Modeling Antileukemic Activity of Carboquinones with Electrotopological State and Chi Indices

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The antileukemic activity (medium effective dose, MED) of a set of 37 carboquinones was modeled using a combination of the electrotopological state (E-state) and molecular connectivity indices with multiple linear regression. A four-variable model gave good statistics: $r^2 = 0.90$, $s = 0.21$. Using the leave-one-out method, the cross-validation statistics indicate a model useful for prediction: $r^2_{press} = 0.85$, $s_{press} = 0.26$. The same variables were used to model the optimum effective dose (OD): $r^2 = 0.88$, $s = 0.19$. The cross-validation statistics indicate a model useful for prediction: $r^2_{press} = 0.83$, $s_{press} = 0.23$. The descriptor variables are interpreted in terms of the molecular structure.

BACKGROUND

It has been shown that QSAR methodology is a successful means for describing the relation of biological activity of drugs to structure information. Models based on structure lend themselves to structure interpretation. These models can be used to suggest effective compounds whose activity can be predicted by the model. It has been further shown that χ and κ shape indices as well as the electrotopological states are effective structure descriptors. Using these structure descriptors we have examined the data set forth by Yoshimoto et al.,[1] the potency against leukemia of a set of carboquinines. Potency measures the dose required to slow the disease process or preserve life for a longer period of time.

In drug research it is beneficial to predict activity of unsynthesized compounds. Quantitative structure−activity relationships (QSAR) have been shown to be a reliable methodology for activity prediction of organic compounds.[2] Numerous QSAR analyses have been published in which various aspects of medicinal potency have been analyzed.[3−6] Specific attention has also been given to structure-toxicity analysis, including the use of topological indices, for various measures of toxicity and for several biological systems in which toxicity is measured.[7−13] The topological indices most widely used for biological properties have been the molecular connectivity χ indices.[14,15]

The electrotopological state (E-state) was introduced in 1990 as a new approach to molecular structure representations.[16] The E-state is a novel combination of electronic and topological information provided at the atom level.[17−24] Most other topological indices, such as χ indices, deal with the whole molecule as a sum over subgraphs of the hydrogen-suppressed molecular graph. In the E-state formalism, an index is computed (as a graph invariant) for each atom in the molecular graph (molecular skeleton or hydrogen suppressed graph). Further, this atom level index combines the electronic state of the bonded atom with its topological nature in the context of the whole molecule. The E-state indices have been used for a variety of QSAR studies.[16,17]

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Table 1. Intrinsic State Values

atom hydride group	intrinsic state	atom hydride group	intrinsic state
>C<	1.250	−SH	3.222
>CH−	1.333	−O−	3.500
$-CH_2-$	1.500	=S	3.667
>C=	1.667	≡CH, $-NH_2$	4.000
−S−	1.833	−Cl	4.111
$-CH_3$, =CH−, >N−	2.000	=NH	5.000
−I	2.120	≡N, −OH	6.000
≡C−, −NH−	2.500	=O	7.000
−Br	2.750	−F	8.000
$=CH_2$, =N−	3.000		

An extension of the E-state indices has recently been introduced, called the atom-type E-state.[14] In this extended approach, each atom in the molecule is assigned a valence-state atom-type by a classification scheme. All atoms of the same type are grouped, and their E-state values summed to make the atom-type E-state index. This atom-type index lends itself to a use which is similar to group additive schemes in which an index appears in a QSAR model for each atom-type in the molecule. For many QSAR cases, only a few atom-type indices may be required for a particular investigation, particularly in biological studies in which only a few atom-types may be required to represent the structure−activity relation. In another approach, for several biological QSARs reported to date, the method of skeletal superposition has also been used so that the individual E-state values for corresponding atoms were entered as variables in regression analysis.[16,17,19−24] We refer to this approach as topological superposition. It is pointed out that no three-dimensional information is required in either approach.

