Hindawi
Heteroatom Chemistry
Volume 2022, Article ID 6078017, 8 pages
https://doi.org/10.1155/2022/6078017

Research Article

Synthesis, Structure, and Antifungal Activities of 3-(Difluoromethyl)-Pyrazole-4-Carboxylic Oxime Ester Derivatives

Bin Wang,[1,3] Wei-Ting Chen,[1,3] Li-Jing Min,[2] Liang Han,[1] Na-Bo Sun,[3] and Xing-Hai Liu[1]

[1]*College of Chemical Engineering, Zhejiang University of Technology, Hangzhou 310014, China*
[2]*College of Life Science, Key Laboratory of Vector Biology and Pathogen Control of Zhejiang Province, Huzhou University, Huzhou 313000, Zhejiang, China*
[3]*College of Biology and Environmental Engineering, Zhejiang Shuren University, Hangzhou 310015, Zhejiang, China*

Correspondence should be addressed to Na-Bo Sun; 600421@zjsru.edu.cn and Xing-Hai Liu; xhliu@zjut.edu.cn

Received 9 April 2022; Revised 25 June 2022; Accepted 18 July 2022; Published 28 August 2022

Academic Editor: David Barker

Copyright © 2022 Bin Wang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Fifteen new pyrazole-4-carboxylic oxime ester derivatives were conveniently synthesized, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR, HRMS, and X-ray diffraction. Antifungal assays indicated that some of these compounds possessed good activity against *S. sclerotiorum, B. cinerea, R. solani, P. oryae,* and *P. piricola* at 50 ppm. Structure-activity relationships (SAR) were studied by molecular docking simulation.

1. Introduction

Nitrogen-linked heterocycles are an important skeleton in synthetic chemistry or natural product chemistry because of their diversity of structure and activity [1–5]. Among these nitrogen-linked heterocycles; pyrazole compounds, especially pyrazole carboxamide compounds, exhibit diverse activity, with examples possessing nematocidal [6–10], insecticidal [11, 12], antibacterial [13], IRAK4 inhibitor [14], antiproliferative [15], antimicrobial [16], immunomodulatory [17], and fungicidal activity [18–20]. Some pyrazole amide compounds have been commercialized as fungicides [21] or insecticides [22]. For example, benzovindiflupyr, a new succinate dehydrogenase inhibitor (SDH) fungicide developed by Syngenta. In these SDH fungicides, the pyrazole ring and carboxamide group are the key functional groups accounting for their activity.

In our previous work, many nitrogen-linked heterocyclic compounds with diverse activity were synthesized [23–27], including many fungicidal pyrazole carboxamide derivatives. In this work, the carboxamide group was replaced by an oxime ester group (Figure 1). In this paper, a set of pyrazole oxime esters were synthesized, and their fungicidal activity was assessed. This data was used to assess the structure-activity relationship (SAR) using molecular docking.

2. Materials and Methods

2.1. Instruments. Melting points were measured by an X-4 apparatus (Gongyi, China) and the temperature was uncorrected. ^{1}H NMR and ^{13}C NMR spectra were tested on a Bruker AV III-500 instrument and ^{13}C NMR spectra were tested on a Bruker AV-400 instrument in $CDCl_3$. DART-HRMS was measured on a JEOL AccuTOF instrument. Single crystal diffraction was performed on a Bruker CCD area detector diffractometer.

2.2. Chemicals. All benzaldehydes (98% purity) were purchased from Duodian Chemical Co. Ltd, China. Ethyl difluoroacetate and methyl hydrazine were purchased from Taizhou Yongxiang Pharmaceutical company; triethyl orthoformate, acetic acid, ethanol, hydroxylamine hydrochloride, and dichlorosulfoxide were purchased from

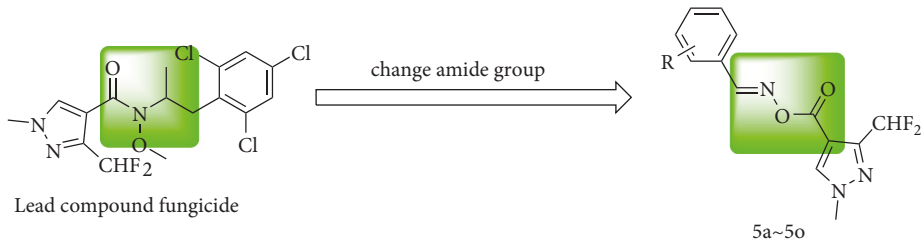


Figure 1: Design strategy of pyrazole oxime ester compounds 5a~5o.

Mclean; sodium hydroxide was purchased from Yongda Reagent company; potassium carbonate, hydrochloric acid, and DCM were purchased from Sinopharm Chemical Reagent Co. Ltd.; TEA was purchased from Qidian Reagent company.

2.3. Experimental Methods

2.3.1. Synthesis of Intermediate Oximes. Benzaldehyde (9.5 mmol) was added to a mixture of Na_2CO_3 (0.5 g, 4.7 mmol) in ethanol (10 mL) and the mixture was stirred at room temperature. After 30 min, $NH_2OH{\cdot}HCl$ (0.7 g, 10.4 mmol) was added, and the reaction was monitored by TLC. The water phase was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated brine (3 × 10 mL), dried with $MgSO_4$, and evaporated in vacuo. The crude product was recrystallized from ethanol and used without further purification.

*2.3.2. Synthesis of Target Compounds **5a-5o**.* The two key intermediates: benzaldehyde oxime and 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonyl chloride were synthesized according to our previous reported work [26].

A solution of intermediate benzaldehyde oxime (7.5 mmol) and NEt_3 (1 mL) in dichloromethane (20 mL), 3-(difluoromethyl)-1-methyl-1*H*-pyrazole-4-carbonyl chloride (7.5 mmol) was added dropwise at ice bath condition, then the mixture was stirred at 20°C. When the reaction was complete (TLC monitoring ($V_{EA}/V_{PE} = 1/2$)), the solvent was removed *in vacuo*, and the crude products were purified by flash chromatography to afford the title compound **5a-5o**.

*2.3.3. (E)-Benzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime **5a**.* White solid, yield 73%, m.p. 171–177°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.46 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.80–7.76 (m, 2H, Ph), 7.52–7.42 (m, 3H, Ph), 7.12 (t, J = 53.8 Hz, 1H, CHF_2), 4.01 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.2, 156.8, 146.7, 146.5 (t, J = 26.3 Hz, Py-CHF_2), 146.2, 135.3, 131.9, 129.8, 128.9, 128.5, 109.3 (t, J = 238.4 Hz, CHF_2), 110.8, 39.81; HRMS (DART) for $C_{13}H_{11}F_2N_3O_2$ m/z: calculated, 280.0892, found, 280.0897 $[M+H]^+$.

