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A topological study of prodrugs of 5-fluorouracil

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Abstract

Various physicochemical properties are correlated with the first-order connectivity index for a series of prodrug derivatives of 5-fluorouracil. Partition coefficient data available in the literature were complemented by calculated log *P* values using the CLOGP program. The first-order connectivity index correlated quite well with the experimental log *P* values ($n = 16$) while the correlation with ClogP improved with the removal of compounds VI, VII and XVII. A molecular modelling study provided data for the molecular area and volume of all prodrugs studied. The regression equations obtained showed that there was good correlation between the topological index and the molecular area and volume. The connectivity index is an adequate topological descriptor. The first-order valence index was preferred over that of order two. Comparison of ClogP values provides group contribution values while the comparison of molecular volume data provides information on the volumes of individual substituents relative to that of hydrogen.

Keywords: 5-Fluorouracil (5-FU); Prodrugs; Connectivity index; Partition coefficient; Molecular area; Molecular volume

1. Introduction

5-Fluorouracil (5-FU) (Fig. 1) ($R_1 = R_2 = H$), is a fluorinated pyrimidine antimetabolite that functions as an antineoplastic agent (Saad and Hoff, 2001). It has been used in the treatment of certain skin diseases. However, because of its low lipophilicity, it does not produce optimal topical bioavailability. Research has focussed on the development of transient chemical modifications of 5-FU that show increased lipophilicity. *N*-Acyloxyalkylation of NH-acidic compounds such as carboxamides, carbamates, ureas, imides and other amide-type structures has generally been considered as a useful approach to obtain prodrug forms of such agents since *N*-acyloxyalkyl derivatives combine a high in vitro stability with enzymatic lability (Bundgaard and Nielsen, 1987). *N*-1-Acyloxymethyl derivatives were shown to penetrate the skin about five times faster than the parent compound and to be metabolised rapidly (Møllgaard et al., 1982). The hydrolysis kinetics and physicochemical properties of a series of bioactive derivatives of 5-fluorouracil have been studied (Buur and Bundgaard, 1984; Buur et al., 1985). The structure and hydrolysis kinetics of *N*-acyl derivatives has also been studied (Buur and Bundgaard, 1984; Beall et al., 1993). N_1-Dea-

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cylation proceeds much faster than N_3-deacylation and shows a pH-dependence that could be ascribed to the water-catalysed and hydroxide-ion-catalysed reactions. The pH-rate profiles obtained for N_3-deacylation were accounted for in terms of spontaneous and hydroxide-ion-catalysed hydrolysis of undissociated N_3-acyl derivatives as well as the hydroxide-ion-catalysed hydrolysis of the anionic derivatives (Buur and Bundgaard, 1984). The physicochemical properties of 1-alkoxycarbonyl derivatives have also been studied (Buur and Bundgaard, 1986, 1987). The antitumour activity of some derivatives has been examined (Marchal et al., 1999; Ozaki et al., 1997; Nakanishi et al., 1999) along with the degree of their incorporation into liposomes (Sasaki et al., 1987; Gulati et al., 1998; Jee et al., 1995).

Calculative procedures have been developed to allow a proper quantification of drug lipophilicity (Kristl et al., 1999; Mannhold and Rekker, 2000; Leo and Hoekman, 2000). The log $P_{oct/water}$ values are calculated using the CLOGP program (Chou and Jurs, 1980; Mannhold et al., 1990). Along with these parameters, the topological index developed by Kier and Hall is also calculated (Kier and Hall, 1976; Kier, 1980). The connectivity index has been employed in many structure–activity studies (Basak et al., 1984; Casaban-Ros et al., 1999; de Gregorio et al., 1998; Gough and Hall, 1999; Kier and Hall, 1993; Rouvray, 1986; Shapiro and Guggenheim, 1998). These parameters are correlated with the molecular area and volume calculations.

A relatively simple formalism such as molecular connectivity is able to easily and quickly characterise molecular structures. Each molecule is assimilated to a graph, where atoms are represented by points called vertices and bonds are represented by edges between vertices. These indices can be correlated with many physical, chemical and biological properties of molecules. Their use in the prediction of diverse physical, chemical and biological properties of various types of compounds have been shown. This paper will examine the structure–property relationships, taking a range of 5-fluorouracil derivatives as a model set of compounds. New lead drugs have been obtained using this method (Gálvez et al., 1995; García-Domenech et al., 1997; Pastor et al., 1999). The chemical structures of the 5-fluorouracil derivatives under investigation are listed in Table 1, while the values of δ^v applicable to the ring system of 5-fluorouracil are given in Table 2. The vertex valence value for fluorine is listed as $(-)7$ with an understanding that the subgraph term for a C–F bond is subtracted in computing the valence indices (Kier and Hall, 1976).