The more recent development of atom-type E-state values provides the basis for application to a wider range of problems to which the E-state formalism is applicable without the need for superposition.[18] The atom-type E-state method combines several aspects of structure representation: (1) encoding electronic and topological structure information, electron accessibility, for each structure feature (atom or hydride group such as −F, =O, $-CH_3$, −OH, etc.); (2) indicating the presence or absence of structure features; and (3) including the count of structure features. For this

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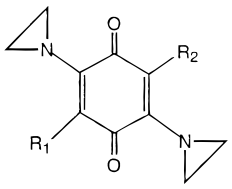
Table 2. Antileukemic Activity as Medium Effective Dose (MED) for Carboquinones



ID	substituents		pMED	calc	res	pres
	R_1	R_2				
1	C_6H_5	CH_5	4.33	4.17	0.16	0.34
2	CH_3	$(CH_2)_3C_6H_5$	4.47	4.73	−0.26	−0.33
3	C_5H_{11}	C_5H_{11}	4.63	4.54	0.09	0.14
4	$CH(CH_3)_2$	$CH(CH_3)_2$	4.77	5.20	−0.43	−0.69
5	CH_3	$CH_2C_6H_5$	4.85	4.96	−0.11	−0.13
6	C_3H_7	C_3H_7	4.92	5.06	−0.14	−0.16
7	CH_3	$CH_2OC_6H_5$	5.15	4.97	0.18	0.21
8	$CH_2OCON(CH_3)_2$	$CH_2OCON(CH_3)_2$	5.16	5.32	−0.16	−0.22
9	C_2H_5	C_2H_5	5.46	5.47	−0.01	−0.01
10	CH_3	$(CH_2)_2OCH_3$	5.57	5.70	−0.13	−0.13
11	CH_3O	CH_3O	5.59	5.76	−0.17	−0.22
12	CH_3	$CH(CH_3)_2$	5.60	5.57	0.03	0.04
13	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	5.63	5.81	−0.18	−0.20
14	CH_3	CH_3	5.66	5.93	−0.27	−0.31
15	H	$CH(CH_3)_2$	5.68	5.56	0.12	0.13
16	CH_3	$CH(OCH_3)C_2H_5$	5.68	5.43	0.25	0.27
17	C_3H_7	CH_2CH_2OCONH	5.68	5.94	−0.26	−0.28
18	$CH_3OC_2H_4$	$CH_3OC_2H_4$	5.69	5.46	0.23	0.25
19	C_2H_5	$(CH_3O)CH_2OCONH_2$	5.76	5.71	0.05	0.05
20	(CH_3)	$(CH_2)_2OCONH_2$	5.78	5.90	−0.12	−0.12
21	CH_3	$(CH_2)_3$DIMER	5.82	5.70	0.12	0.14
22	CH_3	C_2H_5	5.86	5.70	0.16	0.18
23	CH_3	$CH(OC_2HSOCOCH_3)CH_2OCONH_2$	6.03	5.95	0.08	0.09
24	CH_3	$CH_2CH(CH_3)OCONH_2$	6.14	6.04	0.10	0.10
25	C_2H5	$CH(CH_2OCONH_2)OCH_3$	6.16	6.02	0.14	0.15
26	CH_3	$CH(CH_2CH_3)CH_2OCONH_2$	6.18	6.24	−0.06	−0.07
27	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	6.18	5.95	0.23	0.25
28	CH_3	$(CH_2)_3OCONH_2$	6.18	6.22	−0.04	−0.04
29	CH_3	$(CH_2)_2OCONH_2$	6.21	6.38	−0.17	−0.18
30	C_2H_5	$(CH_2)_2OCONH_2$	6.25	6.15	0.10	0.11
31	CH_3	C_2H_5OH	6.39	6.39	−0.00	−0.01
32	CH_3	$CH(CH_3)CH_2OCONH_2$	6.41	6.33	0.08	0.09
33	CH_3	$CH(OCH_3)CH_2OCONH_2$	6.41	6.26	0.15	0.16
34	H	$N(CH_2)_2$	6.45	6.66	−0.21	−0.25
35	$(CH_2)_2OH$	$(CH_2)_2OH$	6.54	6.84	−0.30	−0.36
36	CH_3	$N(CH_2)_2$	6.77	6.67	0.10	0.12
37	CH_3	$CH(OCH_3)CH_2OH$	6.90	6.27	0.63	0.67

reason the E-state method represents a significant advantage over traditional methods.

