Research Article

Microwave Assisted Synthesis, Antifungal Activity, and DFT Study of Some Novel Triazolinone Derivatives

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A series of some novel 1,2,4-triazol-5(4H)-one derivatives were designed and synthesized under microwave irradiation via multistep reaction. The structures of 1,2,4-triazoles were confirmed by $^1$H NMR, MS, FTIR, and elemental analysis. The antifungal activities of 1,2,4-triazoles were determined. The antifungal activity results indicated that the compounds 5c, 5f, and 5h exhibited good activity against Pythium ultimum, and the compounds 5b and 5c displayed good activity against Corynespora cassicola. Theoretical calculation of the compound 5c was carried out with B3LYP/6-31G (d). The full geometry optimization was carried out using 6-31G(d) basis set, and the frontier orbital energy and electrostatic potential were discussed, and the structure-activity relationship was also studied.

1. Introduction

Nowadays, nitrogen-containing heterocycles became a research hot spot because they displayed excellent activities [1–9]. 1,2,4-Triazole derivatives, especially triazolinone compounds, exhibited diverse activities, such as the commercial antidepressant medicine Trazodone, herbicide azafenidin, and herbicides amicarbazone, sulfentrazone, and carfentrazone-ethyl. So the synthesis of substituted triazolinone compounds is one of the important fields for many researchers. Many references reported that triazolinone derivatives showed other interesting activities, including angiotensin II AT(1) receptor antagonists [10–12], anti-human immunodeficiency virus (HIV) activity [13, 14], acetolactate synthase (ALS) inhibitors [15, 16], protoporphyrinogen oxidase inhibitors [17], antioxidant activities [18–20], anticancer activity [21, 22], and anti-inflammatory activity [23].

Microwave-assisted technique is a green method in current organic synthesis [24–28]. It is attractive, offering reduced pollution, low cost, and high yields. The green technique can often shorten the reaction time.

In our previous work [29–33], some 1,2,4-triazole compounds were designed and synthesized. They showed good antifungal activities. In this paper, fifteen novel 1,2,4-triazole derivatives were designed and synthesized under microwave irradiation. Their chemical structures were confirmed by $^1$H NMR, FTIR, MS, and elemental analysis. The antifungal activity of 1,2,4-triazoles was determined in vivo.

2. Results and Discussion

2.1. Synthesis. The synthetic route of target compounds was outlined in Scheme I. All the reported syntheses of O-methyl carbonisothiocyanatidate involve reaction of a thiocyanate salt (e.g., Pb$^{2+}$, NH$_4^+$, K$^+$, and Na$^+$) with methyl carbonochloridate. If we use equal molar amounts of potassium thiocyanate and methyl carbonochloridate, approximately equal amounts of both isomers will be obtained. When the methyl carbonochloridate was reacted with potassium thiocyanate, the potassium thiocyanate was excess, while the drop speed must be slow, as fast speed decreased the yield of product. The intermediate 2 was easily prepared by the reaction of methoxycarbonyl isothiocyanate and methanol. In the synthesis process of intermediate 3, the intermediate 2 cyclized with hydrazine hydrate. Because it is an equilibrium reaction it is reacted under nitrogen atmosphere in order to off hydrogen sulfide gas and increase the yield of intermediate 3. The intermediate 3 exhibits two NH groups, which may
be both methylated with \((\text{CH}_3)_2\text{SO}_4\). We found that the pH values of two NH groups are different. Therefore, pH value is controlled preferably about 8 to 9 which is given the intermediate 4. The target compounds 5a–5o were synthesized using microwave irradiation method. The signal of NCH proton appeared around \(\delta \ 3.66–5.04 \text{ ppm}\). The infrared spectrum of the title compounds 5a–5i showed absorption bands around 2930 cm\(^{-1}\) for CH\(_2\) stretching. The characteristic stretching vibration \(\nu \ (\text{C}=\text{O})\) appears at 1720 cm\(^{-1}\). The mass spectrum results showed that molecular ion is in accordance with its molecular formula. The elemental analysis results are in accordance with the calculated results.