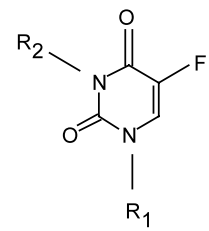

Fig. 1. Prodrugs of 5-fluorouracil (5-FU).

Table 1
Chemical structure of 5-fluorouracil and various derivatives investigated

Compound	R_1	R_2
I (5-FU)	H	H
II	CH_3COOCH_2	H
III	$C_2H_5COOCH_2$	H
IV	$CH_3(CH_2)_2COOCH_2$	H
V	$(CH_3)_3CCOOCH_2$	H
VI	CH_3COOCH_2	CH_3COOCH_2
VII	$(CH_3)_3CCOOCH_2$	$(CH_3)_3CCOOCH_2$
VIII	H	CH_3COOCH_2
IX	H	CH_3CO
X	H	C_2H_5CO
XI	H	C_6H_5CO
XII	CH_3CO	H
XIII	C_2H_5CO	H
XIV	C_6H_5CO	H
XV	CH_3CO	CH_3CO
XVI	C_2H_5CO	C_2H_5CO
XVII	C_6H_5CO	C_6H_5CO
XVIII	CH_3OCO	H
XIX	C_2H_5OCO	H
XX	$(CH_3)_2CHOCO$	H
XXI	$(CH_3)_3CCOCO$	H
XXII	CH_3HNCO	H
XXIII	$(CH_3)_2NCO$	H

The overall structure is shown in Fig. 1.

Table 2
Values of δ^v for various groups

Group	δ^v
=O	6
–O–	6
–N(–)H	4
–N(–)(–)	5
–F	(–)7
(–)(–)C^1=C^2(H)(–)	4 (C1); 3 (C2)
(–)(–)C=C(–)(–)	4

2. Materials and methods

2.1. The connectivity index

Connectivity indices may be derived from the adjacency matrix and are defined as:

$$^m\chi_t = \sum_{j=1}^{N_m} {}^mS_j \quad (1)$$

where m is the subgraph order (i.e. the number of edges or bonds in the subgraph) and N is the number of subgraphs of type t. For $m \leq 2$, all subgraphs are of the *path* type (i.e. all subgraph valencies are not greater than 2 and the subscript t in the above equation is superfluous. ^mS_j is a factor defined for each subgraph as

$$^mS_j = \prod_{i=1}^{m+1} (\delta_i\ \delta_j)^{-1/2} \quad (2)$$

where j denotes the particular set of edges (bonds) that constitutes the subgraph and δ_i is the valence of each vertex within the subgraph. In this work we calculate both the first- and second-order indices ($m = 1$ and 2). The valence values are used for heteroatoms and the vertex valencies are assigned as follows:

$$\delta_i^v = Z^v - h_i \quad (3)$$

where Z^v is the number of valence electrons and h_i is the number of hydrogen atoms attached to the heteroatom.

The first-order index is thus defined as

$$^1\chi^v = \sum_{i,j} (\delta_i\delta_j)^{-1/2} \quad (4)$$

where atoms (vertices) i and j are joined.

The second-order index is defined as

$$^2\chi^v = \sum_{s=1}^{N_m} \sum_{i,j,k} (\delta_i\delta_j\delta_k)^{-1/2} \quad (5)$$

where N_m is the number of subgraphs with two adjacent edges (bonds) and s identifies the particular subgraph.

2.2. Molecular area and volume

The molecular modelling was carried out using SPARTAN (www.wavefun.com). The calculations involved geometry optimisation using semi-empirical methods with minimum neglect of differential overlap (MNDO).

2.3. ClogP calculations

The ClogP calculations were carried out using the CLOGP program (www.biobyte.com) by inputting the SMILES notation for a particular compound.

3. Results and discussion

Acyloxymethyl derivatives are more lipophilic than the parent compound and prodrugs substituted at either (II–V, VIII) or both (VI, VII) nitrogen atoms were studied. These compounds undergo hydrolysis to 5-fluorouracil via the *N*-hydroxyalkyl compound.

N-Acylation of amide or imide-type compounds may be a useful prodrug approach. N_1-Acyl (XII–XIV), N_3-acyl (IX–XI) and N_1,N_3-diacyl derivatives (XV–XVII) were also studied. N_1-Acyl compounds proved to be extremely unstable while the N_3-acyl compounds were promising prodrug forms of 5-fluorouracil (Buur and Bundgaard, 1984; Beall et al., 1993). A series of four 1-alkoxycarbonyl derivatives (Buur and Bundgaard, 1986, 1987), XVIII–XXI, were included in the study along with the two carbamoyl derivatives (Buur et al., 1985), XXII and XXIII. The *N*,*N*-dimethylcarbamoyl derivative (XXIII) proved to be highly stable.

The first-order connectivity index (Eq. (4)) is calculated for the complete set of prodrugs while

the second-order index (Eq. (5)) is calculated for compounds I–X (Table 3). In all cases the values of $^{1}\chi^{v}$ are greater than those of $^{2}\chi^{v}$.

