

Advances in structural design and biological activity of pyridine-based agrochemicals

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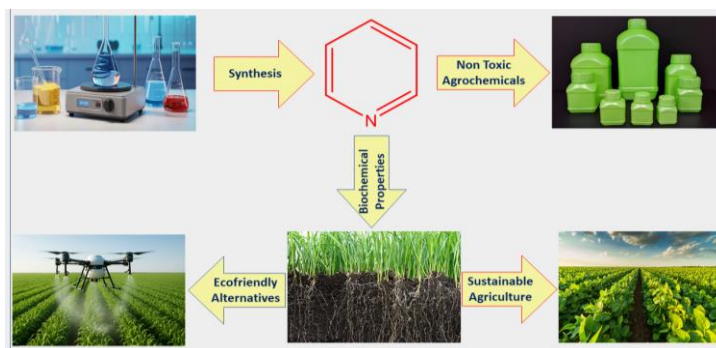
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Abstract

Pyridine derivatives contribute to a significant advancement in agrochemical research due to their structural flexibility and diverse biological functions. Recent advances in organic synthesis have enabled the development of novel pyridine-based compounds serving as key components in fertilizers, pesticides, plant growth regulators, and soil conditioners. Structurally, pyridine rings can serve as substitutes for traditional benzene structures. This substitution allows for variations in electron distribution and hydrogen bond formation and often increases metabolic stability. As a result, agrochemicals become more effective in the field, safer to handle, and less harmful to the environment. This review critically examines the structure-activity relationships of pyridine scaffolds, highlighting their role in resistance development, optimizing plant growth, and ensuring environmental safety. By integrating perspectives from synthetic organic chemistry and practical agricultural needs, the assessment demonstrates how pyridine chemistry influences eco-friendly developments.



Keywords: Pyridines, fertilizers, insecticides, herbicides, SAR, safety

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1. Introduction

Heterocyclic agrochemicals are essential elements in modern agricultural production. In the "pre-chemical era," the global population was around 2 billion in 1927. As of mid-November 2022, this number has reached 8 billion, marking an increase of 2 billion since 1998 and 1 billion since 2010. It took approximately 37 years from 1950 for the human population to double, surpassing 5 billion in 1987. Projections indicate that the global population may double again in over 70 years, potentially exceeding 10 billion by 2059.¹ With limited arable land available, intensifying farming practices are the only feasible approach to feed the growing population. Factors such as varietal characteristics, weather conditions, climate, and irrigation impact agricultural crop productivity, alongside losses attributed to pests, diseases, and weeds. To satisfy the increasing global demand for food, modern agriculture must incorporate integrated pest management.² Several factors drive the current search for new agricultural chemicals, including global warming, limited land for crop production, and emerging resistance in weeds and pests. At the same time, any new product must comply with increasingly strict environmental regulations and high ecotoxicological standards. Replacing a benzene ring with pyridine

does more than just make the structure look similar; it directly improves how the molecule breaks down and functions within a living organism. Its lower electron density and higher molecular polarity make the molecule more stable against metabolic breakdown compared to the original benzene structure. This behavior highlights a complex structural and functional change that goes far beyond a simple structural swap.³⁻⁶

Reviews highlight the application of the pyridine scaffold in developing pesticides through intermediate derivatization methods.^{7, 8} By improving compound efficacy, this strategy reduces the amount of active ingredients needed, minimizing environmental risks. It also provides practical solutions for pest resistance and allows the design of new, legally protected structures. Developing pyridine-containing neonicotinoids (such as imidacloprid and acetamiprid) and carboxamide fungicides (such as boscalid) proves that minor changes to the heterocycle can successfully avoid intellectual property restrictions. This strategy produces potent commercial products and can sometimes alter the activity spectrum of the compounds for better field performance.⁷ Several reviews focus on agrochemicals derived from the pyridine scaffold.⁹⁻¹² In recent years, research on pyridine-based agrochemicals has shifted toward designing molecules that exhibit enhanced selectivity, reduced environmental persistence, and innovative modes of action.

Recent studies have shown that modifying the substituents on the pyridine ring can produce compounds that are highly effective against resistant pest species while demonstrating minimal toxicity to non-target organisms and beneficial insects.^{13, 14} Furthermore, the incorporation of computational modeling and high-throughput screening has expedited the discovery of promising pyridine derivatives as potential plant growth regulators and pesticide candidates.¹¹ These advancements not only broaden the chemical diversity of agrochemicals but also promote sustainable agriculture by encouraging the use of safer, more biodegradable products and easing regulatory acceptance. At present, this review is primarily based on structure-activity relationship (SAR) data and theoretical predictions. We acknowledge that there is a current scarcity of comprehensive field validation studies for many pyridine-based agrochemicals.

2. Fertilizers

Pyridine derivatives have attracted significant interest in fertilizer technology because of their ability to support plant nutrition and improve crop yields. Recent studies show that these compounds are especially valuable for improving micronutrient chelation, with pyridine-based ligands being used to bind essential elements like iron, zinc, and copper. This enhances their availability and uptake by plants, particularly in difficult soil conditions, and certain chelators such as *N,N'*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**1**) (Figure 1) have demonstrated superior stability and performance compared to conventional agents.^{15,16}

The ligand **1** serves as an excellent example of how pyridine chemistry can be used to improve micronutrient delivery in challenging agricultural soils. The problem with conventional aliphatic chelators like EDTA is that they often fail in alkaline or calcareous soils (pH > 7.5) due to competitive precipitation. Pyridine-based ligands handle these conditions much better. This capability comes down to the nitrogen atom in the pyridine ring. Its lone pair of electrons sits in an sp^2 orbital and stays localized because it does not participate in the aromatic π -system. This makes the nitrogen a highly accessible Lewis base for coordinating transition metals like Fe^{3+} , Zn^{2+} , and Cu^{2+} . Together with the flexible ethylenediamine backbone, ligand **1** wraps around the metal cation to form a tight, structurally stable hexadentate complex.

By fully encapsulating the metal, the ligand blocks it from reacting with soil anions. This keeps the micronutrients from turning into insoluble hydroxides or carbonates, meaning they stay soluble in the soil solution. Plants can then easily absorb them through their roots and translocate them where needed.

Additionally, some pyridine derivatives like nicotinic acid and its analogues serve as plant growth stimulants, promoting root development, seed germination, and resilience to stress, which makes them valuable additions to modern fertilizer formulations.^{17, 18, 19} Advances have also been made in developing pyridine-containing polymers and coatings for controlled-release fertilizers, ensuring nutrients are delivered steadily over time and reducing environmental loss.

In addition, pyridine-functionalized nanomaterials have emerged to allow more targeted nutrient delivery.²⁰ There is growing evidence that combining pyridine derivatives with traditional fertilizers can boost crop yield and quality while lowering costs and minimizing environmental impact. As research progresses, the versatility and environmentally friendly nature of pyridine-based fertilizers are likely to drive continued innovation in sustainable agriculture.

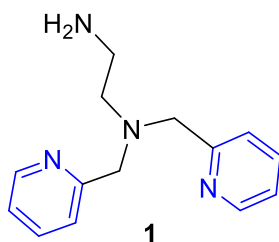


Figure 1. Chemical structure *N,N'*-bis(pyridin-2-ylmethyl)ethane-1,2-diamine (**1**).

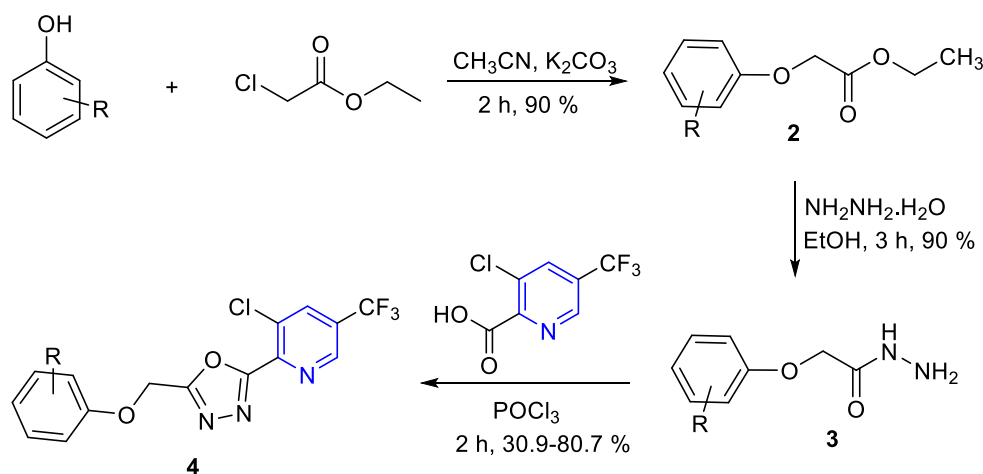
3. Insecticides

The pyridine ring serves as a crucial pharmacophore in widely used insecticides, particularly in the neonicotinoid category. These substances function as powerful agonists that engage the nicotinic acetylcholine receptors (nAChRs) within the insect central nervous system. In this category, the market sub-classes that primarily contain chloropyridinylmethyl units lead the market, as evidenced by the success of insecticides like imidacloprid, acetamiprid, and nitenpyram.¹⁰ These well-defined molecules depend significantly on the electronic characteristics of the pyridine core to attain elevated binding affinity to insect receptors while ensuring reduced toxicity in [mammals](#). In addition to neonicotinoids, the pyridine framework is crucial to various other classes of active ingredients available in the market. For example, flonicamid, a derivative of pyridine carboxamide, operates as a selective inhibitor of homopteran feeding by targeting particular potassium channels. In a comparable manner, pymetrozine is another extensively utilized azomethine insecticide containing pyridine, exhibiting distinctive systemic efficacy against sap-sucking pests. Although these commodity chemicals have shaped contemporary crop protection for many years, the prevalence of insect resistance has propelled current investigations toward structurally innovative pyridine frameworks. The novel derivatives outlined below seek to circumvent these established resistance mechanisms by modifying the substitution configurations on the heterocycle.^{3, 10}

