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Cyclobutane Carboxamide Inhibitors of Fungal Melanin: Biosynthesis and their Evaluation as Fungicides

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Abstract—A new fungicide lead has been identified by enzyme screening of a focused combinatorial library. The lead compound **4**, a potent inhibitor of scytalone dehydratase (SD), exhibits fungicidal activity upon foliar application but does not show systemic activity. The X-ray crystal structure of the enzyme–inhibitor complex and an appreciation for the relationship between physical properties and systemic activity enabled us to rapidly improve upon this initial lead. The geminal halogen–methyl group combination was found to be optimal for interaction with the bounding serine and asparagine side-chain residues. Replacement of CF_3 with methyl was a key discovery, giving inhibitors with slightly diminished enzyme inhibition potency while significantly increasing systemic activity. Amides prepared from amines with 2,4-dichloro substitution on the phenyl ring gave the most potent enzyme inhibitors. Two compounds from this series showed systemic activity comparable to the commercial standard and were selected for outdoor testing in flooded plots which simulate rice paddies.

Introduction

Blast disease, caused by the pathogen *Pyricularia grisea*,[1] is a major cause of damage to growing rice plants, resulting in decreased per acre yield of grain. Consequently, the discovery of fungicides able to control blast disease is an important objective for many agrochemical businesses. Desirable attributes of rice blasticides are high intrinsic potency, systemic activity, low toxicity to non-pathogens, and the absence of growth-stunting effects on the crop plant. Interference in a mechanism by which a pathogen infects its host, rather than intervention in the biological processes common to all higher organisms, is an attractive strategy. In order to infect its host, *P. grisea* must melanize an infection structure (the appresorium) to penetrate the leaf surface.[2] Consequently, the enzymes of the melanin biosynthetic pathway are biochemical targets for the design of rice blasticides.

The fungal melanin biosynthesis pathway includes a series of successive reductions and dehydrations of 1,3,6,8-tetrahydroxynaphthalene to yield 1,8-dihydroxynapthalene, the last identified precursor of fungal melanin. Scytalone dehydratase (SD) catalyzes the dehydration of scytalone and vermelone in this pathway.[3] Carpropamid (**1**) (Fig. 1), a potent inhibitor of SD catalytic activity, has recently been commercialized by Bayer as an agricultural fungicide useful for the control of rice blast.[4] Two additional inhibitors of SD, diclocymet (**2**)[5] and AC 382042 (**3**),[6] have been announced as rice fungicides under development. Carpropamid is characterized by high selectivity toward the target pathogen and low toxicity to mammals and fish.[4a] Refined, high-resolution structures of SD-inhibitor complexes have been obtained,[7] and the detailed structural information has enabled structure-based design of novel inhibitors.[8] We have reported the successful application of combinatorial chemistry and in vitro screening for the identification of a novel scytalone dehydratase inhibitor, **4**.[9] We report here the results of our efforts to optimize systemic activity of this potent in vitro inhibitor.

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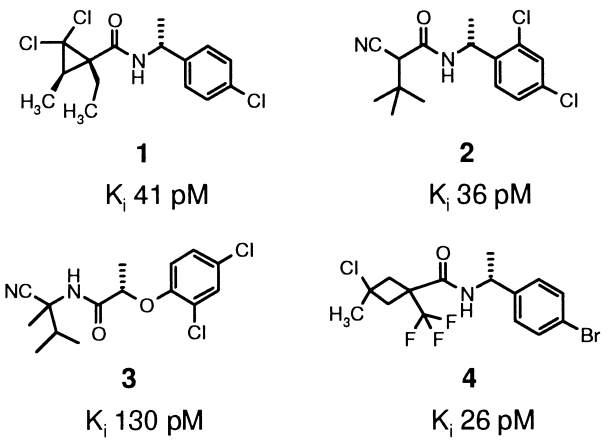


Figure 1. Inhibitors of scytalone dehydratase (SD).

Results and Discussion

While the lead compound **4** shows strong in vitro potency and exhibits good in vivo fungicidal activity upon foliar application, it lacks systemic activity. Thus, we sought to alter the structure of **4** in such a way as to impart systemic activity while maintaining SD inhibition potency. Soil uptake and translocation within the plant are related to hydrophobicity and our experience is that a partitioning coefficient between octanol and water (LogP) of 3.0 to 4.0 is optimal for systemic activity. Thus, our strategy was to use our understanding of the interaction of the inhibitor with the protein-binding site to design less lipophilic yet potent inhibitors.

The crystal structure of **4** bound to SD was solved at 1.8 Å resolution and provided an excellent model of the inhibitor binding pocket.[9] Major interactions with hydrophilic residues are shown in Figure 2. The crystal structure implies hydrogen bonding interactions between the inhibitor amide N1 and a bound water molecule and between the amide O and the hydroxyl group of the Tyr50 side-chain. Investigations of other SD inhibitors by our group have shown that this hydrogen bonding network provides considerable energy of binding and modifications that disrupt this network are often deleterious.[8a] The crystal structure also shows the chlorine and methyl substituents of the cyclobutane ring oriented towards the Asn131 side chain of SD, apparently making a complimentary electrostatic interaction. These substituents do not completely fill their respective binding pockets. The trifluoromethyl group, phenyl group and bromine atom occupy lipophilic pockets. The trifluoromethyl group is directed towards the π-face of Phe53, which has been implicated as an important recognition element for SD inhibitors.[7a,8] A Connolly surface[10] (Fig. 3) of the inhibitor binding pocket shows that there was an unoccupied region accessible from the 2-position of the aromatic ring of **4**. This pocket could accommodate one or two heavy atoms. Additionally, examination of the overlay of crystal structures of SD-inhibitor complexes from other analogue series demonstrated the potential for side chains of the protein residues in this region to move.[8c]

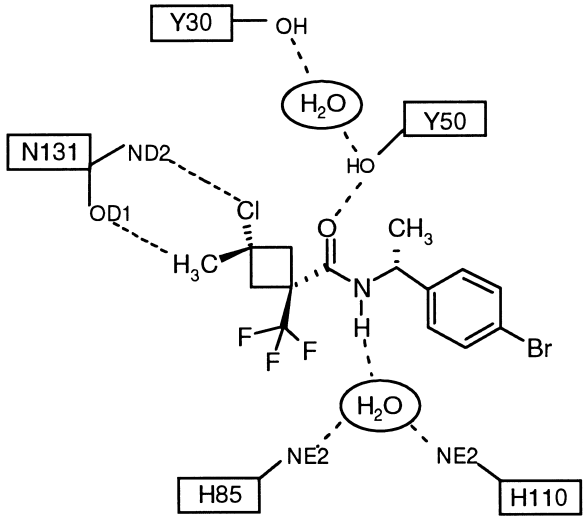


Figure 2. A schematic drawing of the interactions between **4** and SD.

Chemistry

Cyclobutane carboxylic acid **10** was synthesized following the procedure of Hall et al.[11] with some minor modifications (Scheme 1). Thermolysis of the cyanohydrin acetyl ester **7** in a Pyrex tube packed with helices gave the trifluoromethylacrylonitrile **8**. Thermal cycloaddition of allene with **8** at 200 °C afforded product in only 25% yield following distillation. The nitrile was hydrolyzed with base, and the resulting acid was reacted with concentrated aqueous HCl to give the acid **10** as a 1:1 mixture of isomers. Alternatively, **9** could be converted directly to **10** by reaction with concentrated HCl in a pressure vessel heated to 100 °C.

Replacement of CF_3 with other substituents was achieved by analogous 2+2 cycloadditions. The 3-chloro-1,3-dimethylcyclobutane carboxylic acid **16** was synthesized following a similar route (Scheme 2). Cycloaddition of either methacrylonitrile or ethyl methacrylate with allene afforded the corresponding methylene cyclobutanes **12** or **15** in 23–30% yield. ^{1}H NMR of the crude products prior to distillation indicated that the major product was octahydronaphthlene **13**, which results from the cascade [4+2] cycloaddition of methacrylonitrile with the dimer of allene, 1,2-dimethylene cyclobutane.[12] Repeating the reaction with an excess of ethyl methacrylate was operationally simpler and gave the desired product **15** in 41% yield. Carboxylic acid **19** was prepared from 2-chloroacrylonitrile following a similar route (Scheme 2).

