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ORIGINAL PAPER

Synthesis of fungicidally active succinate dehydrogenase inhibitors with novel difluoromethylated heterocyclic acid moieties

Harald Walter[1] · Clemens Lamberth[1] · Camilla Corsi[1]

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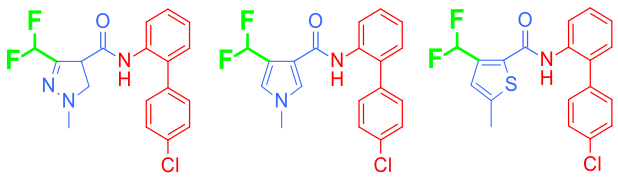
Abstract

Novel fungicidally active succinate dehydrogenase inhibitors have been prepared, which either carry a difluoromethyl and methyl-bearing pyrazoline, pyrrole, or thiophene ring in the acid component, mimicking similar-substituted pyrazole carboxamides. As five-membered heterocyclic systems with such a special substitution pattern are barely known, unique synthesis routes had to be developed, which rely, e.g., on the van Leusen pyrrole synthesis and the halogen dance reaction. Synthesis and biological activity against selected Ascomycete pathogens of these difluoromethylated pyrazoline, pyrrole, and thiophene derivatives are reported.

Graphical abstract



Keywords Fungicide · Thiophene · Pyrrole · Pyrazoline · Succinate dehydrogenase inhibitor

Introduction

The succinate dehydrogenase inhibitors (SDHIs, also called complex II inhibitors) are currently the fastest growing broad-spectrum mode of action class on the fungicide market, being applied against all kinds of phytopathogens including seed- and soilborne diseases, such as take-all disease and fusarium head blight, many different foliar cereal, fruit, and vegetable diseases, such as molds and stem rots, leaf and net blotch, powdery mildew and rusts including the important well as Asian soybean rust. Their historical name "carboxamides" points to the fact that the central amide function is the only common ground of the so far 20 commercialized active ingredients of this compound class [1–5]. Although the chemical scope of the amine part is relatively broad and reaches from aniline derivatives over benzylamine derivatives to phenethylamine derivatives, the structure–activity relationship requirements of the acid portion seem to be much more restricted. The oxathiine ring system of carboxin (**1**), the very first complex II inhibitor which was launched in the 1960s, bears a methyl group next to its carboxyl function. A first breakthrough towards a broader spectrum was the introduction of boscalid (**2**), which carries a chloro-substituent in the *ortho*-position of the carboxamide function. However, the evolution of 50 years SDHI optimization culminated in a CHF_2 group next to the acid function being optimum for fungicidal efficacy. This is demonstrated by the highly successful 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid as structural motif of the very recent commercialized products benzovindiflupyr

✉ Clemens Lamberth
clemens.lamberth@syngenta.com

[1] Chemical Research, Syngenta Crop Protection AG, Schaffhauserstrasse 101, 4332 Stein, Switzerland

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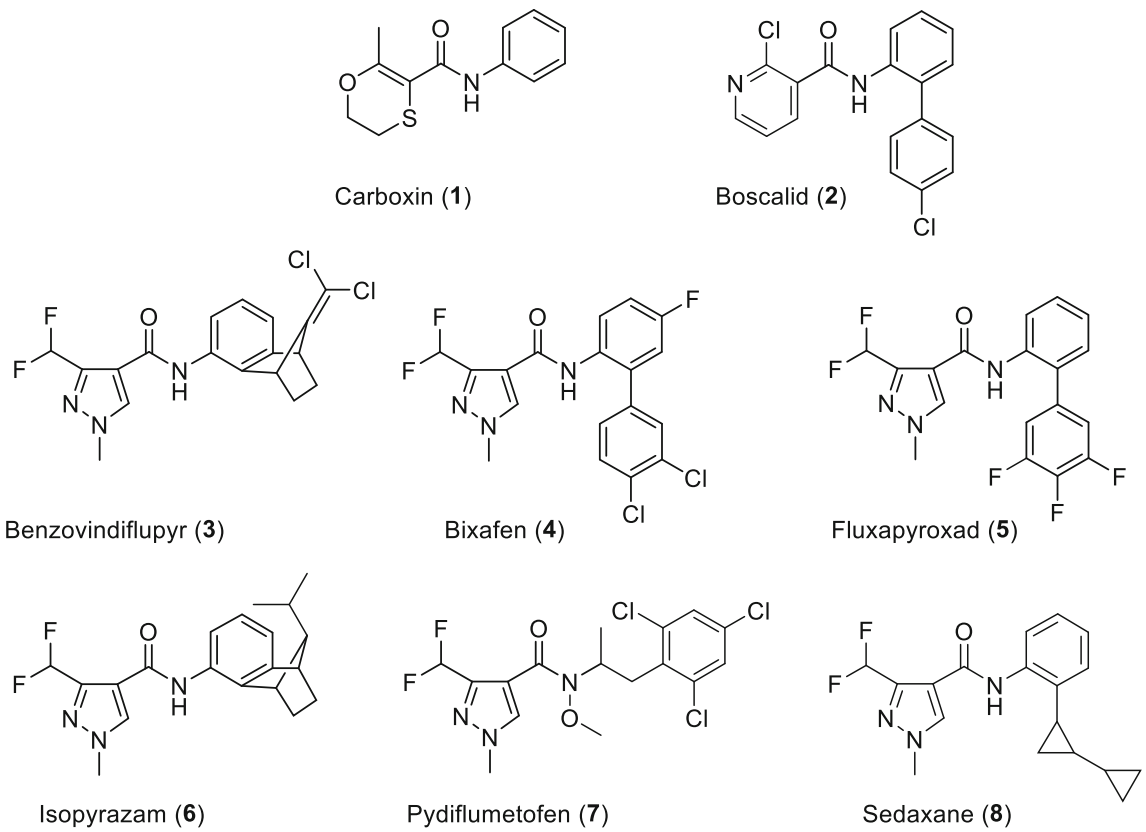


Fig. 1 Different commercialized succinate dehydrogenase inhibitors

(**3**), bixafen (**4**), fluxapyroxad (**5**), isopyrazam (**6**), pydiflumetofen (**7**), and sedaxane (**8**) (Fig. 1).

