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Use of Artificial Intelligence in Structure-Activity Correlations of Anticonvulsant Drugs

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SUMMARY

The Computer-Automated Structure Evaluation Program, a new expert system capable of automatically developing relevant descriptors for structure-activity relationships, has been used to analyze experimental anticonvulsant activity data of a series of 1,3-dihydro-2*H*-1,4-benzodiazepine-2-one derivatives. Some significant correlations are observed between the activity of 99 benzodiazepines against pentylenetetrazole and some relevant molecular fragments identified by the program. The utility of the observed relationships and the predictive power of the method are discussed.

INTRODUCTION

Structure-activity relationships of anticonvulsant drugs have been extensively investigated in the past few years (1–5). Particular attention has been devoted to the 1,4-benzodiazepines which exhibit a wide spectrum of powerful effects on the central nervous system. Included in this series are the clinically useful drugs diazepam, oxazepam, and flurazepam (6). It is well recognized also that 1,4-benzodiazepines possess remarkable activity in the Met[1] test (7, 8), an experimental model of epilepsy that has predictive power for compounds of potential therapeutic value in petit mal (absence) symptom (9). The need for better anticonvulsant drugs in this category makes it desirable to extend our actual knowledge about the structural factors responsible for activity. Unfortunately, not only is the mechanism of anticonvulsant action unknown, but also, a satisfactory correlation between the anti-Met activity of these drugs and molecular structure descriptors has not yet been obtained.

Although molecular orbital theory has been employed with increasing success to assist in the definition of electronic descriptors of drug action, few efforts in this line have involved the anticonvulsant activity of 1,4-benzodiazepines. Recently, a CNDO/2 study of the 1,3-dihydro-5-phenyl-1,4-benzodiazepine-2-ones was reported by Lucek *et al.* (10) in an attempt to correlate the anti-Met activity with lipophilicity and with some electronic molecular indices such as the total electronic charge on atomic centers and the highest occupied and lowest occupied molecular orbital energies. The most significant descriptor appeared to be the electronic density on the p_y orbital of the aromatic carbon adjacent to the amide nitrogen. Another MO study of benzodiazepine derivatives has been reported by Blair and Webb (11). The most relevant finding in their correlations was the negative dependence of anti-Met activity on the total molecular dipole moment. This result appears to be consistent with other studies of miscellaneous compounds (12–14).

Previous correlation between molecular structure and biological activity in this series had been done mainly in qualitative terms (15, 16). Among the few efforts devoted to the search of QSAR involving molecular structure descriptors, mention should be made of the work of Camerman and Camerman (17, 18). In this work, the authors demonstrated that the possession of certain hydrophobic areas and electrophilic functions which occupy relatively similar positions in space, regardless of the gross conformational features of the molecule, was responsible for activity. These observations led the authors to propose that these stereochemical features form the common structural basis for anticonvulsant action, and that any anticonvulsant potential in new compounds, even noncongenerics, might be predictable from this knowledge. However, in a recent review, Jones and Woodbury (19) opposed this point of view and showed that it did not work when it was applied to several other cases involving known anticonvulsant chemicals. These authors went on to state that molecular structure descriptors seem to provide only a very limited amount of information and that they are frequently unsuitable for quantitative correlations. They suggested that the use of physicochemical parameters (mainly electronic molecular indices obtained from quantum chemical calculations) are more desirable for QSAR studies in anticonvulsant chemistry.

It is apparent that such a belief had been prompted mainly by the fact that no method existed that was capable of performing quantitative correlations between molecular structure and biological activity in a large

The abbreviations used are: Met, metrazole (pentylenetetrazole); CASE, computer-assisted structure evaluation; QSAR, quantitative structure-activity relationships.