Fluoromethyl acrylate ester **22** was prepared as shown in Scheme 3. This intermediate was reacted with allene following the standard procedure but the crude reaction mixture contained little or none of the desired cyclobutane **23** as judged by ^{1}H NMR. The cyclobutane carboxylic acid **26** was prepared by alkylation of the dianion of 3-methylenecyclobutane carboxylic acid with ethyl iodide followed by hydrolysis with HCl (Scheme 4).

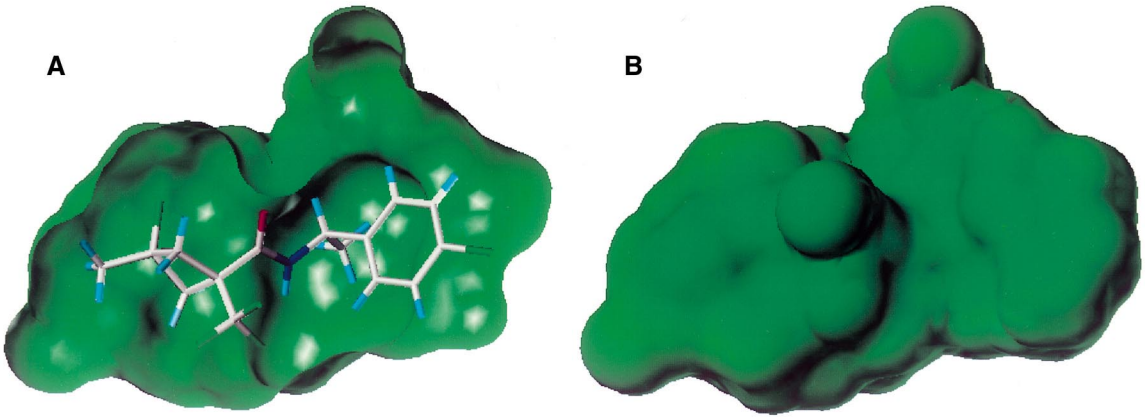
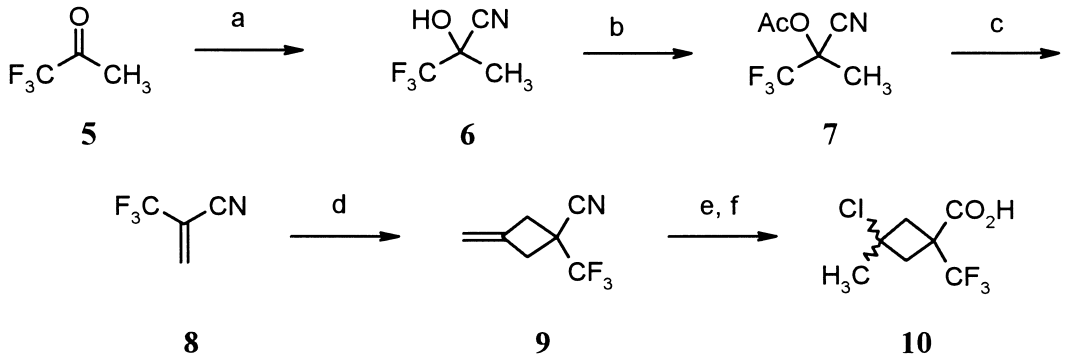
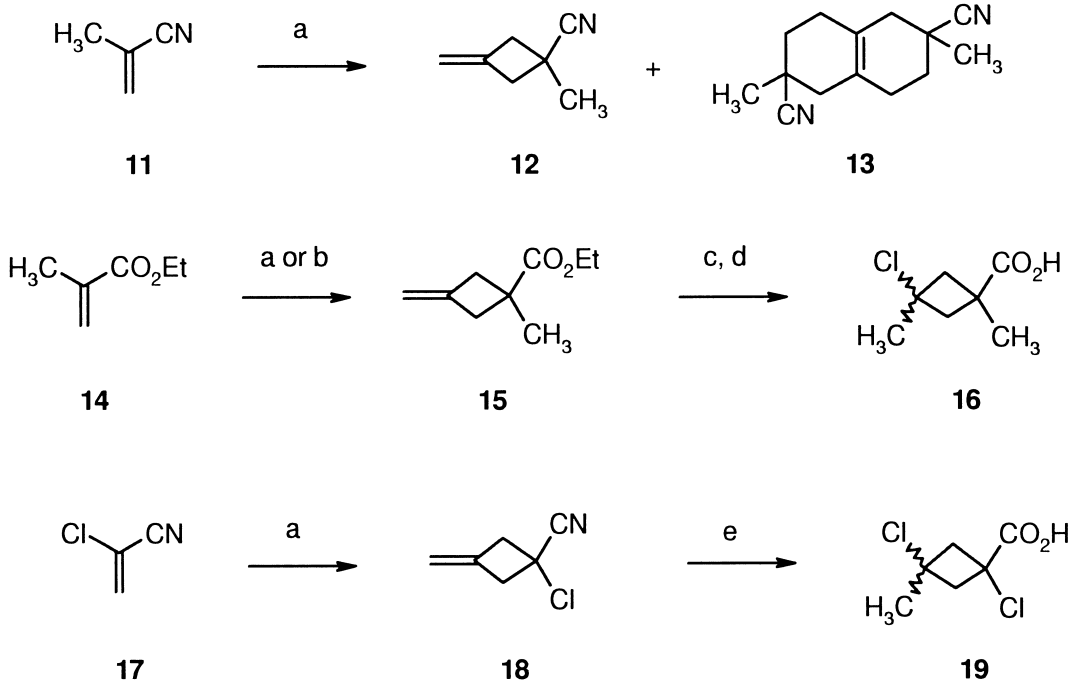


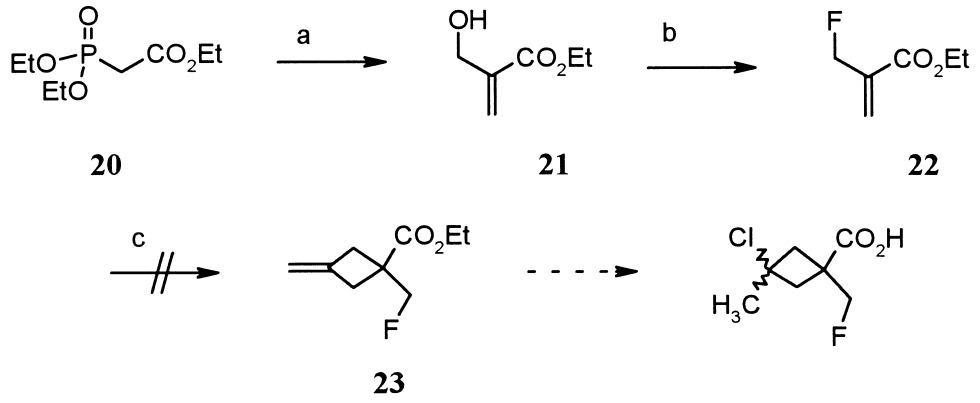
Figure 3. (A) Cross section of the Connolly surface of the SD binding pocket showing **4**. (B) Connolly surface of the SD binding pocket generated from the crystal structure of the SD-**4**.



