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Computer Automated Structure Evaluation (CASE) of the teratogenicity of retinoids with the aid of a novel geometry index

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SUMMARY

The CASE (Computer Automated Structure Evaluation) program, with the aid of a geometry index for discriminating *cis* and *trans* isomers, has been used to study a set of retinoids tested for teratogenicity in hamsters. CASE identified 8 fragments, the most important representing the non-polar terminus of a retinoid with an additional ring system which introduces some rigidity in the isoprenoid side chain. The geometry index helped to identify relevant fragments with an all-*trans* configuration and to distinguish them from irrelevant fragments with other configurations.

INTRODUCTION

Retinoids are compounds which are structurally related to retinol, more commonly known as vitamin A. The basic structure of vitamin A is that of a diterpene with a hydrophobic ring on one end and an isoprenoid side chain containing a polar hydroxyl group on the other. It has long been known that vitamin A has at least three distinct functions in supporting mammalian life, i.e., systemic, optic, and reproductive. Its systemic functions are necessary for general good health and growth, and include the maintenance of epithelial tissues, the nervous system, bone formation, and endocrine functions [1–3]. Vitamin A is also required for the maintenance of vision since it is used in the biosynthesis of the visual pigments. The importance of vitamin A in maintaining fetal growth and development has also been shown in studies with rats [4,5]. These studies show that vitamin A deficiency leads to fetal death.

Retinoic acid, the acid form of vitamin A (Fig. 1), and its esters when included in the diet of rats, can cure the symptoms of vitamin A deficiency relating to its systemic functions, but not its optic and reproductive functions. Indeed, rats fed with this diet grew normally and appeared heal-

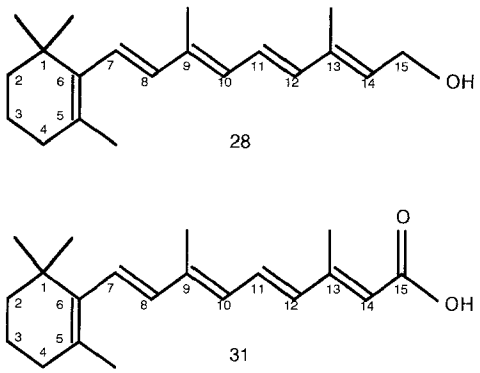


Fig. 1. Retinol and retinoic acid.

thy but they lost their sight [2]. Furthermore, when female rats were given retinoic acid or its methyl ester instead of retinol, they were able to conceive normally but they failed to carry their litters. Hence, the essential role of vitamin A in vision and reproduction was clearly established.

Although retinoic acid and other retinoids are not very useful as vitamin A substitutes in the diet, they have been found to possess therapeutic value in treating dermatologic conditions. Isotretinoin, 13-*cis* retinoic acid (cpd **29**, see Fig. 2), and etretinate (cpd **32**, see Fig. 2), effective agents in treating tough and persistent types of acne, have been approved for use in the U.S. with a warning against use on pregnant women [6]. Nevertheless, since the approval of isotretinoin in September 1982 up to 1984, a total of 35 pregnant women were reported to have used this retinoid. Of these, 29 experienced spontaneous abortion and/or teratogenesis, i.e., congenital malformations [7]. Some of the reported exposures to isotretinoin occurred even before conception. Considering the fact that most adolescent and young adult pregnancies are unplanned [8], the danger of untimely exposure is quite high. In view of this, it is important to determine which structural features in retinoids are related to teratogenicity in the hope of designing a useful retinoid devoid of this side effect.

A number of studies have been made on the relation that may exist between the structure of retinoids and their teratogenic activity. Willhite et al. have published a series of papers specifically dealing with the effects of retinoid structure on teratogenic activity [9–11]. We have used in the past the Computer Automated Structure Evaluation (CASE) methodology to study successfully several databases for structure–activity relationships such as the mutagenicity of non-fused-ring nitroarenes [12], antileukemic activity of 9-anilinoacridines [13], antibacterial activity of quinolones [14], and glyoxalase I inhibition of flavonoids [15], just to mention a few. However, retinoids present an interesting challenge because of the potential importance of cis-trans isomerism. In the past, CASE isolated linear fragments devoid of any geometry. The isoprenoid side chain, with its four double bonds, can have a number of geometrical isomers, all of which are seen as identical by the CASE program. An example of a situation where this could be a problem was found after manual examination of the database used in a CASE analysis of the mutagenicity of a set of mononuclear nitroarenes [12]. In this case, it was found (see Fig. 3) that the fragment

