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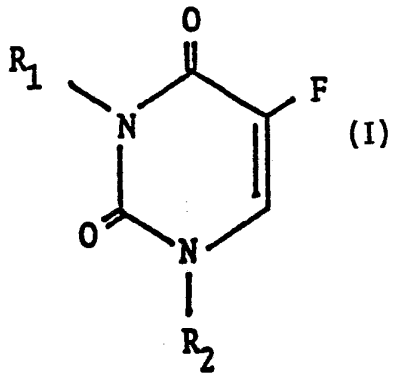

(I)

(57) Abstract

A pharmaceutical composition in unit dosage form adapted for topical administration to a human or non-human animal in need thereof comprising a pharmacologically effective amount of a prodrug of 5-fluorouracil having formula (I), wherein R_1 and R_2 may be the same or different and are selected from the group consisting of H, R_3CO- and R_4-O-CO with the proviso that both R_1 and R_2 may not be H; or a non-toxic pharmaceutically acceptable salt, adduct, oxide or other derivative thereof; a pharmaceutically acceptable, topically administratable carrier therefor; and a method for topically applying the composition. R_3 and R_4 comprise groups such that the prodrug (1) has an enhanced delivery across topical membranes and (2) hydrolyzes after delivery to 5-fluorouracil.

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"TOPICAL 5-FLUOROURACIL PRODRUG COMPOSITION AND METHOD"

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to certain 5-fluorouracil prodrug compositions and methods for their topical administration.

Description of the Prior Art

Considerable research has been conducted in an attempt to solve the problem of enhancing the delivery of topically applied drugs across the topical skin membrane.

Many drugs have been found to be useful for the treatment of various skin disease states such as psoriasis and atopic dermatitis when they are given orally, but are not effective when applied topically. However, the use of a drug in a topical manner to treat a topical disease state is desirable in that only a locally effective concentration of the drug needs to be attained in the skin. On the other hand, an oral dose develops a systemic (whole body) concentration of the drug.

Although 5-fluorouracil (5-FU) is the only widely accepted topical treatment for skin malignancies and is successful in treating superficial lesions such as actinic keratoses [Dillaha et al, Arch. Dermatol., Vol. 92, page 410 (1965)] and basal cell carcinomas [Sloan et al, Int. J. Pharm., Vol. 44, page 87 (1988)], it is ineffective in treating deeper lesions or actinic keratoses of the extremities. Therefore, a more effective and less irritating therapy is generally conceded as being desirable.

There are two general approaches to enhancing the dermal delivery of any drug. The first is by a formulation approach and the second is by a prodrug approach [Waranis et al, J. Pharm. Sci., Vol. 76, page 587 (1987)].

Prodrugs comprise derivatized or other chemical and/or physically modified forms of the drug species and are designed to more readily penetrate topical barriers. Upon transport across the topical membrane, they are converted in situ to the active form, whereupon they perform their intended biological function in the target organ. These prodrugs are also designed to resist metabolic conversions and other forms of degradation until they have crossed the barrier.

5-FU is conventionally employed in a formulation containing propylene glycol (a solubilizer) and a penetration enhancer. See U.S. Patent Nos. 3,991,203; 4,411,893; 4,415,563; 4,714,703 and 4,853,388; and Japanese Patent No. 83-79915 [abstracted in Chem. Abs., Vol. 99:58911h (1983)]. Propylene glycol is very irritating to the skin over extended courses of treatment which can last for several weeks.

Polar, high-melting, heterocyclic drugs such as 5-FU which are relatively insoluble in lipids and in water have presented a challenge to pharmaceutical chemists for some time in their efforts to improve the topical delivery of such agents so that they can be used effectively in clinical situations. One approach to meeting this challenge has been to use N-acyloxyalkyl prodrug derivatives which are lower-melting and more lipophilic than the parent drugs. Recently, a number of examples of the application of this approach to modifying heterocyclic drugs have been described [Bodor et al, U.S. Patent No. 4,061,753; CA 87:152278 (1977) and

Sloan et al, Int. J. Pharm., Vol. 12, pages 299-313 (1982); Stella et al, U.S. Patent No. 4,163,058; CA 91:193312 (1979); Ozaki et al, U.S. Patent No. 4,267,326; Mollgaard et al, Int. J. Pharm., Vol. 12, pages 153-162 (1982); and Sloan et al, J. Pharm. Sci., Vol. 72, pages 372-378 (1983)].