### 2.2. Antifungal Activity

The \textit{in vivo} antifungal activity results of 1,2,4-triazol-5(4H)-ones against \textit{Phytophthora infestans}, \textit{Botrytis cinerea}, \textit{Corynespora cassicola}, \textit{Rhizoctonia solani}, and \textit{Pythium ultimum} were shown in Table 1; dimethoxynil, fludioxonil, chlorothalonil, validamycin, and zhongshengmycin were used as controls. From Table 1, it is shown that compounds 5c, 5f, and 5h exhibited good control efficacy against \textit{Pythium ultimum} at 500 ppm. Compounds 5a, 5g, 5i, 5m, and 5n showed moderate control efficacy against \textit{Pythium ultimum}. The control zhongshengmycin had no control efficacy against \textit{Pythium ultimum}. For the \textit{Rhizoctonia solani}, most of the title compounds displayed no control efficacy, except compounds 5f and 5h. Surprisingly, all the compounds can not only inhibit the \textit{Botrytis cinerea}, but also promote the \textit{Botrytis cinerea} growth. Most of 1,2,4-triazol-5(4H)-ones displayed weak control efficacy against \textit{Corynespora cassicola}; only compounds 5b and 5c showed good antifungal activity (about 70%) against \textit{Corynespora cassicola}, which is higher than that of control chlorothalonil.

Unfortunately, the title compounds exhibited weak activity against \textit{Phytophthora infestans}.

### 2.3. DFT Calculation

Molecular total energy and frontier orbital energy levels are listed in Table 2. Energy gap between HOMO and LUMO was calculated by B3LYP.

According to the frontier molecular orbital theory, HOMO and LUMO are the most important factors that affect the bioactivity. HOMO has the priority to provide electrons, while LUMO can accept electrons firstly [34–36]. Thus, study on the frontier orbital energy can provide useful information about the biological mechanism. From Figure 1, the HOMO of compound 5c is mainly located on the OCH\(_2\) group, 2,4-Cl\(_2\) benzene ring, and 1,2,4-triazol-5(4H)-one ring, while the LUMO of compound 5c is located on the OCH\(_2\) group, 2,4-Cl\(_2\) benzene ring, and 1,2,4-triazol-5(4H)-one ring. The fact that the compound 5c has strong affinity suggests the importance of the frontier molecular orbital in the \(\pi-\pi\) stacking or hydrophobic interactions. From Figure 1, the electron transfer process of the HOMO and LUMO implies that 2,4-Cl\(_2\) phenyl ring had important impact on the antifungal activity.

The electrostatic potential of compound 5c was also calculated. From Figure 2, it is clear that the oxygen atom at the 1,2,4-triazole ring possessed the greatest negative charges and it is therefore possible that the oxygen atom had some interaction with the receptor or acceptor.

Furthermore, the combination of MO provided meaningful clues as to the structural features of these new family fungicides that will be helpful in the design of more potent compounds in the future.

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Scheme 1: The synthetic route of title compounds.

5a: R = 3,4-Cl\(_2\) Ph;
5b: R = 4-Br Ph;
5c: 3,4-Cl\(_2\) Ph;
5d: R = 4-Cl Ph;
5e: R = 4-CN Ph;
5f: R = 2-(phenyl)-2-(methoxyimino)acetate;
5g: R = undecyl;
5h: R = 3-Cl Ph;
5i: R = 2-Cl Ph;
5j: R = 3-CN Ph;
5k: R = 4-MeO Ph;
5l: R = 3-F Ph;
5m: R = 4-F Ph;
5n: R = 5-chloropyridin-2-yl;
5o: R = 2-F Ph
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3. Materials and Methods

3.1. Instruments. Melting points were measured using an X-4 melting apparatus and were uncorrected. $^{1}$H NMR spectra were determined on a Bruker AC-P400 instrument (400 MHz) using TMS as an internal standard and CDCl$_3$ as solvent. Mass spectra were determined on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were recorded on a Yanaco MT-3CHN elemental analyzer. Microwave activation was carried out with CEM Discover Focused Microwave (2450 MHz, 300 W). All the reagents are of analytical grade or freshly prepared before use. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF 254.