CH=CH–C=C–CH=CH

was randomly distributed among the active and inactive molecules and was thus not believed to

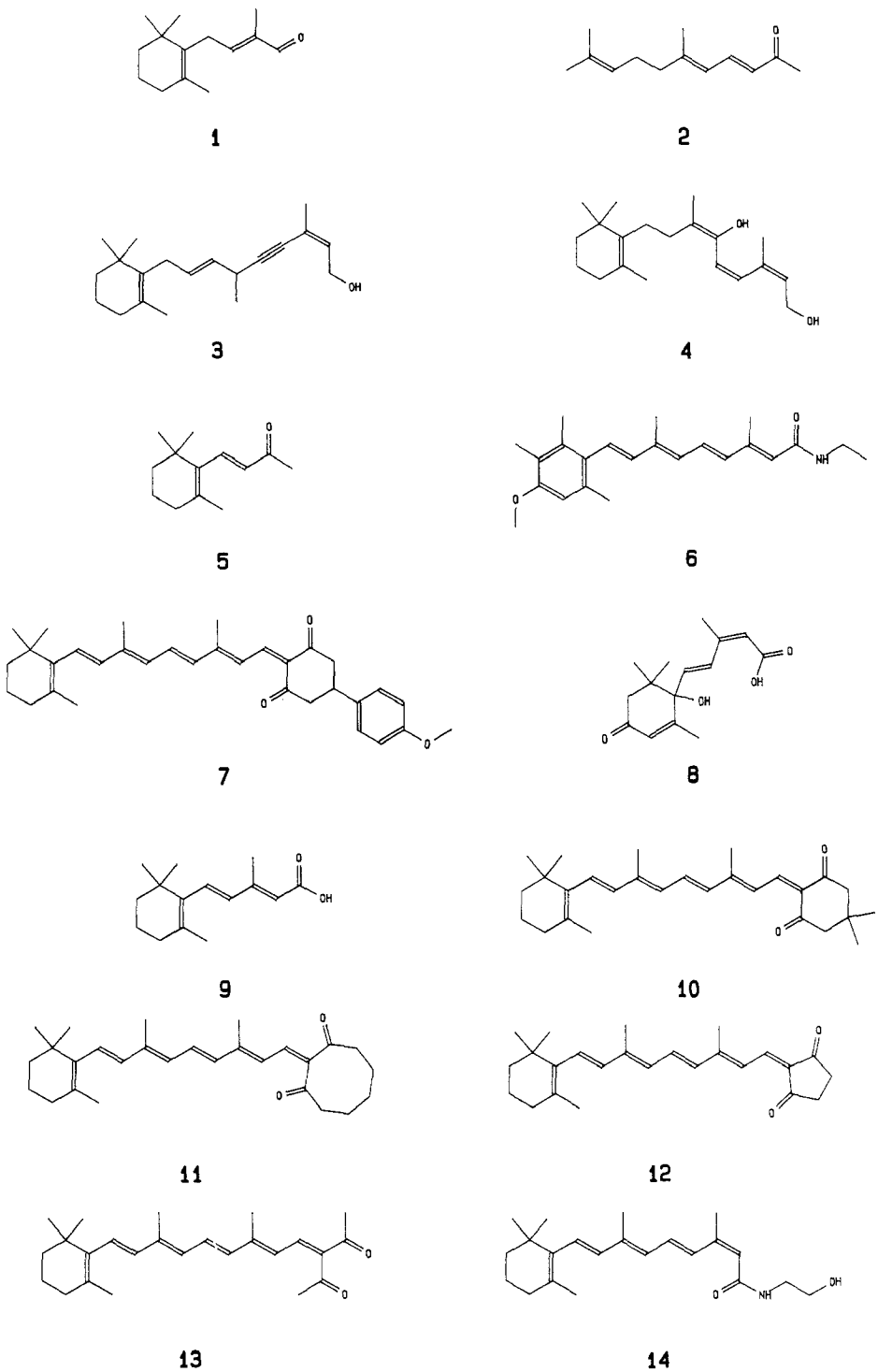
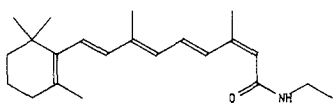