Although no examples of prodrugs have been reported where both water and lipid solubility have been optimized in order to obtain enhanced delivery of drugs across topical membranes, there are a number of prodrugs which incorporate an amino group into the derivative and exhibit enhanced lipid solubility and dermal delivery [Sloan, U.S. Patent No. 4,206,220; CA 93:8017 (1980); Sloan and Little, CA 96:104087 (1982); Sloan, CA 97:144855 (1982); and Bodor et al, Int. J. Pharm., Vol. 10, pages 307-321 (1982)].

Although the topical membrane or skin is a "biological membrane," it differs substantially from other membranes in that the barrier to absorption of drugs is the stratum corneum which comprises a dead, dry (5-10% H_2O), compact keratin-containing material. All other biological membranes comprise live, essentially aqueous (75-80% H_2O) material. Obviously, therefore, the considerations bearing on the transport or delivery of drug species across other biological membranes are altogether different from those bearing on the delivery of drugs across the topical skin membrane.

A high degree of lipophilicity is necessary in any prodrug designed to effectively cross the skin membrane. However, the prodrug must substantially immediately convert to the parent active drug species after transport across the stratum corneum.

It has been suggested heretofore to employ certain N-Mannich type bases as prodrugs for oral or parenteral administration. See, for example, Pitman. Med. Res. Rev., Vol. 1, No. 2, pages 189-214 (1981); Johansen et al, Arch. Pharm. Chem. Sci., Ed. 8, pages 141-151, 207-214 (1980); Johansen et al, Arch. Pharm. Chem. Sci., Ed. 10, pages 111-121 (1982); Bundgaard et al, Int. J. Pharm., Vol. 7, pages 119-127, 129-136 (1980); Bundgaard et al, J. Pharm. Sci., Vol. 69, No. 1, pages 44-47 (1980); Bundgaard et al, Acta. Pharm. Suec., Vol. 18, pages 129-134 (1981); Bundgaard et al, Int. J. Pharm., Vol. 8, pages 183-192 (1981); and Bundgaard et al, Int. J. Pharm., Vol. 9, pages 7-16 (1981). There is no suggestion in the prior art, however, as to the utilization of such N-Mannich bases as topical prodrugs.

There is disclosed in U.S. Patent No. 4,412,994 the use of Mannich base hydroxamic acid prodrugs for topical administration to warm-blooded animals. The parent drugs from which the prodrugs are derived, however, are limited to "acyl residues of non-steroidal anti-inflammatory agents containing a carboxylic acid function."

The use of Mannich bases or aminomethyl derivatives for topical delivery involves the intact prodrug partitioning from a non-protic solvent (in which it is stable) into the skin (in which it is not stable because of the presence of water) where it reverts to the parent compound. On the other hand, the use of Mannich bases or aminomethyl derivatives for oral or parenteral use take advantage of increased water solubility and increased dissolution properties of the derivatives to enhance the bio-availability of the parent drug, but it is the parent drug and not the prodrug that is actually

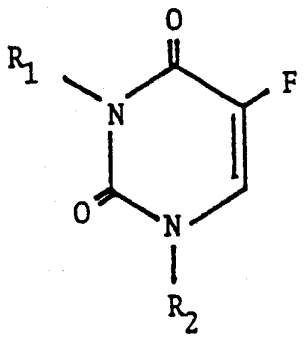
involved in the partitioning from the aqueous environment (in which the prodrug is not stable) into the membranes and from there ultimately the systemic circulation. Thus, the topical delivery depends on the superior partitioning properties of the intact prodrug while the oral or parenteral delivery still depends on partitioning properties of the parent drug and gains its only advantage from the more immediate and higher solution concentrations of the parent drug that develop from the use of the prodrugs.

Sloan (U.S. Patent No. 4,845,081) describes certain aminomethyl derivatives of 5-FU as well as other biologically active organic compounds which function successfully as topically applied prodrugs having an enhanced delivery or transport across the topical membrane.

It is an object of the present invention to provide novel 5-fluorouracil prodrug compositions and methods for their topical administration.

SUMMARY OF THE INVENTION

The above and other objects are realized by the present invention which provides a pharmaceutical composition in unit dosage form adapted for topical administration to a human or non-human animal in need thereof comprising a pharmacologically effective amount of a prodrug of 5-fluorouracil having the formula:



wherein: R_1 and R_2 may be the same or different and are selected from the group consisting of H, R_3CO- and R_4-O-CO with the proviso that both R_1 and R_2 may not be H;

or a non-toxic pharmaceutically acceptable salt, adduct, oxide or other derivative thereof; and a pharmaceutically acceptable, topically administrable carrier therefor; said R_3 and R_4 comprising groups such that the prodrug (1) has an enhanced delivery across topical membranes of the animal upon topical application of the composition as compared with 5-fluorouracil and (2) hydrolyzes after delivery across the topical membrane to yield a pharmacologically effective amount of 5-fluorouracil.

