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REGULAR ARTICLE

An efficient approach for the synthesis, characterization, and antifungal studies of chlorantraniliprole carboxamide derivatives

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BB: Experimental Data Collection, Data Analysis, Manuscript Writing;
ST: Manuscript Writing, Manuscript Revision, Supervision, and Funding Acquisition.

Abstract

The structural modification of established agrochemical scaffolds remains a powerful strategy for developing next-generation fungicidal agents with enhanced efficacy and safety. In this study, an efficient and mild peptide-coupling approach was developed for the synthesis of a new series of chlorantraniliprole (CTPR)-based carboxamide derivatives (1a–1j). The protocol employs a 1-hydroxybenzotriazole/1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (HOBt/EDC·HCl)-mediated amide bond formation between 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid and a diverse set of aromatic, aliphatic, and cyclic amines under ambient conditions, affording the target compounds in good to excellent yields (65.33–93.68%). The method is operationally simple, reproducible, and avoids harsh reagents or elevated temperatures. Structural elucidation of the synthesized compounds was accomplished using ^{1}H NMR, FTIR, and ESI–MS analyses. The antifungal potential of all derivatives was evaluated in vitro against five major phytopathogenic fungi, such as *Alternaria*, *Fusarium*, *Rhizoctonia*, *Helminthosporium*, and *Aspergillus,* using the poisoned food technique, with hexaconazole as the reference fungicide. The biological results revealed a strong dependence of antifungal activity on amine substitution. Compounds bearing short-chain aliphatic or heterocyclic amines exhibited markedly superior activity compared to aromatic analogues. In particular, derivatives 1c, 1h, 1i, and 1j demonstrated broad-spectrum antifungal efficacy, frequently outperforming hexaconazole and, in some cases, achieving complete growth inhibition at higher concentrations. Structure-activity relationship (SAR) analysis indicated that smaller open-chain amines and polar heterocyclic substituents significantly enhance antifungal performance, likely due to improved hydrophobic and hydrogen-bonding interactions with fungal targets. Overall, this work presents a practical synthetic route to CTPR-based carboxamides and identifies several promising lead compounds for the development of novel, effective, and potentially eco-friendly fungicidal agents.

Keywords

1-Hydroxybenzotriazole; Antifungal Activity; Carboxamide Derivatives; Mild Reaction; Substituted Amines.

Introduction

Heterocyclic compounds constitute a central class of molecular architectures in modern agrochemical and pharmaceutical research due to their structural diversity and wide-ranging biological activities. The incorporation of heteroatoms such as nitrogen, oxygen (Kumar et al., 2025), or sulfur into aromatic ring systems (Singh et al., 2023; Tiwari et al., 2023) often imparts unique physicochemical and bioactive properties, making heterocycles indispensable scaffolds in drug and pesticide discovery. Indeed, a substantial proportion of commercially successful agrochemicals and pharmaceuticals are based on heterocyclic frameworks (Lamberth and Dinges, 2012; Kumar et al., 2021). Given their widespread importance, the specialized field of heterocyclic chemistry has emerged, focusing exclusively on the synthesis, properties, and applications of these compounds. Researchers across the globe continue to explore and report novel heterocyclic structures, as reflected in a growing body of recent literature (Kumar et al., 2025; Verma et al., 2020; Tiwari et al., 2022). These compounds serve as foundational frameworks in agrochemical design, exhibiting diverse biological activities such as insecticidal (Fahmy et al., 2018), bactericidal (Rusu et al., 2023), fungicidal (Ramadan et al., 2021), nematocidal (Wang et al., 2023), rodenticidal (Kaddah et al., 2023), and herbicidal (Kumar et al., 2025) effects. Among nitrogen-containing heterocycles, pyridine- and pyrazole-based systems have received considerable attention owing to their broad-spectrum biological activities. Chlorantraniliprole (CTPR), a representative anthranilic diamide insecticide, is a prominent example of a pyridine-containing agrochemical with exceptional efficacy and selectivity (Tiwari et al., 2022). CTPR exhibit insecticidal

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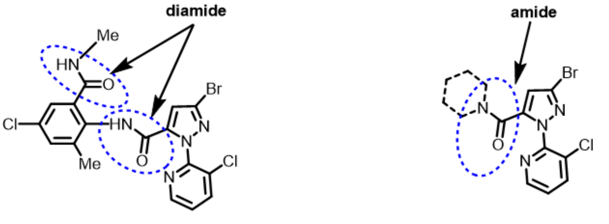
action by selectively activating insect ryanodine receptors, resulting in uncontrolled calcium release, muscle paralysis, and eventual insect death (Xiang et al., 2024). Importantly, its negligible interaction with mammalian ryanodine receptors confers an excellent safety profile, making it an attractive lead scaffold for further structural modification. CTPR belongs to the novel class of anthranilic diamide insecticides, which act selectively on insect ryanodine receptor channels (RyRs) (Bentley et al., 2010). RyRs play a central role in regulating intracellular calcium release, essential for muscle contraction (Zucchi and Ronca-Testoni, 1997). CTPR induces uncontrolled calcium release, leading to lethargy, paralysis, and eventual death in target insects.

Crucially, CTPR exhibits a favorable safety profile in mammals. It does not interact with mammalian RyRs, shows no acute toxicity via oral, dermal, or inhalation exposure, and does not cause skin irritation or sensitization. Furthermore, no reproductive toxicity or significant health risks to agricultural workers or manufacturers have been reported. These attributes make CTPR an important lead compound for the design and development of structurally modified derivatives with improved or broadened insecticidal properties.

Recent research has intensified around the synthesis and biological evaluation of CTPR derivatives. (Ren et al., 2022) reported the synthesis of a novel fluorinated CTPR derivative, while (Chen et al., 2015) explored the structure–activity relationship (SAR) and insecticidal properties of novel anthranilic diamides. Furthermore, Wang et al. conducted SAR studies on CTPR analogues with modified amide bridges, identifying a trifluoro-substituted derivative as a promising lead compound. These studies highlight the amide linkage as a critical structural component in CTPR derivatization (Xu et al., 2025; Wang et al., 2025). Recognizing the high market potential of insecticides and herbicides, we identified CTPR as one of the most widely used and commercially successful insecticides globally. It is applied across a broad spectrum of crops. CTPR is the first diamide-based insecticide with a wide range of pest control activity. It was developed globally by DuPont and belongs to a new class of selective insecticides characterized by a novel mode of action (Sparks and Bryant, 2022). It effectively targets a variety of pests, particularly from the orders Lepidoptera and, to a lesser extent, Coleoptera, Diptera, and Isoptera. CTPR acts by activating muscular calcium channels, specifically the ryanodine receptor, leading to rapid paralysis and eventual death of susceptible insect species (Du et al., 2023; Zhang and Qiang, 2021). Its selective affinity for insect ryanodine receptors accounts for its excellent safety profile, including low mammalian toxicity. CTPR primarily acts through ingestion, with a secondary effect via contact exposure **Figure 1**.