Linear regression studies were carried out with the parameters under study (Table 3). The log P values determined by Buur and Bundgaard (1987), the calculated ClogP values, the connectivity data and the calculated molecular area and volume are included in Table 3.

The values of log P determined at physiological pH are lower than those obtained at low pH due to the effects of ionisation. This is described by the following equation:

$$\log P_{app} = \log P + \log\left(\frac{a_H}{a_H + K_a}\right) \quad (6)$$

Since P and P_{app} are related via the term α, the degree of ionisation

$$P = P_{app}(1-\alpha)^{-1} \quad (7)$$

and hence

$$\log P_{app} = \log P + \log(1-\alpha) \quad (8)$$

where

$$\alpha = (10^{pK_a - pH} + 1)^{-1} = \left(\frac{K_a}{a_H + K_a}\right) \quad (9)$$

for a weak acid. These equations are consistent with Eq. (6) above. For $pH < pK_a - 2$, $\alpha \sim 0$ and for $pH > pK_a + 2$, $\alpha \sim 1$.

From the above equations

$$\log P_{app} = \log P - \log(10^{pH-pK_a} + 1) \quad (10)$$

The values of log P_{app} are plotted against pH for compounds II and XIX (Fig. 2). These data are calculated using Eq. (10) from the log P and pK_a values quoted by Buur and Bundgaard (1987) and Buur et al. (1985). The pK_a values cited for II and XIX are 7.3 and 6.9, respectively. At low pH,

Table 3
Connectivity indices, molecular areas and volumes, and partition data for a series of prodrugs of 5-FU

Compound	log P [a]	ClogP	Δ [b]	$^{1}\chi^{v}$	$^{2}\chi^{v}$	Area (Å^2)	Volume (Å^3)
I (5-FU)	−0.83	−0.973 [c]	0.143	1.797	1.013	145.0	125.3
II	−0.67	−0.262	0.408	3.253	2.064	227.6	204.2
III	−0.11	0.267	0.377	3.814	2.298	250.1	225.0
IV	0.47	0.796	0.326	4.314	2.694	273.2	245.9
V	0.90	0.975	0.075	4.503	2.610	290.2	265.7
VI	−0.37	−1.727	1.357	4.713	3.085	310.1	282.7
VII	2.54	0.747	1.793	7.213	4.177	453.7	405.7
VIII	−0.42	−0.448 [c]	0.028	3.257	1.888	226.1	203.8
IX	−0.34	−0.337	0.003	2.672	1.550	192.4	171.7
X	0.19	0.192	0.002	3.232	1.778	216.3	192.5
XI	0.80	0.402	0.398	4.332		255.9	240.1
XII		−1.299		2.667		188.0	170.4
XIII		−0.770		3.228		210.0	186.1
XIV		0.136		4.328		257.8	240.3
XV		−0.852		3.542		242.4	218.3
XVI		0.206		4.664		288.5	260.0
XVII		2.684		6.864		386.6	355.0
XVIII	−0.68 [d]	−0.677	0.003	2.780		201.9	181.8
XIX	−0.17 [d]	−0.148	0.022	3.367		229.7	204.0
XX	0.20 [d]	0.161	0.039	3.762		253.0	225.0
XXI		0.560		4.076		270.4	245.2
XXII	−0.20	−0.099	0.101	2.917		211.0	187.2
XXIII	−0.37	−0.371	0.001	3.286		230.5	207.9

[a] Buur et al. (1985).
[b] $\Delta = |(\log P - \text{ClogP})|$.
[c] ClogP = −0.819 (I) and 0.243 (VIII) (from www.daylight.com/daycgi/clogp).
[d] Buur and Bundgaard (1987).