The hybrid **4** was developed by combining the structural stability of the pyridine framework with the polar, heterocyclic character of a 1,3,4-oxadiazole linker. The synthesis process consists of three steps. The first step is the etherification of various phenols with ethyl chloroacetate, which produces the intermediate esters **2**. This is followed by a quantitative hydrazinolysis using hydrazine hydrate to produce 2-phenoxyacetohydrazides **3**. Finally, hydrazides **3** go through a crucial dehydrative cyclization with 3-chloro-5-(trifluoromethyl)picolinic acid, which is accelerated by refluxing phosphorus oxychloride as a condensing

agent, resulting in functionalized scaffolds **4**. From a design standpoint, this hard frame limits the scaffold's flexibility, promoting an ideal structure for target-receptor interaction.²¹

The insecticidal activity of compound **4**, a trifluoromethylpyridine derivative featuring a 1,3,4-oxadiazole moiety, was thoroughly evaluated against two major agricultural pests: *Mythimna separata* (Oriental armyworm) and *Plutella xylostella* (Diamondback moth). Bioassay results revealed that many of these synthesized compounds, including several variants of compound **4**, exhibited exceptional insecticidal efficacy. At a concentration of 500 mg/L, most derivatives achieved 100% mortality against both pests, while at 250 mg/L, the mortality rate was still above 90% for the most active compounds. Median lethal concentration (LC₅₀) values for selected derivatives ranged from 54.5 to 160.7 mg/L, with certain variants demonstrating greater potency than the commercial insecticide chlorpyrifos.²¹ Structure-activity relationship analysis indicated that the presence of strong electron-withdrawing groups such as CF₃, CN, Cl, and OCF₃ especially at the para position of the benzene ring, significantly enhanced insecticidal activity. In contrast, compounds with electron-donating groups or bulky alkyl substituents displayed reduced or negligible activity. These findings suggest that compound **4** and its optimized derivatives hold strong potential as next-generation insecticides, combining high efficacy with the ability to overcome resistance issues prevalent in current pest management.²¹



Scheme 1. The multi step synthetic route leading to novel trifluoromethyl pyridine derivatives **4**.

The synthetic pathways for pyridine derivatives **6** and **9** both begin with the conversion of 3-cyano-4,6-dimethylpyridine-2(1*H*)-one **5**. Compound **6** is produced *via* the deoxychlorination of compound **5** utilizing POCl₃, which adds a chlorine atom at the 2-position of the pyridine ring. To synthesize compound **9**, the distyryl derivative **8** is first synthesized, then reacted with *p*-methoxy chloroacetanilide and sodium acetate while refluxing in ethanol. This procedure produces 2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)-*N*-(4-methoxyphenyl)acetamide **9** (Scheme 2).²²

The insecticidal activity of compounds **6** and **9** was evaluated against both nymphs and adults of the *Aphis craccivora* (cowpea aphid), with their efficacy benchmarked against the commercial insecticide acetamiprid. Both compounds demonstrated remarkable bioefficacy. After 48 hours of treatment, compound **6** exhibited an LC₅₀ value of 0.017 ppm for nymphs and 0.103 ppm for adults, indicating very high toxicity that approaches the efficacy of acetamiprid (LC₅₀ = 0.006 ppm for nymphs, 0.023 ppm for adults). Compound **9** also showed excellent insecticidal activity, with LC₅₀ values of 0.021 ppm for nymphs and 0.213 ppm for adults after 48 hours.²²

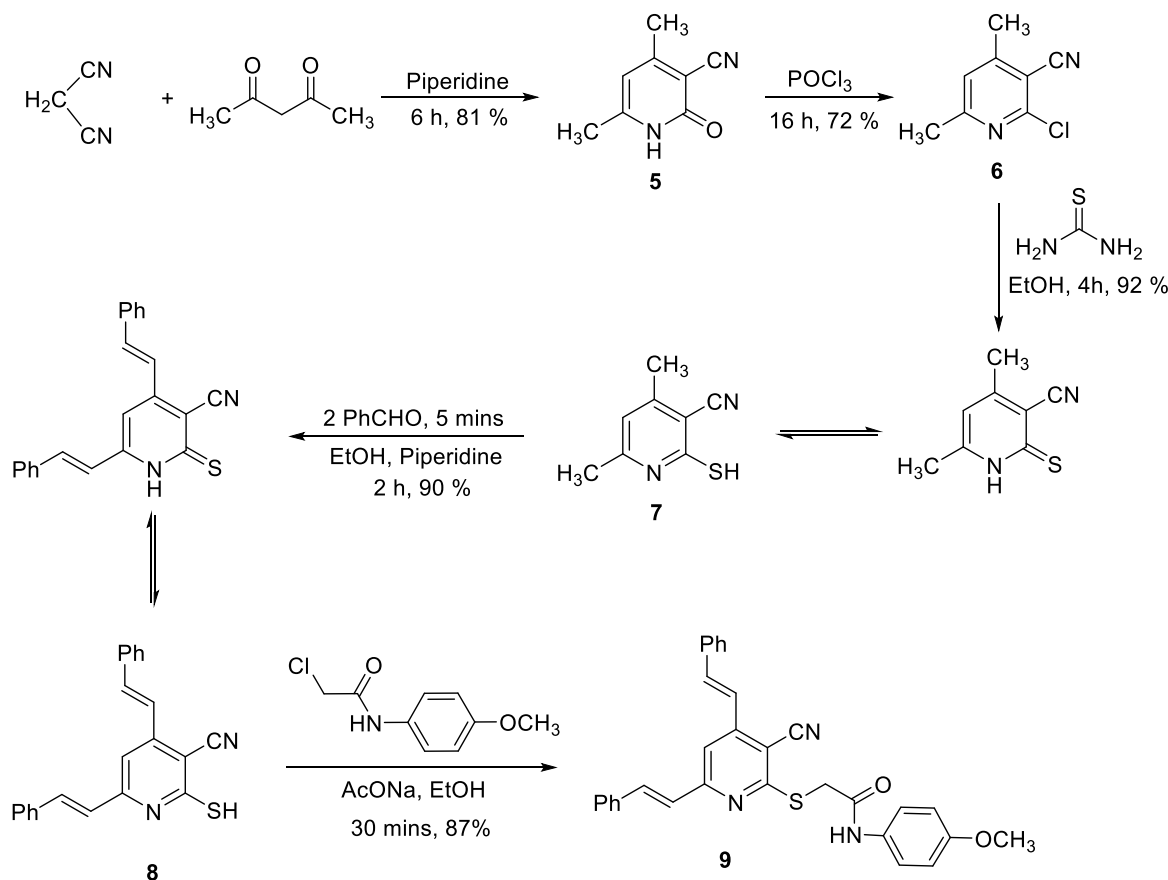
These results reflect that both compounds are highly effective, especially against the nymph stage, where their LC_{50} values are only slightly higher than those of acetamiprid. The strong performance of **6** may be attributed to the chlorine substituent at the 2-position of the pyridine ring, which appears to enhance insecticidal potency. For compound **9**, the combination of a distyrylpyridine core and a 4-methoxyphenyl moiety likely contributes to its bioactivity, as the presence of the methoxy group is known to increase biological activity in various agrochemical scaffolds.²²

Overall, the data suggest that both compounds **6** and **9** are promising candidates for development as new insecticides, combining potent activity with structural diversity. Their high activity, particularly at low concentrations, highlights their potential utility in integrated pest management strategies targeting resistant or difficult-to-control aphid populations. The structure-activity relationship (SAR) analysis provides further insight into the factors driving the potent insecticidal effects of these compounds. For compound **6** (2-chloro-3-cyano-4,6-dimethylpyridine), a chlorine atom at the 2-position of the pyridine ring significantly enhances its bioactivity compared to other dimethylpyridine derivatives. This halogen substitution likely improves the compound's interaction with insect targets or its physicochemical properties for bioavailability. In the case of compound **9** (2-((3-cyano-4,6-distyrylpyridin-2-yl)thio)-*N*-(4-methoxyphenyl)acetamide), the distyrylpyridine core is a crucial structural motif associated with elevated insecticidal efficacy. Additionally, the 4-methoxyphenyl moiety attached to the acetamide group further boosts activity, likely due to electron-donating effects of the methoxy group, which can enhance interaction with biological receptors. The cyano group present in compound **9** is another feature that correlates with higher insecticidal activity, as compounds retaining this group generally display greater potency than their analogues lacking it.²² SAR indicates that halogenation (Cl) of the pyridine ring, the presence of a distyrylpyridine scaffold, and incorporation of electron-donating substituents like the 4-methoxy group all contribute to the notable insecticidal activity observed in compounds **6** and **9**.

2-Amino-4-(4-chlorophenyl)-6-(*p*-tolyl)nicotinonitrile **10** was synthesised through a one-pot multicomponent reaction, which involved the integration of an appropriate aldehyde, *p*-toluidine, and malononitrile under standard heating and microwave irradiation, as shown in Scheme 3. Ethyl 4-amino-2-methyl-1,8-naphthyridine-3-carboxylate (**11**) was obtained by refluxing compound **10** with ethyl acetoacetate for 8 hours. During this process, the acetoacetate nucleophile reacted with the electrophilic cyano group, leading to cyclisation and the formation of the core structure, ethyl 4-amino-5-(4-chlorophenyl)-2-methyl-7-(*p*-tolyl)-1,8-naphthyridine-3-carboxylate. The compound 3-amino-4-(4-chlorophenyl)-6-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonitrile **12** was produced by alkylating the amino group of **10** with chloroacetonitrile, followed by base-mediated cyclisation to form the fused pyridine-pyrrole structure (Scheme 3).²³

The insecticidal activity of compounds **10**, **11**, and **12** was evaluated against third instar larvae of *Culex pipiens* (common house mosquito), revealing significant structure-dependent variations in potency. 2-Amino-4-(4-chlorophenyl)-6-(*p*-tolyl)nicotinonitrile **10** serves as a key intermediate, exhibited moderate larvicidal activity, which is attributed to its basic 2-amino-3-cyanopyridine scaffold substituted at the 4- and 6-positions with aryl groups. However, its lack of additional fused or condensed rings and limited functionalization resulted in less pronounced activity compared to its derivatives.²³ On the other hand, ethyl 4-amino-5-(4-chlorophenyl)-2-methyl-7-(*p*-tolyl)-1,8-naphthyridine-3-carboxylate **11** displayed a marked increase in larvicidal potency, with an LC_{50} value of 0.137 $\mu\text{g/mL}$, ranking it among the most active compounds in the series. This enhanced activity is closely related to the presence of the 1,8-naphthyridine core, which extends the π -system and increases molecular rigidity, facilitating better interaction with the insect target site. The ester group at position 3 and the amino group at position 4 further boost polarity and hydrogen-bonding potential, improving both solubility and binding affinity. The chloro and *p*-tolyl aryl substituents at positions 5