Another embodiment of the invention comprises a method of administering 5-fluorouracil to a human or non-human animal in need thereof comprising topically applying to the animal a pharmacologically effective amount of the above-described composition.

DETAILED DESCRIPTION OF THE INVENTION

Several of the above-described compounds have been characterized in the prior art as prodrugs for the improved rectal or oral delivery of 5-FU. See Kametani et al, J. Med. Chem., Vol. 23, pages 1324-1329 (1980) and J. Med. Chem., Vol. 25, pages 1219-1222 (1982); J. Pharm. Sci., Vol. 75, No. 5, pages 522-527 (1986); and Acta. Pharm. Suec., Vol. 23, pages 205-216 (1986).

The present invention is predicated on the discovery that these and related compounds are also effective prodrugs for the enhanced delivery or transport of 5-FU across topical membranes.

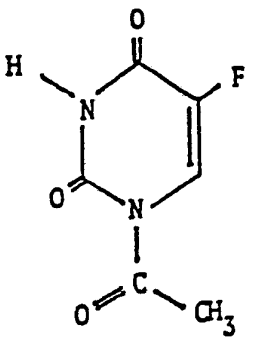
In the structural formula set forth above, R_3 and R_4 may be the same or different and are selected from the group consisting of (a) cycloalkyl groups having one to ten carbon atoms, (b) straight or branched chain alkyl groups of one to ten carbon atoms, (c) straight or branched chain alkenyl or alkynyl groups of two to ten carbon atoms, wherein the chains of (a), (b) or (c) thereof (1) may be interrupted by one or more N, S or O atoms, or (2) may be substituted at any point on the chain by one or more members selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$ and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S, hydrocarbyl aryl groups, aryl groups substituted by at least one member selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$, OR_5, halogen, SR_5, $N(R_5)_2$, NO_2 and R_5, and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S.

Most preferably, R_3 is CH_3 or C_2H_5, and R_4 is C_2H_5.

R_5 is selected from the group consisting of cycloalkyl or straight or branched chain alkyl groups of one to ten carbon atoms, and alkenyl or alkynyl groups of two to ten carbon atoms.

Either of R_1 or R_2 may be H; however, as will be apparent, both may not be H since the resulting compound would be 5-FU.

Preferred embodiments of the invention are those compositions and methods wherein the structural formula of the prodrug is: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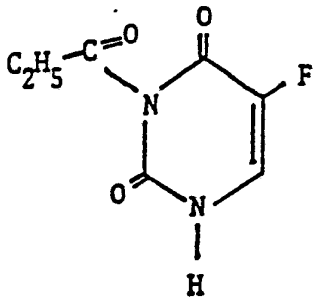
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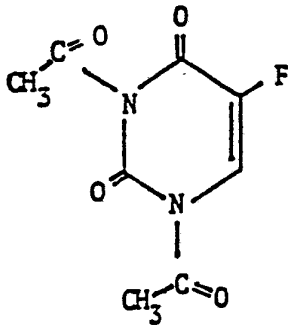
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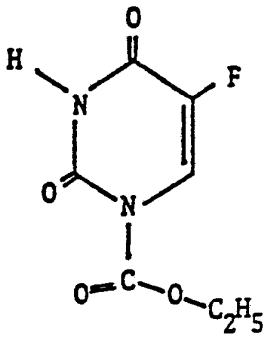


The compositions of the invention for both veterinary and for human use of the present invention comprise the prodrug together with one or more acceptable carriers therefor and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations, not deleterious to the recipient thereof and suitable for topical application. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the prodrug with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the prodrug with the carrier(s) and then, if necessary, dividing the product into unit dosages thereof.

It should be understood that excluded from the scope of the present invention are non-sterile mixtures which are merely solutions or suspensions of the known

prodrugs in solvents and liquids known in the literature for use in their synthesis and/or isolation by the methods described therein. Included within the scope of the present invention are such solutions and suspensions of the known substances which are pharmaceutically acceptable to the intended recipient thereof and which contain in addition at least one other pharmaceutically acceptable substance.

Suitable non-toxic pharmaceutically acceptable carriers for use with the prodrugs will be apparent to those skilled in the art. See, for example, Remington's Pharmaceutical Sciences, 4th edition (1970). Obviously, the choice of suitable carriers will depend upon the exact nature of the particular dosage form selected, as well as upon the identity of the prodrug species.

