UDC 547.732:615.01
DOI https://doi.org/10.32782/pcsd-2025-4-9

Yuliia KHARCHENKO
Candidate of Chemical Sciences, Associate Professor, Associate Professor at the Department of Human Biology, Chemistry and Methodology of Teaching Chemistry, Sumy State Pedagogical University named after A. S. Makarenko, 87 Romenska str., Sumy, Ukraine, 40002
***ORCID:** 0000-0002-8960-2440*
***Scopus Author ID:** 24921271000*

To cite this article: Kharchenko, Yu. (2025). Amidni pokhidni 1,2,4-oksadiazolu yak perspektyvni ahenty z podviinoiu funhitsydnoiu ta nematotsydnoiu diieiu [Amide derivatives of 1,2,4-oxadiazole as promising agents with dual fungicidal and nematicidal activity]. *Problems of Chemistry and Sustainable Development*, 4, 69–78, doi: https://doi.org/10.32782/pcsd-2025-4-9

AMIDE DERIVATIVES OF 1,2,4-OXADIAZOLE AS PROMISING AGENTS WITH DUAL FUNGICIDAL AND NEMATICIDAL ACTIVITY

Fungal and nematode pathogens, which often act synergistically, pose a significant threat to food security. Conventional plant protection methods involve the use of separate fungicides or nematicides, which increases chemical load and promotes the development of resistance. A promising approach is the design of dual-action molecules that can simultaneously suppress both fungal and nematode pathogens. Particular attention is drawn to amide derivatives of 1,2,4-oxadiazole due to their chemical modularity, heteroatomic composition, and favourable toxicity profile. These compounds exhibit a high level of succinate dehydrogenase (SDH) inhibition, leading to the blockade of electron transport, disruption of oxidative phosphorylation, and energy depletion in pathogens.

This study employed a systematic review of publications in Scopus, Web of Science, and PubMed. A comparative analysis of synthetic strategies for amide 1,2,4-oxadiazoles was conducted, and data on their fungicidal and nematicidal activities were systematised using structure-activity relationship (SAR) analysis to identify key structural-activity patterns. The analysis demonstrated that maximal activity is achieved through the combination of heteroaromatic substituents (notably pyridyl groups), optimal halogenation, and a flexible amide linker, which ensures proper orientation of the molecule within the enzyme's active site.

Key structural fragments responsible for high biological efficacy were identified, and recommendations for optimizing synthetic protocols were proposed. Further optimization can be achieved through modular molecular design, balancing hydrophobicity, and integrating secondary mechanisms of action, including reactive oxygen species generation, while minimizing toxicity and the risk of bioaccumulation (ecological SAR). The introduction of amide 1,2,4-oxadiazole derivatives as innovative dual-action agents presents prospects for enhancing crop productivity, reducing the frequency of applications, and mitigating the development of resistance.

***Keywords:** 1,2,4-oxadiazole, amide derivatives, synthesis, fungicidal activity, nematicidal activity, succinate dehydrogenase (SDH), structure-activity relationships (SAR).*

Юлія ХАРЧЕНКО
кандидат хімічних наук, доцент, доцент кафедри біології людини, хімії та методики навчання хімії, Сумський державний педагогічний університет імені А. С. Макаренка, вул. Роменська, 87, м. Суми, Україна, 40002
***ORCID:** 0000-0002-8960-2440*
***Scopus Author ID:** 24921271000*

Бібліографічний опис статті: Харченко, Ю. (2025). Амідні похідні 1,2,4-оксадіазолу як перспективні агенти з подвійною фунгіцидною та нематоцидною дією. *Проблеми хімії та сталого розвитку*, 4, 69–78, doi: https://doi.org/10.32782/pcsd-2025-4-9

АМІДНІ ПОХІДНІ 1,2,4-ОКСАДІАЗОЛУ ЯК ПЕРСПЕКТИВНІ АГЕНТИ З ПОДВІЙНОЮ ФУНГІЦИДНОЮ ТА НЕМАТОЦИДНОЮ ДІЄЮ

Грибкові та нематодні патогени, що часто діють синергічно, становлять серйозну загрозу продовольчій безпеці. Традиційні методи захисту рослин передбачають застосування окремих фунгіцидів або нематицидів, що підвищує хімічне навантаження та сприяє розвитку резистентності. Перспективним підходом є розробка молекул подвійної дії, здатних одночасно пригнічувати грибкові та нематодні патогени. Особливу увагу привертають амідні похідні 1,2,4-оксадіазолу завдяки їх хімічній модульності, гетероатомному складу та сприятливому профілю токсичності. Ці сполуки демонструють високий рівень інгібування сукцинатдегідрогенази (SDH), що призводить до блокування електронного транспорту, порушення окислювального фосфорилювання та енергетичного виснаження патогенів.

У роботі використано систематичний огляд публікацій у базах Scopus, Web of Science та PubMed. Проведено порівняльний аналіз синтетичних стратегій амідних 1,2,4-оксадіазолів та систематизовано дані щодо їх фунгіцидної та нематоцидної активності з застосуванням SAR-аналізу для виявлення структурно-активних закономірностей. Аналіз показав, що максимальна активність досягається при поєднанні гетероароматичних замісників (зокрема піридильних), оптимального галогенування та гнучкого амідного лінкера, що забезпечує правильну орієнтацію молекули у активному сайті ферменту.

Виявлено ключові структурні фрагменти, що визначають високу біологічну ефективність, та запропоновано рекомендації щодо оптимізації синтетичних протоколів. Подальша оптимізація може бути здійснена шляхом модульного дизайну молекул, досягнення балансу гідрофобності та інтеграції вторинних механізмів дії, зокрема генерації активних форм кисню, із зменшенням токсичності та ризику біоакумуляції (екологічний SAR). Впровадження амідних похідних 1,2,4-оксадіазолу як інноваційних агентів подвійної дії відкриває перспективи підвищення продуктивності агрокультур, зменшення частоти обробок та стримування розвитку резистентності.

Ключові слова: *1,2,4-оксадіазол, амідні похідні, синтез, фунгіцидна активність, нематоцидна активність, сукцинатдегідрогеназа (SDH), структурно-активні зв'язки (SAR).*

Relevance of the Problem. Global food security remains under constant pressure from biotic factors, including pathogens and pests, which cause substantial damage to agricultural crops. According to expert estimates, crop losses worldwide due to their impact can reach 20–40 % (Yu, 2025).

A particular threat arises from the simultaneous infection of plants by fungi and nematodes, which often results in synergistic interactions: cumulative losses exceed the additive effect of individual pathogens (Liu, 2022). Among known plant pathogens, more than 8,000 fungal species cause diseases, including *Fusarium graminearum*, *Botrytis cinerea*, *Sclerotinia sclerotiorum*, *Rhizoctonia solani*, *Blumeria* spp., *Pythium* spp., *Colletotrichum* spp., *Puccinia* spp., and *Phytophthora* spp., accounting for approximately 85 % of all crop diseases (Dang, 2011). Concurrently, plant-parasitic nematodes such as *Meloidogyne incognita*, *Aphelenchoides besseyi*, and *Bursaphelenchus xylophilus* inflict severe damage on agriculture (Xie, 2019). Their combined synergistic impact highlights the urgent need for universal control agents, including the development of new chemical compounds with dual activity capable of simultaneously targeting both classes of pests (Liu, 2022).