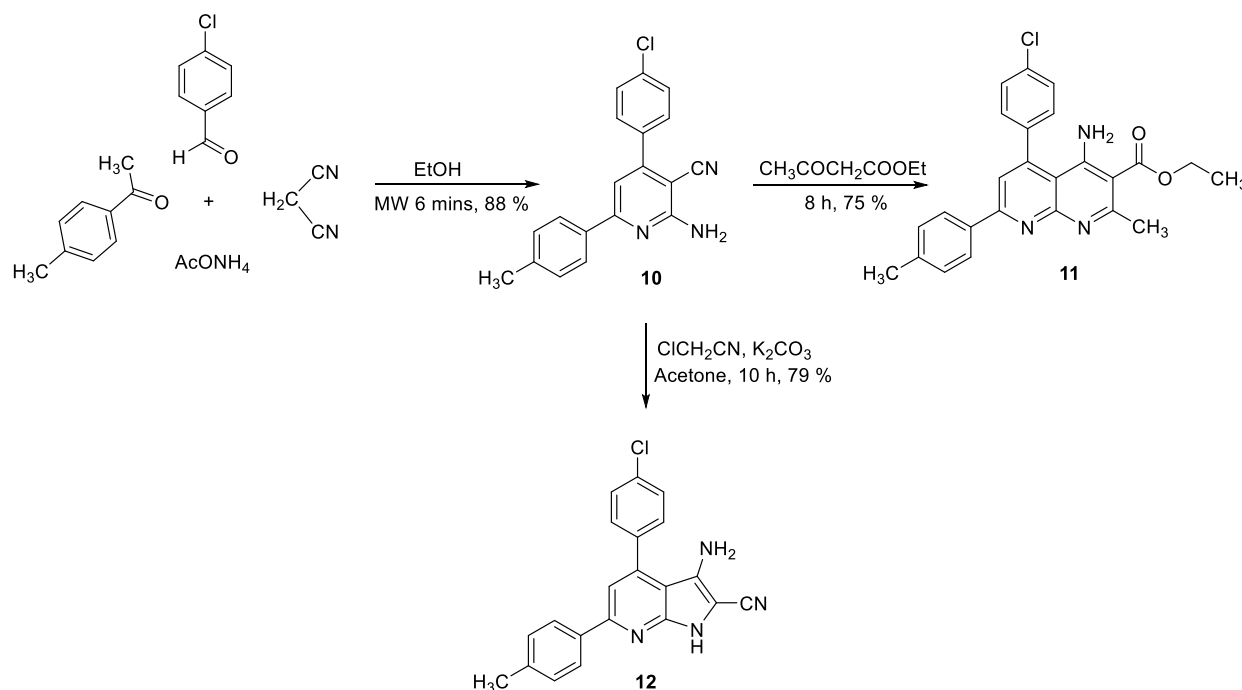
and 7, respectively, increase lipophilicity, aiding cuticle penetration and bioavailability. The synergistic effects of these substituents and the fused ring structure collectively contribute to its high insecticidal efficacy.



Scheme 2. Multistep synthesis of polyfunctionalized pyridine derivatives with potential insecticidal activity.

Notably, 3-amino-4-(4-chlorophenyl)-6-(*p*-tolyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonitrile **12** was the most potent larvicide in the study, exhibiting an LC_{50} of 0.118 $\mu\text{g/mL}$. Its exceptional activity is primarily attributed to the fused pyridine-pyrrole framework (7-azaindole system), which provides a planar, electron-rich scaffold that enhances resonance stability and facilitates strong π - π stacking, hydrophobic, and hydrogen bonding interactions with key residues at the target site. The electron-donating amino group and the electron-withdrawing cyano group create a highly conjugated system, further increasing binding affinity and biological activity. The chloro and *p*-tolyl substituents play a dual role in boosting lipophilicity and fine-tuning the electronic environment of the molecule. Structure-activity relationship (SAR) analysis confirms that the fusion of the pyrrole ring significantly amplifies insecticidal potency compared to the parent scaffold in compound **10**.²³

Overall, the SAR findings highlight the importance of ring fusion (naphthyridine or pyrrole), electron-withdrawing groups (cyano, chloro), and electron-donating groups (amino, *p*-tolyl) in maximizing insecticidal activity. Increasing molecular rigidity and conjugation, introducing polar groups for receptor interaction, and optimizing lipophilicity for cuticle penetration all play synergistic roles. Thus, compounds **11** and **12**, by incorporating these features, clearly outperform the parent compound **10** and stand out as promising candidates for further insecticidal development.²³



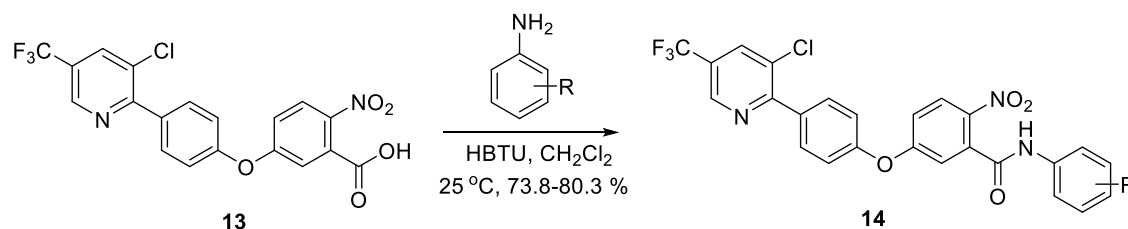
Scheme 3. Synthesis of polyfunctionalized pyridine and pyrrolo[2,3-*b*]pyridine derivatives **10-12** via sequential alkylation and cyclization.

The synthesis of 5-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)phenoxy)-2-nitro-*N*-arylbenzamide derivatives **14** from intermediate **13** was achieved via an efficient amidation reaction. In this step, 5-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)phenoxy)-2-nitrobenzoic acid **13** was reacted with various substituted anilines in the presence of HBTU (*O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate) and triethylamine as coupling agents. The reaction was performed in dichloromethane at room temperature with stirring for 8 hours, allowing the carboxylic acid group of **13** to form an amide bond with the amino group of the aniline derivative (Scheme 4).²⁴

The insecticidal activity of 5-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)phenoxy)-2-nitro-*N*-arylbenzamide derivatives **14** was systematically evaluated against three pest species: *Mythimna separata*, *Aphis craccivora*, and *Tetranychus cinnabarinus* (carmine spider mite). The results revealed that these 2-phenylpyridine derivatives containing *N*-phenylbenzamide moieties exhibited potent and selective activity, particularly against *Mythimna separata* larvae. Several analogs, such as **14b** ($\text{R} = 3\text{-Cl}$), **14d** ($\text{R} = 2\text{-OCH}_3$), **14g** ($\text{R} = 2\text{-CH}_3$, 5-Cl), **14h** ($\text{R} = 3\text{-OCF}_3$), and **14k** ($\text{R} = 4\text{-CH}_3\text{CO}$) demonstrated 100% inhibition of *M. separata* at 500 mg/L, matching the efficacy of the commercial insecticide chlorantraniliprole. In contrast, most compounds showed only moderate or negligible activity against *A. craccivora* and were ineffective against *T. cinnabarinus*.²⁴

SAR analysis indicated that the nature and position of substituents on the *N*-phenyl ring were critical for insecticidal potency. Compounds with electron-withdrawing groups, such as chlorine (**14b**, **14g**), trifluoromethyl (**14j**), or trifluoromethoxy (**14h**), or an electron-donating methoxy group in the ortho position (**14d**), generally exhibited the highest activity against *M. separata*. The presence of a chloro group in the 3-position or a methoxy group in the 2-position of the aniline moiety was especially beneficial. Conversely, derivatives with methyl or fluorine substituents at certain positions showed reduced or no activity, suggesting that both the electronic and steric environment around the amide bond significantly influence biological performance. The inactivity against *T. cinnabarinus* across all derivatives underscores the selectivity of this

scaffold. These findings highlight the potential of tailored 2-phenylpyridine-benzamide derivatives for targeted pest control and guide further optimization through strategic substitution on the aromatic rings.²⁴

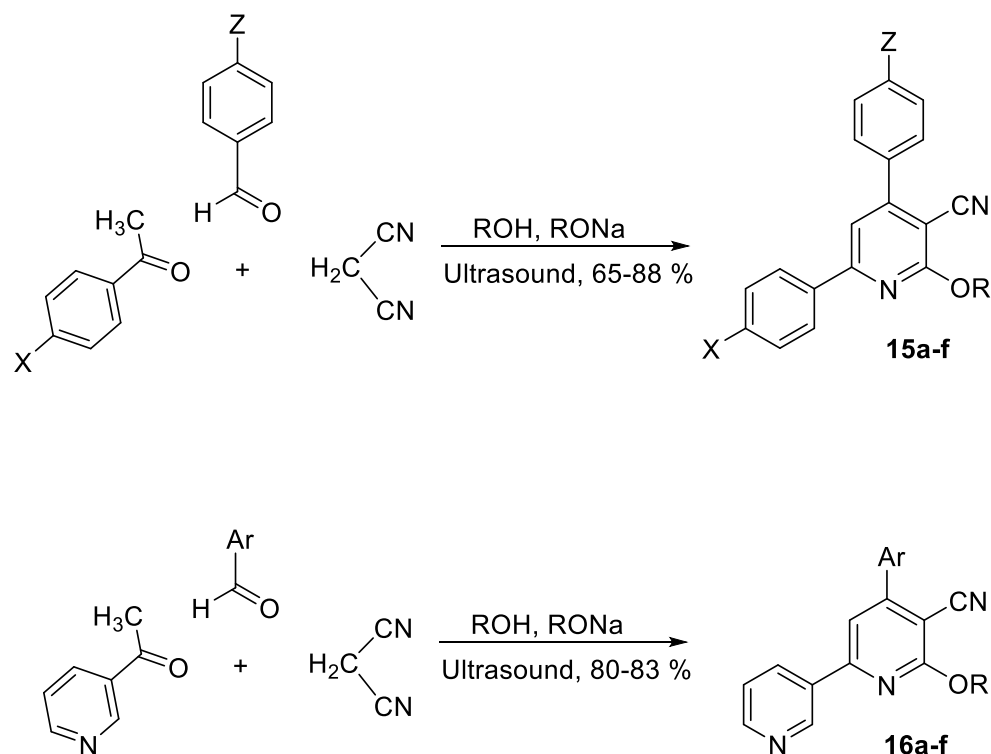


Scheme 4. Amidation-Based Synthesis of 5-(4-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)phenoxy)-2-nitro-*N*-arylbenzamide derivatives.