Although the synthesis of 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid has been thoroughly optimized and well described in the meantime [6–10], other difluoromethylated heterocyclic carboxylic acids are rarely known. In this paper, we report the synthesis of the fungicidally active SDHIs **9**–**11**, for which we developed the synthesis of three completely novel difluoromethylated heterocycles, which are 3-(difluoromethyl)-1-methylpyrazoline and 3-(difluoromethyl)-pyrrole with a carboxylic function in position 4 as well as 3-(difluoromethyl)-5-methylthiophene-2-carbonyl fluoride (Fig. 2).

Results and discussion

Chemical synthesis

Because of the fact that 3-(difluoromethyl)-1-methyl-1H-pyrazole is part of six successful active ingredients, we wanted to prepare some novel analogs, which are closely related by structure to it. One isosteric replacement, which came immediately to our mind, was to exchange the pyrazole ring by its partially saturated pyrazoline (dihydropyrazole) derivative. So far, difluoromethylated pyrazolines have been only rarely described in the scientific literature. Although there have been some methods known for the synthesis of *N*-methylpyrazoline-4-carboxylic acid

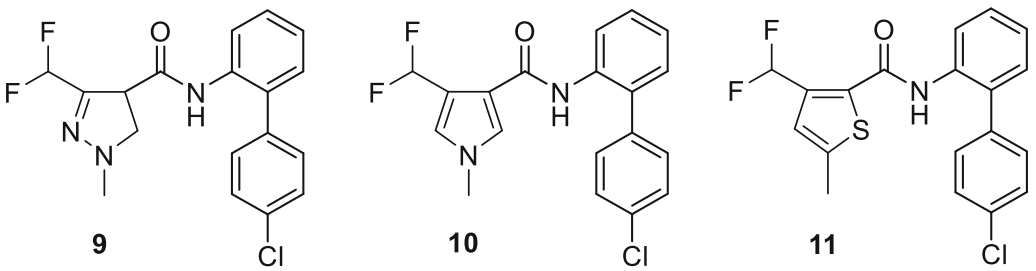


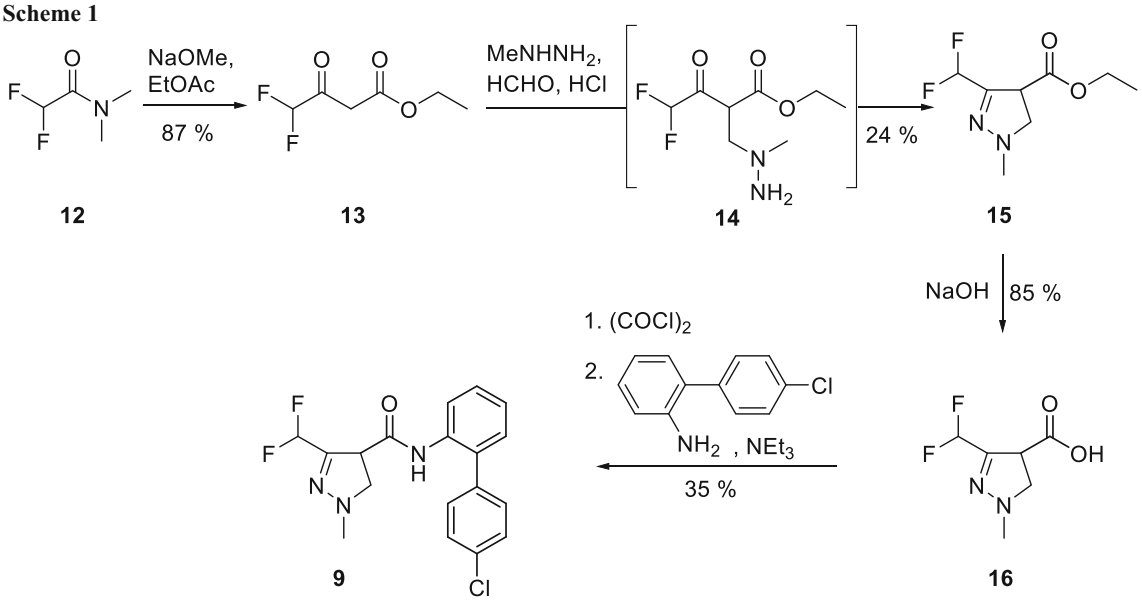
Fig. 2 The three target compounds **9**–**11** with novel difluoromethylated heterocyclic acid portions

derivatives, such as the 1,3-dipolar cycloaddition of *N*-methylnitrilimines to acrylates [11] and of α-silylnitrosamines to fumarates [12], or the transformation of *N*-dimethylaminopyrroles with dimethyl acetylenedicarboxylate [13], we decided to use the 4,4-difluoroacetoacetate **13** for our synthesis, as this important building block of the manufacturing routes of benzovindiflupyr (**3**), isopyrazam (**6**), pydiflumetofen (**7**), and sedaxane (**8**) is readily available as a mixture of methyl and ethyl esters in only one step by Claisen condensation of *N*,*N*-dimethyldifluoroacetamide (**12**) with ethyl acetate [1, 3, 7]. This β-ketoester **13** was then converted in a Mannich-type reaction with methylhydrazine and an aqueous solution of formaldehyde in the presence of catalytic amounts of hydrochloric acid in boiling ethanol to the Mannich adduct **14**, which cyclizes spontaneously to the desired 3-(difluoromethyl)-1-methylpyrazoline ester **15** as major product. The isomeric 5-(difluoromethyl) substituted pyrazole, in which the methyl group is linked to the ring nitrogen next to the difluoromethyl function was formed in less than 10%. After saponification of ester **15** to the pyrazoline acid **16**, subsequent transformation into the acid chloride and amidation with 4′-chlorobiphenyl-2-amine delivered the target compound **9** (Scheme 1) [14].

