



A curcuminoid reduces anthracnose severity caused by *Colletotrichum lindemuthianum* in common bean

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Abstract Common bean (*Phaseolus vulgaris*), a key component of human nutrition, is highly susceptible to infection by *Colletotrichum lindemuthianum*, a fungus that rapidly develops fungicide resistance. Since this phytopathogen represents a challenge to common bean crops, new fungicides are needed to control it. Thus, curcuminoids have emerged as potential antifungal candidates. In this study, we synthesised 18 monoketone curcuminoids (MKCs) and evaluated their antifungal activity against *C. lindemuthianum*. We also employed in silico methods to identify the *C. lindemuthianum* protein targeted by the most active MKC. MKCs were synthesised via aldol condensations (yield=38%–97%). Compound **9** (curcumin A or (1*E*,4*E*)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one) was the most active

curcuminoid against *C. lindemuthianum* in vitro, with a minimum inhibitory concentration of 62.5 µg/mL, which was similar to that of the commercial fungicide thiophanate-methyl (60.9 µg/mL) under the same conditions. In experiments conducted on *P. vulgaris* inoculated with *C. lindemuthianum*, curcumin A (**9**) reduced anthracnose severity from 7.31 to 2.13, similar to the severity with thiophanate-methyl application (2.59). In silico analysis showed that curcumin A and protein kinase inhibitors had similar three-dimensional structures and affinities for protein kinase, suggesting that curcumin A inhibits this type of enzyme in the fungus. These results show that compound **9** is a potentially useful lead compound for developing new fungicides to control *C. lindemuthianum* in common bean.

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Introduction

Common bean (*Phaseolus vulgaris* L.) is a key component of the human diet (Karavidas et al., 2022; Punia et al., 2020; Uebersax et al., 2023). Furthermore, because common bean fixes nitrogen, it is used in agricultural practices, such as crop rotation schemes and intercropping, to support the cultivation of non-legumes, including cereals (Ntatsi

et al., 2020). In 2022, India, Brazil, and Myanmar ranked first, second, and third, respectively, in the 28-million-ton global production of dry common bean (FAOSTAT, 2024).

The genus *Colletotrichum* (Sordariomycetes, Ascomycota) includes numerous plant pathogens, such as the fungus *Colletotrichum lindemuthianum* (Sacc. & Magnus) Briosi & Cavara, which causes anthracnose in common bean (Cheewangkoon et al., 2021; Da Silva et al., 2020; Guevara-Suarez et al., 2022; Richard et al., 2021). Crop losses can reach up to 100% when seeds infected with this fungus are cultivated in a cool and humid environment (Nabi et al., 2022). Sequencing of common bean and *C. lindemuthianum* genomes has improved our understanding of this pathogen and contributed to resistant cultivar development. However, new virulence phenotypes of the fungus, usually classified as *C. lindemuthianum* races, are constantly emerging, posing a threat to these cultivars (Paulino et al., 2021). Therefore, preventive management, such as crop rotation and the use of certified resistant seeds, are key to reducing pathogen levels in crops. In Brazil, common bean farmers often use harvested grains as seed for the next year, which can spread pathogens between seasons. In this case, phytosanitary management with fungicides is an essential management strategy (Pandey et al., 2023). Unfortunately, the wide pathogenic variability of *C. lindemuthianum* enables it to develop fungicide resistance (Davide & Souza, 2009; Pinto et al., 2012; Zhan et al., 2015), highlighting the need for new antifungals (Sparks & Lorschbach, 2017).

Computational advances are of great importance in improving agricultural yield. There are several tools that enable the alignment and comparison of protein sequences, the classification and prediction of protein structures, and the study of interactions between small organic molecules and proteins (Mu et al., 2022; Pal et al., 2006). These tools can determine the specificity of complex formation between biomacromolecules and endogenous or exogenous bioactive compounds, which can be performed, for example, with the use of molecular docking (Hou et al., 2023; Iñiguez-Luna et al., 2025). This can be useful for the rational synthesis of substances that are more active than the initial chemical structure (Huang et al., 2016). Consequently, the number of studies using this technique has increased from approximately 900 per

year in 2000 to approximately 9000 per year in 2020 (Muhammed & Aki-Yalcin, 2024).

Curcumin (**I**, Fig. 1) and curcuminoids display antifungal properties (Tavares et al., 2022). For example, curcumin is active against *Phytophthora infestans* (Mont.) de Bary, *Puccinia recondita* Rob-erge ex Desm., *Phytophthora japonica* Waterhouse, and *Rhizoctonia solani* Kühn (Kim et al., 2003; Moghadamtousi et al., 2014). Due to the highlighted antifungal potential of these compounds, several acetone-derived monoketone curcuminoids (MKCs), also known as “monocarbonyl curcuminoids” or “diarylpentanoids”, have been synthesised and evaluated for their antifungal activity (Nagargoje et al., 2020; Seker et al., 2018). MKCs can be obtained through Claisen–Schmidt condensation (CSC) (Vieira et al., 2024). Although CSC is a classical reaction, it remains an attractive synthetic method because it requires a very simple reaction setup and yields satisfactory to good quantities of MKCs in relatively short reaction times (less than 24 h). Moreover, in many cases, MKCs can be isolated by vacuum filtration and purified by recrystallisation and, thus, do not require the use of chromatographic methods for product isolation (Vieira et al., 2024). Furthermore, the CSC-based synthetic approach employed here aligns with some “Green Chemistry” principles, such as the use of non-toxic solvents (e.g., ethanol) (Anastas & Eghbali, 2010).