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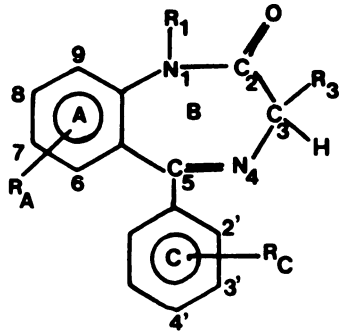
TABLE 1

Structure and experimental anti-Met activities of 1,4-benzodiazepines under study



Compound number	Substituents			Experimental activity[a]
	RA	RB	RC	
1	H	H	H	−0.53
2	7-F	H	H	−0.50
3	7-Cl	H	H	1.65
4	7-Br	H	H	2.22
5	7-CN	H	H	2.30
6	7-NO_2	H	H	2.60
7	7-CF_3	H	H	2.48
8	7-CH_3	H	H	0.16
9	7-$N(CH_3)_2$	H	H	0.84
10	7-SCH_3	H	H	1.15
11	7-SC_2H_5	H	H	0.57
12	7-$SOCH_3$	H	H	1.01
13	7-SO_2CH_3	H	H	−0.28
14	7-Phenyl	H	H	−0.41
15	6-Cl	H	H	0.13
16	8-Cl	H	H	−0.09
17	9-Cl	H	H	−0.47
18	9-NO_2	H	H	−0.46
19	7-NO_2, 9-CH_3	H	H	1.56
20	7,9-Cl	H	H	1.57
21	7,9-CH_3	H	H	−0.48
22	7,8-CH_3	H	H	0.30
23	7-Cl	H	2′-F	3.46
24	7-Cl	H	3′-F	1.86
25	7-Cl	H	4′-F	−0.44
26	7-Cl	H	2′-Cl	2.88
27	7-Cl	H	2′-Br	2.76
28	7-Cl	H	2′-OCH_3	1.60
29	7-Cl	H	4′-OCH_3	−0.43
30	7-Cl	H	2′-CH_3	1.56
31	7-Cl	H	3′-CH_3	0.85
32	7-Br	H	2′-F	2.82
33	7-CN	H	2′-F	2.63
34	7-NO_2	H	2′-F	3.00
35	7-NO_2	H	2′-Cl	3.30
36	7-NO_2	H	2′-CF_3	2.70
37	7-NO_2	H	2′-NO_2	2.97
38	7-NO_2	H	3′-NO_2	0.82
39	7-Cl	H	2′,4′-Cl	−0.37
40	7-NO_2	H	2′-F,3′-NO_2	−0.37
41	7-Cl	1-CH_3	H	2.31
42	7-Cl	1-CH_3	H	2.63
43	7-SCH_3	1-CH_3	H	0.60
44	7-$N(CH_3)_2$	1-CH_3	H	1.69
45	7-Cl	1-CH_3	2′-F	2.88
46	7-Cl	1-CH_3	2′-Cl	3.03
47	7-NO_2	1-CH_3	2′-F	3.50
48	7-NO_2	1-CH_3	2′-Cl	3.92