CTPR diamide chemistry

Functional diversification of CTPR

Figure 1. Structural diversification of CTPR-based diamide and amide derivatives.

The chemical structure of CTPR, we have designed our molecules to maintain the integrity of CTPR acid within the system and various amines coupled with the acid (Main et al., 2023). A new class of carboxamide has been synthesized based on various amines, and their efficacy trials have been studied. Recent studies have demonstrated that modification of the amide linkage in CTPR analogues can significantly influence biological activity, providing opportunities to expand its application beyond insect control. In particular, the introduction of diverse amine substituents offers a rational approach to tuning molecular interactions with biological targets. Motivated by the growing demand for effective and environmentally benign fungicides, the present work focuses on the synthesis of novel CTPR-based carboxamide derivatives and the systematic evaluation of their antifungal potential.

Materials and methods

Experimental Section: After preliminary optimization, the generality of the developed coupling protocol was examined using a wide range of amines, including aromatic, aliphatic, and heterocyclic derivatives. The key intermediate, 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (2a), was coupled with the corresponding amines using 1-hydroxybenzotriazole (HOBt) and EDC·HCl as activating agents, with triethylamine as the base. Dichloromethane was identified as the optimal solvent, affording the highest yields under mild reaction conditions. The optimized protocol involved stirring the reaction mixture at room temperature under a nitrogen atmosphere for 8 h. The desired carboxamide derivatives (1a–1j) were isolated in yields ranging from 65.33% to 93.68%. The method was found to be operationally simple, reproducible, and tolerant of diverse functional groups. After establishing the optimal reaction conditions for our model system, we next sought to evaluate the generality of the developed methodology across a variety of substrates bearing diverse functional groups. A broad range of amine derivatives, including aromatic, aliphatic, and heterocyclic substituents, were subjected to the reaction (Busto et al., 2011; Procopio et al., 2024), affording the corresponding amide products (1a–1j) in good to excellent yields. Notably, during the optimization process, aliphatic amines yielded higher results compared to their aromatic counterparts. The influence of ring strain was also investigated using cyclopropylamine (3g), which was well tolerated under the reaction conditions, yielding the desired product in a slightly reduced but still appreciable yield of 74%.

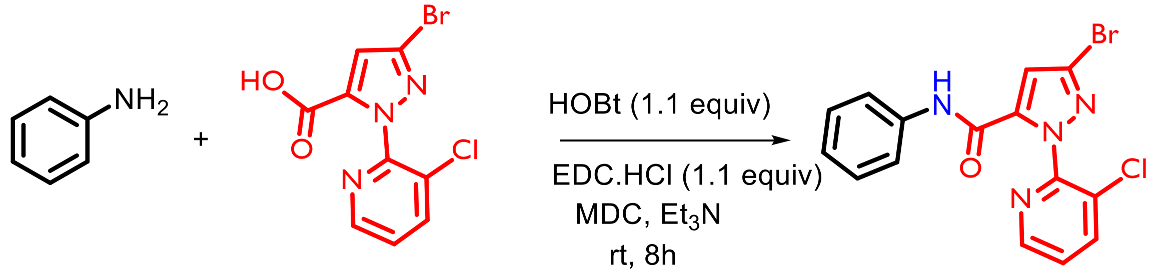
To determine the optimal conditions for the proposed peptide coupling reaction, we examined several key reaction parameters using 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (2a) and aniline (3a) as model substrates. The coupling was carried out in the presence of 1.1 eq. each of hydroxybenzotriazole (HOBt) and 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) as coupling reagents, and trimethylamine (Et_3N) as the base, in THF at room temperature under a nitrogen atmosphere for 8–10 hours (Albeiicio et al., 2001; Chan and Cox, 2007). Under these conditions, the desired product 1a was obtained in good yield, validating the efficiency of the optimized protocol. (Entry 1; **Table 1**). In the next attempt, we used EDC·HCl as both the reagent and catalyst along with Et_3N (3 eq.) in N, N-Dimethylformamide (DMF), but this significantly reduced the yield to just 24% (Entry 4, **Table 1**), indicating that HOBt is crucial for the model reaction (Nozaki, 2006). We then tested dioxane as the solvent, but the results remained unsatisfactory (Entry 5, **Table 1**).

Subsequently, we employed Dichloromethane (DCM) in anticipation of a better outcome; this condition afforded a significantly improved yield of 87% after 8 hours at room temperature (Entry 6, Table 1). Furthermore, we evaluated O-(7-azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluorophosphate (HATU) as a peptide coupling reagent in combination with Et_3N (3 eq.) in N, N-dimethylformamide (DMF), but only 35% of product 1a was obtained after 8 hours of stirring (Marchán and Grandas, 2007; Slingerland et al., 2023) (Entry 7, Table 1). This outcome confirmed that peptide coupling agents were less effective for this transformation, and the combination of HOBt/EDC·HCl was chosen for further optimization. We next investigated the effect of temperature. However, increasing the temperature and reaction time did not result in any notable improvement compared to the previously optimized conditions (Entry 8, Table 1).

A reaction was performed using 1.0 eq. of acid 2a, 0.95 eq. of amine 3a, base (3.0 eq.) in 10 mL of solvent under N_2 atmosphere. [b] Isolated yields. [C] HATU as peptide reagent. In a subsequent experiment, HOBt alone was employed as both reagent and catalyst with triethyl amine Et_3N (3 eq.) in DMF, but only 50% of the product was isolated (Entry 9, Table 1). We also explored the use of inorganic bases such as sodium carbonate (Na_2CO_3) (2 eq.) and hydrated potassium phosphate ($K_3PO_4 \cdot 3H_2O$) (2.5 eq.) (Entries 10 and 11, Table 1), but no product formation was observed even after 8 hours of stirring. Finally, we tested 1,2-dichloroethane (DCE) as a solvent, which gave a moderate yield of 75% (Entry 12, Table 1). After comprehensive optimization involving various solvents, bases, coupling reagents, and reaction conditions, we concluded that the optimal conditions for our model reaction involved Et_3N (3 eq.), HOBt (1.1 eq.), EDC·HCl (1.1 eq.) in 10 mL DCM, stirred for 8 hours at room temperature under a nitrogen atmosphere.