Curcumin (**I**) and curcuminoids demethoxycurcumin (**II**) and bisdemethoxycurcumin (**III**, Fig. 1) have antifungal effects on *Colletotrichum coccodes* (Wallr.) S. Hughes, *Colletotrichum gloeosporioides* (Penz.) Penz. & Sacc., and *Colletotrichum acutatum* J.H.Simmonds, which cause anthracnose (Bui et al., 2021; Cho et al., 2006). However, to the best of our knowledge, there are no studies on the antifungal

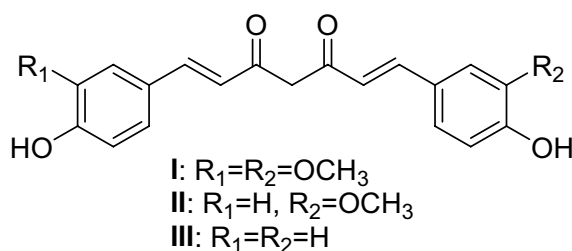


Fig. 1 Chemical structures of curcumin (**I**), demethoxycurcumin (**II**), and bisdemethoxycurcumin (**III**)

effects of curcumin, MKCs, and other curcuminoids against *C. lindemuthianum*. Thus, based on previous reports indicating that curcumin and curcuminoids may also act against *C. lindemuthianum* (Cho et al., 2006) and that MKCs **1–9** (Fig. 2) and similar compounds have antimicrobial activity (Nagargoje et al., 2020; Seker et al., 2018; Vieira et al., 2018), in this study, we synthesised 18 MKCs, evaluated their activity against *C. lindemuthianum* *in vitro*, and assessed the most active curcuminoid in common bean (*P. vulgaris*). We also conducted *in silico* studies to identify which protein is targeted by the most active curcuminoid.

Materials and methods

Curcuminoid synthesis

Acetone-derived monocarbonyl curcuminoids **1–9** were synthesised by CSC between acetone and an

aromatic aldehyde, as previously reported (Crotti et al., 2018; Vieira et al., 2018). Compounds **1–8** were synthesised under basic catalysis by adding an aqueous sodium hydroxide solution (2.5 mol/L) to ethanol (20 mL) (Fig. 2). The resulting solution was added to a 100-mL round-bottom flask containing acetone (13 mmol) and an aromatic aldehyde (26 mmol). The reaction mixture was stirred at 0 °C for 0.5–24 h, depending on the employed aldehyde. The precipitate was vacuum-filtered, purified by recrystallisation in hexane (Hex):ethanol, and vacuum-dried. Compound **9** (curcumin A) was synthesised under acidic conditions, which was achieved by saturating acetic acid (50 mL) with gaseous HCl at 0 °C (Fig. 2). Gaseous HCl was generated by dropping sulfuric acid into concentrated HCl. This acidified acetic acid solution was added to a mixture of acetone (580 mg, 10 mmol) and vanillin (20 mmol), and the reaction mixture was stirred at 0 °C for 24 h. The reaction mixture was then poured into cold water (200 mL) and extracted with ethyl

