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ORIGINAL PAPER

Synthesis and biological activity of 3-substituted isoxazolecarboxamides

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Abstract A series of novel 3-substituted isoxazolecarboxamides have been prepared. A key step was 1,3-dipolar cycloaddition of nitrile oxides to α,β-unsaturated esters. Some of these compounds exhibited high fungicidal activities against *Alternaria alternata*, *Botrytis cinerea*, *Rhizoctonia solani*, *Fusarium culmorum*, and *Phytophthora cactorum*.

Keywords Cycloaddition · Fungicides · Chlorination · Regioselectivity

Introduction

Climatic changes and the quick appearance of resistance in pathogenic organisms induce a continuous quest for new protective plant agents that show selective activity against pests and proper durability in the environment. The biological activity of carboxamides has been known for a long time. Herbicidal potency results from inhibiting phytoenone desaturase, an enzyme involved in the biosynthesis of carotenoids [1]. Fungicidal activity of some phenyl amides such as methalaxyl methyl originates from inhibition of ribosomal RNA synthesis, and the activity of heteroaromatic carboxamides, such as carboxine and thifluzamide, and aromatic amides (mepronil) lies in the inhibition of succinic dehydrogenase complex II from the pathogen respiration chain [2]. However, simple derivatives of isoxazole show also biological activity, e.g., hymexazole (3-hydroxy-5-methylisoxazole), disturbs the RNA metabolism of fungi [3]. These results induced us to prepare a series of new heterocyclic amide derivatives of 5- and 4-isoxazolecarboxylic acids as potential protective plant agents.

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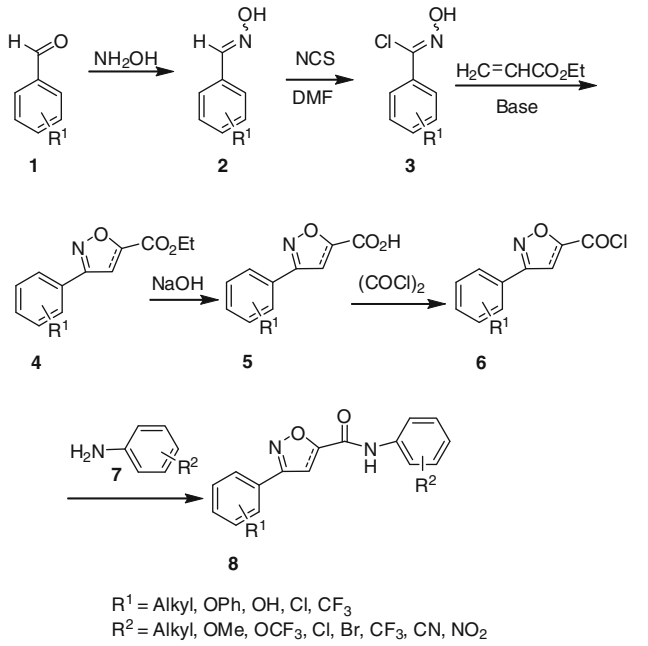
Results and discussion

Synthesis of intermediates

A key step in the synthesis was 1,3-dipolar cycloaddition of nitrile oxides to α,β-unsaturated esters resulting in 2-isoxazoline- or isoxazolecarboxylates, which were transformed into amides via acid chlorides. Starting materials were aldehydes, which were oximated with hydroxylamine and chlorinated with *N*-chlorosuccinimide (NCS) in DMF to form an imine group [4]. 4-Phenoxybenzaldehyde was prepared in an Ullmann reaction of 4-bromobenzaldehyde with phenol in DMF solution in the presence of anhydrous pyridine [5]. The course of the reaction of aldoximes with NCS depended on the solvent. In acetonitrile in the presence of half a molar equivalent of pyridine the major products for substrates with electron-donating groups (EDG) were nitriles, whereas benzaldoxime and oximes of aliphatic aldehydes afforded starting aldehydes [6]. For the majority of oximes chlorination with NCS in DMF proceeded smoothly, and nitrile oxides were generated in situ in the presence of tertiary amines, usually triethylamine (Huisgen method) [7] or on a basic Amberlyst A-21 column [8] (Scheme 1).

Apart from the commercial ethyl acrylate, esters were prepared by esterification of the corresponding acids or transesterification of some esters. Methyl cinnamates were synthesized from aryl aldehydes via Knoevenagel condensation and acidic esterification. Reactions of monosubstituted esters (acrylates) and α,α-disubstituted esters are



Scheme 1

highly regioselective and afford 3-substituted-4,5-dihydroisoxazole-5-carboxylates. α,β-Disubstituted esters show lower and opposite regiochemistry, and 4-substituted esters are the major compounds. In an asymmetric version of the reaction, we used chiral complexes of lanthanide triflates with 2,2′-binaphthol (BINOL) and obtained a series of 3-aryl-2-isoxazolines with enantioselectivities up to 89% [9]. Regioselectivity of the reaction depended on the steric demand of the ester group, and for *t*-butyl (*E*)-2-pentenecarboxylate the 4-ester was the only product. The electronic character of the dipole substituent was also important, since reactions with dipoles bearing electron-donating substituents (4-*i*-Pr, 4-OMe) showed higher regioselectivity than reactions with electron-withdrawing groups.

