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Synthesis, Bioevaluation and Structure-Activity Relationships of Novel *N*-Aryl Carbamate Derivatives as Potential Fungicidal Agents

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Abstract

The exploitation of natural products as lead compounds continues to serve as a vital strategy for the discovery of novel fungicidal agents. This work designed and synthesized a series of carbamate derivatives based on the natural product physostigmine and commercial carbamate fungicides. The title compounds were synthesized from readily available aromatic aldehydes via green Curtius rearrangement. The antifungal activities of those compounds were evaluated in vitro against eight phytopathogenic fungi. Many of the carbamate compounds exhibited good fungicidal activities. Among those molecules, compounds **3a9**, **3b1**, **3b2** and **3b12** outperformed the potency of the positive control azoxystrobin against certain fungi. Moreover, compounds **3b2**, **3b3**, and **3b12** showed outstanding and broad-spectrum in vitro antifungal activities against seven fungi with an inhibition rate of over 70% at 50 μg/mL. The preliminary structure-activity relationship (SAR) investigations demonstrated that *N*-aryl carbamates bearing a chlorine atom(s) or two bromine atoms on the di-substituted phenyl ring showed superior antifungal potency. This work might lay the foundation for investigating natural-source-based green fungicides, which exhibited great potential as novel antifungal lead compounds.

Keywords: carbamates; antifungal activities; green Curtius rearrangement; plant pathogenic fungi; structure-activity relationship

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1. Introduction

Plant diseases, caused by phytopathogenic fungi, lead to substantial crop yield losses and can even result in complete crop failure [1–3]. These pathogens infect a wide range of crops, including grains, vegetables, and fruits, damaging various plant tissues [4]. Furthermore, some fungi produce toxins that pose a significant threat to human health [5]. Currently, chemical fungicides remain crucial for crop protection, significantly reducing losses from plant diseases and ensuring crop yield and quality [6]. However, reliance on traditional chemical control can lead to negative impacts, including environmental residue issues and the development of fungal resistance due to the long-term use of single-site inhibitors [7]. Consequently, there is an urgent need to discover novel fungicides with

high efficiency, environmental compatibility, and broad-spectrum activity to overcome the limitations of existing agrochemicals.

Natural products, known for their chemical diversity, potent biological activities, environmental compatibility (e.g., facile degradation, low residue and non-target selectivity), and suitability as scaffolds for structural optimization, serve as vital sources for pesticide discovery [8–10]. As such, they are considered crucial precursors or lead compounds for developing new pesticides [11,12].

Physostigmine, a carbamate plant alkaloid isolated from *Physostigma venenosum*, possesses diverse biological activities, including insecticidal and medicinal properties [13,14]. Its structure has inspired the development of commercial carbamate pesticides [15] (Figure 1). The carbamate moiety is a key pharmacophore in many fungicides, often exhibiting broad-spectrum activities by targeting thio-containing enzymes in phytopathogenic fungi [16]. In addition, carbamate fungicides are generally considered to have a reduced environmental impact because they hydrolyze rapidly in the field, resulting in minimal residue [17]. This combination of efficacy and favorable environmental profile makes carbamates one of the most important classes of commercial fungicides. Several novel carbamate fungicides have been developed and commercialized in recent years, such as Pyribencarb [18], Triclopyricarb [19], Picarbutrazox [20], and Tolprocarb [21] (Figure 2).

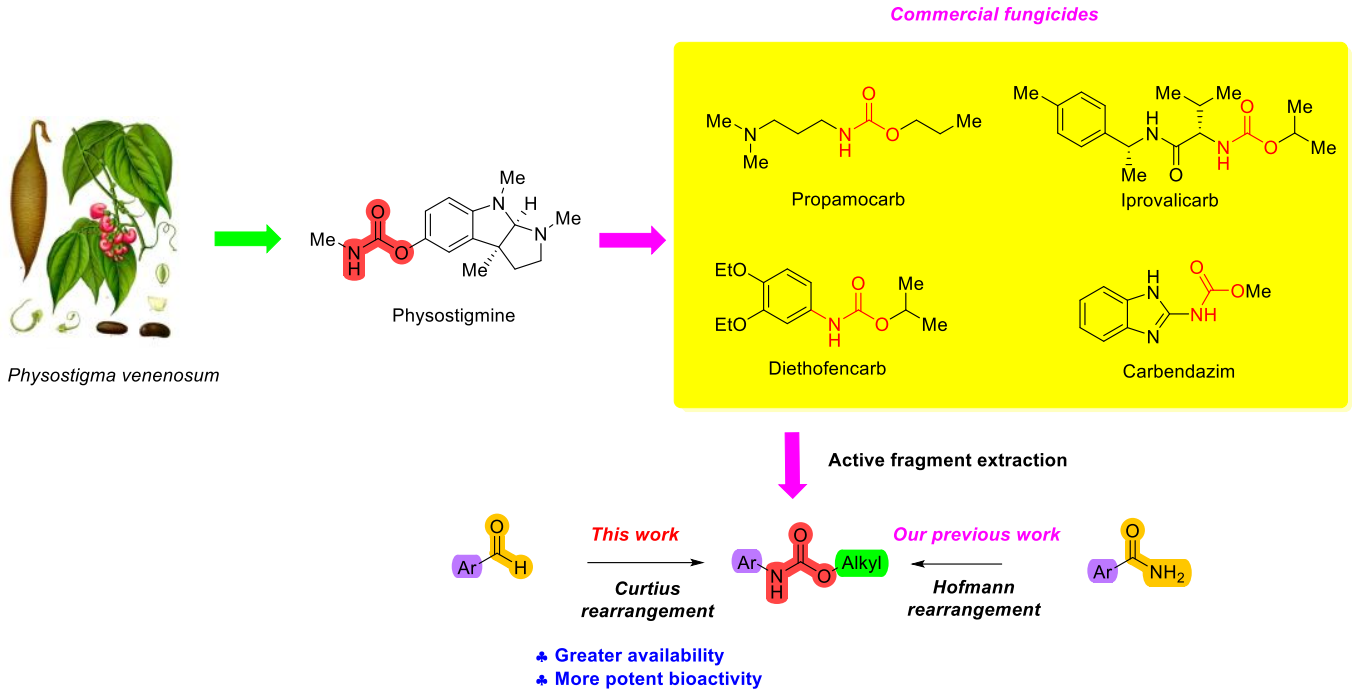


Figure 1. Design strategy of target compounds.