Fig. 2. The compounds in the database of 39 retinoids including the four compounds (**4**, **16**, **21**, and **39**) randomly isolated for use as a test set. →



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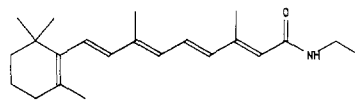

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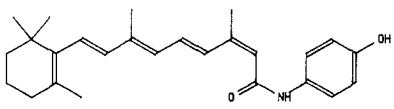

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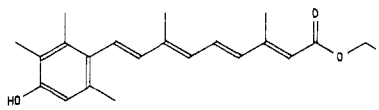

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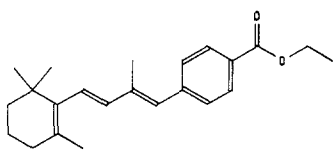

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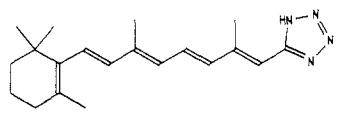

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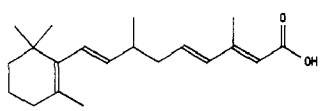

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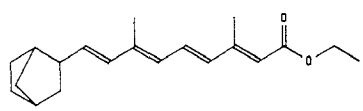

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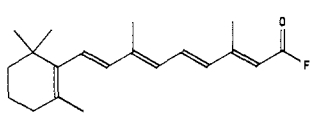

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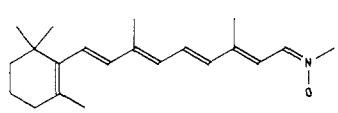

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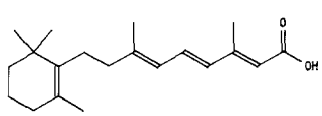

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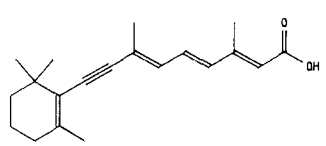

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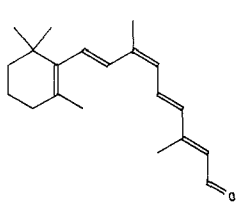

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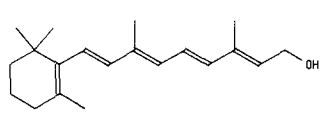

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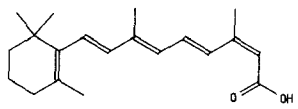
Fig. 2. (continued)



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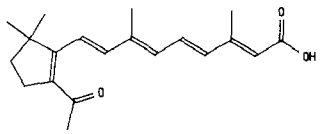

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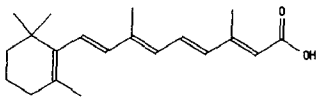

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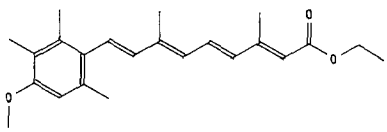

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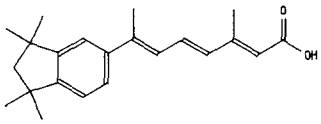

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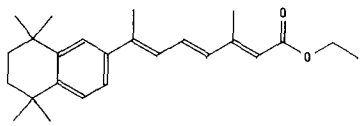

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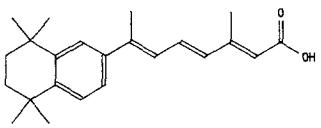

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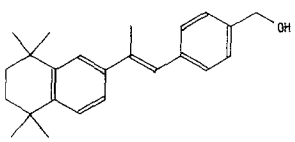

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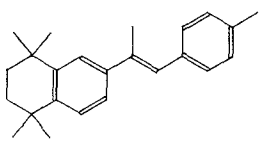

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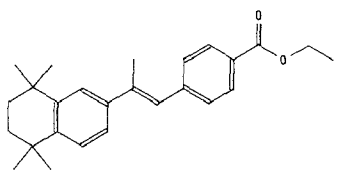

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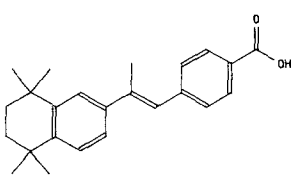

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g. 2. (continued)

be relevant to activity. However, when resolved into its two occurrences, the distribution of the fragment in the phenyl compounds was found to be inactivating and in the biphenyls, activating. In the phenyl compounds, the fragment represents ortho substitution whereas in the biphenyl compounds, the fragment represents free ortho positions. This may suggest that ortho substitution in phenyls inhibits activity while free ortho positions in biphenyls enhances activity.