The E-state index for an atom in a molecule represents the electron accessibility of that atom. It is a combination of electron richness or deficiency together with topological accessibility. The E-state index value for atom i in a molecule is defined as S_i:

$$S_i = I_i + \sum_j \Delta I_{ij} \quad (1)$$

The summation is over all other atoms j within the molecular skeleton.[16,17] The term for perturbation of atom i by atom j is defined as

$$\Delta I_{ij} = (I_i - I_j)/r_{ij}^2 \quad (2)$$

in which the separation, r_{ij}, is given as the number of atoms in the shortest path between atoms i and j. The intrinsic state for an atom is obtained from the ratio of its valence state electronegativity to the number of skeletal bonds, that is, the avenues over which electron density may be distributed. The intrinsic state value, I_i, is given as follows:

$$I_i = ((2/N_i)^2\delta_i^v + 1)/\delta_i \quad (3)$$

where N is the principal quantum number for the valence electrons, δ^v and δ are the molecular connectivity valence and simple delta values which contain counts of the number of σ, π, and lone pair electrons in atom i.[16,17] Intrinsic state values for common groups are given in Table 1. The E-state value for an atom is equal to the intrinsic state value perturbed by all other atoms in the molecule. Atoms with larger I values diminish the E-state value of other atoms; atoms with smaller I values augment the E-state value of other atoms. The development of these relations is given in several references along with illustrations of their computation and use.[17−25]

The E-state indices have been correlated with ^{17}O NMR frequencies[17,19−21] for ethers, aldehydes, and ketones; receptor binding including a series of indolealkylamines binding to

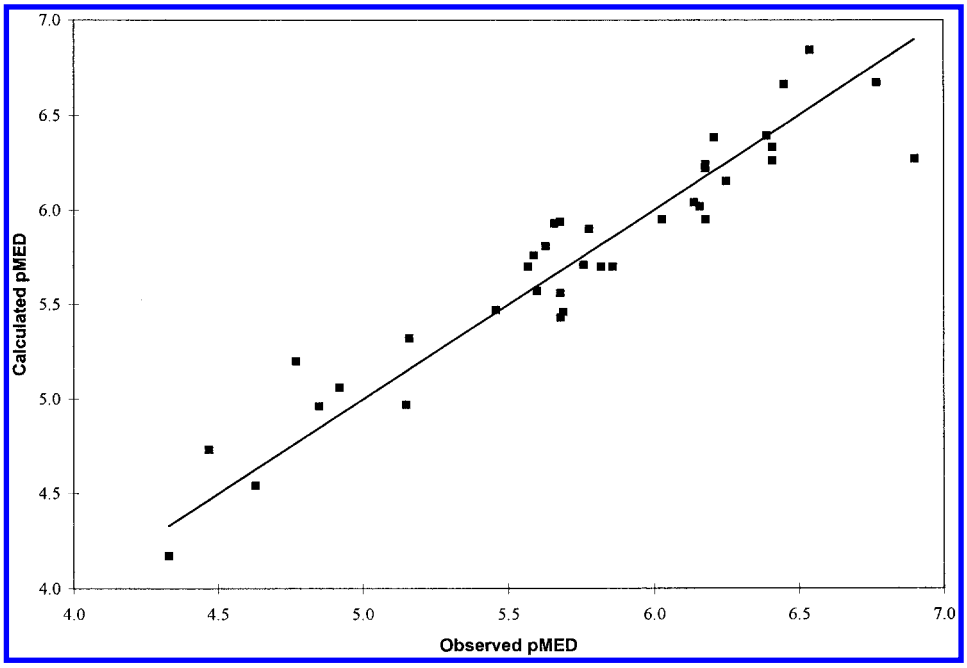


Figure 1. The plot of calculated versus observed pMED (medium effective dose) for 37 carboquinones based on a four-variable model using molecular connectivity χ and E-state variables.

5-HT_2 receptors[17,23] and binding of barbiturates to β-cyclodextrin;[15] receptor binding QSAR including affinity of β-carbolines[18] as well as dopamine D-2 receptor binding of salicylamides;[23] inhibition of flu virus by benzimidazoles[16] and inhibition of MAO by hydrazides[22] with a later comparison to MO parameters;[24] and the binding of corticosteroids.[25]

METHODS AND MATERIALS

The activity (MED and OD data) was obtained from Yoshimoto et al.[1] The values are reported in the form of log [1/(mol/kg)] as shown in Table 1 for the MED data. The MED is a potency measure at the dose that gives a 40% increase in lifespan. The OD is the dose given that produces the longest increase in life.