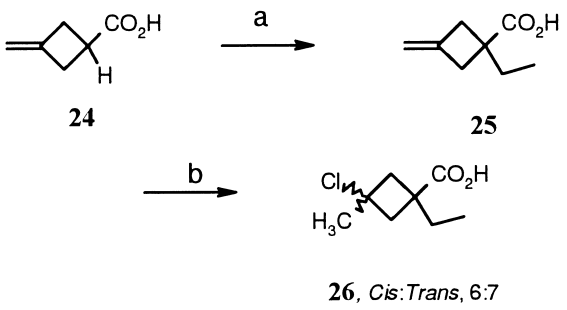
Scheme 1. Synthesis of cyclobutane carboxylic acid **10**. (a) KCN, H_2SO_4, 60%; (b) AcCl, reflux, 84%; (c) pyrolysis at 520 °C, 66%; (d) allene (1.6 equiv), hydroquinone (catalytic), benzene, 200 °C, 25%; (e) NaOH, H_2O, 100 °C, 96%; (f) concd HCl, rt, 68%.



Scheme 2. Synthesis of cyclobutane carboxylic acids **16** and **19**. (a) Allene (1.66 equiv), hydroquinone (catalytic), benzene, 200 °C, 23–30%; (b) allene (0.25 equiv), hydroquinone (catalytic), benzene, 200 °C, 41%; (c) NaOH, H_2O, 100 °C, quantitative; (d) concd HCl, rt, 77%; (e) concd HCl, 100 °C, 40%.



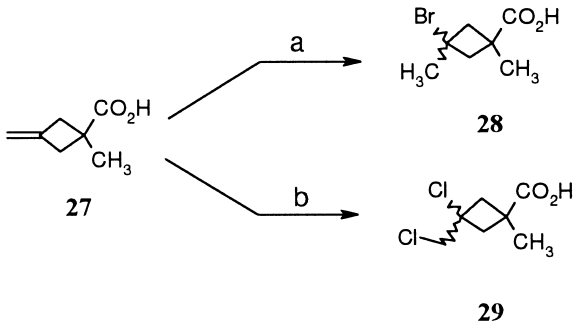
Scheme 3. Attempted preparation of fluoromethyl cyclobutane carboxylic acid. (a) Formaldehyde, H_3PO_4, K_2CO_3, 69%; (b) DAST, CH_2Cl_2, 45%; (c) allene, hydroquinone (catalytic), benzene, 200 °C.



Scheme 4. Preparation of cyclobutane carboxylic acid **26**. (a) LDA, THF, then EtI, 68%; (b) concd HCl, 100%.

Owing to the ring strain of the cyclobutane ring, the methylene group of intermediate **27** was highly reactive. Hydrogen bromide was added across the double bond at room temperature (Scheme 5). Chlorination of **27** using dichloroiodobenzene gave the chloro-chloromethyl cyclobutane carboxylic acid **29**. The product **29** was shown to be a 1:1 mixture of isomers by ^{1}H NMR.

Substituents other than methyl were introduced into the cyclobutane 3-position by the following route (Scheme 6). 3-Methylene cyclobutane carboxylic acid **27** was reacted with ozone, and the intermediate ozonide was decomposed with dimethylsulfide to give the cyclobutanone **30**. The cyclobutanone was reacted with ethylmagnesium bromide and lithium TMS acetylide to give the hydroxy compounds **31** and **32**, respectively. The TMS group of **32** was removed by basic hydrolysis. The 3,3-difluoro analogue **35** was prepared by reaction of the cyclobutanone **34** with DAST.



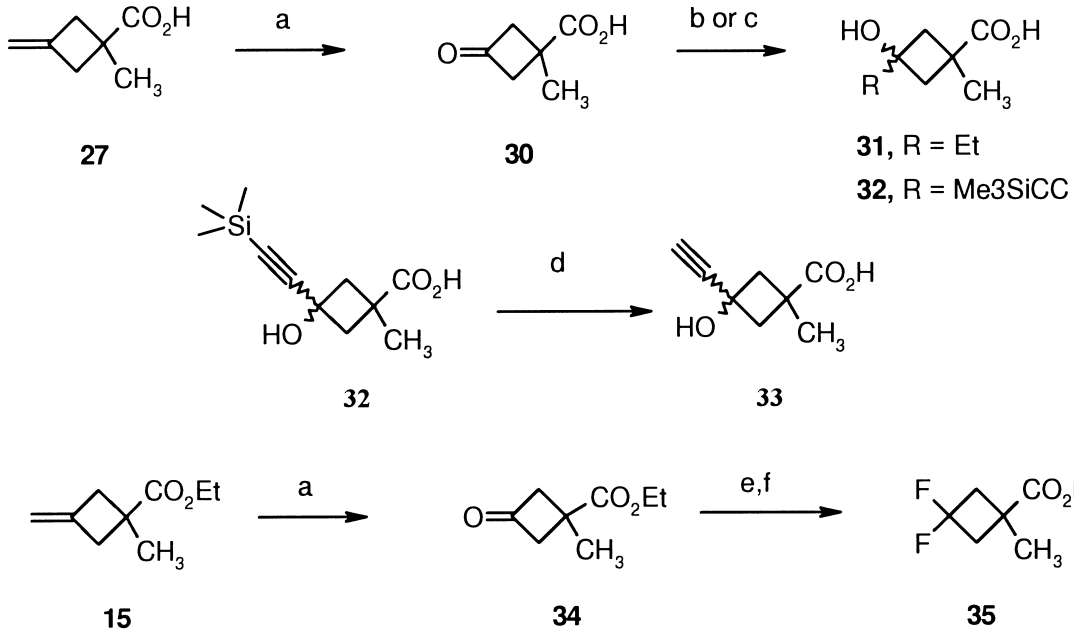
Scheme 5. Synthesis of substituted cyclobutanecarboxylic acids **28** and **29**. (a) HBr, 66%; (b) dichloroiodobenzene, CH_2Cl_2, 46%.

The cyclobutane carboxylic acids were converted to their corresponding acid chlorides using either thionyl chloride or oxalyl chloride/DMF for acylation of amines (Scheme 7). Where possible, *cis* and *trans* isomers of the formed amides were separated by chromatography. The identity of the separate isomers was determined by NOE experiment. Typically, the isomer with the lower R_f has the halogen substituent *cis* to the carboxamide functionality.

Biological evaluation

Cyclobutane carboxamides were evaluated for activity in an SD inhibition assay[8a] and in vivo for their ability to protect rice plants from infection by *P. grisea* (Tables 1–3). The soil systemic assay rates disease control of rice seedlings in flooded culture tubes 7–10 days after inoculation with *P. grisea*. The SD inhibiting fungicide carpropamid is included for comparison (Table 1, entry 6).

1-Trifluoromethylcyclobutane carboxamides. The *cis* and *trans* isomeric forms of the substituted cyclobutane ring have a significant effect on activity (Table 1, entries 1 and 2). The isomers with the chlorine atom *cis* to the carboxamide functionality are typically 10-fold more potent than the *trans* isomers. The model of the SD-inhibitor complex clearly shows the interaction of the chlorine substituent on the cyclobutane ring with the Asn131 side-chain carboxamide. Though we cannot ascertain the orientation of the Asn131 side-chain carboxamide from the X-ray crystal structure of the SD-inhibitor complex, we hypothesize that the observed significant preference for binding of the *cis* isomer pairs the 3-chlorine atom with the NH_2 on the Asn131 side-chain. 2,4-Disubstitution with chlorine on the phenyl ring increases potency of enzyme inhibition by a small extent, as anticipated. Extension of the bridge between the amide and phenyl group from one to three atoms is tolerated (**39**). However, with the three atom spacer, substituents in the 4-position of the phenyl ring are not tolerated (data not shown). Instead 2- and 2,5-disubstitution is best.[8b,c] The *R*-configuration of the chiral

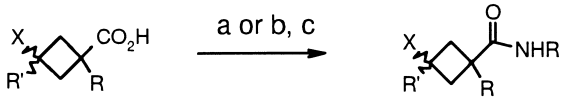


Scheme 6. Preparation of cyclobutane carboxylic acids **31**, **33** and **35**. (a) O_3, CH_2Cl_2, then $(CH_3)_2S$, 78%; (b) EtMgBr, THF, 64%, *cis* and *trans* isomers separated by chromatography; (c) lithium TMS acetylide, THF, 85%, *cis* and *trans* isomers separated by chromatography; (d) NaOH, MeOH, 70%; (e) DAST, CH_2Cl_2; (f) NaOH, H_2O, 100 °C, 43% (two steps).

center was found to be critical for good binding and disease control.