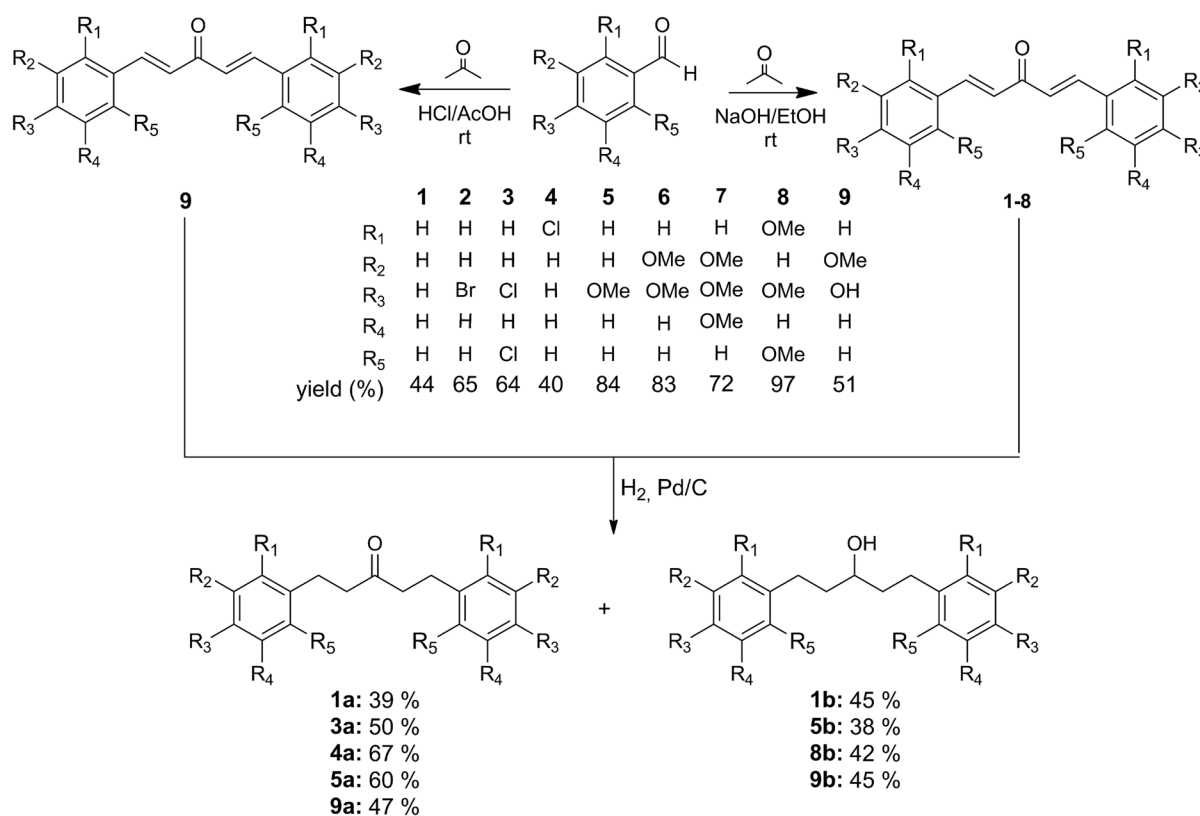


Fig. 2 Synthesis of MKCs **1–9** and their reduced derivatives

acetate (EtOAc; 4×100 mL) (Crotti et al., 2018; Vieira et al., 2018). The combined organic layers were dried over anhydrous MgSO₄ and filtered, and the solvent was removed under reduced pressure in a rotary evaporator. The resulting solid was purified using silica gel flash column chromatography with isocratic elution with Hex:EtOAc 1:1 (v:v), resulting in compound **9** as an orange powder with a 51% yield (Fig. 2).

Derivatives **1a**, **1b**, **3a**, **4a**, **5a**, **5b**, **8b**, **9a**, and **9b** were obtained by catalytic hydrogenation. In this procedure, MKCs **1**, **3–5**, **8**, and **9** were completely dissolved in high-performance liquid chromatography (HPLC)-grade EtOAc together with the catalyst (Pd/C 10 mol%) and transferred to a high-pressure reactor under stirring, with a pressure of 100 psi in a H₂ atmosphere at room temperature for 18 h (Crotti et al., 2018; Vieira et al., 2018). The reaction mixtures were filtered under reduced pressure in celite to remove the catalyst, and the solvent was removed in a rotary evaporator to provide a white solid. This solid was purified by column chromatography over flash silica gel, yielding compounds **1a**, **1b**, **3a**, **4a**, **5a**, **5b**, **8b**, **9a**, and **9b**. The following eluents were used: Hex:EtOAc 9:1 (v:v) for compounds **3** and **4**, Hex:EtOAc 8:2 (v:v) for compounds **5** and **8**, and Hex:AcOEt 1:1 (v:v) for compounds **1** and **9** (Fig. 2).

All compounds displayed a minimal purity of 95%, as confirmed by HPLC before the *in vitro* assays. The HPLC chromatograms of all compounds and the spectrometric data for the identification of the synthesised compounds are available in the Supplementary Material.

C. lindemuthianum inoculum

C. lindemuthianum strain UFLALV134 (origin: Lavras (MG), Brazil), belonging to race 65, was cultured in M3 medium (Tu, 1985) in the dark at 22 °C. Small pieces of the fungal mycelium were transferred to sterile common bean pods in glass tubes and incubated in the dark at 22 °C for 15 days. The conidial suspension was prepared by adding liquid M3S medium (7 mL) (Tu, 1985) to each tube, and the suspension was filtered through a Miracloth layer. Liquid M3S medium was added to the suspension to reach a final concentration of 1.2×10^6 conidia/mL, as described by Francisco et al. (2023).

In vitro assay with *C. lindemuthianum*

Adapting the method described in the literature (Francisco et al., 2023; Pereira et al., 2022), each compound (Fig. 2) was dissolved in dimethylsulfoxide (DMSO) to obtain a 2000 µg/mL stock solution, which was then diluted with M3S medium to 1000, 500, 250, 125, and 62.5 µg/mL. Commercial fungicide Cercobin 700WP™ (Ihara, Cajuru do Sul, Sorocaba (SP), Brazil; active ingredient: thiophanate-methyl) was dissolved in DMSO and diluted with M3S to 1400 µg/mL, which was diluted to 700, 350, 175, 87, and 44 µg/mL. The diluted concentrations of Cercobin 700WP™ correspond to 490, 245, 122.5, 60.9, and 30.8 µg/mL thiophanate-methyl (positive control), respectively. The negative control was a DMSO solution in M3S medium (5 µL + 95 µL, respectively). In a microtube, each of the prepared solutions (100 µL) was added to an aqueous suspension (100 µL) containing *C. lindemuthianum* (1.2×10^6 conidia/mL) and kept in the dark at 23 °C for five days. For each compound, the minimum inhibitory concentration (MIC; the lowest concentration of each compound that inhibited fungal development) was determined by visual inspection without magnification, in duplicate.