TABLE 1—*Continued*

Compound number	Substituents			Experimental activity[a]
	RA	RB	RC	
49	7-F	1-CH_3	2′-F	0.27
50	7-$N(CH_3)_2$	1-CH_3	2′-Cl	2.82
51	7-Cl	1-$C2H_5$	H	1.90
52	7-Cl	1-CH_2COCH_3	H	2.28
53	7-Cl	1-$(CH_2)_3N(CH_3)_2$	H	0.38
54	7-Cl	3-CH_3	H	1.15
55	7-Cl	3-OH	H	2.50
56	7-Cl	1-CH_3,3-OH	H	2.63
57	7-NO_2	3-$OCOCH_3$	H	0.36
58	7-NO_2	1-CH_3,3-OH	H	1.93
59	7-Cl	3-CH_2CH_3	H	−0.43
60	7-Cl	3-Phenyl	H	−0.36
61	H	5-C_5H_{11}[b]		−0.44
62	7-Br	5-CH_3		−0.32
63	7-Cl	5-C_4H_3S[c]		0.44
64	H	5-Pyridyl		−0.23
65	7-Br	5-Pyridyl		2.66
66	H	H[d]	H	−0.23
67	7-$N(CH_3)_2$	1-CH_3[d]	H	−0.31
68	7-Cl	H[e]	2′-Cl	1.59
69	7-Cl	1-CH_3[e]	2′-Cl	2.68
70	7-Br	5-Pyridyl[e]	—	0.50
71	7-SC_4H_7	H	H	0.80
72	7-Cl	H	3′-OCH_3	2.16
73	7-CF_3	H	2′-CF	2.00
74	7-CN	1-CH_3	H	2.48
75	7-NO_2	1-CH_3	2′-CF	2.72
76	H	1-CH_3	2′-F	1.52
77	7-Cl	1-$(CH_2)_2CH(CH_3)_2$	H	2.00
78	7-Cl	1-$(CH_2)_3OH$	H	1.36
79	7-Cl	1-$(CH_2)_2N(C_2H_5)_2$	H	2.08
80	7-Cl	1-$(CH_2)_2N(CH_3)_2$	H	1.76
81	7-Cl	1-$(CH_2)_2N(C_2H_5)_2$	2′-F	2.40
82	7-Cl	1-$(CH_2)_3N(CH_3)_2$	2′-F	1.76
83	7-CF_3	1-$(CH_2)_2N(CH_3)_2$	H	1.74
84	7-NO_2	1-$(CH_2)_2N(CH_3)_2$	H	1.68
85	7-NO_2	1-$(CH_2)_3N(CH_3)_2$	H	1.28
86	7-NO_2	1-$(CH_2)_2CH(CH_3)_2$	H	1.84
87	7-NO_2	1-$CH_2CONHCH_3$	H	2.32
88	7-Cl	3-$OCOCH_3$	H	2.64
89	7-Cl	3-NH_2	H	1.12
90	7-Cl	3-CH_2COCH_3	H	0.80
91	7-Cl	1,3-CH_3	H	1.92
92	7-Cl	1-CH_3,3-$OCOH_3$	H	1.04
93	7-Cl	1-$(CH_2)_2N(CH_3)_2$,3-OH	H	1.20
94	7-Cl	1-$(CH_2)_2N(CH_3)_2$,3-$COCH_3$	H	1.36
95	7-Cl	1-$COCH_3$, 3-$OCOCH_3$	H	0.72
96	7-Cl	1-CH_3,3-OCH_3	H	2.32
97	7-NO_2	3-OH	H	2.00
98	7-NO_2	1-CH_3, 3-$OCOCH_3$	H	2.56
99	7-NO_2	1-CH_3, 3-OH	H	1.92

[a] Activity expressed as log $(1/C)$, where C is the dose in millimoles/kg required to suppress completely the seizures induced by administration of 125 mg/kg of metrazole in 50% of the treated animals. For details concerning the biological test see Ref. 18.

[b] C_5H_{11} = cyclohexyl group.

[c] C_4H_3S = 2-thienyl group.

[d] Secondary amine at N-4.

[e] The carbonyl oxygen atom has been replaced by a sulfur atom.

database. To us, this represents a sort of challenge which we would like to take up with our recently developed CASE methodology.

The purpose of this communication is to report the results of the CASE analysis of the anti-Met activity of 99 substituted 1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones. Special attention was devoted to the identification of the most relevant structural features responsible for activity and to the illustration of the reliability of the artificial intelligence procedure for developing automat-

ically the most prevalent molecular structure descriptors for anti-Met activity.

METHODOLOGY

The CASE Program. The CASE program (20, 21) is an expert system capable of reading molecular structure and manipulating it to generate potential descriptors. Elaborate statistical analysis provides decisions as to what factors are relevant to the property being examined and suitable descriptors are then automatically generated. In the current program, these descriptors consist exclusively of molecular fragments of various size and shape similar to those originally proposed by Free and Wilson (22).

Specifically, the method consists of tabulating for each molecule the type of fragments that can be formed by breaking the molecule into structural subunits containing between 3 and 10 heavy atoms together with their attached hydrogen atoms. Each fragment is labeled positive if it belongs to an active molecule and negative if it belongs to an inactive one. The fragments obtained are collected and analyzed statistically. Any significant discrepancy from a random distribution of structural subunits between the active and inactive pool is taken as an indication that the subunit is relevant to the property being examined.