The carbamate skeleton is a privileged structure in agrochemical discovery [22–30]. However, conventional synthetic routes to carbamates often involve hazardous reagents, cumbersome procedures, and are not environmentally benign [31]. In response, we recently developed a green and unified method for the oxidation of amides and aldehydes using an oxone-KBr-NaN_3 system, generating key intermediates (*N*-halo amides and acyl azides) that undergo Hofmann or Curtius rearrangements to isocyanates, which are subsequently trapped by alcohols to yield carbamates [32]. In our previous work, we applied the Hofmann rearrangement variant to synthesize carbamate derivatives with promising antifungal activities [33]. Building on these results, we herein report the design and synthesis of a new series of carbamate compounds via the green Curtius rearrangement

of readily available aldehydes (Scheme 1). Their antifungal activities were evaluated against eight plant pathogenic fungi in vitro, and the structure-activity relationships were investigated. This work provides valuable insights for developing promising carbamate-based lead compounds as prospective fungicides (Figure 1).

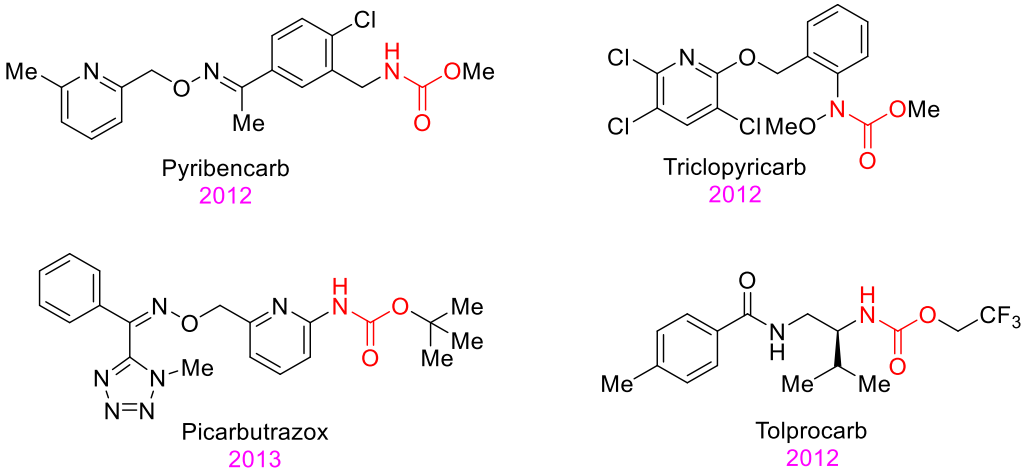
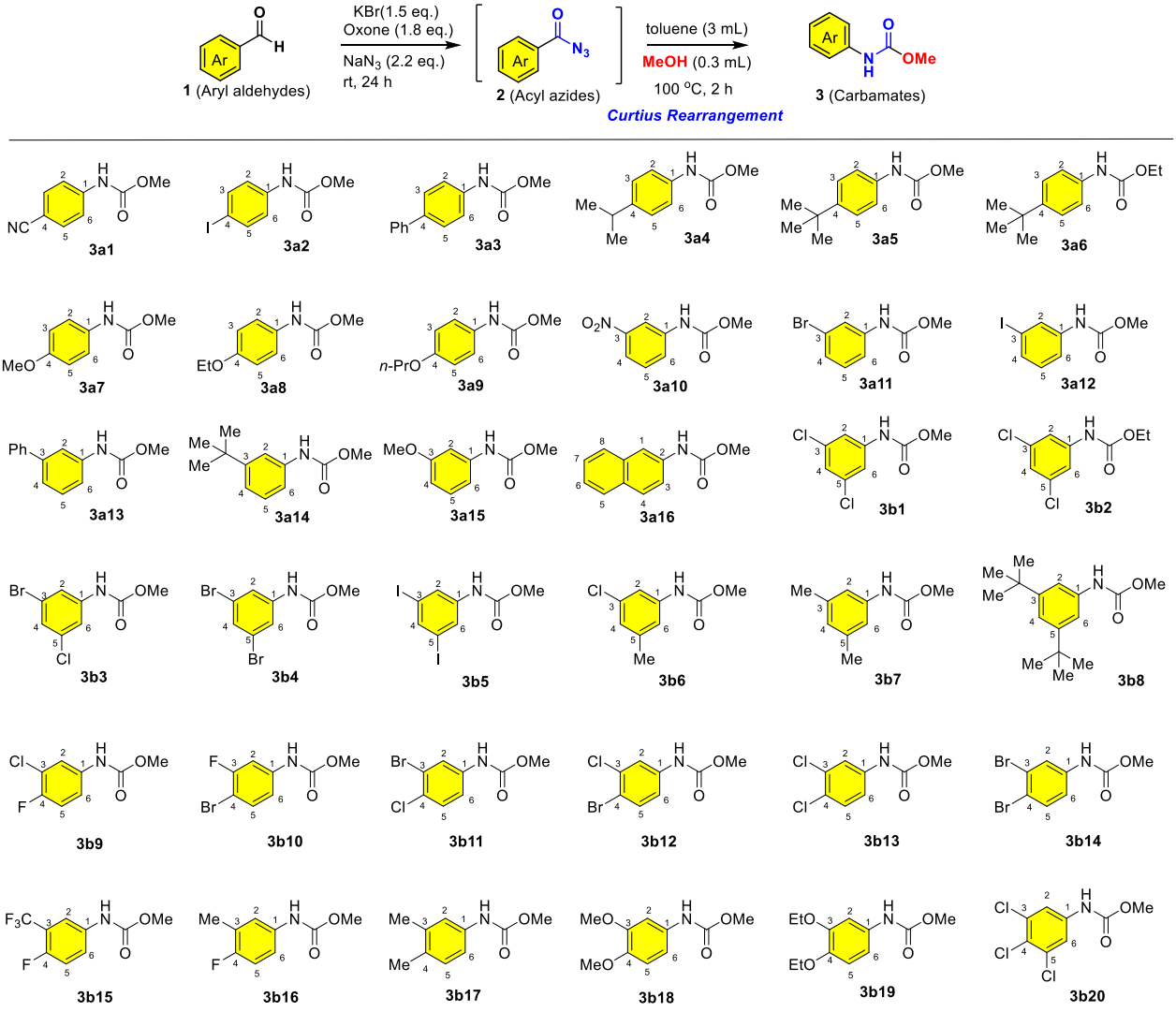


Figure 2. Commercialized carbamate fungicides since the 2010s.



Scheme 1. Synthetic route of the target molecules.

