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Structure-intestinal transport and structure-metabolism correlations of some potential cancerostatic pyrimidine nucleosides in isolated rat jejunum

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Summary. *Both transport and biotransformation processes for a series of pyrimidine nucleobases, ribonucleosides, 2'-deoxyribonucleosides, and acetyl and 5'-substituted derivatives of the cancerostatic agent araC were studied in the isolated everted rat jejunum with a continuous perfusion technique. Metabolic alterations during penetration were assessed by HPLC. 5'-Halogeno and 5'-deoxy derivatives of cytosine nucleosides exhibited higher transport rates and higher stability towards the deamination reaction than did unsubstituted derivatives. Octanol-buffer partition coefficients were estimated for the study compounds, and fragmental constants for the sugar moieties of nucleosides were assessed. With the present study compounds there was no correlation between lipophilicity and transport rate, as previously reported, but there was a correlation between lipophilicity and metabolic alteration of araC derivatives ($r = 0.99$, $n = 5$).*

Introduction

In the previous paper [7], the kinetics of transport and metabolism of the cytostatic agent araC and its acetyl derivatives across the isolated rat jejunum were investigated and compared with those of the natural nucleoside cytidine. The stability of the cytosine nucleoside amino group to deaminase [13] and during transport [7] was also followed. Cyclocytidine undergoes a deamination reaction during intestinal transport [7], though it was one of the most stable compounds against cytidine hydrolase [13]. Therefore, more attention was paid to the other analogs of araC, and in particular to the biologically active ones [10]. For further clarification of the effect of structure modification on kinetics of transport and metabolism during intestinal permeation our previous study was extended to include pyrimidine nucleobases, pyrimidine ribonucleosides, pyrimidine deoxyribonucleosides, and some 5'-substituted derivatives, in particular, in an effort to find out metabolically a more stable derivative that might be suitable as an oral congener of the antileukemic agent araC. Generally, for drugs administered PO, transport across the intestinal barrier is the first step towards reaching the systemic circulation and consequently the site of action for production of the appropriate effect. Therefore, we selected the everted rat intestine as a model for testing compounds with reference both to processes of intestinal absorption and to metabolism. Moreover, on the basis of the measured partition coefficient we have applied the method of Rekker [17, 18] to calculate fragmental constants, which also characterize the lipophilicity.

Materials and methods

The study compounds were synthesized according to the references indicated in Table 1.

The series of study compounds included pyrimidine nucleobases cytosine, uracil, thymine; pyrimidine ribonucleosides cytidine (Cyd), uridine (Urd); arabinosylcytosine derivatives arabinosylcytosine (araC) and its *N*-acetyl (*N*-Ac-araC), tri-*O*-acetyl (Ac_3araC), tetra-acetyl derivatives (Ac_4araC), cyclocytidine (cC); arabinosyluracil (araU), cyclouridine (cU); deoxyribonucleosides deoxycytidine (dCyd), deoxyuridine (dUrd), thymidine; and 5'-deoxy derivatives 5'-chlorocyclocytidine (5'-Cl-cC), 5'-chlorocytidine (5'Cl-Cyd), 5'-chloroarabinosylcytosine (5'-Cl-araC), and 2',5'-anhydroarabinosylcytidine (2',5'-anhydro-araC). The nucleobases and nucleosides are commercial products (Pharma-Waldhof GmbH, Mannheim). The details of the everted jejunal preparation with continuous perfusion and the design of permeation studies have been described earlier [7, 25]. Briefly, a 10-cm length of fasted everted rat jejunum was cannulated from both ends with tygon cannula, put in an organ bath connected with the outflow from a peristaltic pump on one side and to a UV concentration monitor on the other, and the outflowing solution from the concentration monitor was returned to a reservoir for recirculation. The organ bath contained the compound under study at a concentration of 8.2 m*M* in 30 ml Krebs-Ringer bicarbonate (mucosal fluid). The circulating solution was also Krebs-Ringer bicarbonate, but a volume of 100 ml was used and it contained no drug at the beginning of the experiment (serosal fluid). The entire system was kept oxygenated with a constant temperature of 37° C and tested for functional integrity. The cumulative mucosal to serosal transport of compounds was recorded usually up to 60 min, when 10-μl samples of both mucosal and serosal fluids were used for HPLC measurements of nucleosides and their metabolites. The concentration measurements necessary for the evaluation of transport parameters and for the determination of the partition coefficients were performed by high-performance liquid chromatography (HPLC) in the reversed-phase mode. The liquid chromatography consisted of