Generally, however, the prodrugs of the present invention for use in topical applications should be restricted to use in non-protic, anhydrous vehicles (e.g., plastibase, petrolatum, isopropyl, myristate, etc.) at concentrations of from about 0.1 to about 20% by weight. The stability of the prodrug in a particular vehicle will depend upon the vehicle employed.

The therapeutic dosage ranges for administration of the prodrugs will generally be the same as, or less than, those characteristically used in this art for administration of the active drug species. Obviously, such therapeutic dosage ranges will vary with the size of the patient, the condition for which the prodrug is administered, the particular dosage form employed and the like. The quantity of given dosage form required to deliver the desired dose of the active drug 5-FU will, of course, depend upon the concentration of the prodrug in any given pharmaceutical composition dosage thereof.

The invention is illustrated by the following non-limiting examples.

EXAMPLE 1

Syntheses

The 1-alkylcarbonyl derivatives (1-6) in Tables 1 and 2 were synthesized from the reaction of the potassium salt of 5-FU with the corresponding acyl chlorides in acetone or acetonitrile at ice-bath temperature. The 1-alkyloxycarbonyl derivatives (7-12) in Tables 3-5 were synthesized from the reaction of the potassium salt of 5-FU with the corresponding alkyl chloroformates in acetone at room temperature for one hour. The 3-alkylcarbonyl derivatives (13-16) in Tables 6-8 were synthesized from the reaction of the corresponding 1,3-bisalkylcarbonyl derivatives with one equivalent of t-butylamine in ether at room temperature until the reaction was complete by TLC. The 1,3-bisalkylcarbonyl derivatives (17-20) in Tables 9 and 10 were synthesized from the reaction of 5-FU with three equivalents of the corresponding acyl chlorides in the presence of three equivalents of triethylamine at room temperature for three hours.

EXAMPLE 2

Diffusion Cell Experiments

The diffusion cell experiments were conducted as described by Sloan et al in J. Invest. Dermatol., Vol. 87, page 244 (1986), and Sherertz et al in J. Invest. Dermatol., Vol. 89, page 147 (1987). The results from these experiments are recorded in the tables as J_i (flux of 5-FU through the skin indicating the relative extent of transdermal delivery), C_s (a measure of the amount of 5-FU in the skin after the

applied formulation of prodrug was removed indicating the relative extent of dermal delivery) and J_j (flux of a standard drug/formulation through the skin after the application of the prodrug/formulation indicating the relative amount of damage caused by the prodrug/formulation).

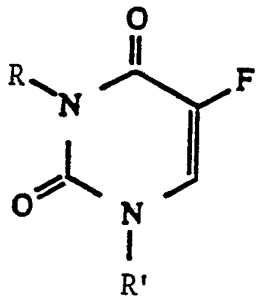
EXAMPLE 3

Physicochemical Properties

The results from the determination of the physicochemical properties are recorded in the tables as C_{IPM} (the saturated solubility of the prodrug in the isopropyl myristate (IPM) vehicle/formulation in which the prodrug was applied to the mouse skins), K (the partition coefficients of the prodrug between IPM and a pH 4.0 acetate buffer) and C_w (the solubility of the prodrug in pH 4.0 acetate buffer calculated from the partition coefficient and the IPM solubility). Because some of the prodrugs were so unstable in the presence of protic solvents, the partition coefficients were determined by vigorously shaking 0.5 to 1.0 ml of the IPM solutions from the IPM solubility determinations with 0.5 - 1.0 ml of the buffer for ten seconds, allowing the layers to separate for sixty seconds, and analyzing the IPM solutions for intact prodrug immediately.

TABLE 1

PHYSICOCHEMICAL PROPERTIES OF
1-ALKYLCARBONYL DERIVATIVES OF 5-FU



Compound	MP °C	K[a]	C_w[b]
1. R = H, R' = (C = O)CH_3	126-127	0.185	20.7
2. R = H, R' = (C = O)C_2H_5	127-128	0.764	8.86
3. R = H, R' = (C = O)C_3H_7	142-143	2.69	1.30
4. R = H, R' = (C = O)C_4H_9	117-118	11.3	0.745
5. R = H, R' = (C = O)C_5H_{11}	98-99	42.9	0.662
6. R = H, R' = (C = O)C_7H_{15}	81-82	----	----

a Partition coefficient between IPM and pH 4.0 acetate buffer at 23 ± 1°C.

b Solubility in mg/ml of pH 4.0 acetate buffer at 23 ± 1°C calculated from partition coefficient between IPM and pH 4.0 acetate buffer and the solubility of derivative in IPM.