The greatest advantage of this method is that the choice of descriptors, usually painstakingly done by the investigators, is performed automatically here. As a result, this choice is not constrained by prejudices or procedural requirements. Furthermore, the pool of potential descriptors is very large, easily ranging in the thousands for 50–100-compound database. This is clearly out of reach of human evaluation, but it guarantees that no important structural features are overlooked. Once the database has been analyzed, new structures can be submitted and examined for activating/deactivating fragments and the expected activity/inactivity will be then projected. It is also important to note that, with more and more data, the program's accuracy at predictions should increase. It is essentially a "learning" machine.

A basic assumption in the present approach (which is quite a general postulate in most QSAR studies), is that a functional dependence exists between the observed biological data and some relevant structural or electronic properties of the drugs. In our case, this functional form is assumed to be the sum of independent contributions of the most relevant activating/deactivating fragments automatically selected by the program. A term accounting for possible interactions between fragments has not been introduced in the current version of the program, but work is actually in progress in order to include this potentially important term.

The only input needed to generate a database, other than the biological activity, is the chemical structure. This information is entered into the computer using a simple line notation similar to the Wiswesser line notation, but specially adapted to the program for coding a variety of molecular structures rapidly and easily (23).

RESULTS AND DISCUSSION

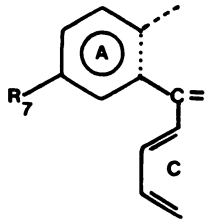
The CASE analysis was performed on a series of 99 substituted 1,3-dihydro-2*H*-1,4-benzodiazepine-2-ones with a variety of substituents at different positions (the general structure is reported at the top of Table 1). The anti-Met activity data are expressed as log $(1/C)$, where C is the dose in millimoles/kg required to suppress completely the seizures induced by administration of 125 mg/kg of pentylenetetrazole in 50% of a sample of mice. These values were obtained from the work developed by Sternbach *et al.* (16) who used the standard protocol proposed by Everett and Richards (24). This database has been analyzed by other procedures in the literature (11, 25) and represents a reliable and uniform set of data suitable for structure-activity analysis.

An important aspect to any structure-activity study concerns the error in the estimates of biological activities. In the present case, we are assuming that, since all drugs were tested by a standard technique, the values obtained were normally distributed and had an equal error. Thus, the variance of the dependent variable is supposed to be the same for any set of independent variables.

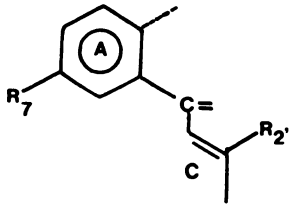
Another factor which is worth emphasizing is that the experimental estimates of potency are based on the amount of drug administered. Such data are usually inaccurate because the influence of absorption, distribution, and elimination precludes a good estimate of the concentration of the drug at the receptor site. However, for the purpose of looking for a qualitative analysis, this *in vivo* model has an acceptable degree of reliability (19).

The first step in our procedure was to code the compounds numbered 1–70 in Table 1 and label them as inactive if $\log(1/C) < 0$, or active if $\log(1/C) > 0$. It is important to emphasize here that, due to the relative nontoxic character of these compounds, high doses were chosen for the screening (16). This is an unusual case and may introduce some arbitrariness in labeling a compound as inactive. However, for the purpose of looking for the structural features that maximize or suppress anti-Met activity, this choice ensures that no essential information is overlooked. As a result, 19 of these compounds were inactive, 10 were marginal, and 41 were active. Only those subunits found in distributions that would be observed with less than 15% probability if their occurrence was random were kept for further analysis. The statistical analysis performed within this confidence level generated 64 activating fragments and five inactivating ones. At this stage, we were interested in identifying those fragments that contain the most fundamental structural features relevant for anti-Met activity. Four subunits were found to be the most relevant for activity: three activating, fragments I—III, and one inactivating, fragment IV. They are explicitly displayed in Fig. 1, together with their distribution and probabilities.