*2.3.4. (E)-2-Methylbenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime **5b**.* White solid, yield 72%, m.p. 120–123°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.71 (s, 1H, CH), 8.04 (d, J = 1.0 Hz, 1H, pyrazole), 7.88 (dd, J = 7.8, 1.4 Hz, 1H, Ph), 7.38 (td, J = 7.5, 1.4 Hz, 1H, Ph), 7.28–7.24 (m, 2H, Ph), 7.14 (t, J = 53.8 Hz, 1H, CHF_2), 4.01 (s, 3H, CH_3), 2.51 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:159.2, 155.7, 146.6 (t, J = 26.3 Hz, Py-CHF_2), 138.2, 135.1, 131.5, 131.0, 128.3, 128.2, 126.3, 110.8, 109.2 (t, J = 238.4 Hz, CHF_2), 39.8, 19.9; HRMS (DART) for $C_{14}H_{13}F_2N_3O_2$ m/z: calculated, 294.1049, found, 294.1054 $[M+H]^+$.

*2.3.5. (E)-3-Methylbenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime **5c**.* White solid, yield 71%, m.p. 119–123°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.42 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.65 (d, J = 2.1 Hz, 1H, Ph), 7.53 (d, J = 7.3 Hz, 1H, Ph), 7.34–7.26 (m, 2H, Ph), 7.12 (t, J = 53.8 Hz, 1H, CHF_2), 4.00 (s, 3H, CH_3), 2.39 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:159.2, 156.7, 146.5 (t, J = 26.3 Hz, Py-CHF_2), 138.8, 135.2, 132.7, 129.7, 128.7, 128.5, 126.0, 110.8, 109.3 (t, J = 238.4 Hz, CHF_2), 39.8, 21.1; HRMS (DART) for $C_{14}H_{13}F_2N_3O_2$ m/z: calculated, 294.1049, found, 294.1054 $[M+H]^+$.

*2.3.6. (E)-4-Methylbenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime **5d**.* White solid, yield 71%, m.p. 147–150°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.42 (s, 1H, CH), 8.02 (s, 1H, Pyrazole), 7.67 (d, J = 8.1 Hz, 2H, Ph), 7.24 (d, J = 8.0 Hz, 2H, Ph), 7.12 (t, J = 53.8 Hz, 1H, CHF_2), 4.00 (s, 3H, CH_3), 2.40 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz), δ: 159.3, 156.7, 146.4 (t, J = 26.3 Hz, Py-CHF_2), 142.5, 135.3, 129.6 (2C, Ph), 128.4 (2C, Ph), 126.9, 110.9, 109.3 (t, J = 238.1 Hz, CHF_2), 39.8, 21.6; HRMS (DART) for $C_{14}H_{13}F_2N_3O_2$ m/z: calculated, 294.1049, found, 294.1054 $[M+H]^+$.

*2.3.7. (E)-2-Methoxybenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime **5e**.* Light yellow solid, yield 70%, m.p. 116–120°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.86 (s, 1H, CH), 8.02–8.01 (m, 2H, pyrazole, Ph), 7.46 (ddd, J = 8.8, 7.5, 1.8 Hz, 1H, Ph), 7.16 (t, J = 53.8 Hz, 1H, CHF_2), 7.00 (t, J = 7.5 Hz, 1H, Ph), 6.93 (dd, J = 8.5, 0.9 Hz, 1H, Ph), 4.00 (s, 3H, CH_3), 3.89 (s, 3H, CH_3O), 1.26 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 159.3, 158.4, 152.7, 146.4 (t, J = 26.3 Hz, Py-CHF_2), 135.1, 133.2, 127.4, 120.7, 118.1, 111.0, 110.8, 109.1 (t, J = 238.4 Hz, CHF_2), 55.5, 39.7; HRMS (DART) for $C_{14}H_{13}F_2N_3O_3$ m/z: calculated, 310.0998, found, 310.1003 $[M+H]^+$.

2.3.8. (E)-4-Methoxybenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5f***. Light yellow solid, yield 70%, m.p. 131–138°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.40 (s, 1H, CH), 8.02 (s, 1H, pyrazole), 7.73 (d, J = 8.8 Hz, 2H, Ph), 7.12 (t, J = 53.8 Hz, 1H, CHF_2), 6.96 (d, J = 8.8 Hz, 2H, Ph), 4.00 (s, 3H, CH_3), 3.86 (s, 3H, CH_3O); ^{13}C NMR ($CDCl_3$, 101 MHz), δ: 162.5, 159.4, 156.3, 146.4 (t, J = 26.3 Hz, Py-CHF_2), 135.3, 132.3, 130.2 (2C, Ph), 122.2, 114.4 (2C, Ph), 109.3 (t, J = 237.1 Hz, CHF_2), 55.4, 39.4; HRMS (DART) for $C_{14}H_{13}F_2N_3O_3$ m/z: calculated, 310.0998, found, 310.1003 $[M+H]^+$.

2.3.9. (E)-3,4,5-Trimethoxybenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5g***. White solid, yield 68%, m.p. 153–157°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.37 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.10 (t, J = 53.8 Hz, 1H, CHF_2), 6.99 (s, 2H, Ph), 4.00 (s, 3H, CH_3), 3.91 (d, J = 3.4 Hz, 9H, CH_3O); ^{13}C NMR (101 MHz, $CDCl_3$) δ:159.2, 156.7, 153.4, 146.3 (t, J = 26.3 Hz, Py-CHF_2), 141.1, 135.3, 125.0, 110.7, 109.3 (t, J = 237.0 Hz, CHF_2), 105.5, 60.7, 56.2 (2C, OCH_3), 39.7; HRMS (DART) for $C_{14}H_{13}F_2N_3O_3$ m/z: calculated, 370.1209, found, 370.1213 $[M+H]^+$.

