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Article

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Synthesis and Quantitative Structure-Activity Relationship (QSAR) Study of Novel *N*-Arylsulfonyl-3-Acylindole Arylcarbonyl Hydrazone Derivatives as Nematicidal Agents

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Abstract

In continuation of our program aimed at the discovery and development of natural-product-based pesticidal agents, fifty-four novel *N*-arylsulfonyl-3-acylindole arylcarbonyl hydrazone derivatives were prepared, and their structures were well characterized by ^{1}H NMR, ^{13}C NMR, HRMS, ESI-MS, and mp. Their nematicidal activity was evaluated against the pine wood nematode, *Bursaphelenchus xylophilus in vivo*. Among all the derivatives, especially **V-12** and **V-39** displayed the best promising nematicidal activity with the LC_{50} values of 1.0969 and 1.2632 mg/L, respectively. It suggested that introduction of R^1 and R^2 together as the electron-withdrawing substituents, R^3 as the methyl group, and R^4 as the phenyl with the electron-donating substituents could be taken into account for further preparation of this kind of compounds as nematicidal agents. Six selected descriptors are a WHIM descriptor (E1m), two GETAWAY descriptors (R1m+ and R3m+), a Burden eigenvalues descriptor (BEHm8), and two edge adjacency indices descriptors (EEig05x and EEig13d). Quantitative structure-activity relationship (QSAR) studies demonstrated that the structural factors, such as molecular masses (a negative correlation with the bioactivity) and molecular polarity (a positive correlation with bioactivity), are likely to govern the nematicidal activities of these compounds. For this model, the correlation coefficient ($R^2_{\text{training set}}$), the leave-one-out cross-validation correlation coefficient (Q^2_{LOO}) and the seven-fold cross-validation correlation coefficient ($Q^2_{\text{7-fold}}$) were 0.791, 0.701 and 0.715, respectively. And the external cross-validation correlation coefficient (Q^2_{ext}) and the root mean square error for the test set ($RMSE_{\text{test set}}$) were 0.774 and 3.412, respectively. It will pave the way for future design, structural modification and development of indole derivatives as nematicidal

agents.

KEYWORDS: Indole, hydrazone, structural modification, botanical pesticide, nematicidal activity, QSAR, *Bursaphelenchus xylophilus*

INTRODUCTION

Pine wood nematode, *Bursaphelenchus xylophilus*, has caused pine wilt disease which has been devastating forests worldwide.[1] Moreover, at present there are only few commercial nematicides left in use, and their repeated applications over the years have led to the enhancement of biodegradation mechanisms in soil and the development of pest resistance.[2-4] To prevent the pine wilt disease and overcome the problems about resistance development and environment pollution, therefore, the research and development of efficacy nematicidal agents has received much attention internationally in recent years.[5-11] In the meantime, during the long period of evolution, plants must resist attackers over their lifetime by producing and exuding secondary metabolites, and pesticides produced from plant secondary metabolites may result in less or slower resistance development and lower pollution.[12,13] Hence, the discovery of new pesticidal compounds directly from plant secondary metabolites, or by using them as the lead compounds for further structural modifications has recently been one of the important procedures for research and development of new pesticides.[14-17] Some botanical pesticides such as nicotine, pyrethrum and neem extracts are the characteristic examples made from plants as defenses against pests.[18]

Indole (**I-1**, Scheme 1), an aromatic heterocyclic compound, is a constituent of many natural plants, such as Robinia pseudacacia, jasmines, certain citrus plants and orange blossoms. Due to its crucial heterocyclic skeleton, extensive efforts by using **I-1** as a lead compound have been made for the preparation of potent anti-human immunodeficiency virus type 1 (HIV-1) inhibitors (*e.g.*, delavirdine),[19,20] hepatitis C virus (HCV) inhibitors,[21] antimicrobial agents,[22] glutamate carboxypeptidase II (GCPII) inhibitors,[23] antifungal agents,[24] and so on. In contrast, to the best of our knowledge, little work has been conducted

on the structural modifications of indoles as nematicidal agents against the pine wood nematode, *B. xylophilus*. Recently, we have found that some fraxinellone-based hydrazone derivatives exhibited the pronounced insecticidal activity,[25] and some *N*-arylsulfonyl-3-acetylindoles showed the potent anti-HIV-1 activity.[26] In continuation of our program aimed at the discovery and development of novel natural-product-based pesticidal agents,[24-28] consequently, we herein synthesized fifty-four novel *N*-arylsulfonyl-3-acylindole arylcarbonyl hydrazone derivatives (**V-1**~**V-54**, Scheme 3) by introduction of the hydrazone fragments on the *N*-arylsulfonyl-3-acylindolyl skeleton. Their nematicidal activity was evaluated against *B. xylophilus*. In addition, the quantitative structure-activity relationship (QSAR) studies of **V-1**~**V-54** were also investigated.

MATERIALS AND METHODS

General: All reagents and solvents were of reagent grade or purified according to the standard methods before use. Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography (PTLC) were performed with silica gel plates using silica gel 60 GF_{254} (Qingdao Haiyang Chemical Co., Ltd.). Melting points were determined on a XT-4 digital melting-point apparatus (Beijing Tech Instrument Co., Ltd.) and were uncorrected. Infrared spectra (IR) were recorded on a Bruker TENSOR 27 spectrometer. Nuclear magnetic resonance spectra (NMR) were recorded on a Bruker Avance DMX 300, 400 or 500 MHz instrument in $CDCl_3$ or DMSO-d_6 (^{1}H at 300, 400 or 500 MHz and ^{13}C at 125 MHz) using TMS (tetramethylsilane) as the internal standard. Electrospray iontrap mass spectrometry (ESI-TRAP-MS) and electron ionization mass spectra (EI-MS) were carried out with Bruker ESI-TRAP Esquire 6000 plus mass spectrometry instrument, and HP 5988 instrument, respectively. High-resolution mass spectra (HR-MS) were carried out with IonSpec 4.7 Tesla

FTMS instrument.

*Synthesis of 3-Formylindoles (**II-1~II-4**):* A mixture of *N*,*N*-dimethylformamide (DMF, 5 mL) and phosphorus oxychloride ($POCl_3$, 0.5 mL) was stirred at 0 °C for 20 min. Then a solution of indoles (**I-1~I-4**, 5 mmol) in DMF (2 mL) was added dropwise to the above mixture. After adding, the mixture was stirred at 35 °C for 1 h, and water was added, followed by adding 30% aqueous sodium hydroxide (NaOH) to adjust pH value to 8-9. The mixture was then refluxed for 1 h. On cooling, the mixture was poured into ice water, and the precipitated product was collected, washed by water, and recrystallized from absolute methanol to afford **II-1~II-4** in 84-95% yields.

*Data for **II-1**:* Yield = 91%, pink solid. mp = 190-192 °C [literature, 195-198 °C].[29] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.93 (s, 1H), 8.29 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.20–7.28 (m, 2H). EI-MS, *m/z* (%): 145 (M^+, 96).

*Data for **II-2**:* Yield = 95%, brown solid. mp =187-189 °C [literature, 186-188 °C].[29] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.89 (d, J = 2.0 Hz, 1H), 8.21 (s, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 2.41 (s, 3H). EI-MS, *m/z* (%): 159 (M^+, 68).

*Data for **II-3**:* Yield = 88%, yellow solid. mp = 241-243 °C [literature, 244-245 °C].[29] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.01 (s, 1H), 8.52 (s, 1H), 8.47 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H); 7.65 (d, J = 8.0 Hz, 1H). EI-MS, *m/z* (%): 170 (M^+, 70).

*Data for **II-4**:* Yield = 84%, yellow solid. mp > 300 °C [literature, 312-313.3 °C].[30] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.03 (s, 1H), 8.94 (d, J = 2.0 Hz, 1H), 8.58 (s, 1H), 8.15 (dd, J = 2.4, 9.2 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H). EI-MS, *m/z* (%): 190 (M^+, 100).

