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# Quantitative structural–activity relationship (QSAR) study for fungicidal activities of thiazoline derivatives against rice blast

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**Abstract**—For the development of new fungicides against rice blast, the quantitative structural–activity relationship (QSAR) analyses for fungicidal activities of thiazoline derivatives were carried out using multiple linear regression (MLR) and neural network (NN). We have studied the substituent effects at *para* site of $R^1$ and at three sites (*ortho*, *meta*, or *para*) of $R^2$ aromatic rings in compounds. The results of MLR and NN analyses in the training set of Set-3 showed good correlations ($r^2$ values of 0.829 and 0.966, respectively) between the descriptors and the fungicidal activities. Five descriptors including the non-overlap steric volume ($SV_{R^2C_2}$), Connolly surface area ($SA_{R^1}$), hydrophobicity ($\sum \pi_{R^2}$), and Hammett substituent constants ($\sigma_{pR^1}$ and $\sigma_{mR^2}$) were selected as important factors of fungicidal activities. Although the descriptors of optimum MLR model were used in NN, the results were improved by NN. This means that the descriptors used in MLR model include non-linear relationships.


Rice is one of the major human staple crops for almost half of the world's population, particularly in East and Southeast Asia. However, rice blast which is caused by *Magnaporthe grisea*, is a leading constraint to rice production.[1–3] A screening experiment is carried out with candidate compounds in the glasshouse for the development of new fungicides against such fungus.[4] The in vivo assays in this procedure give the most accurate means to predict the field activities which reflect not only the intrinsic potency of the molecule but also its salient physical and chemical properties such as stability, uptake, and redistribution within host plants. The functional features are defined by the specific structural–properties of compounds that exhibit a particular activity against the same target. These results could be used effectively for the development of new fungicides by QSAR analyses which are carried out with various descriptors (structural, electronic, and physicochemical properties).

All derivatives of compounds used in our study for the development of new fungicides against this plant disease contained thiazoline as five-membered heterocyclic ring which has various physicochemical specificities from two double bonds (endo and exo) and un-paired electrons in sulfur and nitrogen atoms. The synthetic procedures of these have been reported through solid[5] and solution phase combinatorial synthetic methods.[6] We have tested the fungicidal activities of these derivatives against six fungi (*M. grisea*, *Rhizoctonia solani*, *Botrytis cinerea*, *Phytophthora infestans*, *Puccinia recondite*, and *Erysiphe graminis f.* sp. *hordei*) in 250 ppm concentration.[7,8] Among fungicidal activities against various fungi, compounds which substituted with phenylcarbamoyl-methyl at 4-site in a thiazoline ring have very high fungicidal activities against *M. grisea* and *B. cinerea*. However, compounds that are replaced with phthalimidyl at this site have extremely low activities against these targets. In the case of compounds substituted with phenyl at 2-imino site in the thiazoline ring, they have more selective fungicidal activities against the two fungi

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mentioned above than those compounds replaced with alkyl at this site. According to the results of the above mentioned, compounds that have a phenylimino group at C-2, methyl at N-3, phenylcarbamoyl-methyl at C-4, and hydrogen at C-5 on the thiazoline skeleton were found to be the most active fungicide against *M. grisea* compared to the others.

We studied the substituent effects in thiazoline derivatives of the fungicidal activities against *M. grisea* based on the results of the screening experiment in a more decreased concentration (100 ppm) as a continuous procedure. The multiple linear regression (MLR) and neural network (NN) were carried out to find out the relationship between the structural specificities of various substituents and fungicidal activities against this fungus. The back-propagation algorithm was used for NN analysis. The models that derived from QSAR studies could be used as significant information for the development of a new fungicide.