Spectral Characterization: All synthesized compounds were fully characterized by spectroscopic techniques. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6, and chemical shifts are reported in ppm relative to TMS. FTIR spectroscopy confirmed the presence of characteristic amide functional groups, while ESI–MS provided molecular ion peaks consistent with the proposed structures. ^1H NMR (400 MHz) spectra were recorded in trichloro(deuterio)methane ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6). Chemical shifts (δ) for carbon are reported in parts per million (ppm) relative to tetramethylsilane (TMS) and referenced to the residual solvent peak. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets), coupling constants (J) in Hertz (Hz), and integration.

Table 1. Optimization of the reaction conditions



3a 2a 1a

Entry	Catalyst/reagent	Base (eq.)	Solvent	(°C)/(h)	Yield (%)
1	HOBt /EDC.HCl	Et_3N (3)	THF	rt / 6	51%
2	HOBt / EDC.HCl	Et_3N (3)	Toluene	rt / 6	45%
3	/EDC.HCl	Et_3N (3)	DMF	rt / 8	65%
4	EDC.HCl	Et_3N (3)	DMF	rt / 8	24%
5	/EDC.HCl	Et_3N (3)	Dioxane	rt / 8	54%
6	**HOBt/EDC.HCl**	**Et_3N (3)**	**DCM**	**rt / 8**	**87%**
7	HATU [c]	Et_3N (3)	DMF	rt / 8	35%
8	HOBt/EDC.HCl	Et_3N (3)	THF	50^0C / 10	52%
9	HOBT	Et_3N (3)	DMF	rt / 8	50%
10	HOBt/EDC.HCl	Na_2CO_3(2.5)	Dioxane	rt / 8	00%
11	HOBt/EDC.HCl	$K_3PO_4.3H_2O$ (2)	Dioxane	rt / 8	00%
12	HOBt/EDC.HCl	Et_3N (3)	EDC	rt / 8	75%

Mass spectra were obtained using an electrospray ionization (ESI) mass spectrometer. FTIR spectra were recorded on a PerkinElmer Spectrum 65 FTIR spectrometer using KBr pellets, and characteristic absorption bands are reported in wave numbers (cm^{-1}). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates. Spots were visualized under UV light or by staining with iodine (I_2) or ninhydrin solution.

Biological Activity: Post-harvest pathogenic fungi such as *Alternaria* (Gudmestad et al., 2013)*, Fusarium* (Vavre et al., 2020)*, Rhizoctonia* (Varma, 2019)*, Helminthosporium* (Yu, 2019) and *Aspergillus* (Subhash et al., 2022) were isolated from the crop and crop soil of the agricultural land of G.B. Pant University of Agriculture and Technology, under the guidance of the Department of Plant Pathology, College of Agriculture. Potato dextrose agar was used as a growth medium, and temperature conditions were kept at 27 ± 2 °C. (Ribeiro et al, 25). For bioassay results, only actively growing colonies were considered. All the fungi cultures were inoculated on autoclaved and cooled PDA medium in sterilized glass Petri-plates, under aseptic conditions (Wang et al., 2013). Different concentrations of molecules listed in Table 2 (25, 50, 100, 500 mg/mL) were prepared separately and were added aseptically to PDA medium. The medium was transferred to Petri plates (90 mm diameter, 20 mL each) and incubated under aseptic conditions. A 20 distilled water solution (1.0 %, v/v) was used as a control. Each treatment in the experiment was used as a triplicate (Chauhan et al., 2020).

Results and discussion

In the study, aimed to utilize peptide coupling methodologies to modify CTPR. Specifically, 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid (2a) was reacted with a series of aromatic, heterocyclic, and aliphatic amines using EDC·HCl and HOBt as coupling agents in dichloromethane as the solvent. This reaction afforded the corresponding amide derivatives in yields ranging from 65.33% to 93.68% **(Table 2)**.

Plausible Mechanistic Pathways: As elongation occurs, the root cap differentiates and becomes tapered, displaying a yellowish coloration. Based on the existing literature, we propose a plausible mechanistic pathway for the transformation of compounds 2 and 3 into the target products 1a–1j. The reaction is initiated by the deprotonation of 3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxylic acid (2a), generating a carboxylate anion intermediate (I). This nucleophilic intermediate (I) then attacks the electrophilic carbon of the EDC reagent, leading to the formation of a reactive O-acylcarbamidic intermediate (II). Subsequently, intermediate (II) undergoes a nucleophilic substitution with HOBt, resulting in the release of EDC-urea as a by-product and the formation of an activated O-acylated intermediate (III). The generation of EDC-urea likely serves as a thermodynamic driving force, facilitating the progression of the reaction toward intermediate (III). In the final step, intermediate (III) is attacked by an amine derivative (3), leading to the displacement of HOBt and formation of the desired product 1 (1a–1j), **Figure 2**.

Although anhydrous HOBt is known to be sensitive to humidity and pressure, the present work employs only the commercially available hydrated/stabilized form of HOBt, which is widely recognized as significantly safer for routine laboratory use. All reactions were performed on a small scale under controlled conditions, without exposure to elevated pressure or mechanical stress. Under these conditions, HOBt functions as a mild and reliable coupling additive, and no safety-related concerns were encountered during the study.

Spectral Characterization of Representative: (3-bromo-1-(3-chloropyridin-2-yl)-N-phenyl-1H-pyrazole-5-carboxamide) **(1a)** was synthesized by 3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazole-5-carboxylic acid **(2a)** with aniline **(3a)** inpresence of base and peptide coupling reagents. The product was obtained as colorless needles in 87% yield with m.p. 161–162 °C.