In all cases, 1-trifluoromethylcyclobutane carboxamides, while being potent enzyme inhibitors, and having foliar disease control, lacked systemic activity. This is consistent with our experience that a LogP higher than 4.0 frequently precludes plant translocation. The LogP of **37** was determined to be 4.25 by high performance liquid chromatography (HPLC). Therefore, we focused on making changes to the substituents on the cyclobutane ring which would decrease lipophilicity.

Cyclobutane modification. A series of cyclobutane carboxylic acids were synthesized and coupled to (*R*)-1-(4-bromophenyl)ethylamine (Table 2). Deletion of substituents on C1 or C3 has a deleterious effect on enzyme inhibitory potency (**40** and **41**). Replacement of CF_3 with halogen gives good enzyme inhibitors which lacked systemic activity (**42** and **44**), presumably due to higher lipophilicity. Replacement of CF_3 with methyl gives an inhibitor with slightly diminished potency (**45**). However, this modification significantly improved its systemic activity. **45** protected rice plants from *P. grisea* infection in the systemic test at 3 ppm concentration whereas **4** failed to protect the plants from infection at that rate.



Scheme 7. Preparation of cyclobutane carboxamides (a) (i) $(COCl)_2$, cat. DMF, CH_2Cl_2; (ii) RNH_2, Et_3N; (b) (for X=OH) EDC, RNH_2, Et_3N; (c) separate isomers by chromatography.

Since the crystal structure showed room in the binding pocket adjacent to the C3-methyl on the cyclobutane ring, we sought analogues with larger, lipophilic substituents here. We reasoned that the decrease in lipophilicity made by making the switch from CF_3 to methyl would balance the lipophilicity increase of larger C3 substituents. Modeling indicated that the chloromethyl group *trans* to the carboxamide group would be well accommodated. Surprisingly, both *cis* and *trans* isomers are very potent inhibitors of SD (**46** and **47**). Perhaps protein side chains bounding the upper side of the cyclobutane binding pocket are able to move to accommodate the chloromethyl group of **46** in a fashion that

Table 1. Inhibition of SD and control of blast disease in systemic assays by 1-trifluoromethyl cyclobutane carboxamides

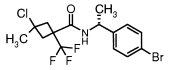
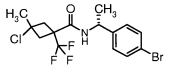
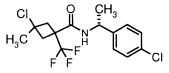
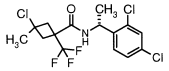
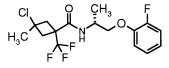
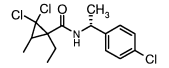
Compd no.	Structure	K_i (nM)	Systemic assay
4		0.026 ± 0.002	68 at 3 ppm 50 at 0.8 ppm 0 at 0.2 ppm
36		0.43 ± 0.03	13 13 0
37		0.067 ± 0.002	82 35 31
38		0.011 ± 0.001	0 0 0
39		0.350 ± 0.030	64 0 0
1		0.041 ± 0.001	98 78 27

Table 2. Inhibition of SD and control of blast disease in systemic assays by cyclobutane carboxamides

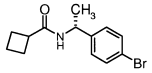
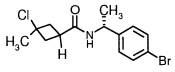
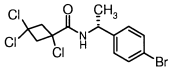
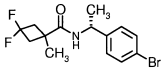
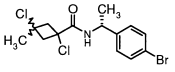
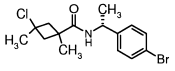
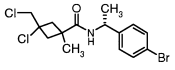
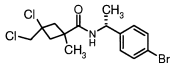
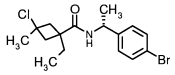
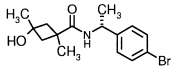
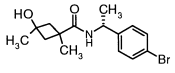
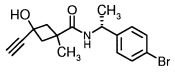
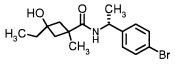
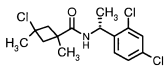
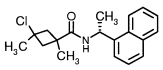
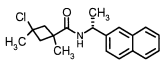
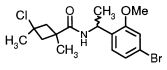
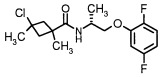
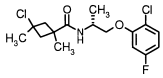
Compd no.	Structure	K_i (nM)	Systemic assay
40		520 ± 50	Not tested
41		44 ± 1	Not tested
42		0.45 ± 0.009	17 at 3 ppm 0 at 0.8 ppm 0 at 0.2 ppm
43		6 ± 0.3	93 0 0
44		0.310 ± 0.02	46 0 0
45		0.100 ± 0.005	99 38 22
46		0.027 ± 0.001	96 0 31
47		0.016 ± 0.002	93 79 0
48		0.021 ± 0.003	Not tested
49		480 ± 40	Not tested
50		16 ± 1	Not tested
51		28 ± 0.5	Not tested
52		3.2 ± 0.1	Not tested

Table 3. Inhibition of SD and control of blast disease in systemic assay by 1-methylcyclobutane carboxamides

Compd no.	Structure	K_i (nM)	Systemic assay
53		0.012 ± 0.003	98 at 3 ppm 100 at 0.8 ppm 48 at 0.2 ppm
54		3.2 ± 0.2	0 0 0
55		0.016 ± 0.002	93 0 25
56		0.030 ± 0.002	100 100 98
57		0.420 ± 0.02	99 65 16
58		0.057 ± 0.008	21 0 0

was not anticipated by modeling experiments. Alternatively, the inhibitor may adopt a new orientation that shifts the position of the cyclobutane relative to the binding pocket.

Although we observed that hydrogen accepting substituents on the cyclobutane ring are making favorable contacts with the hydrogen donating carboxamide NH_2 of Asn131 (Fig. 2), we were interested to see if hydrogen donating substituents might donate a hydrogen to the carboxamide carbonyl. We were able to make a number of cyclobutane carboxamides substituted with hydroxyl groups (**49**–**52**). However, in all cases potency was adversely affected. Presumably the increased cost to desolvate the more hydrophilic inhibitors contributed to the poor inhibition constants observed.

Amine modification. The phenyl group occupies a hydrophobic region of the SD inhibitor binding pocket. A large number of analogues made on other series of SD inhibitors[8b,c] delineates the modifications and substitution patterns tolerated in this region of the enzyme active site. Accordingly, we synthesized a small set of amines that included those known to afford high inhibitory potency and those that addressed opportunities presented by the steric demands of the binding pocket Connolly surface.

As anticipated, for hydrophobic substituents that are shaped correctly, potency increases with increased buried hydrophobic surface area (**53**, **55** and **56**) (Table 3). Lower activity of the inhibitor **54** prepared from 1-(α-naphyl)ethylamine demonstrates that the hydrophobic pocket cannot accommodate this substituent. Amides prepared from phenoxypropylamines with halogen substitution in a 2,5-configuration gave potent inhibitors that were also found to have good systemic activity (**57**, **58**).

Conclusions

The available model of the enzyme–inhibitor complex and an appreciation for the relationship between physical properties and systemic activity enabled us to focus our synthetic effort on modifications likely to improve activity of our initial lead **4**. The geminal halogen–methyl group combination seemed optimal for electrostatic interaction with the asparagine sidechain bounding the end of the cyclobutane binding pocket. No modification otherwise at the cyclobutane 3-position is superior. Replacement of CF_3 of **4** with methyl was a key discovery, giving inhibitors with slightly diminished enzyme potency but superior systemic activity. Amides prepared from amines with 2,4-dichloro substitution on the phenyl ring gave the most potent enzyme inhibitors. Two compounds from this series (**47** and **55**) were identified as being on par with carpropamid and were selected for outdoor testing in flooded plots which simulate real rice paddies.