The molecular structure was represented by a group of topological descriptors. All indices were calculated with the Molconn-Z software package.[26] The indices included electrotopological state, molecular connectivity, and κ shape indices. All statistical analyses were carried out using the SAS System.[27] All structures were entered into a computer data file using the MOLCONN structure format.[26] This form of connection table allows the 14 invariant skeletal atoms to be numbered consistently for all molecules. This numbering scheme has been illustrated in Table 2 for compound no. **13**, showing the atom level E-state values along with the atom-type E-state indices.

RESULTS

The E-state, including hydrogen E-state[16] (both atom level and atom-type),[18] molecular connectivity χ,[14] and κ shape indices[14] (computed by Molconn-Z) were entered into a data matrix and subjected to principal component analysis using SAS. Pairwise correlations were examined for correlation coefficients greater than 0.80. For each such pair one of the variables was eliminated.

The following variables were retained for further analysis:

E-state atom level:	sl, s2, s3, s4, s5, s6, s7, s8, s9, s10, sll, s12, s13, s14

(The symbol s1 refers to the E-state index for atom number 1 as labeled in Table 2.)

hydrogen E-state:	hs1
atom-type E-state:	SsCH3, SssCH2, SsssCH, SdssC, SaaCH, SaasC, SaaaC, SsssN, SsOH, SssO, SdO
molecular connectivity χ:	${}^1\chi^v$, ${}^4\chi^v_{PC}$
κ shape:	${}^2\kappa_\alpha$, ${}^3\kappa_\alpha$

Principal component analysis revealed that eight eigenvectors cover 95% of the data variation, that is, there are eight independent pieces of information among the variables selected above.

Using the RSQUARE option of "proc reg", models were examined for all combinations of one to four variables. There are three atom-type E-state descriptors for aromatic carbon atoms. These structure descriptors appeared, in various combinations, in most of the models with three or four variables. It was decided to create a combination variable, including all three in a new variable Sarom: Sarom = SaaCH + SaasC + SaaaC. The four-variable model with the best statistics was selected for further analysis. The best four-variable model contained two E-state descriptors: SsCH3 and Sarom. These two E-state variables produce the following statistics in a two-variable model:

$$r^2 = 0.70, \quad s = 0.36, \quad r^2_{press} = 0.65, \quad s_{press} = 0.38$$

The statistics are an indication of the useful structure descriptive nature of these variables. A four-variable model for the MED data was chosen based on its regression

statistics as well as its cross-validation statistics:

$$\text{pMED} = -0.208\ (\pm 0.040)^1\chi^v + 2.112\ (\pm 0.289)^4\chi^v_{PC} - 0.338\ (\pm 0.030)\text{SsCH}_3 - 0.128\ (\pm 0.009)\ \text{Sarom} + 5.071\ (\pm 0.436)$$

$$r^2 = 0.90,\quad s = 0.21,\quad n = 37,\quad F = 70,\quad r^2_{press} = 0.85,\quad s_{press} = 0.26 \quad (5)$$

The observed, calculated, and the residual pMED are given in Table 2. The plot of calculated versus observed pMED is shown in Figure 1. A plot of residual versus observed pMED (not sown) shows no trends and appears random.

It is expected that the same variables describe the important structure features in the OD data set. Thus the same variables were used to model the OD data. A statistically sound model was also found. The data set was subjected to statistical analysis to search for a better four-variable model but none was found. The model selected was as follows:

$$\text{pOD} = -0.207\ (\pm 0.035)^1\chi^v + 1.474\ (\pm 0.253)^4\chi^v\text{PC} - 0.264\ (\pm 0.027)\text{SsCH}_3 - 0.097\ (\pm 0.008)\text{Sarom} + 5.401\ (\pm 0.383)$$

$$r^2 = 0.88,\quad s = 0.19,\quad n = 37,\quad F = 61,\quad r^2_{press} = 0.83,\quad s_{press} = 0.23 \quad (6)$$

The observed, calculated, and the residual pOD are in Table 4. The plot of calculated versus observed pOD is shown in Figure 2. A plot of residual versus observed pOD (not sown) shows no trends and appears random.