In order to solve this problem, a descriptor containing information regarding the geometry of a fragment was developed so that CASE would be able to discriminate between geometric isomers.

THEORETICAL

(1) The CASE methodology

The CASE methodology has been described before and hence only a brief discussion follows.

The CASE program is a fully automated system that analyzes the biological activities and structures of a given set of compounds and identifies structural descriptors believed to be responsible for the activity or inactivity of the compounds [12–18].

The input to the CASE program is a database made up of the coded molecular formulas, each one associated with an index of biological activity. CASE takes each molecule in the database and breaks it up into all possible fragments of 2–10 linearly connected heavy atoms each [16]. These fragments are marked as active or inactive depending on whether the parent molecule is active or not. The fragments are then subjected to a series of statistical tests to determine which of them have a distribution that is markedly skewed toward either activity or inactivity. Those that are selected as significant are subjected to a Quantitative Structure Activity Relationship (QSAR) analysis, based on the frequency of occurrences of the relevant fragments, to yield a linear regression equation that best describes the activity of the compounds in the database. The common logarithm of the partition coefficients (log P) of the compounds in an octanol/water system is also considered as a potential descriptor. The new version of the CASE program has the ability to discriminate between *cis* and *trans* isomers by virtue of a geometry index.

(2) The geometry index

In developing a suitable geometry descriptor or index, certain considerations have to be taken into account. First, the descriptor has to be compact so as not to take up too much space in the CASE data files. Second, the descriptor has to be generated before the fragment is separated from its parent compound. Third, once generated, it has to be independent of the parent compound since references to the original structure will be inefficient and time-consuming during the CASE analysis of the fragments.

Several models were considered. For instance, the fragment could be placed on a two-dimensional rectangular grid where the atoms could only occupy points on the grid and movement from point to point is restricted to 135° angles. In this model, the descriptor considered was the sum of the horizontal and vertical distances between the two ends of the fragment. However, the positioning of each fragment on this grid was cumbersome since the complete geometry of the parent compound had to be known and accessed for each fragment generated. Another model consid-

ered was to use the geometric distance between the two ends of the fragment. For this, the geometry of the compound had to be calculated and the geometric distances between all atoms calculated and stored in a matrix. Hence, for each fragment of the compound, the distance between the end atoms can be looked up in the geometric distance matrix, without any reference to the original structure. The idea was sound, however, the problem with this model was that the distance index was a real number and hence, not compact. After considerable study, we found a way of describing the geometry of a fragment in a single 7-bit geometry index.

The index we propose is a 7-bit number where each bit serves to encode the geometry of each 1,4 pair in a linear fragment. Since there are seven 1,4 pairs in a linear fragment of 10 atoms, a single byte of information is more than adequate to characterize the *cis-trans* configuration of a whole fragment. To generate the index, the coded structure is first decoded into a connectivity matrix. If the original code contained any geometry data, it is likewise stored in the matrix. An analysis is performed to determine the presence of rings in the structure. A table of all 1,4 pairs is generated after the analysis and each pair is characterized as being *cis* or *trans*. By default, a pair is marked *trans*. A pair is marked *cis* if any of the following conditions is met:

(a) Both atoms are originally encoded to be of *cis* configuration,

(b) Both atoms are the opposite pair of *cis*-encoded atoms,

(c) Both atoms are members of the same ring of size 8 or less,

(d) Both atoms are substituents of the same ring.

At the end of this process, the 1,4 table contains all pertinent information for the characterization of any fragment of any length. All that is required is to determine which atoms in the original structure make up the fragment and look up each 1,4 pair in the table of the original structure.

For example, the fragment in Fig. 3 has six heavy atoms in the chain. The chain contains three 1,4 pairs. In the phenyl compounds, the geometry of each 1,4 pair is cis-cis-cis. In the biphenyl compounds, the geometry of each one is trans-trans-trans. Hence, with 1 indicating cis and 0 meaning trans, the geometry indices for each example would be 7 (111 binary) and 0 (000 binary), respectively.