In vivo assay with common bean plants inoculated with *C. lindemuthianum*

Following Pereira et al. (2022), compounds **9** and **9a** were dissolved in 0.04 g/mL aqueous Tween 80 solutions to achieve the concentration (C) calculated according to the following formula: $C = (A \times B) / D$, where A represents the MIC of each compound; B is the thiophanate-methyl (positive control) concentration; and D is the MIC of thiophanate-methyl. Water, 0.04 g/mL Tween 80, and 0.7 mg/mL thiophanate-methyl (Cercobin700 WP™) were used as controls. Common bean (*Phaseolus vulgaris* L. 'Pérola') seeds were sown in 162-cell polystyrene trays filled with Tropstrato HT® commercial substrate (Vida Verde, Mogi Mirim (SP), Brazil). Eight-day-old plants (stage V2: fully expanded primary leaves) were treated with a solution (1.3 mL) of one of the tested compounds or controls. Each solution was applied with a brush to primary, fully expanded leaves. After 4 h, an aqueous suspension containing *C. lindemuthianum* conidia (1.2×10^6 conidia/mL) was sprayed

on the leaf surface and stems until the suspension began to drip. The plants were kept in a greenhouse under 80% relative humidity at 22 °C for eight days. Anthracnose severity was evaluated using the 1–9 scale developed by Schoonhoven & Pastor-Corrales (1987). The experiment followed a randomised complete block design with four replicates, with each plot consisting of four plants, and was carried out twice with a one-week interval between repetitions. The data from both experiments were tested for normality (Shapiro & Wilk, 1965) and homoscedasticity (Bartlett, 1937). They were subjected to analysis of variance (ANOVA) (Kaufmann & Schering, 2014), and means were compared using the Scott–Knott test ($P \leq 0.05$) (Scott & Knott, 1974) in R 4.4.0 (R Core Team, 2024).

Initial in silico protein selection

The three-dimensional structure of compound **9** was built using Marvin Sketch 19.21 (<http://www.chemaxon.com/marvin>) and subjected to a conformational search with OpenBabel 3.0.0 (O’Boyle et al., 2011), Open3Dalign 2.3 (Tosco et al., 2011), and Mopac2016 (<http://OpenMOPAC.net/>, Version 22.234L, J.J.P. Stewart, Stewart Computational Chemistry, Colorado Springs, CO, USA), as described for other organic compounds (Mota et al., 2017). All conformations representing at least 1.5% of the total conformations, according to the Boltzmann distribution, were used by LiSiCa 1.0.1 (Lešnik et al., 2015) to search for similar three-dimensional structures in the Ligand Expo database (Feng et al., 2004) (<http://ligand-expo.rcsb.org/>). All proteins with ligands presenting a Tanimoto score ≥ 0.5 , that is, ligands located in protein cavities but not chemically bound to the proteins, were selected for the next stage of computational work. Multiple alignments of the amino acid sequences of the proteins were performed by applying the Clustal Omega 1.2.4 algorithm (Sievers et al., 2011), contained in Ugene 39 (Okonechnikov et al., 2012). The same computer program was used to calculate the Hamming dissimilarity (%) by considering the gaps, and the similarity (%) was determined as $100 - \text{Hamming dissimilarity} (\%)$. When a pair of amino acid sequences had 100% similarity, one of the components of the pair was excluded. The remaining sequences were employed in searches of *Colletotrichum* spp. (taxid:5455) genomes

contained in the standard databases of the National Center for Biotechnology Information-NCBI (Sayers et al., 2025). For this purpose, Blastp 2.14.1+ (Altschul, 1997; Schaffer, 2001) was used. Only proteins with total scores equal to or greater than 200 in relation to the protein sequences translated from the *Colletotrichum* spp. genomes were selected for the next part of the study.

Molecular docking

The three-dimensional structure of the biological unit of the proto-oncogene serine/threonine-protein kinase (PIM-1) 3T9I (Nishiguchi et al., 2011), produced by *Homo sapiens*, and the structures of other PIM-1 sharing 100% amino acid sequence similarity with 3T9I were downloaded from the RCSB Protein Data Bank (Berman, 2000) (<https://www.rcsb.org>). Structures with mutations or missing amino acids in or surrounding the binding site were excluded. The remaining PIM-1 structures were three-dimensionally aligned to the 3T9I structure using Lovoalign 21.027 (Martínez et al., 2007), which was also used to calculate the root mean square deviation of atomic positions (RMSD) between the protein pairs. The pdb files of the selected proteins were converted to pdbqt format using MGLTools 1.5.7rc1 (Morris et al., 2009). Assuming pH 7, OpenBabel 3.0.0 (O’Boyle et al., 2011) was used to add hydrogen atoms to the PIM-1 inhibitors, which were complexed to the three-dimensional structures of the protein in the biological units, and converted to pdbqt format with MGLTools 1.5.7rc1 (Morris et al., 2009). The most stable conformations of compound **9** and the PIM-1 inhibitors were docked to a parallelepiped region measuring $32.29 \times 27.47 \times 29.73 \text{ \AA}^3$ (x, y, z), centred on the binding site of the PIM-1 inhibitors, using QuickVina 2 (Alhossary et al., 2015). Except for exhaustiveness, which was raised to 128, all other program parameters were employed at their default values. The obtained affinity values were subjected to Anderson–Darling’s normality (Marsaglia & Marsaglia, 2004) and Bartlett’s homoscedasticity (Bartlett, 1937) tests. The remaining statistical calculations were performed as described for the *in vivo* test.