2. Materials and Methods

2.1. General Information

The commercially available chemical reagents and solvents were purchased from Bidepharm (Shanghai, China) and used directly without further purification. Proton and Carbon nuclear magnetic resonance (NMR) spectra were recorded on Bruker AVIII 400 MHz spectrometers (Bruker, Rheinstetten, Germany). ^{1}H NMR and ^{13}C NMR chemical shifts are reported in ppm (δ) with the solvent (chloroform-d) peaks utilized as the internal standard (7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). Data are documented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet), coupling constants (Hz), and integration. High-resolution mass spectra (HRMS) were obtained using a Thermo Scientific LTQ Orbitrap XL instrument (ThermoFisher, Waltham, MA, USA) via electron spray ionization (ESI).

2.2. Synthetic Procedures

General Synthetic Procedure for Carbamates 3: Aromatic aldehydes (1.0 mmol) were dissolved in a mixture of acetonitrile (5 mL) and water (5 mL). Potassium bromide (0.2 mmol), sodium azide (1.5 mmol), and Oxone® (2.0 mmol) were added sequentially at 0 °C. The reaction mixture was stirred at room temperature for 2–4 h (monitored by TLC). Upon completion, the resulting acyl azide intermediate was heated to 60–70 °C for 1–2 h to facilitate the Curtius rearrangement. The corresponding alcohol (methanol or ethanol, 5 mL) was then added, and the mixture was stirred for an additional 2 h. After completion, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford the pure carbamate products **3**.

Carbamates **3** were synthesized in one-pot two-step reactions according to our previous report [32]. The title compounds **3a1**–**3a3**, **3a5**, **3a7**, **3a10**–**3a12**, **3a15**–**3a16**, **3b1**, **3b4**, **3b9**–**3b10**, **3b15**–**3b18** were known compounds and were already in store in our laboratory [32]. The remaining compounds were synthesized following the general procedure above. Twelve of these compounds (**3a4**, **3a6**, **3a8**, **3a13**–**3a14**, **3b2**–**3b3**, **3b6**–**3b8**, **3b13**, **3b19**) were known and their corresponding references are listed. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. Known compounds showed spectral data consistent with the literature values. The characterization data of newly prepared compounds are listed as follows:

3a4 [34]. 40.5 mg, 70% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (2H, d, *J* = 8.0 Hz, H-2, H-6), 7.19–7.14 (2H, d, H-3, H-5), 6.68 (1H, bs, N-H), 3.77 (3H, s, OMe), 2.87 (1H, sep, *J* = 6.9 Hz, $CH(CH_3)_2$), 1.23 (6H, d, *J* = 7.0 Hz, $CH(CH_3)_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3 (C=O), 144.2 (C-4), 135.5 (C-1), 126.9 (C-2, C-6), 118.9 (C-3, C-5), 52.3 (OMe), 33.5 ($CH(CH_3)_2$), 24.1 ($CH(CH_3)_2$).

3a6 [35]. 47 mg, 71% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (4H, s, H-2, H-3, H-5, H-6), 6.66 (1H, bs, N-H), 4.23 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.30 (3H, t, *J* = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.8 (C=O), 146.3 (C-1), 135.3 (C-4), 125.9 (C-2, C-6), 118.6 (C-3, C-5), 61.2 (OCH_2), 34.3 ($C(CH_3)_3$), 31.4 ($C(CH_3)_3$), 14.6 (OCH_2CH_3).

3a8 [36]. 34.5 mg, 59% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.7 Hz, H-2, H-6), 6.86–6.81 (2H, m, H-3, H-5), 6.56 (1H, bs, N-H), 3.99 (2H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.75 (3H, s, OMe), 1.39 (3H, t, *J* = 7.0 Hz, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.4 (C-4), 154.5 (C=O), 130.8 (C-1), 120.7 (C-2, C-6), 114.9 (C-3, C-5), 63.7 (OCH_2CH_3), 52.3 (OMe), 14.9 (OCH_2CH_3).

3a9. *Methyl (4-propoxyphenyl)carbamate*. 35 mg, 56% yield; white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.6 Hz, H-2, H-6), 6.87–6.81 (2H, m, H-3, H-5), 6.59 (1H,

bs, N-H), 3.88 (2H, t, *J* = 6.6 Hz, OCH_2), 3.75 (3H, s, OMe), 1.83–1.74 (2H, m, OCH_2CH_2), 1.02 (3H, t, *J* = 7.4 Hz, $OCH_2CH_2CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.6 (C-4), 154.5 (C=O), 130.7 (C-1), 120.8 (C-2, C-6), 114.9 (C-3, C-5), 69.8 (OCH_2), 52.3 (OMe), 22.6 (OCH_2CH_2), 10.5 ($OCH_2CH_2CH_3$). **HRMS** (ESI) *m*/*z* calculated for $C_{11}H_{16}O_3N^+$ $[M+H]^+$ 210.1125, found 210.1124.

3a13 [37]. 52 mg, 76% yield; yellowish solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1H, s, H-2), 7.62–7.57 (2H, m, H-2″, H-6″), 7.44 (2H, t, *J* = 7.5 Hz, H-3″, H-5″), 7.40–7.34 (3H, m, H-4, H-6, H-4″), 7.33–7.29 (1H, m, H-5), 6.86 (1H, bs, N-H), 3.80 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.2 (C=O), 142.2 (C-1), 140.7 (C-1″), 138.3 (C-3), 129.5 (C-3″, C-5″), 128.8 (C-5, C-4″), 127.5 (C-2″, C-6″), 127.2 (C-6), 122.4 (C-2), 117.5 (C-4), 52.4 (OMe).

3a14 [34]. 47 mg, 75% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46–7.37 (1H, m, H-5), 7.28–7.22 (2H, m, H-2, H-6), 7.15–7.09 (1H, m, H-4), 6.80 (1H, bs, N-H), 3.78 (3H, s, OMe), 1.32 (9H, s, $C(CH_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3 (C=O), 152.3 (C-3), 137.6 (C-1), 128.7 (C-2, C-5), 120.6 (C-6), 116.0 (C-4), 52.3 (OMe), 34.8 ($C(CH_3)_3$), 31.3 ($C(CH_3)_3$).

3b2 [38]. 55 mg, 79% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 1.8 Hz, H-2, H-6), 7.03 (1H, t, *J* = 1.8 Hz, H-4), 6.74 (1H, bs, N-H), 4.23 (2H, q, *J* = 7.1 Hz, OCH_2CH_3), 1.32 (3H, t, *J* = 7.1 Hz, OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.1 (C=O), 139.9 (C-1), 135.3 (C-3, C-5), 123.3 (C-2, C-6), 116.8 (C-4), 61.8 (OCH_2CH_3), 14.5 (OCH_2CH_3).