Conventional plant protection strategies rely on the separate application of fungicides or nematicides, necessitating the combination of multiple agents, which increases costs and environmental load. Dual-activity molecules that simultaneously suppress both fungi and nematodes offer a more efficient approach to pathogen control while reducing overall pesticide burden.

One promising strategy for developing dual-action agrochemicals is the use of the 1,2,4-oxadiazole scaffold. Its advantages include:

– heteroatomic nature: the presence of oxygen and nitrogen atoms facilitates specific interactions with biological targets, particularly enzymes.

– chemical modularity: variations in substituents on the ring carbon atoms and functional groups (amides, halogens, CF_3, etc.) allow fine-tuning of physicochemical properties (pKa, lipophilicity) and bioactivity.

– safety and stability: the 1,2,4-oxadiazole structure is already employed in known agrochemicals (e.g., the nematicide thioxazafen) (Ju, 2023), demonstrating a favourable toxicity profile and synthetic accessibility.

The integration of 1,2,4-oxadiazole-based dual-action molecules into crop protection systems presents a promising approach for the simultaneous control of fungal and nematode pathogens,

reduction of chemical load, and enhancement of agroecosystem resilience.

Analysis of Recent Studies and Publications. Nitrogen-containing heterocyclic structures, particularly oxadiazole derivatives, occupy a prominent position in contemporary medicinal chemistry and the development of new bioactive compounds. Notably, approximately three-quarters of modern herbicides and pesticides contain at least one heterocyclic ring (Gomtsyan, 2012). The high biological activity of these structures is attributed to their ability to participate in a wide range of intramolecular interactions – van der Waals, hydrophobic, hydrogen bonding, and coordination – which facilitates effective binding to catalytic centres and allosteric sites of biological targets (Kumar, 2022). Consequently, oxadiazole heterocycles are regarded as one of the most valuable pharmacophores today.

In recent years, the 1,2,4-oxadiazole core has established itself as a versatile structural scaffold, both in the design of pharmaceutical agents (fig. 1) (Biernacki, 2020, Kumar, 2024) and in the development of highly active agrochemicals (Fu, 2024, Zhao, 2024, Zhong, 2023, Chen, 2025).

A key trend in recent years has been the growing interest in 1,2,4-oxadiazole as a scaffold for designing succinate dehydrogenase inhibitors (SDHIs) (Hu, 2025, Yu, 2025). SDHIs have long held a leading position in the fungicide market, but pathogen resistance and the structural conservatism of their mechanism of action underscore the need for new molecular classes. In this context, amide-substituted 1,2,4-oxadiazoles emerge as a promising direction: their electronic structure, aromaticity, and ability to form specific intermolecular interactions make the oxadiazole scaffold suitable for precise modulation of interactions within the SDH Q-domain. Thus, amide 1,2,4-oxadiazoles represent a natural extension of this trend, offering a novel approach to inhibiting the respiratory chain of fungal and nematode pathogens.

In agrochemical design, the principle of active substructure splicing – combining multiple biologically relevant substructures into a single hybrid molecule – is widely employed. For amide 1,2,4-oxadiazoles, this involves linking two or more aromatic or heteroaromatic fragments via the oxadiazole ring and the amide moiety (Ou, 2025).

Recently, several new nematicides containing amide fragments with broad-spectrum and sufficiently high activity have been reported (Flemming, 2025, Liu, 2022, Lahm, 2017, Schleker, 2022, Thompson, 2024). Among them are fluopyram, fluazaindolizine, and cyclobutrifluram (fig. 2).

Notably, fluopyram has demonstrated high efficacy against a broad spectrum of phytoparasitic nematodes (Jeschke, 2017, Miles, 2014, Schleker, 2022), confirming the effectiveness of the amide fragment in designing novel nematicides. The amide moiety is not merely a chemical linker; it serves as a critical molecular bridge with dual functional significance. First, the amide provides structural flexibility necessary for optimal ligand orientation within the SDH active pocket. Second, it contains key donor and acceptor sites (NH and C═O groups) to form stabilising hydrogen bonds with amino acid residues of the target protein. As demonstrated by recent studies (Liu, 2022), newly synthesised compounds containing an amide fragment exhibit biological activity comparable to modern commercial fungicides, highlighting the pivotal role of the amide bridge in enzyme inhibition.

Analysis of recent literature indicates that SDH inhibitors remain one of the most dynamic areas in the development of new fungicides (Liu, 2022, Wang, 2021, Yan, 2018). Their mechanism of action involves blocking SDH, an enzyme simultaneously involved in the tricarboxylic acid cycle and the mitochondrial respiratory chain (Cecchini, 2003, Sun, 2005). Molecular modification via the amide bridge allows the creation of a novel enzyme binding mode, potentially circumventing existing