*Synthesis of N-Arylsulfonylindoles (**III-1~III-17**):* A mixture of **I-1~I-4** (1 mmol), benzyltriethylammonium chloride (TEBA, 0.1 mmol), NaOH (1.8 mmol), and arylsulfonyl

chlorides (1.2 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature. After stirring for 1-2 h, the reaction was complete according to TLC analysis, and water (10 mL) was added to the mixture, which was extracted with CH_2Cl_2 (30 mL × 3). Subsequently, the combined organic phase was washed by brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated under the reduced pressure to give **III-1**~**III-17** in 73-99% yields. The example data of **III-1** and **III-2** are shown as follows, whereas data of **III-3**~**III-17** can be found in the Supporting Information.

*Data for **III-1**:* Yield = 97%, white solid. mp = 78-79 °C [literature, 78-79 °C].[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, J = 8.4, 4.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 3.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.6 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H). EI-MS, *m/z* (%): 257 (M^+, 85).

*Data for **III-2**:* Yield = 96%, white solid. mp = 83-84 °C [literature, 87-88 °C].[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J = 10.8 Hz, 1H), 7.75 (d, J = 10.8 Hz, 2H), 7.56 (d, J = 4.4 Hz, 1H), 7.97 (d, J = 10.0 Hz, 1H), 7.20 (m, 4H), 6.65 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H). EI-MS, *m/z* (%): 271 (M^+, 100).

*Synthesis of 3-Formyl-N-Arylsulfonylindoles (**IV-1**~**IV-13**):* A mixture of **II-1**~**II-4** (2 mmol), arylsulfonyl chlorides (4 mmol), and K_2CO_3 (6 mmol) in dry CH_2Cl_2 (10 mL) was refluxed for 12-20 h. Then the reaction mixture was filtered. The corresponding filtrate was collected, concentrated under the reduced pressure, and purified by PTLC to produce **IV-1**-**IV-13** in 64-99% yields. The example data of **IV-1** and **IV-2** are shown as follows, whereas data of **IV-3**~**IV-13** can be found in the Supporting Information.

*Data for **IV-1**:* Yield = 71%, white solid. mp = 148-150 °C [literature, 149 °C].[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.09 (s, 1H), 8.25 (d, J = 7.5 Hz, 1H), 8.22 (s, 1H), 7.95 (d, J = 8.0 Hz,

1H), 7.85 (d, J = 8.5 Hz, 2H), 7.34-7.42 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H). ESI-MS, *m/z* (%): 300 ($[M+H]^+$, 100).

*Data for **IV-2**:* Yield = 75%, white solid. mp = 137-139 °C [literature, 137 °C].[33] ^{1}H NMR (500 MHz, $CDCl_3$) δ: 10.08 (s, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.22 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.89-7.91 (m, 2H), 7.34-7.42 (m, 2H), 6.94 (d, J = 9.0 Hz, 2H), 3.81 (s, 3H). ESI-MS: *m/z* (%): 316 ($[M+H]^+$, 25).

*Synthesis of 3-Acyl-N-Arylsulfonylindoles (**IV-14~IV-33**):* To a stirred mixture of $AlCl_3$ (3 mmol) and R^3COCl (acetyl chloride, propionyl chloride or *n*-hexanoyl chloride, 1.5 mmol) in dry CH_2Cl_2 (5 mL) at room temperature, a solution of **III-1~III-17** (1 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise. After adding, the mixture was stirred at room temperature for 1.5-2 h, and the reaction process was checked by TLC analysis. Then water (10 mL) was added to the mixture, which was extracted with CH_2Cl_2 (30 mL × 3). Subsequently, the combined organic phase was washed with saturated aqueous $NaHCO_3$ (30 mL × 2) and brine (30 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by PTLC to afford **IV-14~IV-33** in 62-99% yields. The example data of **IV-14** and **IV-15** are shown as follows, whereas data of **IV-16~IV-33** can be found in the Supporting Information.

*Data for **IV-14**:* Yield = 72%, white solid. mp = 158–159 °C [literature, 159–160 °C].[34] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.32-8.34 (m, 1H), 8.21 (s, 1H), 7.92-7.97 (m, 3H), 7.48-7.61 (m, 3H), 7.34-7.39 (m, 2H), 2.58 (s, 3H). EI-MS *m/z* (%): 299 (M^+, 74).

*Data for **IV-15**:* Yield = 91%, white solid. mp = 142–144 °C [literature, 145–146 °C].[35] ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31-8.34 (m, 1H), 8.21 (s, 1H), 7.90-7.94 (m, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.26-7.37 (m, 4H), 2.57 (s, 3H), 2.36 (s, 3H). EI-MS *m/z* (%): 313 (M^+, 35).

*Synthesis of N-Arylsulfonyl-3-Acylindole Arylcarbonyl Hydrazone Derivatives (**V-1~V-54**):* A

mixture of **IV-1**~**IV-33** (0.5 mmol), the corresponding hydrazides (0.5 mmol) and HOAc (two drops) in ethanol (5 mL) was refluxed for 2-6 h. When the reaction was complete according to TLC analysis, the mixture was allowed to cool, and filtered to give the solid, which was further recrystallized from absolute ethanol to produce target compounds **V-1**~**V-54** in 74-97% yields. The example data of **V-1**~**V-20** are shown as follows, whereas data of **V-21**~**V-54** can be found in the Supporting Information.

*Data for **V-1***: Yield = 90%, white solid. mp = 215-216 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.63 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.92-7.98 (m, 5H), 7.61 (d, J = 6.5 Hz, 1H), 7.56 (d, J = 7.0 Hz, 2H), 7.40-7.44 (m, 4H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 146.3, 142.6, 135.2, 134.2, 133.9, 132.1, 130.8, 130.3, 128.9, 128.0, 127.4, 127.3, 126.3, 124.7, 123.8, 118.7, 113.5, 21.5. ESI-MS: *m/z* (%): 418 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{23}H_{20}N_3O_3S$ ([M+H])$^+$, 418.1219; found, 418.1226.

*Data for **V-2***: Yield = 83%, white solid. mp = 182-183 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.64 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 7.97-8.00 (m, 3H), 7.95 (d, J = 7.5 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.4, 142.7, 135.2, 133.9, 132.1, 130.3, 129.8, 128.9, 128.4, 128.0, 127.4, 126.2, 124.6, 123.7, 118.5, 115.6, 113.5, 56.3. ESI-MS: *m/z* (%): 434 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{23}H_{20}N_3O_4S$ ([M+H])$^+$, 434.1169; found, 434.1161.

*Data for **V-3***: Yield = 79%, white solid. mp = 267-268 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.64 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.33 (s, 1H), 7.93-8.00 (m, 5H), 7.79 (d, J = 8.0 Hz, 2H), 7.55-7.61 (m, 3H), 7.39-7.45 (m, 2H), 2.05 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 169.6, 163.4, 145.2 142.6, 135.2, 133.9, 132.1, 130.3, 130.1, 128.9, 128.8, 128.0, 127.4,

126.2, 124.6, 123.7, 119.3, 118.5, 113.5, 24.5. ESI-MS: *m/z* (%): 483 ($[M+Na]^+$, 100). HRMS (ESI): calcd for $C_{24}H_{21}N_4O_4S$ $([M+H])^+$, 461.1278; found, 461.1284.

Data for ***V-4***: Yield = 97%, white solid. mp = 208-209 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.63 (s, 1H), 8.47 (d, J = 7.5 Hz, 1H), 8.39 (s, 1H), 8.08 (d, J = 8.5 Hz, 2H), 7.94-7.99 (m, 3H), 7.70 (d, J = 7.0 Hz, 2H), 7.62 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.48 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 142.4, 140.5, 135.8, 135.2, 133.8, 132.2, 130.6, 130.2, 129.2, 128.9, 128.1, 127.5, 126.5, 124.9, 123.9, 119.1, 113.5. ESI-MS: *m/z* (%): 460 ($[M+Na]^+$, 100). HRMS (ESI): calcd for $C_{22}H_{17}N_3O_3SCl$ $([M+H])^+$, 438.0673; found, 438.0681.