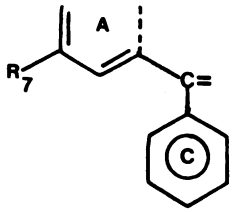
Fragments I and III, which if present cause a compound to be active at almost 100% of confidence, were found to be present in 53 and 31 compounds, respectively. Both fragments essentially exhibit substitution at position 7 of ring A. Fragment II was found to be present in 20 benzodiazepines (of which 1 was inactive, 1 was mar-



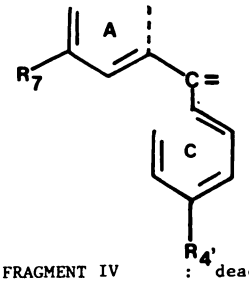
FRAGMENT I : activating
Probability : 100%
Distribution : (6,8,39)



FRAGMENT II : activating
Probability : 100%
Distribution : (1,1,18)



FRAGMENT III : activating
Probability : 100%
Distribution : (6,6,19)



FRAGMENT IV : deactivating
Probability : 87.5%
Distribution : (3,0,0)

FIG. 1. *Structure and statistical data of the most relevant descriptors of anti-Met activity*

Probability values measure the probability that the fragment is causally related to activity. For distribution, the values (*Na*,*Nb*,*Nc*) refer to the number of inactive, marginal, and active compounds, respectively, where the corresponding subunit was found to be present. R = Cl, Br, NO_2, CN, CF_3 $N(CH_3)_2$. R′ = nonhydrogen substituent.

ginal, and 18 were active) and exhibits substitution at position 7 of ring A and at position 2′ of ring C. Finally, fragment IV which occurs in three inactive molecules, presents substitution at position 7 of ring A and at position 4′ of ring C.

It is interesting to note some similarities between the descriptors displayed in Fig. 1. Comparison between fragments I and III leads to the conclusion that substitution at position 7 of ring A is required for anti-Met activity. On the other hand, a comparison between these fragments and subunits II and IV leads to the conclusion that substitution at position 2′ of ring C (*ortho*) has a strong activating effect, while substitution at position 4′ of ring C (*para*) prevents anti-Met activity.

From the above considerations and taking into account the nature of these substituents, we may speculate that the receptor with which these compounds interact must contain at least two active sites: one of them should be suitable for the interaction with electronegative groups at positions 7 and 2′, and one should be a site (probably anionic) suitable for the interaction with a hydrogen atom at position 4′.

Based on these four selected descriptors, a multivariate regression analysis was carried out, and Eq. 1 was obtained

$$\log(1/C) = -0.27 + 0.56n_I(F_I) + 2.36n_{II}(F_{II}) + 0.20n_{III}(F_{III}) - 2.79n_{IV}(f_{IV}) \quad (1)$$

$$R = 0.884; \quad S = 0.97; \quad N = 70$$

where $n_i(F_i)$ is the number of times fragment F_i is present in the molecule considered. Eq. 1 was used to estimate the anti-Met activity of compounds 1–70. The results are displayed in Table 2. It may be seen that the presence of fragments I–III coupled with the absence of fragment IV allowed us to identify correctly 50 of the 51 active or marginally active compounds. The marginal activity of compound 15, a 6-substituted 1,4-benzodiazepine, could not be accounted for on the basis of the structural descriptors considered in the present work. On the other hand, 12 compounds which lack fragments I–III and/or contain fragment IV were correctly identified as inactive molecules. Inactivity of compounds 2, 13, 14, 21, 40, 59, and 60 was not reproduced correctly by regression Eq. 1. The failure to explain inactivity is a common problem inherent in any kind of drug activity regression analysis (11). In our case, it may be due to the fact that the database under analysis is weighted somewhat in favor of active compounds instead of being the ideal 50:50 distribution of actives versus inactives. This problem eventually could be corrected by adding more inactive molecules when these data become available.