3b3 [39]. 60 mg, 76% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 (1H, t, *J* = 1.8 Hz, H-2), 7.39 (1H, t, *J* = 2.1 Hz, H-6), 7.19 (1H, t, *J* = 1.8 Hz, H-4), 6.86 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6 (C=O), 139.9 (C-1), 135.5 (C-3), 126.2 (C-5), 122.9 (C-4), 119.6 (C-6), 117.3 (C-2), 52.8 (OMe).

3b5. *Methyl (3,5-diiodophenyl)carbamate*. 81 mg, 67% yield; white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (2H, d, *J* = 1.4 Hz, H-2, H-6), 7.74 (1H, t, *J* = 1.4 Hz, H-4), 6.58 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.4 (C=O), 140.1 (C-3, C-5), 139.8 (C-1), 126.5 (C-4), 94.6 (C-2, C-6), 52.8 (OMe). **HRMS** (ESI) *m*/*z* calculated for $C_8H_8O_2NI_2^+$ $[M+H]^+$ 403.8639, found 403.8632.

3b6 [39]. 60 mg, 72% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (1H, s, H-2), 7.04 (1H, s, H-4), 6.85 (1H, s, H-6), 6.83 (1H, bs, N-H), 3.75 (3H, s, OMe), 2.26 (3H, s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.9 (C=O), 140.5 (C-1), 138.8 (C-3), 134.4 (C-6), 124.2 (C-4), 117.4 (C-5), 115.9 (C-2), 52.5 (OMe), 21.3 (CH_3).

3b7 [40]. 39 mg, 73% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.02 (2H, s, H-2, H-6), 6.73 (1H, s, H-4), 6.61 (1H, bs, N-H), 3.78 (3H, s, OMe), 2.28 (6H, s, 3-CH_3, 5-CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1 (C=O), 138.8 (C-3, C-5), 137.7 (C-1), 125.2 (C-2, C-6), 116.5 (C-4), 52.3 (OMe), 21.4 (3-CH_3, 5-CH_3).

3b8 [41]. 46.5 mg, 59% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 4.2 Hz, H-2, H-6), 7.15 (1H, t, *J* = 1.7 Hz, H-4), 6.75 (1h, bs, N-H), 3.77 (3H, s, OMe), 1.32 (18H, s, 3-$C(CH_3)_3$, 5-$C(CH_3)_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3 (C=O), 151.7 (C-3, C-5), 137.2 (C-1), 117.7 (C-2, C-6), 113.2 (C-4), 52.3 (OMe), 34.9 (3-$C(CH_3)_3$, 5-$C(CH_3)_3$), 31.4 (3-$C(CH_3)_3$, 5-$C(CH_3)_3$).

3b11. *Methyl (3-bromo-4-chlorophenyl)carbamate*. 63 mg, 80% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77–7.71 (1H, m, H-2), 7.34 (1H, d, *J* = 8.7 Hz, H-5), 7.27 (1H, dd, *J* = 8.7 and 2.4 Hz, H-6), 6.79 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7 (C=O), 137.4 (C-1), 130.4 (C-5), 128.6 (C-6), 123.4 (C-4), 122.6 (C-2), 118.6 (C-3), 52.7 (OMe). **HRMS** (ESI) *m*/*z* calculated for $C_8H_8O_2NClBr^+$ $[M+H]^+$ 263.9422, found 263.9422.

3b12. *Methyl (4-bromo-3-chlorophenyl)carbamate*. 64 mg, 81% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 2.6 Hz, H-2), 7.50 (1H, d, *J* = 8.7 Hz, H-5), 7.14 (1H, dd, *J* = 8.7 and 2.6 Hz, H-6), 6.74 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR**

(100 MHz, $CDCl_3$) δ 153.6 (C=O), 138.1 (C-1), 134.9 (C-5), 133.8 (C-3), 120.2 (C-2), 118.1 (C-6), 115.8 (C-4), 52.7 (OMe). **HRMS** (ESI) *m*/*z* calculated for $C_8H_8O_2NClBr^+$ $[M+H]^+$ 263.9422, found 263.9418.

3b13 [42]. 53.5 mg, 81% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 2.5 Hz, H-2), 7.34 (1H, d, *J* = 8.7 Hz, H-5), 7.20 (1H, dd, *J* = 8.7 and 2.5 Hz, H-6), 6.73 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7 (C=O), 137.4 (C-1), 132.9 (C-3), 130.6 (C-5), 126.7 (C-6), 120.3 (C-4), 117.9 (C-2), 52.7 (OMe).

3b14. *Methyl (3,4-dibromophenyl)carbamate*. 64.5 mg, 70% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (1H, s, H-2), 7.50 (1H, d, *J* = 8.7 Hz, H-5), 7.20 (1H, d, *J* = 8.7 Hz, H-6), 6.71 (1H, bs, N-H), 3.78 (3H, s, OMe). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.6 (C=O), 138.0 (C-1), 133.7 (C-4), 125.0 (C-5), 123.3 (C-6), 118.7 (C-3), 118.2 (C-2), 52.7 (OMe). **HRMS** (ESI) *m*/*z* calculated for $C_8H_8O_2NBr_2^+$ $[M+H]^+$ 307.8917, found 307.8922.

3b19 [34]. 37 mg, 51% yield; colorless solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23–7.08 (1H, m, H-5), 6.80 (1H, d, *J* = 8.5 Hz, H-6), 6.73 (1H, dd, *J* = 8.6 and 2.5 Hz, H-2), 6.59 (1H, bs, N-H), 4.06 (4H, dq, *J* = 10.3 and 7.0 Hz, 3-OCH_2CH_3, 4-OCH_2CH_3), 3.76 (3H, s, OMe), 1.43 (6H, dt, *J* = 8.3 and 7.0 Hz, 3-OCH_2CH_3, 4-OCH_2CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.3 (C=O), 149.1 (C-4), 144.9 (C-3), 131.6 (C-1), 114.2 (C-6), 110.7 (C-5), 105.5 (C-2), 65.1 (4-OCH_2), 64.5 (3-OCH_2), 52.3 (OMe), 14.9 (4-OCH_2CH_3), 14.7 (3-OCH_2CH_3).