Experimental

Methods and materials

Thin-layer chromatography (TLC) and flash chromatography were performed with E. Merck silica gel (230–400 mesh). Compounds were visualized on TLC using 10% phosphomolybdic acid in EtOH. Except where indicated, anhydrous solvents and reagents were used as received. All melting points are uncorrected. ^{1}H NMR spectra, except where noted, were recorded at 300 MHz in $CDCl_3$. ^{19}F NMR spectra were recorded at 282 or 376 MHz in $CDCl_3$. Mass spectra were obtained on a Micromass Platform 2 using atmospheric pressure chemical ionization detection at 3.5 kV positive ion and 2.5 kV negative ion. Accurate mass elemental composition measurements were performed on a Finnigan MAT900XL mass spectrometer using electron multiplier detection at 1.80 kV positive ion and 1.90 kV negative ion.

Starting materials

(*R*)-(+)-1-(4-Bromophenyl)ethylamine was purchased from Fluka Chemie AG, (*R*)-(+)-1-(4-chlorophenyl)-ethylamine was purchased from Celgene, (*R*)-(+)-1-(1-naphthyl)ethylamine was purchased from the Aldrich Chemical Company, and (*R*)-(+)-1-(2-naphthyl)ethylamine was purchased from Fluka Chemie AG. *cis*- and *trans*-3-Chloro-3-methyl-1-trifluoromethylcyclobutane carboxylic acid (**10**), *cis*- and *trans*-3-chloro-1,3-dimethylcyclobutanecarboxylic acid (**16**), 3-methylenecyclobutane carboxylic acid (**24**) and 3-methylene-1-methylcyclobutane carboxylic acid (**27**) were made following the published procedures[11] with minor modifications as described in the text. (*R*)-3-[(2-fluorophenyl)oxy]propyl-2-amine, (*R*)-3-[(2,5-difluorophenyl)oxy]propyl-2-amine, and (*R*)-3-[(2-chloro-5-fluorophenyl)oxy]propyl-2-amine were made following our published procedure.[8b,13] (*R*)-1-(2,4-Dichlorophenyl)ethylamine[14] was prepared from (*R*)-1-(4-chlorophenyl)ethylamine by the method of Polniaszek and Lichti.[15] The known ±1-(4-bromo-2-methoxyphenyl)ethylamine[16] was prepared by Fries rearrangement[17] of 1-acetoxy-3-bromobenzene followed by methylation of the hydroxy group and reductive amination of the resulting ketone.[18]

***cis*- and *trans*-1,3-Dichloro-3-methylcyclobutanecarboxylic acid (19).** 3-Chloro-3-cyanomethylene cyclobutane[19] (**18**) (5.53 g, 43.35 mmole) was dissolved in concentrated aqueous HCl (45 mL). The solution was stirred at rt overnight and then refluxed for another 30 min. The product was extracted from the aqueous layer with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated. 40% Of the desired carboxylic acid was obtained as a 1:1 ratio of isomers which were not separated. ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.64 (s, 3H), 1.86 (s, 3H), 2.90–3.05 (m, 4H), 3.30–3.37 (m, 4H), 13.75 (br s, 2H).

1-Ethyl-3-methylenecyclobutanecarboxylic acid (25). Diisopropyl amine (4.44 g, 6.08 mL, 44 mmol) was dissolved in THF (100 mL) under N_2 and cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 20 mL, 50 mmol) was carefully added and the mixture was stirred at rt for 30 min. To the resulting LDA solution was added 3-methylenecyclobutanecarboxylic acid (2.24 g, 20 mmol) in 10 mL of THF and the mixture was heated at 50 °C for 1 h. The reaction mixture was then cooled to 0 °C, iodoethane (3.10 g, 1.6 mL, 20 mmol) was added, and the resulting mixture was stirred at rt for 2 h. Upon completion of the reaction, THF was removed by evaporation in vacuo, aq NaOH (1M, 100 mL) was added to the residue and excess amine was extracted from the basic aq layer with CH_2Cl_2 (3×50 mL). The aq layer was acidified with concd HCl (∼10 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined CH_2Cl_2 extracts were dried ($MgSO_4$), concentrated in vacuo and purified by chromatography (EtOAc:hexanes, 1:4) to provide a yellow oil (1.90 g, 68%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91 (t, J = 7.4 Hz, 3H), 1.85 (q, J = 7.4 Hz, 2H), 2.56 (m, 2H), 3.14 (m, 2H), 4.86 (m, 2H); MS (APCI$^-$) 139 (M-1).

***cis*- and *trans*-1-Ethyl-3-chloro-3-methylcyclobutanecarboxylic acid (26).** 1-Ethyl-3-methylenecyclobutanecarboxylic acid (**25**) (1.50 g, 10.7 mmol) was added dropwise to a stirred solution of concd HCl (20 mL). The mixture was stirred at rt for 2 h under N_2. The product was extracted with CH_2Cl_2 (3×20 mL) and the combined CH_2Cl_2 extracts were washed with H_2O (20 mL), dried ($MgSO_4$) and evaporated in vacuo to provide a white solid (1.89 g, 100%): mp 54–56 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of *cis* and *trans* isomers) δ 0.89 (t, J = 7.4 Hz, 3H), 1.73 and 1.74 (two s, 3H), 1.81 and 2.01 (two q, J = 7.4 Hz, 2H), 2.35 and 2.57 (two d, J = 13.7 and 14.3 Hz, 2H), 2.87 and 3.09 (two d, J = 13.7 and 14.3 Hz, 2H).

***cis*- and *trans*-3-Chloro-3-(chloromethyl)-1-methylcyclobutanecarboxylic acid (29).** To iodobenzenedichloride[20] (2.4 g, 9.72 mmol) in 9 mL CH_2Cl_2 was added 3-methylene-1-methylcyclobutane carboxylic acid (**27**) (1.0 g, 7.93 mmol) in 2 mL CH_2Cl_2. The solution was stirred at ambient temperature for 1 h, refluxed for 1 h, and allowed to cool. The solution was extracted once with 1 M NaOH and the aq phase was acidified with concd HCl. The product precipitated as an oil upon acidification. The product was extracted with CH_2Cl_2, dried and concentrated to provide the product as a colorless oil (0.71 g, 46%) as an equal mixture of *cis* and *trans* isomers which were not separated: ^{1}H NMR ($CHCl_3$) δ: 1.46 (s, 3H), 1.65 (s, 3H), 2.48 (d, J = 15 Hz, 2H), 2.61 (d, J = 15 Hz, 2H), 3.05 (d, J = 19 Hz, 2H), 3.10 (d, J = 19 Hz, 2H), 3.78 (s, 2H), 3.83 (s, 2H).

1-Methyl-3-oxocyclobutanecarboxylic acid (30). 1-Methyl-3-methylenecyclobutane carboxylic acid (**27**) (3.0 g, 19 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to −78 °C. Ozone from an ozone generator was bubbled through the solution while stirring for 30 min, in which time the reaction mixture turned blue. Oxygen was bubbled through the solution followed by N_2 until the blue color disappeared. Dimethyl sulfide (4.3 mL, 58 mmol) was added to the clear solution and the mixture was stirred overnight at rt. The reaction mixture was washed with H_2O, dried ($MgSO_4$) and evaporated in vacuo to provide the ketone as an off-white solid

(3.8 g, 75%): mp 62–65 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 3H), 2.95 (d, J = 19.6 Hz, 2H), 3.39 (d, J = 19.6 Hz, 2H), 12.65 (s,1H); MS(APCI$^-$) 127 (M-1).