3.2. Synthetic Procedures. The synthetic route is shown in Scheme 1.

3.2.1. Synthesis of Intermediates 1 and 2. The potassium thiocyanate (10.69 g, 0.11 mol) and pyridine (0.40 g) were dissolved in methyl isobutyl ketone (50 mL); methyl chloroformate (9.45 g, 0.10 mol) was added dropwise at 55°C, and the mixture was stirred for 4 h. Then MeOH (20 mL) was added to the mixture and stirred for 16 h. The mixture was washed with concentrated hydrochloric acid (3 mL) and H$_2$O.
(50 mL). After filtration and evaporation of the solvent, the crude intermediate 2 was collected without further purification: white solid, yield 80%, $^1$H NMR (400 MHz, CDCl$_3$) δ: 3.77 (s, 3H, COOCH$_3$), 4.12 (s, 3H, CSOCH$_3$), 8.56 (s, 1H, NH).

3.2.2. Synthesis of Intermediate 3. To a solution of intermediate 2 (50 mmol) in MeOH (75 mL) were added 80% NH$_2$NH$_2$·H$_2$O (4.07 g, 65 mmol) and KOH (45%, 0.81 g, 6.5 mmol) at 0°C; then the mixture was stirred at 30°C for 5 h. After evaporation of the solvent, the crude intermediate 3 was recrystallized by EtOH to give white crystal 3; yield 78%, m.p. 172–173°C. $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 4.02 (s, 3H, triazoline-OCH$_3$), 10.51 (s, 1H, NH).

3.2.3. Synthesis of Intermediate 4. To a solution of 3 (65 mmol) and K$_2$CO$_3$ (9.52 g) in CH$_3$CN (100 mL) was added (CH$_3$)$_2$SO$_4$ (68 mmol) at 55°C, and the mixture was stirred for another 2 h. The organic phase was extracted with CH$_2$Cl$_2$ (3 × 10 mL). After drying over sodium sulphate and evaporation of the solvent, the crude was collected without being purified to give the corresponding intermediate 4.

3.2.4. General Procedure for Theoester 5. DMF (5 mL), 4 (0.25 g, 1.00 mmol), RCH$_2$Cl (1.10 mmol), and NaOH (0.05 g, 1.20 mmol) were charged into a CEM designed 10 mL pressure-rated vial. Then it was irradiated in a CEM Discover Focused Synthesizer (150 w, 90°C, 200 psi, 15 minutes). The mixture was cooled below 50°C. The mixture was poured into crushed ice and the title compound 1,2,4-triazole was collected after being recrystallized.

1-(3,4-Dichlorobenzyl)-3-methoxy-4-methyl-1H-1,2,4-triazole-5(4H)-one (5a). m.p. 136–140°C. Yield 88%, $^1$H NMR (400 M, CDCl$_3$): 3.16 (s, 3H, N-CH$_3$), 3.96 (s, 3H, OCH$_3$), 4.83 (s, 2H, NCH$_2$), 7.18–7.21 (m, 1H, Ph), 7.40–7.45 (m, 2H, Ph); IR/cm$^{-1}$: 3449.33, 2957.94, 1710.43, 1615.33, 1518.36, 1470.76, 1425.27, 1403.40, 1307.42, 1233.37 1135.45, 1009.21, 914.98, 812.11, 743.63, 662.08, 595.11; ESI-MS: 289 [M+H]$^+$

Elemental anal. (%), calculated: C, 45.85; H, 3.85; N, 14.58; found: C, 45.98; H, 3.77; N, 14.43.

1-(4-Bromobenzyl)-3-methoxy-4-methyl-1H-1,2,4-triazole-5(4H)-one (5b). m.p. 138–140°C. Yield 84%, $^1$H NMR (400 M, CDCl$_3$): 3.15 (s, 3H, N-CH$_3$), 3.95 (s, 3H, OCH$_3$), 4.84 (s, 2H, NCH$_2$), 7.24 (d, $J = 6.4$ Hz, 2H, Ph), 7.47 (d, $J = 6.4$ Hz, 2H, Ph); IR/cm$^{-1}$: 3450.50, 2942.58, 1711.13, 1607.26, 1458.33, 1424.33, 1382.18, 1301.13, 1067.47, 1008.00, 910.76, 847.46, 798.29, 727.42, 600.46; ESI-MS: 299 [M+H]$^+$

Elemental anal. (%), calculated: C, 44.31; H, 4.06; N, 14.09; found: C, 44.25; H, 3.92; N, 14.21.

