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Correlation of drug absorption with molecular charge distribution

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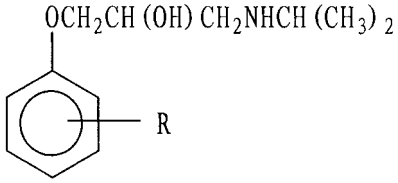
In the selection of orally bioavailable drug candidates it is important to predict the absorption properties of new compounds. Although the drug permeability in Caco-2 cell monolayers is a good predictor of drug absortion in humans for structurally diverse drugs [1], the experimental determination of drug permeability is time-consuming and expensive. Other simpler predictors are needed. The partition coefficient between octanol and water or buffer (pH 7.4) has therefore been used to predict passive drug absorption *in vivo*, but the predictor is valid only for series of homologous compounds and becomes unreliable when structural diversity introduced [2, 3].

In this paper, we are using quantum chemical parameters related with molecular charge distribution to correlate them with drug absorption properties of a series of β-adrenoreceptor antagonists. The molecular charge distributions of the compounds are calculated with the semiempirical self-consistent field molecular orbital calculation CNDO/2 method, using the minimum energy confirmation obtained from the optimization of the standard molecular geometry with the molecular mechanics MM+ method.

Table 1 lists the molecular structures, permeability coefficients in Caco-2 cell monolayers (P_c, cm/s) and appearent permeability coefficients in excised rat intestinal segments (P_{app}, cm/s) of eight β-adrenoreceptor antagonists and their quantum chemical parameters related to molecular charge distribution ($\Sigma Q_{N,O,H}$ and $\Sigma Q'_{N,O,H}$). $\Sigma Q_{N,O,H}$ is the sum of the absolute values of net atomic charges of all hydrogen, nitrogen and oxygen atoms and $\Sigma Q'_{N,O,H}$ is the sum of the absolute of net atomic charges of all nitrogen and oxygen atoms plus the hydrogen atoms attached to them. P_c and P_{app} are taken from literatures [4, 5]. The correlation equations between P_c or P_{app} and these parameters are listed in Table 2.

The equations in Table 2 show that all the permeability coefficients in Caco-2 cell monolayers, excised rat ileum and excised rat colon correlate well with $\Sigma Q_{N,O,H}$ or $\Sigma Q'_{N,O,H}$, much better than with $LogD_{oct,7.4}$ ($D_{oct,7.4}$ is the partition coefficient between octanol and buffer at pH 7.4, $r^2 = 0.725$, 0.728 and 0.659 in Caco-2 cell monolayers, rat ileum and colon, respectively [4, 5]). These facts indicate that the hydrogen bonding interaction is very important when β-adrenoreceptor antagonists are transported across cells, because $\Sigma Q_{N,O,H}$ and $\Sigma Q'_{N,O,H}$ can be considered as the parameters related with hydrogen bonding capacity. This is in accordance with the conclusion of van de Waterbeemd et al. [6], saying that membrane permeability is primarily determined by the hydrogen bonding capacity and the molecular size. Since the β-adrenoreceptor antagonists have similar molecular volumes

Table 1: Quantum chemical parameters and permeability coefficients of β-adrenoreceptor antagonists



				$P_c \times 10^6$ (cm/s)	$P_{app} \times 10^6$ (cm/s)	
Compound	R	$\Sigma Q_{N,O,H}$	$\Sigma Q'_{N,O,H}$	Caco-2 cell	Ileum	Colon
Athenolol	p-CH_2CONH_2	1.7158	1.8274	1.02 ± 0.10	5.0 ± 1.0	1.92 ± 0.20
Practonol	p-$NHCOCH_3$	1.6256	1.6069	3.46 ± 0.53	5.5 ± 1.3	2.44 ± 0.55
Pindolol	2,3-(CH_2=CHNH)	1.0318	1.1587	54.7 ± 0.6	24.9 ± 4.5	34.7 ± 9.7
Metoprolol	p-$CH_2CH_2OCH_3$	0.9072	1.1131	91.9 ± 4.0	40.5 ± 9.8	96 ± 22
Oxprenolol	o-OCH_2CH=CH_2	0.9732	1.1083	119.6 ± 6	50 ± 25	62 ± 17
Alprenolol	o-CH_2CH=CH_2	0.7601	0.8995	242 ± 14	68 ± 11	116 ± 18
H95/71	p-NHCHO	1.3971	1.5238	3.75 ± 0.34		
H244/45	p-$NHCOC_2H_5$	1.4779	1.5412	6.03 ± 0.26		

Table 2: Correlation equations between permeability coefficients of β-adrenoreceptor antagonists and quantum chemical parameters