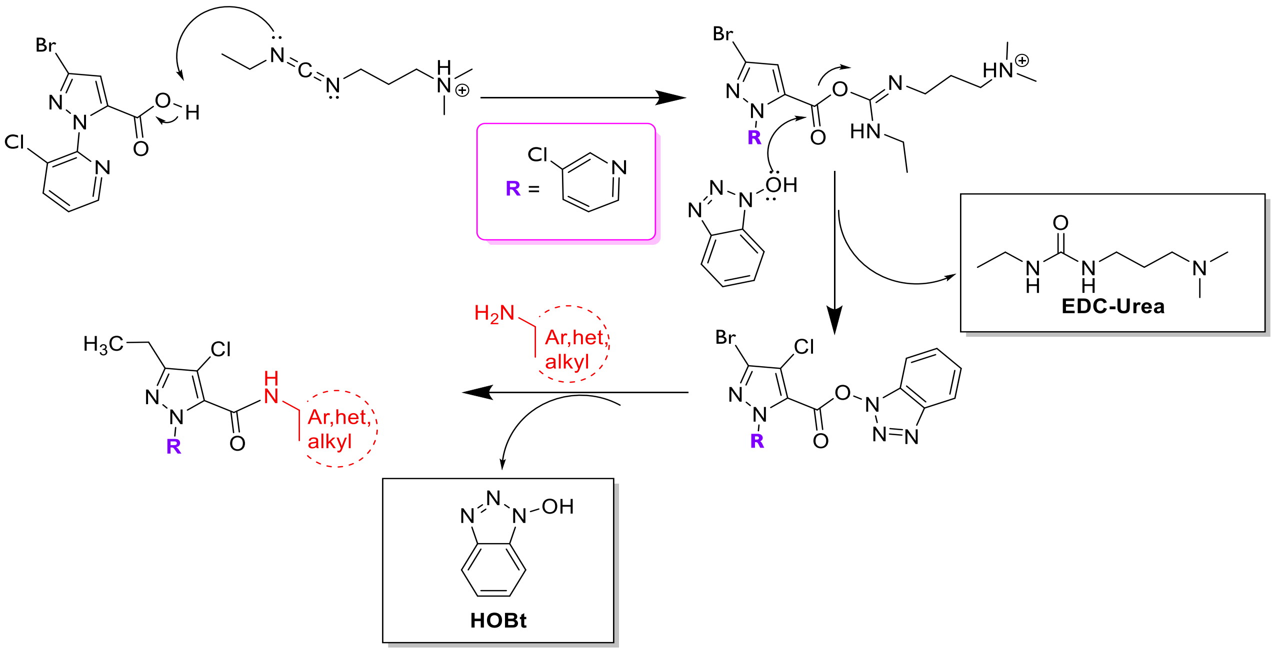
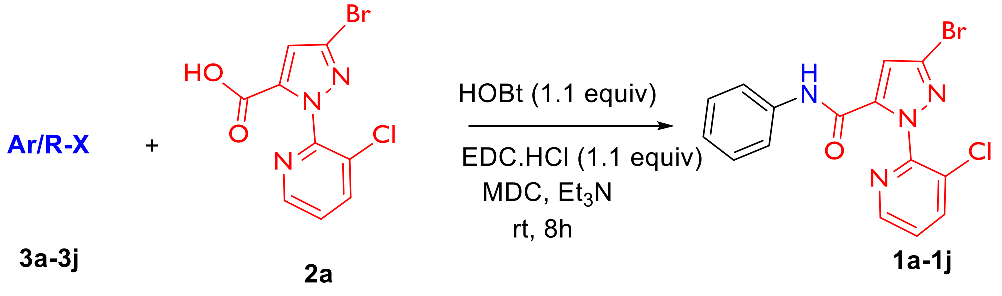


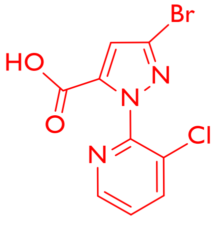
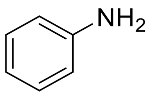
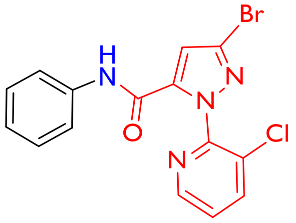
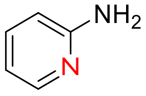
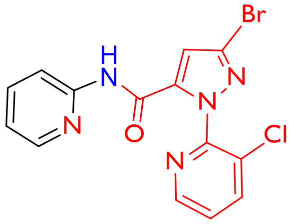
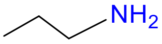
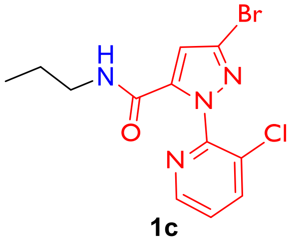
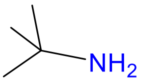
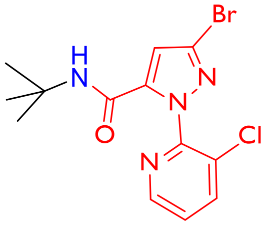
Figure 2. Plausible mechanism of the synthesized compounds

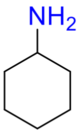
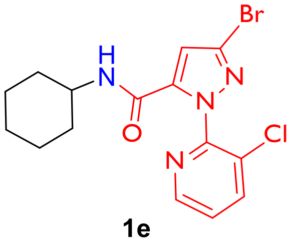
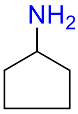
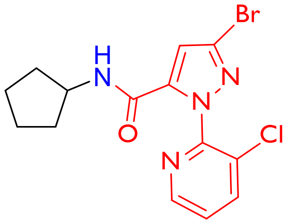
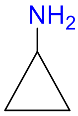
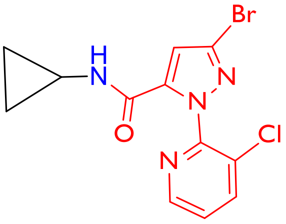
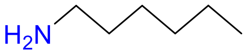
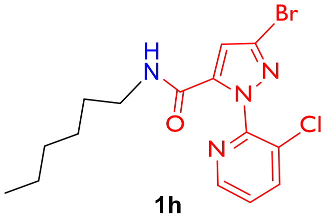
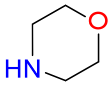
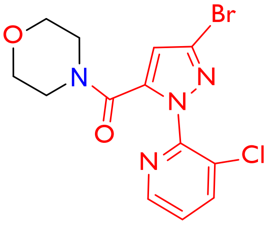
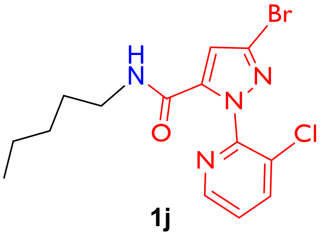
The structure of compound **1a** was established on the basis of spectral data analysis. In the ^{1}H NMR spectrum in DMSO-d_6 at 400 MHz, the characteristic peak of amide linkage -NH appeared at δ 8.23 ppm, and a singlet appeared at δ 7.47 ppm corresponds to –CH of pyrazole ring, respectively. The peaks of all other protons. Its liquid chromatography mass spectrometry showed $[M+H]^+$ peak at 378.62, which confirmed its molecular formula to be $C_{15}H_{10}BrClN_4O$ **(Table 2)**.