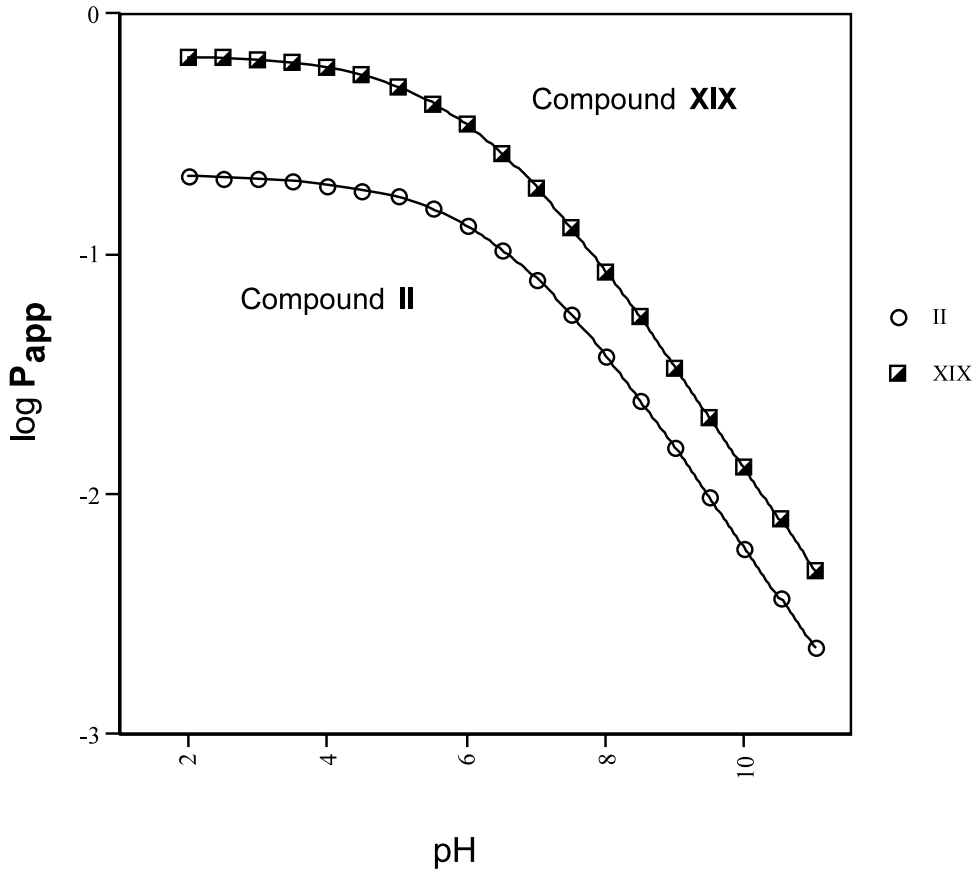

Fig. 2. The variation of log P_{app} with pH for compounds II and XIX.

the log P_{app} values are virtually invariant, but decrease monotonically with increasing pH at higher pH. This is due to the increasing ionisation of the molecule (i.e. increasing α). As α approaches 0, log P_{app} approaches log P asymptotically (Eq. (8) and Fig. 2). From the log P value (-0.17) of compound XIX, log P_{app} at pH 7.4 is -0.79 (Eq. (10)), which is identical to the literature value (Buur and Bundgaard, 1987). Fig. 2 illustrates the dramatic decrease in log P_{app} with increasing pH for both the N_1-acetoxymethyl and the N_1-acetoxycarbonyl derivatives. At any given pH, the latter is more lipophilic.

Compounds VI and VII are much more lipophilic (Buur et al., 1985) than the predictions obtained using CLOGP would suggest. The calculated values are lower (higher hydrophobicity) than the observed values and the Δ values are 1.36 and 1.79, respectively. These prodrugs are *N*-acyloxymethyl derivatives substituted at both nitrogen atoms. The agreement is reasonable for all other prodrugs studied. The 1,3-bis(pivaloyloxymethyl) derivative (VII) is more lipophilic than compound VI due to the presence of the *t*-butyl substituents.

The values of log P for compounds I–X were correlated with both the first-order ($^1\chi^v$) and second-order ($^2\chi^v$) connectivity indices. The correlation coefficient was higher in the case of the former (0.88) and all further calculations were carried out using the first-order index. In the case of other properties (calculated molecular area and volume), this index was the preferred one.

The first-order index was correlated with the experimental values of log P where these are available ($n = 16$), as shown in Fig. 3. The regression equation obtained is:

$$\log P = 0.613\ (^1\chi^v) - 2.209$$

$$(n = 16;\ s = 0.40;\ r = 0.89)$$

The calculated values of log P (ClogP) were also correlated with the connectivity index (Fig. 4). The regression equation obtained is:

$$\text{ClogP} = 0.490\ (^1\chi^v) - 1.924$$

$$(n = 23;\ s = 0.68;\ r = 0.68)$$

Evidently there is some scatter in the ClogP versus connectivity index graph. In the ClogP–$^1\chi^v$ plot, compounds VI, VII and XVII may be regarded as outliers. Compounds VI and VII are the only disubstituted *N*-acyloxymethyl derivatives in the series and, as mentioned above, exhibit relatively large Δ values. The correlation coefficient is 0.79 when these three derivatives are removed from the series.