Similar procedures were adopted to dock inhibitors and compound **9** to casein kinase II subunit alpha (CK2) 6RCB (Dalle Vedove et al., 2020), dual specificity tyrosine-phosphorylation-regulated

kinase 1A (DYRK1A) 7FHS (Miyazaki et al., 2022), and similar protein structures. The sizes of the docking regions in the proteins measured $30.40 \times 28.55 \times 22.80 \text{ \AA}^3$ (x, y, z) and $26.07 \times 25.83 \times 25.39 \text{ \AA}^3$ (x, y, z) for CK2 and DYRK1A, respectively.

Results and discussion

Curcuminoid synthesis

For compounds **1–8**, the reaction times varied depending on the substituent on the benzaldehyde. For instance, an increasing number of mesomeric electron-releasing methoxyl groups on the benzaldehyde aromatic ring slowed the reaction compared to compounds **2**, **3**, and **4**, which have a halide (a Cl in **3** and **4**, or a Br in **2**) on the same ring. Cl and Br increase the electrophilicity of the carbonyl carbon and make it more susceptible to nucleophilic attack by negatively charged enolates, accelerating the reaction, as previously reported by Mak et al. (2007).

Compounds **1–9** were obtained in yields varying from fair (**1**, 44%; and **4**, 40%) to excellent (**8**, 97%). However, ketones **1a**, **3a**, **4a**, **5a**, and **9a** and alcohols **1b**, **5b**, **8b**, and **9b** were obtained in yields ranging from low (38% for **5b**) to good (67% for **4a**) by the catalytic hydrogenation of **1**, **3**, **4**, **5**, **8**, and **9**. Hydrogenation of **1**, **5**, and **9** produced a mixture of **1a** (39%) and **1b** (45%), **5a** (60%) and **5b** (38%), and **9a** (48%) and **9b** (45%), respectively. Hydrogenation of **3** and **4** produced only saturated ketones **3a** (50%) and **4a** (67%), respectively, while hydrogenation of **8** yielded alcohol **8b** (42%). The alcohols were generally obtained in yields slightly lower than those for the saturated ketones. This difference in the yields of alcohols and saturated ketones is due to the higher chemoselectivity of hydrogenation reactions for carbon–carbon double bonds (C=C) compared to carbonyl (C=O) groups under the conditions used in this study (Mahata et al., 2012). These results are very similar to those previously reported by Vieira et al., (2018) and make the approach suitable for scaling up the synthesis of compounds **1–9** and converting them into derivatives **1a**, **1b**, **3a**, **4a**, **5a**, **5b**, **8b**, **9a**, and **9b**.

In vitro assay with *C. lindemuthianum*

Compound **9** (https://www.ebi.ac.uk/chembl/compound_report_card/CHEMBL128729) was the most active against *C. lindemuthianum*. Its MIC (62.5 µg/mL) resembled that of the commercial fungicide thiophanate-methyl (60.9 µg/mL) under the same conditions (Table 1). When the C=C double bond or the ketone carbonyl of compound **9** was hydrogenated, yielding compounds **9a** and **9b**, respectively, the antifungal activity decreased, as the MIC increased to two and four times that obtained for compound **9**, respectively. However, when the C=C double bond or ketone carbonyl of compound **1** was hydrogenated, generating compounds **1a** and **1b**, respectively, the antifungal activity increased because the MIC fell to 25% of the value observed for compound **1**. Similarly, the MIC was reduced by at least 50% when compound **4a** was obtained from compound **4**. These results suggest that electron-withdrawing groups (such as F, Br, and NO₂) at the *ortho* position (R¹ or R⁵ group) relative to the carbon chain linked to the aromatic ring increase the antifungal activity after C=C double bond or ketone carbonyl hydrogenation.

Table 1 Minimum inhibitory concentration (MIC) of curcuminoids in an *in vitro* assay carried out with *Colletotrichum lindemuthianum*

Curcuminoid	MIC (µg/mL)
1	500.0
1a	125.0
1b	125.0
2	500.0
3	500.0
3a	> 500.0
4	> 500.0
4a	250.0
5	> 500.0
5a	500.0
5b	> 500.0
6	500.0
7	125.0
8	250.0
9	62.5
9a	125.0
9b	250.0
Thiophanate-methyl (positive control)	60.9

In vivo assay with common bean inoculated with *C. lindemuthianum*

Compound **9** provided the best result *in vitro*; thus we evaluated it *in vivo*. We also tested compound **9a**, a hydrogenated derivative of compound **9**. The *in vivo* results (Table 2) agreed with the *in vitro* results (Table 1). The ratio between the severity values of anthracnose for compound **9** (2.13) and thiophanate-methyl (2.59) was approximately equal to the ratio between the MIC values of compound **9** (62.5 µg/mL) and thiophanate-methyl (60.9 µg/mL). A similar behaviour was observed for compound **9a** compared to thiophanate-methyl, whose corresponding ratios between their severities and MIC values were approximately equal to 2. Furthermore, these results confirm that compound **9** is the most promising for controlling *C. lindemuthianum* infection in common bean. First isolated from the rhizomes of *Curcuma longa* L. (Masuda et al., 1993), compound **9** (curcumin A) has been extensively studied in the treatment of human diseases (Meng et al., 2026). However, its antifungal activity has not yet been reported.