Table 2. Legend: Synthesis of Chlorantraniliprole carboxamide derivatives.



Ar = Aromatic
R = Aliphatic, Heterocyclic
X = -NH$_2$, -NH

Entry	Substrate	Amine	Product	Yield	m.p.
1.	 **2a**	 **3a**	 **1a**	87%	261–262 °C
2.	**2a**	 **3b**	 **1b**	65.33%	246-247 °C
3.	**2a**	 **3c**	 **1c**	93%	186-187 °C
4.	**2a**	 **3d**	 **1d**	92%	189-191 °C

5.	**2a**	 **3e**	 **1e**	90.7%	200-202 °C
6.	**2a**	 **3f**	 **1f**	93%	222-223 °C
7.	**2a**	 **3g**	 **1g**	74.7%	145-147 °C
8.	**2a**	 **3h**	 **1h**	91.43%	210-212 °C
9.	**2a**	 **3i**	 **1i**	86.84%	195-196 °C
10.	**2a**	 **3j**	 **1j**	89.84%	220-222 °C

3-bromo-1-(3-chloropyridin-2-yl)-N-phenyl-1H-pyrazole-5-carboxamide (1a): The product was obtained as a colorless needle (3.35 g, 87.05% yield); m.p. 161-162 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.52 (d, *J* = 3.6 Hz, 1H), 8.23 (d, *J* = 4 Hz, 1H), 7.65 (dd, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.43 (s, 1H), 7.32 (m, 2H), 7.13 (m, 1H) ppm. LCMS (ESI): calcd. for $C_{15}H_{10}BrClN_4O$ $[M+H]^+$ 378.62; found 378.62.

3-bromo-1-(3-chloropyridin-2-yl)-*N*-(pyridin-2-yl)-1*H*-pyrazole-5-carboxamide (1b): The product was obtained as a light yellow colour (2.46 g, 65.33% yield); m.p. 246-247 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 8.39 (d, 1H), 8.53 (d, *J* = 3.60 Hz, 1H,), 8.24 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.65 (m, 2H), 7.18 (m, 1H) ppm.

LCMS (ESI): calcd. for $C_{14}H_9BrClN_5O$ $[M+H]^+$ 379.61; found 380.09.

3-bromo-1-(3-chloropyridin-2-yl)-*N*-propyl-1*H*-pyrazole-5-carboxamide (1c): The product was obtained as a white colour solid (3.17 g, 93% yield); m.p. 186–187 °C. ^{1}H NMR (400 MHz, DMSO–d_6): δ 8.71 (d, 1H), 8.5 (d, *J* = 1.2 Hz, 1H), 8.19 (d, *J* = 1.2 Hz, 1H), 7.62 (m,1H), 7.19 (s, 1H), 3.07 (m, 2H), 1.45 (m,2H), 0.84 (t, 3H) ppm. LCMS (ESI): calcd. for $C_{12}H_{12}BrClN_4O$ $[M+H]^+$ 344.61; found 345.08.

N-tert-butyl-3-bromo-1-(3-chloropyridin-2-yl)-1H-pyrazole-5-carboxamide (1d)

The product was obtained as a light yellow colour solid (5.42 g, 92% yield); m.p. 189–191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 7.2 Hz, 1H), 8.24 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.89 (dd, *J* = 4.8 Hz, 1H), 6.51 (s, 1H), 1.38 (s, 9H) ppm. LCMS (ESI): calcd. for $C_{13}H_{14}BrClN_4O$ $[M+H]^+$ 357.02; found 357.01.

3-bromo-1-(3-chloropyridin-2-yl)-N-cyclohexyl-1H-pyrazole-5-carboxamide (1e): The product was obtained as a white colour solid (5.74 g, 90.7% yield); m.p. 200–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 7.2 Hz, 1H), 8.22 (s, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.73 (dd, *J* = 4.8 Hz, 1H), 6.43 (s, 1H), 3.53 (m, 1H), 1.79 (m, 2H), 1.59 – 1.43 (m, 8H) ppm. LCMS (ESI): calcd. for $C_{15}H_{16}BrClN_4O$ $[M+H]^+$ 383.10; found 383.05.

3-bromo-1-(3-chloropyridin-2-yl)-N-cyclopentyl-1*H*-pyrazole-5-carboxamide (1f): The product was obtained as an off-white colour solid (3.41g, 93% yield); m.p. 222–223 °C. ^{1}H NMR (400 MHz, DMSO–d_6): δ 8.5 (d, *J* = 6 Hz, 1H), 8.49 (d, *J* = 1.6 Hz, 1H), 7.62 (dd, *J* = 4.8 Hz, 1H), 7.23 (s, 1H), 4.01 (m, 1H), 1.80 (q, 2H), 1.65 (q, 2H), 1.45 (m, 4H) ppm. LCMS (ESI): calcd. for $C_{14}H_{14}BrClN_4O$ $[M+H]^+$ 370.64; found 371.1.

3-bromo-1-(3-chloropyridin-2-yl)-N-cyclopropyl-1H-pyrazole-5-carboxamide (1g): The product was obtained as an off-white colour solid (4.21 g, 74.7% yield); m.p. 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 7.2 Hz, 1H), 8.21 (s, 1H), 8.18 (d, *J* = 7.2 Hz, 1H), 7.81 (dd, *J* = 4.8 Hz, 1H), 6.40 (s, 1H), 2.54 (m, 1H), 1.79 (m, 2H), 0.57 – 0.42 (m, 2H) ppm. LCMS (ESI): calcd. for $C_{12}H_{10}BrClN_4O$ $[M+H]^+$ 341.02; found 341.01.

3-bromo-1-(3-chloropyridin-2-yl)-N-hexyl-1H-pyrazole-5-carboxamide (1h): The product was obtained as a white colour solid (5.82 g, 91.43% yield); m.p. 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 7.2 Hz, 1H), 8.19 (s, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.78 (dd, *J* = 4.8 Hz, 1H), 6.46 (s, 1H), 3.01 (m, 2H), 1.65 (q, 2H), 1.39 (m, 4H), 1.21 (m, 2H), 0.91 (t, 3H) ppm. LCMS (ESI): calcd. for $C_{15}H_{18}BrClN_4O$ $[M+H]^+$ 385.05; found 385.04.