In Caco-2-cell monolayers				
$LogP_c = -1.778 - 2.398\ \Sigma Q_{N,O,H}$	n = 8	$r^2 = 0.964$	s = 0.182	F = 159
$LogP_c = -1.055 - 2.736\ \Sigma Q'_{N,O,H}$	n = 8	$r^2 = 0.983$	s = 0.123	F = 356
In excised rat ileum				
$LogP_{app} = -3.248 - 1.217\ \Sigma Q_{N,O,H}$	n = 6	$r^2 = 0.974$	s = 0.088	F = 152
$LogP_{app} = -2.923 - 1.395\ \Sigma Q'_{N,O,H}$	n = 6	$r^2 = 0.947$	s = 0.127	F = 71.4
In excised rat colon				
$LogP_{app} = -2.331 - 1.991\ \Sigma Q_{N,O,H}$	n = 6	$r^2 = 0.989$	s = 0.093	F = 365
$LogP_{app} = -1.922 - 2.206\ \Sigma Q'_{N,O,H}$	n = 6	$r^2 = 0.946$	s = 0.208	F = 70.0

n is the number of samples, r is the correlation coefficient, s is the standard deviation, F is the F-statistic

(242–272 Å^3), the hydrogen bonding potential appears to be the only determining factor.

Although the correlations between $LogP_c$ and the quantum chemical parameters are very similar to those between $LogP_{app}$ and the quantum chemical parameters, they are somewhat different. Maybe $\Sigma\ Q'_{N,O,H}$ is the better parameter to predict the cell permeability in Caco-2 cell monolayers and $\Sigma\ Q_{N,O,H}$ is the better one in rat ileum and colon.

Because of their simplicity and excellent correlation with drug absorption, the quantum chemical parameters related to molecular charge distribution can be used to predict drug absorption.

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A new cyclolanostanol arabinoside from the rhizome of *Cimicifuga racemosa*

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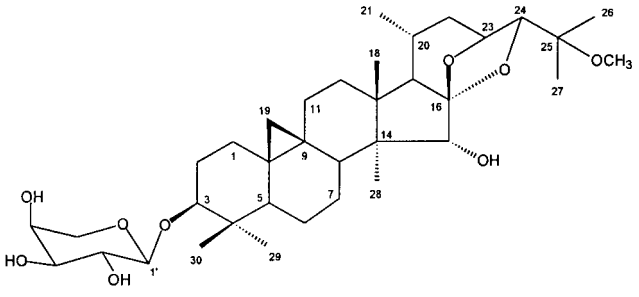
The most popular phytotherapeutic agent used in treatment of menopausal symptoms is the extract of *Cimicifuga racemosa* (L.) Nutt. which has been used in European phytotherapy for over 50 years. During a series of chemical investigations of *Cimicifuga* species, 9,19-cyclolanostane-type triterpenoids [1–3], fukiic and piscidic acid esters [4], and chromones have been isolated [5]. Our previous studies led to the isolation of a number of 9,19-cyclolanostane-type triterpenes from *C. racemosa* [6], and we have developed an analytical method for the separation of the main triterpene glycosides [7]. As a continuation of this work, a new triterpene glycoside has been isolated, 25-*O*-methylcimigenol-3-*O*-α-L-arabinopyranoside (**1**). This paper deals with the isolation and the structural elucidation of **1**.

The IR spectrum of **1** showed a strong hydroxyl absorption band at 3364 cm^{-1}. High resolution electrospray ionization mass spectrometry (HRESIMS) of **1** showed an ion peak for $[M + Na]^+$ at m/z 657.3933, in agreement with the molecular formula $C_{36}H_{58}O_9$. The ^{1}H NMR spectrum of **1** (Table) displayed signals characteristic of cyclopropane-methylene protons as an AX system (δ 0.28, 0.52, J = 3.0 Hz), a methoxy group [δ 3.18 ($OC\underline{H}_3$)], and six tertiary [1.26, 1.24 (×2), 1.17, 1.13 and 1.01] and a secondary methyl (δ 0.83, d, J = 6.4 Hz) group. Additionally, one anomeric proton signal was observed at δ 4.77 (d, J = 6.9 Hz). Thus, compound **1** was considered to be a 9,19-cyclolanostane-type triterpene monoglycoside. The ^{13}C NMR spectrum of **1** exhibited 36 signals. Thirty signals were accounted for the aglycon moiety. The remaining signals were in accordance with the presence of one pentose and one methoxy group. Full assignments of the proton and carbon signals of the aglycone part of **1** were secured by DQF-COSY and HMQC spectra. The carbon resonances attributed to the aglycon moiety supported the presence of 25-*O*-methyl-cimigenol as sapogenol moiety glycosylated at C-3 (δ 88.8 d) [1]. The glycosylation shifts observed for this carbon suggested that **1** was a monodesmosidic saponin. The structure of the sugar moiety was achieved using DQF-COSY and HMQC. The results of the DQF-COSY experiment allowed the sequential assignments of all proton resonances within the sugar resi-



Cimiracemoside B