4-((3-Methoxy-4-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)benzonitrile (5e). m.p. 160–162°C. Yield 89%, $^1$H NMR (400 M, CDCl$_3$): 3.15 (s, 3H, N-CH$_3$), 3.96 (s, 3H, OCH$_3$), 4.94 (s, 2H, NCH$_2$), 7.44 (d, $J = 8.16$ Hz, 2H, Ph), 7.64 (d, $J = 8.16$ Hz, 2H, Ph); IR/cm$^{-1}$: 3434.79, 2955.79, 2229.46, 1715.92, 1613.56, 1523.56, 1421.90, 1230.01, 1016.35, 857.47, 735.86, 640.39, 596.36, 552.70; ESI-MS: 245 [M+H]$^+$

Elemental anal. (%), calculated: C, 59.01; H, 4.95; N, 22.94; found: C, 58.88; H, 5.12; N, 23.13.

(E)-Methyl 2-((3-Methyl-4-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)phenyl-2-(methoxymino)acetate (5f). m.p. 103–107°C. Yield 89%, $^1$H NMR (400 M, CDCl$_3$): 3.15 (s, 3H, N-CH$_3$), 3.96 (s, 3H, OCH$_3$), 4.94 (s, 2H, NCH$_2$), 7.44 (d, $J = 8.16$ Hz, 2H, Ph), 7.64 (d, $J = 8.16$ Hz, 2H, Ph); IR/cm$^{-1}$: 3455.02, 2936.45, 2710.46, 1611.72, 1522.17, 1431.39, 1230.32, 1005.55, 86.57, 741.29, 711.75, 681.57, 598.40, 572.80; ESI-MS: 245 [M+H]$^+$

Elemental anal. (%), calculated: C, 53.89; H, 5.43; N, 16.76; found: C, 53.98; H, 5.13; N, 16.88.
3-Methoxy-4-methyl-1-undecyl-1H-1,2,4-triazol-5(4H)-one (5g). m.p. 102–105°C, Yield 78%, 1H NMR (400 M, CDCl3): 0.86 (t, J = 6.71 Hz, 3H, CH3), 1.24–1.29 (m, 16H, CH2), 1.66–1.68 (m, 2H, CH2), 3.10 (s, 3H, N-CH3), 3.66 (s, J = 7.21 Hz, 2H, NCH2), 3.95 (s, 3H, OCH3); IR/cm−1: 3446.77, 2941.81, 1708.02, 1622.82, 1258.48, 1131.46, 1016.03, 763.78, 661.94; ESI-MS: 285 [M+H]+. Elemental anal. (%), calculated: C, 63.57; H, 10.31; N, 14.83; found: C, 63.76; H, 10.52; N, 14.97.

1-(3-Chlorobenzyl)-3-methoxy-4-methyl-1H-1,2,4-triazol-5(4H)-one (5h). m.p. 97–100°C, Yield 90%, 1H NMR (400 M, CDCl3): 3.17 (s, 3H, N-CH3), 3.96 (s, 3H, OCH3), 4.87 (s, 2H, NCH2), 7.27–7.34 (m, 4H, Ph); IR/cm−1: 3441.67, 2960.00, 1716.14, 1621.83, 1520.80, 1391.88, 1267.10, 1228.92, 814.96, 789.51, 740.97, 593.84; ESI-MS: 254 [M+H]+. Elemental anal. (%), calculated: C, 52.08; H, 4.77; N, 16.56; found: C, 52.21; H, 4.87; N, 16.77.

1-(2-Chlorobenzyl)-3-methoxy-4-methyl-1H-1,2,4-triazol-5(4H)-one (5i). m.p. 120–122°C, Yield 87%, 1H NMR (400 M, CDCl3): 3.19 (s, 3H, N-CH3), 3.97 (s, 3H, OCH3), 5.04 (s, 2H, NCH2), 7.19–7.25 (m, 2H, Ph), 7.37–7.39 (m, 2H, Ph); IR/cm−1: 3439.30, 2947.24, 1718.79, 1614.24, 1523.69, 745.45, 595.23; ESI-MS: 254 [M+H]+. Elemental anal. (%), calculated: C, 52.08; H, 4.77; N, 16.56; found: C, 52.22; H, 4.88; N, 16.67.