(3-bromo-1-(3-chloropyridin-2-yl)-1*H*-pyrazol-5-yl) (morpholino) methanone (1i): The product was obtained as a white colour solid (3.2 g, 86.84 % yield); m.p. 195–196 °C. ^{1}H NMR (400 MHz, DMSO–d_6): δ 8.52 (d, *J* = 1.6 Hz,1H), 8.24 (d, *J* = 1.2Hz, 1H), 7.61 (s, 1H), 7.03(s, 1H), 3.68 (m,6H), 3.48 (m, 2H) ppm. LCMS (ESI): calcd. for $C_{13}H_{12}BrClN_4O_2$ $[M+H]^+$ 372.62; found 373.1.

3-bromo-1-(3-chloropyridin-2-yl)-N-pentyl-1H-pyrazole-5-carboxamide (1j): The product was obtained as a white colour solid (5.51 g, 89.84% yield); m.p. 220–222 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 7.2 Hz, 1H), 8.22 (s, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.82 (dd, *J* = 4.8 Hz, 1H), 6.43 (s, 1H), 3.21 (m, 2H), 1.83 (q, 2H), 1.38-1.30 (m, 4H), 0.93 (t, 3H) ppm. LCMS (ESI): calcd. for $C_{14}H_{16}BrClN_4O$ $[M+H]^+$ 371.05; found 371.04.

Biological Activity (Antifungal): The *in-vitro* Antifungal activity of compounds 1a-1j was determined against isolated fungal cultures of *Alternaria, Fusarium, Rhizoctonia, Helminthosporium,* and *Aspergillus* using potato dextrose media in 90mm petri plates. Different solution concentrations starting from 25 ppm to 200 ppm of the compound were prepared using 200 ppm of the stock solution and its serial dilution methods. Cultures were inoculated, and different concentrations of compounds were mixed along with PDA media. Untreated and market controls were also taken during the experimental phase. % of Minimum inhibitory concentrations (MIC) were recorded and calculated based on known methods. Observations were made after 14 days in the control environment by using BOD incubators. No other microbial contaminations were observed during experiments. % MIC is summarized in the supplementary file tables. We have evaluated compounds to increase the fungicidal activity of carboxamide; for that, we have made carboxamide using aromatic amines of anilines and pyridines. We have seen that effective controls against all the fungi are significantly lower than the market standard of hexaconazole 5% SC (compare entries 1, 2, and 13) at almost all concentration levels. So, it was observed that no significant controls of MIC have been observed in aromatic substitutions. To increase the number of controls, we have replaced aromatic amines with aliphatic and cyclicamine groups having C-3 to C-6 hydrocarbon.

(a) Antifungal activity of synthesized compounds against *Alternaria*

The synthesized compounds exhibited variable antifungal activity against *Alternaria*, with a clear dose-dependent trend. Compound 2a showed the weakest effect, reaching only 30% inhibition at the highest concentration. Similarly, 1a, 1b, and 1e demonstrated only moderate activity, with inhibition levels not exceeding ~57%. Compounds 1fand the standard fungicide Hexaconazole produced identical inhibition profiles (35–79%), confirming the reliability of 1f as a potential substitute for Hexaconazole. On the other hand, compounds 1c, 1d, 1g, 1h, 1i, and 1j showed significantly stronger antifungal activity. Among these, 1c and 1i were the most potent, achieving 100% inhibition at 200 ppm, while 1d, 1g, 1h, and 1j also maintained high activity (≥90%). This indicates the strong fungicidal potential of these compounds against *Alternaria* **Figure 3**.

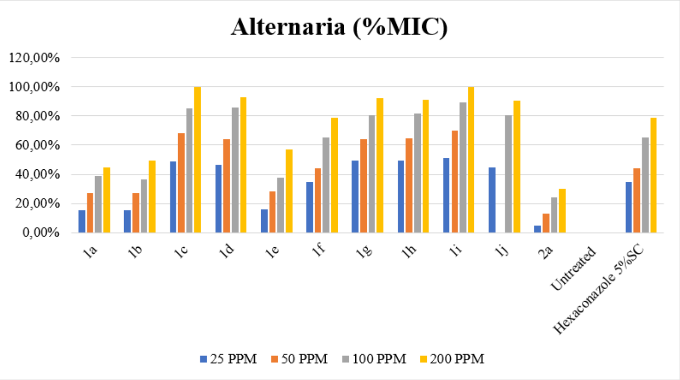


Figure 3. Antifungal activity of synthesised compounds against *Alternaria*.

Compounds such as 1a, 1b, and 1e showed moderate antifungal potential, whereas 2a was least effective, indicating structural or functional limitations in its activity profile. The superior activity of compounds 1i and 1c highlights their potential as strong candidates for further development. Their high efficacy suggests possible applications as eco-friendly antifungal agents, reducing reliance on conventional fungicides that often pose environmental and resistance-related concerns. Overall, the findings highlight the importance of rational molecular design in enhancing antifungal efficacy and pave the way for sustainable crop protection strategies. The significant inhibition observed, especially for the highly effective compounds, underlines the importance of these synthesized molecules in developing eco-friendly and efficient antifungal agents for plant disease management. The findings demonstrate that antifungal efficacy against *Alternaria* is strongly concentration-dependent and varies between compounds. Compounds 1c and 1i emerged as the most effective, completely inhibiting fungal growth, while1d, 1g, 1h, and 1j also provided near-complete protection. Compound 1f matched the performance of Hexaconazole, confirming its utility as an alternative. In contrast, 2a, 1a, 1b, and 1e exhibited weak to moderate inhibition, indicating limited application.

(a) Antifungal activity of synthesized compounds against *Fusarium*

The antifungal study against *Fusarium* clearly shows that the synthesized compounds differ greatly in their effectiveness. Some compounds, such as 2a, 1a, 1b, and 1e, were weak to moderately active, providing only limited protection even at higher concentrations. Compounds like 1d and 1f showed moderate to good activity, with 1f being almost equal to the standard fungicide Hexaconazole, suggesting it could serve as a suitable substitute. On the other hand, compounds 1c, 1g, 1h, 1i, and 1j proved to be highly effective, giving strong inhibition that in some cases was even better than Hexaconazole. Among these, 1h was the most powerful compound, completely stopping fungal growth at the highest tested concentration, while 1c and 1j also showed very high levels of inhibition **Figure 4**.