2.3.10. (E)-2-Bromobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5h***. Light yellow solid, yield 70%, m.p. 124–130°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.86 (s, 1H, CH), 8.11 (dd, J = 7.6, 2.0 Hz, 1H, Ph), 8.05 (s, 1H, pyrazole), 7.63 (dd, J = 7.8, 1.5 Hz, 1H, Ph), 7.39–7.33 (m, 2H, Ph), 7.14 (t, J = 53.8 Hz, 1H, CHF_2), 4.01 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:158.9, 155.8, 146.6 (t, J = 26.3 Hz, Py-CHF_2), 135.1, 133.1, 132.9, 129.3, 128.6, 127.7, 124.8, 110.3, 109.1 (t, J = 238.4 Hz, CHF_2), 39.7. HRMS (DART) for $C_{13}H_{10}{}^{79}BrF_2N_3O_2$ m/z: calculated, 357.9997, found, 358.0003 $[M+H]^+$; for $C_{13}H_{10}{}^{81}BrF_2N_3O_2$ m/z: calculated, 359.9977, found, 359.9972 $[M+H]^+$.

2.3.11. (E)-4-Bromobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5i***. Light yellow solid, yield 69%, m.p.180–183°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.41 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.66 (d, J = 8.5 Hz, 2H, Ph), 7.60 (d, J = 8.5 Hz, 2H, Ph), 7.09 (t, J = 53.8 Hz, 1H, CHF_2), 4.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 155.7, 153.7, 145.9 (t, J = 25.6 Hz, Py-CHF_2), 135.5, 132.3 (2C, Ph), 129.8 (2C, Ph), 128.8, 126.5, 109.3 (t, J = 237.3 Hz, CHF_2), 49.1, 40.2; HRMS (DART) for $C_{13}H_{10}{}^{79}BrF_2N_3O_2$ m/z: calculated, 357.9997, found, 358.0003 $[M+H]^+$; for $C_{13}H_{10}{}^{81}BrF_2N_3O_2$ m/z: calculated, 359.9977, found, 359.9977 $[M+H]^+$.

2.3.12. (E)-2-Nitrobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5j***. White solid, yield 73%, m.p. 146–149°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:9.09 (s, 1H, CH), 8.19 (ddd, J = 17.1, 8.0, 1.4 Hz, 2H, Ph), 8.06 (s, 1H, pyrazole), 7.76 (td, J = 7.6, 1.3 Hz, 1H, Ph), 7.70 (td, J = 7.8, 1.5 Hz, 1H, Ph), 7.13 (t, J = 53.7 Hz, 1H, CHF_2), 4.02 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:158.8, 153.6, 148.0, 146.9 (t, J = 24.8 Hz, Py-CHF_2), 135.3, 134.1, 132.0, 130.1, 125.5, 125.1, 110.2, 109.1 (t, J = 237.3 Hz, CHF_2), 39.9; HRMS (DART) for $C_{13}H_{10}F_2N_4O_4$ m/z: calculated, 325.0743, found, 325.0748 $[M+H]^+$.

2.3.13. (E)-3-Nitrobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5k***. Light yellow solid, yield 71%, m.p.172–176°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.59 (t, J = 1.9 Hz, 1H, Ph), 8.56 (s, 1H, CH), 8.35 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H, Ph), 8.21 (dt, J = 7.9, 1.4 Hz, 1H, Ph), 8.06 (s, 1H, pyrazole), 7.67 (t, J = 8.0 Hz, 1H, Ph), 7.07 (t, J = 53.8 Hz, 1H, CHF_2), 4.02 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 157.7, 153.4, 145.8, 145.5 (t, J = 27.3 Hz, Py-CHF_2), 145.3, 134.6, 132.5, 130.8, 129.1, 125.2, 122.5, 108.4 (t, J = 238.4 Hz, CHF_2), 38.9; HRMS (DART) for $C_{13}H_{10}F_2N_4O_4$ m/z: calculated, 325.0743, found, 325.0748 $[M+H]^+$.

2.3.14. (E)-4-Fluorobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5l***. Light yellow solid, yield 71%, m.p. 144–147°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.43 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.79 (dd, J = 8.8, 5.3 Hz, 2H, Ph), 7.14 (t, J = 8.6 Hz, 2H, Ph), 7.14 (t, J = 53.8 Hz, 1H, CHF_2), 4.00 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 159.1, 155.50, 146.4 (t, J = 26.3 Hz, Py-CHF_2), 135.3, 130.5 (d, J = 8.1 Hz, 2C, Ph), 126.1 (d, J = 3.0 Hz, Ph), 116.3 (d, J = 11.1 Hz, 2C, Ph), 110.7, 109.3 (t, J = 238.4 Hz, CHF_2), 39.8; HRMS (DART) for $C_{13}H_{10}F_3N_3O_2$ m/z: calculated, 298.0798, found, 298.0803 $[M+H]^+$.

2.3.15. (E)-4-(Trifluoromethyl)benzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5m***. White solid, yield 70%, m.p. 129–133°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.51 (s, 1H, CH), 8.05 (s, 1H, pyrazole), 7.90 (d, J = 8.1 Hz, 2H, Ph), 7.70 (d, J = 8.2 Hz, 2H, Ph), 7.08 (t, J = 53.8 Hz, 1H, CHF_2), 4.01 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:158.9, 155.3, 146.3 (t, J = 25.3 Hz, Py-CHF_2), 135.8, 135.6 (2C, Ph), 133.3, 128.7 (2C, Ph), 125.9 (q, J = 3.8 Hz, Ph), 124.9 (q, J = 272.8 Hz, CF_3), 110.0, 109.3 (t, J = 236.9 Hz, CHF_2), 39.8; HRMS (DART) for $C_{14}H_{10}F_5N_3O_2$ m/z: calculated, 348.0766, found, 348.0771 $[M+H]^+$.

2.3.16. (E)-4-Chlorobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5n***. White solid, yield 69%, m.p.163–169°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.43 (s, 1H, CH), 8.03 (s, 1H, pyrazole), 7.73 (d, J = 8.5 Hz, 2H, Ph), 7.44 (d, J = 8.5 Hz, 2H, Ph), 7.09 (t, J = 53.8 Hz, 1H, CHF_2), 4.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 101 MHz), δ: 159.0, 155.5, 146.5 (t, J = 24.3 Hz, Py-CHF_2), 138.0, 135.4, 132.3, 129.6 (2C, Ph), 129.3 (2C, Ph), 128.3, 109.3 (t, J = 237.0 Hz, CHF_2), 39.9; HRMS (DART) for $C_{13}H_{10}{}^{35}ClF_2N_3O_2$ m/z: calculated, 314.0502, found, 314.0508 $[M+H]^+$; for $C_{13}H_{10}{}^{37}ClF_2N_3O_2$ m/z: calculated, 316.0502, found, 316.0508 $[M+H]^+$.