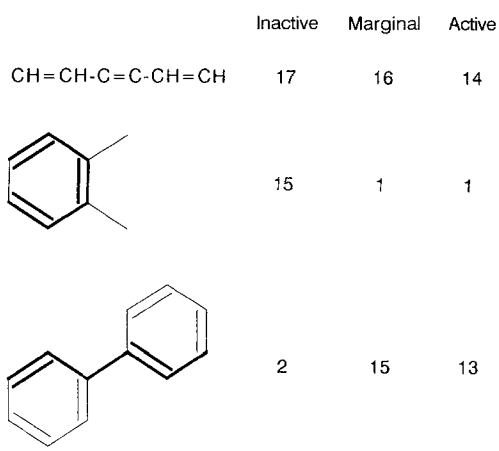


Fig. 3. Problem of fragment geometry taken from a database of non-fused ring nitroarenes and related compounds. Shown are the distributions of the fragment with and without geometry distinction.

EXPERIMENTAL DATA

The data were acquired from Willhite [19]. Syrian Golden Hamsters were given a single oral retinoid dose on day 8 of gestation and sacrificed on day 14. The litters were examined for resorp-

TABLE I
LIST OF COMPOUNDS SUBMITTED FOR CASE ANALYSIS WITH EXPERIMENTAL AND CALCULATED ACTIVITIES

No.	Common name/code	Experimental		Calculated activity[b]
		TD_{50}^{a}	Activity	
1	β-C_{14} Aldehyde	980	–	–
2	Pseudoionone	960	–	–
3	Oxenin	750	–	–
5	β-Ionone	480	–	–
6	Motretinid/Ro11-1430	330	–	–
7	all-*trans*-2-Retinylidene-5-*p*-methoxyphenyl-1,3-cyclohexanedione	250	–	–
8	Abscisic acid	250	–	–
9	C_{15} Acid	220	–	–
10	Retinylidene dimedone	210	–	–
11	all-*trans*-2-Retinylidene-1,3-cyclooctanedione	210	–	–
12	all-*trans*-2-Retinylidene-1,3-cyclopentanedione	190	–	–
13	Retinylidene acetylacetone	190	–	–
14	13-*cis*-*N*-(2-Hydroxyethyl)retinamide	173	–	–
15	Ro13-3987	163	–	–
17	13-*cis*-*N*-(4-Hydroxyphenyl)retinamide	139	–	–
18	Ro11-4768	87	+	++
19	*trans*-Aryltriene analog of retinoic acid ethyl ester	84	+	++
20	all-trans-5-[2,6-Dimethyl-8-(2,6,6-trimethylcyclohexen-1-yl)-1,3,5,7-octatetren-1-yl]tetrazole	81	+	–
22	2-Norbornenyl ethyl ester	75	+	++
23	15-Fluororetinone	54	++	++
24	all-*trans*-Retinylidene methyl nitrone	39	++	–
25	7,8-Dihydroretinoic acid	38	++	++
26	7,8-Dehydroretinoic acid	37	++	++
27	9-C-Retinal	23.2	++	++
28	all-*trans* Retinol	22.9	++	–
29	13-*cis*-Retinoic acid/Ro4-3780	22.3	++	++
30	Ro8-7699	10.9	+++	+++
31	all-*trans* Retinoic acid/Ro1-5488	10.5	+++	+++
32	Etretinate/Ro10-9359	5.7	++++	++
33	Ro13-4306	4.7	++++	++++
34	Ro13-2389	0.70	++++	++++
35	Ro13-6307	0.66	++++	++++
36	Ro13-8320	0.036	++++	++++
37	Ro13-9272	0.032	++++	++++
38	Ro13-6298	0.023	++++	++++

[a]Concentration in mg equiv. of vitamin A/kg body wt. of 50% occurrence of teratogenesis.
[b]Using Eq. 1.

TABLE 2
LIST OF COMPOUNDS TAKEN OUT OF THE LEARNING SET TO BE SUBMITTED FOR CASE ANALYSIS AS A TEST SET

No.	Common name/code	Experimental	
		TD_{50}^{a}	Activity
4	Hydroxenin	510	−
16	Ro8-4968	163	−
21	9,10-Dihydroretinoic acid	76	+
39	TTNPB/Ro13-7410	0.019	++++

[a]See Table 1.

tions, deaths, and live fetuses. A litter was considered affected if it contained one or more malformed or dead fetuses or three or more resorptions [11]. The retinoid doses were measured in molar equivalents to all-trans retinoic acid (cpd **31**, see Fig. 2). The dose in mg compound per kg body weight required for 50% of the test set to exhibit teratogenesis is the TD_{50} value.