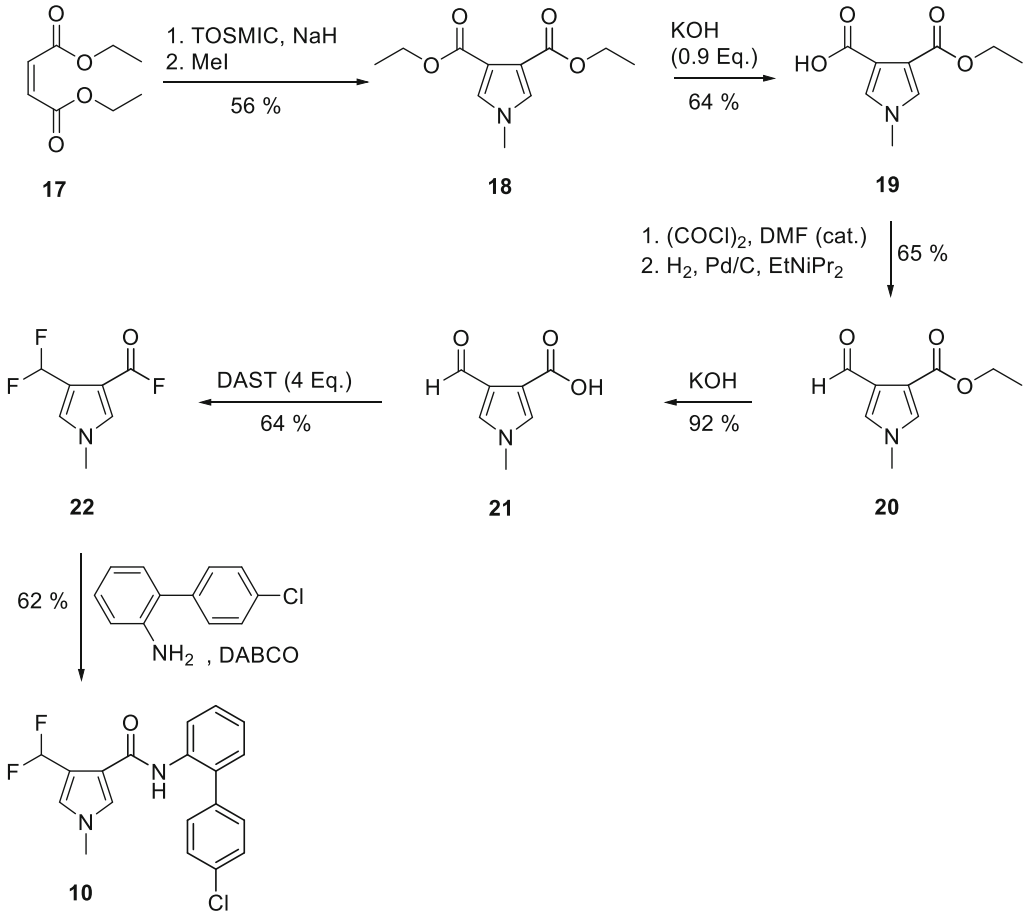
Another ring system, which would be closely related to the 3-(difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid moiety of the commercial fungicides **2**–**7**, is the corresponding pyrrole, in which one of the two ring nitrogen of the pyrazole has been replaced by a carbon atom. Also difluoromethylated pyrrole derivatives are, as it was the case for the pyrazoline scaffold, not known in the literature at all; therefore, we had to develop a completely new synthesis route [15]. We used diethyl maleate (**17**) as starting material, which was converted with TosMIC into the 3,4-dicarbethoxy-substituted pyrrole **18**. The synthesis of this diester has been described already by Paal–Knorr cyclization of a 2,3-diformylsuccinate [16], by a three-component condensation of methylamine with two equivalents of ethylpropiolate [17] and by dehydrogenation of the corresponding pyrrolidine with manganese dioxide [18], but never by the van Leusen pyrrole synthesis with TosMIC [19–23], as reported herewith by us. One of the two ester functions of **18** were then saponified to the carboxylic acid **19** and transformed into the acid chloride, which underwent a Rosenmund reduction to the aldehyde **20**. The saponification of the remaining ester of **20** delivered the pyrrole derivative **21**. Both aldehyde and carboxylic acid functions of **21** were converted with diethylaminosulfur trifluoride (DAST) [24, 25] to the difluoromethyl-substituted pyrrole acid fluoride **22** [15], which delivered the desired target compound **10** by amidation with 4′-chlorobiphenyl-2-amine (Scheme 2) [26].

