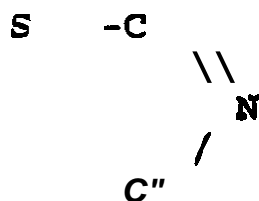


The molecule contains the Toxicophore



*** 5 out of the known 5 molecules (100%) containing such Biophore are Mouse carcinogens with an average activity of 62.

(conf.level=97%)

** This Biophore exists in a significantly different environment than in the data base (i.e. 5.45); It may not be relevant

*** QSAR Contribution : Constant is 64.00

** Total projected QSAR activity 64.00

*** The probability that this molecule is a Mouse carcinogen is 05.7%

** The projected Mouse carcinogenic potency is 64.0 CASE units **

Figure 19.6. Prediction of the carcinogenicity in mice of epitholone A. The structure of epitholone A (toxicophore shown in bold) is given in Fig. 19.7.

that operate like a "black box." The latter simply provides a likelihood that a test chemical is active or inactive. When, however, the SAR prediction is accompanied by documentation of the basis of that forecast, the human expert can determine whether it is justified and whether it applies to the specific test chemical.

Thus, the mucolytic agent *N*-acetyl-L-cysteine is predicted to have a potential to induce allergic contact dermatitis by virtue of the biophore **SH—CH₂** (Fig. 19.5). Moreover, examination of the chemicals that contribute to that toxicophore reveals that indeed they all have the substructure in an environment that is similar to the one found in *N*-acetyl-L-cysteine (Table 19.3). On the other hand, the tubulin polymerization perturber (and potential anti-neoplastic agent) epitholone A (Fig. 19.6) is predicted to be a mouse carcinogen by virtue of the toxicophore units shown in bold. That toxicophore is present in five molecules in the learning set. The presence of that toxicophore

is associated with an 89% probability of carcinogenicity and a potency of 63 units, which corresponds to a TD₀₁ value of 0.039 mmol/kg per day (40). However, the program flags the toxicophore because its environment in epitholone A is significantly different from that of the molecules in the learning set (Fig. 19.6). In fact, examination of the structures of the molecules that contribute to the biophore (Fig. 19.7) indicates that indeed the molecules are quite different from that of epitholone A, and hence, the prediction of carcinogenicity can be disregarded (however, also see below).

Moreover the molecules that contributed to this toxicophore (Fig. 19.7), even though they contain the **S—C=N—C=** moiety (Fig. 19.6), also contain functionalities (i.e., "structural alerts") that are associated with carcinogenicity/genotoxicity such as nitro, amino, and hydrazino groups. In fact, these could be responsible for the murine carcinogenicity of these chemicals. Obviously, these latter functionalities are absent in epitholone A.