RESULTS AND DISCUSSION

The molecular structures of the compounds in the database were encoded using KLN, a line notation method [20]. Structures containing *cis-trans* data were encoded as such. Each compound was associated with an index of teratogenic activity in hamsters, i.e., TD_{50}.

The names, experimental activities and CASE calculated activities of the compounds submitted for analysis are listed in Table 1. A total of 39 compounds were available for analysis. The structures of these compounds are shown in Fig. 2. The activity of the compounds was categorized as follows: for concentrations greater than 100 mg/kg, inactive; 75–100, marginal; 20–75, active; 10–20, very active; and below 10, extremely active. With this scale, the 39 compounds contained 17 actives, 5 marginals, and 17 inactives.

Four (**4**, **16**, **21** and **39**, see Fig. 2) of the 39 compounds were selected at random and set aside to serve as a test set. These compounds are listed in Table 2. The remaining 35 compounds were taken as the learning set and submitted for CASE analysis to determine which fragments are most relevant to activity. A total of 18,423 fragments were generated. In the QSAR analysis, fragments were selected through a forward stepwise regression analysis and the result is shown in Eq. 1. At each stage of adding a parameter to Eq. 1, the partial F test was evaluated to ensure that each descriptor was significant at least at the 95% level.

$$\log(1/C) = -2.44 + 0.92n_1F_1 + 0.69n_2F_2 - 1.30n_3F_3 + 0.65n_4F_4 + 0.65n_5F_5 + 1.21n_6F_6 \quad (1)$$

with $r^2 = 0.896$, $s = 0.42$, $n = 35$, $F(6,28,0.05) = 40.07$.

The six fragments selected by the QSAR analysis are shown in Fig. 4. The occurrence of these fragments in the compounds of the learning set is shown in Table 3. Eq. 1 was used to calculate the activities of the 35 compounds and the results are in Table 1, column 3. With this equation, 14 of the 16 actives and 15 of the 15 inactives are correctly described. Of the four marginals,

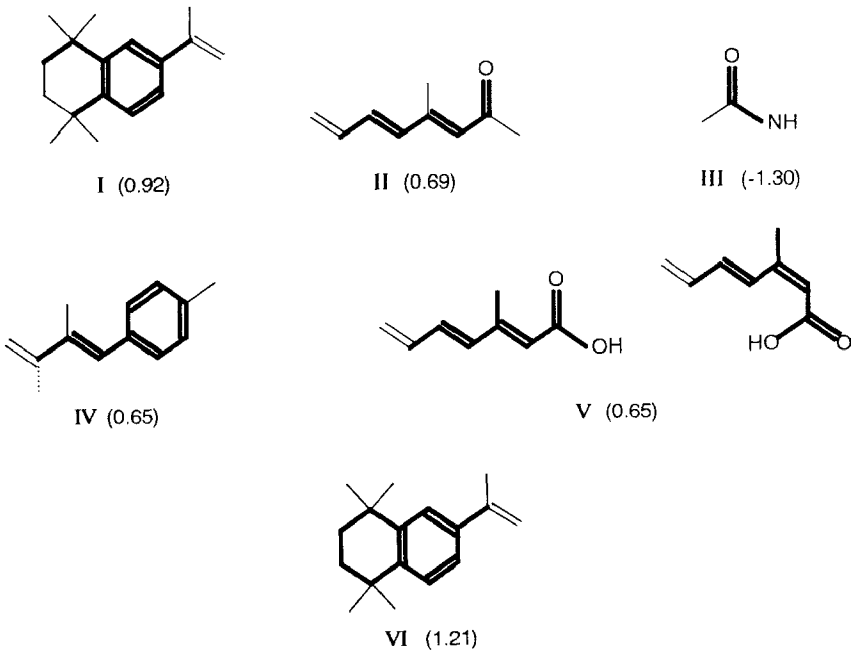


Fig. 4. Fragments selected by QSAR analysis along with their QSAR coefficients.

three were calculated as active and one as inactive. The remaining two active compounds (**24** and **28**, see Fig. 2) were calculated to be inactive due to the absence of any fragments found in Eq. 1.