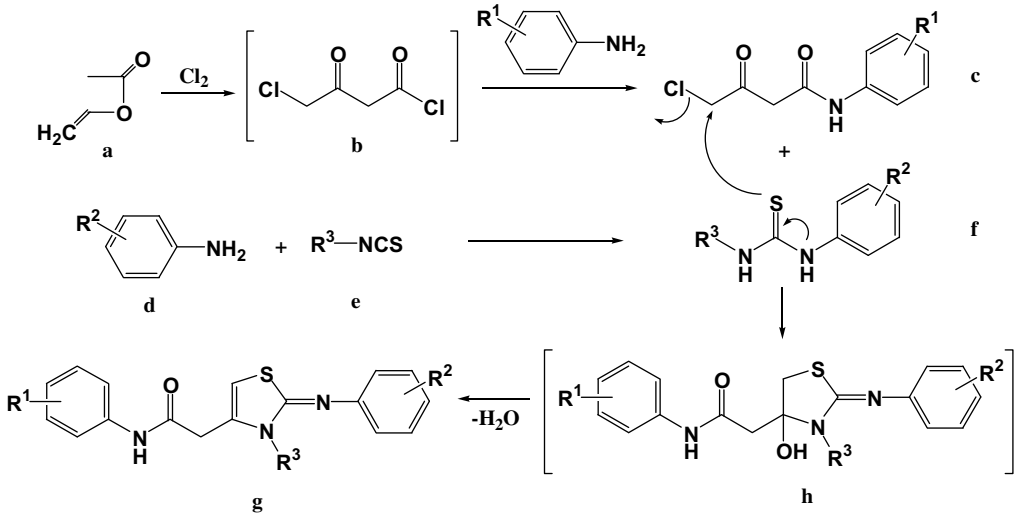
The synthesis of 2-phenylimino-1,3-thiazolines **g** were achieved according to the outlined pathway as reported[5,6] and summarized in Scheme 1. Thus, the reaction of γ-chloroacetoacetanilide derivatives **c** which were prepared by the subsequent treatment of diketene **a** with chlorine and anilines ($R^1NH_2$) in methylene chloride at −78 °C with thioureas **f**, obtained by the reaction of anilines ($R^2NH_2$) **d** and isothiocyanates **e** in ethanol at refluxing temperature, afforded 2-phenylimino-1,3-thiazoline **g** in moderate to high yields. The thiazoline derivatives that have various substituents at *para* sites in $R^1$ and $R^2$ aromatic rings were synthesized. The melting points (°C) were measured with an Electrothermal IA 9000 series digital melting point apparatus and they were not altered. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on Varian Gemini 300 (300 MHz), Bruker Avance 300 (300 MHz), or Varian 600 (600 MHz) spectrometer using TMS as an internal standard (chemical shifts in ppm and coupling constants (*J*) in hertz). Fourier conversion infrared (FT-IR) analysis was obtained on Perkin-Elmer 16FC-PC FT-IR, and was reported in $cm^{-1}$. HRMS data were obtained through a JMS-700 Mass spectrometer. Electrospray mass spectral analysis was obtained from a Micromass Quattro micro™ spectrometer for the ES-MS analysis by the direct injection of the sample dissolved in methanol.

The fungicidal activities of thiazoline derivatives were tested against rice blast which was caused by *M. grisea*.[1,2] Rice (*Oryza sativa* L., cv. Nakdong) plants were grown in vinyl pots (4.5 cm diameter) in the greenhouse at 25 ± 5°C for 3–4 weeks. Seedlings were sprayed until runoff with **h** dissolved in water + dimethyl sulfoxide (99 + 1 by volume) containing Tween 20 (250 mg/L). Control plants were treated with Tween 20 solution containing 1% dimethyl sulfoxide. The treated plant seedlings were allowed to stand for 24 h. For the development of rice blast, the treated rice seedlings of the third-leaf stage were inoculated with *M. grisea* by spraying with a spore suspension ($5 \times 10^8$ spores/ml) of the fungus. After the incubation of the seedlings in the dark for 1 day at 25°C and 100% RH, they were transferred to a growth chamber maintaining at 25 °C and 70–80% RH. Disease severity was determined by the percentage of infected leaf area 5 days after the inoculation. The pots were arranged as a randomized complete block with three replicates per treatment. Three estimates for each treatment were converted into percentage fungal control value (*A*) as in Eq. 1.

$$A = \%\ \text{control value} = 100[(a-b)/a] \qquad (1)$$

where *a* is the area of infection (%) on leaves sprayed with Tween 20 solution alone, *b* is the area of infection (%) on treated leaves.[7,8] In this study, experimental activities were used as logarithm ($\log A$) of the percentage (%) fungal control values of Eq. 1.

Table 1 shows the results of screening experiments against *M. grisea* for compounds used in this study. We have used the X-ray crystal structure (CCDC 659065) of thiazoline derivative (**62**) as a template to construct various derivative structures in this study.[9]




**Scheme 1.** Overall reaction pathway for synthesis of 2-phenylimino-1,3-thiazoline derivatives (g).