If the N_1 or N_3-substituents introduced into 5-fluorouracil are relatively non-lipophilic, the net result may be a decrease in the octanol–water partition coefficient. The ClogP value of the 1,3-bis(acetoxymethyl)-5-fluorouracil derivative (VI)

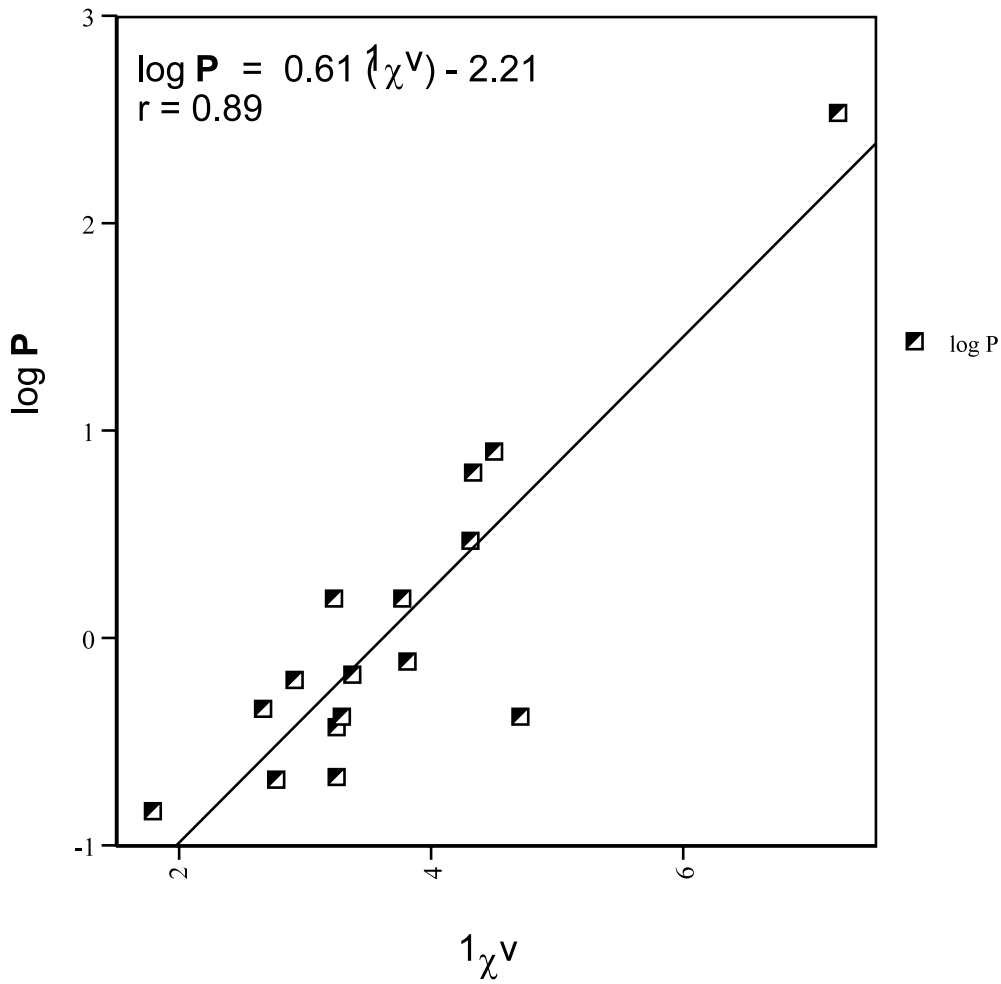

Fig. 3. A plot of experimental log P values vs. ($^1\chi^v$) for prodrugs of 5-fluorouracil.