TABLE 2

RATES OF DELIVERY OF 5-FU THROUGH HAIRLESS MOUSE SKIN BY 1-ALKYLCARBONYL DERIVATIVES OF 5-FU

Compound	C_{IPM}[a]	J_i[b]	C_s[c]	J_j[d]
5-FU	0.0064	0.0311	0.48	0.215
1	3.80 (2.87)	1.213	8.85	0.296
2	6.77 (4.73)	0.560	8.96	0.219
3	3.48 (2.26)	0.168	1.07	0.185
4	8.39 (5.10)	0.133	2.08	0.144
5	25.7 (14.6)	0.146	1.42	0.084
6	28.4 (14.4)	0.078	1.58	0.129

a Solubility in mg/ml of IPM at 23 ± 1°C (equivalent mg of 5-FU/ml).

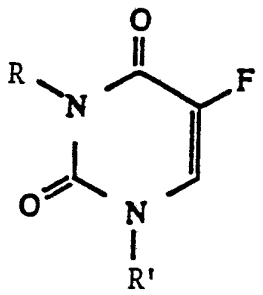
b Flux in mg/cm^2 hour of 5-FU from suspensions of prodrugs in IPM.

c Amount of 5-FU in mg leached from hairless mouse skin in 24 hours subsequent to application of prodrug in vehicle for 48 hours.

d Flux in mg/cm^2 hour of theophylline from suspension in PG.

TABLE 3

PHYSICOCHEMICAL PROPERTIES OF
1-ALKYLOXYCARBONYL DERIVATIVES OF 5-FU



	Compound	MP °C	K^a	$C_w{}^b$
7.	R=H,R'=(C=O)OCH_3	158-160	0.026	16.0
8.	R=H,R'=(C=O)OC_2H_5	126.5-128.5	0.0757	35.2
9.	R=H,R'=(C=O)OC_3H_7	124-126	0.359	9.2
10.	R=H,R'=(C=O)OC_4H_9	97-98	1.46	5.36
11.	R=H,R'=(C=O)OC_6H_{13}	66-77	31.1	1.17
12.	R=H,R'=(C=O)OC_8H_{17}	97-98	----	----

a Partition coefficient between IPM and pH 4.0 acetate buffer at 23 ± 1°C.

b Solubility in mg/ml of pH 4.0 acetate buffer at 23 ± 1°C calculated from partition coefficient between IPM and pH 4.0 acetate buffer and the solubility of derivative in IPM.

TABLE 4

PHYSICOCHEMICAL PROPERTIES OF
1-ALKYLOXYCARBONYL DERIVATIVES OF 5-FU[a]

Compound	log K[b]	C_w[c]	Half-Lives (min)[d]	
			Buffer	80% Plasma
5-FU	-0.83	11.1		
7	-0.68	23.3	190	---
8	-0.17	6.9	550	2.1
9	---	---	---	---
10	0.89	5.9	550	3.1
11	2.04[e]	1.5[e]	550[e]	2.0[e]
12	---	---	---	---

a From J. Pharm. Sci., Vol. 75, page 522, Buur et al (1986).

b Octanol-pH 4.0 acetate buffer partition coefficient determined at 22°C.

c Solubility in mg/ml at pH 4.0 acetate buffer at 22°C.

d Half-lives determined at 37°C in 0.05 M phosphate buffer at pH 7.4. Plasma was human plasma.

e From Int. J. Pharm., Vol. 36, page 41, Buur et al (1987).

TABLE 5

RATES OF DELIVERY OF 5-FU THROUGH HAIRLESS MOUSE SKIN BY 1-ALKYLOXYCARBONYL DERIVATIVES OF 5-FU

Compound	C_{IPM}[a]	J_i[b]	C_s[c]	J_j[d]
7	0.400 (0.277)	0.343	1.08	0.337
8	2.64 (1.70)	0.770	2.38	0.357
9	3.28 (1.98)	0.294	0.65	0.300
10	7.77 (4.39)	0.284	0.54	0.321
11	28.7 (14.4)	0.195	1.38	0.321
12	10.4 (4.72)	0.037	0.41	0.323

a Solubility in mg/ml of IPM at 23 ± 1°C (equivalent mg of 5-FU/ml).

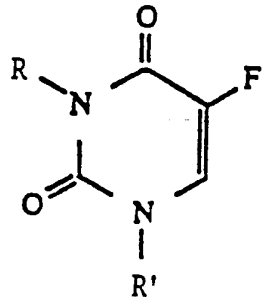
b Flux in mg/cm^2 hour of 5-FU from suspensions of prodrugs in IPM.

c Amount of 5-FU in mg leached from hairless mouse skin in 24 hours subsequent to application of prodrug in vehicle for 48 hours.

d Flux in mg/cm^2 hour of theophylline from suspension in PG.