2.3.17. (E)-2,4-Dichlorobenzaldehyde O-(3-(Difluoromethyl)-1-methyl-1h-pyrazole-4-carbonyl) Oxime ***5o***. White solid, yield 67%, m.p. 173–176°C; ^{1}H NMR ($CDCl_3$, 500 MHz), δ:8.83 (s, 1H, CH), 8.10 (d, J = 8.5 Hz, 1H, Ph), 8.05 (s, 1H, pyrazole), 7.47 (d, J = 2.1 Hz, 1H, Ph), 7.33 (ddd, J = 8.5, 2.0, 0.7 Hz, 1H, Ph), 7.11 (t, J = 53.8 Hz, 1H, CHF_2), 4.01 (s, 3H, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ:158.9, 152.7, 146.8 (t, J = 26.3 Hz, Py-CHF_2), 138.4, 135.7, 135.3, 129.9, 129.2, 127.9, 126.4, 110.4, 109.2 (t, J = 238.4 Hz, CHF_2), 39.9; HRMS (DART) for $C_{13}H_9{}^{35}Cl_2F_2N_3O_2$ m/z: calculated, 348.0113, found, 348.0118 $[M+H]^+$; for $C_{13}H_9{}^{37}Cl_2F_2N_3O_2$ m/z: calculated, 350.0113, found, 350.0118 $[M+H]^+$.

2.4. Structure Determination. One colorless crystal was cultivated in EtOH by self-volatilization with dimensions of 0.28 mm × 0.22 mm × 0.14 mm for X-ray on a Bruker CCD area detector diffractometer equipped with a graphite-monochromatic MoKα radiation (λ = 0.71073 Å). The structure of compound **5d** was solved using direct methods by ShelXS [28] structure solution program and refined with the ShelXL [29] refinement package using least squares minimization in Olex2 software [30]. The detailed crystal data are listed in Table 1.

2.5. Fungicidal Activity. Fungicidal activities of pyrazole-4-carboxylic oxime ester derivatives **5a**~**5o** were tested according to reported work [31, 32]. The antifungal activities of compounds **5a**-**5o** and fluxapyroxad were tested *in vitro* against *Gibberella zeae* (GZ), *Fusarium oxysporum* (FO), *Phytophthora infestans* (PI), *Phytophthora capsici* (PC), *Rhizoctonia solani* (RS), *Sclerotinia sclerotiorum* (SS), *Alternaria solani* (AS), *Physalospora piricola* (PP), *Cercospora arachidicola* (CA), and *Botrytis cinerea* (BC). The relative percent inhibition (%) has been determined using the mycelium growth rate method. The inhibition of the test compounds compared to the blank assay was calculated *via* the following equation:

$$\text{inhibition}\,(\%) = \frac{(\text{CK} - \text{CI})}{\text{CK}} \times 100\%, \quad (1)$$

where CK is the average diameter of mycelia in the blank test and CI is the average diameter of mycelia in the presence of those compounds. All experiments were replicated three times.

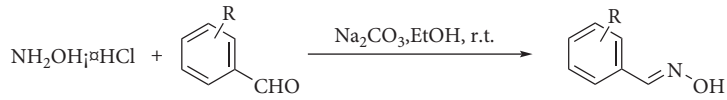
3. Results and Discussion

3.1. Chemistry. The intermediate **4** (pyrazole-4-carbonyl chloride) was prepared by a previously reported method [20] in four synthetic steps from commercial starting materials. For the intermediate substituted-benzaldehyde oximes (Scheme 1), commercially available substituted benzaldehydes were condensed with excess $NH_2OH{\cdot}HCl$ and were used without purification. Finally, the oximes were condensed with acid chloride **4** to afford the target compounds as white or light-yellow solids **5a**-**5o** (Scheme 2). From Figure 2, the torsion angles, C (6)-O (2)-N (3)-C (7) was 172.50 (15)°, which indicated the two C=N groups are *E* configuration.

Table 1: Crystal data of compound **5d**.

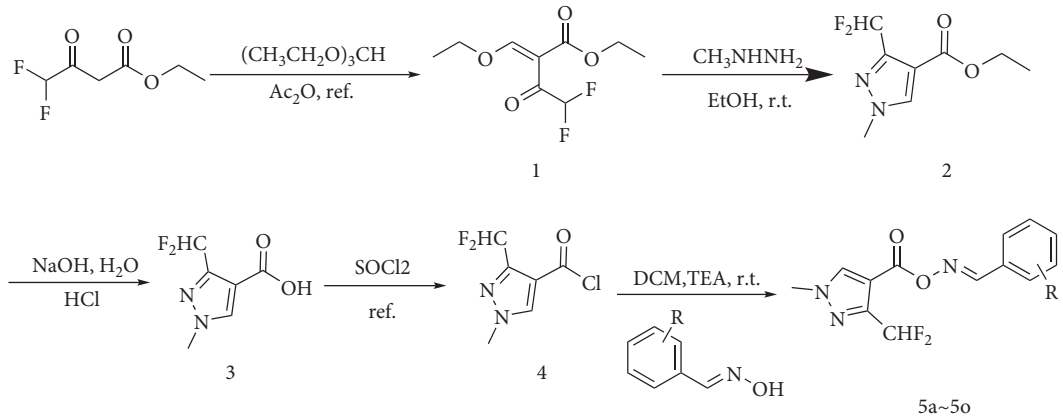
Name	5d
Empirical formula	$C_{14}H_{13}F_2N_3O_2$
Formula weight	293.27
Temperature/K	296 (2)
Crystal system	Monoclinic
Crystal size/mm^3	0.36 × 0.34 × 0.32
Space group	C2/c
a/Å	16.6161 (11)
b/Å	15.7963 (9)
c/Å	12.9160 (8)
α/°	90
β/°	124.693 (2)
γ/°	90
Volume/Å	2787.4 (3)
Z	8
ρ_{calc}g/cm^3	1.398
μ/mm^{-1}	0.114
F (000)	1216.0
Radiation	MoKα (λ = 0.71073)
2^Θ range for data collection/°	5.964 to 54.944
Index ranges	$-21 \le h \le 21$, $-20 \le k \le 20$, $-16 \le l \le 16$
Reflections collected	32252
Independent reflections	3192 [R_{int} = 0.0505, R_{sigma} = 0.0285]
Data/restraints/parameters	3192/0/192
Goodness-of-fit on F^2	1.046
Final R indexes ($I \ge 2\sigma$ (I))	R_1 = 0.0491, wR_2 = 0.1243
Final R indexes (all data)	R_1 = 0.0763, wR_2 = 0.1394
Largest diff. peak/hole/e Å^{-3}	0.23/-0.24