3b20. *Methyl (3,4,5-trichlorophenyl)carbamate*. 48 mg, 63% yield; colorless solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.64 (2H, s, H-2, H-6), 3.77 (3H, s, OMe), NH (not observed). **^{13}C NMR** (100 MHz, CD_3OD) δ 154.4 (C=O), 139.1 (C-1), 133.6 (C-3, C-5), 123.5 (C-4), 117.9 (C-2, C-6), 51.5 (OMe). **HRMS** (ESI) *m*/*z* calculated for $C_8H_7O_2NCl_3^+$ $[M+H]^+$ 253.9537, found 253.9545.

2.3. Bioassays

The in vitro antifungal activity of the desired compounds against eight plant pathogenic fungi was measured by the mycelial growth inhibition method [33]. The assay was performed against the following fungi: *Botrytis cinerea*, *Magnaporthe oryzae*, *Pythium aphanidermatum*, *Fusarium graminearum*, *Colletotrichum destructivum*, *Valsa mali*, *Colletotrichum siamense*, and *Fusarium oxysporum*. Briefly, compounds were dissolved in DMSO to create stock solutions, which were incorporated into Potato Dextrose Agar (PDA) medium to achieve a final concentration of 50 μg/mL for preliminary screening. The final DMSO concentration in the medium was 0.5% (*v*/*v*). Mycelial disks (5 mm diameter) from the edge of a freshly growing fungal colony were inoculated at the center of the compound-amended PDA plates. Plates inoculated with DMSO (0.5% in PDA) served as the negative control, and plates containing the commercial fungicide azoxystrobin at 50 μg/mL served as the positive control. All plates were incubated at 25 °C in the dark until the mycelial growth in the negative control plates nearly covered the entire plate surface. The diameter of the fungal colony was measured, and the percentage inhibition of mycelial growth was calculated using the formula: Inhibition (%) = $[(C - T)/C] \times 100$, where C is the average diameter of fungal growth in the negative control, and T is the average diameter of fungal growth in the treatment. Each treatment was performed in triplicate.

For the active compounds, the median effective concentration (EC_{50}) was determined. A series of concentrations (e.g., 100, 50, 25, 12.5, 6.25, 3.125 μg/mL) of the test compounds was prepared in PDA, and the bioassay was conducted as described above. The EC_{50} values and their 95% confidence intervals were calculated using SPSS 22.0 software (Probit analysis). The detailed experimental procedure is described in the Supplementary Materials.

3. Results

3.1. Chemistry

In this work, two sets of novel carbamate derivatives, which were prepared from readily and/or commercially available aldehydes, were designed and synthesized via green oxidation of aldehydes and subsequent Curtius rearrangement. The synthetic routes and chemical structures of the target compounds are presented in Scheme 1. The starting material, aromatic aldehydes 1, are easily prepared or readily available from commercial sources. Upon treatment of our oxone-KBr-NaN_3 system, the corresponding acyl azides 2 were generated from aromatic aldehydes via a green and sustainable approach, enabling the subsequent heat-prompted Curtius rearrangement and capture with alcohols (methanol or ethanol), which led to the synthesis of the target compounds 3 characterized with the carbamate motif. Two series of structural diversity-guided target compounds were secured and characterized through ^{1}H NMR, ^{13}C NMR, and HRMS analyses. The corresponding data are presented in the manuscript.

3.2. In Vitro Antifungal Activity

The in vitro fungicidal potential of all target derivatives was systematically assessed against eight plant pathogenic fungi by the mycelial growth inhibition method. Preliminary evaluations were carried out at a concentration of 50 μg/mL with the commercialized broad-spectrum fungicide azoxystrobin as a positive control. The results are summarized in Table 1.

Table 1. Preliminary in vitro antifungal activity of compounds against eight fungi at 50 μg/mL.

