Communications to the Editor

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THE SUBSTITUENT ENTROPY CONSTANT σ_{s° USED IN THE QSAR INVESTIGATION OF DIHYDROFOLATE REDUCTASE INHIBITION BY BAKER TRIAZINES

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QSAR analysis of dihydrofolate reductase inhibition by Baker triazines — 4,6-diamino-1,2-dihydro-2,2-dimethyl-(x-substitutedphenyl)-s-triazines — was achieved for 21 congeners by the linear combination of the four kinds of parameters $(\sigma_{s^\circ})^2$, σ_{s°, σ_i and σ_π.

The successful result is expressed by the equation,

$$\log(1/C) = -25.29\ (\pm 7.58)(\sigma_{s^\circ})_2^2 + 7.04\ (\pm 2.64)\ \sigma_{s^\circ 3,4} + 3.22\ (\pm 1.68)\ |\sigma_i|_{3,4} + 3.68\ (\pm 3.22)\ |\sigma_\pi|_{3,4} + 6.37$$

$$r = 0.981,\ SE = 0.09,\ F = 103.7^{**}$$

Subscripts 2,3 and 4 denote the positions of the x substituents.

This suggests that a four parameter analysis of this type is the most promising in QSAR analyses.

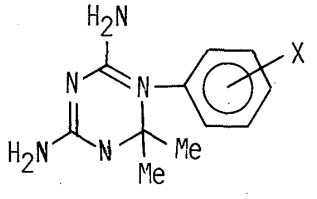
KEYWORDS — substituent entropy constant σ_{s° ; QSAR analyses ; Baker triazines ; dihydrofolate reductase inhibition ;substituent constant ; regression analyses

In a previous report[1] we presented many kinds of the substituent entropy constant σ_{s° and reported that a linear combination of the enthalpy term expressed by the substituent constant σ_i or σ_π[2] and the entropy term expressed by the quadratic equation of σ_{s° is one of the most reliable methods for QSAR analysis of the biological response (BR) of the drug. The general expression is Eq. 1,

$$BR = a\ (\sigma_{s^\circ})^2 + b\ \sigma_{s^\circ} + c\ |\sigma_i| + d\ |\sigma_\pi| + e\ , \qquad (1)$$

where $|\sigma_i|$ and $|\sigma_\pi|$ are orthogonal to σ_{s°, and $a\ (\sigma_{s^\circ})^2 + b\ \sigma_{s^\circ}$ denotes the maximum biological response as given by the entropy term.

This work is concerned with the QSAR of dihydrofolate reductase inhibition by Baker triazines (I). This topic has been investigated recently by Hansch *et al.*[3] and Hopfinger[4], but the parameters used in their regression analysis lack the explicit physical or chemical values of the independent variables.



(I)

The results are as follows.

1. 2-substituted series

n = 9 X = H, F, Cl, Br, I, Me, OMe, 2,4-Cl_2, 2,5-Cl_2

a	b	e	r	F	SE
223.15 (± 205.27)	-52.64 (± 26.96)	+ 6.87	0.949	27.3**	0.13

2. 3- and 4-substituted series

n = 13 X = H, 3-OMe, 3-Ph, 3-NO_2, 3-Cl, 3-CF_3, 3-CH_2Ph, 3-$(CH_2)_2$Ph, 3-$(CH_2)_4$Ph, 3,4-Cl_2, 4-$(CH_2)_2$Ph, 4-$(CH_2)_4$Ph, 4-CH_2Ph

b	c	d	e	r	F	SE
5.56 (± 2.31)	+ 3.18 (± 1.36)	-6.37 (± 2.55)	+ 6.80	0.927	18.3**	0.08

For all 21 congeners ;

a_2	b_2	$b_{3,4}$	$c_{3,4}$
210.57 (± 152.30)	- 50.32 (± 19.16)	+ 5.66 (± 2.39)	- 3.22 (± 1.42)

$d_{3,4}$	e	r	F	SE
-6.34 (± 2.67)	+ 6.77	0.988	125.1**	0.07

	b_2	$b_{3,4}$	$c_{3,4}$
	- 25.29 (± 7.58)	+ 7.04 (± 2.64)	+ 3.68 (± 1.68)

d	e	r	F	SE
-6.03 (± 3.22)	+ 6.37	0.981	103.7	0.09

** : $P < 0.01$ (F test).

This method has the following advantages compared with the regression analysis of Hansch's group and Hopfinger :

1. The number of independent variables is reduced.
2. The physicochemical meaning of the parameter is explicit.
3. The neccesary and sufficient thermodynamic conditions are satisfied.

These advantages indicate the distinctive merit of the method of four parameter analysis including σ_s in the QSAR. Details of this work will be reported in a subsequent paper.

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