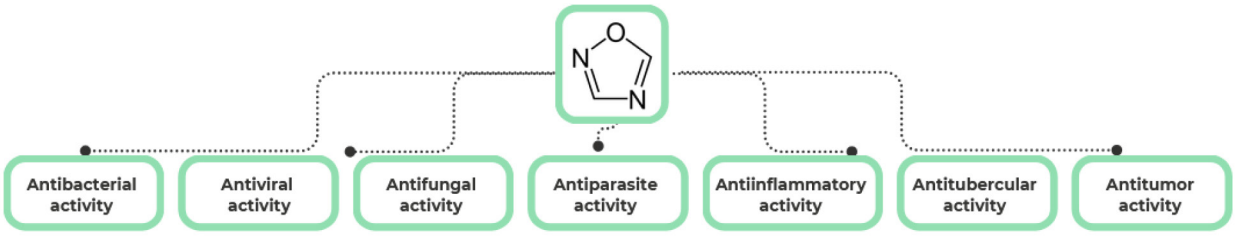


Fig. 1. Pharmacological activity of 1,2,4-oxadiazole derivatives

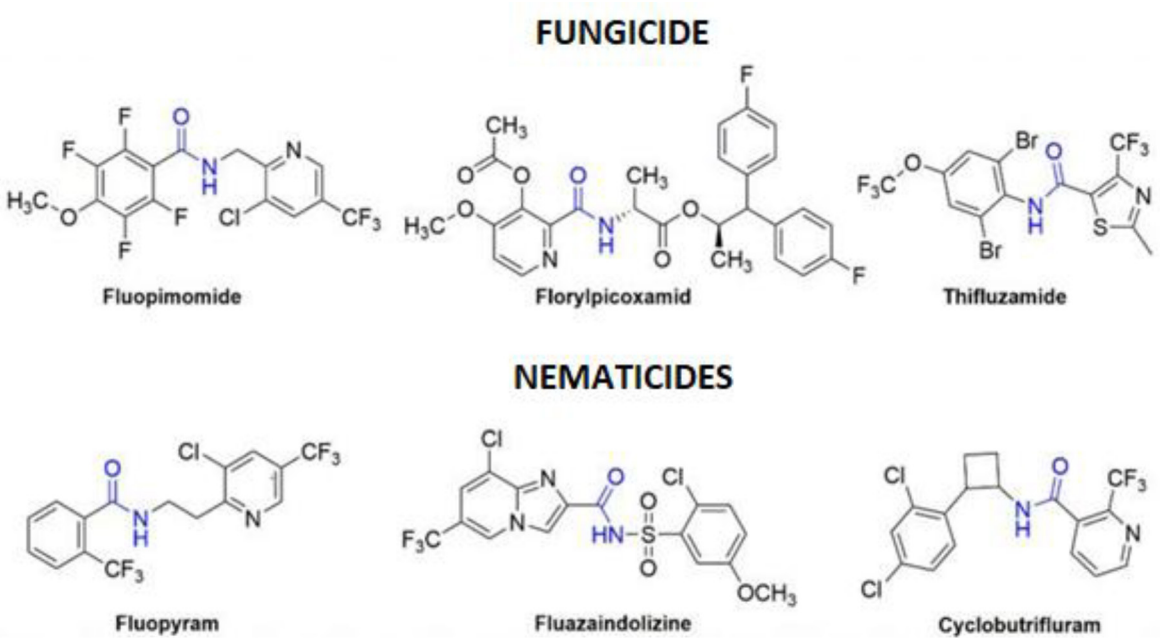


Fig. 2. Structures of reported antifungal and nematicidal compounds containing amide or 1,2,4-oxadiazole fragments

resistance (Miyamoto, 2020, Wang, 2021). Notably, well-known SDHI fungicides – fluopimomid, florilpicozamide, tifluzamid – and nematicides fluazaindolizine and cyclobutrifluram (fig. 2) all contain an amide linkage. This highlights that incorporating amide fragments into the structures of new 1,2,4-oxadiazoles is a key strategy for developing selective fungicides and nematicides.

Research Objective. The objective of this study is to summarise current data on the structural features, synthetic strategies, and SAR profiles of amide-substituted 1,2,4-oxadiazoles as a promising class of dual-action agrochemicals with simultaneous fungicidal and nematicidal activity, and to identify the key factors that determine their biological efficacy.

Presentation of the Main Research Material. The synthesis of amide 1,2,4-oxadiazoles typically involves two key stages: the formation of the heterocyclic core (Kumar, 2024) (fig. 3) and subsequent functionalisation with an amide moiety. The primary pathways for constructing the 1,2,4-oxadiazole ring involve cyclisation reactions, particularly the reaction of hydroxamidochlorides with nitriles, which yields a compact and stable scaffold. After formation of the heterocyclic core, the introduction of the amide fragment is a critical step for modulating biological activity.

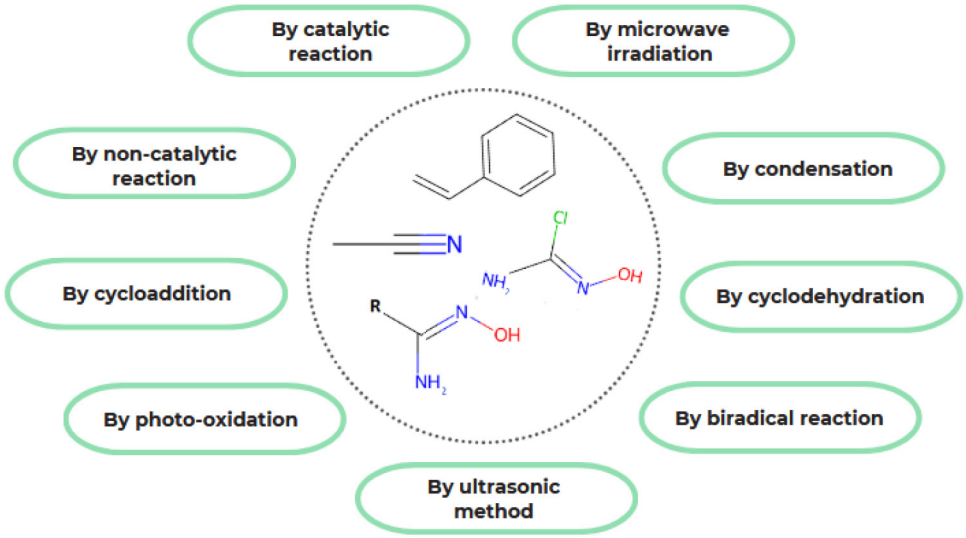


Fig. 3. Synthetic approaches for obtaining the 1,2,4-oxadiazole ring

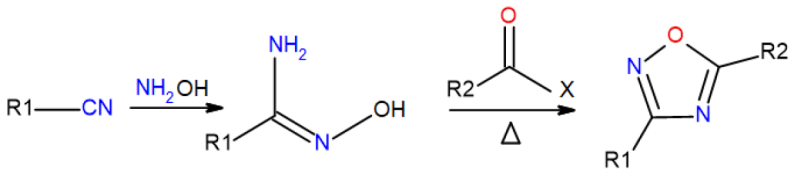


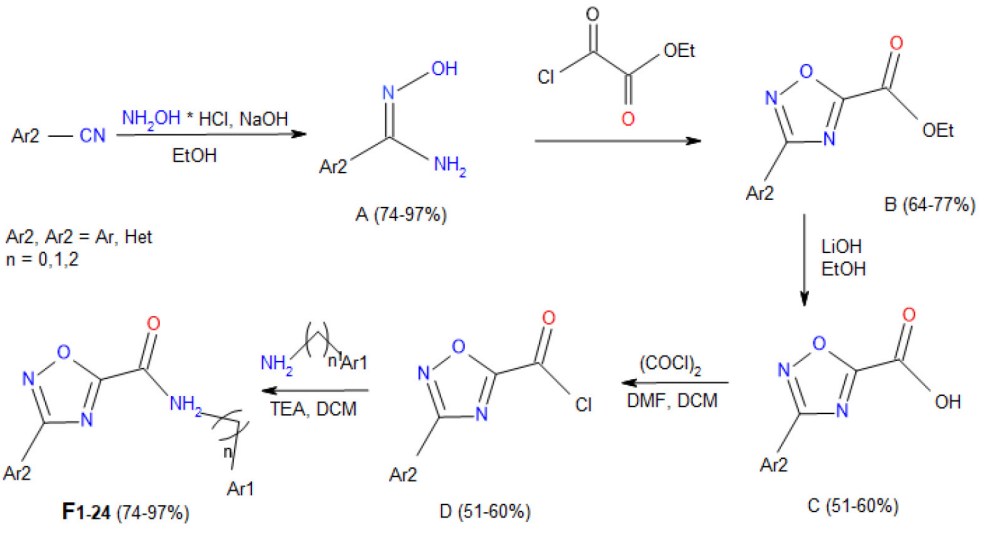
Fig. 4. General approach to the synthesis of the 1,2,4-oxadiazole ring

A typical standard synthetic approach, employed by numerous authors (Fu, 2024, Kharchenko, 2008, Kharchenko, 2009, Liu, 2019, Liu, 2022, Liu, 2025, Ou, 2025, Zhong, 2023, Zhu, 2025), involves the synthesis of amidoximes via the reaction of substituted nitriles with hydroxylamine hydrochloride, followed by cyclocondensation of the resulting amidoximes with anhydrides or acyl chlorides of carboxylic acids or their synthetic equivalents (Fig. 4).