Synthesis of carboxamides

Some 3-aryl-4,5-dihydroisoxazolecarboxylates with halo- and trifluoromethylaryl substituents were dehydrated to the corresponding isoxazoles in a two-step reaction involving NBS bromination and potassium acetate induced dehydrobromination [10]. Esters were saponified with aqueous-ethanolic sodium hydroxide solution to carboxylic acids. Acid chlorides were prepared by reaction of the carboxylic acids with oxalyl chloride in benzene and further used to acylate a series of aromatic, heteroaromatic, and aliphatic amines typically in the presence of triethylamine (method A). Yields were usually good; only in cases of weakly nucleophilic aromatic amines with EWG were they modest, and some side reactions took place because of degradation of acid chlorides to 3-arylisoxazoles, 3-aryl-2-isoxazolines, and aryl nitriles [11]. Efficiency of the acylation reaction was much improved by formation of lithium amides with *n*-butyl lithium in diethyl ether solution (method B) or with *t*-butyl lithium (method C) reacting with acyl chlorides. However, acylation in THF resulted mainly in formation of *n*-butyl esters by cleavage of THF by butyl lithium. Four types of amides (**8**–**11**) were prepared (Scheme 2).

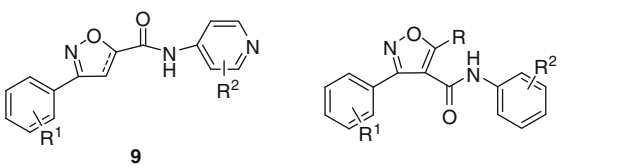
The obtained amides were screened for herbicidal, insecticidal, acaricidal and fungicidal activity. The best activity was found against fungus isolates (Table 1). The commercial fungicide chlorothalonil was tested as a reference compound under the same conditions as the isoxazole carboxamides.

Structure-activity relationship

Amides with electron-donating groups (EDG) at the aldehyde-derived phenyl ring showed low fungicidal activity; a smaller negative effect of EDGs at the other phenyl ring was also observed. High biological activity was found for compounds with electron-withdrawing groups (EWG) in both aromatic functions, and was particularly outstanding in case of CF_3 and F substituted amides **8i**, **9a**, **9c**, and **9f**. The last compound was more potent than the reference pesticide chlorothalonil. An increase of activity with a number of halide atoms in the first aromatic ring was found (cf. **8e**, **8h**, **8i**, and **9a**); however, a second CF_3 group lowered the activity.

The substitution pattern was also crucial. Amides with a CF_3 group at position 4 and 3 were similarly active, whereas 2-substituted products were devoid of activity. The same trend was observed also for the other aromatic ring. Introduction of another isoxazoline substituent (alkyl or phenyl) at positions 4/5 was also detrimental (compounds **10** and **11**).

In conclusion, biological activity is influenced by a combination of electronic and steric effects. High biological activity can be correlated with low electron density of the ring systems. Effective conjugation of the phenyl and the isoxazole rings is also essential, and ortho substitution in both rings is a detrimental factor causing the loss of



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R^1 = F, CF_3; R^2 = Cl, F

10 R = Me; R^1 = Cl; R^2 = Br
11 R = 4-$CF_3C_6H_4$; R^1 = *i*-Pr; R^2 = Br

Scheme 2

Table 1 Fungicidal inhibitory activities of compounds **8–11** at 200/20 μg cm^{-3}