3-((3-Methoxy-4-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl)methyl)benzonitrile (5j). m.p. 130°C, Yield 89%, 1H NMR (400 M, CDCl3): 3.17 (s, 3H, N-CH3), 3.97 (s, 3H, OCH3), 4.91 (s, 2H, NCH2), 7.46–7.48 (m, 1H, Ph), 7.58–7.62 (m, 3H, Ph); IR/cm−1: 3446.70, 2946.35, 2231.17, 1706.17, 1522.05, 1453.60, 1399.59, 1236.83, 1134.53, 1012.73, 783.64, 701.50; ESI-MS: 256 [M+H]+. Elemental anal. (%), calculated: C, 47.16; H, 4.35; N, 22.00; found: C, 47.32; H, 4.44; N, 22.12.

3.3. Antifungal Activities. The biological activities of title compounds against Phytophthora infestans, Botrytis cinerea, Corynespora cassiicola, Rhizoctonia solani, and Pythium ultimum were evaluated according to [37–40], and a potted plant test method was adopted. Germination was conducted by soaking cucumber seeds in water for 2 h at 50°C and then keeping the seeds moist in 24 h at 28°C in an incubator. When the radicles were 0.5 cm, the seeds were grown in plastic pots containing a 1:1 (v/v) mixture of vermiculite and peat. Cucumber and tomato plants used for inoculations were at the stage of two seed leaves. Tested compounds and commercial fungicides were sprayed with a hand spray on the surface of the seed leaves. Tested compounds and commercial fungicides were found to be active in detecting the disease index. The relative control efficacy (%), calculated: C, 55.69; H, 5.10; N, 17.71; found: C, 55.47; H, 5.12; N, 17.88.

1-((5-Chloropyridin-2-yl)methyl)-3-methoxy-4-methyl-1H-1,2,4-triazol-5(4H)-one (5n). m.p. 111–113°C, Yield 88%, 1H NMR (400 M, CDCl3): 3.15 (s, 3H, N-CH3), 3.95 (s, 3H, OCH3), 4.48 (s, 2H, NCH2), 7.30–7.33 (m, 3H, Ph), 7.68 (d, J = 8.0 Hz, 1H, Py), 8.42 (s, 1H, Py); IR/cm−1: 3436.68, 2959.93, 1711.34, 1611.26, 1519.05, 1399.59, 1235.83, 1134.81, 1012.73, 783.64, 701.50; ESI-MS: 256 [M+H]+. Elemental anal. (%), calculated: C, 47.16; H, 4.35; N, 22.00; found: C, 47.32; H, 4.44; N, 22.12.

3.4. DFT Calculation. DFT-B3LYP/6-31G (d) methods in Gaussian 03 package [41] were used to optimize the structure.
4. Conclusion

In summary, this paper reported some novel 1,2,4-triazol-5(4H)-one derivatives were successfully synthesized. The bioassay results showed that some of the title compounds exhibited considerable antifungal activity. The bioactivity of these novel compounds deserves further investigation.

Conflict of Interests

The authors declare that they have no conflict of interests.

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References

[1] M. S. Mohamed, S. A. Ali, D. H. A. Abdelaziz, and S. S. Fathallah, “Synthesis and evaluation of novel pyroles and pyrrolopyrimidines as anti-hyperglycemic agents,” BioMed Research International, vol. 2014, Article ID 249780, 13 pages, 2014.

[2] S.-L. Yan, M.-Y. Yang, Z.-H. Sun et al., “Synthesis and antifungal activity of 1,2,3-thiadiazole derivatives containing 1,3,4-thiadiazole moiety,” Letters in Drug Design & Discovery, vol. 11, no. 7, pp. 940–943, 2014.

[3] N. M. Khalifa and M. A. Al-Omar, “Synthesis and biological evaluation of 2-thioxopyrimidin-4(1H)-one derivatives as potential non-nucleoside HIV-1 reverse transcriptase inhibitors,” International Journal of Molecular Sciences, vol. 15, no. 11, pp. 20723–20735, 2014.

[4] M.-Y. Yang, W. Zhao, Z.-H. Sun, C.-X. Tan, J.-Q. Weng, and X.-H. Liu, “Synthesis and biological activity of acylthiourea derivatives contain 1,2,3-thiazole and 1,3,4-thiazole,” Letters in Drug Design & Discovery, vol. 12, no. 4, pp. 314–318, 2015.