For example, the authors of the work (Liu, 2022) conducted a synthesis (fig. 5) based on various (hetero)aromatic nitriles with hydroxylamine. Amidoximes **A** were synthesised and then treated with ethyl oxalyl chloride in acetonitrile. The resulting esters **B** were hydrolysed with LiOH in ethanol to yield acids **C**. Compounds **C** reacted with oxalyl chloride to form chloroanhydrides **D**, which were subsequently converted into target amides **F1–F24** via reaction with primary amines.

This modular approach allows for rapid variation of the Ar1 and Ar2 substituents, typically halogenated phenyls or heterocycles (fig. 5), enabling straightforward modification of one of the aromatic substituents for quick investigation of structure-activity relationships (SAR).

According to Liu (2022), all obtained compounds (**F1–F24**) exhibited moderate to high mycelial growth inhibition at a concentration of 50 mg/mL. Notably, compounds **F3**, **F15**, **F18** and **F20** showed good antifungal activity against *B. cinerea*, with inhibition rates of 56.8 %, 58.2 %, 55.9 % and 55.8 %, respectively. These values, however, were lower than those for reference agents fluopyram (87.3 %) and tifluzamid (80.3 %) (fig. 1). In contrast, compounds **F1**, **F3**, **F9**, **F14** and **F15** exhibited high antifungal activity against *S. sclerotiorum*, with inhibition rates of 73.2 %, 84.85 %, 61.1 %, 65.2 % and 89.3 %, respectively. Compound **F15** demonstrated particularly high efficacy against *S. sclerotiorum* ($EC_{50} \approx 2.9$ mg/mL),



F1: Ar1 = C_6H_5, Ar2 = 2-Py, n = 2;
F2: Ar1 = C_6H_5, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2;
F3: Ar1 = C_6H_5, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F4: Ar1 = C_6H_5, Ar2 = 2,4-di-Cl-C_6H_3, n = 0;
F5: Ar1 = 4-CH_3-C_6H_4, Ar2 = 2-Py, n = 2;
F6: Ar1 = 4-CH_3-C_6H_4, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2;
F7: Ar1 = 4-CH_3-C_6H_4, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F8: Ar1 = 4-CH_3-C_6H_4, Ar2 = 2,4-di-Cl-C_6H_3, n = 0;
F9: Ar1 = 4-Cl-C_6H_4, Ar2 = 2-Py, n = 2;
F10: Ar1 = 4-Cl-C_6H_4, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2
F11: Ar1 = 4-Cl-C_6H_4, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F12: Ar1 = 4-Cl-C_6H_4, Ar2 = 2,4-di-Cl-C_6H_3, n = 0;
F13: Ar1 = thienyl, Ar2 = 2-Py, n = 2;
F14: Ar1 = thienyl, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2;
F15: Ar1 = thienyl, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F16: Ar1 = thienyl, Ar2 = 2,4-di-Cl-C_6H_3, n = 0;
F17: Ar1 = 6-Br-3-Py, Ar2 = 2-Py, n = 2;
F18: Ar1 = 6-Br-3-Py, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2;
F19: Ar1 = 6-Br-3-Py, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F20: Ar1 = 6-Br-3-Py, Ar2 = 2,4-di-Cl-C_6H_3, n = 0;
F21: Ar1 = 3-Cl-5-CF_3-2-Py, Ar2 = 2-Py, n = 2;
F22: Ar1 = 3-Cl-5-CF_3-2-Py, Ar2 = 3-Cl-5-CF_3-2-Py, n = 2;
F23: Ar1 = 3-Cl-5-CF_3-2-Py, Ar2 = 2,4-di-F-C_6H_3, n = 1;
F24: Ar1 = 3-Cl-5-CF_3-2-Py, Ar2 = 2,4-di-Cl-C_6H_3, n = 0.

Fig. 5. Synthetic scheme

which is comparable to tifluzamid (4.3 mg/mL) and fluopyram (1.2 mg/mL) (Li, 2022). Morphological analysis revealed that **F15** induced abnormal collapse and wrinkling of *S. sclerotiorum* hyphae, thereby directly inhibiting pathogen growth.

SAR analysis of these 1,2,4-oxadiazoles showed that the presence of an aryl substituent at C(3) and β-arylethylamine groups resulted in higher activity against *B. cinerea* and *S. sclerotiorum* for compounds with an unsubstituted pyridine ring compared to those with trifluoromethyl or chloro-substituted pyridine. This is exemplified by the following activity profiles of 1,2,4-oxadiazoles bearing substituted and unsubstituted pyridine rings against *S. sclerotiorum* and *B. cinerea*: **F1** (73.2 % and 24.2 %) > **F2** (48.6 % and 23.6 %); **F5** (56.3 % and 24.9 %) > **F6** (56.0 % and 22.9 %); **F9** (61.1 % and 26.7 %) > **F10**(48.6 % and 24.2 %). When a heterocyclic substituent was introduced at C3, the trend shifted as follows: **F14** (65.2 % and 36.4 %) > **F13** (41.1 % and 27.3 %); **F18** (34.9 % and 55.9 %) > **F17** (10.1 % and 27.6 %); **F22** (37.6 % and 45.2 %) > **F21** (35.1 % and 38.8 %). The highest activity was observed for compounds with n = 1 and a 2,4-difluorophenyl group: **F3** (41.1 % and 27.3 %) > **F1** (73.2 % and 24.2 %); **F15** (89.3 % and 58.2 %) > **F13** (41.1 % and 27.3 %). Additionally, the antifungal effect of thiophenyl-substituted compounds was significantly higher than that of compounds with other substituents: **F15** (89.3 % and 58.2 %) > **F3** (41.1 % and 27.3 %) > **F7** (56.4 % and 46.4 %) > **F11** (44.9 % and 44.2 %) > **F23** (34.6 % and 41.5 %). Comparison of series with identical substituents showed the lowest activity for compounds with a 2,4-dichlorophenyl group and n = 0 (**F15** (89.3 % and 58.2 %) > **F14** (65.2 % and 36.4 %) > **F13** (41.1 % and 27.3 %) > **F16** (39.6 % and 25.5 %). At the same time, introducing the 2,4-difluorophenyl moiety at n = 1 (**F15**) led to superior antifungal activity toward both *B. cinerea* and *S. sclerotiorum*. These results indicate that a large steric load of the R substituent generally has a negative effect on fungicidal activity.