DISCUSSION

In our proposed model, the structure has been represented by two different types of indices. In this model both the $^4\chi^v_{PC}$ and $^1\chi^v$ variables are molecular connectivity indices. The χ indices are a whole molecule descriptor, a single value computed over the whole molecule to represent the whole molecule. The other two variables, SsCH3 and Sarom, are atom-type E-state indices in which the index reflects structure information for an individual atom (or atom-type) but encoded from all atoms in the molecule.

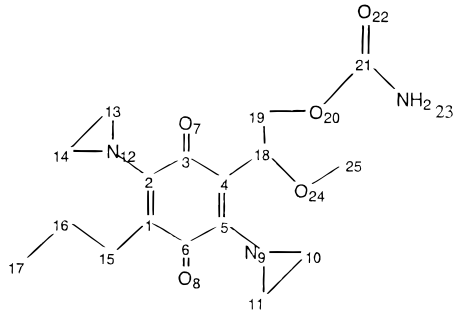
For each variable in the model the fraction contribution to calculated potency is computed from the product of its coefficient times the value of the index for a given molecule. In the MED data set the average percentage for each variable are as follows: $^1\chi^v$, 22.9%; $^4\chi^v_{PC}$, 55.6%; SsCH3, 15.2%; Sarom, 6.34%. For the OD data set the values are $^1\chi^v$, 29.2%; $^4\chi^v_{PC}$, 49.6%; SsCH3, 15.1%; Sarom, 6.13%.

The first order χ valence index is the summation of contributions from all paths of length one edge in the molecular graph. The contribution for each path-one subgraph is based on the local topology and the electronic state (δ^v value) of the two atoms within each path. The index decreases with increased chain branching. The coefficient for the $^1\chi^v$ variable is negative, meaning that as branching increases, activity increases. This index contributes about one-fifth of the calculated potency within the MED data set, ranging from 17 to 29%.

The $^4\chi^v_{PC}$ index is the summation over all subgraphs with an isobutane skeleton. The index increases with increased adjacency (the index is greater for 3,4,5-trimethylheptane than for 2,4,6-trimethylheptane). Since the coefficient for $^4\chi^v$PC is positive, increased adjacency increases activity. The index covers from 45 to 68% of the calculated MED across the data set. As the value of $^4\chi^v$PC increases, the percentage calculated MED also tends to increase. Thus, to design molecules with greater MED activity, molecules should be considered with greater branching and with branch points adjacent.

Both χ indices are of the valence type. For both $^1\chi^v$ and $^4\chi^v_{PC}$ nitrogen and oxygen atoms increase the index value over that for carbon atoms. Hence, in this model adding nitrogen and oxygen tends to increase $^1\chi^v$ but decreases calculated MED, whereas the opposite effect is observed for $^4\chi^v_{PC}$. Since $^4\chi^v_{PC}$ has more than twice the effect in calculating MED, molecules with nitrogen and oxygen

Table 3. The Electrotopological State Indices for Compound Number 13 in Table 2, Along with the Atom-Type Electrotopological State Indices



atom id[a]	atom type	intrinsic values[b]	E-state values[c]
1	dssC	1.667	0.585
2	dssC	1.667	0.480
3	dssC	1.667	−0.206
4	dssC	1.667	0.271
5	dssC	1.667	0.388
6	dssC	1.667	−0.114
7	dO	7.000	13.237
8	dO	7.000	13.130
9	sssN	2.000	1.862
10	ssCH2	1.500	0.726
11	ssCH2	1.500	0.726
12	sssN	2.000	1.907
13	ssCH2	1.500	0.767
14	ssCH2	1.500	0.767
15	ssCH2	1.500	0.566
16	ssCH2	1.500	0.785
17	sCH3	2.000	1.986
18	sssCH	1.333	−0.822
19	ssCH2	1.500	−0.200
20	ssO	3.500	4.834
21	dssC	1.667	−0.945
22	dO	7.000	10.944
23	sNH2	4.000	5.028
24	ssO	3.500	5.379
25	sCH3	2.000	1.419

atom-type E-state symbol[d]	atom-type E-state value	atom-type E-state symbol[d]	atom-type E-state value
SdssC	0.458	SsssN	3.770
SssCH	−0.822	SssNH2	5.028
SssCH2	4.136	SdO	37.312
SsCH3	1.419	SssO	10.213

[a] Atom id is the number of the atom as given in the drawing above. [b] Intrinsic state value for each atom. [c] The electrotopological state value for each atom. [d] Symbol for sum of E-state values for all atoms of the designated type.