Cyanopyridines **15a-f** and **16a-f** are functionalized pyridine derivatives synthesized using a four-component reaction that includes aromatic aldehydes, acetyl aryls, sodium alkoxide, and malononitrile (for **15a-f**) or 3-acetylpyridine (for **16a-f**). The reaction is carried out in methanol or ethanol under ultrasound irradiation at 50-60°C, resulting in greener and more efficient conditions than traditional methods. Acetophenone derivatives, aryl carbaldehydes, malononitrile, and sodium methoxide/ethoxide are used in the reactions **15a-f**. The strategy for **16a-f** is extended to include 3-acetylpyridine as a building block in the synthesis of bipyridine derivatives (Scheme 5).²⁵

All compounds were tested for insecticidal activity against nymphs and adults of the *Aphis craccivora*. To compare toxicities, we used the LC₅₀ values. Among the compounds **15a-f**, 6-(*p*-chlorophenyl)-2-ethoxy-4-phenyl-3-cyanopyridine **15f** showed the highest activity, with an LC₅₀ of 0.080 mg/L for nymphs and 0.498 mg/L for adults. 6-(*p*-Chlorophenyl)-2-methoxy-4-(*p*-methoxyphenyl)-3-cyanopyridine **15d** demonstrated strong activity (LC₅₀ = 0.098 mg/L for nymphs; 0.593 mg/L for adults). Compounds **15c** and **15b** demonstrated moderate activity (LC₅₀ for nymphs: 0.127 and 0.185 mg/L, respectively). The reference insecticide, acetamiprid, had LC₅₀ values of 0.045 mg/L for nymphs and 0.267 mg/L for adults. This suggests that the most potent synthesized compounds approach the activity of commercial standards. Bipyridine derivatives **15a-c** exhibited lower activity than **15a-f** (LC₅₀ for nymphs: 0.304-0.388 mg/L).²⁵

SAR analysis reveals that the presence of a 4-chlorophenyl group (as shown in **15f** and **15d**) significantly increases insecticidal activity. This group, along with the cyano and ethoxy/methoxy substituents, appears to be crucial for bioactivity. Compounds with ethoxy groups (e.g., **15f**) are more active than those with methoxy groups (e.g., **15a**), indicating that the substituent's size and electron-donating nature influence potency. Adding a second pyridine ring (as in **16a-f**) decreased activity when compared to mono-pyridine analogues, indicating that increasing molecular bulk or changing electronic distribution may reduce binding or uptake in the target insect. All compounds were more toxic to nymphs than to adults, which could be attributed to physiological differences or increased susceptibility in young insects. Nymphs have an overall activity trend of **15f** > **15d** > **15c** > **15b** > **15e** > **15a** > **16b** > **16a** > **16c**. Ultrasound-assisted synthesis efficiently produces diverse pyridine derivatives with promising insecticidal properties. Compounds **15f** and **16d** have the highest potency, approaching commercial insecticide standards. SAR analysis emphasizes the importance of chlorophenyl and ethoxy/methoxy groups in achieving optimal activity. These findings encourage the further development and optimization of pyridine-based insecticides as potential alternatives to commercial neonicotinoids.²⁵



Scheme 5. Ultrasound-assisted synthesis of cyanopyridine and bipyridine derivatives *via* three-component reactions

4. Herbicides

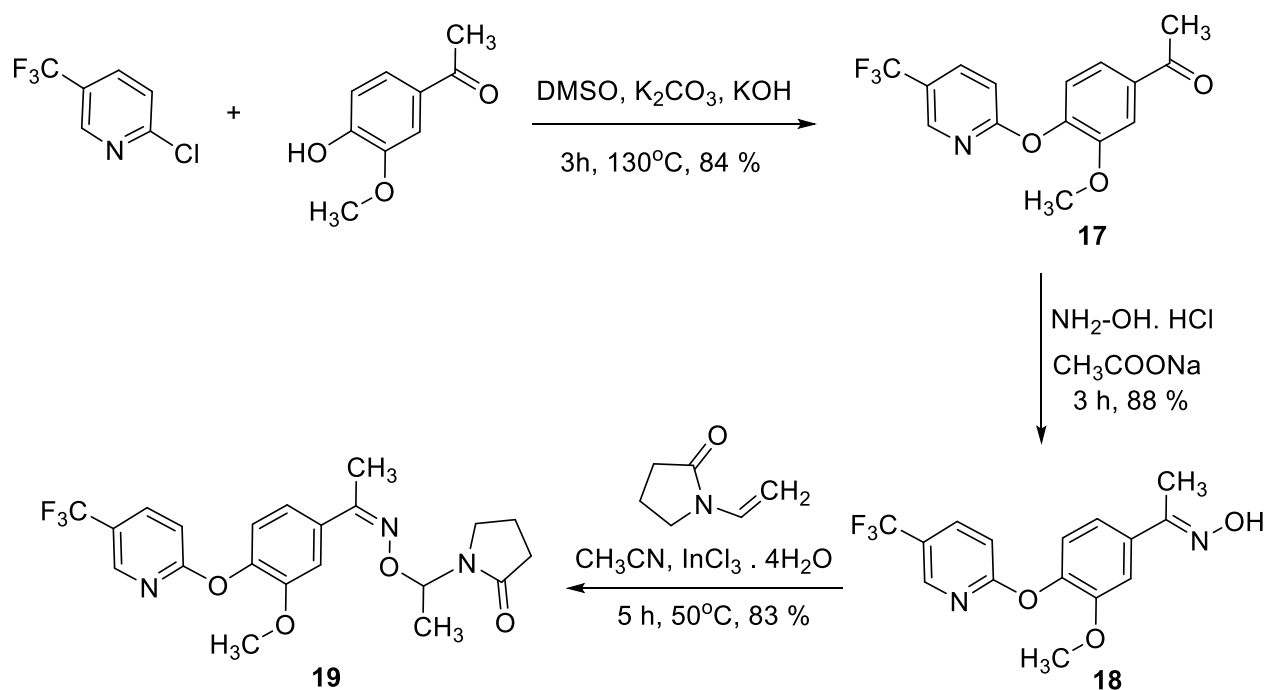
Pyridine derivatives have emerged as a significant class of herbicides in modern agriculture, valued for their selective weed control and compatibility with environmental standards. These compounds typically disrupt essential plant growth processes, such as auxin biosynthesis or transport, resulting in effective and targeted weed management while minimizing harm to crops.⁷

Recent studies have shown that pyridine-based herbicides display high efficacy against a broad spectrum of weed species, including those that are resistant to older classes of herbicides. Their selectivity allows for use in various crops without causing phytotoxicity, making them important tools in integrated weed management.^{12, 13} Many newer pyridine herbicides also have a favorable degradation profile, leading to lower environmental persistence and reduced risk of groundwater contamination. However, resistance in some weed populations has been reported, highlighting the need for integrated management strategies and the rotation of herbicide modes of action.²⁶ Recent advances in this field focus on synthesizing novel pyridine derivatives with enhanced activity, lower application rates, and improved environmental safety. Innovations in formulation technology have further optimized their delivery and reduced off-target effects. Ongoing research aims to balance efficacy with sustainability, ensuring that new pyridine herbicides meet both agricultural productivity and ecological standards.²⁷

A derivative of phenoxy pyridine-2-pyrrolidinone **19** was produced through the reaction of oxime **18** with *N*-vinyl-2-pyrrolidone using a Lewis acid catalyst ($\text{InCl}_3 \cdot 4\text{H}_2\text{O}$), and the resulting structure was confirmed by single-crystal X-ray analysis (Scheme 6). Following assessment, compound **19** exhibited exceptional effectiveness as a protoporphyrinogen oxidase (PPO) enzyme inhibitor, with an IC_{50} value of 0.041 mg/L,

slightly exceeding that of the commercial herbicide oxyfluorfen, which has an IC_{50} of 0.043 mg/L. In evaluations of herbicidal effectiveness, the compound achieved total elimination of the weed *Abutilon theophrasti* at a rate of 150 g/ha, matching or exceeding oxyfluorfen. Notwithstanding a lowered application rate of 75 g/ha, pyrrolidinone derivative **19** demonstrated significant weed control (95% damage), while the effectiveness of oxyfluorfen slightly decreased to 90%. In addition to its heightened potency, it significantly reduced the concentrations of chlorophyll a and b in the targeted weeds, indicating strong herbicidal characteristics that were somewhat more evident than those of oxyfluorfen. The new compound showed considerable tolerance in rice, cotton, and peanut plants, leading to minimal to no crop harm even at high application rates, though it displayed diminished selectivity for maize relative to oxyfluorfen. Field trials further demonstrated that **19**, administered at 600 g/ha, achieved 95% effectiveness in weed control, slightly surpassing oxyfluorfen's 85%.²⁷

Molecular modeling revealed that the compound shows a greater attraction to the active site of the PPO enzyme than oxyfluorfen, thereby creating further stabilizing interactions. In conclusion, compound **19** is recognized as a powerful PPO inhibitor and herbicide, providing efficient weed control, superior crop safety, and improved enzyme affinity, making it a highly promising candidate for future herbicide development.²⁷