The in vitro results were confirmed in vivo for the leading compound **F15**: it effectively controlled *S. sclerotiorum*-induced disease on cabbage leaves, demonstrating protective and curative effects of 62.3 % and 71.0 % at a dose of 100 mg/mL. Moreover, the application of **F15** visibly disrupted the hyphal morphology of *S. sclerotiorum*.

Another study (Schleker, 2022) focused on the structural modification of fluopyram. The flexible ethyl linker connecting the amide and pyridine fragments was replaced in target compounds with a rigid 1,2,4-oxadiazole ring. A one-pot procedure was developed involving the cyclisation of amidoximes with benzoyl chlorides, followed by the removal of the tert-butoxycarbonyl protecting group from the intermediates, yielding free amino intermediates that were acylated in situ to obtain the target compounds. All target amide 1,2,4-oxadiazoles were tested for nematicidal activity, and some demonstrated very promising results.

The analysis of SAR and positional effects of the amide fragment in the target compounds revealed two key aspects: the site of attachment and the nature of the linker. The amide fragment can be introduced at the C(3) position (series **A**) or C(5) position (series **B**, **C**) of the 1,2,4-oxadiazole ring (Ou, 2025) (fig. 6).

Studies of nematicide series **A–C** showed that amide introduction at either position maintains high activity (Ou, 2025). However, within series **A**, when the amide fragment was introduced at position

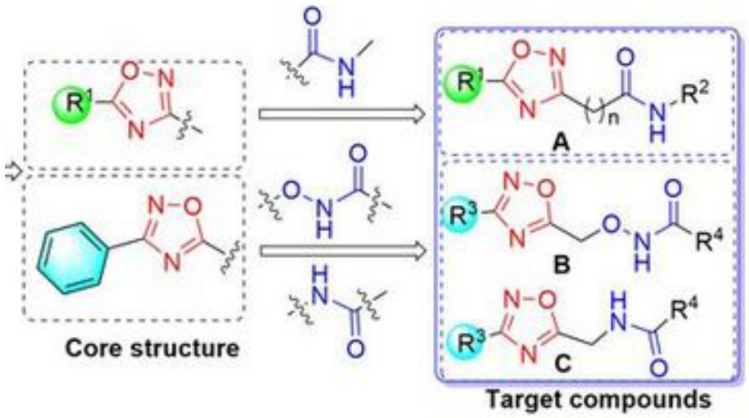


Fig. 6. Target product structures (Ou, 2025)

3 and *R*1 = 2-CF_3-C_6H_4 of 1,2,4-oxadiazole, the activity of the monosubstituted *R*2 compound was higher than that of the disubstituted *R*2 counterpart; e.g., **A13** (*R*2 = 4-CF_3-C_6H_4, 35.5 %) > **A11** (*R*2 = 2-Cl-4-CF_3-C_6H_3, 27.1 %). The position of the substituent in the aryl *R*2 group also matters. Ortho-substituted R2 aryl groups enhance nematicidal activity against *B. xylophilus*. For example, with *R*1 = 2-CF_3-C_6H_4, introducing a CF_3 group at the 2-position of the benzene ring *R*2 increases activity: **A14** (*R*2 = 2-CF_3-C_6H_4, 45.3 %) > **A13** (*R*2 = 4-CF_3-C_6H_4, 35.5 %). Bulky ortho-substituents (e.g., 2-trifluoromethylphenyl in *R*2) further enhance activity, likely due to optimal filling of the nematode SDH active site (Wang, 2024).

Another critical factor is the nature and length of the amide linker. Comparative analysis of nematicidal activity between series **C** and **B** showed that the absence of an oxygen atom in the linker (i.e., using an amide instead of another linkage type) increased activity by nearly 30 %. This may be explained by the more hydrophobic environment around the linker, optimising interactions with the SDH active site in nematodes. Oxygen presence can create undesired hydrogen bonds and increase molecular polarity, reducing efficacy (Ou, 2025). Meanwhile, for the fungicidal compound **F15** (Liu, 2022), a spacer *n* = 1 was used, representing an additional methylene linker between the oxadiazole core and the amide group. Control over linker nature and length enables the tuning of lipophilicity (log P), which is crucial for compound penetration into pathogen cells and for influencing the ecotoxicological profile.

Interestingly, introduction of an electron-withdrawing group R3 in series **C** target compounds (Ou, 2025) enhanced nematicidal activity against *B. xylophilus*, e.g., **C1** (*R*3 = 4-F-C_6H_4, 38.8 %) > **C2** (R3 = 4-Cl-C_6H_4, 32.5 %) > **C5** (*R*3 = C_6H_5, 29.8 %) > **C4** (*R*3 = 4-CH_3-C_6H_4, 25.6 %). Conversely, introducing an acceptor group at **R4** = 2-CF_3-C_6H_4 with an ortho-chloro atom in *R*3 reduced activity: **C3** (*R*3 = 4-CF_3-C_6H_4, 90.7 %) > **C6** (*R*3 = 2-Cl-4-CF_3-C_6H_3, 30.8 %).

Thus, recent studies confirm the high fungicidal activity of amide 1,2,4-oxadiazoles, which is comparable to that of commercial SDHI fungicides.

Conclusions and Prospects for Further Research. The analysis of recent scientific literature reveals a sustained increase in interest in dual-action molecules that exhibit both fungicidal and nematocidal activity, driven by the prevalence of combined infections and the emergence of pathogen resistance to conventional SDHI-based agents. Amidic 1,2,4-oxadiazoles represent a promising class of such dual-active agents capable of effectively suppressing pathogenic fungi and nematodes. Their bioactivity is primarily associated with the inhibition of succinate dehydrogenase (SDH), leading to the blockade of electron transport, disruption of oxidative phosphorylation, and rapid energy depletion in the pathogens.

SAR analysis confirmed that maximal biological activity is achieved through the combination of heteroaromatic substituents, optimal halogenation, and a flexible amidic linker, which ensures proper molecular orientation within the enzyme's active site. The hydrophobic–hydrophilic balance (log P) determines the compounds' ability to penetrate pathogen tissues while maintaining sufficient solubility. A comparative evaluation of the fungicidal and nematocidal effects indicates that amidic 1,2,4-oxadiazole derivatives can serve as a foundation for the development of innovative dual-action agrochemicals.

Future research should focus on the modular design of molecules to maintain stable interactions with SDH while preserving the flexibility of the amidic linker, as well as optimal combinations of hydrophobic and heteroaromatic fragments. Additionally, it should assess secondary modes of action and eco-SAR to minimise toxicity and reduce the risk of bioaccumulation.

The implementation of such compounds opens new prospects for the development of effective, safe, and sustainable next-generation agrochemicals.