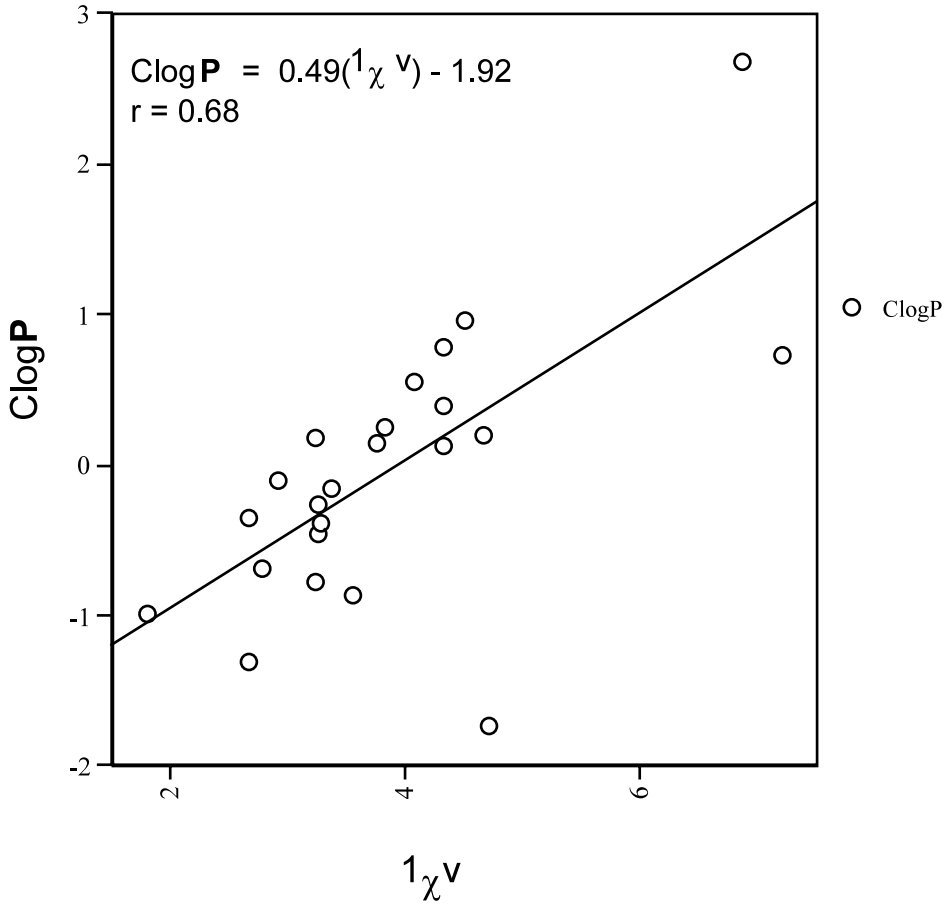

Fig. 4. A plot of ClogP values vs. ($^1\chi^v$) for all derivatives of 5-fluorouracil.

is rather low (Fig. 4 and Table 3). The N_1,N_3-diacylated derivative (compound XVIII) exhibited a more positive ClogP value, presumably due to the presence of the phenyl ring system. Derivatives VI and XVII show large deviations of ClogP from the regression equation. The ClogP value increases dramatically as the size of the substituent increases (compounds XV–XVII). This is also observed for monoacylated compounds (IX–XIV). The N_3-monoacyl derivatives are weak acids due to the dissociation of the N_1-hydrogen atom, the pK_a values being about 7. The pK_a values for 5-FU are 8.0 (N_1–H) and about 13 (N_3–H), indicating the better leaving ability of the N_1-anion. Thus, the N_3-acyl derivatives are more hydrolytically stable. However, the N_3–H group in 1-acetyloxymethyl-5-FU (II) exhibited a pK_a of 7.3 (Buur et al., 1985), whereas the corresponding 3-derivative (VIII) exhibited a pK_a value of 8.0 (Buur et al., 1985) for the N_1–H group. Thus, the N_3-anion is more stable. The 3-acyl-5-FU derivatives hydrolyse more slowly than the 1-acyl-5-FU derivatives as the 3-acyl group is perpendicular to and the 1-acyl group is coplanar with the 5-FU ring (Buur and Bundgaard, 1984). The N_3-monoacylated prodrugs (IX–XI) are more lipophilic than the corresponding N_1-monoacylated compounds (XII–XIV), based on ClogP data. All acylated derivatives (IX–XVII) are more lipophilic than the parent 5-FU.

The group contributions for both methyl and methylene groups may be ascertained by compar-

ing the calculated log *P* values (ClogP). By comparing the pairs II and III, III and IV, IX and X and XVIII and XIX, the contribution of the methylene group is invariant at 0.53, i.e. ΔClogP (CH_2) = 0.53. The value of ΔClogP for the pair XV and XVI is 1.058 representing the two methylene groups. The value per methylene moiety (0.53) agrees with the value quoted. Similarly, the contribution of a methyl group is found to be 0.62 (by comparing couples VI/VII and II/V). The acyloxycarbonyl derivatives (XVIII–XXI) show an increase in the ClogP value as the size of the acyl group increases. The increase on going from the 1-methoxycarbonyl derivative to the 1-ethyloxycarbonyl derivative amounts to 0.53, which agrees with the π value of 0.5 for the methylene group. For this series of prodrugs, the ClogP values agree quite well with available experimental values.

The relatively poor water solubility of uracil is largely due to the high crystal lattice energy in the molecule due to intermolecular hydrogen bonds formed between NH protons in one molecule and a carboxyl group in another molecule. Disruption or decrease of such hydrogen bonding by the replacement of the N1 and/or the N3 protons in uracil by other substituents results in greatly increased solubility. That the melting points play a major role in the relationship between aqueous solubility and octanol–water partition coefficients of crystalline solutes is well recognised. Regression equations have been obtained using these parameters (Buur and Bundgaard, 1984; Buur et al., 1985).