Compounds	Average Inhibition Rate ± SD (%) (*n* = 3) [a]							
No.	***B. c.***	***M. o.***	***P. a.***	***F. g.***	***C. d.***	***V. m.***	***C. s.***	***F. o.***
3a1	6.50 ± 0.74	0.27 ± 0.87	3.75 ± 2.08	1.12 ± 3.22	7.11 ± 0.66	0	0	15.97 ± 0.67
3a2	58.97 ± 2.57	60.88 ± 2.13	56.30 ± 0.25	52.02 ± 3.47	53.60 ± 0.90	50.68 ± 0.66	34.06 ± 0.57	54.15 ± 0.82
3a3	35.70 ± 4.27	32.65 ± 0.70	42.91 ± 1.40	47.71 ± 1.42	30.19 ± 2.22	45.83 ± 1.34	48.37 ± 0.60	50.75 ± 1.20
3a4	58.93 ± 0.83	51.25 ± 1.00	61.69 ± 1.28	41.97 ± 0.98	48.11 ± 1.36	52.29 ± 0.76	19.44 ± 2.80	47.58 ± 1.37
3a5	60.10 ± 0.43	60.73 ± 0.53	63.45 ± 0.45	69.49 ± 0.64	39.22 ± 1.41	61.95 ± 0.76	21.67 ± 0.9	63.48 ± 0.63
3a6	45.55 ± 1.37	50.71 ± 0.61	51.86 ± 1.39	58.22 ± 1.12	8.50 ± 1.68	47.38 ± 1.13	50.34 ± 2.42	42.74 ± 1.23
3a7	0	0	3.43 ± 1.91	10.71 ± 0.31	8.35 ± 0.41	0.61 ± 0.91	7.66 ± 3.58	16.42 ± 0.92
3a8	20.05 ± 1.18	16.78 ± 1.25	13.36 ± 0.86	52.67 ± 1.48	73.86 ± 1.08	14.87 ± 3.20	14.00 ± 4.48	26.62 ± 0.73
3a9	67.58 ± 1.20	67.41 ± 1.36	68.79 ± 0.95	77.40 ± 1.07	83.65 ± 0.57	52.14 ± 2.03	50.67 ± 2.73	59.58 ± 0.71
3a10	0	0	0	12.07 ± 3.07	0	0.87 ± 1.76	11.46 ± 2.29	9.80 ± 0.83
3a11	35.66 ± 2.15	31.60 ± 2.05	35.74 ± 1.56	43.38 ± 0.57	22.64 ± 8.76	35.70 ± 1.37	48.57 ± 1.65	33.79 ± 0.73
3a12	44.7 ± 0.86	37.53 ± 2.80	36.66 ± 3.22	28.65 ± 1.59	33.19 ± 1.99	40.31 ± 0.87	40.54 ± 0.99	43.72 ± 0.79
3a13	75.20 ± 0.94	75.76 ± 0.73	77.52 ± 0.97	75.16 ± 0.58	63.42 ± 0.28	73.73 ± 1.46	86.51 ± 1.74	65.67 ± 0.38
3a14	52.83 ± 0.59	55.33 ± 0.92	56.61 ± 1.17	60.05 ± 1.79	45.86 ± 1.06	51.55 ± 1.17	18.04 ± 2.50	39.10 ± 0.95
3a15	9.58 ± 1.18	4.64 ± 1.56	15.16 ± 1.37	18.26 ± 3.83	10.73 ± 0.31	18.34 ± 5.42	15.94 ± 2.03	16.21 ± 0.80
3a16	69.06 ± 0.27	67.68 ± 0.36	68.08 ± 0.83	28.73 ± 1.52	44.35 ± 1.73	66.93 ± 0.65	62.23 ± 1.31	62.56 ± 0.97
3b1	82.40 ± 0.74	83.45 ± 0.61	80.28 ± 0.36	75.43 ± 1.94	60.03 ± 2.15	78.24 ± 1.31	60.89 ± 2.90	70.11 ± 1.15
3b2	85.79 ± 0.45	76.31 ± 0.37	82.95 ± 0.91	89.45 ± 2.10	61.97 ± 1.55	87.29 ± 0.86	81.24 ± 1.79	83.54 ± 0.61
3b3	87.36 ± 0.26	88.94 ± 0.3	85.61 ± 0.97	98.43 ± 1.14	72.33 ± 0.76	89.48 ± 0.60	86.89 ± 1.56	83.58 ± 0.77
3b4	77.66 ± 0.42	77.86 ± 0.59	78.24 ± 0.51	69.71 ± 3.06	53.34 ± 1.09	74.55 ± 1.04	56.96 ± 1.47	65.78 ± 0.48
3b5	28.63 ± 0.99	28.98 ± 1.29	36.83 ± 0.83	46.09 ± 1.10	4.38 ± 1.16	24.94 ± 0.98	19.65 ± 5.27	19.94 ± 0.83
3b6	68.11 ± 0.65	65.76 ± 1.07	73.39 ± 0.95	71.63 ± 0.81	62.26 ± 0.83	55.37 ± 1.80	57.00 ± 2.02	67.68 ± 1.54
3b7	28.78 ± 1.36	25.57 ± 0.91	30.07 ± 0.47	24.59 ± 0.10	2.63 ± 0.83	16.06 ± 1.30	21.88 ± 4.39	32.07 ± 2.34
3b8	8.85 ± 1.69	7.37 ± 0.97	9.53 ± 0.89	10.37 ± 1.52	0	5.32 ± 1.47	4.51 ± 3.48	12.39 ± 0.73
3b9	36.14 ± 5.51	35.52 ± 4.69	34.73 ± 1.78	38.64 ± 8.35	37.18 ± 2.83	39.00 ± 1.73	31.51 ± 0.46	37.37 ± 1.47
3b10	59.67 ± 1.11	57.35 ± 2.16	58.16 ± 2.11	56.67 ± 1.58	41.66 ± 1.25	56.12 ± 2.04	27.38 ± 5.31	51.26 ± 1.01
3b11	81.83 ± 0.66	78.55 ± 0.65	81.51 ± 1.45	83.13 ± 1.13	73.56 ± 0.98	74.21 ± 1.23	90.68 ± 0.84	78.31 ± 0.63
3b12	82.97 ± 0.26	80.04 ± 1.32	85.42 ± 0.98	85.78 ± 0.57	76.70 ± 0.53	84.32 ± 0.97	97.86 ± 0.28	83.50 ± 1.72
3b13	76.42 ± 0.44	76.45 ± 1.41	80.80 ± 0.48	94.12 ± 0.87	70.87 ± 0.41	78.41 ± 1.14	80.69 ± 1.66	77.54 ± 0.83
3b14	77.83 ± 0.50	76.86 ± 2.18	82.31 ± 1.26	87.87 ± 0.76	62.13 ± 0.48	79.01 ± 1.45	89.88 ± 1.80	78.66 ± 1.18
3b15	39.09 ± 1.05	35.33 ± 0.52	43.80 ± 1.54	59.13 ± 1.33	49.47 ± 0.48	40.63 ± 0.93	37.95 ± 1.52	42.31 ± 0.68
3b16	19.55 ± 2.26	9.93 ± 2.04	12.50 ± 0.92	14.58 ± 3.95	13.65 ± 1.01	23.23 ± 2.35	18.69 ± 1.69	17.66 ± 0.45
3b17	20.91 ± 1.06	27.94 ± 1.03	17.02 ± 0.44	1.81 ± 1.42	15.94 ± 1.46	12.74 ± 1.29	33.56 ± 1.15	18.65 ± 1.13
3b18	4.54 ± 2.23	0	4.26 ± 0.73	6.58 ± 1.95	6.63 ± 1.70	1.31 ± 1.11	1.30 ± 2.51	13.53 ± 0.97
3b19	12.24 ± 0.83	5.18 ± 1.06	12.45 ± 1.21	6.70 ± 1.12	15.28 ± 1.38	10.93 ± 1.79	9.44 ± 7.49	10.47 ± 1.27
3b20	62.24 ± 1.86	60.47 ± 1.15	59.87 ± 1.30	64.61 ± 1.44	57.14 ± 0.67	57.49 ± 0.68	71.12 ± 0.76	54.01 ± 1.17
AZO	54.39 ± 0.24	59.94 ± 0.24	56.40 ± 0.87	58.17 ± 0.22	53.46 ± 0.90	63.14 ± 0.66	54.79 ± 0.67	62.50 ± 2.14

[a] *B. c.*, *Botrytis cinerea*; *M. o.*, *Magnaporthe oryzae*; *P. a.*, *Pythium aphanidermatum*; *F. g.*, *Fusarium graminearum*; *C. d.*, *Colletotrichum destructivum*; *V. m.*, *Valsa mali*; *C. s.*, *Colletotrichum siamense*; *F. o.*, *Fusarium oxysporum*; AZO, azoxystrobin. <60% > 60% > 70% > 80%.

Key findings from the preliminary screening are summarized as follows:

Broad-Spectrum Activity: Compounds **3b1**, **3b2**, **3b3**, **3b11**, and **3b12** exhibited notable broad-spectrum activity, showing high inhibition rates (>70–80%) against most of the eight fungi tested.