3.2. Fungicidal Activity. Fungicidal activities of compounds **5a**~**5o** and positive control fluxapyroxad against *Rhizoctonia solani* ***(RS)***, *Phytophthora capsici* ***(PC)***, *Alternaria solani* ***(AS)***, *Pyricularia oryae* ***(PO)***, *Gibberella zeae* ***(GZ)***, *Botrytis cinerea* ***(BC)***, *Sclerotinia sclerotiorum* ***(SS)***, *Fusarium oxysporum* ***(FO)***, *Physalospora piricola* ***(PP)***, and *Cercospora arachidicola* were tested at 50 ppm, the results are shown in Table 2. The fungicidal activity results showed some compounds exhibited good inhibition against *S. sclerotiorum, B. cinerea, P. oryae, R. solani,* and *P. piricola*. For the *P. oryae*, compounds **5g** (85.7%) and **5j** (71.4%) possessed good inhibition, compared to that of the control fluxapyroxad (27.3%). Compound **5k** (42.9%) exhibited moderate activity against *P. oryae*. For *S. sclerotiorum*, compounds **5f** (60.7%) and **5i** (71.4%) possessed good inhibition, but was weaker than that of fluxapyroxad (96.4%). While compound **5b** (44.6%), **5g** (44.6%), **5h** (53.6%), **5k** (50.0%), and **5n** (44.6%) displayed moderate activity against *S. sclerotiorum*. For *R. solani*, compound **5e** (62.1%) possessed good inhibition, however, it was weaker than the control fluxapyroxad (88.4%). Compound **5c** (43.1%), **5f** (44.8%), **5h** (50.0%), and **5j** (55.2%) exhibited moderate activity against *R. solani*. For *B. cinerea*, only compound **5h** (75.0%) possessed good inhibition. For *P. piricola*, compound **5e** (53.1%), **5h** (46.9%), **5j** (62.5%), and **5o** (56.3%) possessed moderate activity. Most of the title pyrazole oxime ester compounds showed weak activity against *A. solani, G. zeae, P. capsici, F. oxysporum,* and *C. arachidicola.*



R: 1=H;2=2-CH_3;3=3-CH_3;4=4-CH_3;5=2-CH_3O; 6=4-CH_3O;7=3,4,5-tri-CH_3O; 8=2-Br;
9=4-Br;10=2-NO_2;11=3-NO_2;12=4-F;13=4-CF_3;14=4-Cl;15=2,4-di-Cl;16=2,4,6-tri-CH_3

Scheme 1: The synthetic route of substituted oxime.



5a R=H;5b R=2-CH_3; 5c R=3-CH_3; 5d R=4-CH_3; 5e R=2-CH_3O; 5f R=4-CH_3O;
5g R=3,4,5-tri-CH_3O; 5h R=2-Br; 5i R=4-Br;5j R=2-NO_2; 5k R=3-NO_2; 5l R=4-F;
5m R=4-CF_3; 5n R=4-Cl;5o R=2,4-di-Cl

Scheme 2: Design strategy of pyrazole oxime ester compounds **5a~5o**.

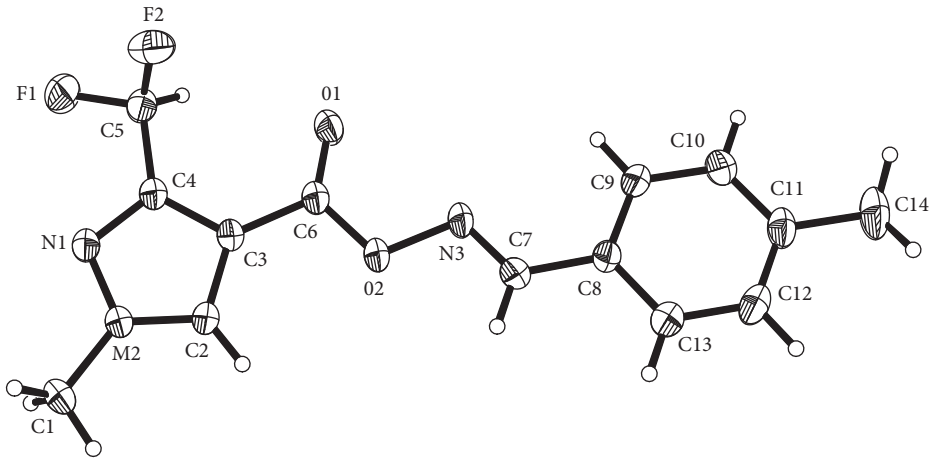


Figure 2: Molecular structure of (*E*)-4-methylbenzaldehyde (*O*)-(3-(difluoromethyl)-1-methyl-1 (*H*)-pyrazole-4-carbonyl) oxime.

3.3. Docking Study. In order to study the mode of action of these compounds, molecular docking was carried out between the compound **5g** and the enzyme SDH (PDB:2FBW) using DS 2.5. The docking results indicated that compound **5g** can well occupy the active site of SDH (Figure 3). From Figure 3 (above), two π-cation interactions exist between Arg 43 amino acid residue of SDH and the compound **5g** with the distances of 3.6 Å and 3.9 Å, respectively. There are two hydrogen bonds between the compound **5g** and SDH. One is between the Ser 39 amino acid residue of SDH and the O atom of carboxamide group in compound **5g** and with the distance of 2.3 Å. The other is between the Tyr 58 amino acid residue of SDH and the O atom of MeO group with the distance of 2.0 Å. From the docking results, the pyrazole ring and amide group are key active groups in this fungicide, which is the same as the lead compound pydiflumetofen (Figure 3).

Table 2: The fungicidal activity of compounds **5a~5o** at 50 ppm.

