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QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP FOR THE COMPUTATIONAL PREDICTION OF CARCINOGENICITY’S NITROCOMPOUNDS.

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Abstract

The presence of nitrocompounds in the environment, in foodstuffs and drugs, together with their biological reactivity, represents a potentially serious risk to human health. Several nitro derivatives have been screened for carcinogenicity in rodents, but this is a lengthy and expensive process, taking two years and typically costing 2.5 million dollars, and uses large numbers of animals that can suffer adverse welfare. There is, therefore, much impetus to develop suitable alternative methods, particularly for screening large numbers of chemicals for carcinogenicity. One possible way of predicting carcinogenicity is to use quantitative structure-activity relationships (QSARs). QSARs have been widely utilized for toxicity testing, thereby contributing to a reduction in the need for experimental animals. It is even possible to undertake virtual screening of candidate molecules before they are synthesized. This paper describes the results of applying a TOPological Sub-Structural Molecular Design (TOPS-MODE) approach for predicting the rodent carcinogenicity of nitro-derivatives by using data from bioassays in the female rat. This approach is based on the calculation of the spectral moments of the bond matrix of molecular graph which have been used to generate graph-theoretical descriptors, expressing physical and biological properties in terms of sub-structural features of molecules. The model described 79.10 % of the experimental variance, with a standard deviation of 0.424 (S). The predictive power of the model was validated by leave-one-out validation, with a determination coefficient of 0.666 (q²). In addition, this approach enabled the contribution of different fragments to carcinogenic potency to be assessed, thereby making the relationships between structure and carcinogenicity to be transparent. It was found that the carcinogenic activity of the chemicals analysed was increased by the presence of a primary amine group bonded to the aromatic ring, a manner that was proportional to the ring aromaticity. The nitro group bonded to an aromatic carbon atom is a more important determinant of carcinogenicity than the nitro group bonded to an aliphatic carbon. The TOPS-MODE approach was compared with four other predictive models (BCUT, Gálvez topological charges index, Randić molecular profile and geometrical descriptors), but none of these could explain more than 66 % of the variance in the carcinogenic potency in the database, when the same number of descriptors was involved.