***cis*- and *trans*-3-Ethyl-3-hydroxy-1-methylcyclobutanecarboxylic acid (31).** 1-Methyl-3-oxocyclobutanecarboxylic acid (1.00 g, 7.8 mmol) was dissolved in 15 mL of anhyd THF and cooled to 0 °C under N_2. EtMgBr (1 M in THF, 17.0 mL, 17.0 mmol) was added to the solution dropwise. The mixture was warmed to rt and stirred for 2 h. The reaction mixture was then treated with 1 M HCl to pH 2 and extracted with EtOAc. The combined EtOAc extracts were dried ($MgSO_4$) and evaporated in vacuo to provide the crude product. Purification by column chromatography (EtOAc:hexanes 1:1) provided the *cis* and *trans* isomers: *trans*-isomer, light yellow oil, 0.43 g, 35%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (t, J = 7.2 Hz, 3H), 1.55 (s, 3H), 1.63 (q, J = 7.2 Hz, 2H), 1.97 (d, J = 13.9 Hz, 2H), 2.64 (d, J = 13.9 Hz, 2H). *cis*-isomer, light yellow oil, 0.29 g, 24%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, J = 7.2 Hz, 3H), 1.40 (s, 3H), 1.63 (q, J = 7.2 Hz, 2H), 2.10 (d, J = 14.2 Hz, 2H), 2.52 (d, J = 14.2 Hz, 2H).

***cis*- and *trans*-3-Hydroxy-1-methyl-3-trimethylsilylethynylcyclobutanecarboxylic acid (32).** *n*-BuLi (2.5 M in hexanes, 6.9 mL, 17.2 mmol) was added dropwise to a solution of TMS acetylene (1.70 g, 2.4 mL, 17.2 mmol) in 20 mL of THF under N_2 at −78 °C. The mixture was stirred for 30 min. A solution of 1-methyl-3-oxocyclobutanecarboxylic acid (1.00 g, 7.8 mmol) in THF (5 mL) was added dropwise and the mixture was warmed to rt and stirred for 2 h. The reaction mixture was then treated with 1 M HCl to pH 2 and extracted with EtOAc. The combined EtOAc extracts were dried ($MgSO_4$) and evaporated in vacuo to provide a brown oil (1.48 g, 84%): ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of *cis* and *trans* isomers) δ 0.16 (two s, 9H), 1.55 (br s, 3H), 2.52 (overlapping d, 2H), 2.82 (overlapping d, 2H); MS(APCI$^-$) 225 (M-1).

***cis*- and *trans*-3-Ethynyl-3-hydroxy-1-methylcyclobutanecarboxylic acid (33).** A mixture of 3-hydroxy-1-methyl-3-trimethylsilylethynylcyclobutanecarboxylic acid (2.50 g, 11.0 mmol) and aq NaOH (1 M, 11.5 mL, 11.5 mmol) in 15 mL of MeOH was stirred overnight at rt. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in Et_2O, washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo to provide an orange solid (1.2 g, 70%): mp 88–91 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of *cis* and *trans* isomers) δ 1.55 (s, 3H), 2.26 and 2.50 (two d, J = 13.8 Hz, 2H), 2.60 and 2.63 (two s, 1H), 2.82 and 3.06 (two d, J = 13.8 Hz, 2H); HRMS m/e calcd for $C_8\ H_9\ O_3$ (M-1)$^-$ 153.0552. Found: 153.0557.

3,3-Difluoro-1-methylcyclobutanecarboxylic acid (35). A solution of ethyl 1-methyl-3-oxocyclobutane carboxylate (**34**) in 15 mL CH_2Cl_2 under N_2 was treated with DAST (1.15 mL, 8.92 mmol) and stirred overnight at rt. The reaction mixture was poured over ice and extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated in vacuo to yield the corresponding difluoro ester as an orange oil (0.40 g, 76%). Saponification of the ester provided a brown oil quantitatively: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 3H), 2.47 (m, 2H), 3.09 (m, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −92.5 (d), −88.2 (d).

Standard conditions for the coupling of cyclobutane carboxylic acids to amines were as follows.

Method A. A solution of 0.240 g (1.11 mmol) of 3-chloro-3-methyl-1-trifluoromethylcyclobutane carboxylic acid in 5 mL $SOCl_2$ was heated at reflux for 1 h. Solvent was removed in vacuo. The residue was added to a solution of Na_2CO_3 (0.176 g, 1.66 mmol) and (*R*)-(+)-1-(4-bromophenyl)ethylamine (0.172 g, 1.11 mmol) in 6 mL of 1:1 dioxane:water, pre-cooled to 0 °C. After stirring at rt overnight, the mixture was poured into 50 mL water and extracted twice with 50 mL EtOAc. Drying ($MgSO_4$) and removal of the solvent gave an oil which was chromatographed on silica gel, eluting with 25% hexane–CH_2Cl_2, to afford the isomeric cyclobutane carboxamides **4** and **36**.

Method B. To 0.30 g (2.0 mmol) of 3,3-difluoro-1-methylcyclobutane carboxylic acid (**36**) in CH_2Cl_2 (8 mL) under N_2 was added 1 drop DMF and oxalyl chloride (0.21 mL, 2.4 mmol). The mixture was stirred overnight at rt under N_2. A solution of (*R*)-(+)-(4-bromophenyl)ethylamine hydrochloride (0.47 g, 2.0 mmol) and triethylamine (0.61 mL, 4.4 mmol) in CH_2Cl_2 (5 mL) was added to the reaction mixture and stirring was continued overnight at rt. The reaction mixture was diluted with CH_2Cl_2 and washed with water, 1 M HCl and 1 M NaOH. The organic phase was dried ($MgSO_4$) and evaporated in vacuo to yield **43** (0.49 g, 74%).

Method C. To a mixture of 3-ethynyl-3-hydroxy-1-methyl cyclobutane carboxylic acid (**33**) (0.30 g, 1.9 mmol), (*R*)-(+)-1-(4-bromophenyl)ethylamine hydrochloride (0.46 g, 1.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (0.41 g, 2.1 mmol) in CH_2Cl_2 under N_2 was added Et_3N (0.54 mL, 3.9 mmol). The mixture was stirred at rt for 24 h. The reaction mixture was then diluted with CH_2Cl_2, washed with 0.5 M HCl, $NaHCO_3$ and H_2O, dried ($MgSO_4$) and the solvent was removed by evaporation under reduced pressure. The residue was chromatographed on a silica gel column eluting with EtOAc:hexanes, 1:1, to obtain **51** and its *trans* isomer.

Products **4, 36–58** were prepared following these procedures. Characterization data for these compounds are as follows:

***cis*- and *trans*-(*R*)-3-Chloro-3-methyl-1-trifluoromethy-*N*-[1-(4-bromophenyl)ethyl] cyclobutanecarboxamide (4 and 36).** Method A, *cis* isomer **36** isolated as a white solid (38% yield): mp 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (d, J = 6.8 Hz, 3H), 1.54 (s, 3H), 2.86–2.95 (m, 2H), 2.97–3.02 (m, 2H), 5.05–5.12 (m, 1H), 5.85 (br s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.13 (s); irradiation at −73.13 ppm showed no NOE enhancement on C-3 methyl. HRMS m/e calcd for $C_{15}H_{17}Br\ Cl\ F_3\ N\ O$:

398.0134. Found 398.0148. *trans* Isomer **4** isolated as a white solid (39%): mp 142–144 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 6.8 Hz, 3H), 1.74 (s, 3H), 2.80–2.88 (m, 2H), 3.10–3.16 (m, 2H), 5.15 (m, 1H), 5.85 (br s, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.71 (s); irradiation at −73.71 ppm showed positive NOE enhancement on C-3 methyl; HRMS *m*/*e* calcd for C_{15} $H_{17}BrClF_3NO$: 398.0134. Found. 398.0147.

***trans*-(*R*)-3-Chloro-3-methyl-1-trifluoromethy-*N*-[1-(4-chlorophenyl)ethyl]cyclobutane carboxamide (37).** Method A, *cis* isomer isolated as a white solid (11%): mp 129–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (d, J = 6.9 Hz, 3H), 1.67 (s, 3H), 2.82–3.05 (m, 4H), 5.05-5.15 (m, 1H), 5.85 (br s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H); HRMS *m*/*e* calcd for $C_{15}H_{17}Cl_2F_3NO$: 354.0639. Found: 354.0627. *trans* Isomer **37** isolated as a white solid (19%): mp 145–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (d, J = 6.9 Hz, 3H), 1.74 (s, 3H), 2.79–2.86 (m, 2H), 3.05–3.15 (m, 2H), 5.10–5.20 (m, 1H), 5.85 (br s, 1H), 7.23 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H); HRMS *m*/*e* calcd for $C_{15}H_{17}Cl_2F_3NO$: 354.0639. Found: 354.0623.