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The abbreviations used in this paper are defined in *Materials and methods*

Table 1. Transport and metabolic changes of different nucleobases and nucleosides during mucosal to serosal penetration across everted rat jejunum

No.	Compound tested	$\bar{v}$ (μmol/h)[a] (Total transport)	Percent of compounds found[b]				log P[c]
			Mucosal side		Serosal Side		
1	Cytosine	29.5 ± 1.4	Cytosine	100	Cytosine	100	− 1.49
2.	Uracil	28.2 ± 1.2	Uracil	100	Uracil	100	− 1.11
3.	Thymine	20.2 ± 1.0	Thymine	100	Thymine	100	− 0.57
4.	Cyd	9.0 ± 2.1	Cyd	100	Cyd	97.5	− 2.51
					Urd	2.5	
5.	Urd	5.1 ± 1.2	Urd	100	Urd	100	− 1.98
6.	AraC [3, 4, 6]	13.6 ± 0.8	AraC	100	AraC	85	− 2.05
					AraU	15	
7.	N-Ac-araC	4.3 ± 0.7	N-Ac-araC	100	N-Ac-araC	87.5	− 1.35
					AraC	7	
					AraU	5.5	
8.	Ac_3araC. HCl [1]	6.8 ± 1.5	Ac_3araC	100	Ac_3araC	65	− 0.80
					Ac_3araU	35	
9.	Ac_4araC [14]	4.0 ± 0.2	Ac_4araC	100	Ac_4araC	45	− 0.16
					N-AcAraC	16	
					Ac_3araU	39	
10.	AraU [6]	12.0 ± 3.4	AraU	100	AraU	100	− 1.71
11.	cC. HCl [2]	9.2 ± 1.1	cC	100	cC	62	− 4.03
					cU	29	
					AraU	9	
12.	cU [26]	14.5 ± 0.1	cU	99	cU	99.5	− 2.85
			AraU	1	AraU	0.5	
13.	dCyd	10.6 ± 2.3 (8.8[d])	dCyd	100	dCyd	81.5	− 1.90
					dUrd	1.5	
					Uracil	17	
14.	dUrd	11.8 ± 3.9 (4.7[d])	dUrd	96	dUrd	40	− 1.62
			Uracil	4	Uracil	60	
15.	Thymidine	13.4 ± 0.1 (7.0[d])	Thymidine	100	Thymidine	52	− 0.93
					Thymine	48	
16.	5′-Cl-Cyd [11]	17.6 ± 0.3	5′-Cl-Cyd	100	5′-Cl-Cyd	97	− 1.05
					Uracil	3	
17.	5′-Cl-araC [11]	16.2 ± 1.0	5′-Cl-araC	100	5′-Cl-araC	100	− 0.71
18.	5′-Cl-cC. HCl [11]	15.2 ± 0.2	5′-Cl-cC	1.5	5′-Cl-araC	100	− 3.10
			5′-Cl-araC	98.5			
19.	2′,5′-Anhydro-araC [11]	22.2 ± 0.2	2′,5′-Anhydro-araC	100	2′,5′-Anhydro-araC	100	− 1.64