Finally, we also wanted to check, which results a difluoromethyl- and methyl-substituted thiophene analog of the successful pyrazole carboxylic acid part of products **3**–**8** would deliver in our assays. As it was the case for pyrazolines and pyrroles, also difluoromethylated thiophenes are completely unknown so far. We started the synthesis of target compound **11** bearing the sulfur atom adjacent to the carboxamide function with the regioselective bromination of 2-methylthiophene (**23**). The resulting 2-bromo-5-methylthiophene (**24**) was subjected to a lithium diisopropylamide (LDA)-induced halogen dance reaction [27–31], in which the migrated carbanion could be

Scheme 1



Scheme 2



trapped with carbon dioxide delivering the thienyl acid **25**. Previously, several different electrophiles have been added to the lithium salt in thiophene position 2 resulting from the halogen dance reaction of 2-bromo-5-methylthiophene (**24**) [32, 33], but so far never carbon dioxide delivering a carboxylic acid. The synthesis of the trisubstituted thiophene derivative **25** has been described already [34, 35], but not via a halogen dance reaction as in our approach. Another lithiation, this time with butyl lithium, led by exchange of the bromo-substituent with a formyl function to **26**, which was subsequently converted with excess of bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-fluor) [24, 25] to the difluoromethylated thiophene-2-carboxyl acid fluoride **27** (Scheme 3).

Biological evaluation

The three target compounds **9**–**11** have been evaluated for their fungicidal activity against different phytopathogens. As we were especially interested in the control of cereal diseases, we chose *Blumeria graminis* (wheat and barley powdery mildew), *Pyrenophora teres* (barley net blotch), and *Zymoseptoria tritici* (wheat leaf blotch), all belonging to the family of Ascomycota, as fungal test species. Because **9**–**11** bear exactly the same amine portion as boscalid (**2**), this commercial product was used as reference. As shown in Table 1, all three novel succinate dehydrogenase inhibitors show at the very low rate of 20 ppm interesting efficacy. It seems that the pyrazoline derivative **9** and the pyrrole carboxamide **10** have a strength in the control of powdery mildew, whereas the thiophene **11** shows a similar profile as its pyridine analog boscalid, because both compounds show excellent control of the leaf spot diseases *P. teres* and *Z. tritici*.

Conclusion

We have introduced three novel difluoromethylated acid motifs into the family of succinate dehydrogenase inhibitors. These previously unknown pyrazoline, pyrrole, and thiophene derivatives have been prepared on completely

Scheme 3

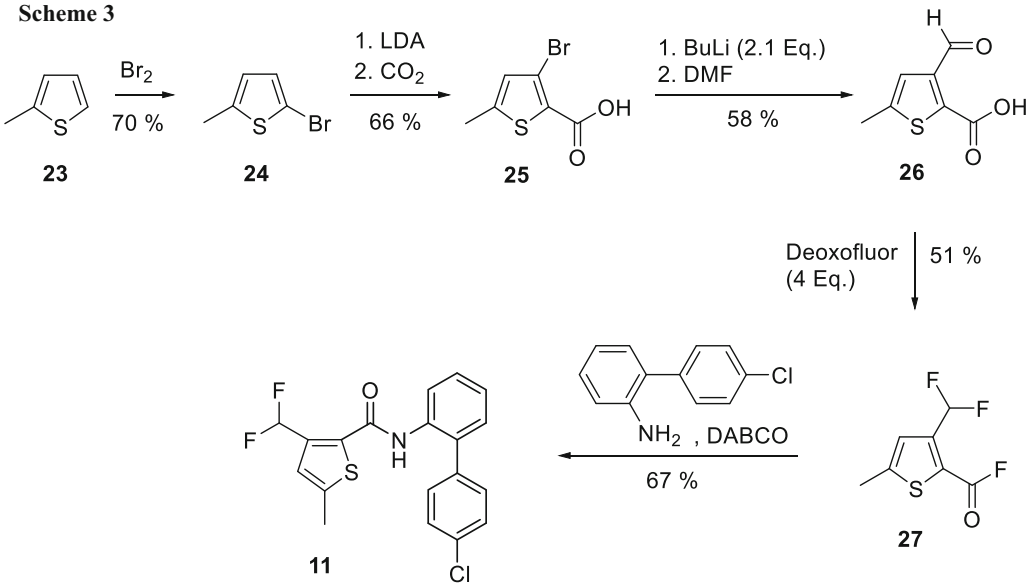


Table 1 Fungicidal activity of the target compounds against different cereal pathogens

Compound	*Blumeria graminis* (cereal powdery mildew)	*Pyrenophora teres* (barley net blotch)	*Zymoseptoria tritici* (wheat leaf blotch)
9	80	50	30
10	70	30	35
11	30	70	80
2 (boscalid)	20	80	70

Results are given in % activity at 20 ppm

different routes from simple starting materials, such as *N*,*N*-dimethyldifluoroacetamide, diethyl maleate, and 2-methylthiophene, either using a Mannich reaction, a van Leusen pyrrole synthesis, or a halogen dance reaction as the key step. These novel specifically substituted five-membered ring carboxamides show potent activity against the economically important Ascomycete phytopathogens *B. graminis*, *P. teres*, and *Z. tritici*.

Experimental

All new compounds were characterized by standard spectroscopical methods. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield from the standard ($\delta = 0.00$), coupling constants in Hz. LC–MS spectra were determined using the following apparatus: ACQUITY UPLC from Waters, Phenomenex Gemini C18, 3 mm particle size, 110 Angström, 30 × 3 mm column, 1.7 cm^3/min., 60 °C, H_2O + 0.05% HCOOH (95%)/CH_3CN/MeOH 4:1 + 0.04% HCOOH (5%)—2 min—CH_3CN/MeOH 4:1 + 0.04% HCOOH (5%)—0.8 min; ACQUITY SQD Mass Spectrometer from Waters, ionization method: electrospray (ESI), polarity: positive ions, capillary 3.00 kV, cone 20.00 V, extractor 3.00 V, source temperature 150 °C, desolvation temperature 400 °C, cone gas flow 60 dm^3/h, desolvation gas flow 700 dm^3/h. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F524 precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 μm, E. Merck). Unless otherwise stated, all reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents.