TABLE 6

PHYSICOCHEMICAL PROPERTIES OF
3-ALKYLCARBONYL DERIVATIVES OF 5-FU



	Compound	MP °C	K^b	C_w^c
13.	R=(C=O)CH_3,R'=H	114-117[a]	0.040	18.5
14.	R=(C=O)C_2H_5,R'=H	99-102[a]	0.088	29.9
15.	R=(C=O)C_3H_7,R'=H	111-112	0.97	4.59
16.	R=(C=O)C_4H_9,R'=H	110-111	1.65	1.19

a From J. Med. Chem., Vol. 23, page 1324, Kametani et al (1980).

b Partition coefficient between IPM and pH 4.0 acetate buffer at 23 ± 1°C.

c Solubility in mg/ml of pH 4.0 acetate buffer at 23 ± 1°C calculated from partition coefficient between IPM and pH 4.0 acetate buffer and the solubility of derivative in IPM.

TABLE 7

PHYSICOCHEMICAL PROPERTIES OF
3-ALKYLCARBONYL DERIVATIVES OF 5-FU[a]

Compound	log K[b]	C_w[c]	Half-Lives (min)[d]	
			Buffer	80% Plasma
13	-0.34	42.8	43	4.6
14	0.19	35.3	50	20
15	0.67	----	58	28

a From Int. J. Pharm., Vol. 21, page 349, Buur et al (1984).

b Octanol-pH 4.0 acetate buffer partition coefficient determined at 22°C.

c Solubility in mg/ml at pH 4.0 acetate buffer at 22°C.

d Half-lives determined at 37°C in 0.05 M phosphate buffer at pH 7.4. Plasma was human plasma.

TABLE 8

RATES OF DELIVERY OF 5-FU THROUGH HAIRLESS MOUSE SKIN BY 3-ALKYLCARBONYL DERIVATIVES OF 5-FU

Compound	C_{IPM}[a]	J_i[b]	C_s[c]	J_j[d]
13	0.074 (0.56)	0.575	1.77	0.282
14	2.62 (1.83)	0.673	2.00	0.318
15	4.44 (2.89)	0.291	0.86	0.204
16	1.96 (1.19)	0.071	0.38	0.194

a Solubility in mg/ml of IPM at 23 ± 1°C (equivalent mg of 5-FU/ml).

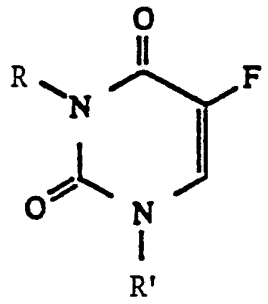
b Flux in mg/cm^2 hour of 5-FU from suspensions of prodrugs in IPM.

c Amount of 5-FU in mg leached from hairless mouse skin in 24 hours subsequent to application of prodrug in vehicle for 48 hours.

d Flux in mg/cm^2 hour of theophylline from suspension in PG.

TABLE 9

PHYSICOCHEMICAL PROPERTIES OF
1,3-BISALKYLCARBONYL DERIVATIVES OF 5-FU



	Compound	MP °C	K^a	$C_w{}^b$
17.	R=R'=(C=O)CH_3	109-111	2.93	1.91
18.	R=R'=(C=O)C_2H_5	97-99	33.8	0.80
19.	R=R'=(C=O)C_3H_7	46-48	----	----
20.	R=R'=(C=O)C_4H_9	44-46	----	----

a Partition coefficient between IPM and pH 4.0 acetate buffer at 23 ± 1°C.

b Solubility in mg/ml of pH 4.0 acetate buffer at 23 ± 1°C calculated from partition coefficient between IPM and pH 4.0 acetate buffer and the solubility of derivative in IPM.

TABLE 10

RATES OF DELIVERY OF 5-FU THROUGH HAIRLESS MOUSE SKIN BY 1,3-BISALKYLCARBONYL DERIVATIVES OF 5-FU

Compound	C_{IPM}[a]	J_i[b]	C_s[c]	J_j[d]
17	5.60 (3.40)	0.291	1.24	0.282
18	17.4 (9.35)	0.090	0.51	0.288
19	169 (81.4)	0.127	1.54	0.190
20	352 (154)	0.124	1.14	0.156

a Solubility in mg/ml of IPM at 23 ± 1°C (equivalent mg of 5-FU/ml).

b Flux in mg/cm^2 hour of 5-FU from suspensions of prodrugs in IPM.

c Amount of 5-FU in mg leached from hairless mouse skin in 24 hours subsequent to application of prodrug in vehicle for 48 hours.