Activity against Specific Fungi:

Against *B. cinerea*, 14 compounds showed >60% inhibition, with five compounds (**3b1**, **3b2**, **3b3**, **3b11**, **3b12**) exceeding 80% inhibition, outperforming azoxystrobin (54.4%). Against *M. oryzae*, 13 compounds showed >60% inhibition; compounds **3b1**, **3b3**, and **3b12** were particularly active (>80%). Against *P. aphanidermatum*, seven compounds (**3b1**, **3b2**, **3b3**, **3b11**, **3b12**, **3b13**, **3b14**) showed >80% inhibition, significantly higher than azoxystrobin (56.4%). Against *F. graminearum*, six compounds (**3b2**, **3b3**, **3b11**, **3b12**, **3b13**, **3b14**) demonstrated remarkable activity (>80%), with **3b3** and **3b13** achieving 98.4% and 94.1% inhibition, respectively. Against *C. destructivum*, compound **3a9** was the most active (>80% inhibition), and ten compounds showed >60% inhibition. Against *V. mali*, compounds **3b2**, **3b3**, and **3b11** showed >80% inhibition. Against *C. siamense*, seven compounds showed >80% inhibition, with **3b11** and **3b12** being the most potent (90.7% and 97.9%, respectively). Against *F. oxysporum*, seven compounds showed >70% inhibition, with **3b2**, **3b3**, and **3b12** exceeding 80%. In summary, the screening identified several potent compounds, with **3b1**, **3b2**, **3b3**, **3b11**, and **3b12** showing particularly promising broad-spectrum activity.

Based on the preliminary screening results, the EC_{50} values of the most active compounds (showing >80% inhibition at 50 μg/mL) were determined against the eight fungi (Table 2).

Table 2. EC_{50} values (μg/mL) of selected compounds against eight fungi in vitro.

Compound	Regression Equation	R^2	EC_{50} (μg/mL, 95% CI) [a,b]
	B. cinerea		
3b1	y = 3.605x + 4.008	0.966	12.94 (8.56–17.74)
3b2	y = 3.826x + 4.728	0.993	17.21 (14.93–19.70)
3b3	y = 4.387x + 5.829	0.994	21.31 (18.80–24.11)
3b11	y = 4.810x + 6.903	0.985	27.24 (24.22–30.63)
3b12	y = 4.610x + 6.221	0.998	22.36 (19.81–25.20)
azoxystrobin	y = 0.608x + 0.764	0.916	18.06 (4.97–37.44)
	M. oryzae		
3b1	y = 4.028x + 4.698	0.971	14.67 (9.77–20.41)
3b3	y = 4.328x + 5.578	0.995	19.44 (17.11–22.02)
3b12	y = 4.601x + 6.167	0.989	21.90 (19.40–24.69)
azoxystrobin	y = 0.529x + 0.476	0.986	7.93 (0.08–17.84)
	P. aphanidermatum		
3b1	y = 3.996x + 4.732	0.983	15.28 (13.27–17.44)
3b2	y = 4.578x + 6.065	0.949	21.12 (14.48–30.25)
3b3	y = 4.791x + 6.384	0.990	21.50 (19.10–24.17)
3b11	y = 5.622x + 8.391	0.990	31.08 (27.94–34.64)
3b12	y = 4.202x + 5.753	0.998	23.41 (20.60–26.58)
3b13	y = 6.011x + 8.930	0.997	30.60 (27.60–33.95)
3b14	y = 4.500x + 6.375	0.996	26.12 (23.12–29.52)
azoxystrobin	y = 0.534x + 0.612	0.968	13.98 (1.08–30.50)
	F. graminearum		
3b2	y = 4.136 + 4.050	0.921	9.53 (5.03–13.92)
3b3	y = 4.674x + 5.835	0.913	17.72 (9.24–30.75)
3b11	y = 4.005 + 4.603	0.943	14.10 (7.65–22.06)
3b12	y = 4.983x + 5.645	0.902	13.58 (8.31–20.11)
3b13	y = 4.376x + 5.061	0.944	14.34 (8.74–21.22)
3b14	y = 3.268x + 3.736	0.993	13.90 (6.93–22.20)
azoxystrobin	y = 0.552x + 0.561	0.971	10.35 (0.48–21.80)
	C. destructivum		
3a9	y = 2.927x + 3.579	0.901	16.70 (5.73–33.15)
azoxystrobin	y = 0.673x + 0.996	0.998	30.14 (15.25–74.79)
	V. mali		
3b2	y = 3.871 + 4.767	0.997	17.04 (14.79–19.48)

Table 2. *Cont.*

Compound	Regression Equation	R^2	EC_{50} (μg/mL, 95% CI) [a,b]
3b3	y = 4.394x + 5.932	0.999	22.39 (19.76–25.33)
3b12	y = 3.996x + 5.351	0.985	21.83 (19.11–24.88)
azoxystrobin	y = 0.593 + 0.398	0.956	4.70 (0.06–11.32)
	C. siamense		
3a13	y = 3.439x + 4.522	0.987	20.66 (17.80–23.87)
3b2	y = 4.311x + 5.146	0.935	15.62 (8.76–24.75)
3b3	y = 4.005x + 5.044	0.934	18.18 (9.07–32.16)
3b11	y = 4.180x + 5.275	0.884	18.28 (7.03–38.57)
3b12	y = 4.528x + 5.387	0.999	15.48 (1.57–49.40)
3b13	y = 4.546x + 5.680	0.904	17.76 (8.08–33.78)
3b14	y = 3.538x + 4.325	0.942	16.70 (7.44–30.14)
azoxystrobin	y = 0.504x + 0.678	0.998	22.12 (4.01–73.56)
	F. oxysporum		
3b2	y = 3.464x + 4.218	0.996	16.51 (14.13–19.08)
3b3	y = 4.138x + 5.233	0.991	18.39 (16.10–20.90)
3b12	y = 4.401x + 5.971	0.985	22.73 (20.07–25.72)
azoxystrobin	y = 0.809x + 0.930	0.978	14.15 (5.66–23.54)

[a] Average of three replicates. [b] Red color: better than positive control. Green color: close to positive control.

The EC_{50} results revealed the following key points. Several compounds demonstrated potency superior or comparable to azoxystrobin against specific fungi. Against *B. cinerea*, compounds **3b1** (EC_{50} = 12.94 μg/mL) and **3b2** (17.21 μg/mL) were more potent than azoxystrobin (18.06 μg/mL). Against *F. graminearum*, compound **3b2** (EC_{50} = 9.53 μg/mL) was more effective than azoxystrobin (10.35 μg/mL). Against *C. destructivum*, compound **3a9** (EC_{50} = 16.70 μg/mL) was significantly more active than azoxystrobin (30.41 μg/mL). Against *C. siamense*, multiple compounds, particularly **3b12** (EC_{50} = 15.48 μg/mL), showed higher potency than azoxystrobin (22.12 μg/mL). While the title compounds showed good activity against *V. mali* (EC_{50} = 17.04–21.83 μg/mL for top compounds), their activity was lower than that of azoxystrobin (4.70 μg/mL). Compounds **3b2**, **3b3**, and **3b12** emerged as the most promising broad-spectrum candidates, exhibiting significant activity against seven of the eight fungi.