Synthesis protocols

***Ethyl 4,4-difluoro-3-oxobutanoate* (13)** A 21% solution of sodium ethoxide in ethanol (32 cm^3, 0.1 mol) was added dropwise to a solution of 11.2 g 2,2-difluoro-*N*,*N*-dimethylacetamide (**12**, 91 mmol) in 150 cm^3 of ethyl acetate. The resulting mixture was stirred for 1 h at 80 °C, then cooled to room temperature, poured on ice-water, acidified with

2 N hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under in vacuo. The residue was purified by distillation under reduced pressure to deliver 13.2 g ethyl 4,4-difluoro-3-oxo-butanoate (**13**, 79 mmol, 87%) as a colorless oil. B.p.: 50–53 °C (18 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.32$ (t, 3H, $J = 7.5$ Hz), 4.34 (q, 2H, $J = 7.5$ Hz), 5.40 (s, 2H), 5.98 (t, 1H, $J = 54.0$ Hz) ppm; LC–MS: $t_R = 1.85$ min; MS: $m/z = 167$ ($[M+1]^+$).

Ethyl 3-(difluoromethyl)-1-methyl-4,5-dihydro-1H-pyrazole-4-carboxylate **(15, $C_8H_{12}F_2N_2O_2$)** Ethyl 4,4-difluoro-3-oxobutanoate (5.0 g, 30 mmol) was dissolved in 35 cm^3 of ethanol and the solution was cooled to 0 °C. A 37% aqueous solution of formaldehyde (2.5 g, 30 mmol) was added and the mixture was stirred for 15 min at 0 °C. Methylhydrazine (1.4 g, 30 mmol) was added and the reaction mixture was heated to reflux. After reaching the reflux temperature, 0.5 cm^3 of concentrated hydrochloric acid was added, then refluxing was continued for 16 h. Subsequently the mixture was cooled to room temperature and evaporated in vacuo. The remainder was taken up in water and extracted with ethyl acetate. The organic layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure. The remainder was purified by chromatography on silica gel, using ethyl acetate and hexane 1:2 as eluents to deliver 1.5 g ethyl 3-(difluoromethyl)-1-methyl-4,5-dihydro-1H-pyrazole-4-carboxylate (**15**, 7.3 mmol, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.14$ (t, 3H, $J = 7.3$ Hz), 2.77 (s, 3H), 3.53–3.61 (m, 1H), 3.76–3.80 (m, 1H), 4.07 (q, 2H, $J = 7.4$ Hz), 5.67 (t, 1H, $J = 54.2$ Hz), 6.48 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.8$, 15.4, 17.3, 39.0, 44.9, 129.1, 143.2, 158.7 ppm; LC–MS: $t_R = 2.01$ min; MS: $m/z = 207$ ($[M+1]^+$).

3-(Difluoromethyl)-1-methyl-4,5-dihydro-1H-pyrazole-4-carboxylic acid **(16, $C_6H_8F_2N_2O_2$)** Aqueous sodium hydroxide solution (1 N, 1.5 cm^3, 1.5 mmol) was added to a solution of 0.15 g ethyl 3-(difluoromethyl)-1-methyl-4,5-dihydro-1*H*-pyrazole-4-carboxylate (0.7 mmol) in 2 cm^3 of dioxane. The reaction mixture was stirred for 2 h at room temperature, then acidified to pH 2 by addition of concentrated hydrochloric acid. The solvent was removed under reduced pressure and the remainder extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated to deliver 0.1 g 3-(difluoromethyl)-1-methyl-4,5-dihydro-1*H*-pyrazole-4-carboxylic acid (**16**, 0.6 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.69$ (s, 3H), 3.51–3.59 (m, 1H), 3.78–3.86 (m, 1H), 5.73 (t, 1H, $J = 55.1$ Hz), 6.50 (s, 1H), 12.31 (bs, 1H) ppm; LC–MS: $t_R = 1.54$ min; MS: $m/z = 179$ ($[M+1]^+$).

N-[2-(4-Chlorophenyl)phenyl]-3-(difluoromethyl)-1-methyl-4,5-dihydro-1H-pyrazole-4-carboxamide **(9, $C_{18}H_{16}ClF_2N_3O$)** 3-(Difluoromethyl)-1-methyl-4,5-dihydro-1*H*-pyrazole-4-carboxylic acid (0.1 g, 0.6 mmol) was dissolved in 2 cm^3 of dichloromethane containing one drop of *N*,*N*-dimethylformamide. A solution of 78 mg oxalyl chloride (0.6 mmol) in 2 cm^3 of dichloromethane was added at room temperature. This mixture was stirred for 1 h at room temperature and then slowly added to a mixture of 0.11 g 4′-chlorobiphenyl-2-amine (0.6 mmol) and 85 mg triethylamine (0.8 mmol) in 2 cm^3 of dichloromethane. The reaction mixture was stirred for 16 h at room temperature, then poured on water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate/heptane 1:3 as eluent, to deliver 40 mg *N*-[2-(4-chlorophenyl)phenyl]-3-(difluoromethyl)-1-methyl-4,5-dihydro-1H-pyrazole-4-carboxamide (**9**, 0.2 mmol, 35%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.83$ (s, 3H), 3.59–3.68 (m, 2H), 5.72 (t, 1H, $J = 54.5$ Hz), 6.44 (s, 1H), 7.12–7.22 (m, 5H), 7.31–7.43 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 24.7$, 108.3, 110.0, 113.2, 117.5, 117.9, 121.8, 123.6, 124.8, 126.1, 129.2, 129.7, 130.4, 133.3, 134.02, 135.1, 136.7, 160.6 ppm; LC–MS: $t_R = 1.73$ min; MS: $m/z = 364$ ($[M+1]^+$).