As expected, excellent correlations were obtained when the molecular area and volume were correlated with the connectivity index. The data are shown in Figs. 5 and 6, respectively. The regression equations obtained are as follows:

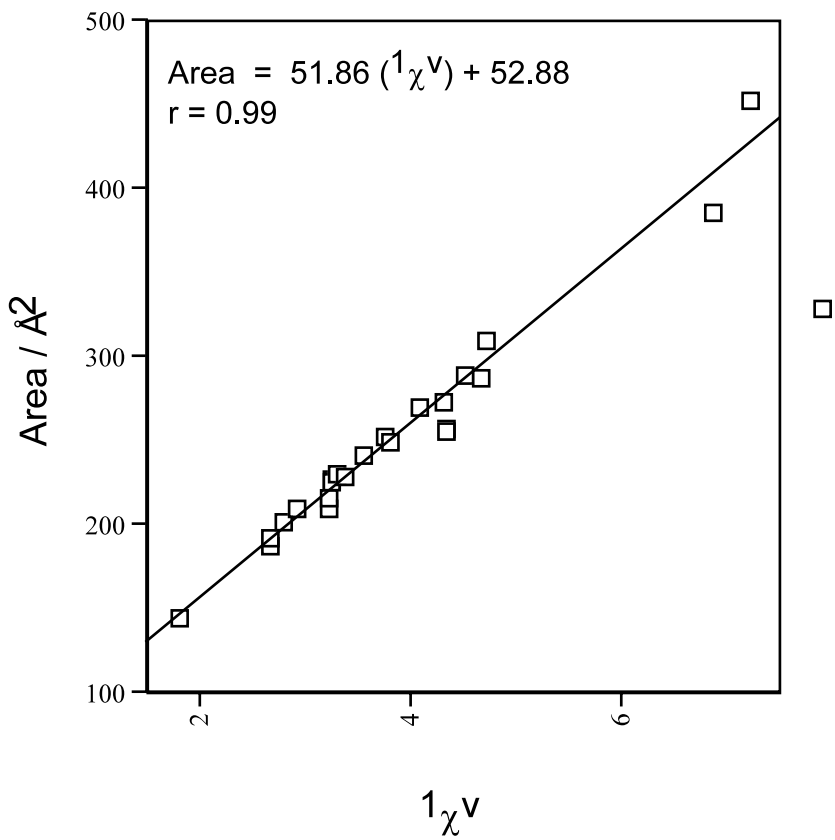

Fig. 5. A plot of the calculated molecular area (Å^2) vs. ($^1\chi^v$) for all derivatives of 5-fluorouracil studied.

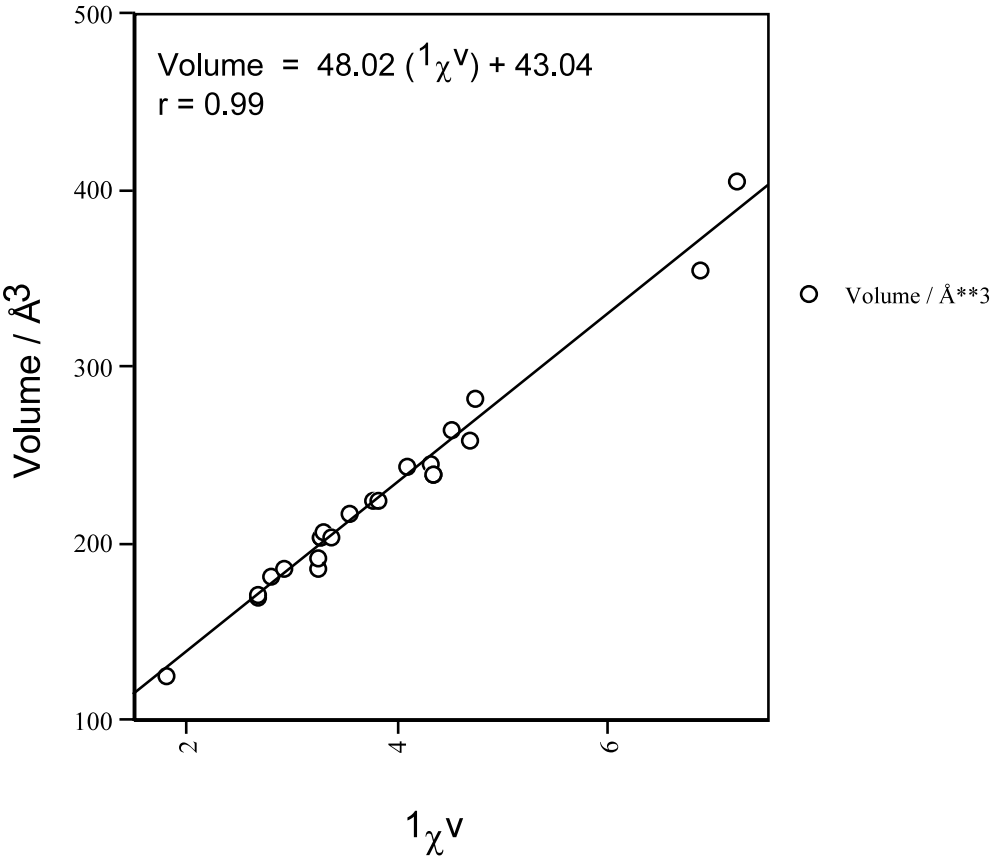

Fig. 6. A plot of the calculated molecular volume (Å^3) vs. ($^1\chi^v$) for all derivatives of 5-fluorouracil studied.