***trans*-(*R*)-3-Chloro-3-methyl-1-trifluoromethy-*N*-[1-(2,4-dichlorophenyl)ethyl]cyclobutanecarboxamide (38).** Method A, *cis* isomer isolated as a white solid (9%): mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 7.5 Hz, 3H), 1.70 (s, 3H), 2.82–3.05 (m, 4H), 5.30–5.40 (m, 1H), 6.05 (br s, 1H), 7.18–7.28 (m, 3H); HRMS *m*/*e* calcd for $C_{15}H_{16}Cl_3F_3NO$: 388.0250. Found: 388.0253. *trans* Isomer **38** isolated as a white solid (9%): mp 180–181 °C; ^{1}H NMR ($CDCl_3$) δ 1.52 (d, J = 7.5 Hz, 3H), 1.74 (s, 3H), 2.80–2.90 (m, 2H), 3.10–3.20 (m, 2H), 5.30–5.40 (m, 1H), 6.05 (br s, 1H), 7.22 (s, 2H), 7.40 (s, 1H); HRMS *m*/*e* calcd for $C_{15}H_{16}Cl_3F_3NO$: 388.0250. Found: 388.0268.

***trans*-(*R*)-3-Chloro-3-methyl-1-trifluoromethy-*N*-[3-(2-fluorophenyl)oxy-2-propyl] cyclobutanecarboxamide (39).** Method A, *cis* isomer isolated as a white solid (27%): mp 70–72 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J = 7.2 Hz, 3H), 1.67 (s, 3H), 2.83–2.90 (m, 1H), 2.97–3.05 (m, 3H), 4.0–4.10 (m, 2H), 4.35–4.45 (m, 1H), 6.05 (br s, 1H), 6.90–6.98 (m, 2H), 7.01–7.12 (m, 2H), ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.59(s), −135.08 (s); HRMS *m*/*e* calcd for $C_{16}H_{19}ClF_4NO_2$: 368.1040. Found: 368.1033. *trans* isomer **39** isolated as a white solid (35%): mp 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J = 7.2 Hz, 3H), 1.75 (s, 3H), 2.80–2.85 (m, 2H), 3.05–3.20 (m, 2H), 4.0–4.12 (m, 2H), 4.42–4.52 (m, 1H), 6.10 (br s, 1H), 6.90–7.0 (m, 2H), 7.01–7.12 (m, 2H), ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.98 (s), −135.195 (s), Irradiation at −73.98 ppm showed positive NOE enhancement on C-3 methyl. HRMS *m*/*e* calcd for $C_{16}H_{19}ClF_4NO_2$: 368.1040. Found: 368.1034.

(*R*)-*N*-[1-(4-Bromophenyl)ethyl]cyclobutanecarboxamide (40). Method A, isolated as a white solid (83%): mp 140–150 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.30 (d, J = 6.9 Hz, 3H), 1.75–2.18 (m, 6H), 3.05 (m, 1H), 4.85 (m, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 7.5 Hz, 1H); HRMS *m*/*e* calcd for C_{13} $H_{17}BrNO$: 282.0494. Found: 282.0494.

***cis*-(*R*)-3-Chloro-3-methyl-*N*-[1-(4-bromophenyl)ethyl]-cyclobutanecarboxamide (41).** Method A, isolated as a white solid (7%): mp 110–131 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.30 (d, J = 7.13 Hz, 3H), 1.72 (s, 3H), 2.46–2.70 (m, 4H), 2.85–2.95 (m, 1H), 4.90–4.95 (m, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.50 ppm (d, J = 8.4 Hz, 2H), 8.30 (d,J = 7.5 Hz, 1H); HRMS *m*/*e* calcd for $C_{14}H_{18}ClNO$: 330.0260. Found: 330.0251.

(*R*)-1,3,3-Trichloro-*N*-[1-(4-bromophenyl)ethyl]cyclobutanecarboxamide (42). Method A, isolated as a white solid (42%): mp 149–151 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.40 (d, J = 6.9 Hz, 3H), 3.45–3.55 (m, 2H), 3.85–3.95 (m, 2H), 4.85–4.95 (m, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 8.85 (d, J = 7.5 Hz, 1H); HRMS *m*/*e* calcd for $C_{13}H_{14}Cl_3BrNO$: 383.9324. Found: 383.9339.

(*R*)-3,3-Difluoro-1-methyl-*N*-[1-(4-bromophenyl)ethyl]-cyclobutanecarboxamide (43). Method B, isolated as an orange solid (72%): mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, J = 7.2 Hz, 3H), 1.58 (s, 3H), 2.40 (m, 2H), 3.01 (m, 2H), 5.06 (m, 1H), 5.66 (d, J = 7.2 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −93.3 (s), −87.4 (s); HRMS *m*/*e* calcd for $C_{14}H_{17}BrF_2NO$: 332.0462. Found: 332.0476.

***cis*- and *trans*-(*R*)-1,3-Dichloro-3-methyl-*N*-[1-(4-bromophenyl)ethyl]cyclobutanecarboxamide (44).** Method A, isolated in 13% yield as a 1:1 mixture of two isomers which were not separated: mp 109–113 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (d, J = 7.0 Hz, 3H), 1.80 (s, 3H), 2.85–2.95 (m, 2H), 3.30–3.40 (m, 2H), 4.90–5.00 (m, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 8.70 (d, J = 7.5 Hz, 1H).

***cis*-(*R*)-3-Chloro-1,3-dimethyl-*N*-[1-(4-bromophenyl)ethyl]-cyclobutanecarboxamide (45).** Method A, isolated as an orange solid (3%): mp 128–139 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.30 (overlapping doublet and singlet, 6H), 1.75 (s, 3H), 2.25–2.35 (m, 2H), 2.90–3.00 (m, 2H), 4.85–4.95 (m, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 8.09 (d, J = 7.5 Hz, 1H).

***cis*- and *trans*-(*R*)-3-Chloro-3-(chloromethyl)-1-methyl-*N*-[1-(4-bromophenyl)ethyl] cyclobutanecarboxamide (46 and 47).** Method A, *trans* isomer **46** isolated as a white solid (24%): mp 96–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (d, J = 7.0 Hz, 3H), 1.61 (s, 3H), 2.38–2.44 (m, 2H), 3.00–3.06 (m, 2H), 3.80 (d, J = 3.75 Hz, 2H), 4.97–5.07 (m, 1H), 5.61 (br s, 1H), 7.18 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H); irradiation at 3.80 ppm showed no NOE enhancement on C-1 methyl; HRMS *m*/*e* calcd for $C_{15}H_{19}Cl_2BrNO$: 378.0027. Found: 378.0036. *cis* Isomer **47** isolated as a white solid (24%): mp 102–117 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 3H), 1.50 (d, J = 7.0 Hz, 3H), 2.57–2.62 (m, 2H), 2.88–2.95 (m, 2H), 3.77 (s, 2H), 5.07–5.17 (m, 1H), 5.81 (br s, 1H), 7.20 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H); irradiation at 3.77 ppm showed positive NOE

enhancement on C-1 methyl. HRMS *m/e* calcd for $C_{15}H_{15}Cl_2BrNO$: 378.0027. Found: 378.0042.

***cis*-(*R*)-3-Chloro-1-ethyl-3-methyl-*N*-[1-(4-bromophenyl)-ethyl]cyclobutanecarboxamide (48).** Method B, *cis* isomer isolated as a white solid (29%): mp 127.5–129 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (t, J = 7.4 Hz, 3H), 1.49 (d, J = 7.2 Hz, 3H), 1.72 (q, J = 7.4 Hz, 2H), 1.73 (s, 3H), 2.34 (d, J = 15 Hz, 2H), 2.93 (d, J = 15 Hz, 2H), 5.13 (m, J = 7.2 Hz, 1H), 5.75 (d, J = 7.2 Hz, 1H), 7.21 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H); HRMS *m/e* calcd for $C_{16}H_{22}ClBrNO$: 358.0573. Found: 358.0570.