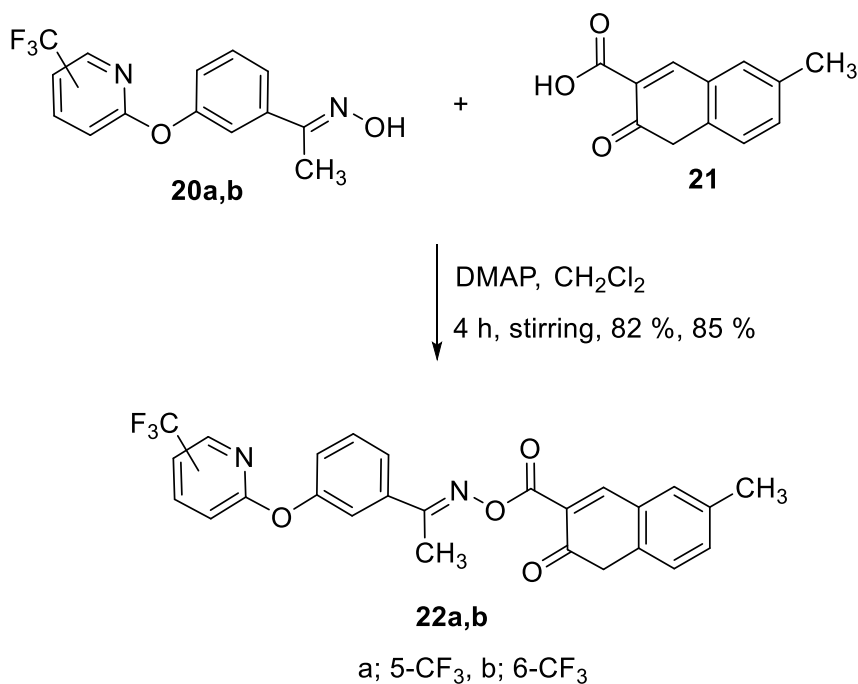


Scheme 6. Structural synthesis of a highly active phenoxy-pyridine-2-pyrrolidinone derivative **19** as a novel herbicidal agent.

In this study, different phenoxy-pyridine derivatives **22a** and **22b** as new herbicidal compounds were synthesized by coupling the phenoxy-pyridine skeleton with the coumarin moiety based on the inherent allelopathic properties of coumarins. The synthesis was achieved by coupling coumarin **20** with phenoxy-pyridine **21** in the presence of EDCI and DMAP as catalysts in dichloromethane to give the target compounds **22a** and **22b**, which were purified by chromatography (Scheme 7). Biological testing revealed that **22a** and **22b** are very potent inhibitors of the protoporphyrinogen oxidase (PPO) enzyme with IC_{50} values of 0.02653 mg/L for **22a** and 0.01937 mg/L for **22b**, respectively. These compounds were superior to the

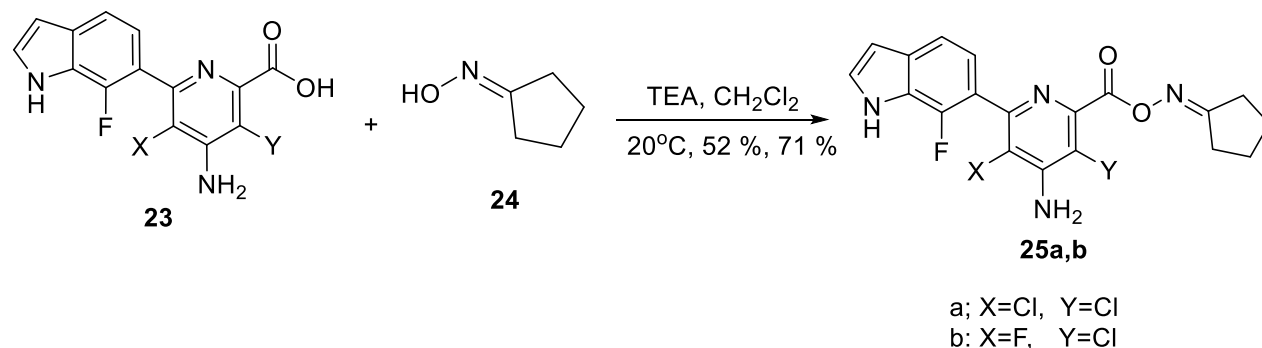
commercial herbicide oxyfluorfen ($IC_{50} = 0.04943$ mg/L). In greenhouse studies, these materials gave near 100% weed control at 300 g/ha and were notably effective against broadleaf species such as *Abutilon theophrasti* and *Amaranthus retroflexus*. Their increased activity was due to the presence of the CF_3 group in their makeup.²⁸

Field trials revealed that **22b** was as effective as oxyfluorfen at 300 g/ha, while **22a** needed a higher dosage of 450 g/ha for complete control. Importantly, **22b** displayed excellent crop selectivity compatible with maize, soybean, and cotton but not with rice and wheat. Molecular docking studies showed that **22a** and **22b** interacted with the PPO enzyme active site with high binding affinity and hydrogen bonding and π -stacking. The π -interaction is like that of the reference compound, oxyfluorfen, which indicates their high efficacy. To summarize, **22a** and **22b** can be viewed as potential herbicides due to their good weed control, strong enzyme inhibition, and selective safety to key crops (maize, soybean, and cotton).²⁸



Scheme 7. Design and synthesis of phenoxy pyridine derivatives **22a,b** linked to natural coumarins for selective herbicidal activity.

Derivatives of 6-indolylpyridine oxime **25a** and **25b** were developed from the reaction of indolyl picolinic acid derivatives with cyclopentanone oxime. The products were evaluated for their herbicidal activity. When applied at a rate of 30 g/ha, both substances demonstrate significant herbicidal effectiveness, achieving 90% to 100% suppression of persistent grassy weeds, such as *Echinochloa crus-galli* and *Digitaria sanguinalis*. Remarkably, even at a lower application rate of 7.5 g /ha, these pyridine derivatives maintain over 90% efficacy against major broadleaf weeds, comparable to the effectiveness of established commercial benchmarks like halauxifen-methyl. In biochemical terms, in vitro enzymatic studies revealed that compounds **25a** and **25b** exhibit strong auxin-disrupting properties, with IC_{50} values of 6.15 μ M and 4.39 μ M against indole-3-acetic acid (IAA) pathways, respectively, significantly exceeding halauxifen-methyl (9.06 μ M). Furthermore, assessments of crop tolerance verified the excellent selective safety profiles of **25a** and **25b**, indicating their suitability for comprehensive weed control in active wheat and rice farming environments without harming the crops.²⁹



Scheme 8. Synthesis and development of 6-indolylpyridine oxime derivatives **25a,b** as auxin-disrupting herbicides with crop selectivity.

5. Fungicides

Recent developments have brought additional pyridine-based fungicides to the forefront. For example, fluazinam (3-chloro-*N*-[3-chloro-2,6-dinitro-4-(trifluoromethyl)phenyl]-5-(trifluoromethyl)pyridin-2-amine) (**26**) (Figure 2), a widely used fungicide in horticulture, acts by uncoupling oxidative phosphorylation in fungal mitochondria and is effective against a broad spectrum of pathogens, including the mold *Botrytis cinerea* (gray mold) and *Phytophthora* species (oomycete pathogen). It offers exceptional control against *Phytophthora infestans*, the infamous pathogen responsible for potato late blight. Due to the limited number of effective chemical agents available for managing this highly destructive organism and the rapid development of resistance, the effectiveness of pyridine-based fungicides, such as fluazinam, serves as a crucial tool in crop protection. Its unique mode of action helps prevent cross-resistance with other fungicide classes.³⁰ Furthermore, research on pyriofenone ((5-chloro-2-methoxy-4-methyl-pyridinyl)-(2,3,4-trimethoxy-6-methylphenyl) methanone) (**27**) (Figure 2) another pyridine-containing fungicide shows promising activity against powdery mildew by inhibiting fungal cell wall formation. Field studies demonstrate that these fungicides not only control resistant strains but also contribute to integrated disease management programs. Including results from recent trials and mechanistic studies provides a more comprehensive picture of the current landscape and emerging trends in pyridine-based fungicidal innovation.³¹

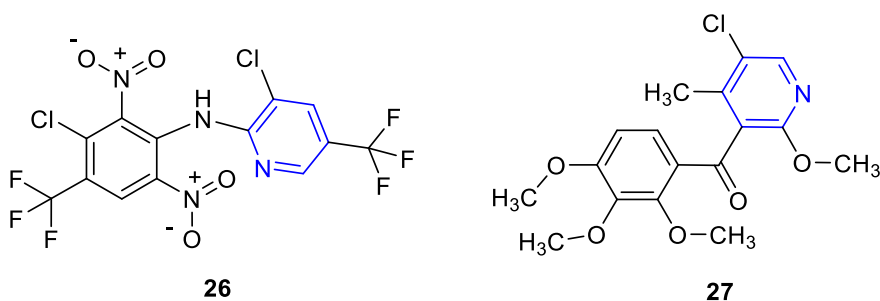
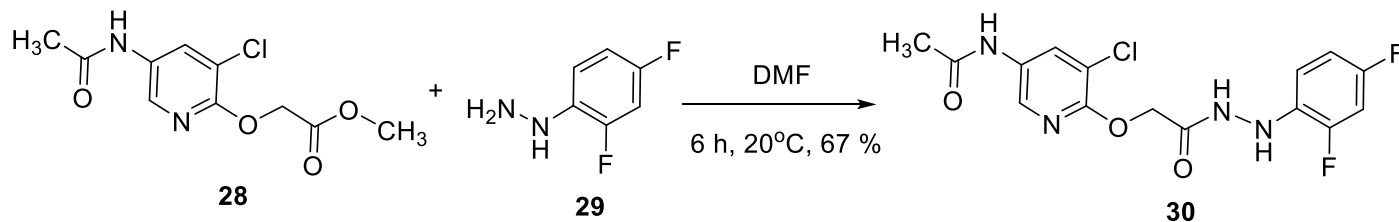


Figure 2. The chemical structures of Fluazinam (**26**) and Pyriofenone (**27**).