Curcumin (**I**, 16.9%), in combination with ar-turmerone (35.03%), demethoxylcurcumin (**II**, 15.22%), and bisdemethoxylcurcumin (**III**, 14.03%), has been effective in controlling litchi anthracnose caused by *C. gloeosporioides* in field trials (Bui et al., 2021). Curcumin (**I**), demethoxylcurcumin (**II**), and bisdemethoxylcurcumin (**III**) at concentrations between 0.4 and 100 µg/mL also effectively inhibit the mycelial growth of three red pepper anthracnose pathogens: *C. coccodes*, *C. gloeosporioides*, and *C. acutatum* (Cho et al., 2006). Therefore, the antifungal potential of curcumin (**I**) and curcuminoids **II** and **III** against *Colletotrichum* spp. is well-reported. However, this

is the first report on the antifungal activity of MKCs against *C. lindemuthianum*. Compound **9** (or curcumin A, Fig. 2), the most active MKC against *C. lindemuthianum*, is the monocarbonyl analog of curcumin (**I**, Fig. 1). The similarities between the structures of curcumin (**I**) and curcumin A (**9**) indicate that curcumin A could also be active against other *Colletotrichum* spp. Conversely, the results of this study indicate that curcumin (**I**) and curcuminoids **II** and **III** are also active against *C. lindemuthianum*.

Initial in silico protein selection

When we searched for protein ligands with three-dimensional structures resembling that of compound **9**, we identified 14 proteins. Only three of these proteins—3T9I, 6RCB, and 7FHS—provided scores above 200 when aligned with the amino acid sequences extracted from *Colletotrichum* spp. genomes. The similarity of the three-dimensional structures of compound **9** and the inhibitors of these proteins suggests that compound **9** also inhibits them (Fernández-Torras et al., 2022; Kubinyi, 2002). Furthermore, the amino acid sequences of 3T9I, 6RCB, and 7FHS resemble the amino acid sequences of enzymes produced by *Colletotrichum* spp.; thus, inhibitors of the proteins may also inhibit analogous enzymes in *Colletotrichum* spp. because closely related amino acid sequences usually indicate structural similarity, particularly in the active sites or binding domains of proteins (Jemth, 2025; Kennedy et al., 2022).

Molecular docking

Docking compound **9** in the binding sites of the three-dimensional structures of PIM-1 showed that this compound has an intermediate affinity for PIM-1 (-8.8 ± 0.4 kcal/mol) compared to PIM-1 inhibitors (Fig. 3). For inhibitors LXG and HUL, which afforded affinities similar to that calculated for compound **9**, the values were -8.8 ± 0.8 and -8.7 ± 0.6 kcal/mol, respectively. The inhibitors with the strongest affinity for the enzyme were 26L, STU, and IOB, with values of -11 ± 1 , -10.9 ± 0.6 , and -10.8 ± 0.6 kcal/mol, respectively. Those with the weakest affinity for the enzyme were 985, 971, and 596, all with values of -1.2 ± 0.1 kcal/mol. Therefore, compound **9** may also inhibit PIM-1.

Table 2 Severity of anthracnose caused by *Colletotrichum lindemuthianum* in common bean (*Phaseolus vulgaris* L.) treated with compounds **9** (curcumin A) and **9a**

Treatment	Severity*
Water (control)	7.34a
Aqueous Tween 80 (control)	7.31a
9	2.13c
9a	5.81b
Thiophanate-methyl (control)	2.59c

* Means followed by the same letter do not differ statistically according to the Scott–Knott test ($P < 0.05$)