Of the six fragments selected, Fragment I seems to be the most important. Alone, it could account for 69% of the data. This structure introduces some rigidity in the backbone of the retinoid by incorporating the C5–C8 carbons of the retinoid structure (Fig. 1) into a ring, which seems to enhance teratogenic activity. Fragment I is actually embedded in Fragment VI which specifies that the non-polar terminus should be a six-membered ring. Thus, the presence of Fragment VI contributes a total of 2.13 units to the log(1/C) of teratogenic activity.

Fragment II is the next most relevant fragment. It contains the conjugated double bonds of the retinoid backbone with the acid or acid derivative terminus and a substituent, typically a methyl group, at position 13. Its configuration is all-*trans* suggesting that the *trans* configuration of the double bonds may be important for teratogenic activity. It is interesting to realize that all the molecules that contain the all-*trans* version of Fragment V also contain Fragment II since II is embedded in V. Thus it is appropriate to evaluate these two fragments together. Noting that Fragment V includes both *cis* and *trans* configurations around the C13–C14 bond but is limited to the acid version, one can evaluate the contribution of various chains as shown in Table 4. Hence, the all-*trans* configuration of Fragment II enhances the value of log(1/C) by 0.69 units over that contributed by the C13-C14 *cis* chain. This shows that while teratogenic molecules can have both *cis* and *trans* chains, those with an all-*trans* configuration are expected to be more potent.

Fragment III, an amide group, represents a deactivating functionality which, as shown in Table 4, is potent enough to nullify any contribution of Fragment II to teratogenic activity. This group is found in 4 of the 35 compounds in the learning set, all of which are inactive.

TABLE 3
OCCURRENCES OF QSAR FRAGMENTS IN THE LEARNING SET OF 35 RETINOIDS

No.	Calculated activity[a]	QSAR fragment[b]					
		I	II	III	IV	V	VI
1	−	.	.	.	.	.	.
2	−	.	.	.	.	.	.
3	−	.	.	.	.	.	.
5	−	.	.	.	.	.	.
6	−	.	×	×	.	.	.
7	−	.	.	.	.	.	.
8	−	.	.	.	.	.	.
9	−	.	.	.	.	.	.
10	−	.	.	.	.	.	.
11	−	.	.	.	.	.	.
12	−	.	.	.	.	.	.
13	−	.	.	.	.	.	.
14	−	.	.	×	.	.	.
15	−	.	.	×	.	.	.
17	−	.	.	×	.	.	.
18	++	.	×	.	.	.	.
19	++	.	.	.	×	.	.
20	−	.	.	.	.	.	.
22	++	.	×	.	.	.	.
23	++	.	×	.	.	.	.
24	−	.	.	.	.	.	.
25	++	.	.	.	.	×	.
26	++	.	.	.	.	×	.
27	++	.	×	.	.	.	.
28	−	.	.	.	.	.	.
29	++	.	.	.	.	×	.
30	+++	.	×	.	.	×	.
31	+++	.	×	.	.	×	.
32	++	.	×	.	.	.	.
33	++++	×	.	.	.	×	.
34	++++	×	.	.	.	.	×
35	++++	×	.	.	.	×	×
36	++++	×	.	.	×	.	×
37	++++	×	.	.	×	.	×
38	++++	×	.	.	×	.	×

[a]See Table 1.
[b] × means the fragment occurs at least once in the compound.

Fragment IV occurs in the three most active compounds (cpds **36**–**38**, see Fig. 2) and one marginally active compound (cpd **19**, see Fig. 2) in the learning set. This fragment has a *trans* configuration across the C9-C10 position and constrains the C11-C14 atoms into a para-substituted phenyl ring. Having carbons C11-C14 in a phenyl ring fixes the configuration at this part of the retinoid

TABLE 4
CONTRIBUTIONS OF DIFFERENT SIDE CHAINS TO TERATOGENICITY IN Log(1/C) UNITS BASED ON QSAR FRAGMENTS II, III, AND V

Side chain	Individual contributions	Total contribution
all-*trans* acid	0.69+0.65	1.34
all-*trans* other	0.69	0.69
all-*trans* amide	0.69−1.30	−0.61
C13-C14-*cis* acid	0.65	0.65
C13-C14-*cis* other	0.00	0.00
C13-C14-*cis* amide	−1.30	−1.30

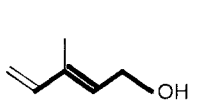
backbone into a *cis* arrangement. This conformational restriction seems to enhance activity considerably.

