until TLC indicated that the starting material was no longer present. The solution was poured into water, neutralized with acetic acid, and extracted with chloroform. Addition of hexane to the residue obtained on removal of the solvent from the dried (K_2CO_3) extracts gave a crystalline material which was recrystallized from the appropriate solvent.

2-Alkylmercapto-4-aminopyrimidines. 2-Mercapto-4-aminopyrimidine (from[18] dithiouracil) and KOH (excess) were dissolved in ethanol and the corresponding alkyl halide was added. The mixture was refluxed for ca. 3 h and then poured into water and extracted with chloroform. Evaporation of the dried extracts gave an oil which was crystallized from chloroform–hexane.

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Quantitative Structure–Activity Relationships for 5-Substituted 8-Hydroxyquinolines as Inhibitors of Dental Plaque

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Fourteen 8-hydroxyquinolines were tested for antiplaque activity by measuring their minimum inhibitory concentrations [MIC (M)] against *Streptococcus mutans* No. 6715. Linear regression analysis was conducted with the MIC (M) values and hydrophobic (log *P*), electronic (σ, pK_a^{OH}, pK_a^{N}), and steric [molar refractivity (MR), molecular weight (mol wt)] parameters. The best correlation ($r^2 = 0.90$) was obtained with MR, log *P*, and σ. The smaller the steric contribution of the 5-substituent, the more active the compound. The parent 8-hydroxyquinoline was the most active. The negative contribution toward activity by 5-substituents larger than hydrogen can be overcome by the positive contributions of groups that are lipophilic and electron withdrawing; for example, the 5-chloro derivative is as active as the parent 8-hydroxyquinolines.

Predicting the activity of a compound has been a primary goal of structure–activity relationship (SAR) studies for many years. When quantitative biological data are available for a series of congeners, then quantitative structure–activity relationship (QSAR) methods may be useful. There are three major approaches in the study of QSAR: (1) the semiempirical linear free-energy related model proposed by Hansch,[1] (2) the empirical mathematical model proposed by Free and Wilson,[2] and (3) quantum chemical approaches.[3]

In order to make the problem manageable in the linear free-energy approach, it is customary to study a congeneric series of compounds in which a parent molecule is modified by the presence of one or more substituents. Implicit in this approach is the assumption that all members of the series act on the biological system by the same mechanism and only their quantitative potency is modified by the substituents. The appearance over the last 10 years of a large number of successful SAR correlations in the literature supports this assumption. The biological activity data must be obtained under uniform conditions, and the biological response should be of low complexity.[4]

The bacteria *Streptococcus mutans* No. 6715 play a major role in the formation of dental plaque. Dental plaque in turn is the primary cause of caries and periodontal disease. One approach for the prevention of these diseases has involved use of antibacterial agents. 8-Hydroxyquinolines have been shown to be some of the most potent in vitro inhibitors of *S. mutans* No. 6715.[5-7] Initial studies indicated that 8-hydroxyquinolines with log *P* values between 1 and 4 display the best activity against this organism.[5] As part of our continuing studies of dental plaque inhibitors, we synthesized and tested a series of 5-substituted 8-hydroxyquinolines.[6,7] These analogues were chosen since the substituent would be some distance from the portion of the molecule involved in chelation. It has been shown that chelation with iron or copper ions is required for antibacterial activity. In the absence of these ions, the 8-hydroxyquinolines are not toxic to microorganisms. Substitution near the nitrogen atom or the phenolic group reduces or eliminates biological activity and the ability of the compound to chelate metal ions.[8,9] We concluded from the preliminary results that the use of the single parameter, log *P*, was not adequate to accurately predict antiplaque activity. For example, 5-methoxymethyl-8-hydroxyquinoline and 5-cyanomethyl-8-hydroxyquinoline have log *P* values which differ by only 0.03; yet, the compounds show[6] 20 and 80% inhibition of *S. mutans* at 10^{-4} M, respectively.

To delineate the structural requirements for optimal antibacterial activity, we have investigated 14 compounds as inhibitors of *S. mutans* No. 6715. The antibacterial activities were measured by determining the minimum molar concentrations of the agents required for total inhibition of bacterial growth. These are recorded as the MIC (M) values in Table I. In Table I are also given the