[5] S. Bala, S. Kamboj, A. Kajal, V. Saini, and D. N. Prasad, “1,3,4-Oxadiazole derivatives: synthesis, characterization, antimicrobial potential, and computational studies,” BioMed Research International, vol. 2014, Article ID 172791, 18 pages, 2014.

[6] N.-N. Su, Y. Li, S.-J. Yu, X. Zhang, X.-H. Liu, and W.-G. Zhao, “Microwave-assisted synthesis of some novel 1,2,3-triazoles by click chemistry, and their biological activity,” Research on Chemical Intermediates, vol. 39, no. 2, pp. 759–766, 2013.

[7] G.-X. Sun, Z.-H. Sun, M.-Y. Yang, X.-H. Liu, Y. Ma, and Y.-Y. Wei, “Design, synthesis, biological activities and 3D-QSAR of new N,N′-diacylhydrazines containing 2,4-dichlorophenoxymoieties,” Molecules, vol. 18, no. 12, pp. 14876–14891, 2013.

[8] X. H. Liu, X. Y. Xu, C. X. Tan, J. Q. Weng, J. H. Xin, and J. Chen, “Synthesis, crystal structure, herbicidal activities and 3D-QSAR study of some novel 1,2,4-triazol[4,3-a]pyrimidine derivatives,” Pest Management Science, vol. 71, no. 2, pp. 292–301, 2015.

[9] L.-J. Zhang, M.-Y. Yang, Z.-H. Sun et al., “Synthesis and antifungal activity of 1,3,4-thiadiazole derivatives containing pyridazine group,” Letters in Drug Design & Discovery, vol. 11, no. 9, pp. 1107–1111, 2014.

[10] A. Parate and S. C. Chaturvedi, “Structural insights for 3H-1, 2, 4 triazolines as angiotensin II receptor antagonists using QSAR techniques,” Medicinal Chemistry Research, vol. 19, no. 4, pp. 375–391, 2010.

[11] S. K. Sivan and V. Manga, “Molecular docking and 3D-QSAR studies on triazoline and pyridazinone, non-nucleoside inhibitor of HIV-1 reverse transcriptase,” Journal of Molecular Modeling, vol. 16, no. 6, pp. 1169–1178, 2010.

[12] M. C. Sharma, S. Sharma, P. Sharma, A. Kumar, and K. S. Bhadoriya, “Comparative QSAR and pharmacophore analysis for a series of 2,4-dihydro-3H-1,2,4-triazol-3-ones derivatives as angiotensin II AT1 receptor antagonists,” Medicinal Chemistry Research, vol. 23, no. 5, pp. 2486–2502, 2014.

[13] B. Côté, J. D. Burch, E. Asante-Appiah et al., “Discovery of MK-1439, an orally bioavailable non-nucleoside reverse transcriptase inhibitor potent against a wide range of resistant mutant HIV viruses,” Bioorganic and Medicinal Chemistry Letters, vol. 24, no. 3, pp. 917–922, 2014.

[14] Z. K. Sweeney, S. Acharya, A. Briggs et al., “Discovery of triazoline non-nucleoside inhibitors of HIV reverse transcriptase,” Bioorganic and Medicinal Chemistry Letters, vol. 18, no. 15, pp. 4348–4351, 2008.

[15] Z. Liu, L. Pan, Y.-H. Li, S.-H. Wang, and Z.-M. Li, “Synthesis and herbicidal activity of novel sulfonureas containing 1,2,4-triazoline moiety,” Chemical Research in Chinese Universities, vol. 29, no. 3, pp. 466–472, 2013.

[16] L. Pan, Y. W. Chen, Z. Liu, Y. H. Li, and Z. M. Li, “Synthesis, crystal structure and herbicidal activity of novel sulfonureas containing triazoline moiety,” Chinese Journal of Organic Chemistry, vol. 33, no. 3, pp. 542–550, 2013.

[17] Z. Yang, Y. Sheng-Gang, L. Yan-Ping et al., “Design and synthesis of 1-benzothiazol-5-yl)-1H-1,2,4-triazol-5-ones as protoporphyrinogen oxidase inhibitors,” Bioorganic & Medicinal Chemistry, vol. 21, no. 11, pp. 3245–3255, 2013.