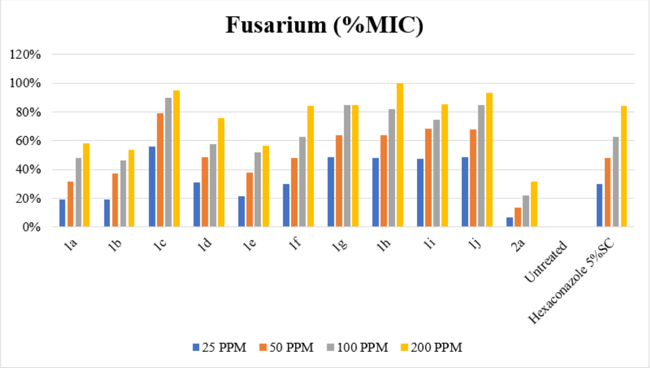


Figure 4. Antifungal activity of synthesised compounds against *Fusarium*.

The findings highlight that the antifungal activity of these compounds is strongly dose-dependent, and that 1h, 1c, and 1j stand out as the most promising candidates for developing effective antifungal agents, whereas 2a is the least useful.

(c) Antifungal activity of synthesized compounds against *Rhizoctonia*

The antifungal screening of synthesized compounds against *Rhizoctonia* showed a distinct dose-dependent response. Compounds 2a, 1a, 1b, and 1e were the least effective, with inhibition not exceeding 55% even at 200 ppm, making them poor candidates. Compounds 1d and 1f exhibited moderate to strong inhibition (32.79–89.00%), and notably, their activity was exactly eq. alent to the standard fungicide Hexaconazoleacross all concentrations, indicating they could be considered as effective substitutes. In contrast, compounds 1c, 1h, 1i, and 1j demonstrated very strong antifungal activity, showing inhibition rates above 80% at higher concentrations. Among these, 1h was the most potent compound, reaching nearly complete inhibition (98.17%) at 200 ppm.Compounds 1c (91.17%), 1j (95.17%), and 1i (89.89%)also displayed high activity, outperforming Hexaconazole at the same concentrations. Compound 1g showed moderate inhibition at lower doses but only reached ~70% at the highest concentration, indicating limited effectiveness compared to the strongest candidates **Figure 5**.

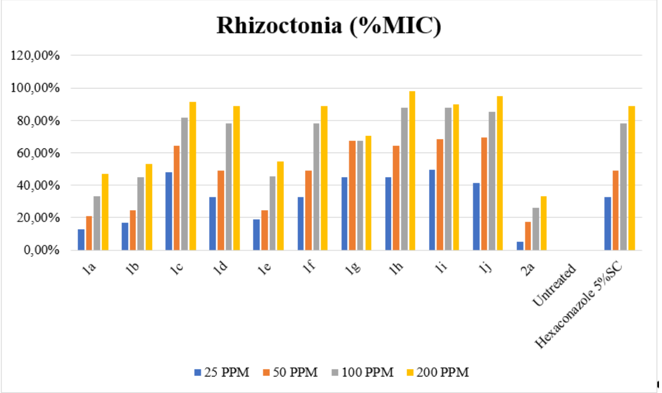


Figure 5. Antifungal activity of synthesized compounds against *Rhizoctonia*

Overall, the data suggest that the antifungal activity of these compounds against *Rhizoctonia* is strongly concentration-dependent. Compounds 1h, 1c, and 1j emerged as the most promising antifungal agents, with inhibition levels higher than the standard fungicide Hexaconazole. Compounds 1d and 1f were equally effective as Hexaconazole, suggesting potential as reliable alternatives. Conversely, 2a, 1a, 1b, and 1e showed weak activity and are less suitable for practical applications.

(d) Antifungal activity of synthesized compounds against *Helminthosporium*

The antifungal activity of the synthesized compounds against *Helminthosporium* showed variable effectiveness, with a clear dose-dependent increase in inhibition. The weakest activity was observed with 2a, which only reached ~26.29% inhibition at 200 ppm. Similarly, compounds 1a, 1b, and 1e exhibited relatively low inhibition (≤54%), making them less promising candidates. Compounds 1d and 1f showed inhibition profiles identical to the standard fungicide Hexaconazole (29.71–73.00%), suggesting their potential as substitutes. Compound 1g demonstrated moderate inhibition (41.45–70.37%) but plateaued at higher doses, indicating limited potency. On the other hand, compounds 1c, 1h, 1i, and 1j displayed strong antifungal activity, significantly outperforming Hexaconazole at eq. alent concentrations. Among them, **1i** showed the highest activity (95.17% at 200 ppm), followed closely by 1h (94.17%) and 1j (93.17%), while 1c also maintained high inhibition (85.00%) **Figure 6**.

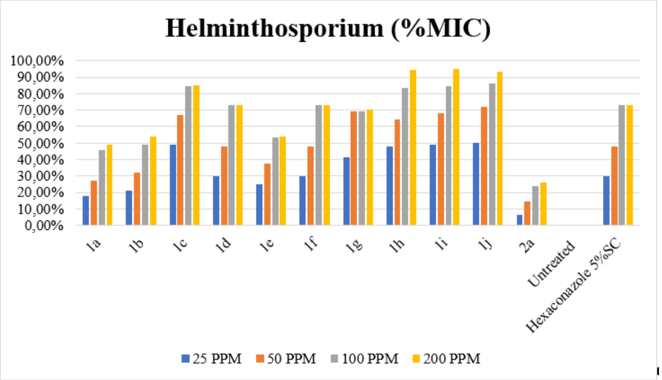


Figure 6. Antifungal activity of synthesized compounds against *Helminthosporium*.

The results demonstrate that the antifungal activity of the compounds against *Helminthosporium* is concentration dependent, with 1i, 1h, and 1j emerging as the most potent candidates, showing inhibition levels well above the standard fungicide. Compound 1c also proved highly effective. Compounds 1d and 1f, while not superior, were eq.alent to Hexaconazole, confirming their reliability as alternatives. In contrast, 2a, 1a, 1b, and 1e were the least effective, indicating limited scope for practical antifungal application.