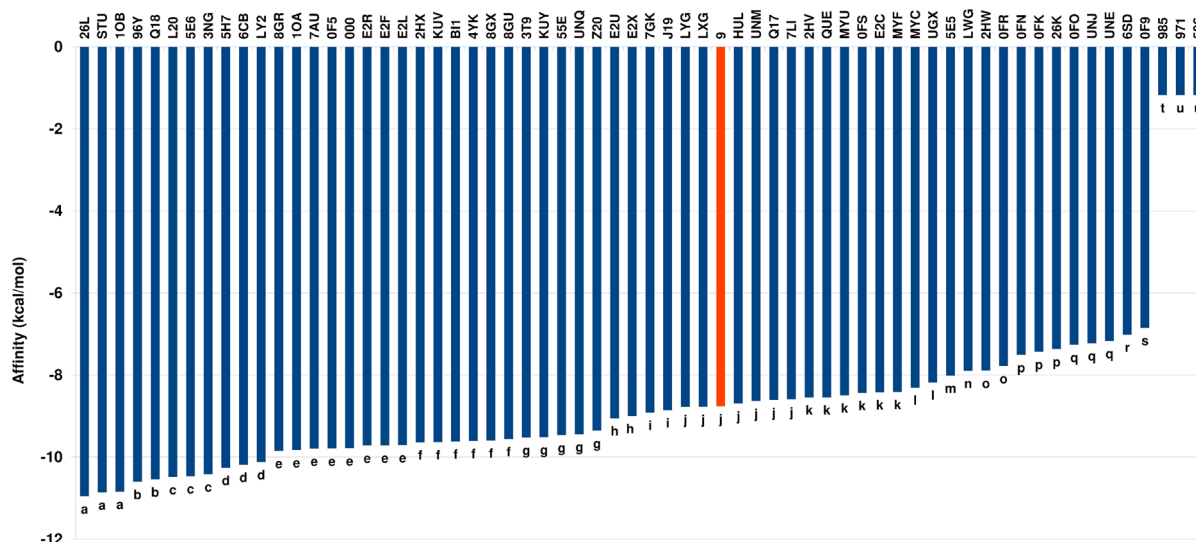


Fig. 3 Affinities of compound **9** and inhibitors of the proto-oncogene serine/threonine-protein kinase (PIM-1) for PIM-1, according to calculations performed with QuickVina 2 (Alhossary et al., 2015). Bars with the same letters correspond to

statistically equal affinities according to the Scott–Knott test at 5% significance. The three-letter and/or number codes correspond to PIM-1 inhibitors according to the RCSB Protein Data Bank (<https://www.rcsb.org>)

The results for the docking of compound **9** in the binding sites of CK2 (Fig. 4) were similar. Compound **9** showed an affinity of -8.8 ± 0.7 kcal/mol, while the inhibitors with values closest to that calculated for compound **9**, K1B and JWQ, showed

values of -8.9 ± 0.6 and -8.8 ± 0.6 kcal/mol, respectively. The lowest and highest affinity values were calculated for ligands E1B (-10.6 ± 0.8 kcal/mol) and V55 (-6.2 ± 0.2 kcal/mol), respectively.

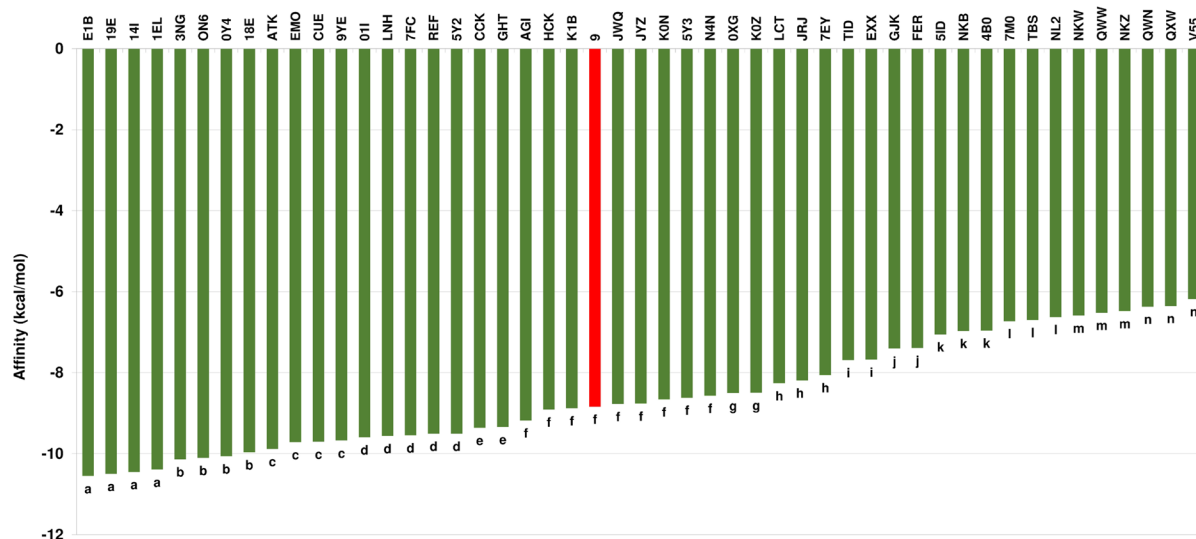


Fig. 4 Affinities of compound **9** and casein kinase II subunit alpha (CK2) inhibitors for CK2, based on calculations performed with QuickVina 2 (Alhossary et al., 2015). Bars with the same letters correspond to statistically equal affinities

according to the Scott–Knott test at 5% significance. Three-letter and/or number codes correspond to CK2 inhibitors according to the RCSB Protein Data Bank (<https://www.rcsb.org>)

Similarly, the affinity of compound **9** for the DYRK1A site was -8.7 ± 0.6 kcal/mol, while the enzyme inhibitors with affinities closest to that calculated for compound **9**, JHW and HRM, had values of -8.8 ± 0.9 and -8.7 ± 0.8 kcal/mol, respectively (Fig. 5). The lowest and highest affinity values were calculated for inhibitors B6N (-11.1 ± 1.3 kcal/mol) and ANP (-4.8 ± 2.2 kcal/mol), respectively.