If the molecular structure descriptors selected by the CASE program represent a true causal relationship for anti-Met activity, then it should be expected that the correlation with drug activity should remain valid, irrespective of changes in substituents attached to the framework. With this test in mind, Eq. 1 was applied to

TABLE 2

Experimental and estimated anti-Met activities from Eq. 1

Compound number	Presence of selected fragments: Activation I	II	III	Deactivation of IV	Anti-Met[a] activity: Observed	Calculated	p^b
							%
1	0	0	0	0			0.0
2	2	0	2	0		++	99.7
3	2	0	2	0	+++	++	100
4	2	0	2	0	+++	++	100
5	2	0	2	0	+++	++	100
6	2	0	2	0	++++	++	100
7	2	0	2	0	++++	++	97.2
8	2	0	2	0	+	++	100
9	2	0	2	0	++	++	100
10	2	0	2	0	++	++	100
11	2	0	2	0	+	++	100
12	2	0	2	0	++	++	97.2
13	2	0	2	0		++	97.2
14	2	0	2	0		++	99.6
15	0	0	0	0	+		NB[c]
16	0	0	0	0			0.0
17	0	0	0	0			0.0
18	0	0	0	0			0.0
19	0	0	2	0	+++	+	100
20	0	0	2	0	+++	+	99.1
21	0	0	2	0		+	92.1
22	0	0	2	0	+	+	100
23	1	1	0	0	++++	++++	100
24	1	0	0	0	+++	+	100
25	0	0	0	2			0.0
26	1	1	0	0	++++	++++	100
27	1	1	0	0	++++	++++	100
28	1	1	0	0	+++	++++	100
29	0	0	0	2			0.0
30	1	1	0	0	+++	++++	100
31	1	0	0	0	++	+	100
32	1	1	0	0	++++	++++	100
33	1	1	0	0	++++	++++	100
34	1	1	0	0	++++	++++	100
35	1	1	0	0	++++	++++	100
36	1	1	0	0	++++	++++	100
37	1	1	0	0	++++	++++	100
38	1	0	0	0	++	+	100
39	0	1	0	1			0.0
40	1	0	0	0		+	100
41	2	0	2	0	+++	++	100
42	2	0	2	0	++++	++	100
43	2	0	2	0	+	++	100
44	2	0	2	0	+++	++	100
45	1	1	0	0	++++	++++	100
46	1	1	0	0	++++	++++	100
47	1	1	0	0	++++	++++	100
48	1	1	0	0	++++	++++	100
49	1	1	0	0	+	++++	100
50	1	1	0	0	++++	++++	100
51	2	0	2	0	+++	++	100
52	2	0	2	0	+++	++	100
53	2	0	2	0	+	++	100
54	2	0	2	0	++	++	100
55	2	0	2	0	++++	++	100
56	2	0	2	0	++++	++	100
57	2	0	2	0	+	++	100
58	2	0	2	0	+++	++	100
59	2	0	2	0		++	100
60	2	0	2	0		++	0.0[d]
61	0	0	0	0			0.0
62	0	0	0	0			NB[c]
63	1	0	0	0	+	+	100
64	0	0	0	0			0.0
65	1	0	0	0	++++	+	100
66	0	0	0	0			0.0
67	0	0	0	0			0.0
68	1	1	0	0	+++	++++	100
69	1	1	0	0	++++	++++	100
70	1	0	0	0	+	+	100

[a] To express the ranges of activity, the following notation has been adopted: +, marginally active; ++, moderately active; +++, active; ++++, extremely active. A blank means that the compound is inactive.

[b] Overall probability of being active against the Met test, based on fragments with $p < 15\%$ (see the text for further details).

[c] NB, no basis to support activity; the compond is assumed to be inactive.

[d] Although regression Eq. 1 predicts this compound to be moderately active, the probability criterion (based on fragments with $p < 15\%$) predicts this compound to be inactive.

estimate the anti-Met activity of compounds numbered 71–99 in Table 1. Included in this set are compounds with varied substituents at different positions of rings A, B, and C. Again, by using the presence of fragments I–III as an indication of activity and the absence of fragments I–III or the presence of fragment IV as an indication of inactivity, the results displayed in Table 3 were obtained. As can be seen, the activity of all the members of this set were qualitatively accounted for by Eq. 1.