Data for ***V-5***: Yield = 76%, yellow solid. mp = 155-156 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.62 (s, 1H), 8.50-8.53 (m, 3H), 8.46 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.90-7.93 (m, 3H), 7.62 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.51 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 148.6, 142.3, 138.3, 135.2, 133.8, 133.0, 132.5, 132.2, 130.2, 129.9, 128.9, 128.0, 127.6, 126.7, 125.2, 124.0, 122.0, 119.6, 113.5. ESI-MS: *m/z* (%): 471 ($[M+Na]^+$, 70). HRMS (ESI): calcd for $C_{22}H_{17}N_4O_5S$ $([M+H])^+$, 449.0914; found, 449.0917.

Data for ***V-6***: Yield = 78%, yellow solid. mp = 217-218 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.81 (s, 1H), 8.63 (s, 1H), 8.48 (d, J = 7.5 Hz, 1H), 8.41 (s, 1H), 8.34-8.35 (m, 1H), 8.02-8.04 (m, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H), 7.51 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 148.3, 142.2, 136.8, 135.1, 134.2, 133.8, 132.4, 132.2, 131.7, 130.1, 128.9, 128.1, 127.6, 126.7, 125.2, 124.7, 124.0, 119.6, 113.6. ESI-MS: *m/z* (%): 483 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{22}H_{16}ClN_4O_5S$ $([M+H])^+$, 483.0524; found, 483.0531.

*Data for **V-7***: Yield = 89%, white solid. mp = 242-243 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.60 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.27 (s, 1H), 7.92-7.93 (m, 4H), 7.78 (s, 1H), 7.62 (t, J = 7.0 Hz, 1H), 7.55 (t, J = 7.0 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.0 Hz, 1H), 2.47 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 146.2, 142.7, 136.0, 135.6, 134.3, 133.9, 132.1, 130.8, 129.8, 128.9, 128.0, 127.3, 126.1, 125.2, 123.4, 118.7, 113.5, 21.9, 21.5. ESI-MS: *m/z* (%): 454 ([M+Na]$^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_3S$ ([M+H])$^+$, 432.1376; found, 432.1385.

*Data for **V-8***: Yield = 82%, white solid. mp = 224-225 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.60 (s, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.26 (s, 1H), 8.00 (d, J = 9.0 Hz, 2H), 7.95 (d, J = 7.5 Hz, 2H), 7.79 (s, 1H), 7.61 (t, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 9.0 Hz, 2H), 3.79 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 164.4, 142.7, 136.0, 135.6, 134.0, 133.9, 132.1, 129.8, 129.7, 128.9, 128.5, 128.0, 126.0, 125.2, 123.4, 118.5, 115.5, 113.5, 56.3, 22.0. ESI-MS: *m/z* (%): 448 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_4S$ ([M+H])$^+$, 448.1325; found, 448.1330.

*Data for **V-9***: Yield = 84%, white solid. mp = 234-235 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.59 (s, 1H), 8.28-8.31 (m, 2H), 8.08 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 7.5 Hz, 2H), 7.78 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.62 (t, J = 7.0 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.25 (d, J = 8.0 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 142.5, 140.4, 136.3, 135.9, 135.6, 133.8, 132.2, 130.6, 129.6, 129.2, 128.9, 128.0, 126.3, 125.2, 123.5, 119.1, 113.4, 21.9. ESI-MS: *m/z* (%): 452 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{23}H_{19}N_3O_3SCl$ ([M+H])$^+$, 452.0830; found, 452.0832.

*Data for **V-10***: Yield = 82%, yellow solid. mp = 189-190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.70 (s, 1H), 8.59 (s, 1H), 8.52 (dd, J = 8.0 Hz, 1.5 Hz, 2H), 8.40 (s, 1H), 8.32 (d, J = 8.0

Hz, 1H), 7.91-7.94 (m, 3H), 7.85 (s, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.55 (t, J = 7.5 Hz, 2H), 7.26 (d, J = 8.0 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.4, 148.6, 142.4, 138.4, 136.6, 135.6, 133.8, 133.0, 132.5, 132.2, 129.8, 129.7, 128.9, 128.0, 126.5, 125.3, 123.6, 122.0, 119.6, 113.5, 21.9. ESI-MS: *m/z* (%): 463 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{23}H_{19}N_4O_5S$ ([M+H])$^+$, 463.1070; found, 463.1078.

Data for ***V-11***: Yield = 79%, white solid. mp = 219-220 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.83 (s, 1H), 8.64 (s, 1H), 8.59 (s, 1H), 8.17 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 7.0 Hz, 2H), 7.87 (d, J = 9.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.5, 146.9, 141.7, 137.0, 133.8, 133.6, 132.3, 132.1, 131.0, 129.3, 128.9, 128.5, 128.1, 127.5, 119.5, 118.1, 114.8, 107.4, 21.5. ESI-MS: *m/z* (%): 443 ([M+H]$^+$, 100). HRMS (ESI): calcd for $C_{24}H_{19}N_4O_3S$ ([M+H])$^+$, 443.1172; found, 443.1174.

Data for ***V-12***: Yield = 93%, yellow solid. mp = 250-251 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.82 (s, 1H), 8.75 (s, 1H), 8.70 (s, 1H), 8.62 (d, J = 2.5 Hz, 1H), 8.56 (t, J = 6.5 Hz, 2H), 8.23 (d, J = 8.5 Hz, 1H), 7.88-7.95 (m, 4H), 7.62 (d, J = 7.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.6, 148.7, 141.4, 138.0, 137.0, 133.6, 133.2, 132.7, 132.3, 132.0, 130.3, 129.7, 128.9, 128.5, 128.1, 127.7, 122.4, 119.4, 118.9, 114.9, 107.8. ESI-MS: *m/z* (%): 474 ([M+H]$^+$, 100). HRMS (ESI): Calcd for $C_{23}H_{16}N_5O_5S$ ([M+H])$^+$, 474.0866; found, 474.0878.

Data for ***V-13***: Yield = 74%, yellow solid. mp = 157-158 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 9.30 (s, 1H), 8.67 (s, 1H), 8.63 (s, 1H), 8.32 (dd, J = 9.5 Hz, 2.0 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 7.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 7.96 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ:

162.9, 146.9, 146.5, 144.2, 142.1, 141.3, 137.5, 133.2, 133.1, 131.7, 130.5, 128.4, 128.0, 127.5, 127.0, 126.8, 121.1, 118.4, 21.0. ESI-MS: *m/z* (%): 463 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{23}H_{19}N_4O_5S$ $([M+H])^+$, 463.1070; found, 463.1081.

Data for ***V-14***: Yield = 93%, white solid. mp = 205-206 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.74 (d, J = 4.0 Hz, 1H), 8.34 (s, 1H), 8.09 (d, J = 7.5 Hz, 2H), 7.92-7.97 (m, 3H), 7.72 (t, J = 7.0 Hz, 1H), 7.58-7.63 (m, 3H), 7.53-7.54 (m, 2H), 7.36-7.41 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.9, 150.7, 136.6, 134.7, 133.9, 131.4, 129.8, 128.2, 127.8, 127.4, 126.7, 125.4, 124.6, 124.1, 121.7, 112.7, 14.7. ESI-MS: *m/z* (%): 418 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{23}H_{20}N_3O_3S$ $([M+H])^+$, 418.1219; found, 418.1228.

Data for ***V-15***: Yield = 84%, white solid. mp = 201-202 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.72 (d, J = 5.5 Hz, 1H), 8.33 (s, 1H), 8.09 (d, J = 7.5 Hz, 2H), 7.98 (d, J = 7.0 Hz, 1H), 7.72 (t, J = 7.5 Hz, 3H), 7.63 (t, J = 7.5 Hz, 2H), 7.36-7.40 (m, 4H), 2.47 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.9, 150.6, 140.3, 137.5, 136.6, 134.7, 133.8, 132.0, 129.8, 128.1, 127.8, 127.4, 126.7, 125.4, 125.0, 124.1, 121.7, 112.7, 20.8, 14.7. ESI-MS: *m/z* (%): 432 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_3S$ $([M+H])^+$, 432.1376; found, 432.1382.