Fragments II, III and V represent different possible functionalities at the polar terminus of the retinoid structure. Fragments II and V consist of acids or acid precursors. The appearance of these fragments suggests that an acidic terminus is required to have activity.

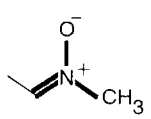
The two active compounds which were not correctly classified each contained a fragment which was unique to each one. These two fragments are shown in Fig. 5. Although these singly occurring fragments may not be statistically significant, these fragments were the only distinguishing factors between these active compounds and the inactive compounds in the database. Thus, it may be useful to study these fragments further. It could be noted that Fragment VII may be taken as an acid precursor and hence be related to Fragment V. Furthermore, the hydrogens on the *N*-methyl group of Fragment VIII may have a relatively high pKa such as in nitromethane which has a pKa of 11. This may also be representative of an acidic terminus.

Using Eq. 1, the four test compounds were evaluated and the results are shown in Table 5. As can be seen, the QSAR equation correctly predicted the activities of the two inactive compounds (**4** and **16**, see Fig. 2) and the one extremely active compound (**39**, see Fig. 2). The marginally active compound (**21**, see Fig. 2) was calculated to be inactive due to the absence of any of the fragments found in the QSAR equation.

Since the data base studied is congeneric, it should be noted that the fragments selected by the QSAR analysis should be considered within the general retinoid backbone. Hence, Fragments I and VI refer to the nonpolar cyclic end of the retinoid, Fragment IV refers to the side chain section, and Fragments II, III and V refer to the polar terminus.



VII



VIII

Fig. 5. Singly occurring fragments found in compounds **28** and **24**.

TABLE 5
OCCURRENCES OF QSAR FRAGMENTS IN THE TEST SET OF THE 4 RETINOIDS TAKEN OUT OF THE LEARNING SET

No.	Activity		QSAR fragment[b]					
	Actual	Calculated[a]	I	II	III	IV	V	VI
4	−	−	.	.	.	.	.	.
16	−	−	.	×	×	.	.	.
21	+	−	.	.	.	.	.	.
39	++++	++++	×	.	.	×	.	×

[a]See Table 1
[b] × means the fragment occurs at least once in the compound.

Of the six fragments, three (II, IV, and V) have sufficient length to be characterized by a geometry index. The total occurrences of each of the four fragments are found in Table 6. The geometry index was sufficient to distinguish similar fragments occurring with different configurations. On one hand, it can be seen in the case of Fragment IV that the separation of the *trans* isomer from the *cis* is quite meaningful. On the other hand, with Fragment V, it is apparent that the difference in geometry around the C13-C14 bond does not affect activity to a great extent and hence both configurations are included in the QSAR equation.

CONCLUSIONS

An improved version of the CASE program capable of distinguishing different geometries of linear fragments has been used to study a set of 39 retinoids characterized for teratogenic activity. It was found that the all-*trans* configuration across the 4 double bonds of the isoprenoid side chain is activating. Apparently, a *cis* configuration around the C12-C13 single bond brought about by inclusion in a phenyl ring enhances activity while *cis* around the C13-C14 somewhat decreases it. Furthermore, if the polar terminus of the retinoid is acidic or can be metabolized to an acidic functionality, then the retinoid will probably be strongly teratogenic.

TABLE 6
DISTRIBUTION OF QSAR FRAGMENTS AND THEIR GEOMETRIC ISOMERS

Fragment	Geometry	Inactive	Marginal	Active
II	all-*trans*	1	2	10
	others	3	0	1
IV	all-*trans*	0	0	3
	others	1	1	1
V	all-*trans*	0	0	6
	others	0	0	1

The geometry index introduced into the CASE program has been used successfully in this study. It has allowed the discrimination between similar fragments with different geometries and separated the fragments when geometry seemed to be a useful factor.

With the descriptors determined in this study the next step would be to see which structural features of retinoids are related to their beneficial effects. From there, it may be possible to design useful retinoids with minimal or no teratogenic side effects.

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