(e) Antifungal activity of synthesized compounds against *Aspergillus*

The antifungal activity of the synthesized compounds against *Aspergillus* showed clear variability among the tested samples. Compound 2a exhibited the weakest inhibition, reaching only 36.21% at 200 ppm. Similarly, 1b and 1e showed relatively low to moderate inhibition (≤72%), indicating limited potency. Compound 1fdisplayed inhibition exactly eq.alent to the standard fungicide Hexaconazole (37.00–77.00%), suggesting its potential as a reliable substitute. In contrast, compounds 1c, 1d, 1g, 1h, 1i, and 1j exhibited stronger inhibition than Hexaconazole at most concentrations. Among these, 1d was the most active compound, achieving 95.13% inhibition at 200 ppm and consistently showing superior activity across all doses. Compounds 1c (89.32%), 1j (89.13%), 1i (83.13%), 1g (83.13%), and 1h (83.13%)also showed high antifungal efficacy, outperforming the standard fungicide **Figure 7**.

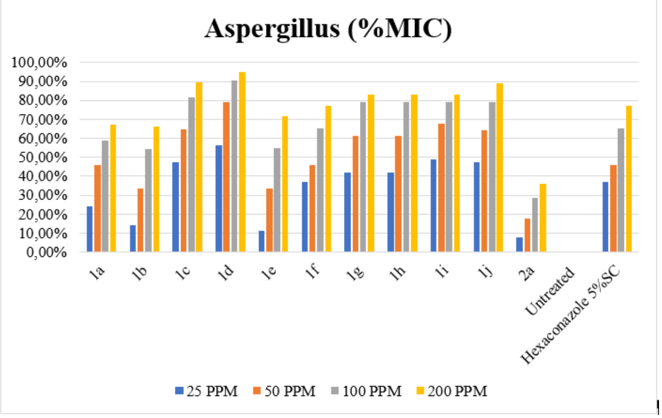


Figure 6. Antifungal activity of synthesized compounds against *Aspergillus*.

The results confirm that the antifungal activity against *Aspergillus* is dose-dependent, with several compounds showing much higher effectiveness than Hexaconazole. Compound 1d emerged as the most promising candidate, followed by 1c and 1j, all of which exhibited strong inhibition above 89% at the highest concentration. Compounds 1g, 1h, and 1i also showed consistently high inhibition levels. In contrast, 2a, 1b, and 1ewere weakly active, whereas 1f matched Hexaconazole in performance but did not surpass it.

The antifungal evaluation of synthesized compounds against five phytopathogenic fungi (*Alternaria*, *Fusarium*, *Rhizoctonia*, *Helminthosporium*, and *Aspergillus*) revealed both broad-spectrum and selective inhibitory effects. In almost all cases, inhibition was dose-dependent, increasing with higher concentrations, and showed distinct variations among compounds. Compounds 2a, 1a, 1b, and 1e consistently exhibited the weakest activity across all fungi, rarely exceeding 55–60% inhibition even at 200 ppm. Their limited efficacy indicates poor antifungal potential and makes them unsuitable for practical application. Compounds 1d and 1f showed moderate to strong activity across fungi, with inhibition patterns almost identical to the commercial fungicide Hexaconazole. In particular, 1f consistently matched

Hexaconazole's profile (up to ~79% inhibition), while 1d exceeded the standard in some cases, notably against *Aspergillus* (95.13%). These findings suggest that 1d and 1f are dependable substitutes or complements to conventional fungicides. The most promising results were observed for 1c, 1g, 1h, 1i, and 1j, which demonstrated broad-spectrum and high antifungal activity, frequently outperforming Hexaconazole.

Surprisingly, we found that propyl carboxamide gave us 100% control against all fungi. We increased branching on the hydrocarbon chain and used tert-butyl amine, and observed that the efficacy was excellent and comparable to the propyl chain on Alternaria, Rhizoctonia, and Aspergillus, as shown in entries 3 & 4. Based on these findings, we replaced the chain with cyclic amines to understand their efficacy. Surprisingly, we discovered that larger cyclic groups have less efficacy than smaller groups like cyclopropane and cyclopentane, as seen in entries 5, 6, & 7. Additionally, entry 7 showed excellent efficacy against Alternaria and Fusarium, while entry 6 performed well against Fusarium and Rhizoctonia. However, entry 5 did not demonstrate strong efficacy against any fungi, indicating that larger cyclic groups do not interact hydrophobically with fungal proteins. To explore this further, we increased the aliphatic open hydrocarbon chain from propyl to hexyl and compared entries 3, 8 & 10. We found that increasing the hydrocarbon chain length had little effect on bioefficacy, with efficacy remaining almost equal across all cases. For further evaluation, we introduced morpholine as an amide substitution. Surprisingly, we found that oxygen plays a vital role in increasing bioefficacy, as the polar oxygen atom in morpholine likely forms hydrogen bonds with water molecules in the protein cavity, enhancing efficacy, as seen in entry 9. We also tested core molecules such as pyrazole acid; however, efficacy was quite low, as shown in entry 11. From these observations, we conclude that amine groups significantly contribute to making pyrazole acid effective against fungi.

Compound 1c was consistently strong, achieving complete inhibition of *Alternaria* (100%) and showing >85% inhibition against all other fungi. Compound 1h was particularly effective against *Fusarium* (100%) and *Rhizoctonia* (98.17%), as well as strong activity against *Helminthosporium* and *Aspergillus*. Compound 1i emerged as one of the broadest and most potent agents, completely inhibiting *Alternaria* (100%) and achieving high efficacy against *Helminthosporium* (95.17%) and *Aspergillus* (83–89%). Compound 1jalso maintained consistently high inhibition across all fungi (≥89% at higher concentrations), showing near-complete activity. Compound 1g showed good activity (70–92% range), though slightly less potent than the top performers. Overall, 1c, 1h, 1i, and 1j stand out as broad-spectrum antifungal agents, displaying superior inhibition against multiple pathogens, often exceeding the performance of Hexaconazole. Compound 1d showed selective enhancement against *Aspergillus*, while 1f matched Hexaconazole across all fungi, making it a reliable alternative. Conversely, 2a, 1a, 1b, and 1e were consistently weak, suggesting minimal practical value.

Conclusions

In summary, we have successfully developed a robust reaction methodology for the synthesis of substituted CTPR carboxamide derivatives, characterized by high molecular complexity and obtained in good to excellent yields. This protocol employs a 1-hydroxybenzotriazole (HOBt)-mediated peptide coupling strategy, demonstrating high efficiency and reproducibility. Given the broad scope for structural diversification, this approach holds significant potential for generating diverse libraries of bioactive CTPR carboxamide analogues using peptide chemistry techniques. Additionally, we have established that 1c, 1h, 1i, and 1j exhibit broad-spectrum, promising antifungal activity; different chains of amines behave differently. Smaller open-chain hydrocarbons show greater efficacy against larger and cyclic chains.

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