BIBLIOGRAPHY:

1. Biernacki K., Daśko M., Ciupak O., Kubiński K., Rachon J., Demkowicz S. Novel 1,2,4-oxadiazole derivatives in drug discovery. *Pharmaceuticals (Basel)*. 2020. Vol. 13(6). 111. DOI: https://doi.org/10.3390/ph13060111

2. Cecchini G. Function and structure of complex II of the respiratory chain. *Annual Review of Biochemistry*. 2003. Vol. 72. P. 77–109. DOI: https://doi.org/10.1146/annurev.biochem.72.121801.161700

3. Chen X., Wang S., Du T., Zhang Y., Zhao X., Chen J. Design, synthesis, and nematicidal activity of novel amide derivatives containing a 1,2,4/1,3,4-oxadiazole moiety against *Bursaphelenchus xylophilus. J. Agric. Food Chem.* 2025. Vol. 73(12). P. 7166–7178. DOI: https://doi.org/10.1021/acs.jafc.4c13159

4. Dang Q. L., Kim W. K., Nguyen C. M., Choi Y. H., Choi G. J., Jang K. S., et al. Nematicidal and antifungal activities of annonaceous acetogenins from *Annona squamosa* against various plant pathogens. *J. Agric. Food Chem*. 2011. Vol. 59. P. 11160–11167. DOI: https://doi.org/10.1021/jf203017f

5. Flemming A., Guest M., Luksch T., O'Sullivan A., Screpanti C., Dumeunier R., et al. The discovery of Cyclobutrifluram, a new molecule with powerful activity against nematodes and diseases. *Pest Management Science*. 2025. Vol. 81. P. 2480–2490. DOI: https://doi.org/10.1002/ps.8730

6. Fu W., Yuan Q., Zhang H., Li X., Lu Y., Yan W., et al. Novel SDH inhibitors as antifungal leads: From azobenzene derivatives to the 1,2,4-oxadiazole compounds. *J. Agric. Food Chem*. 2024. Vol. 72. P. 24272–24282.

7. Gomtsyan A. Heterocycles in drugs and drug discovery. *Chemistry of Heterocyclic Compounds*. 2012. Vol. 48. P. 7–10.

8. Hu X., Miao J., Tian Y., Luo W., Shang J., Liu R., Lu H. Design, synthesis and herbicidal activity of 1,2,4-oxadiazole compounds as novel light-dependent protochlorophyllide oxidoreductase inhibitors. *Molecules*. 2025. Vol. 30(19). 3970. DOI: https://doi.org/10.3390/molecules30193970

9. Jeschke P. Latest generation of halogen-containing pesticides. *Pest Management Science*. 2017. Vol. 73(6). P. 1053–1066. DOI: https://doi.org/10.1002/ps.4540

10. Kharchenko Y., Detistov O., Orlov V. Polycyclic systems containing 1,2,4-oxadiazole ring 2. 4-(1,2,4-Oxadiazol-5-yl)pyrrolidin-2-ones: Synthesis and prediction of biological activity. *Chemistry of Heterocyclic Compounds*. 2008. Vol. 44. P. 600–605. DOI: https://doi.org/10.1007/s10593-008-0080-y

11. Kharchenko J. V., Detistov O. S., Orlov V. D. Synthesis of substituted 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1H)-thiones. *Journal of Combinatorial Chemistry*. 2009. Vol. 11(2). P. 216–219. DOI: https://doi.org/10.1021/cc800111h

12. Kumar G., Kumar R., Mazumder A., Salahuddin H., Singh U., Kumar M. M. A., Shahar Yar N., Kumar N. Insight into the synthesis, biological activity, and structure–activity relationship of 1,2,4-oxadiazole and analogs: A comprehensive review. *Letters in Drug Design & Discovery*. 2024. Vol. 21(9). P. 1437–1464. DOI: https://doi.org/10.2174/1570180820666230330105308

13. Kumar N., Goel N. Heterocyclic compounds: Importance in anticancer drug discovery. *Anticancer Agents in Medicinal Chemistry*. 2022. Vol. 22. P. 3196–3207. DOI: 10.2174/1871520622666220404082648

14. Lahm G. P., Desaeger J., Smith B. K., Pahutski T. F., Rivera M. A., Meloro T., et al. The discovery of fluazaindolizine: A new product for the control of plant parasitic nematodes. *Bioorganic & Medicinal Chemistry Letters*. 2017. Vol. 27(7). P. 1572–1575. DOI: https://doi.org/10.1016/j.bmcl.2017.02.029

15. Liu D., Luo L., Wang Z., Ma X., Gan X. Design, synthesis and antifungal/nematicidal activity of novel 1,2,4-oxadiazole derivatives containing amide fragments. *Int. J. Mol. Sci*. 2022. Vol. 23(3). 1596. DOI: https://doi.org/10.3390/ijms23031596

16. Liu M. M., Liang Y. R., Zhu Z. Z., Wang J., Cheng X. X., et al. Discovery of novel aryl carboxamide derivatives as hypoxia-inducible factor 1α signaling inhibitors with potent anticancer metastasis activity. *Journal of Medicinal Chemistry*. 2019. Vol. 62. P. 9299–9314. DOI: https://doi.org/10.1021/acs.jmedchem.9b01313

17. Liu X.-H., Fu C.-H., Wang J., Wei Y.-C., Tan C.-X., Weng J.-Q., et al. Novel 5-(trifluoromethyl)-1,2,4-oxadiazole-based pyrimidin-4-ether HDAC inhibitors for controlling rust disease. *J. Agric. Food Chem*. 2025. Vol. 73(8). P. 4563–4573. DOI: https://doi.org/10.1021/acs.jafc.4c09039

18. Miles T. D., Miles L. A., Fairchild K. L., Wharton P. S. Screening and characterization of resistance to succinate dehydrogenase inhibitors in *Alternaria solani*. *Plant Pathology*. 2014. Vol. 63(1). P. 155–164. DOI: https://doi.org/10.1111/ppa.12077

19. Miyamoto T., Hayashi K., Okada R., Wari D., Ogawara T. Resistance to succinate dehydrogenase inhibitors in field isolates of *Podosphaera xanthii* on cucumber. *Pesticide Biochemistry and Physiology*. 2020. Vol. 169. 104646. DOI: https://doi.org/10.1016/j.pestbp.2020.104646

20. Ou Y., Guo X., Zhang Q., Zhang W., Gan X. Design, synthesis, and nematicidal activity of novel 1,2,4-oxadiazole derivatives containing amide fragments. *Molecular Diversity*. 2025. Vol. 29. P. 2293–2304. DOI: https://doi.org/10.1007/s11030-024-10992-9

21. Schleker A. S. S., Rist M., Matera C., Damijonaitis A., Collienne U., et al. Mode of action of fluopyram in plant-parasitic nematodes. *Scientific Reports*. 2022. Vol. 12(1). 11954. DOI: https://doi.org/10.1038/s41598-022-15782-7

22. Sun F., Huo X., Zhai Y., Wang A., Xu J., Su D., Bartlam M., Rao Z. Crystal structure of mitochondrial respiratory membrane protein complex II. *Cell*. 2005. Vol. 121. P. 1043–1057. DOI: https://doi.org/10.1016/j.cell.2005.05.025

23. Thompson H., Peris-Felipo F. J., Peranginangin N., Pocock M., Gayan-Quijano A. L. Cyclobutrifluram (TYMIRIUM® technology): Low risks… *Crop Protection*. 2024. Vol. 184. 106822. DOI: https://doi.org/10.1016/j.cropro.2024.106822.