These results suggest that compound **9** can inhibit multiple protein kinases in the fungus, aligning with the prediction of Pharos (Kelleher et al., 2023), a user interface to the Knowledge Management Center (KMC). According to a prediction made by Pharos (<https://pharos.nih.gov/targets>), on September 27, 2024, compound **9** inhibits the following kinases: nuclear factor kappa-B kinase subunits alpha and beta, hepatocyte growth factor receptor, NF-kappa-B essential modulator, RAC-alpha serine/threonine-protein kinase, epidermal growth factor receptor, glycogen synthase kinase-3 beta, tyrosine-protein kinase SYK, and calcium/calmodulin-dependent protein kinase type II subunit alpha.

Protein phosphorylation by protein kinases constitutes an essential means of transducing extracellular signals into the cell nucleus (Lee & Adams, 1995) and regulates the functions of proteins involved in

fungal processes (Dickman & Yarden, 1999). For example, protein kinases are essential for the pathogenicity of *Colletotrichum* spp. in plants (Jiang et al., 2022). Consequently, protein kinase inhibitors have been studied for the development of antifungals (Heinisch, 2005). This has led to the selection of *N*-substituted diaminopyrimidine, sorafenib derivatives, thiadiazole derivatives, pyrazole derivatives, and fludioxonil as antifungals that act by inhibiting protein kinases (Sun et al., 2023). However, the action of curcuminoids against fungi through protein kinase inhibition has not yet been reported.

Conclusions

The screening of nine MKCs obtained through CSC and nine of their alcohols and saturated ketone derivatives enables the identification of curcumin A (**9**) as the most active compound against *C. lindemuthianum* in the *in vitro* tests, with a MIC of $62.5 \mu\text{g/mL}$, a value similar to that observed for the commercial fungicide thiophanate-methyl ($60.9 \mu\text{g/mL}$). In an experiment with bean seedlings, curcumin A at a concentration of 0.72 mg/mL reduced anthracnose severity from 7.34 to 2.13, while thiophanate-methyl at a

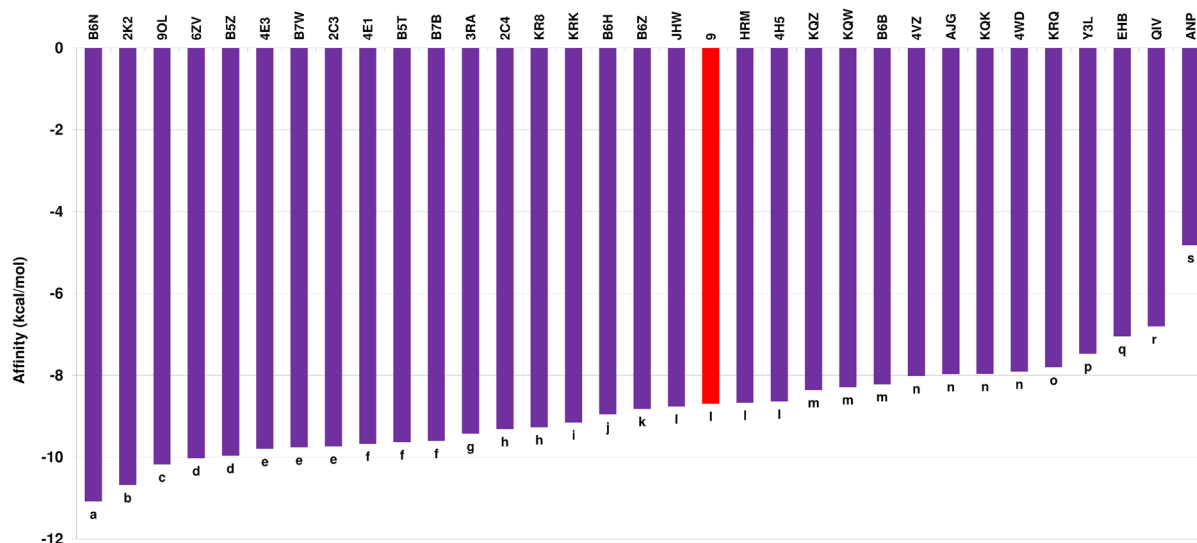


Fig. 5 Affinities of compound **9** and dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A) inhibitors for DYRK1A based on calculations performed with QuickVina 2 (Alhossary et al., 2015). Bars with the same letters corre-

spond to statistically equal affinities according to the Scott-Knott test at 5% significance. Three-letter codes and/or numbers correspond to DYRK1A inhibitors according to the RCSB Protein Data Bank (<https://www.rcsb.org>)

concentration of 0.7 mg/mL reduced the severity to 2.59. Therefore, curcumin A shows potential for use in the development of a new fungicide controlling *C. lindemuthianum*. An in silico search for protein ligands with chemical structures similar to curcumin A resulted in the selection of organic compounds complexed to 14 proteins, among which only three kinases possessed amino acid sequences similar to those found in *Colletotrichum* spp. genomes. Molecular docking of curcumin A and inhibitors of these kinases at their active sites revealed that curcumin A has affinities for these enzymes with values that are intermediate between those calculated for the inhibitors. Therefore, the in silico study suggests that compound **9** inhibits several protein kinases, its probable targets in the fungus.

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Data availability All data generated or analysed during this study has been included in the published article or in its supplementary material. There are no additional data that were generated as part of this study. If there is any further information needed regarding the data, please contact the corresponding author.

Declarations

Ethics approval, consent to participate and human and animal rights Not applicable.

Consent for publication All authors approve the publication of the manuscript and the associated data.

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