[18] O. G. Kol, H. Yuksek, and F. Islamoglu, “Synthesis and in vitro antioxidant activities of novel 4-(methyl-2-thienylmethyleneamino)-4,5-dihydro-1H-1,2,4-triazol-5-one derivatives with their acidic properties,” Journal of the Chemical Society of Pakistan, vol. 35, no. 4, pp. 1179–1190, 2013.

[19] H. Yuksek, O. Akyildirim, M. L. Yola, Ö. Gürsoy-Kol, M. Çelebi, and D. Kart, “Synthesis, in vitro antimicrobial and antioxidant activities of some new 4,5-dihydro-1H-1,2,4-triazol-5-one derivatives,” Archiv der Pharmazie, vol. 346, no. 6, pp. 470–480, 2013.

[20] H. Yuksek, O. Akyildirim, and O. G. Kol, “Synthesis and in vitro antioxidant evaluation of new 1,3,5-Tri-2-methoxy-4-[4,5-dihydro-1H-1,2,4-triazol-5-ony (4-yl)azo]methine]-phenoxycarbonyl-benzene derivatives,” Journal of Chemistry, vol. 2013, Article ID 517420, 8 pages, 2013.

[21] M. Sharma, S. Garigipati, B. Kundu et al., “Discovery of novel 1,2,4-triazol-5-ones as tumor necrosis factor-alpha inhibitors for the treatment of neuropathic pain,” Chemical Biology and Drug Design, vol. 80, no. 6, pp. 961–970, 2012.
[22] M. Pitucha and J. Rzymowska, “Anticancer screening and structure activity relationship study of some semicarbazides and 1,2,4-Triazolin-5-ones,” *Letters in Drug Design and Discovery*, vol. 9, no. 6, pp. 568–572, 2012.

[23] R. J. Singh and D. K. Singh, “Reaction of 4-amino-4,5-dihydro-1H-1,2,4-triazole-5-one with some carboxylic acid anhydrides and their antiinflammatory activity,” *Asian Journal of Chemistry*, vol. 22, no. 4, pp. 2664–2668, 2010.

[24] X.-H. Liu, J.-Q. Weng, B.-L. Wang, Y.-H. Li, C.-X. Tan, and Z.-M. Li, “Microwave-assisted synthesis of novel fluorinated 1,2,4-triazole derivatives, and study of their biological activity,” *Research on Chemical Intermediates*, vol. 40, no. 8, pp. 2605–2612, 2014.

[25] G.-X. Sun, M.-Y. Yang, Y.-X. Shi et al., “Microwave assistant synthesis, antifungal activity and DFT theoretical study of some novel 1,2,4-triazole derivatives containing pyridine moiety,” *International Journal of Molecular Sciences*, vol. 15, no. 5, pp. 8075–8090, 2014.

[26] X.-H. Liu, Z.-H. Sun, M.-Y. Yang et al., “Microwave assistant one pot synthesis, crystal structure, antifungal activities and 3D-QSAR of Novel 1,2,4-triazolo[4,3-a]pyridines,” *Chemical Biology & Drug Design*, vol. 84, no. 3, pp. 342–347, 2014.

[27] Z. H. Sun, Z. W. Zai, M. Y. Yang, X.-H. Liu, C.-X. Tan, and J.-Q. Weng, “Microwave assistant synthesis and dimeric crystal structure of 2-(((6-chloropyridin-3-yl)methyl)thio)-5-(pyridin-4-yl)-1,3,4-thiadiazole,” *Chinese Journal of Structural Chemistry*, vol. 33, pp. 1779–1783, 2014.

[28] L. J. Zhang, M. Y. Yang, B. Z. Hu et al., “Microwave assisted synthesis of novel 8-chloro-1,2,4-triazolo[4,3-a]pyridine derivatives,” *Turkish Journal of Chemistry*, 2015.

[29] N.-B. Sun, Y.-X. Shi, X.-H. Liu et al., “Design, synthesis, antifungal activities and 3D-QSAR of new N,N'-diacetylhydrazines containing 2,4-dichlorophenoxy moiety,” *International Journal of Molecular Sciences*, vol. 14, no. 11, pp. 21741–21756, 2013.

