The Application of Classical QSAR to Agrochemical Research

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ABSTRACT

Since the first paper for the QSAR procedure was published in 1962, a number of agrochemical QSAR studies have been accumulated. Among them, some studies were to construct models to design new compounds of the improved activity profiles. Others were to search for a clue for molecular mechanisms of action and/or physicochemical backgrounds for some “compulsory or favorable” substructures and substituents within the compound series. In this article, some examples of studies from these two categories are reviewed.

KEYWORDS

Agrochemical QSAR, Molecular Mechanisms of Action, Physicochemical, QSAR

1. INTRODUCTION

As a general approach to examining relationships between structure and biological activity, the classical QSAR (quantitative structure-activity relationship) procedure was published some 55 years ago by Corwin Hansch and his coworkers including the present author (Hansch et al., 1963; Hansch & Fujita, 1964). The original project at that time was to get an insight into (sub)molecular mechanism of action of the plant growth regulators/herbicides of substituted phenoxyacetic acid series through analyzing substituent effects on their structure-activity relationship (Hansch et al., 1963). Thus, the classical QSAR of the Hansch-type stems from agrochemistry. Since then, a number of the classical QSAR studies have been published not only in agrochemical (Draber & Fujita, 1992; Hansch & Fujita, 1995) but also more in medicinal/pharmaceutical chemistry area (Fujita, 1990; Hansch & Leo, 1995). We could expect two categories of consequences from analyses of the structure-activity relationships for series of bioactive compounds. One is to extract guiding principles and construct models to design and synthesize new compounds the activity profiles of which are improved over those of existing series members. The second is to obtain an insight into the (sub)molecular mechanism of the biological action. In this article, examples of agrochemical QSAR studies from two categories carried out in some Japanese institutions are reviewed.

2. DESIGN AND SYNTHESSES OF COMMERCIALIZED AGROCHEMICALS

2.1. Design of a Novel Herbicidal N-Benzylacylamide, Bromobutide

At around 1970, chemists at Sumitomo Chemical, Takarazuka, recognized that the steric effects of substituents in some pesticide series are very important in governing variations of their potency. They actually analyzed the effect of aliphatic substituents including normal, branched, and cycloalkyls as well as the effect of various substituents attached to different positions of the aromatic ring of “aralkyl” agrochemical activities, quantitatively. One of their QSAR consequences was such that the bulkier and the more...
α-branched the N-alkyl substituents R in a series of RNHCH₂CN, the higher was the fungicidal activity against soil-borne fungi (Kirino et al., 1980). Another was that, in herbicidal N-chloroacetyl-N-phenylglycine ethyl esters (I in Figure 1), the higher the bulk of such aromatic substituents as alkyl, alkoxy, halogen, acyl, NO₂, CF₃, and Ph at ortho and meta positions to the di-substituted amino side chain, the more potent was the activity (Fujinami et al., 1976). They considered that the steric bulk of substituents played a role in protecting compounds against certain detoxification mechanisms and that the stability in soil or plants was the critical factor determining above two types of agrochemical potency. Kirino and coworkers at Sumitomo applied above considerations to the structural optimization of a series of herbicidal N-dimethylbenzylacylamides (II in Figure 1) newly discovered in those days (Kirino et al., 1983). Systematic modification of the structure was carried out to make the substituent R in the structure (II) bulkier and bulkier to increase protection against the possible hydrolytic detoxication mechanism (Kirino et al., 1983). Then, indices of the biological activity measured were examined with physicochemical substituent parameters and the regression analysis using the least squares method.

The analysis for the first synthesized set, in which R in II varies from simple normal and branched alkyls to such congested substituents as t-BuCHCl-, t-BuCHBr-, i-PrCMe₂- and Me₂CBrCHBr-, gave Equation 1.

\[
p_{I_{50}}(M) = -0.151 (\pm 0.093) \pi^2 + 0.983 (\pm 0.457) \pi - 0.350 (\pm 0.070) E_s^c + 2.877 (\pm 0.465) \quad (1)
\]

\[n = 41, \ r = 0.933, \ s = 0.267, \ F = 83.00\]

In this and the following QSAR equations, n is the number of compounds included in the analysis, r is the correlation coefficient, s is the standard deviation, F is the ratio of regression and residual variances, and figures in parentheses are the 95% confidence intervals. Unless otherwise noted, the terms insignificant above the 95% level were discarded. I₅₀ is the molar concentration required for 50% inhibition of shoot elongation of the seedlings of the bulrush, Scirpus juncoides, a perennial pest weed species in paddy fields. π is the hydrophobicity constant of substituent R based on 1-octanol/water partition coefficients. \(E_s^c\) is a variation of the Taft \(E_s\) steric substituent constant. It emphasizes here the effect of α-branching of alkyl groups in addition to the bulk of R, but does not correct for the hyperconjugation effect (MacPhee, Panaye, & Dubois, 1978; Takayama, Akamatsu, & Fujita, 1985). The higher the bulk as well as the α-branching, the more negative is defined the value. Compounds where R = CH₂Br and CH₂Cl are not included in Equation 1, since their \(p_{I_{50}}\) values are about 1.5 units higher than those predicted by Equation 1. This was attributed to a higher reactivity of their halogen substituents, probably in an alkylation reaction. The structural feature of groups having primary halogens at the α-position, however, is not necessarily favorable to the activity, since the \(E_s^c\) value is made less negative and the π value is not modified greatly. The \(p_{I_{50}}\) values of compounds with α-haloalkyl groups where the halogen atom is not primary fit Equation 1 quite well, as do those of compounds without haloalkyl groups. This indicates that the activity of this series of compounds is not entirely due to their alkyllating property, even though they have α-haloacetyl substituents. Substituents R having a double bond at the α,β-position and those having a β-halogen, which could give an α,β-
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