Diethyl 1-methylpyrrole-3,4-dicarboxylate **(18)** A solution of 19.5 g *p*-toluenesulfonylmethyl isocyanide (TosMIC, 0.1 mol) in 200 cm^3 of *N*-methylpyrrolidone was added during 1 h at 0 °C to a suspension of 60% sodium hydride (8.8 g, 0.2 mol) in 150 cm^3 of *N*-methylpyrrolidone. The resulting suspension was stirred for further 30 min at 0 °C, then a solution of 17.2 g diethyl maleate (**17**, 0.1 mol) in 50 cm^3 of *N*-methylpyrrolidone was slowly added. The reaction mixture was stirred for 2 h at 0 °C and for 1 h at 10 °C, then 28.4 g methyl iodide (0.2 mol) was added and stirring was continued for further 3 h at room temperature. Subsequently the reaction mixture was cooled to 0 °C and quenched by addition of 100 cm^3 of saturated aqueous ammonium chloride solution. The resulting mixture was poured on brine and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The remainder was purified by chromatography on silica gel, using ethyl acetate/heptane 1:4 as eluent, to deliver 12.7 g diethyl 1-methylpyrrole-3,4-dicarboxylate (**18**, 56 mmol, 56%). M.p.: 48–50 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (t, 6H, $J = 5.3$ Hz), 3.66 (s, 3H), 4.27 (q, 4H, $J = 5.2$ Hz), 7.18 (s, 2H) ppm; LC–MS: $t_R = 1.95$ min; MS: $m/z = 226$ ($[M+1]^+$).

4-Ethoxycarbonyl-1-methylpyrrole-3-carboxylic acid **(19, $C_9H_{11}NO_4$)** A mixture of 12.7 g diethyl 1-methylpyrrole-3,4-dicarboxylate (**18**, 56 mmol) and 3.3 g powdered

potassium hydroxide (50 mmol) in 140 cm^3 of ethanol was heated for 4 h to 80 °C. Subsequently the reaction mixture was stirred for 16 h at room temperature and then evaporated under reduced pressure. The residue was taken up in ethyl acetate, stirred for 15 min, and filtered. The filtrate was diluted with water and the phases were separated. The aqueous phase was acidified to pH 2 by addition of 2 N hydrochloric acid. The resulting suspension was filtered and the solid remainder was washed with cold water and dried in high vacuum to deliver 7.1 g 4-ethoxycarbonyl-1-methylpyrrole-3-carboxylic acid (**19**, 36 mmol, 64%). M.p.: 160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$ (t, 3H, $J = 5.3$ Hz), 3.73 (s, 3H), 4.39 (q, 2H, $J = 5.4$ Hz), 7.33 (d, 1H, $J = 2.5$ Hz), 7.47 (d, 1H, $J = 2.5$ Hz), 13.66 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.5$, 36.3, 59.1, 114.3, 121.5, 121.9, 127.4, 163.8, 165.6 ppm; LC–MS: $t_R = 0.96$ min; MS: $m/z = 198$ ($[M+1]^+$).

***Ethyl 4-formyl-1-methylpyrrole-3-carboxylate* (20, $C_9H_{11}NO_3$)** A solution of 8.0 g oxalyl chloride (63 mmol) in 20 cm^3 of dichloromethane was slowly added at room temperature to a solution of 11.8 g 4-ethoxycarbonyl-1-methylpyrrole-3-carboxylic acid (**19**, 60 mmol) and 7 drops of *N*,*N*-dimethylformamide in 60 cm^3 of dichloromethane. The reaction mixture was stirred for 2 h at room temperature and then heated to reflux for 1 h. Subsequently it was cooled to room temperature and evaporated under reduced pressure to deliver the crude 4-ethoxycarbonyl-1-methylpyrrole-3-carboxylic acid chloride. This acid chloride was dissolved in 200 cm^3 of tetrahydrofuran. After addition of 7.7 g *N*,*N*-diisopropylethylamine (Hünig's base, 60 mmol), the mixture was treated with hydrogen in the presence of a 10% palladium on charcoal at 5 °C for 5 h. The catalyst was filtered off and the solvent removed in vacuo. The remainder was purified by chromatography on silica gel, using *tert*-butyl methyl ether/heptane 1:5 as eluent, to deliver 7.1 g ethyl 4-formyl-1-methylpyrrole-3-carboxylate (**20**, 39 mmol, 65%). M.p.: 75–76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.36$ (t, 3H, $J = 5.3$ Hz), 3.72 (s, 3H), 4.33 (q, 2H, $J = 5.3$ Hz), 7.25 (d, 1H, $J = 2.6$ Hz), 7.30 (d, 1H, $J = 2.6$ Hz), 10.39 (s, 1H) ppm; LC–MS: $t_R = 1.55$ min; MS: $m/z = 182$ ($[M+1]^+$).