No.	R	AS	GZ	PO	PC	SS	BC	RS	FO	CA	PP
5a	H	27.8 ± 0.1	12.2 ± 0.1	28.6 ± 0.4	5.3 ± 0.1	17.9 ± 0.3	9.4 ± 0.3	32.8 ± 0.2	7.7 ± 0.1	17.6 ± 0.1	15.6 ± 0.2
5b	2-CH_3	11.1 ± 0.2	12.2 ± 0.1	17.1 ± 0.4	10.5 ± 0.1	44.6 ± 0.3	12.5 ± 0.4	20.7 ± 0.1	19.2 ± 0.3	17.6 ± 0.1	25.0 ± 0.2
5c	3-CH_3	16.7 ± 0.2	12.2 ± 0.1	14.3 ± 0.5	10.5 ± 0.2	17.9 ± 0.1	3.1 ± 0.3	43.1 ± 0.3	15.4 ± 0.1	23.5 ± 0.1	31.3 ± 0.2
5d	4-CH_3	33.3 ± 0.3	12.2 ± 0.3	17.1 ± 0.2	5.3 ± 0.1	25.0 ± 0.4	9.4 ± 0.3	37.9 ± 0.1	7.7 ± 0.1	17.6 ± 0.1	31.3 ± 0.1
5e	2- OCH_3	27.8 ± 0.3	29.3 ± 0.1	14.3 ± 0.1	13.2 ± 0.1	17.9 ± 0.3	12.5 ± 0.1	**62.1 ± 0.3**	19.2 ± 0.4	29.4 ± 0.1	**53.1 ± 0.1**
5f	4- OCH_3	16.7 ± 0.1	22.0 ± 0.1	28.6 ± 0.1	5.3 ± 0.2	**60.7 ± 0.1**	18.8 ± 0.1	44.8 ± 0.1	19.2 ± 0.4	17.6 ± 0.1	9.4 ± 0.2
5g	3,4,5-tri-OCH_3	33.3 ± 0.1	12.2 ± 0.1	**85.7 ± 0.1**	7.9 ± 0.2	44.6 ± 0.4	18.8 ± 0.1	29.3 ± 0.1	15.4 ± 0.1	17.6 ± 0.1	3.1 ± 0.1
5h	2-Br	16.7 ± 0.2	17.1 ± 0.3	14.3 ± 0.1	5.3 ± 0.1	53.6 ± 0.1	**75.0 ± 0.3**	50.0 ± 0.3	23.1 ± 0.3	29.4 ± 0.3	46.9 ± 0.3
5i	4-Br	11.1 ± 0.4	12.2 ± 0.1	28.6 ± 0.4	5.3 ± 0.1	71.4 ± 0.1	18.8 ± 0.1	37.9 ± 0.1	15.4 ± 0.1	11.8 ± 0.1	31.3 ± 0.1
5j	2-NO_2	5.6 ± 0.2	12.2 ± 0.1	**71.4 ± 0.1**	18.4 ± 0.2	7.1 ± 0.3	25.0 ± 0.4	55.2 ± 0.1	23.1 ± 0.1	47.1 ± 0.1	**62.5 ± 0.1**
5k	4-NO_2	5.6 ± 0.1	12.2 ± 0.2	42.9 ± 0.1	5.3 ± 0.1	50.0 ± 0.1	12.5 ± 0.1	27.6 ± 0.5	19.2 ± 0.1	17.6 ± 0.4	3.1 ± 0.3
5l	4-F	11.1 ± 0.1	12.2 ± 0.1	28.6 ± 0.2	10.5 ± 0.3	21.4 ± 0.3	34.4 ± 0.1	34.5 ± 0.1	7.7 ± 0.3	17.6 ± 0.1	12.5 ± 0.1
5m	4-CF_3	5.6 ± 0.3	12.2 ± 0.1	14.3 ± 0.1	5.3 ± 0.1	32.1 ± 0.1	9.4 ± 0.5	17.2 ± 0.3	7.7 ± 0.3	5.9 ± 0.3	28.1 ± 0.3
5n	4-Cl	16.7 ± 0.3	17.1 ± 0.1	17.1 ± 0.3	5.3 ± 0.1	44.6 ± 0.1	25.0 ± 0.1	37.9 ± 0.1	19.2 ± 0.1	17.6 ± 0.1	28.1 ± 0.3
5o	2,4-di-Cl	11.1 ± 0.2	12.2 ± 0.1	14.3 ± 0.1	5.3 ± 0.1	7.1 ± 0.3	12.5 ± 0.2	20.7 ± 0.5	15.4 ± 0.4	17.6 ± 0.2	**56.3 ± 0.4**
CK		88.9 ± 0.2	28.6 ± 0.2	27.3 ± 0.2	16.7 ± 0.2	96.4 ± 0.2	63.6 ± 0.2	88.4 ± 0.2	29.4 ± 0.2	100 ± 0.2	63.6 ± 0.2