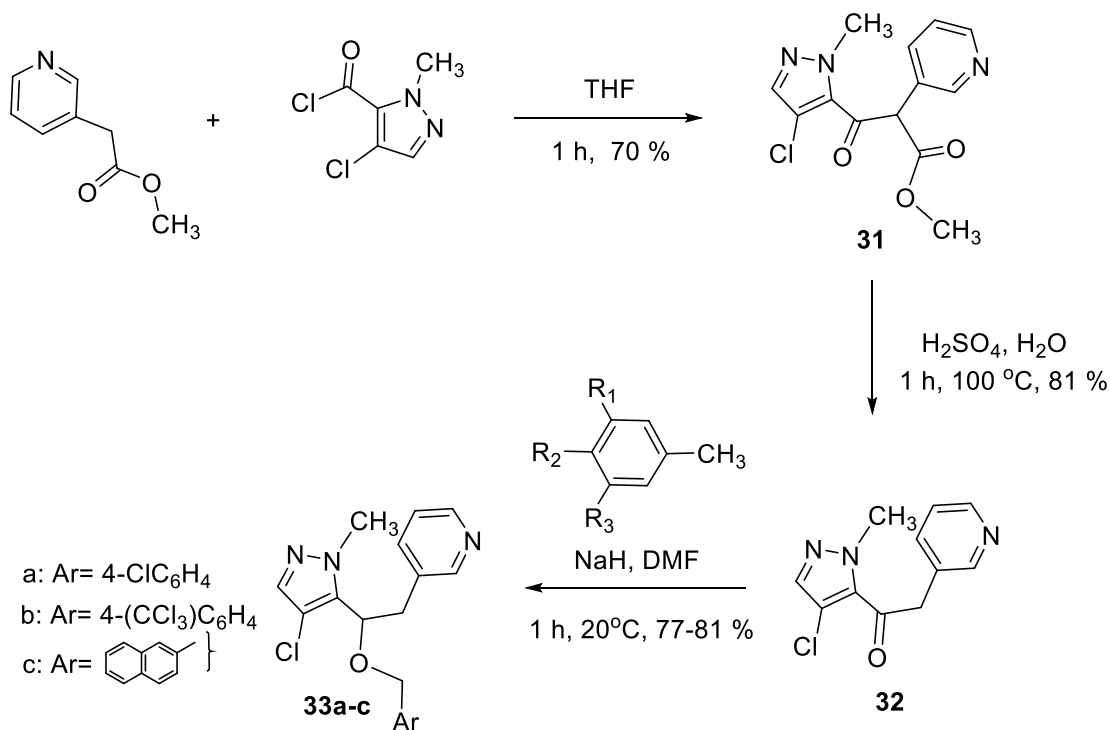
N-(5-chloro-6-(2-(2-(3,4-difluorophenyl)hydrazinyl)-2-oxoethoxy)pyridin-3-yl)acetamide (**30**) was obtained from the reaction of acetamidopyridine derivative **28** with (2,4-difluorophenyl)hydrazine (**29**) and

screened for their *in vitro* fungicidal activity against *Rhizoctonia solani* and *Fusarium graminearum* with low EC₅₀ values. It also demonstrates high *in vivo* preventive efficacy at 100 µg/mL, with mechanisms involving lipid metabolism disruption and plasma membrane contraction, while maintaining promising environmental compatibility.³²



Scheme 9. Synthesis of *N*-(5-chloro-6-(2-(2-(3,4-difluorophenyl)hydrazinyl)-2-oxoethoxy)pyridin-3-yl)acetamide (**30**).

Derivatives of 4-chloropyrazole-based pyridine **33a**, **33b**, and **33c** were developed and evaluated for their fungicidal activities. Bioassay results indicated the compounds displayed notable and diverse antifungal activities, comparable to the positive controls, imazalil and triadimefon. The mode of action of the active compounds was further investigated through microscopy observations, Q-PCR, and enzyme inhibition assays. It was found that these target compounds disrupt fungal sterol biosynthesis by interfering with the RcCYP51 enzyme system. These findings confirm that their fungicidal mechanism continues to target the cytochrome P450-dependent 14α-demethylase, as initially intended in the molecular design. Overall, the results strongly suggest that our rational molecular design protocol is both practical and effective.³³

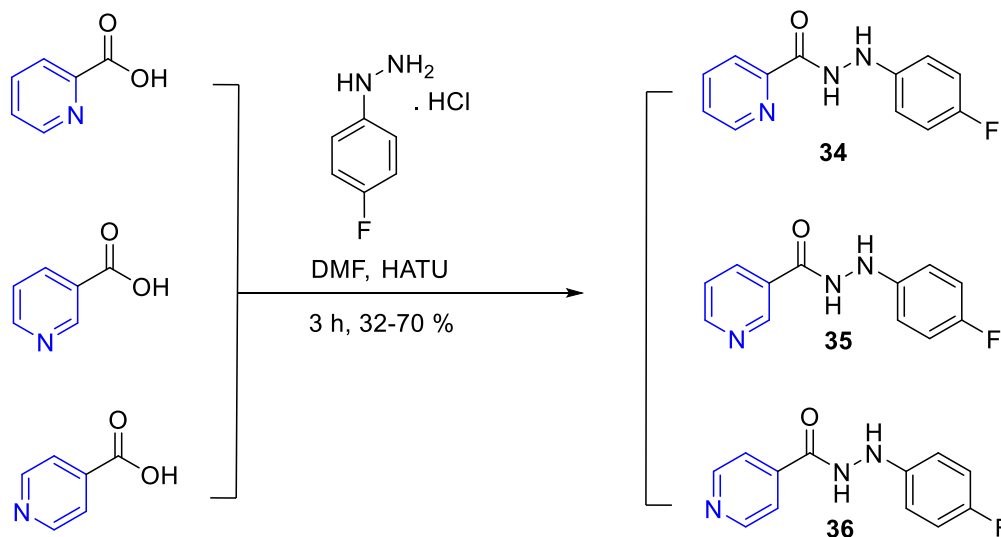


Scheme 10. Synthetic route for the preparation of 4-chloropyrazole-based pyridine derivatives **33a-c**.

The pyridinecarbohydrazide analogs **34-36** were produced by reaction of the corresponding isomeric pyridinecarboxylic acids (nicotinic, isonicotinic, and picolinic acid) with 4-fluorophenylhydrazine under basic conditions using HATU (2-(7-azabenzotriazole)-*N,N,N',N'*-tetramethylurea hexafluorophosphate) as the condensing agent in DMF.

The three compounds were assayed for their antifungal (herbicidal) activity against the major citrus pathogen *Penicillium italicum* strain PiR2, resistant to prochloraz. Safety studies have shown that *N'*-(4-fluorophenyl)-2-pyridinecarbohydrazide (**34**) is much less toxic than prochloraz. At the highest concentration tested (400 µg/mL), it showed a net hemolysis rate of only 1.1% in comparison to prochloraz, which caused over 92% hemolysis at comparable doses. The structure-activity relationship analysis indicated that the most potent antifungal and herbicidal activity was observed for the 2-pyridinecarbohydrazide isomer **34**, followed by **35** and **36**, indicating the position of the hydrazide linkage on the pyridine ring has a great impact on activity. These results suggest that ortho substitution of the pyridine ring is favorable for binding to SDH and biological activity. The 4-fluorophenyl group is likely to increase the potency of the compound by enhancing interactions with the SDH active site and increasing lipophilicity.³⁴

In conclusion, compound **34** demonstrated greater effectiveness and lower toxicity compared to prochloraz, the commercial fungicide, and exhibited superior activity than compounds **35** and **36** both *in vitro* and *in vivo*. These results indicate that *N'*-(4-fluorophenyl)-2-pyridinecarbohydrazide (**34**) is a promising SDH inhibitor and has potential for development as a postharvest herbicide or fungicide for citrus and other crops.³⁴



Scheme 11. Synthesis of isomeric *N'*-(4-fluorophenyl)-pyridinecarbohydrazide derivatives (**34-36**) as potent SDH inhibitors for antifungal and herbicidal applications.

6. Commercially Available Pyridine-based Agrochemicals

One of the most significant uses of pyridine derivatives is as herbicides. Clopyralid, picloram, triclopyr, and fluroxypyr are among the most used pyridine-based herbicides. These act primarily as synthetic auxins, mimicking natural plant hormones to disrupt growth in susceptible broadleaf weeds.^{35, 36}

6.1. Clopyralid

Clopyralid (3,6-dichloropyridine-2-carboxylic acid) (**37**) (Figure 3) is particularly recognized for its exceptional effectiveness and selectivity in managing thistles and a variety of broadleaf weeds within cereal crops, grasslands, and turf systems.³⁵ A major benefit of clopyralid is its strong selectivity, allowing for broadleaf weed control with little to no negative impact on grass species, making it highly suitable for use in mixed planting environments. Nevertheless, clopyralid does present some limitations. Its persistence in soil and crop residues can be problematic, as it may remain active long after application and negatively affect sensitive crops planted in subsequent rotations. This residual activity requires careful crop planning and management to avoid unintended injury to non-target species.

On a chemical level, clopyralid acts as an auxin mimic, interfering with the hormonal pathways that regulate plant cell growth and division. This disruption results in abnormal development and ultimately leads to the death of susceptible broadleaf weeds, providing targeted and efficient weed control.³⁵

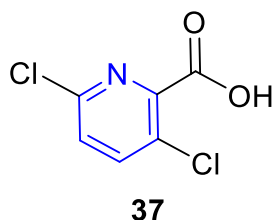


Figure 3. The chemical structure of Clopyralid (**37**).

6.2. Picloram

Picloram (4-amino-3,5,6-trichloropyridine-2-carboxylic acid) (**38**) (Figure 4) is a powerful herbicide frequently chosen for use in rangeland and forestry management, where control of broadleaf weeds and woody plants is particularly challenging. Its broad-spectrum activity allows it to target a wide variety of problematic species, and its residual effectiveness ensures long-term weed suppression after application, reducing the need for frequent re-treatment.^{35, 36} Despite these advantages, picloram's high persistence in soil is a significant drawback. The compound can remain active in the environment for extended periods, increasing the risk of it moving beyond the target area through leaching or runoff. This mobility raises concerns about contamination of groundwater and unintended effects on sensitive crops or natural vegetation nearby. As a result, the use of picloram is often subject to strict regulations and careful management practices to mitigate environmental risks. Chemically, picloram exerts its herbicidal action by mimicking auxin, a natural plant hormone. This mimicry disrupts the plant's normal hormonal regulation, causing uncontrolled cell division and abnormal growth patterns that ultimately kill susceptible weeds and woody plants. While this targeted mechanism contributes to its effectiveness, it also underscores the importance of responsible use to prevent non-target and environmental impacts.