[a] Transport rate: mean of at least five experiments ± SD
[b] Parent compounds and metabolites on mucosal and serosal sides after 60 min
[c] Logarithm of partition coefficient in octanol-buffer
[d] Net deoxynucleoside transport calculated from total transport

a Milton Roy model 396-57 minipump, a model 709 pulse dampener, a model 1203 UV III monitor operated at 254 nm (all from Laboratory Data Control, Riviera Beach, Fla, USA), a home-made septum injector, and a model EZ 13 electronic recorder (Laboratorní přístroje, Prague, Czechoslovakia). The stationary phase was Separon SI C 18 octadecyl-silica with particle size 10 μm (Laboratorní přístroje), packed into a 250 mm × 4.2 mm ID stainless steel column, and mixtures of aqueous acetic acid (0.5 *M* concentration) and methanol were used as the mobile phase. Most substances were chromatographed in 10 vol.% methanol, but higher methanol percentages, as indicated in Table 2, were necessary with the more lipophilic compounds for satisfactory elution from the column. Table 2 gives the pertinent chromatographic data; the capacity factors (k) have been calculated from the basic equation $t_R = t_M (1 + k)$, t_R being the retention time of the compound of interest and t_M the mobile phase holdup time (dead time). This latter quantity was determined as described by Ryba [21]: t_M was 2.34 min for the typical flow rate of 1.0 ml/min; for uracil t_R = 2.76 min; for uridine t_R = 3.04 min. The determination of the partition coefficient (P) was performed as described earlier [7, 20].

Results and discussion

The study compounds and their metabolites on both mucosal and serosal sides of the intestine and their stability were qualitatively and quantitatively assessed, and the results are given in Table 1. It is clear that pyrimidine nucleobases did not undergo metabolic alteration during penetration of the intestinal barrier, which is in agreement with an earlier report [22]. The significantly higher estimated transport rates for nucleobases than for the corresponding nucleosides may be indicative of simultaneous passive and active intestinal transport of the nucleobases, as reported elsewhere [22].

The nucleoside bond of ribo and arabino derivatives is significantly more stable than that of 2′-deoxy ribonucleosides during transport (Table 1). There is no cleavage of the nucleosidic bond of the ribo and arabino derivatives or of cyclonucleosides during transport. In contrast, there was a

considerable cleavage of the nucleosidic bond of 2′-deoxyribonucleosides. For instance, 60%, 48%, and 17% of the nucleobases were observed on the serosal side for deoxyuridine, thymidine, and deoxycytidine, respectively. As indicated, cytosine crosses the intestinal barrier unchanged. Therefore, in the case of deoxycytidine, the uracil detected could not be due to deamination of cytosine, but rather to cleavage of deoxyuridine resulting from the deamination of deoxycytidine. The results are in agreement with the lower chemical stability of the 2′deoxyribonucleoside bond [19, 28, 29], which is further influenced by the character of the pyrimidine base [12, 23, 24], where the protonation of the amino group should precede the cleavage reaction in cytosine derivatives [23].

Apparently 2′-deoxynucleosides were transported to a greater extent than the corresponding ribonucleosides, as could have been predicted from Table 1 (total transport). However, 2′-deoxynucleosides had undergone nucleosidic bond cleavage during transport, which resulted in a high transport rate of formed nucleobases (uracil, thymine) and in lower net transport of the intact deoxynucleosides (deoxycytidine, deoxyuridine, thymidine), the latter corresponding to the transport of ribonucleosides (cytidine, uridine). Therefore it might be concluded that the change of the ribo to the deoxyribo moiety does not increase the transport potentiality of nucleosides, but rather decreases the stability of the nucleoside bond.

From the practical point of view, it is important to know the metabolic changes that might occur for araC derivatives used in the chemotherapy of myeloblastic leukemia. In the present investigation of cytidine analogs during transport across the intestinal barrier different results were obtained from those recorded in the in vitro experiments with isolated deaminase [13]. The natural nucleoside cytidine is deaminated significantly more slowly than its analogs, while its deamination with isolated enzyme was the fastest [13]. Cytidine penetrates the intestinal barrier at a relatively high rate, while its modification resulted in a lower transport rate and concomitantly increased the metabolic alterations during penetration, as seen with acetyl derivatives of araC. During cyclocytidine transport there was also detectable arabinosyluracil on the serosal side, besides cyclocytidine and cyclouridine. There was no detectable araC at the serosal side, although araC is reported [9] as the active therapeutic entity of cyclocytidine in therapeutic application. We assume that araU is a product of deamination of araC, basing this on the observation that cyclouridine is not transformed to araU during transport. During cyclocytidine transport, the amount transported in 1 h was 9.2 μmol, which contained 0.9 μmol arabinosyluracil (9%), while in the experiment with araC during the same period 1.36 μmol was transported, containing 2 μmol (15%) arabinosyluracil. Table 1 also shows that the total deamination of cyclocytidine was 38%, because of the relatively high amount of cyclouridine (29%). Twice as much cyclocytidine as araC was deaminated, which is explained by the simultaneous deamination of the arabinosylcytosine formed and the parent cyclocytidine.