Data for ***V-16***: Yield 90%, white solid. mp = 208-210 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.66 (s, 1H), 8.73 (s, 1H), 8.32 (s, 1H), 8.09 (d, J = 7.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 1H), 7.91 (s, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 2H), 7.39-7.41 (m, 1H), 7.34 (s, 1H), 7.08 (d, J = 8.0 Hz, 2H), 3.85 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 162.3, 137.3, 135.3, 135.2, 130.3, 128.2, 128.0, 127.3, 126.6, 126.5, 125.9, 125.1, 124.5, 122.4, 114.0, 113.3, 55.9, 15.1. ESI-MS: *m/z* (%): 470 ($[M+Na]^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_4S$ $([M+H])^+$, 448.1325; found, 448.1320.

*Data for **V-17***: Yield = 87%, white solid. mp = 196-198 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.93 (s, 1H), 8.72 (d, J = 7.5 Hz, 1H), 8.36 (s, 1H), 8.10 (d, J = 7.0 Hz, 2H), 7.97 (s, 2H), 7.89 (d, J = 7.0 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.41-7.42 (m, 1H), 7.36-7.38 (m, 1H), 2.49 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.1, 151.9, 137.2, 136.4, 135.3, 133.5, 131.8, 130.8, 130.4, 128.7, 128.1, 128.0, 127.3, 127.2, 126.0, 125.1, 124.7, 122.1, 113.3, 15.4. ESI-MS: *m/z* (%): 452 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{23}H_{19}N_3O_3SCl$ $([M+H])^+$, 452.0830; found, 452.0828.

*Data for **V-18***: Yield = 92%, white solid. mp = 220-221 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.72 (d, J = 4.0 Hz, 1H), 8.30 (s, 1H), 7.92-7.95 (m, 5H), 7.59 (d, J = 7.0 Hz, 1H), 7.54 (d, J = 7.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 3H), 7.36 (d, J = 6.5 Hz, 1H), 2.46 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.8, 150.7, 145.6, 139.7, 137.7, 134.7, 133.7, 131.4, 130.2, 128.2, 127.8, 127.4, 126.8, 125.3, 124.5, 124.0, 121.5, 112.7, 20.9, 14.7. ESI-MS: *m/z* (%): 432 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_3S$ $([M+H])^+$, 432.1376; found, 432.1379.

*Data for **V-19***: Yield = 83%, white solid. mp = 189-190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.74 (d, J = 3.0 Hz, 1H), 8.31 (s, 1H), 7.96 (d, J = 7.5 Hz, 3H), 7.74 (s, 2H), 7.37-7.40 (m, 6H), 2.47 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.9, 150.6, 145.6, 137.5, 134.7, 133.7, 132.0, 130.1, 128.1, 127.8, 127.4, 126.8, 125.3, 124.9, 124.5, 123.9, 121.6, 112.7, 20.9, 20.8, 14.7. ESI-MS: *m/z* (%): 446 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{25}H_{24}N_3O_3S$ $([M+H])^+$, 446.1532; found, 446.1541.

*Data for **V-20***: Yield = 86%, white solid; mp = 191-192 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.74 (d, J = 5.0 Hz, 1H), 8.31 (s, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.93-7.96 (m, 3H), 7.59 (d, J

= 7.0 Hz, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.35-7.42 (m, 2H), 7.10 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 163.8, 150.9, 134.7, 133.9, 131.5, 129.3, 128.2, 127.9, 127.8, 127.4, 127.0, 125.3, 124.6, 123.9, 121.4, 115.1, 114.9, 112.7, 55.7, 14.7. ESI-MS: *m/z* (%): 448 ($[M+H]^+$, 100). HRMS (ESI): calcd for $C_{24}H_{22}N_3O_4S$ $([M+H])^+$, 448.1325; found, 448.1321.

Assay of Nematicidal Activity.[36] Acetone solutions of compounds **V-1**~**V-54** and emamectin benzoate (used as a positive control) were firstly prepared at the concentrations of 5, 10, 25, 50, and 100 mg/L, respectively. Then 10 μL of the above solutions were added to the aqueous suspension (90 μL) containing approximate 2500 living nematodes (third-instar and fourth-instar larvae of *B. xylophilus*) per mL. The blank control group was prepared in the same way but lacked the tested compound. Three replicates in each trial were made and kept at 25 ^{o}C for 24 h. Finally, the activities of five concentrations of the tested compounds were monitored under a microscope by recording the death rate of the tested nematodes. Nematodes that did not move when prodded with a needle were considered dead. The LC_{50} values of tested compounds were calculated using the probit method.

QSAR Model Development.

Data Set. The experimental data used in this work contained 54 compounds (**V-1**~**V-54**). The nematicidal activity of 54 compounds was expressed as LC_{50} values (μmol/L) and used as the dependent variable in the following QSAR study.

Molecular Descriptor Calculation. To obtain a QSAR model, the compound was represented by structural descriptors. The molecular descriptors were calculated by the following process. All the compound structures were sketched in HyperChem[37] program and pre-optimized with the MM+ molecular mechanics force filed. In order to obtain more precise optimization, the

semi-empirical quantum chemistry method AM1[38] was used. The resulted minimum energy conformations of 54 compounds were input into DRAGON 5.4[39] software to calculate molecular descriptors.

In DARGON, 1664 molecular descriptors were calculated, which including: (a) 0D-constitutional descriptors, (b) 1D-functional groups counts, atom-centered fragments, (c) 2D-topological descriptors, walk and path counts, connectivity indices, information indices, 2D autocorrelations, edge adjacency indices, Burden eigenvalues, topological charge index, eigenvalue-based index, (d) 3D-Randic molecular profiles, geometrical descriptors, RDF descriptors, 3D-MoRSE descriptors, WHIM descriptors[40], GETAWAY descriptors[41], (e) charge descriptors, (f) molecular properties. The *Handbook of Molecular Descriptors*[42], detail calculation procedure could be found in which. The list of the above-mentioned descriptors and corresponding meanings could be found in the literature references of the DRAGON package.

To obtain the non-redundant information, constant or near-constant variables and two descriptors found to be correlated pairwise (one of any two descriptors with a correlation coefficient greater than 0.99 was removed) were exlcuded. After the pre-reduction step, 851 molecular parameters were obtained. Thus, 851 structural descriptors were retained for subsequent subvariable selection.

Splitting Dataset into Training Set and Test Set. To build and validate the QSAR model, the studied dataset were divided training set was used to develop the model and test set was used to validate the external predictive ability of the proposed model. In this study, the Kennard & Stone (KS) method[43] was used to split dataset into a training set and a test set due to its good performance in other studies. The KS method can be used to rationally select training set and test set based on the descriptor space.

Feature Selection and QSAR Construction by Genetic Algorithm-Multiple Linear Regression (GA-MLR). In this work, the relationship between bioactivity and structural descriptors was built by the Genetic algorithm-Multiple linear regression (GA-MLR) method. Genetic algorithm[44] was performed to search the descriptors pool and select the descriptors relevant to the bioactivity. Multiple linear regression is a classical linear regression method, the model constructed by which is simple and could be interpreted easily. In the present work, GA-MLR procedure were performed by the MobyDigs software[45] using the correlation coefficient of leave-one-out cross validation (LOO) as fitness function. When increasing the number of the descriptors did not increase the cross-validated correlation coefficient (Q^2_{LOO}) value to any significant degree, the GA selection was stopped. The corresponding parameters used in the model building process can be found as follows: population size 100, maximum allowed descriptors in a model 8 and reproduction/mutation trade-off 0.5 and the other parameters were set as default values.

Performance and Applicability Domain Evaluation of the QSAR Model. Several statistic parameters were adopted to assess the quality of the developed QSAR models such as the correlation coefficient (R^2) for fitness ability, Q^2_{LOO} for internal predictive ability and root mean square error (RMSE). Moreover, seven-fold cross-validation correlation coefficient ($Q^2_{\text{7-fold}}$) was also employed to check for reliability and robustness. The external predictive power of the QSAR model was estimated by the external cross-validation correlation coefficient (Q^2_{ext}) defined as follows:

$$Q^2_{ext} = 1 - \frac{\sum_{i=1}^{m}(y_i - y_{pred})^2}{\sum_{i=1}^{m}(y_i - \overline{y}_{tr})^2}$$

where y_{i} and y_{pred} are the experimental and predicted values of the bioactivity of the

389 compounds in the test set, respectively; $\bar{y}_{tr}$ is the averaged value of the dependent variable
390 for the training set; and *m* is the number of the compounds in the test set.