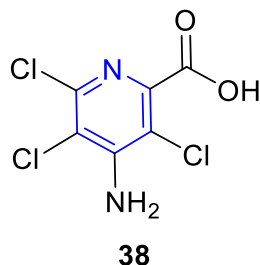


Figure 4. The chemical structure of Picloram (**38**).

6.3. Triclopyr

Triclopyr (2-[(3,5,6-trichloropyridin-2-yl)oxy]acetic acid) (**39**) (Figure 5) exemplifies rational bioisosteric design in agrochemistry, serving as the structural pyridine analogue of the legacy phenoxy herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), a key component of the notorious wartime defoliant "Agent Orange". The transition from the benzene core of 2,4,5-T to the pyridine scaffold of triclopyr offers significant synthetic and environmental advantages. The production of 2,4,5-T was historically hindered by the unavoidable generation of trace amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a highly carcinogenic and persistent dioxin impurity.^{35, 36}

By substituting the benzene ring with an electron-deficient pyridine ring, the modified electronic distribution effectively suppresses hazardous self-condensation pathways during industrial synthesis, thereby completely eliminating dioxin formation and making triclopyr much safer to produce and deploy. Additionally, the incorporation of the nitrogen heteroatom enhances molecular polarity, significantly improving water solubility and facilitating the systemic translocation of the herbicide through dense woody plant tissues. This bioisosteric optimization promotes highly selective brush and weed control at reduced application rates, illustrating how the heteroaromatic replacement mitigates ecotoxicological risks while maintaining potent biological efficacy.^{35, 36}

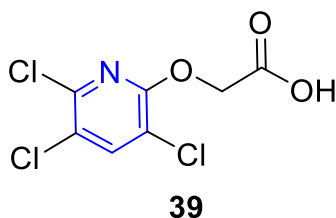


Figure 5. The chemical structure of Triclopyr (**39**).

6.4. Fluroxypyr

Fluroxypyr (2-[(4-amino-3,5-dichloro-6-fluoropyridin-2-yl)oxy]acetic acid) (**40**) (Figure 6) is widely used for managing broadleaf weeds in crops like cereals, maize, and sugarcane. Like triclopyr, it is classified under HRAC Group 4 as a synthetic auxin, falling within the pyridine-carboxylic acid chemical subclass.^{35, 36} The strategic inclusion of both an electron-deficient pyridine ring and a highly electronegative fluorine atom at the 6-position significantly alters the molecule's electronic topology when compared to traditional chlorinated benzene-based analogues. This structural modification enhances its selectivity and metabolic stability in the target plant, as it mimics indole-3-acetic acid to disrupt growth-regulating hormone pathways, ultimately interfering with the normal growth and development of susceptible weeds. Importantly, this molecular architecture facilitates rapid and safe microbial degradation in the soil, allowing fluroxypyr to degrade quickly, with a very short soil half-life of 10-20 days.^{26, 36} This reduces its environmental persistence and mitigates the long-term groundwater contamination risks associated with older, structurally rigid halogenated benzene herbicides. However, since it does not provide comprehensive control over all broadleaf weeds and some species display reduced sensitivity, fluroxypyr is frequently applied in combination with other herbicides to achieve optimal results.

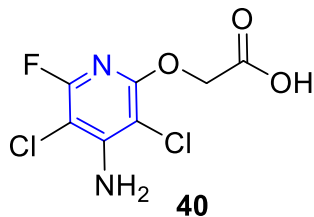


Figure 6. The chemical structure of Fluroxypyr (**40**).

Beyond herbicides, pyridine derivatives also serve as active ingredients in insecticides and fungicides. Pyriproxyfen (4-phenoxyphenyl (*RS*)-2-(2-pyridyloxy)propyl ether) (**41**) is a well-known pyridine-based insect growth regulator that mimics juvenile hormone, interfering with pest development and reproduction (Figure 7).³⁰ Its main advantage is its effectiveness against whiteflies, aphids, and mosquitoes, with minimal plant toxicity. The disadvantage is resistance development in target pests with repeated use and limited action on some insect species. Chemically, it blocks the transition to adult stages in insects, halting population growth.

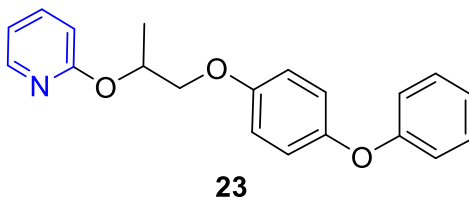


Figure 7. The chemical structure of Pyriproxyfen (**41**).

Similarly, pyribencarb (methyl (2-chloro-5-((1*E*)-1-[(6-methyl-2-pyridylmethoxy)imino]ethyl)benzyl) carbamate) (**42**) (Figure 8) and other pyridine derivatives have been explored for their fungicidal properties, offering new modes of action against resistant pathogens. Pyribencarb displays high efficacy against fungal pathogens, including those resistant to conventional fungicides, but is still under regulatory review in some countries and lacks comprehensive environmental safety data. Biochemically, pyribencarb is a benzylcarbamate fungicide known for its role as a potent inhibitor of mitochondrial respiration. It selectively disrupts fungal growth by binding to the ubiquinol-oxidation center (Qo site) of the cytochrome *bc*₁ complex (Complex III) within the mitochondrial respiratory chain. This interaction blocks electron transport, preventing ATP synthesis through a mechanism similar to that of strobilurin fungicides, which ultimately inhibits fungal spore germination and mycelial growth.³¹

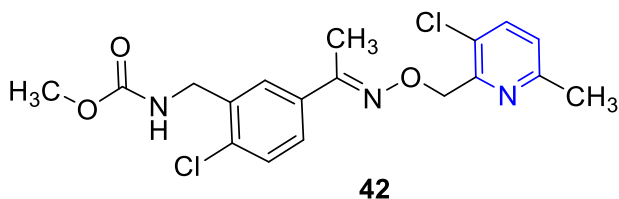


Figure 8. The chemical structure of pyribencarb (**42**).

The popularity of pyridine-based agrochemicals is also due to their relatively favorable environmental profiles. Many degrade rapidly in soil, reducing long-term contamination risks. Still, the rise of herbicide-resistant weeds is a growing concern, prompting research into new pyridine analogues with improved selectivity, efficacy at lower doses, and novel action modes.¹³ Recent innovations focus on advanced synthesis and formulation technologies, such as microencapsulation and controlled release, to enhance efficacy and reduce off-target impacts.²⁰ For instance, the development of phenoxy(trifluoromethyl)pyridine-2-pyrrolidinone inhibitors of protoporphyrinogen oxidase shows progress in designing herbicides with specific molecular targets.²⁷

The structure-activity relationship (SAR) among clopyralid, picloram, triclopyr, fluroxypyr, and pyriproxyfen illustrates how structural variations within the pyridine ring system influence their agrochemical properties and applications. Clopyralid, with its 3,6-dichloropyridine-2-carboxylic acid structure, features two chlorine atoms that enhance herbicidal activity and selectivity against broadleaf weeds, while the carboxylic acid group aids plant uptake and systemic movement, resulting in strong selectivity with minimal impact on grasses. Picloram, distinguished by three chlorine atoms and an amino group on the pyridine ring, demonstrates increased soil persistence and broad-spectrum activity, making it especially potent against a wide range of broadleaf weeds and woody plants. However, this also results in greater environmental persistence and a higher risk of off-target effects (Table 1).

Table 1. Structural features, main activities, originating company, resistance status, and environmental persistence of selected pyridine-based agrochemicals

Compound	Key Functional Groups	Main Activity and mode of action (HRAC/WSSA)	Originating Company & Launch Year	Current Resistance Status	Environmental Persistence (Soil $t_{1/2}$)
Clopyralid	2 Cl, carboxylic acid	Broadleaf herbicide; Auxin mimic (Group 4)	Dow Chemical Co. (1987)	Documented resistance in invasive thistles (<i>Carduus</i> species)	Moderate (30-90 days; stable in plant residues)
Picloram	3 Cl, amino, carboxylic acid	Broadleaf/woody weed; Auxin mimic (Group 4)	Dow Chemical Co. (1964)	Confirmed resistance in several dicot weeds (<i>Centaurea</i> species)	High (90-300 days; high leaching risk)
Triclopyr	3 Cl, ether (oxyacetic acid)	Woody plant herbicide; Auxin mimic (Group 4)	Dow Chemical Co. (1979)	Emerging baseline tolerance; isolated resistant biotypes	High (30-90 days; microbial decay)
Fluroxypyr	2 Cl, F, amino, ether	Broadleaf herbicide; Auxin mimic (Group 4)	Dow Chemical Co. (1985)	Isolated target weed resistance (<i>Bassia scoparia</i> biotypes)	Low–moderate (10-20 days; rapid degradation)
Pyriproxyfen	Pyridine, ether-linked aromatic ring	Insect growth regulator; Juvenile hormone mimic	Sumitomo Chemical (1996)	Reported resistance in whiteflies (<i>Bemisia tabaci</i>) and houseflies	Low (6-10 days; rapid photolysis)

Triclopyr contains an ether-linked oxyacetic acid moiety and multiple chlorine substitutions, which enable efficient translocation within plants and potent activity against woody species; however, its persistence and selectivity profile are like picloram.^{7, 36} Fluroxypyr incorporates a fluorine atom in addition to chlorine substitutions, and possesses an amino group and ether side chain, all of which contribute to improved metabolic stability, rapid soil degradation, and strong selectivity for target broadleaf weeds, with reduced environmental persistence compared to picloram and triclopyr.³⁶ Pyriproxyfen, while also based on a pyridine ring, features an ether-linked aromatic moiety rather than a carboxylic acid, allowing it to function as an insect growth regulator rather than a herbicide. Its unique structure enables it to mimic juvenile hormone in insects, selectively disrupting their development and reproduction, with minimal impact on plants.^{7, 10} Collectively, these structural differences dictate each compound's spectrum of activity, selectivity, and environmental behavior, shaping their roles and effectiveness in modern crop protection strategies.⁷