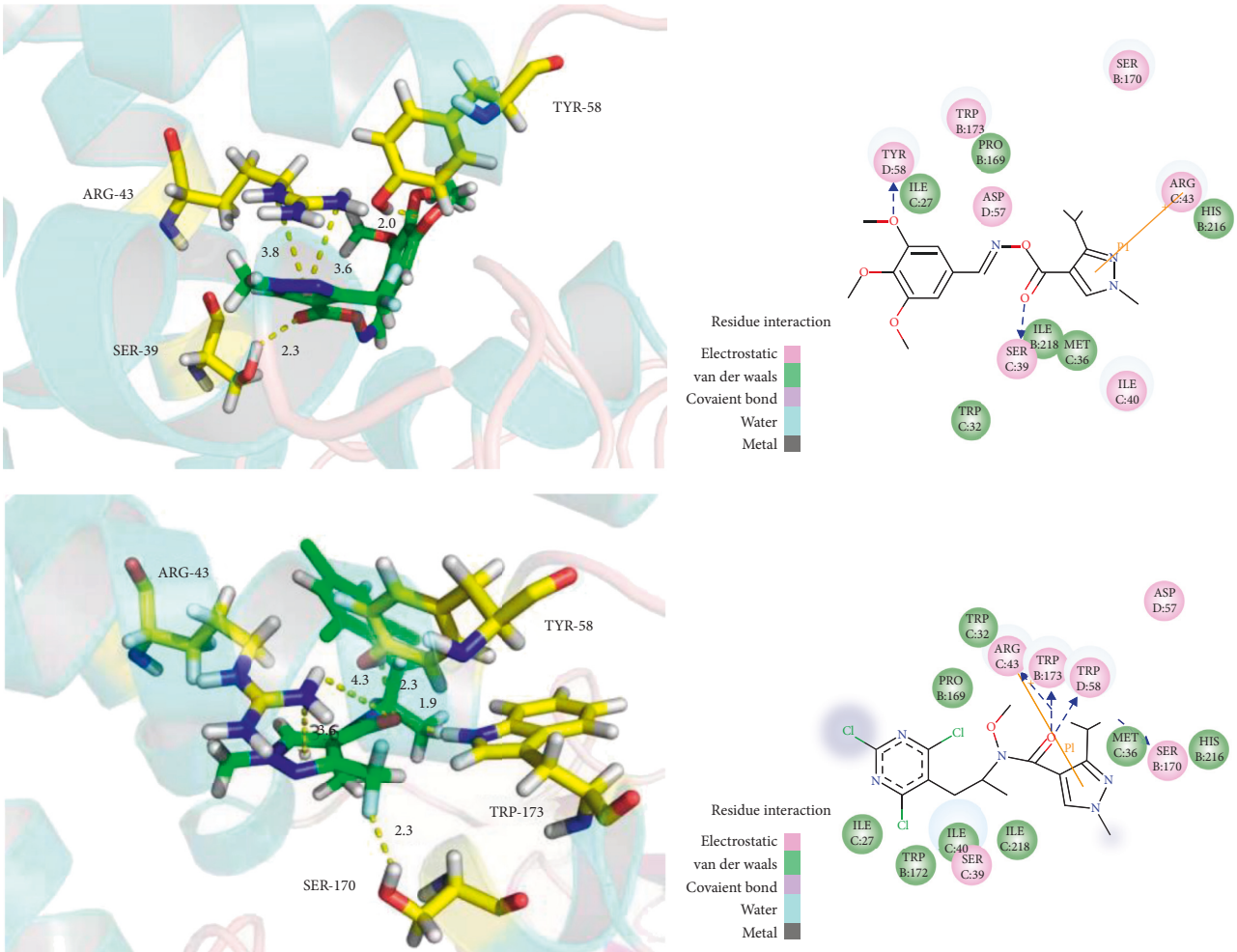


Figure 3: Docking modeling and molecular receptor-ligand interactions of compound 5g (above, left 3D, right 2D) and CK (down, left 3D, right 2D) with SDH.

4. Conclusions

In conclusion, a series of pyrazole-4-carboxylic oxime ester derivatives were synthesized using a bioisosterism strategy. The X-ray analysis results showed that the oxime has an *E* configuration. The antifungal activity of the target pyrazole-4-carboxylic oxime ester compounds against ten fungi was tested at 50 ppm, and some of the target compounds showed good fungicidal activity against *B. cinerea, S. sclerotiorum, R. solani, P. oryae,* and *P. piricola*. These structures can be further optimized for discovering new fungicides.

Data Availability

The data used to support the study can be made available upon request to the corresponding author.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgments

This work was funded in part by Zhejiang Provincial Natural Science Foundation of China (Nos. LY19C140002 and LY19B020009), the Chemical Company for Research (KYY-HX-20210140 and KYY-HX-20190720), and the Opening Foundation of the Key Laboratory of Green Pesticide and Agricultural Bioengineering, Ministry of Education, Guizhou University (No. 2018GDGP0104). The authors thank Dr. Charles L. Cantrell for HRMS.

Supplementary Materials

^{1}H NMR, ^{13}C NMR, and HRMS spectra of compounds prepared in this study are available as a supplementary file. (*Supplementary Materials*)

References

[1] X. H. Liu, W. Yu, L. J. Min et al., "Synthesis and pesticidal activities of new quinoxalines," *Journal of Agricultural and Food Chemistry*, vol. 68, no. 28, pp. 7324–7332, 2020.

[2] Q. Fu, P. P. Cai, L. Cheng et al., "Synthesis and herbicidal activity of novel pyrazole aromatic ketone analogs as HPPD inhibitor," *Pest Management Science*, vol. 76, no. 3, pp. 868–879, 2020.

[3] C. S. Yu, Q. Wang, J. Bajsa-Hirschel, C. L. Cantrell, S. O. Duke, and X. H. Liu, "Synthesis, crystal structure, herbicidal activity and SAR study of novel N-(arylmethoxy)-2-chloronicotinamides derived from nicotinic acid," *Journal of Agricultural and Food Chemistry*, vol. 69, no. 23, pp. 6423–6430, 2021.

[4] X. H. Liu, Y. H. Wen, L. Cheng, T. M. Xu, and N. J. Wu, "Design, synthesis, and pesticidal activities of pyrimidin-4-amine derivatives bearing a 5-(trifluoromethyl)-1, 2, 4-oxadiazole moiety," *Journal of Agricultural and Food Chemistry*, vol. 69, no. 25, pp. 6968–6980, 2021.

[5] Y. H. Wen, L. Cheng, T. M. Xu, X. H. Liu, and N. J. Wu, "Synthesis, insecticidal activities and DFT study of pyrimidin-4-amine derivatives containing the 1, 2, 4-oxadiazole motif," *Frontiers of Chemical Science and Engineering*, vol. 16, no. 7, pp. 1090–1100, 2022.

[6] S. J. Kang, W. Zhao, C. X. Tan, J. Q. Weng, W. L. Peng, and X. H. Liu, "Synthesis, nematicidal activity, and molecular docking of some new pyrazole-5-carboxamide derivatives," *Indian Journal of Heterocyclic Chemistry*, vol. 31, pp. 51–56, 2021.

[7] L. Cheng, W. Zhao, Z. H. Shen et al., "Synthesis, nematicidal activity and docking study of novel pyrazole-4-carboxamide derivatives against *Meloidogyne incognita*," *Letters in Drug Design and Discovery*, vol. 16, no. 1, pp. 29–35, 2018.

[8] L. Cheng, Z. H. Shen, T. M. Xu et al., "Synthesis and nematocidal activity of N-substituted 3-methyl-1H-pyrazole-4-carboxamide derivatives against *Meloidogyne incognita*," *Journal of Heterocyclic Chemistry*, vol. 55, no. 4, pp. 946–950, 2018.

[9] W. Zhao, J. H. Xing, T. M. Xu, W. Peng, and X. Liu, "Synthesis and in vivo nematocidal evaluation of novel 3-(trifluoromethyl)-1H-pyrazole-4-carboxamide derivatives," *Frontiers of Chemical Science and Engineering*, vol. 11, no. 3, pp. 363–368, 2017.

[10] W. Zhao, Z. H. Shen, J. H. Xing et al., "Synthesis, characterization, nematocidal activity and docking study of novel pyrazole-4-carboxamide derivatives," *Journal of Structural Chemistry*, vol. 36, pp. 423–428, 2017.