391 The applicability domain is important for a proposed QSAR model, which is defined by
392 the nature of the chemicals in the dataset and can be characterized in different way. The
393 leverage (*h*) approach[46] is the commonly used methodology, which defined as follows:

394 $$h_i = x_i(X^T X)^{-1} x_i^T \qquad (i = 1, \ldots, n)$$

395 where x_i is the descriptor row-vector of the query chemical, and X is the $n \times k$ matrix of the
396 dataset (*k* is the number of model descriptors and *n* is the number of query compounds). The
397 warning leverage h^* was calculated by $3k'/n$, where k' is the number of variables used in the
398 QSAR model plus one. If the leverage value of a compound is higher than h^*, it is mean that
399 the predicted activity was the result of extrapolation of the model and may be unreliable. The
400 Williams plot (leave-one-out cross-validated standardized errors versus leverage values)
401 could provide an efficient way for verifing the presence of Y outliers (i.e., compounds with
402 cross validated standardized residuals greater than three standard deviation units, >3σ) and X
403 outliers (i.e., compounds with leverage values greater than h^*).

404 **RESULTS AND DISCUSSION**

405 **Synthesis.** As shown in Scheme 1, 3-formylindoles (**II-1**~**II-4**) were easily obtained by
406 Vilsmeier-Haack formylation reaction of indoles (**I-1**~**I-4**) with *N*,*N*-dimethylformamide
407 (DMF) in the presence of phosphorus oxychloride ($POCl_3$). Subsequently, **II-1**~**II-4** reacted
408 with arylsulfonyl chlorides to afford 3-formyl-*N*-arylsulfonylindoles (**IV-1**~**IV-13**).
409 3-Acyl-*N*-arylsulfonylindoles (**IV-14**~**IV-33**) were prepared as shown in Scheme 2. Starting
410 from **I-1**~**I-4**, the arylsulfonyl substituents were firstly introduced at their *N*-1 position to
411 afford *N*-arylsulfonylindoles (**III-1**~**III-17**). Then introduction of the different acyl groups at

412 the C-3 position of **III-1**~**III-17** gave 3-acyl-*N*-arylsulfonylindoles (**IV-14**~**IV-33**). Finally, as
413 described in Scheme 3, *N*-arylsulfonyl-3-acylindole arylcarbonyl hydrazone derivatives
414 (**V-1**~**V-54**) were smoothly prepared by the reaction of **IV-1**~**IV-33** with the corresponding
415 hydrazides. The structures of all target compounds were well characterized by ^{1}H NMR, ^{13}C
416 NMR, HRMS, MS, and mp. Additionally, to confirm the three-dimensional structural
417 information of **V-1**~**V-54**, the single-crystal structure of **V-33** was determined by X-ray
418 crystallography as illustrated in Figure 1. It demonstrated that the substituents on the C=N
419 bond of **V-33** adopted *trans* configuration. And if the substituents on the C=N bond of **V-33**
420 adopted *cis* configuration, big steric effects could be observed between the indolyl ring and
421 the arylcarbonylamino group. Crystallographic data (excluding structure factors) for the
422 structure of **V-33** have been deposited with the Cambridge Crystallographic Data Centre as
423 supplementary publication number CCDC 915720. Copies of the data can be obtained, free of
424 charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44
425 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
426 **Nematicidal Activity.** The nematicidal activity of **V-1**~**V-54** against *B. xylophilus* was
427 indicated in Table 1. Some compounds such as **V-6**, **V-12**, **V-19**, **V-20**, **V-27**, **V-38**, **V-39**, and
428 **V-49** showed the potent nematicidal activity with the LC_{50} values ranging from 1 to 2 mg/L.
429 Especially **V-12** and **V-39** displayed the best promising nematicidal activity with the LC_{50}
430 values of 1.0969 and 1.2632 mg/L, respectively. On the other hand, some interesting results
431 of the structure-activity relationships of **V-1**~**V-54** were also observed: a) When R^3 = H and
432 R^4 = Ph, introduction of R^1 and R^2 together as the electron-withdrawing substituents could
433 lead to the pronounced compound (*e.g.*, **V-12** *vs.* **V-1**~**V-11** and **V-13**). For example, the LC_{50}
434 of **V-12** (containing R^1 = 5-CN and R^2 = 3-NO_2) was 1.0969 mg/L. It is noteworthy that if

introduction of R^2 as two electron-withdrawing substituents (such as NO_2 and Cl) could result in the more potent compound **V-6** than those containing R^2 as one electron-withdrawing substituent (*e.g.*, **V-4** and **V-5**). That is, electron-deficient of the indolyl ring and the phenyl ring of *N*-arylsulfonyl group could favour their nematicidal activity. b) When R^1 = H and R^3 = Me, introduction of R^2 and R^4 together as electron-donating substituents could generally afford the promising compound (*e.g.*, **V-19** *vs.* **V-14**~**V-18** and **V-20**~**V-26**). For example, **V-19** contains R^2 as 4-Me and R^4 as (3-Me)Ph with the LC_{50} value of 1.5955 mg/L. c) When R^1 = 6-Me and R^3 = Me (**V-27**~**V-45**), introduction of R^2 as H, 4-OMe or 4-Cl and R^4 as Ph could produce the promising compounds (*e.g.*, **V-27**, **V-38** and **V-39**). d) When R^3 = Me and R^4 = Ph (**V-46**~**V-51**), introduction of R^1 as 5-NO_2 and R^2 as H could lead to the pronounced compound (*e.g.*, **V-49**). e) Interestingly, the proper chain length of R^3 was essential for the nematicidal activity. For example, the LC_{50} values of **V-52** (R^3 = Et) and **V-53** (R^3 = *n*-pentyl) were 3.7058 and 6.6758 mg/L, respectively; whereas the LC_{50} value of **V-14** (R^3 = Me) was 2.3985 mg/L. All in all, introduction of R^1 and R^2 together as the electron-withdrawing substituents, R^3 as the methyl group, and R^4 as the phenyl with the electron-donating substituents could be taken into account for further preparation of this kind of compounds as nematicidal agents.

QSAR Model. Through the KS method, a training set containing 40 compounds and a test set containing 14 compounds were obtained. To select the molecular parameters that are most relevant to the LC_{50} values of the compounds, 851 structural descriptors calculated by the DRAGON 5.4 were used as the inputs for GA selection procedure. When adding another variable did not improve the performance of the model significiently, the optimal subset size was believed to obtain. In the current work, the LOO cross validation was used to evaluate

458 the proposed QSAR models. On the basis of this principle, the six-variable model was
459 selected as the best model. The corresponding regression equation and the statistical
460 parameters were

461 Y = –0.377EEig05x – 0.421EEig13d + 0.467BEHm8 + 0.967E1m + 0.693R1m+ –
462 0.694R3m+ –17.276

463 Where Y is the LC_{50} values (μmol/L).

464 $n_{\text{training set}}$ = 40 $R^2_{\text{training set}}$ = 0.791 $\text{RMSE}_{\text{training set}}$ = 3.279 Q^2_{LOO} = 0.701

465 RMSE_{LOO} = 3.929 $Q^2_{\text{7-fold}}$ = 0.715 $\text{RMSE}_{\text{7-fold}}$ = 0.370

466 $n_{\text{test set}}$ =14 Q^2_{ext} = 0.774 $\text{RMSE}_{\text{test set}}$ = 3.412

467 The best six-parameter model gave the correlation coefficient ($R^2_{\text{training set}}$), Q^2_{LOO} and
468 $Q^2_{\text{7-fold}}$ were 0.791, 0.701 and 0.715, respectively. The prediction ability of a QSAR model is
469 very important, and statistical parameters for the test set were Q^2_{ext} = 0.774 and $\text{RMSE}_{\text{test set}}$ =
470 3.412, which is satisfactory. From the statistical parameters discussed above, it indicates that
471 the proposed model is stable, robust and predictive. The predicted LC_{50} values by the derived
472 model are listed in Table 2, and the regression plot of the developed best model is shown in
473 Figure 2.