From our previous results [7] and from Table 1 it is clear that the mucosal-serosal transport rate during 60 min was higher for cytosine nucleosides than for uracil nucleosides.

Table 2. Capacity factors (k) of pyrimidine derivatives on octadecyl silica (Separon SI 18) with mobile phases composed of 0.5 *M* acetic acid and methanol

Compound	k		
	10% MeOH	50% MeOH	65% MeOH
Cytosine	0.15	–	–
Uracil	0.18	–	–
Thymine	0.93	–	–
Cyd	0.42	–	–
Urd	0.30	–	–
AraC	0.73	–	–
N-Ac-araC	1.50	–	–
Ac_3araC. HCl	–	–	1.77
Ac_4araC	–	–	0.25
AraU	0.51	–	–
cC. HCl	1.01	–	–
cU	0.25	–	–
dCyd	0.90	–	–
dUrd	0.62	–	–
Thymidine	1.50	–	–
5′-Cl-Cyd	–	0.81	–
5′-Cl-araC	–	0.71	–
5′-Cl-cC. HCl	–	1.55	–
2′,5′-Anhydro-araC	–	0.68	–
Ac_3araU	2.55	–	–

Table 3. Inhibitory activity of araC derivatives

Compound	NSC no.	Leukemia L1210 cells		
		Inhibition of NA synthesis[a]		Inhibition of cell growth[b] IC_{50}, μ*M*
		ED_{50}, μ*M*		
		DNA	RNA	
Arabinosylcytosine	287 459	0.13	> 1,000	0.05
– ,5′-chloro	318 799	4.4	> 1,000	2.4
– ,5′-bromo				24
– ,2′,5′-anhydro	340 843			20
Cyclocytidine	145 668	0.3	36.8	0.08
– ,5′-chloro	318 797			2.5

[a] Micromolar concentration producing a 50% inhibition of nucleic acid synthesis; done at SRI International
[b] Micromolar concentration producing a 50% inhibition of L1210 cell growth; done at Roswell Park Memorial Institute

This shows the importance of the C^4-amino group in the transport process. This is evident from the effect of acetylation of the amino group on the transport rate, which was consequently depressed; tri-*O*-acetyl arabinosylcytosine was transported to greater extent than either *N*-acetyl or tetra-acetyl arabinosylcytosine. It was assumed [7] that such nucleosides are transported across the intestinal barrier by a carrier-mediated process, in which the amino group might somehow play a role in forming a complex with (a) carrier system(s) rather than the sugar moiety. This is also supported by our experimental finding that $HgCl_2$, which was used to block sugar transport in the luminal aspect of the intestine [5], had no effect on nucleoside transport (in the present experimental conditions; unpublished data).

It is interesting that 5′-chloroderivatives of araC are very stable towards metabolic alterations during intestinal transport (Table 1), as in the case of incubation with isolated deaminase [13]. Moreover, the latter compounds were transported at higher rates. This is in contrast to the results with cyclocytidine and acetyl derivatives of arabinosylcytosine, where alterations of arabinosylcytosine molecule decreased both stability and transport. This stresses the importance of substitution of C-5 of the sugar moiety, and shows the potential perspectives for work with these compounds and with 2′,5′-anhydroarabinosylcytosine. We have recently shown interesting biological properties of 5′-substituted derivatives of arabinosylcytosine and cyclocytidine [10]. It was found that araC was the strongest and most specific inhibitor of DNA synthesis, and cyclocytidine efficiently inhibited both DNA and RNA synthesis. Apart from these, 5′-chloroarabinosylcytosine expressed the highest inhibition of DNA synthesis of all the tested derivatives of araC, 5-fluorouracil, and 6-aza pyrimidine nucleosides (in press). Some of these preliminary comparative results are given in Table 3.