***cis*- and *trans*-(*R*)-1,3-Dimethyl-3-hydroxy-*N*-[1-(4-bromophenyl)ethyl]cyclobutanecarboxamide (49 and 50).** Method C, *trans* isomer **49** isolated as a white solid (22%): mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (s, 3H), 1.46 (d, J = 6.9 Hz, 3H), 1.48 (s, 3H), 1.63 (br s, 1H), 1.99 (m, 1H), 2.03 (m, 1H), 2.54 (m, 1H), 2.58 (m, 1H), 5.06 (m, 1H), 5.62 (d, J = 7.5 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.7 Hz, 2H); HRMS *m/e* calcd for $C_{15}H_{21}BrNO_2$: 326.0756. Found: 326.0763. *cis* Isomer **50** isolated in 13% yield as a yellow solid: mp 129–131.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (s, 3H), 1.38 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H), 2.06 (m, 2H), 2.45 (m, 2H), 4.24 (br s, 1H), 5.01 (m, J = 6.9 Hz, 1H), 6.20 (d, J = 6.9 Hz, 1H), 7.17 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 8.3 Hz, 2H); HRMS *m/e* calcd for $C_{15}H_{21}BrNO_2$: 326.0756. Found: 326.0761.

***cis*-(*R*)-3-Ethynyl-3-hydroxy-1-methyl-*N*-[1-(4-bromophenyl)ethyl]cyclobutanecarboxamide (51).** Method C, *cis* isomer isolated as a yellow oil (11%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, J = 6.9 Hz, 3H); 1.50 (s, 3H), 2.23 (d, J = 13.2 Hz, 1H), 2.53 (s, 1H), 2.95 (d, J = 13.2 Hz, 2H), 5.09 (q, J = 6.9 Hz, 1H), 5.70 (br s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 8.4 Hz, 2H); HRMS *m/e* calcd for $C_{16}H_{19}BrNO_2$: 336.0599. Found: 336.0600.

***cis*-(*R*)-3-Ethyl-3-hydroxy-1-methyl-*N*-[1-(4-bromophenyl)-ethyl]cyclobutane carboxamide (52).** Method C, *cis* isomer isolated as a white solid (16%): mp 100–103 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, J = 7.2 Hz, 3H), 1.36 (s, 3H), 1.47 (d, J = 6.6 Hz, 3H), 1.59 (q, J = 7.2 Hz, 2H), 2.01 (m, 1H), 2.05 (m, 1H), 2.30–2.40 (m, 2H), 3.99 (s, 1H), 5.08 (m, 1H), 6.31 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 8.4 Hz, 2H); HRMS *m/e* calcd for $C_{16}H_{23}BrNO_2$: 340.0912. Found: 340.0920.

***cis*-(*R*)-3-Chloro-1,3-dimethyl-*N*-[1-(2,4-dichlorophenyl)-ethyl]cyclobutanecarboxamide (53).** Method A, *cis* isomer isolated as a white solid (25%): mp 182–192 °C, ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.33 (overlapping s and d, J = 6.9 Hz, 6H), 1.75 (s, 3H), 2.25–2.35 (m, 2H), 2.85–3.00 (m, 2H), 5.10–5.20 (m, 1H), 7.43 (s, 2H), 7.56 (s, 1H), 8.24 (d, J = 7.5 Hz, 1H).

***cis*-(*R*)-3-Chloro-1,3-dimethyl-*N*-[1-(1-napthyl)ethyl]cyclobutanecarboxamide (54).** Method A, *cis* isomer isolated as a white solid (14%): mp 153–158 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 3H), 1.70 (d, J = 6.75 Hz, 3H), 1.73 (s, 3H), 2.26–2.31 (m, 2H), 3.0–3.06 (m, 2H), 5.76 (br s, 1H), 5.91–5.96 (m, 1H), 7.43–7.59 (m, 4H), 7.79–7.88 (m, 2H), 8.04–8.10 (m, 1H); HRMS *m/e* calcd for $C_{19}H_{23}ClNO$: 316.1468. Found: 316.1464.

***cis*-(*R*)-3-Chloro-1,3-dimethyl-*N*-[1-(2-napthyl)ethyl]cyclobutanecarboxamide (55).** Method A, *cis* isomer isolated as a white solid (33%): mp 116–126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (s, 3H), 1.61 (d, J = 6.75 Hz, 3H), 1.77 (s, 3H), 2.25–2.37 (m, 2H), 3.0–3.11 (m, 2H), 5.30–5.35 (m, 1H), 5.90 (br s, 1H) 7.43–7.50 (m, 3H), 7.77–7.84 (m, 4H); HRMS *m/e* calcd for $C_{19}H_{23}ClNO$: 316.1468. Found: 316.1458.

***cis*-(±)-3-Chloro-1,3-dimethyl-*N*-[1-(4-bromo-2-methoxyphenyl)ethyl]cyclobutanecarboxamide (56).** Method B, *cis* isomer isolated as a white solid (43%): mp 167–168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.37 (s, 3H), 1.44 (d, J = 6.9 Hz, 3H), 1.77 (s, 3H), 2.33 (m, 2H), 3.01 (m, 2H), 3.88 (s, 3H), 5.20 (m, 1H), 6.49 (d, J = 8.4 Hz, 1H), 7.01–7.10 (m, 3H); HRMS *m/e* calcd for $C_{16}H_{22}ClBrNO_2$: 374.0522. Found: 374.0539.

***cis*-(*R*)-3-Chloro-1,3-dimethyl-*N*-[3-(2,5-difluorophenyl)-oxy-2-propyl]cyclobutanecarboxamide (57).** Method A, *cis* isomer isolated as a white solid (18%): ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.19 (d, J = 6.76 Hz, 3H), 1.30 (s, 3H), 1.75 (s, 3H), 2.20–2.30 (m, 2H), 2.90–3.00 (m, 2H), 3.95–4.05 (m, 2H), 4.05–4.20 (m, 1H), 6.75–6.80 (m, 1H), 7.10–7.30 (m, 2H), 7.62 (d, J = 7.5 Hz, 1H).

***cis*-*R*-3-Chloro-1,3-dimethyl-*N*-[3-(2-chloro-5-fluorophenyl)oxy-2-propyl] cyclobutanecarboxamide (58).** Method A, *cis* isomer isolated as a white solid (29%): mp 77–84 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 1.16 (d, J = 6.3 Hz, 3H), 1.31 (s, 3H), 1.73 (s, 3H), 2.20–2.30 (m, 2H), 2.90–3.00 (m, 2H), 3.94–4.05 (m, 2H), 4.15–4.22 (m, 1H), 6.78–6.83 (m, 1H), 7.16–7.20 (m, 1H), 7.40–7.45 (m, 1H), 7.62 (d, J = 7.5 Hz, 1H); HRMS *m/e* calcd for $C_{16}H_{21}Cl_2FNO_2$: 348.0933. Found: 348.0923.

Rice soil systemic protocol

Nine day old rice seedlings grown in 25 mm×125 mm culture tubes containing 28 mL total water and approximately 30 cc of sifted tama soil are treated with acetone solutions of the test compound at the desired concentration. Seven days after treatment, plants are sprayed with an aqueous suspension of *Pyricularia grisea* conidia (isolate BV0-184) at 50 000/mL. They are then incubated in a dew chamber at 24 °C, 100% relative humidity, for 24 h. After incubation they are moved back to the growth chamber. Infected plants are scored 7–10 days after inoculation by estimating the amount of infected area of the last fully extended leaves at the time of inoculation. Using the scores from the untreated check plants, percent disease control is calculated using the formula [1−(% disease in treatment÷% disease in check)]×100.

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