24. Wang M. L., Du Y., Ling C., Yang Z. K., Jiang B. B., Duan H. X., et al. Design, synthesis and antifungal/anti-oomycete activity of pyrazolyl oxime ethers. *Pest Management Science*. 2021. Vol. 77. P. 3910–3920. DOI: https://doi.org/10.1002/ps.6418

25. Wang Y., Song H., Wang S., Cai Q., Chen J. Design, synthesis, nematicidal activity, and mechanism of novel amide derivatives containing a 1,2,4-oxadiazole moiety. *J. Agric. Food Chem*. 2024. Vol. 72(1). P. 128–139. DOI: https://doi.org/10.1021/acs.jafc.3c04945

26. Xie J. L., Yang F., Wang Y. P., Peng Y. L., Ji H. L. Studies on the efficiency of different inoculation methods of rice white-tip nematode. *Nematology*. 2019. Vol. 21. P. 673–678. DOI: https://doi.org/10.1163/15685411-00003244

27. Yan Z., Liu A., Huang M., Liu M., Pei H., et al. Design, synthesis, DFT study and antifungal activity of pyrazolecarboxamide derivatives. *Eur. J. Med. Chem*. 2018. Vol. 149. P. 170–181. DOI: https://doi.org/10.1016/j.ejmech.2018.02.036

28. Yu L., Yang K., Yao L., Wang N., Kang H., Yao G., et al. Synthesis and antifungal activity of 1,2,4-oxadiazole derivatives. *Molecules*. 2025. Vol. 30(8). 1851. DOI: https://doi.org/10.3390/molecules30081851

29. Zhao L., Wang B., Zhang Y., Zhang C. et al. Design, synthesis, nematicidal, and fungicidal activities of novel azo and azoxy compounds. *J. Agric. Food Chem*. 2024. Vol. 72(10). P. 2473–2481. DOI: https://doi.org/10.1021/acs.jafc.3c04847

30. Zhong L., Wu C., Li M., Wu J., Chen Y., Ju Z., Tan C. 1,2,4-Oxadiazole as a potential scaffold in agrochemistry: A review. *Org. Biomol. Chem*. 2023. Vol. 21(37). P. 7511–7524. DOI: https://doi.org/10.1039/D3OB00934C

31. Zhu M., Du T., Zhang Y., Chen W., Zhu Z., Lu S., Chen J. Novel amide derivatives containing an 1,2,4-oxadiazole moiety as potential SDH inhibitors. *Pest Management Science*. 2025. Vol. 81(9). P. 5234–5249. DOI: https://doi.org/10.1002/ps.8878

REFERENCES:

1. Biernacki, K., Daśko, M., Ciupak, O., Kubiński, K., Rachon, J., & Demkowicz, S. (2020). Novel 1,2,4-oxadiazole derivatives in drug discovery. *Pharmaceuticals (Basel), 13*(6), 111. https://doi.org/10.3390/ph13060111

2. Cecchini, G. (2003). Function and structure of complex II of the respiratory chain. *Annual Review of Biochemistry, 72*, 77–109. https://doi.org/10.1146/annurev.biochem.72.121801.161700

3. Chen, X., Wang, S., Du, T., Zhang, Y., Zhao, X., & Chen, J. (2025). Design, synthesis, and nematicidal activity of novel amide derivatives containing a 1,2,4/1,3,4-oxadiazole moiety against *Bursaphelenchus xylophilus*. *Journal of Agricultural and Food Chemistry, 73*(12), 7166–7178. https://doi.org/10.1021/acs.jafc.4c13159

4. Dang, Q. L., Kim, W. K., Nguyen, C. M., Choi, Y. H., Choi, G. J., Jang, K. S., Park, M. S., Lim, C. H., Luu, N. H., & Kim, J. C. (2011). Nematicidal and antifungal activities of annonaceous acetogenins from *Annona squamosa* against various plant pathogens. *Journal of Agricultural and Food Chemistry, 59*, 11160–11167. https://doi.org/10.1021/jf203017f

5. Flemming, A., Guest, M., Luksch, T., O'Sullivan, A., Screpanti, C., Dumeunier, R., Gaberthüel, M., Godineau, E., Harlow, P., Jeanguenat, A., Kurtz, B., Maienfisch, P., Mondière, R., & Pierce, A. (2025). The discovery of Cyclobutrifluram, a new molecule with powerful activity against nematodes and diseases. *Pest Management Science, 81*, 2480–2490. https://doi.org/10.1002/ps.8730

6. Fu, W., Yuan, Q., Zhang, H., Li, X., Lu, Y., Yan, W., et al. (2024). Novel SDH inhibitors as antifungal leads: From azobenzene derivatives to the 1,2,4-oxadiazole compounds. *Journal of Agricultural and Food Chemistry, 72*, 24272–24282.

7. Gomtsyan, A. (2012). Heterocycles in drugs and drug discovery. *Chemistry of Heterocyclic Compounds, 48*, 7–10.

8. Hu, X., Miao, J., Tian, Y., Luo, W., Shang, J., Liu, R., & Lu, H. (2025). Design, synthesis and herbicidal activity of 1,2,4-oxadiazole compounds as novel light-dependent protochlorophyllide oxidoreductase inhibitors. *Molecules, 30*(19), 3970. https://doi.org/10.3390/molecules30193970

9. Jeschke, P. (2017). Latest generation of halogen-containing pesticides. *Pest Management Science, 73*(6), 1053–1066. https://doi.org/10.1002/ps.4540

10. Kharchenko, Y., Detistov, O., & Orlov, V. (2008). Polycyclic systems containing 1,2,4-oxadiazole ring 2. 4-(1,2,4-Oxadiazol-5-yl)pyrrolidin-2-ones: Synthesis and prediction of biological activity. *Chemistry of Heterocyclic Compounds, 44*, 600–605. https://doi.org/10.1007/s10593-008-0080-y

11. Kharchenko, J. V., Detistov, O. S., & Orlov, V. D. (2009). Synthesis of substituted 5-(1,2,4-oxadiazol-5-yl)-3,4-dihydropyrimidine-2(1H)-thiones. *Journal of Combinatorial Chemistry, 11*(2), 216–219. https://doi.org/10.1021/cc800111h

12. Kumar, G., Kumar, R., Mazumder, A., Salahuddin, H., Singh, U., Kumar, M. M. A., Shahar Yar, N., & Kumar, N. (2024). Insight into the synthesis, biological activity, and structure-activity relationship of 1,2,4-oxadiazole and analogs: A comprehensive review. *Letters in Drug Design & Discovery, 21*(9), 1437–1464. https://doi.org/10.2174/1570180820666230330105308

13. Kumar, N., & Goel, N. (2022). Heterocyclic compounds: Importance in anticancer drug discovery. *Anticancer Agents in Medicinal Chemistry, 22*<, 3196–3207. 10.2174/1871520622666220404082648