[30] W. Ke, N.-B. Sun, and H.-K. Wu, “Microwave assistant synthesis, crystal structure and biological activity of A 1,2,4-triazole compound,” *Journal of the Chemical Society of Pakistan*, vol. 35, no. 4, pp. 1239–1244, 2013.

[31] J. Y. Tong, H. K. Wu, N. B. Sun, and X. H. Liu, “Synthesis, crystal structure and biological activity of a new 1,2,4-triazole derivative,” *Chinese Journal of Structural Chemistry*, vol. 32, pp. 607–611, 2013.

[32] N. B. Sun, X. H. Liu, J. Q. Weng, and C. X. Tan, “An unexpected product N-(3-((2-fluorobenzyl)thio)-5-methyl-1H-1,2,4-triazol-4-yl)acetimidamide: synthesis and structure analysis,” *Journal of the Chemical Society of Pakistan*, vol. 35, pp. 499–502, 2013.

[33] J.-Z. Jin and N.-B. Sun, “Synthesis, crystal structure and fungicidal activity of 3-(((4-Cyclopropyl-5-Methyl-1H-1,2,4-Triazol-3-yl)Methyl)Benzonitrile H2O (1:1) solvent,” *Journal of the Chemical Society of Pakistan*, vol. 35, no. 3, pp. 955–959, 2013.

[34] J.-C. Jin, Z.-H. Sun, M.-Y. Yang, J. Wu, and X.-H. Liu, “Synthesis, crystal structure, and theoretical studies of N(4-((4-chlorobenzyl)oxy)phenyl)-4- (trifluoromethyl) pyrimidine-2-amine,” *Journal of Chemical*, vol. 2013, Article ID 521757, 5 pages, 2013.

[35] Z.-J. Wang, Y. Gao, Y.-L. Hou et al., “Design, synthesis, and fungicidal evaluation of a series of novel 5-methyl-1H-1,2,3-triazole-4-carboxy amide and ester analogues,” *European Journal of Medicinal Chemistry*, vol. 86, pp. 87–94, 2014.

[36] N.-B. Sun, J.-Q. Fu, J.-Q. Weng, J.-Z. Jin, C.-X. Tan, and X.-H. Liu, “Microwave assisted synthesis, antifungal activity and DFT theoretical study of some novel 1,2,4-triazole derivatives containing the 1,2,3-thiadiazole moiety,” *Molecules*, vol. 18, no. 10, pp. 12725–12739, 2013.

[37] M. Y. Yang, W. Zhao, X.-H. Liu, J.-Q. Weng, and C.-X. Tan, “Synthesis, crystal structure and antifungal activity of 4-(5-((2,4-dichlorobenzyl)thio)-4-phenyl-1H-1,2,4-triazol-3-yl)pyridine,” *Chinese Journal of Structural Chemistry*, vol. 34, pp. 203–207, 2015.

[38] C.-X. Tan, Y.-X. Shi, J.-Q. Weng, X.-H. Liu, W.-G. Zhao, and B.-J. Li, “Synthesis and antifungal activity of novel 1,2,4-triazole derivatives containing 1,2,3-thiadiazole moiety,” *Journal of Heterocyclic Chemistry*, vol. 51, no. 3, pp. 690–694, 2014.

[39] L.-J. Min, C.-X. Tan, J.-Q. Weng, and X.-H. Liu, “Synthesis, crystal structure, and biological activity of a novel 1,2,3-thiadiazole compound containing 1,2,4-triazole moiety,” *Phosphorus, Sulfur and Silicon and the Related Elements*, vol. 189, no. 3, pp. 379–386, 2014.

[40] G.-X. Sun, M.-Y. Yang, Z.-H. Sun, H.-K. Wu, X.-H. Liu, and Y.-Y. Wei, “Synthesis and bioactivities of novel 1,3,4-oxadiazole derivatives containing 1,2,3-thiadiazole moiety,” *Phosphorus, Sulfur and Silicon and the Related Elements*, vol. 189, no. 12, pp. 1895–1900, 2014.

[41] M. J. Frisch, G. W. Trucks, H. B. Schlegel et al., *Gaussian 03, Revision C.01*, Gaussian, Wallingford, Conn, USA, 2004.