Table 4. Antileukemic Activity as Optimum Dose (OD) for Carboquinones

	substituents					
ID	R_1	R_2	pOD	calc	res	pres
1	C_6H_5	C_6H_5	4.14	4.05	0.09	0.20
2	CH_3	$(CH_2)_3C_6H_5$	4.21	4.46	−0.25	−0.31
3	C_5H_{11}	C_5H_{11}	4.52	4.28	0.24	0.39
4	$(CH_3)_2CH_2$	$(CH_3)_2CH_2$	4.49	4.77	−0.28	−0.46
5	CH_3	$CH_2C_6H_5$	4.69	4.69	−0.00	−0.00
6	C_3H_7	C_3H_7	4.44	4.77	−0.33	−0.38
7	CH_3	$CH_2OC_6H_5$	4.71	4.70	0.01	0.01
8	$CH_2OCON(CH_3)_2$	$CH_2OCON(CH_3)_2$	4.85'	4.77	0.08	0.12
9	C_2H_5	C_2H_5	5.09	5.13	−0.04	−0.04
10	CH_3	$(CH_2)_2OCH_3$	5.42	5.31	0.11	0.12
11	CH_3O	CH_3O	5.17	5.44	−0.27	−0.34
12	CH_3	$CH(CH_3)_2$	5.21	5.15	0.06	0.07
13	C_3H_7	$CH(OCH_3)CH_2OCONH_2$	5.07	5.28	−0.21	−0.23
14	CH_3	CH_3	5.36	5.53	−0.17	−0.20
15	HC	$H(CH_3)_2$	5.37	5.22	0.15	0.16
16	CH_3	$CH(OCH_3)C_2H_5$	5.33	5.04	0.29	0.32
17	C_3H_7	CH_2CH_2OCONH	5.23	5.44	−0.21	−0.23
18	$CH_3OC_2H_4$	$CH_3OC_2H_4$	5.31	5.09	0.22	0.25
19	C_2H_5	$CH(CH_3O)CH_2OCONH_2$	5.24	5.20	0.04	0.04
20	(CH_3)	$(CH_2)_2OCONH_2$	5.78	5.43	0.35	0.36
21	CH_3	$(CH_2)_3$DIMER	5.39	5.33	0.06	0.07
22	CH_3	C_2H_5	5.37	5.33	0.04	0.05
23	CH_3	$CH(OC_2H_5OCOCH_3)CH_2OCONH_2$	5.39	5.39	0.00	0.00
24	CH_3	$CH_2CH(CH_3)OCONH_2$	5.79	5.51	0.28	0.29
25	C_2H_5	$CH(CH_2OCONH_2)OCH_3$	5.22	5.46	−0.24	−0.26
26	CH_3	$CH(CH_2CH_3)CH_2OCONH_2$	5.66	5.61	0.05	0.06
27	CH_3	$CH(OC_2H_5)CH_2OCONH_2$	5.22	5.41	−0.19	−0.20
28	CH_3	$(CH_2)_3OCONH_2$	5.93	5.67	0.26	0.27
29	CH_3	$(CH_2)_2OCONH_2$	5.75	5.82	−0.07	−0.07
30	C_2H_5	$(CH_2)_2OCONH_2$	5.48	5.62	−0.14	−0.15
31	CH_3	C_2H_5OH	5.79	5.87	−0.08	−0.09
32	CH_3	$CH(CH_3)CH_2OCONH_2$	5.71	5.71	−0.00	−0.00
33	CH_3	$CH(OCH_3)CH_2OCONH_2$	5.66	5.67	−0.01	−0.01
34	H	$N(CH_2)_2$	6.19	6.11	0.08	0.10
35	$(CH_2)_2OH$	$(CH_2)_2OH$	6.05	6.19	−0.14	−0.17
36	CH_3	$N(CH_2)_2$	6.21	6.04	0.17	0.20
37	CH_3	$CH(OCH_3)CH_2OH$	5.75	5.72	0.03	0.04