7. Advances in Formulation Technologies for Pyridine-based Agrochemicals

7.1. Microencapsulation

Microencapsulation is a cutting-edge technique used to enhance the stability, efficacy, and safety of agrochemicals, including pyridine derivatives. In this process, active ingredients are enclosed within microscopic capsules made of polymers or other protective materials. This encapsulation protects the agrochemical from premature degradation due to environmental factors such as light, temperature, or moisture. More importantly, it enables controlled and sustained release of the active ingredient, reducing the frequency of application and minimizing losses through volatilization, leaching, or runoff. Microencapsulation also helps in reducing phytotoxicity and non-target effects, making applications safer for both crops and the environment.³⁷

7.2. Nanotechnology

The use of nanotechnology represents a significant advancement in agrochemical formulation. Nanoparticles, nanocapsules, and nanoemulsions containing pyridine-based compounds are being developed to improve solubility, bioavailability, and targeted delivery. Due to their ultra-small size and high surface area, nanocarriers can penetrate plant tissues more efficiently and protect the active ingredient until it reaches its target site. Additionally, nanotechnology allows for precision agriculture delivering the agrochemical right where it is needed and in optimal amounts. This not only enhances effectiveness but also substantially reduces the total quantity of chemicals applied, lowering the risk of environmental contamination and resistance development in pests or weeds.²⁰

7.3. Green formulations

Green formulations are designed to align with the principles of sustainable agriculture and green chemistry. These include the use of biodegradable carriers, water-based formulations instead of organic solvents, and the incorporation of natural or renewable materials as adjuvants or encapsulation agents. Green formulations aim to decrease the environmental footprint of agrochemicals throughout their life cycle, from production to field application and eventual degradation. For pyridine-based agrochemicals, green formulation strategies may involve enzymatically degradable capsules, solvent-free processing, or the use of plant-derived polymers.²⁰ Such innovations not only meet stricter regulatory standards but also address public and consumer concerns about chemical residues and ecological impact.²⁰

Recent case studies highlight the practical impact of advanced formulation technologies. For instance, microencapsulation of pyridine-based insecticides, such as pyriproxyfen, has led to commercial products with enhanced photostability and reduced environmental leaching, benefitting public health and crop protection initiatives.⁷ Nanoparticle-based formulations, including chitosan or silica nanocarriers loaded with pyridine herbicides, have shown improved uptake and translocation in plants, resulting in greater weed control efficiency at reduced dosages.^{20, 37} Field evaluations of green formulations, such as water-dispersible granules and biodegradable polymer-coated fertilizers, confirm their potential to minimize residues and meet stringent regulatory standards.²⁰ These examples underscore the tangible benefits and growing adoption of innovative formulation strategies in modern agriculture.^{13, 20}

8. Expanded future directions

8.1. AI-Driven molecule design and green chemistry

Emerging technologies are poised to revolutionize pyridine-based agrochemical development. Artificial intelligence (AI) and machine learning are now commonly used to predict the kinetics of screening, assess the biological efficacy and pharmacokinetic performance of novel compounds, optimize formulation parameters, and understand the overall impact on drug development.^{13, 38} These tools help create new pyridine derivatives in a smarter way, accelerating the discovery process and decreasing the need for trial-and-error testing.¹³ In parallel, green chemistry approaches are being implemented to minimize the environmental footprint of agrochemical synthesis. Innovations include the use of renewable starting materials, catalytic and solvent-free processes, and the design of compounds that degrade into non-toxic byproducts.¹³ Such strategies align with global sustainability goals and regulatory requirements, ensuring that future pyridine-based agrochemicals are not only effective but also environmentally responsible.¹³

9. Resistance management: integrated strategies

9.1. Resistance evolution

The repeated and intensive use of pyridine-based agrochemicals has contributed to the evolution of resistance in various pest and weed populations.⁷ Resistance typically arises through mechanisms such as target-site mutations, where genetic alterations reduce the binding affinity of the agrochemical to its intended molecular target, rendering it less effective.³⁹ Another common mechanism is metabolic detoxification, in which enhanced activity of enzymes (e.g., cytochrome P450 monooxygenases, glutathione *S*-transferases) in pests or weeds accelerates the breakdown or sequestration of the active compound before it can exert its toxic effect.²⁶ Recent field studies have documented cases of resistance to pyridine-based herbicides such as fluroxypyr and triclopyr in weed species like *Bassia scoparia* (weed species), often linked to increased metabolic detoxification and altered uptake or translocation patterns.³² Similarly, insect populations have been shown to develop resistance to pyridine-containing insecticides through target-site modifications and upregulated detoxification pathways.^{26, 39}

9.2. Integrated Management

To combat and delay the development of resistance, an integrated resistance management approach is essential.

9.2.1. Rotation of modes of action. Alternating between different classes of agrochemicals with distinct mechanisms of action reduces selection pressure on any single biochemical pathway, thereby slowing the evolution of resistance.^{36, 40}

9.2.2. Synergistic mixtures. Using combinations of pyridine-based products with other agents (such as different chemical classes or biological agents) can produce synergistic effects, enhancing the overall efficacy and reducing the likelihood that pests or weeds will survive and develop resistance.³⁹

9.2.3. Non-Chemical controls. Incorporating biological control agents (predators, parasitoids, or pathogens), crop rotation, and cultural practices such as tillage, staggered planting, or the use of cover crops can reduce reliance on chemical inputs and disrupt pest and weed life cycles.³⁸

9.2.4. Resistance monitoring. Regular field surveillance and the use of molecular diagnostic tools are crucial for the early detection of resistance. Monitoring allows for timely intervention and adjustment of management strategies to prevent resistance from becoming widespread.³⁹

10. Toxicity, Persistence, and Environmental Safety

The safety of pyridine-based agrochemicals has seen significant improvements due to advances in structural design and regulatory standards. Modern pyridine derivatives are increasingly developed with enhanced selectivity and reduced environmental persistence, which helps address concerns about their long-term effects on non-target organisms and ecosystems.¹³ Many newer compounds are formulated to degrade rapidly in soil, minimizing the risk of accumulation and groundwater contamination.^{20, 40} For example, the soil half-life of clopyralid has been reported as 30-90 days,⁴¹ with documented cases of crop injury in rotational plantings due to persistence.⁴² Picloram exhibits even higher environmental persistence, with soil half-lives up to 300 days⁴³ and detectable residues in groundwater.⁴⁴ Acute toxicity data show LC₅₀ values for honeybees exceeding 100 µg/bee for most pyridine herbicides, indicating low acute bee toxicity,³⁴ but chronic effects remain understudied. Regulatory bodies have imposed buffer zones and application restrictions for picloram and clopyralid to mitigate leaching and non-target exposure.⁴⁰ See **Table 2** for a summary of environmental fate and regulatory status of major pyridine-based agrochemicals.

Table 2. Comparative environmental fate, acute toxicity, and regulatory status of selected pyridine-based agrochemicals

Compound	Soil Half-life (days)	LC ₅₀ (Bee, µg/bee)	LC ₅₀ (Fish, mg/L)	Regulatory Status (EU/US)	Bioaccumulation
Clopyralid	30-90	>100	80	Approved/ Restricted	Low
Picloram	90-300	>100	25	Approved/ Restricted	Low–Medium
Triclopyr	30-90	>100	10	Approved	Low
Fluroxypyr	10-20	>100	50	Approved	Low

Structural modifications, such as the strategic placement of electron-withdrawing or electron-donating groups on the pyridine ring, have yielded derivatives that are highly effective against target pests and weeds while displaying low toxicity to beneficial species, including pollinators and natural predators.^{14, 39} In addition, the application of computational modeling and high-throughput screening has facilitated the identification of compounds with favorable safety profiles.¹¹

Nevertheless, some pyridine-based agrochemicals such as picloram and clopyralid are known for their moderate to high persistence in the environment, which can pose risks of carryover to rotational crops and potential leaching into water sources.^{35, 36} These concerns necessitate careful management, including strict adherence to labeled application rates, rotation intervals, and the establishment of buffer zones to mitigate off-target impacts.³⁵

Regulatory approval processes for pyridine-based agrochemicals now require comprehensive toxicological and environmental fate assessments, ensuring that products introduced to the market meet safety standards for both humans and the environment. Innovations in formulation technology, such as controlled-release systems and microencapsulation, further enhance the safety and efficacy of these compounds by reducing off-target exposure and optimizing delivery.²⁰ While advances in formulation have improved safety and environmental compatibility, potential ecological impacts, especially on non-target species, remain underexplored. Further investigation is recommended to understand possible unintended effects and to ensure the safe deployment of these compounds in diverse ecosystems.

11. Conclusions

In summary, while Structure-Activity Relationship (SAR)-based research holds significant promise for the rational design of pyridine-based agrochemicals, it is crucial that laboratory findings are validated through comprehensive field trials to ensure their efficacy and safety in real-world conditions. The considerable advances in the structural development and application of these compounds highlight their essential role in meeting the needs of a growing global population and increasingly challenging agricultural environments. Pyridine derivatives have demonstrated exceptional versatility, serving as herbicides, insecticides, fungicides, plant growth regulators, and components for advanced fertilizers. Their molecular adaptability allows for the precise targeting of pests and weeds, which reduces chemical usage and minimizes off-target effects, while formulation improvements have further enhanced their safety and environmental compatibility.

Ongoing innovation driven by computational methods, high-throughput screening, and bioisosteric modifications will continue to produce new active ingredients that are more selective, effective at lower doses, and biodegradable. Responsible management practices are vital for addressing the environmental persistence of certain compounds and for preventing the development of resistance in target species. This includes the adoption of integrated pest and weed management strategies, rotating modes of action, and adhering to regulatory best practices to protect non-target organisms and water resources. Ultimately, the integration of advanced chemistry with practical agricultural applications will ensure that pyridine-based agrochemicals play a pivotal role in supporting sustainable, high-yield food systems. As research progresses and regulatory frameworks evolve, these compounds will remain central to the development of next-generation crop protection solutions that balance productivity, environmental stewardship, and global food security.

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