474 From a deep analysis of the descriptors used in the proposed model, we could gain some
475 insight into the factors that would influence the bioactivity of the compounds. The relative
476 importance of the descriptors is weighted by the standardized regression coefficient value of
477 the descriptor. The most important descriptor is the E1m (1st component accessibility
478 directional WHIM index/weighted by atomic masses), which is a WHIM descriptor. WHIM
479 descriptors are built in such a way to capture relevant molecular 3D information regarding
480 molecular size, shape, symmetry, and atom distribution with respect to invariant reference

481 frames. R1m+ is a GETAWAY descriptor, which represents R maximal autocorrelation of lag
482 1/weighted by atomic masses. Another important descriptor is R3m+ (R maximal
483 autocorrelation of lag 3/weighted by atomics masses), which also belongs to GETAWAY
484 descriptor. GETAWAY (Geometry, Topology, and Atom-Weights-Assembly) is derived from
485 the leverage matrix which is deduced by the centering all of the atomic coordinates. BEHm8
486 is a Burden eigenvalues descriptor weighted by atomics masses. The above four descriptors
487 all are weighted by atomics masses, that represents atomics masses having an important
488 correlation with the bio-ability. EEig05x represents Eigenvalue 05 from edge adjacency
489 matrix weighted by edge degrees, which belongs to edge adjacency indices. EEig13d is an
490 edge adjacency indices descriptor similar to EEig05x, and the difference is that EEig13d is
491 weighted by dipole moments. It can be seen from the above discussion about the descriptors
492 that the structural factors that are likely to govern the activities of these compounds including:
493 molecular masses (a negative correlation with the bioactivity) and molecular polarity (a
494 positive correlation with bioactivity).

495 QSAR model should be verified by their chemical domain applicability. In this work, as
496 shown in Figure 3, the applicability domain (AD) of the model and the reliability of the
497 prediction were evaluated by the leverage approach expressed as Williams plot. It is obvious
498 that only one compound (**V-6**) in the training set has the hat value higher than the warning h^*
499 value of 0.525, and thus is regarded as a structural outlier. The predicted value of this
500 compound would be more reliable when regarded as extrapolation of the model, but the
501 compound has a small residual, so it is a "good leverage" compound. There is no response
502 outlier both for the training set and test set.

503 In conclusion, fifty-four novel *N*-arylsulfonyl-3-acylindole arylcarbonyl hydrazone

504 derivatives (**V-1~V-54**) were prepared and tested for their nematicidal activity against *B.*
505 *xylophilus in vivo*. Among all the compounds, **V-12** and **V-39** displayed the best promising
506 nematicidal activity with the LC_{50} values of 1.0969 and 1.2632 mg/L, respectively. It
507 generally suggested that introduction of R^1 and R^2 together as the electron-withdrawing
508 substituents, R^3 as the methyl group, and R^4 as the phenyl with the electron-donating
509 substituents can be considered for future preparation of this kind of compounds as
510 nematicidal agents. QSAR model demonstrated that the structural factors, such as molecular
511 masses (a negative correlation with the bioactivity) and molecular polarity (a positive
512 correlation with bioactivity), are likely to govern the nematicidal activities of these
513 compounds.
514

515 **ASSOCIATED CONTENT**

516 **Supporting Information**

517 ^{1}H NMR, HRMS, MS, mp, or ^{13}C NMR data for compounds **III-3~III-17**, **IV-3~IV-13**,
518 **IV-16~IV-33**, and **V-21~V-54**. This material is available free of charge via the Internet at
519 http://pubs.acs.org.

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528 **Notes**

529 The authors declare no competing financial interest.

530

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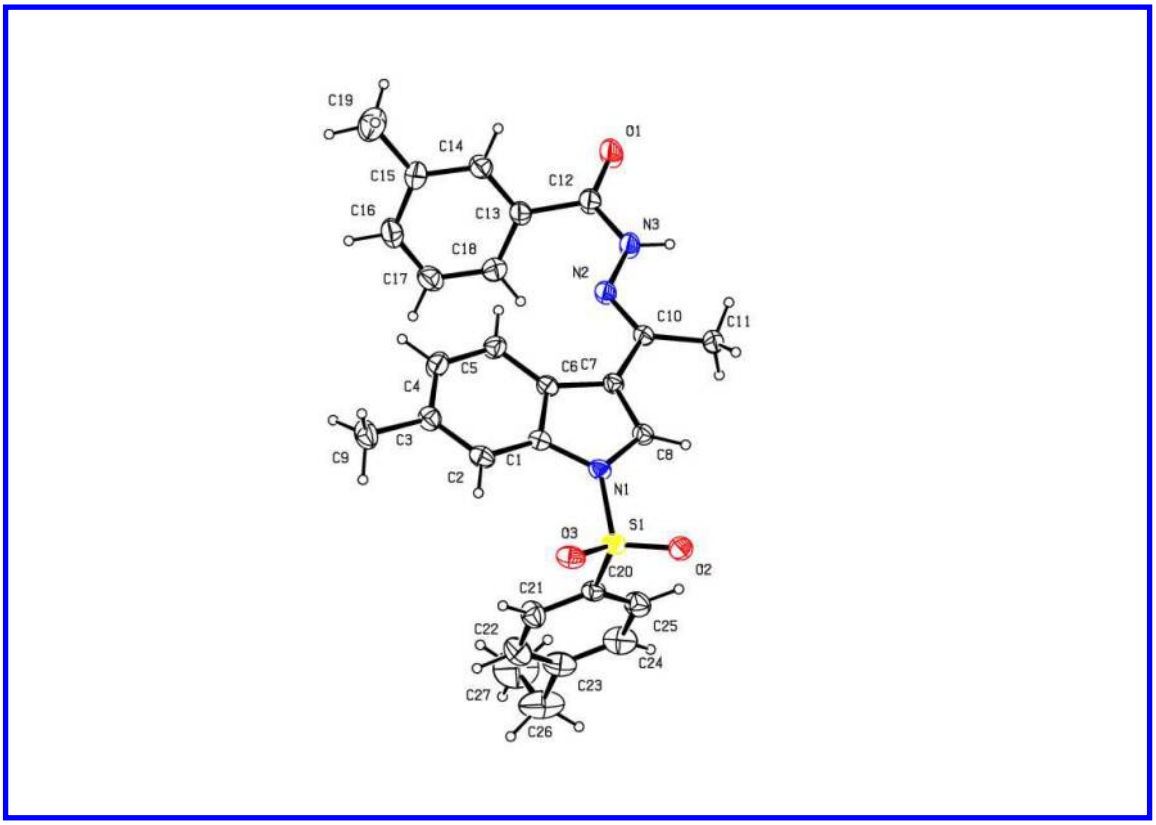


Figure 1. The X-ray crystal structure of **V-33**.

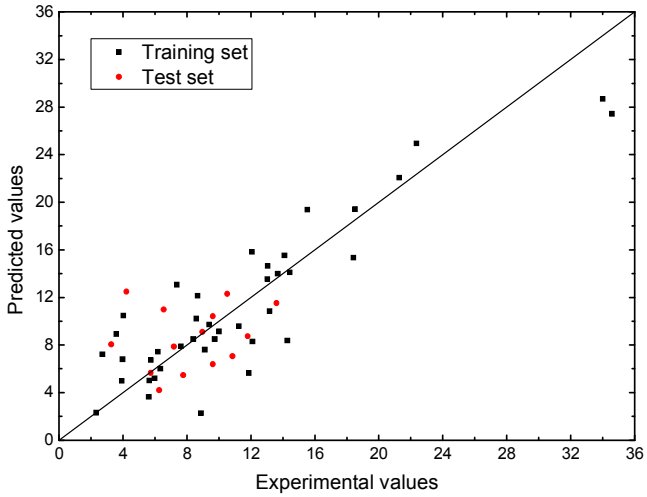


Figure 2. Plot of experimental and predicted biological activity values (LC_{50}, μmol/L) of 54 compounds by GA-MLR model for the training and test set.