Table 4. Estimates of lipophilicity of sugar moiety (fragmental constant)

Sugar moiety	Fragmental constant
1-β-D-Arabinofuranosyl	− 0.39
1-β-D-Ribofuranosyl	− 0.76
2-Deoxy-1-β-D-erythropentofuranosyl	− 0.24
5-Chloro-5-deoxy-1-β-D-arabinofuranosyl	+ 0.97
5-Chloro-5-deoxy-1-β-D-ribofuranosyl	+ 0.63
2,5-Anhydro-1-β-D-arabinofuranosyl	+ 0.04

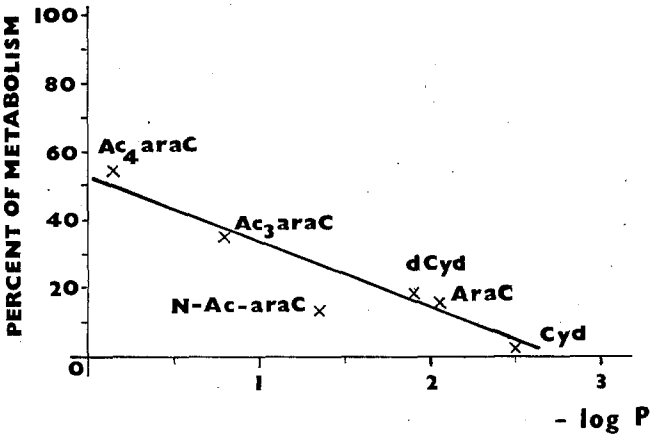

Fig. 1. Relationship between percentage of intestinal metabolic degradation (y) of nucleosides and their lipophilicity (log P). Relationship is expressed by linear equations: $y = 55.9 + 20.7 \log P$ ($r = 0.99$, $n = 5$); $y = 58.2 + 24.0 \log P$ ($r = 0.93$, $n = 6$)

The results on the inhibitory activity of 5′-deoxy-araC derivatives and their behavior during transport across the intestinal wall, where they exhibited higher rates of transport and were practically not biotransformed during penetration, encourages further investigation with regard to their potential oral use compared with the congeners in clinical use. It is known that the intestinal wall represents a complex barrier, which reduces the transport of oral formulations of araC to reach the systemic circulation through biotransformation by intestinal microflora or by intestinal deaminases [7]. The present investigation shows a clearcut stability of 5′-deoxy-araC derivatives compared with araC and with other pyrimidine nucleosides with regard to intestinal permeation under the present experimental conditions. Moreover, the former compounds were more highly resistant to enzymatic deamination in vitro than either araC or cytidine [13]. However, comparative full pharmacokinetic profiles of the aforementioned compounds in vivo must be established to allow an assessment of the sojourn of different compounds and give a more promising effective blood level, to improve their effects as chemotherapeutic agents after oral administration.

It has been reported that lipophilictiy is the main factor in the transport of compounds across biological barriers [15]. Therefore the partition coefficient (log P) of the series of nucleosides studied was measured (as detailed elsewhere [17, 18]) and correlated with their transport rates ($\bar{v}$) (Table 1). It was found that there is no correlation between lipophilicity and transport characteristics of the study nucleosides as reported earlier [7].

From the estimates of partition coefficients given in Table 1, the fragmental constant of the sugar moiety which characterizes the lipophilicity of the studied part of the molecule was calculated according to Rekker et al. [17, 18]. On the basis of the report an estimated fragmental constant for hydrogen of +0.19 was used, and consequently it was possible to calculate the fragmental constant of each sugar moiety of the study compounds (Table 4). The inclusion of a Cl atom in the sugar moiety significantly increased its lipophilicity, irrespective of the configuration, as is evident from the increase in log P (+1.36) for both ribose and arabinose (Table 1). We used the fragmental constants given by Rekker et al. for aliphatic −OH and Cl [17, 18] with the data of Table 4, and found an association between the experimental and the calculated estimates for chloro derivatives. Finally, 2′,5′-anhydro ring formation increased the lipophilicity of the molecule (Table 1; log P −1.64) compared with arabinosylcytosine (log P −2.05), but not to the same extent as chlorination of the molecule (log P −0.71). Nevertheless, the transport rate of the anhydro derivative was higher than that of the 5′-chloro derivative, being the highest of all the compounds studied. This supports the present finding that lipophilicity is not the determinant factor of transport, which more probably is dependent on a specific carrier of the nucleosides [7].