To further sustain the measured EC_{50} values, the inhibitory effects (>80%) at 50 μg/mL of the most potent compounds were shown in Figure 3. For *C. destructivum*, only one compound, **3a9**, exhibited inhibitory effects higher than 80%, which was different from other fungi and depicted in Figure 3.

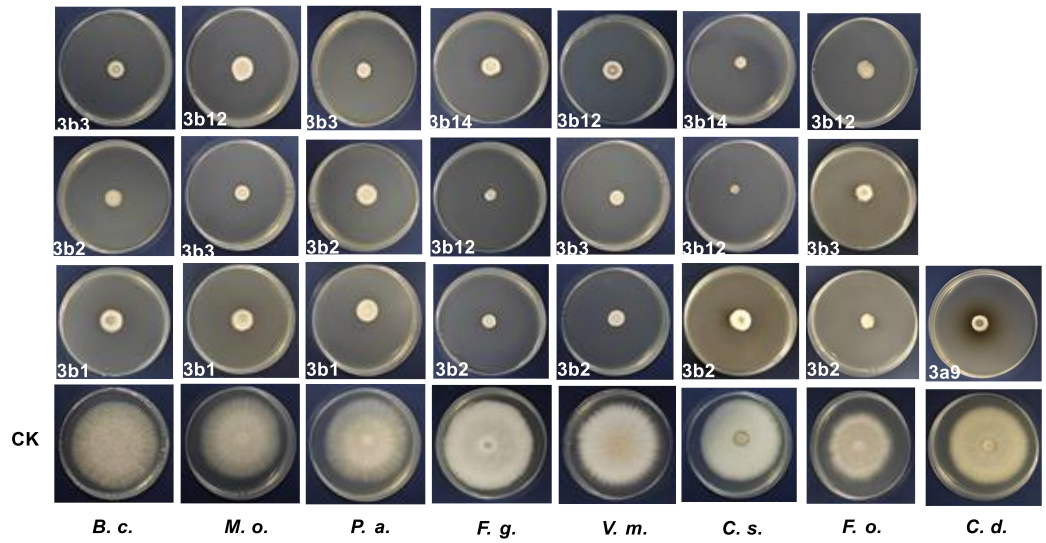


Figure 3. Inhibitory effects (>80%) of the most potent compounds on eight different plant pathogenic fungi at 50 μg/mL with blank control.

4. Discussion

The chemical structures of compounds **3a1**–**3a16**, **3b1**–**3b20** were confirmed by attentively analyzing the aromatic region of proton NMR spectra, referring to the chemical structure of precursors, i.e., aromatic aldehydes, while the methyl carbamate moiety was easily interpreted by the methoxy peak and broad single peak of amide NH. The chemical structure was further substantiated by carbon NMR spectra with the characteristic peaks of carbonyl carbon and OMe as well as the fingerprint peaks of aromatic moiety. Furthermore, the chemical structures of compounds **3a6** and **3b2** were secured by comparing the corresponding spectra with those of **3a5** and **3b1**, for the ethoxy peaks were characteristic while the aromatic moiety was the same.

Based on the in vitro screening results listed in Tables 1 and 2, a preliminary structure-activity relationship (SAR) analysis was performed. The analysis is structured by compound series and substitution patterns.

A-Series (Mono-substituted *N*-aryl carbamates):

Para-substitution: Activity against *C. destructivum* was enhanced by strong electron-donating alkoxy groups (**3a8**, **3a9**). Other substituents at the para-position, regardless of electronic nature, generally resulted in moderate or low activity.

Meta-substitution: Introducing a phenyl group at the *meta*-position (**3a13**) conferred broad-spectrum activity. Other *meta*-substituents led to low or moderate activity. Replacing the phenyl ring with a bulkier β-naphthyl group did not improve activity.

B-Series (Di- or Tri-substituted *N*-aryl carbamates):

Halogen Substitution is Critical: The incorporation of chlorine atoms or two bromine atoms on the phenyl ring significantly enhanced antifungal potency, as seen in compounds **3b1**, **3b2**, **3b3**, **3b4**, **3b11**, **3b12**, **3b13**, and **3b14**. This underscores the positive role of specific halogens (Cl, Br).

Electronic Effects: Electron-donating groups or the replacement of Cl/Br with other halogens (F, I) or groups like CF_3 diminished potency.

Steric Effects: Introducing a third chlorine atom (**3b20**) did not further enhance activity compared to the di-substituted analogues, suggesting an optimal substitution pattern.

5. Conclusions

In summary, thirty-six carbamate derivatives have been designed and synthesized via a green Curtius rearrangement route inspired by physostigmine and commercial carbamate fungicides. The compounds were fully characterized, and their antifungal activities were systematically evaluated in vitro against eight plant pathogenic fungi. The bioassay results identified several potent compounds. Specifically, compounds **3b1** and **3b2** showed superior antifungal activity against *B. cinerea*, compounds **3b2** exhibited higher activity against *F. graminearum*, compound **3a9** significantly inhibited *C. destructivum*, and compound **3b12** was most effective against *C. siamense*, all outperforming azoxystrobin. Furthermore, compounds **3b1**, **3b2**, **3b3**, **3b11**, and **3b12** demonstrated outstanding broad-spectrum in vitro fungicidal activities, making them promising leads for further development. The preliminary SAR study highlighted that di-substituted phenyl rings bearing chlorine or bromine atoms are crucial for high antifungal potency.

However, this study has limitations. The evaluations are preliminary and conducted solely in vitro. Future work should focus on the following: (1) in vivo efficacy studies to confirm activity in plant systems, (2) more detailed mechanistic investigations to elucidate the mode of action, and (3) further structural optimization of the lead compounds (e.g., **3b2**, **3b3**, **3b12**) to improve potency and physicochemical properties. Despite these limitations, these results are anticipated to provide critical insights for the design and development

of novel antifungal agents, theoretically supporting the development of environmentally friendly agrochemicals.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/agronomy15122741/s1, Supplementary File S1: Detailed operation process of biological assays; and ^{1}H NMR, ^{13}C NMR, HRMS spectra of target compounds.

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