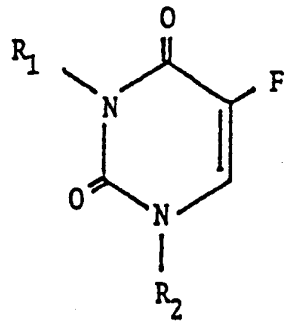
d Flux in mg/cm^2 hour of theophylline from suspension in PG.

While we have described various embodiments in accordance with the present invention, it is understood that the same is not limited thereto, but is susceptible of numerous changes and modifications as known to those skilled in the art. Therefore, we do not wish to be limited to the details described herein, but intend to cover all such changes and modifications as are encompassed by the scope of the appended claims.

TOPICAL 5-FLUOROURACIL PRODRUG COMPOSITION AND METHOD

WE CLAIM:

1. A pharmaceutical composition in unit dosage form adapted for topical administration to a human or non-human animal in need thereof comprising a pharmacologically effective amount of a prodrug of 5-fluorouracil having the formula:



wherein: R_1 and R_2 may be the same or different and are selected from the group consisting of H, R_3CO- and R_4-O-CO- with the proviso that both R_1 and R_2 may not be H;

or a non-toxic pharmaceutically acceptable salt, adduct, oxide or other derivative thereof; and a pharmaceutically acceptable, topically administrable carrier therefor; said R_3 and R_4 comprising groups such that said prodrug (1) has an enhanced delivery across topical membranes of said animal upon topical application of said composition as compared with 5-fluorouracil and (2) hydrolyzes after delivery across said topical membrane to yield a pharmacologically effective amount of 5-fluorouracil.

2. A composition according to claim 1, wherein R_3 and R_4 may be the same or different and are selected from the group consisting of (a) cycloalkyl groups having one to ten carbon atoms, (b) straight or branched chain alkyl groups of one to ten carbon atoms, (c) straight or branched chain alkenyl or alkynyl groups of two to ten carbon atoms, wherein the chains of (a), (b) or (c) thereof (1) may be interrupted by one or more N, S or O atoms, or (2) may be substituted at any point on the chain by one or more members selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$ and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S, hydrocarbyl aryl groups, aryl groups substituted by at least one member selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$, OR_5, halogen, SR_5, $N(R_5)_2$, NO_2 and R_5, and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S; and R_5 is selected from the group consisting of cycloalkyl or straight or branched chain alkyl groups of one to ten carbon atoms, and alkenyl or alkynyl groups of two to ten carbon atoms.

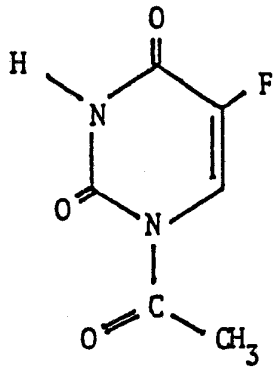
3. A composition according to claim 2, wherein R3 is CH_3 or C_2H_5.

4. A composition according to claim 2, wherein R_4 is C_2H_5.

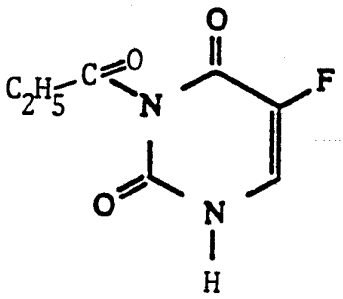
5. A composition according to claim 1, wherein one of said R_1 and R_2 is H.

6. A composition according to claim 1, wherein neither of said R_1 and R_2 is H.

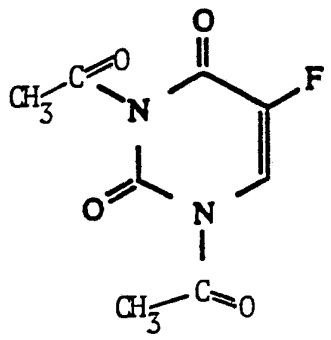
7. A composition according to claim 1, wherein said prodrug of 5-fluorouracil has the formula:



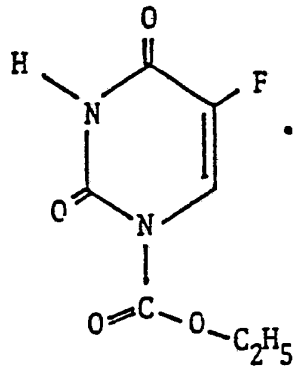
8. A composition according to claim 1, wherein said prodrug of 5-fluorouracil has the formula:



9. A composition according to claim 1, wherein said prodrug of 5-fluorouracil has the formula:



10. A composition according to claim 1, wherein said prodrug of 5-fluorouracil has the formula:



11. A method of administering 5-fluorouracil to a human or non-human animal in need thereof comprising topically applying to said animal a pharmacologically effective amount of a composition according to claim 1.