On the other hand, if the lipophilicity is compared with the degradation of a nucleoside, a good correlation between the partition coefficient (log P) and the percentage metabolism is observed ($r = 0.99$, $n = 5$; Fig. 1). The metabolism of nucleosides by other nonspecific enzymes (esterases, deaminases) is assumed, which should be dependent on the

formation of a complex nucleoside enzyme. As the cleavage of the nucleoside bond at 2′-deoxyribo nucleosides is basically a different reaction, the 2′-deoxynucleosides do not fit into the correlation, except for 2′-deoxycytidine, where the cleavage of the nucleoside bond is dependent on previous deamination to deoxyuridine. The slower deamination of *N*-acetyl araC may be explained by the action of different enzymes at the same position on the nucleoside molecule ($r = 0.93$, $n = 6$).

In conclusion, our preliminary screening results of 5′-deoxy (including of 5′-halogeno) derivatives of araC (Table 3), together with the present study, indicate that this is a potentially interesting new group of biologically active compounds. The results clearly show that 5′-deoxy(halogeno) derivatives are superior in their transport rate and metabolic changes to the clinically used compounds, araC and cyclocytidine, and are the best of all the arabinosylcytosine derivatives tested in the present experimental conditions. The present results stimulate further investigation of the mechanism of action and biological activity of the 5′-deoxy (5′-halogeno) derivatives of araC in in vivo experiments. in particular a comparison of 5′-chloroarabinosylcytosine and araC PO in experimental tumors.

Although there was no correlation between lipophilicity and transport rate, there is a good correlation between lipophilicity and metabolic transformation during intestinal transport of the compounds studied.

The calculated fragmental constants of sugar components should be used more generally for prediction of lipophilic character and nonspecific degradation of other nucleoside analogs.