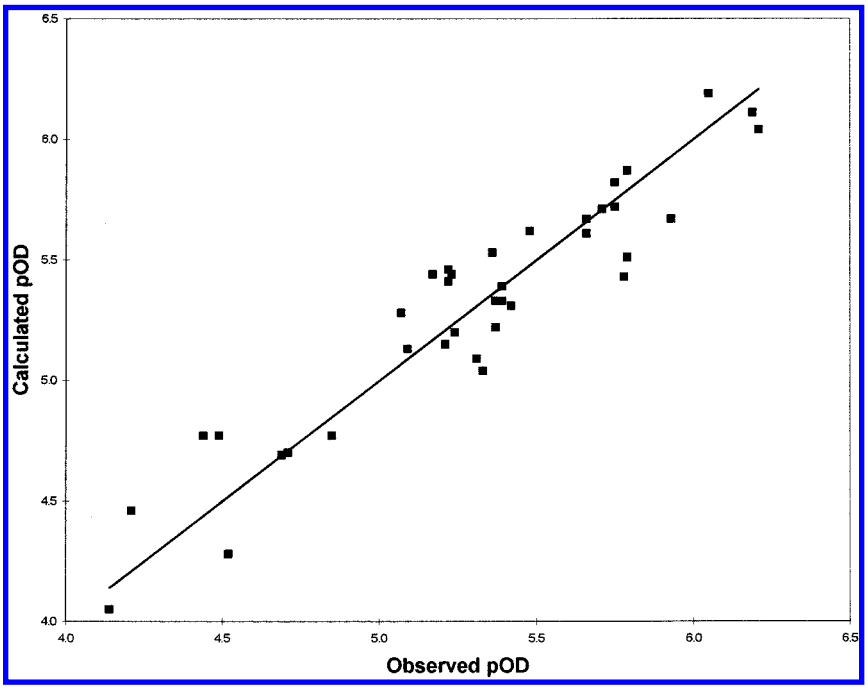


Figure 2. The plot of calculated versus observed pOD (optimum dose) for 37 carboquinones based on a four-variable model using molecular connectivity χ and E-state variables.

heteroatoms may tend to have increased calculated MED values. Designed molecules can be submitted to eq 5 for estimates of MED.

The atom-type E-state index for a structure is the summation of each atom-type E-state over that structure. The value of each index increases as the number of all participat-

ing atoms increase. Because of the negative coefficient for SsCH3, as the presence of methyl groups increases, the activity decreases. It is also important to note that the value of the SsCH3 index is influenced by the atoms surrounding the $-CH_3$ group. Atoms with larger *I* values decrease the SsCH3 and hence tend to increase calculated MED.

The Sarom atom-type E-state also has a negative coefficient. A decrease of this index would lead to an increase in MED activity. A decrease can be obtained by attaching heteroatoms to aromatic carbon atoms. A smaller Sarom can be obtained by attaching groups with larger *I* values, i.e., electron withdrawing groups, such as amines and ethers.

There is much similarity between the MED and OD data and models as reflected in the two models. The structure analysis is essentially the same.

CONCLUSIONS

The models for structure related to potency presented here yield a good statistical account of the data, giving both sound direct statistics as well as the *press* statistics. Further, as a measure of validation, the same variable model was used to predict the OD data for the same compounds. None of the residuals for the MED data are greater than two regression standard deviations, and none of the residuals for the OD data are greater than two standard deviations. Only one predicted residual is greater than two standard deviations, for the MED set, and only one greater than two standard deviations for the OD set. These combined results indicate that these models may be useful for prediction of the potency of antileukemic agents and in the design of new agents. Further the structure features of these molecules are encoded in the four variables included in these models. The nature of these indices may be helpful in the design process. The models presented here should be generally useful for the estimation of MED and OD for similar carboquinones created for antileukemic purposes.

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