14. Liu, D., Luo, L., Wang, Z., Ma, X., & Gan, X. (2022). Design, synthesis and antifungal/nematicidal activity of novel 1,2,4-oxadiazole derivatives containing amide fragments. *International Journal of Molecular Sciences, 23*(3), 1596. https://doi.org/10.3390/ijms23031596

15. Liu, M. M., Liang, Y. R., Zhu, Z. Z., Wang, J., Cheng, X. X., Cheng, J. Y., Xu, B. P., Li, R., Liu, X. H., & Wang, Y. (2019). Discovery of novel aryl carboxamide derivatives as hypoxia-inducible factor 1α signaling inhibitors with potent activities of anticancer metastasis. *Journal of Medicinal Chemistry, 62*, 9299–9314. https://doi.org/10.1021/acs.jmedchem.9b01313

16. Liu, X.-H., Fu, C.-H., Wang, J., Wei, Y.-C., Tan, C.-X., Weng, J.-Q., Min, L.-J., Xu, T.-M., & Wu, N. (2025). Novel 5-(trifluoromethyl)-1,2,4-oxadiazole-based pyrimidin-4-ether histone deacetylase inhibitors for controlling rust disease: Design, synthesis, activity, and structure–activity relationship. *Journal of Agricultural and Food Chemistry, 73*(8), 4563–4573. https://doi.org/10.1021/acs.jafc.4c09039

17. Lahm, G. P., Desaeger, J., Smith, B. K., Pahutski, T. F., Rivera, M. A., Meloro, T., Kucharczyk, R., Lett, R. M., Daly, A., Smith, B. T., Cordova, D., Thoden, T., & Wiles, J. A. (2017). The discovery of fluazaindolizine: A new product for the control of plant parasitic nematodes. *Bioorganic & Medicinal Chemistry Letters, 27*(7), 1572–1575. https://doi.org/10.1016/j.bmcl.2017.02.029

18. Miles, T. D., Miles, L. A., Fairchild, K. L., & Wharton, P. S. (2014). Screening and characterization of resistance to succinate dehydrogenase inhibitors in *Alternaria solani*. *Plant Pathology, 63*(1), 155–164. https://doi.org/10.1111/ppa.12077

19. Miyamoto, T., Hayashi, K., Okada, R., Wari, D., & Ogawara, T. (2020). Resistance to succinate dehydrogenase inhibitors in field isolates of *Podosphaera xanthii* on cucumber: Monitoring, cross-resistance patterns and molecular characterization. *Pesticide Biochemistry and Physiology, 169*, 104646. https://doi.org/10.1016/j.pestbp.2020.104646

20. Ou, Y., Guo, X., Zhang, Q., Zhang, W., & Gan, X. (2025). Design, synthesis, and nematicidal activity of novel 1,2,4-oxadiazole derivatives containing amide fragments. *Molecular Diversity, 29*, 2293–2304. https://doi.org/10.1007/s11030-024-10992-9

21. Schleker, A. S. S., Rist, M., Matera, C., Damijonaitis, A., Collienne, U., Matsuoka, K., Habash, S. S., Twelker, K., Gutbrod, O., Grundler, F. M. W., et al. (2022). Mode of action of fluopyram in plant-parasitic nematodes. *Scientific Reports, 12*(1), 11954. https://doi.org/10.1038/s41598-022-15782-7

22. Sun, F., Huo, X., Zhai, Y., Wang, A., Xu, J., Su, D., Bartlam, M., & Rao, Z. (2005). Crystal structure of mitochondrial respiratory membrane protein complex II. *Cell, 121*, 1043–1057. https://doi.org/10.1016/j.cell.2005.05.025

23. Thompson, H., Peris-Felipo, F. J., Peranginangin, N., Pocock, M., & Gayan-Quijano, A. L. (2024). Cyclobutrifluram (TYMIRIUM® technology): Low risks of a soil applied nematicide and fungicide to non-target soil invertebrates and bees. *Crop Protection, 184*, 106822. https://doi.org/10.1016/j.cropro.2024.106822

24. Wang, M. L., Du, Y., Ling, C., Yang, Z. K., Jiang, B. B., Duan, H. X., An, X., Li, X. H., & Yang, X. L. (2021). Design, synthesis and antifungal/anti-oomycete activity of pyrazolyl oxime ethers as novel potential succinate dehydrogenase inhibitors. *Pest Management Science, 77*, 3910–3920. https://doi.org/10.1002/ps.6418

25. Wang, Y., Song, H., Wang, S., Cai, Q., & Chen, J. (2024). Design, synthesis, nematicidal activity, and mechanism of novel amide derivatives containing an 1,2,4-oxadiazole moiety. *Journal of Agricultural and Food Chemistry, 72*(1), 128–139. https://doi.org/10.1021/acs.jafc.3c04945

26. Xie, J. L., Yang, F., Wang, Y. P., Peng, Y. L., & Ji, H. L. (2019). Studies on the efficiency of different inoculation methods of rice white-tip nematode, *Aphelenchoides besseyi*. *Nematology, 21*, 673–678. https://doi.org/10.1163/15685411-00003244

27. Yan, Z., Liu, A., Huang, M., Liu, M., Pei, H., Huang, L., Yi, H. B., Liu, W. D., & Hu, A. X. (2018). Design, synthesis, DFT study and antifungal activity of the derivatives of pyrazolecarboxamide containing thiazole or oxazole ring. *European Journal of Medicinal Chemistry, 149*, 170–181. https://doi.org/10.1016/j.ejmech.2018.02.036

28. Yu, L., Yang, K., Yao, L., Wang, N., Kang, H., Yao, G., Li, X., & Qin, B. (2025). Synthesis and antifungal activity of 1,2,4-oxadiazole derivatives. *Molecules*, *30*(8), 1851. https://doi.org/10.3390/molecules30081851

29. Zhao, L., Wang, B., Zhang, Y., Zhang, C., Liu, M., Chen, A., et al. (2024). Design, synthesis, nematicidal, and fungicidal activities of novel azo and azoxy compounds. *Journal of Agricultural and Food Chemistry, 72*(10), 2473–2481. https://doi.org/10.1021/acs.jafc.4c00000

30. Zhong L., Wu, C., Li, M., Wu, J., Chen, Y., Ju, Z., & Tan, C. (2023). 1,2,4-Oxadiazole as a potential scaffold in agrochemistry: A review. *Organic & Biomolecular Chemistry, 21*(37), 7511–7524. https://doi.org/10.1039/D3OB00934C

31. Zhu, M., Du, T., Zhang, Y., Chen, W., Zhu, Z., Lu, S., & Chen, J. (2025). Novel amide derivatives containing an 1,2,4-oxadiazole moiety as potential SDH inhibitors: Design, synthesis, and nematicidal activity. *Pest Management Science, 81*(9), 5234–5249. https://doi.org/10.1002/ps.8878

Стаття надійшла: 23.11.2025
Прийнято: 10.12.2025
Опубліковано: 30.12.2025