***4-Formyl-1-methylpyrrole-3-carboxylic acid* (21, $C_7H_7NO_3$)-** A solution of 2.1 g potassium hydroxide (31 mmol) in 22 cm^3 of water was added to a solution of 4.6 g ethyl 4-formyl-1-methylpyrrole-3-carboxylate (**20**, 25 mmol) in 90 cm^3 of ethanol. The reaction mixture was heated for 2 h to 80 °C, then cooled to room temperature and evaporated under reduced pressure. The residue was taken up in water and extracted with ethyl acetate. The aqueous phase was acidified to pH 2 by addition of 2 N hydrochloric acid to pH 2. The resulting suspension was filtered and the solid remainder was washed with cold water and dried in high vacuum to deliver 3.6 g 4-formyl-1-methylpyrrole-3-carboxylic acid (**21**, 23 mmol, 92%). M.p.: 176–179 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 3.84$ (s, 3H), 7.63 (d, 1H, $J = 2.6$ Hz), 7.74 (d, 1H, $J = 2.5$ Hz), 10.22 (s, 1H), 12.72 (s, 1H) ppm; LC–MS: $t_R = 0.87$ min; MS: $m/z = 154$ ($[M+1]^+$).

***4-(Difluoromethyl)-1-methylpyrrole-3-carbonyl fluoride* (22, $C_7H_6F_3NO$)** A solution of 11.0 g diethylaminosulfurtrifluoride (DAST, 68 mmol) in 10 cm^3 of dichloromethane was slowly added at 0 °C to a solution of 2.6 g 4-formyl-1-methylpyrrole-3-carboxylic acid (**21**, 17 mmol) in 70 cm^3 of dichloromethane. The reaction mixture was stirred for 30 min at 0 °C and for 16 h at room temperature, then taken up in ethyl acetate, and washed with water and brine. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure. The remainder was purified by chromatography on silica gel, using ethyl acetate/heptane 1:2 as eluent, to deliver 1.95 g 4-(difluoromethyl)-1-methylpyrrole-3-carbonyl fluoride (**22**, 11 mmol, 64%). M.p.: 53–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.75$ (s, 3H), 6.79–7.17 (m, 2H), 7.38 (d, 1H, $J = 2.6$ Hz) ppm; LC–MS: $t_R = 1.62$ - min; MS: $m/z = 178$ ($[M+1]^+$).

***N*-[2-(4-Chlorophenyl)phenyl]-4-(difluoromethyl)-1-methylpyrrole-3-carboxamide (10, $C_{19}H_{15}ClF_2N_2O$)** A mixture of 0.23 g 4-(difluoromethyl)-1-methylpyrrole-3-carbonyl fluoride (**22**, 1.3 mmol), 0.27 g 4′-chlorobiphenyl-2-amine (1.3 mmol), and 0.2 g 1,4-diazabicyclo[2]octane (DABCO, 1.9 mmol) in 5 cm^3 of acetonitrile was heated to 110 °C for 3 h. The reaction mixture was cooled to room temperature, taken up in ethyl acetate, washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate/heptane 1:2 as eluent, to deliver 0.29 g *N*-[2-(4-chlorophenyl)phenyl]-4-(difluoromethyl)-1-methylpyrrole -3-carboxamide (**10**, 0.8 mmol, 62%). M.p.: 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.66$ (s, 3H), 6.77–6.96 (m, 2H), 7.19–7.45 (m, 8H), 8.27–8.32 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 36.9$, 109.2, 111.7, 114.0, 117.9, 118.5, 122.3, 123.2, 124.1, 124.6, 128.5, 129.2, 130.1, 130.8, 131.6, 134.0, 134.9, 136.8, 161.6 ppm; LC–MS: $t_R = 1.81$ min; MS: $m/z = 361$ ($[M+1]^+$).

***2-Bromo-5-methylthiophene* (24)** A solution of 48.0 g bromine (0.3 mol) in 260 cm^3 of dioxane was slowly added to a solution of 29.4 g 2-methylthiophene (**23**, 0.3 mmol) in 140 cm^3 of dioxane. The reaction mixture was stirred for 3 h at room temperature, then cooled to 0 °C. A saturated aqueous sodium bicarbonate solution was then carefully added and the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The remainder was purified by distillation to deliver

37.2 g 2-bromo-5-methylthiophene (**24**, 0.21 mol, 70%). B.p.: 68–70 °C (20 mbar); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H), 6.51 (d, 1H, $J = 3.6$ Hz), 6.83 (d, 1H, $J = 3.6$ Hz) ppm; LC–MS: $t_R = 1.65$ min; MS: $m/z = 176$, 178 ($[M+1]^+$, $[M+3]^+$).

3-Bromo-5-methylthiophene-2-carboxylic acid **(25, $C_6H_5BrO_2S$)** A 1.6 M solution of butyllithium in hexane (105 cm^3) was slowly added at -30 °C to a solution of 18.4 g diisopropylamine (0.18 mol) in 150 cm^3 of tetrahydrofuran. The mixture was stirred for 30 min at − 30 °C, then cooled to – 70 °C. At this temperature a solution of 24.8 g 2-bromo-5-methylthiophene (**24**, 0.14 mol) in 60 cm^3 of tetrahydrofuran was slowly added. The reaction mixture was stirred for 2 h at – 70 °C, then a stream of carbon dioxide was introduced at the same temperature for 1 h. The addition of carbon dioxide was continued as the mixture warmed up to room temperature. The reaction mixture was acidified to pH 2 by addition of 1 N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated under reduced pressure. The remainder was purified by chromatography on silica gel, using ethyl acetate/heptane 1:3 as eluent, to deliver 20.5 g 3-bromo-5-methylthiophene-2-carboxylic acid (**25**, 66%). M.p.: 190–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.47$ (s, 3H), 6.98 (s, 1H), 13.19 (bs, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.3$, 108.7, 125.5, 129.8, 141.4, 156.3 ppm; LC–MS: $t_R = 1.13$ min; MS: $m/z = 220$, 222 ($[M+1]^+$, $[M+3]^+$).