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References

1. Beránek J, Drašar P (1977) Preparation of 1-(2,3,5-tri-*O*-acetyl-β-D-arabino-pentofuranosyl)cytosine hydrochloride. Collect Czech Chem Commun 42: 366
2. Beránek J, Brokeš J, Hřebabecký H (1977a) Preparation of cyclocytidine hydrochloride. Czech 1501
3. Beránek J, Brokeš J, Hřebabecký H (1977b) Preparation of 1-β-D-arabinofuranosylcytosine. Czech 1502
4. Beránek J, Delia TJ, Drašar P (1977c) One-step synthesis of 1-β-D-arabinofuranosylcytosine. Collect Czech Chem Commun 42: 1588
5. Bihler I, Cybulsky R (1973) Sugar transport at the basal and lateral aspect of the small intestinal cell. Biochim Biophys Acta 298: 429
6. Brokeš J, Beránek J (1974) Synthesis of 1-β-D-arabinofuranosylcytosine. Collect Czech Chem Commun 39: 3100
7. Farghali H, Novotný L, Ryba M, Beránek J, Janků I (1984) Kinetics of transport and metabolism of 1-β-D-arabinofuranosylcytosine and structural analogs by perfused rat jejunum. Biochem Pharmacol 33: 655
8. Garrett ER, Seydel JK, Sharpen AJ (1966) The acid catalyzed solvolysis of pyrimidine nucleosides. J Org Chem 31: 2219
9. Ho DHW, Rodriguez V, Loo TL, Bodey GP, Freireich EJ (1975) Clinical pharmacology of O^2,2′-cyclocytidine. Clin Pharmacol Ther 17: 66
10. Hřebabecký H, Beránek J (1981) A new group of biologically active arabinosylcytosine derivatives, syntheses and activity. Nucleic Acids Symposium Series 9: 99
11. Hřebabecký H, Brokeš J, Beránek J (1980) Reaction of nucleosides with thionyl chloride, preparation of the deoxy derivatives of cytidine and adenosine. Collect Czech Chem Commun 45: 599
12. Hřebabecký H, Brokeš J, Beránek J (1982) Preparation of the 1-(2,5-anhydro-β-D-arabinofuranosyl) derivatives of cytosine and uracil and their cleavage with hydrogen bromide. Collect Czech Chem Commun 47: 2961
13. Kára J, Bártová M, Ryba M, Hřebabecký H, Brokeš J, Novotný L, Beránek J (1982) Sensitivity of some arabinosylcytosine derivatives to enzymatic deamination by cytidine deaminase from mouse kidney. Collect Czech Chem Commun 47: 2824
14. Martinez AP, Lee WW, Goodman L (1966) The acetylation of 1-(β-D-arabinofuranosyl)cytosine. J Med Chem 9: 268
15. Moon AY, Poland DC, Sherage HA (1965) Thermodynamic data from fluorescence spectra. I. The system phenol-acetate. J Phys Chem 69: 2960
16. Nakamura T, Yamada K, Tsuruo T, Kitahara T, Maekawa T, Uzuka Y, Kurita S, Masaoka T, Takaku F, Hirota Y, Amaki I, Osamura S, Nakano N, Oguro M, Inagaki J, Onozawa K (1981) Phase III study of N^4-behenoyl-l-β-D-arabinofuranosylcytosine in adult acute leukemia. (Abstract 687) 12th International Congress of Chemotherapy. Florence, 1981, p 171
17. Nys GG, Rekker RF (1973) Statistical analysis of a series of partition coefficients with special reference to the predictability of folding of drug molecules. Introduction of hydrophobic fragmental constants (f values). Chim Ther 8: 521
18. Nys GG, Rekker RF (1974) The concept of hydrophobic fragmental constants (f values). II. Extension of its applicability to the calculation of lipophilicities of aromatic and heteroaromatic structures. Eur J Med Chem 9: 361
19. Pfitzner KE, Moffatt JG (1964) The synthesis and hydrolysis of 2′,3′-dideoxyuridine. J Org Chem 29: 1508
20. Rekker RF (1977) The hydrophobic fragmental constant. Elsevier, Amsterdam
21. Ryba M (1981) Reversed-phase liquid column chromatography of pyrimidine and purine derivatives. J Chromatogr 219: 245
22. Shanker LS, Tocco DJ (1960) Active transport of some pyrimidines across the rat intestinal epithelium. J Pharmacol Exp Ther 128: 115
23. Shapiro R, Danzig M (1972) Acidic hydrolysis of deoxycytidine and deoxyuridine derivatives. The general mechanism of deoxyribonucleoside hydrolysis. Biochemistry 11: 23
24. Shapiro R, Kang S (1969) Uncatalyzed hydrolysis of deoxyuridine, thymidine, and 5-bromodeoxyuridine. Biochemistry 8: 1806
25. Terziivanov D, Havlík I, Janků I (1982) Evidence for a saturable component in isoniazid transfer across rat small intestine in vitro. J Pharm Pharmacol 34: 817
26. Verheyden JPH, Wagner D, Moffatt JG (1971) Synthesis of some pyrimidine 2′-amino-2′-deoxynucleosides. J Org Chem 36: 250
27. Watanabe KA, Fox JJ (1966) Simple method for selective acylation of cytidine on the 4-amino group. Angew Chem 78: 589
28. York JL (1981) Effect of the structure of the glycon on the acid-catalyzed hydrolysis of adenine nucleosides. J Org Chem 46: 2171
29. Zhuk RA, Berzinja AE, Volynkina GG, Giller SA (1970) Analogi pirimidinnukleozidov. VI. Kinetika kislotnogo gidroliza N_1-(2′-furanidil)- i N_1-(2′-piranidil)proizvodnych uracila, timina i 5-ftoruracila. Khim Geterotsikl Soedin 550

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