Comparison with previous work in this field may provide elements to judge the quality of the descriptors generated with our artificial intelligence program. Borea *et al.* (25, 26) had analyzed the anti-Met activity of a number of compounds included in our database on the basis of a Hansch-type multiple linear regression. They chose as descriptors the Hansch hydrophobic constant of the substituents, the Hammet constant of the substituents at position 7, the field and steric Taft constants for substituents at position 2′, and an additional descriptor accounting for the presence at position 7 of the substituent $N(CH_3)_2$. They concluded that, in addition to the overall lipophilicity of the molecule, activity was increased by highly electron-withdrawing groups at positions 7 and 2′. These conclusions agreed with previous SAR studies (5, 16). The information contained in our fragment II is also consistent with this conclusion.

Another QSAR study involving a variety of central nervous system activities of 59 benzodiazepines, which are also included in the present database, was performed by Blair and Webb (11). They used as descriptors the net atomic charge on the carbonyl oxygen atom, Qo, and the total molecular dipole moment, u. A poor correlation

TABLE 3

Predicted activities for compounds not included in the regression

Compound number	Presence of selected fragments: Activation I	II	III	Deactivation in IV	Anti-Met[a] activity: Observed	Calculated
71	2	0	2	0	++	++
72	1	0	0	0	+++	+
73	1	1	0	0	+++	++++
74	2	0	2	0	++++	++
75	1	1	0	0	++++	++++
76	1	0	0	0	++	+
77	2	0	2	0	+++	++
78	2	0	2	0	++	++
79	2	0	2	0	+++	++
80	2	0	2	0	+++	++
81	1	1	0	0	++++	++++
82	1	1	0	0	+++	++++
83	2	0	2	0	+++	++
84	2	0	2	0	+++	++
85	2	0	2	0	++	++
86	2	0	2	0	+++	++
87	2	0	2	0	+++	++
88	2	0	2	0	++++	++
89	2	0	2	0	++	++
90	2	0	2	0	++	++
91	2	0	2	0	+++	++
92	2	0	2	0	++	++
93	2	0	2	0	++	++
94	2	0	2	0	++	++
95	2	0	2	0	+	++
96	2	0	2	0	+++	++
97	2	0	2	0	+++	++
98	2	0	2	0	++++	++
99	2	0	2	0	+++	++

[a] Activity ranges are as in Table 2.

between Qo, and the anti-Met activity was observed ($r = 0.4430$), while the molecular dipole moment showed a better correlation ($r = 0.6206$). Consideration of both Qo and u did not change significantly the quality of the regression ($r = 0.6238$). This leads to the conclusion that Qo is probably not related to activity and is consistent with the fact that none of the most relevant fragments selected by the CASE program contained the carbonyl oxygen atom. This may also be an indication that the presence of this group is probably not an essential requirement for anti-Met activity. Blair and Webb also discussed the failure of their method to explain the inactivity of some compounds of these series such as our compound number 25, which could not be explained either on the basis of electronic factors or by geometrical features elucidated by X-ray analysis (27). The inactivity of this compound is accounted for, within the present approach, by the presence of fragment IV, which exhibits an open substitution site at position 4′ of ring C. This *para* substitution on ring C had been found to be responsible for greatly decreasing anti-Met activity in previous structure-activity studies in this series (5, 16).

CONCLUDING REMARKS

The application of our artificial intelligence technique for developing automatically relevant descriptors for structure-activity relationships provides significant semiquantitative correlations as well as reliable predictions for the anti-Met activity within the 1,3-dihydro-2*H*-1,4-benzodiazepine-2-one series. The results obtained show CASE's capabilities for identifying causal features responsible for activity. Comparison with previous work that uses electronic molecular indices for quantitative SAR for these drugs suggests that the reliability of the present methodology for drawing a general strategy in the choice of these independent variables is satisfactory.

One important limitation of the current methodology is that eventual interactions between groups in the molecule (i.e., synergism between fragments) are not explicitly taken into account. For example, a fragment which alone displays a low relevance to activity/inactivity in the presence of another fragment, may exhibit a high degree of causality for activity/inactivity. This synergistic pair should be considered as a potential descriptor. Further developments are actually in progress in our laboratory in order to incorporate this potentially important contribution.

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