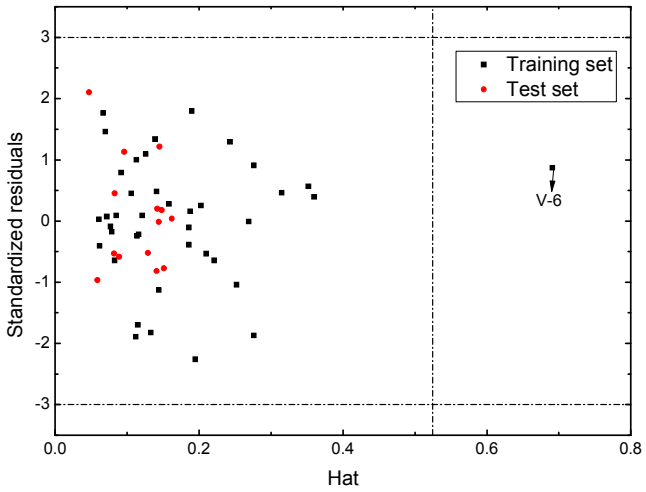
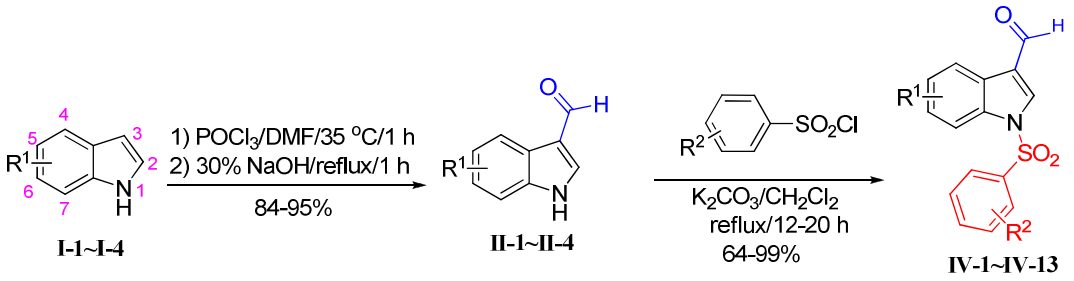


Figure 3. Williams plot for the training and test set by GA-MLR model with six descriptors. The dotted lines are the 3σ limit and the warning value of hat ($h^* = 0.525$).

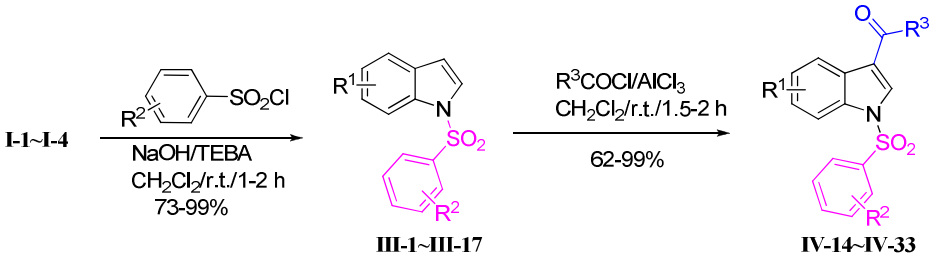


I-1: R^1 = H
I-2: R^1 = 6-Me
I-3: R^1 = 5-CN
I-4: R^1 = 5-NO_2

II-1: R^1 = H
II-2: R^1 = 6-Me
II-3: R^1 = 5-CN
II-4: R^1 = 5-NO_2

IV-1: R^1 = H, R^2 = 4-Me; **IV-2**: R^1 = H, R^2 = 4-OMe;
IV-3: R^1 = H, R^2 = 4-NHAc; **IV-4**: R^1 = H, R^2 = 4-Cl;
IV-5: R^1 = H, R^2 = 3-NO_2; **IV-6**: R^1 = H, R^2 = 3-NO_2, 4-Cl;
IV-7: R^1 = 6-Me, R^2 = 4-Me; **IV-8**: R^1 = 6-Me, R^2 = 4-OMe;
IV-9: R^1 = 6-Me, R^2 = 4-Cl; **IV-10**: R^1 = 6-Me, R^2 = 3-NO_2;
IV-11: R^1 = 5-CN, R^2 = 4-Me; **IV-12**: R^1 = 5-CN, R^2 = 3-NO_2;
IV-13: R^1 = 5-NO_2, R^2 = 4-Me.

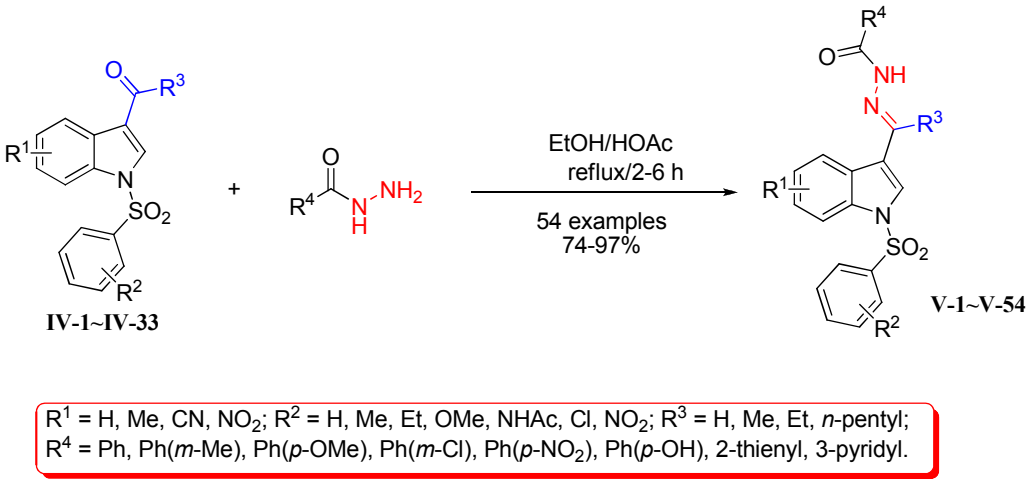
Scheme 1. Synthetic Route for the Preparation of IV-1~IV-13.



III-1: R^1 = R^2 = H; **III-2**: R^1 = H, R^2 = 4-Me; **III-3**: R^1 = H, R^2 = 4-OMe;
III-4: R^1 = H, R^2 = 4-Cl; **III-5**: R^1 = H, R^2 = 3-NO_2; **III-6**: R^1 = 6-Me, R^2 = H;
III-7: R^1 = 6-Me, R^2 = 4-Me; **III-8**: R^1 = 6-Me, R^2 = 4-Et; **III-9**: R^1 = 6-Me, R^2 = 4-OMe;
III-10: R^1 = 6-Me, R^2 = 4-Cl; **III-11**: R^1 = 6-Me, R^2 = 3-NO_2; **III-12**: R^1 = 5-CN, R^2 = H;
III-13: R^1 = 5-CN, R^2 = 4-Me; **III-14**: R^1 = 5-CN, R^2 = 4-Cl; **III-15**: R^1 = 5-NO_2, R^2 = H;
III-16: R^1 = 5-NO_2, R^2 = 4-Me; **III-17**: R^1 = 5-NO_2, R^2 = 4-Cl.

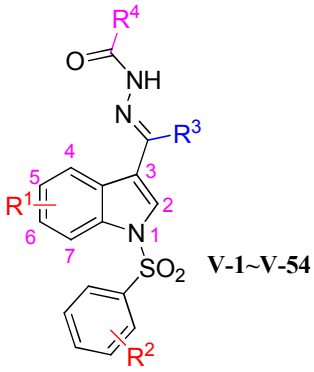
IV-14: R^1 = R^2 = H, R^3 = Me; **IV-15**: R^1 = H, R^2 = 4-Me, R^3 = Me; **IV-16**: R^1 = H, R^2 = 4-OMe, R^3 = Me;
IV-17: R^1 = H, R^2 = 4-Cl, R^3 = Me; **IV-18**: R^1 = H, R^2 = 3-NO_2, R^3 = Me; **IV-19**: R^1 = 6-Me, R^2 = H, R^3 = Me;
IV-20: R^1 = 6-Me, R^2 = 4-Me, R^3 = Me; **IV-21**: R^1 = 6-Me, R^2 = 4-Et, R^3 = Me; **IV-22**: R^1 = 6-Me, R^2 = 4-OMe, R^3 = Me;
IV-23: R^1 = 6-Me, R^2 = 4-Cl, R^3 = Me; **IV-24**: R^1 = 6-Me, R^2 = 3-NO_2, R^3 = Me; **IV-25**: R^1 = 5-CN, R^2 = H, R^3 = Me;
IV-26: R^1 = 5-CN, R^2 = 4-Me, R^3 = Me; **IV-27**: R^1 = 5-CN, R^2 = 4-Cl, R^3 = Me; **IV-28**: R^1 = 5-NO_2, R^2 = H, R^3 = Me;
IV-29: R^1 = 5-NO_2, R^2 = 4-Me, R^3 = Me; **IV-30**: R^1 = 5-NO_2, R^2 = 4-Cl, R^3 = Me; **IV-31**: R^1 = H, R^2 = H, R^3 = Et;
IV-32: R^1 = H, R^2 = H, R^3 = *n*-pentyl; **IV-33**: R^1 = H, R^2 = 4-Me, R^3 = *n*-pentyl.