12. A method according to claim 11, wherein R_3 and R_4 may be the same or different and are selected from the group consisting of (a) cycloalkyl groups having one to ten carbon atoms, (b) straight or branched chain alkyl groups of one to ten carbon

atoms, (c) straight or branched chain alkenyl or alkynyl groups of two to ten carbon atoms, wherein the chains of (a), (b) or (c) thereof (1) may be interrupted by one or more N, S or O atoms, or (2) may be substituted at any point on the chain by one or more members selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$ and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S, hydrocarbyl aryl groups, aryl groups substituted by at least one member selected from the group consisting of COR_5, $COOR_5$, $CON(R_5)_2$, OR_5, halogen, SR_5, $N(R_5)_2$, NO_2 and R_5, and mono- and bi-cyclic saturated or unsaturated heterocyclic rings, each ring consisting of three to seven members selected from the group consisting of C, N, O and S; and R_5 is selected from the group consisting of cycloalkyl or straight or branched chain alkyl groups of one to ten carbon atoms, and alkenyl or alkynyl groups of two to ten carbon atoms.

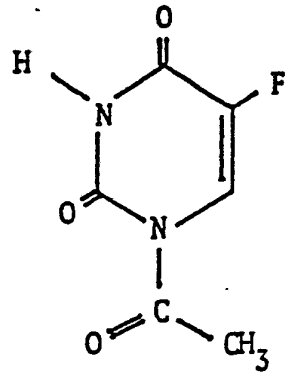
13. A method according to claim 12, wherein R3 is CH_3 or C_2H_5.

14. A method according to claim 12, wherein R_4 is C_2H_5.

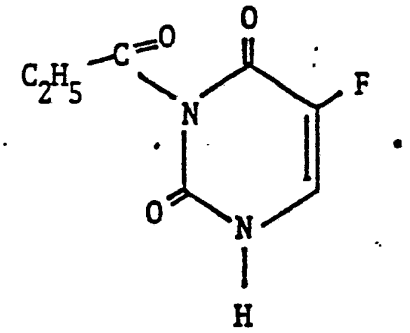
15. A method according to claim 11, wherein one of said R_1 and R_2 is H.

16. A method according to claim 11, wherein neither of said R_1 and R_2 is H.

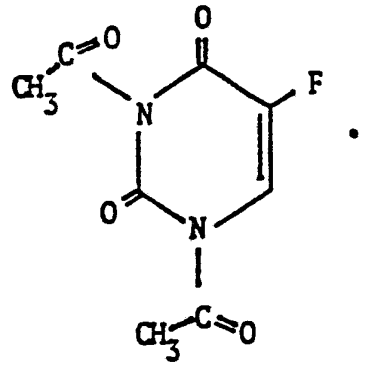
17. A method according to claim 11, wherein said prodrug of 5-fluorouracil has the formula:



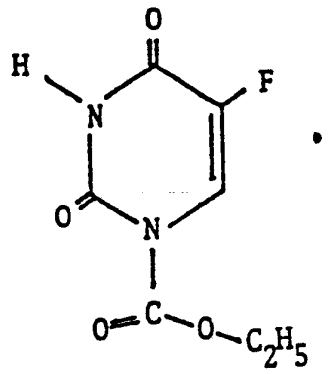
18. A method according to claim 11, wherein said prodrug of 5-fluorouracil has the formula:



19. A method according to claim 11, wherein said prodrug of 5-fluorouracil has the formula:



20. A method according to claim 11, wherein said prodrug of 5-fluorouracil has the formula:



INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/02503

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 31/505
US CL : 514/274

II. FIELDS SEARCHED

Minimum Documentation Searched[4]

Classification System	Classification Symbols
U.S.	514/274

Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched[5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[14]

Category*	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No.[18]
Y	US, A, 4,845,081 (SLOAN) 04 July 1989, see entire document.	1-20
Y	International Journal of Pharmaceutics vol. 21, issued 1984, (ANDERS BURR ET AL.), "Prodrugs of 5-Fluorouracil. I Hydrocysis Kinetics and Physiochemical Properties of Various N-Acyl Derivatives of 5-Fluorouracil", pages 349-364, see entire document.	1-20

* Special categories of cited documents:[15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search[2]	Date of Mailing of this International Search Report[2]
30 JUNE 1992	04 AUG 1992
International Searching Authority[1]	Signature of Authorized Officer[19]
ISA/US	LEONARD SCHENKMAN 7/21/92 A.P.P.