Area = 51.863 ($^1\chi^v$) + 52.875

($n = 23$; $s = 11.35$; $r = 0.99$)

and

Volume = 48.022 ($^1\chi^v$) + 43.037

($n = 23$; $s = 8.44$; $r = 0.99$)

The relationship between the connectivity index and both the molecular area and volume are quite good (Figs. 4 and 5). Apparently, area and volume can be described by this topological index. Within the range under study, this index can be used in a predictive manner.

By calculating the molecular volume of the series of prodrugs it is possible to estimate the volume of individual substituents. Comparing the *N*-acetoxymethyl prodrugs II, VI and VIII with the parent 5-fluorouracil provides an estimate of the volume of the acetoxymethyl substituent relative to a hydrogen atom. The differences in molecular volume are 78.9, 78.5 and 157.4 Å^3 (substitution at both nitrogen atoms), respectively. The agreement is excellent, affording an average value of 78.7 Å^3 for the volume of the acetoxymethyl substituent relative to a hydrogen atom. The increase in volume observed by substituting a hydrogen atom by a pivaloyloxymethyl group may be estimated by comparing compounds V and VII with the parent 5-fluorouracil (I). The increments observed are 140.4 and 280.4 Å^3, respectively. The average value is therefore 140.3 Å^3. The increment in volume observed by substituting a hydrogen atom by an acetyl group is about 46 Å^3, obtained by comparing compounds IX (N_3-acetyl derivative), XII (N_1-acetyl derivative) and XV (N_1,N_3-acetyl derivative) with

the parent 5-fluorouracil (I). The corresponding increment observed by substituting a hydrogen atom by a propionyl group is about 64.5 Å^3, obtained by comparing compounds X, XIII and XVI with the parent compound (I). Similarly, by studying the values for compounds XIV, XI and XVII, the volume of a benzoyl substituent (relative to hydrogen) is 114.8 Å^3.

There is also a high degree of consistency when the volume of a methyl group (relative to hydrogen) is estimated. Examination of the pairs (II and V) and (VI and VII) yields a value of 20.5 Å^3 per methyl substitution. This is consistent with the value of 20.7 Å^3 obtained by comparing the carbamoyl derivatives (XXII and XXIII). A direct estimate of the volume of the methylene group may be obtained by comparing the following pairs: II and III, III and IV, IX and X, XII and XIII, and XV and XVI. The estimated value is 20.8 Å^3.

The regression equations may be used in a predictive manner. Both pentyl-5-fluorouracil-1-acetate [PFA, $R_1 = CH_2CO_2(CH_2)_4CH_3$; $R_2 = H$] and hexyl-5-fluorouracil-1-acetate [HFA, $R_1 = CH_2CO_2(CH_2)_5CH_3$; $R_2 = H$] were synthesised and incorporated into proliposomes (Jee et al., 1995). The first-order connectivity indices of these molecules are 5.31 and 5.81, respectively. The ClogP values determined using the regression equations are 0.68 and 0.92, respectively. The values derived using ClogP deviate to some extent from these results, i.e. 1.70 for PFA and 2.24 for HPA. The molecular area and volume show good agreement between the values predicted from the regression equations and the data from molecular modelling. The regression equations yield 328.4 Å^2 (area) and 298.2 Å^3 (volume) for PFA showing reasonable agreement with the calculated values, i.e. 318.6 Å^2 (area) and 287.7 Å^3 (volume). The corresponding values for HFA are 354.4 Å^2 and 322.2 Å^3 (regression equations) and 341.2 Å^2 and 308.5 Å^3 (calculated values).

4. Conclusions

Molecular connectivity is a useful tool to describe molecular structure and has shown its efficiency to analyse QSAR data (Kier and Hall, 1986, 1993). One of the most interesting advantages of molecular topology is the straightforward calculation of the topological descriptors. In this paper, the correlation between the connectivity index ($^1\chi^v$) and physicochemical properties (lipophilicity, molecular area and volume) has been examined, as applied to prodrugs of 5-fluorouracil. The close correlation of molecular connectivity with partition coefficients demonstrates that these values may reflect the lipophilic character of specific compounds. The relationships with both molecular area and volume would confirm the validity of the connectivity index as a reliable topological descriptor.

The results obtained provide a comparison of ClogP values with the experimental values available in the literature. Large discrepancies between calculated and experimentally determined values have been reported (Kristl et al., 1999). In the present study, a good agreement is observed for the parent compound and all 22 derivatives with the possible exception of the N_1-acetoxymethyl, 1,3-bis-(acetoxymethyl) and 1,3-(pivaloyloxymethyl) derivatives (compounds II, III and VII, respectively).

The good agreement between the values for the molecular area and volume, as calculated using the regression equations, and those measured illustrates the usefulness of the connectivity index as a topological descriptor. Estimates of the volume of both the methyl and methylene substituents have been obtained from the data.

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