Scheme 2. Synthetic Route for the Preparation of IV-14~IV-33.



Scheme 3. Synthetic Route for the Preparation of V-1~V-54.

Table 1. Nematicidal Activity of Compounds V-1~V-54 against *B. xylophilus*.



V-1~V-54

compound	R^1	R^2	R^3	R^4	LC_{50} (mg/L)
V-1	H	4-Me	H	Ph	7.6852
V-2	H	4-OMe	H	Ph	6.7337
V-3	H	4-NHAc	H	Ph	3.3856
V-4	H	4-Cl	H	Ph	14.8897
V-5	H	3-NO_2	H	Ph	6.4652
V-6	H	3-NO_2, 4-Cl	H	Ph	1.8956
V-7	6-Me	4-Me	H	Ph	3.0984
V8	6-Me	4-OMe	H	Ph	4.3049
V-9	6-Me	4-Cl	H	Ph	10.0989
V-10	6-Me	3-NO_2	H	Ph	5.4508
V-11	5-CN	4-Me	H	Ph	2.4815
V-12	5-CN	3-NO_2	H	Ph	1.0969
V-13	5-NO_2	4-Me	H	Ph	2.7624
V-14	H	H	Me	Ph	2.3985
V-15	H	H	Me	(*m*-Me)Ph	4.5374

V-16	H	H	Me	(*p*-OMe)Ph	3.7563
V-17	H	H	Me	(*m*-Cl)Ph	15.6279
V-18	H	4-Me	Me	Ph	3.8666
V-19	H	4-Me	Me	(*m*-Me)Ph	1.5955
V-20	H	4-OMe	Me	Ph	1.8840
V-21	H	4-Cl	Me	Ph	2.9612
V-22	H	3-NO_2	Me	Ph	5.0187
V-23	H	3-NO_2	Me	(*m*-Me)Ph	2.9816
V-24	H	3-NO_2	Me	(*p*-OMe)Ph	4.4858
V-25	H	3-NO_2	Me	(*m*-Cl)Ph	4.3052
V-26	H	3-NO_2	Me	(*p*-NO_2)Ph	6.6147
V-27	6-Me	H	Me	Ph	1.4112
V-28	6-Me	H	Me	(*p*-OMe)Ph	2.9201
V-29	6-Me	H	Me	(*p*-NO_2)Ph	8.8139
V-30	6-Me	4-Me	Me	Ph	4.2817
V-31	6-Me	4-Et	Me	2-thienyl	6.0769
V-32	6-Me	4-Et	Me	3-pyridyl	6.2622
V-33	6-Me	4-Et	Me	(*m*-Me)Ph	6.7608
V-34	6-Me	4-Et	Me	(*p*-OMe)Ph	4.8998
V-35	6-Me	4-Et	Me	(*m*-Cl)Ph	5.9591
V-36	6-Me	4-Et	Me	(*p*-NO_2)Ph	10.7303
V-37	6-Me	4-Et	Me	(*p*-OH)Ph	6.5078

V-38	6-Me	4-OMe	Me	Ph	1.8538
V-39	6-Me	4-Cl	Me	Ph	1.2632
V-40	6-Me	3-NO_2	Me	Ph	4.2262
V-41	6-Me	3-NO_2	Me	2-thienyl	6.3488
V-42	6-Me	3-NO_2	Me	3-pyridyl	3.6371
V-43	6-Me	3-NO_2	Me	(*m*-Cl)Ph	4.7920
V-44	6-Me	3-NO_2	Me	(*p*-NO_2)Ph	3.2280
V-45	6-Me	3-NO_2	Me	(*p*-OH)Ph	2.7766
V-46	5-CN	H	Me	Ph	5.2533
V-47	5-CN	4-Me	Me	Ph	2.6172
V-48	5-CN	4-Cl	Me	Ph	5.7650
V-49	5-NO_2	H	Me	Ph	1.8339
V-50	5-NO_2	4-Me	Me	Ph	3.6960
V-51	5-NO_2	4-Cl	Me	Ph	5.5885
V-52	H	H	Et	Ph	3.7058
V-53	H	H	*n*-pentyl	Ph	6.6758
V-54	H	4-Me	*n*-pentyl	Ph	4.7448
emamectin benzoate	/	/	/	/	0.4102

Table 2. Experimental and Predicted Activity (LC_{50}, μmol/L) by Developed QSAR Model

number	compound	Status	experimental activity	predicted activity
1	**V-1**	Training	18.41	15.34
2	**V-2**	Training	15.53	19.38
3	**V-3**	Training	7.35	13.07
4	**V-4**	Training	34.00	28.68
5	**V-5**	Training	14.42	14.09
6	**V-6**	Training	3.93	4.98
7	**V-7**	Test	7.18	7.87
8	**V-8**	Test	9.62	10.41
9	**V-9**	Training	22.35	24.93
10	**V-10**	Test	11.79	8.74
11	**V-11**	Training	5.61	3.64
12	**V-12**	Training	2.32	2.3
13	**V-13**	Training	5.97	5.2
14	**V-14**	Training	5.75	6.73
15	**V-15**	Test	10.52	12.3
16	**V-16**	Training	8.39	8.5
17	**V-17**	Training	34.58	27.43
18	**V-18**	Test	8.96	9.11
19	**V-19**	Training	3.58	8.91

20	**V-20**	Test	4.21	12.48
21	**V-21**	Test	6.55	10.99
22	**V-22**	Test	10.85	7.05
23	**V-23**	Test	6.26	4.21
24	**V-24**	Training	9.11	7.6
25	**V-25**	Training	8.66	12.14
26	**V-26**	Training	13.03	13.54
27	**V-27**	Test	3.27	8.04
28	**V-28**	Training	6.33	6
29	**V-29**	Training	18.5	19.42
30	**V-30**	Test	9.61	6.4
31	**V-31**	Training	13.05	14.64
32	**V-32**	Test	13.60	11.52
33	**V-33**	Training	14.28	8.37
34	**V-34**	Training	10.00	9.15
35	**V-35**	Training	12.06	15.81
36	**V-36**	Training	21.27	22.06
37	**V-37**	Training	13.68	14
38	**V-38**	Training	4.02	10.48
39	**V-39**	Training	2.71	7.23
40	**V-40**	Training	8.87	2.27
41	**V-41**	Training	13.16	10.84

42	**V-42**	Training	7.62	7.88
43	**V-43**	Training	9.38	9.7
44	**V-44**	Training	6.19	7.43
45	**V-45**	Training	5.64	5.01
46	**V-46**	Training	11.87	5.65
47	**V-47**	Test	5.73	5.67
48	**V-48**	Training	12.09	8.29
49	**V-49**	Training	3.97	6.8
50	**V-50**	Test	7.76	5.46
51	**V-51**	Training	11.25	9.59
52	**V-52**	Training	8.59	10.22
53	**V-53**	Training	14.1	15.54
54	**V-54**	Training	9.73	8.49

TOC

Synthesis and Quantitative Structure-Activity Relationship (QSAR) Study of Novel *N*-Arylsulfonyl-3-Acylindole Arylcarbonyl Hydrazone Derivatives as Nematicidal Agents

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