3-Formyl-5-methylthiophene-2-carboxylic acid **(26, $C_7H_6O_3S$)** A 1.6 M solution of butyllithium in hexane (59 cm^3) was slowly added at – 75 °C to a solution of 10.0 g 3-bromo-5-methylthiophene-2-carboxylic acid (45 mmol) in 220 cm^3 of tetrahydrofuran. The mixture was stirred 30 min at − 75 °C, then a solution of 4.9 g *N*,*N*-dimethylformamide (67 mmol) in 20 cm^3 of tetrahydrofuran was added dropwise. The reaction mixture was stirred for 1 h at – 75 °C, then warmed to room temperature, quenched by addition of 1 N hydrochloric acid, and taken up in ethyl acetate. The phases were separated, the organic layer was washed with brine, dried over sodium sulfate, and evaporated under reduced pressure. The remaining solid was crystallized from water/ethanol 9:1 to deliver 4.5 g 3-formyl-5-methylthiophene-2-carboxylic acid (**26**, 26 mmol, 58%). M.p.: 172–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.56$ (s, 3H), 7.31 (s, 1H), 10.26 (s, 1H), 13.20 (bs, 1H) ppm; LC–MS: $t_R = 1.02$ min; MS: $m/z = 171$ ($[M+1]^+$).

3-(Difluoromethyl)-5-methylthiophene-2-carbonyl fluoride **(27, $C_7H_5F_3OS$)** A solution of 10.6 g Deoxo-fluor (48 mmol) in 20 cm^3 of dichloromethane was added dropwise at 0 °C to a solution of 2.05 g 3-formyl-5-methylthiophene-2-carboxylic acid (**26**, 12 mmol) in 80 cm^3 of dichloromethane. The reaction mixture was stirred for 1 h at 0 °C and 2 h at room temperature, then poured on ice-water. The phases were separated, the organic layer was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The remainder was purified by chromatography on silica gel, using dichloromethane/heptane 2:1 as eluent, to deliver 1.2 g 3-(difluoromethyl)-5-methylthiophene-2-carbonyl fluoride (**27**, 6.1 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.60$ (s, 3H), 7.03–7.28 (m, 2H) ppm; LC–MS: $t_R = 1.95$ min; MS: $m/z = 195$ ($[M+1]^+$).

N-[2-(4-Chlorophenyl)phenyl]-3-(difluoromethyl)-5-methylthiophene-2-carboxamide **(11, $C_{19}H_{14}ClF_2NOS$)** A mixture of 0.38 g 3-(difluoromethyl)-5-methylthiophene-2-carbonyl fluoride (**27**, 0.9 mmol), 0.19 g 4′-chlorobiphenyl-2-amine (0.9 mmol), and 0.16 g 1,4-diazabicyclo[2]octane (DABCO, 1.4 mmol) was heated without solvent to 110 °C for 2 h. The reaction mixture was cooled to room temperature, taken up in ethyl acetate, washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by chromatography on silica gel, using ethyl acetate/heptane 1:4 as eluent, to deliver 0.24 g *N*-[2-(4-chlorophenyl)phenyl]-3-(difluoromethyl)-5-methylthiophene-2-carboxamide (**11**, 0.6 mmol, 67%). M.p.: 149–151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.49$ (s, 3H), 7.03 (s, 1H), 7.18–7.52 (m, 8H), 8.31 (d, 1H, $J = 11.6$ Hz) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.6$, 107.4, 110.0, 112.2, 121.9, 125.0, 125.8, 128.8, 129.3, 130.1, 130.5, 131.7, 132.6, 134.1, 134.2, 136.2, 139.8, 143.3, 159.0 ppm; LC–MS: $t_R = 1.76$ min; MS: $m/z = 378$ ($[M+1]^+$).

Biological assays

Blumeria graminis f. sp. *hordei* (*Erysiphe graminis f.* sp. *hordei*)/barley/leaf disc preventative (powdery mildew on barley)

Barley leaf segments cv. Hasso are placed on agar in multiwell plate (24-well format) and sprayed with the formulated test compound diluted in water. The leaf segments are inoculated by shaking powdery mildew infected plants above the test plates 1 day after application. The inoculated leaf segments are incubated at 20 °C and 60% rh under a light regime of 24 h darkness followed by 12 h light/12 h darkness in a climate chamber and the activity of a compound is assessed as percent disease control compared to untreated when an appropriate level of disease damage appears on untreated check leaf segments (5–7 days after application).

Pyrenophora teres/barley/leaf disc preventative (net blotch)

Barley leaf segments cv. Hasso are placed on agar in a multiwell plate (24-well format) and sprayed with the formulated test compound diluted in water. The leaf segments are inoculated with a spore suspension of the fungus 2 days after application. The inoculated leaf segments are incubated at 20 °C and 65% rh under a light regime of 12 h light/12 h darkness in a climate cabinet and the activity of a compound is assessed as disease control compared to untreated when an appropriate level of disease damage appears in untreated check leaf segments (57 days after application).

Zymoseptoria tritici (*Mycosphaerella graminicola*, *Septoria tritici*)/liquid culture (Septoria leaf blotch)

Conidia of the fungus from cryogenic storage are directly mixed into nutrient broth (PDB potato dextrose broth). After placing a (DMSO) solution of test compound into a microtiter plate (96-well format), the nutrient broth containing the fungal spores is added. The test plates are incubated at 24 °C and the inhibition of growth is determined photometrically 4–5 days after application.

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