[11] J. J. Shi, G. H. Ren, N. J. Wu et al., "Design, synthesis and insecticidal activities of novel anthranilic diamides containing polyfluoroalkyl pyrazole moiety," *Chinese Chemical Letters*, vol. 28, no. 8, pp. 1727–1730, 2017.

[12] X. H. Lv, J. J. Xiao, Z. L. Ren et al., "Design, synthesis and insecticidal activities of N-(4-cyano-1-phenyl-1H-pyrazol-5-yl)-1, 3-diphenyl-1H-pyrazole-4-carboxamide derivatives," *RSC Advances*, vol. 5, no. 68, pp. 55179–55185, 2015.

[13] M. B. Palkar, A. Patil, G. A. Hampannavar et al., "Design, synthesis and QSAR studies of 2-amino benzo[d]thiazolyl substituted pyrazol-5-ones: novel class of promising antibacterial agents," *Medicinal Chemistry Research*, vol. 26, no. 9, pp. 1969–1987, 2017.

[14] J. Lim, M. D. Altman, J. Baker et al., "Identification of N-(1H-pyrazol-4-yl)carboxamide inhibitors of interleukin-1 receptor associated kinase 4: bicyclic core modifications," *Bioorganic & Medicinal Chemistry Letters*, vol. 25, no. 22, pp. 5384–5388, 2015.

[15] H. B. Huo, W. Q. Jiang, F. F. Sun, J. Li, and B. Shi, "Synthesis and biological evaluation of novel steroidal pyrazole amides as highly potent anticancer agents," *Steroids*, vol. 176, pp. 108931–112021, 2021.

[16] K. M. Pandya, S. Battula, and P. J. Naik, "Tetrahedron Pd-catalyzed post-Ugi intramolecular cyclization to the synthesis of isoquinolone-pyrazole hybrid pharmacophores & discover their antimicrobial and DFT studies," *Tetrahedron Letters*, vol. 81, pp. 153353–2021, 2021.

[17] A. S. Hassan, A. A. Askar, A. M. Naglah, A. A. Almehizia, and A. Ragab, "Discovery of new schiff bases tethered pyrazole moiety: design, synthesis, biological evaluation, and molecular docking study as dual targeting DHFR/DNA gyrase inhibitors with immunomodulatory activity," *Molecules*, vol. 25, no. 11, pp. 2593–2020, 2020.

[18] X. W. Hua, W. R. Liu, Y. Chen et al., "Synthesis, fungicidal activity, and mechanism of action of pyrazole amide and ester derivatives based on natural products l-serine and waltherione alkaloids," *Journal of Agricultural and Food Chemistry*, vol. 69, no. 38, pp. 11470–11484, 2021.

[19] L. J. Min, Z. W. Zhai, Y. X. Shi et al., "Synthesis and biological activity of acyl thiourea containing difluoromethyl pyrazole motif," *Phosphorus, Sulfur, and Silicon and the Related Elements*, vol. 195, no. 1, pp. 22–28, 2020.

[20] L. Qiao, Z. W. Zhai, P. P. Cai et al., "Synthesis, crystal structure, antifungal activity, and docking study of difluoromethyl pyrazole derivatives," *Journal of Heterocyclic Chemistry*, vol. 56, no. 9, pp. 2536–2541, 2019.

[21] R. Rajan, H. Walter, and D. Stierli, *Novel Pyrazole-4-Nalkoxycarboxamides as Microbiocides*, 2010, WO 2010063700.

[22] C. Defierer, S. Soergel, D. Saelinger et al., *Novel Pesticidal Pyrazole Compounds*, 2012, WO2012143317.

[23] L. J. Min, L. Qiao, and H. Wang, "Synthesis, crystal structure, herbicidal activity and docking study of 4-Cyclopropyl-3-((4-fluorobenzyl) sulfonyl)-5-methyl-4H-1, 2, 4-triazole," *Chinese Journal of Structural Chemistry*, vol. 38, pp. 1356–1361, 2019.

[24] N. B. Sun, Z. W. Zhai, and J. Y. Tong, "Synthesis, crystal structure and fungicidal activity of 3-(Difluoromethyl)-1-methyl-N-((2(trifluoromethyl)phenyl) carbamoyl)-1H-pyrazole-4-carboxamide," *Chinese Journal of Structural Chemistry*, vol. 38, pp. 706–712, 2019.

[25] T. Jin, Z. W. Zhai, L. Han, J. Q. Weng, C. X. Tan, and X. H. Liu, "Synthesis, crystal structure, docking and antifungal activity of a new pyrazole acylurea compound," *Chinese Journal of Structural Chemistry*, vol. 37, pp. 1259–1264, 2018.

[26] H. Wang, Z. W. Zhai, Y. X. Shi et al., "Novel trifluoromethylpyrazole acyl urea derivatives: synthesis, crystal structure, fungicidal activity and docking study," *Journal of Molecular Structure*, vol. 1171, pp. 631–638, 2018.

[27] X. H. Liu, L. Qiao, Z. W. Zhai et al., "Novel 4-pyrazole carboxamide derivatives containing flexible chain motif: design, synthesis and antifungal activity," *Pest Management Science*, vol. 75, no. 11, pp. 2892–2900, 2019.

[28] G. M. Sheldrick, "A short history of SHEL," *Acta crystallographica*, vol. A64, pp. 112–122, 2008.

[29] G. M. Sheldrick, "Crystal structure refinement with SHELXL," *Acta crystallographica*, vol. C71, pp. 3–8, 2015.

[30] O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard, and H. Puschmann, "OLEX2: a complete structure solution, refinement and analysis program," *Journal of Applied Crystallography*, vol. 42, no. 2, pp. 339–341, 2009.

[31] L. J. Min, H. Wang, J. Bajsa-Hirschel et al., "Novel dioxolane ring compounds for the management of phytopathogen diseases as ergosterol biosynthesis inhibitors: synthesis, biological activities, and molecular docking," *Journal of Agricultural and Food Chemistry*, vol. 70, no. 14, pp. 4303–4315, 2022.

[32] J. X. Mu, C. S. Yu, L. J. Min, and X. H. Liu, "Synthesis, crystal structure, antifungal activity and computational study on 4-(((8-Chloro-3-oxo-[1, 2, 4]-triazolo[4, 3-a]pyridin-2(3H)-yl) thio)methyl)benzonitrile," *Chinese Journal of Structural Chemistry*, vol. 40, pp. 424–430, 2021.