Comp.[a]	R^1	R^2	*Alternaria alternata*	*Botrytis cinerea*	*Fusarium culmorum*	*Phytophtora cactorum*	*Rhizoctonia solani*
8a[a]	4-OPh	2,4,6-Cl_3	0	0	0	0	0
8b[a]	4-Et	2-CN	1	2	1	1	–
8c[a]	4-Et	4-CF_3	0	1	0	0	0
8d[a]	2-OH	4-*sec*-Bu	–	1	–	2	1
8e	2,4-Cl_2	4-Br	–	2	1	1	1
8f	2,4-Cl_2	4-OMe	2	1	0	0	1
8g[a]	2,3,6-Cl_3	4-OCF_3	–	1	0	1	1
8h	2,3,6-Cl_3	4-Br	2	2	2	2	2
8i	4-CF_3	2,6-Cl_2, 4-NO_2	3	2	2	2	2
8j	3,5-$(CF_3)_2$	2,6-Cl_2, 4-NO_2	0	1	1	0	1
9a	4-CF_3	3,5-Cl_2, 2,6-F_2	3	2	3	2	3
9b[a]	4-CF_3	3,5-Cl_2, 2,6-F_2	–	2	1	2	–
9c	4-CF_3	2,3,6-F_3, 6-Cl	–	3/2	2/1	3/2	3/1
9d[a]	2,4,5-F_3	2,3,6-F_3, 5-Cl	–	2	2	3	1
9e	4-CF_3	2,3,5,6-F_4	–	2	2	2	2
9f	3-CF_3	2,3,5,6-F_4	–	3/2	2/1	3/2	3/2
9g	3-CF_3	2,3,6-F_3, 5-Cl	–	2	2	2	2
9h	2-CF_3	2,3,5,6-F_4	–	0	1	0	0
10[a]	2,3,6-Cl_3	4-Br	1	0	1	1	0
11[a]	4-*i*-Pr	4-Br	0	0	0	0	0
Chlorothalonil				2/2	1/0	2/1	3/2

At 0–3 scale: 0 = 0–20% growth inhibition; 1 = 21–50% growth inhibition; 2 = 51–80% growth inhibition; 3 = 81–100% growth inhibition

[a] 4,5-dihydroisoxazole derivative

coplanarity. Further studies are in progress to quantitatively correlate electronic, steric, and hydrophobic effects with fungicidal potency.

Experimental

Reagent grade chemicals were used without further purification unless otherwise noted. Elemental analyses were performed at the Microanalysis Laboratory of Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw. Spectra were obtained as follows: IR spectra on JASCO FTIR-420 spectrometer, ^1H and ^{13}C NMR spectra on Varian 500 UNITY plus-500 and Varian 200 UNITY plus 200 spectrometers in deuterated chloroform using TMS as internal standard, and EI mass spectra on AMD M-40. In ^{13}C NMR spectra, signals of fluorine-substituted carbon atoms and some α-carbons were not observed because of strong ^{19}F–^{13}C coupling. In order to further characterize these compounds, ^{19}F spectra were recorded. Flash chromatography was carried out using silica gel S 230-400 mesh (Merck) and *n*-hexane-ethyl acetate mixtures as an eluent. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF [10]. The synthesis of compounds **4b**, **4e**, and **4g** has already been described [11].

General procedure for the cycloaddition reactions

A solution of 13 mmol chloro-oxime in 15 cm^3 anhydrous toluene was added dropwise over 30 min to a stirred mixture of anhydrous toluene, 6 cm^3 anhydrous NEt_3, 2 g $MgSO_4$, and 8 cm^3 ethyl acrylate (80 mmol). The reaction mixture was stirred overnight at room temperature, diluted with 50 cm^3 toluene, washed with water (5 × 100 cm^3), and evaporated in vacuo.

General procedure for amide synthesis with tertiary amines (method A)

A solution of an aniline derivative (1.2 mmol) in 10 cm^3 anhydrous toluene was added with stirring to an acid chloride followed by 4 cm^3 dry triethylamine (30 mmol). The solution was stirred under reflux for 1 h and overnight at room temperature. Water (10 cm^3) was added, and the organic layer was washed with 3% hydrochloric acid

solution and water, and dried over magnesium sulfate. A crude amide obtained after evaporation of the solvent was purified by crystallization.

General procedure for amide synthesis with n-butyl lithium (method B)

A 2.5-M solution of *n*-BuLi in hexane (0.2 cm^3, 0.5 mmol) was added dropwise at −78 °C to a stirred solution of 4-aminopyridine derivative (0.4 mmol) in dry diethyl ether. Stirring was continued for 1 h, and a solution of acid chloride (0.3 mmol) in dry diethyl ether (or HMPA) was added dropwise. The mixture was stirred for 5 h at 0 °C and overnight at room temperature. The reaction was quenched with ammonium chloride solution, and the product was extracted with methylene chloride and purified by flash chromatography.

General procedure for amide synthesis with t-butyl lithium (method C)

A 1.7-M solution of *t*-BuLi in hexane (1 cm^3, 1.7 mmol) was added dropwise at −78 °C to a stirred solution of an aniline derivative (1.2 mmol) in dry diethyl ether. Stirring was continued for 1, h and a solution of acid chloride (0.4 mmol) in dry HMPA was added dropwise. The mixture was stirred for 4 h at 0 °C and overnight at room temperature. The reaction was quenched with ammonium chloride solution, and the product was extracted with diethyl ether, washed with water, and purified by flash chromatography.

Ethyl 4,5-dihydro-3-(4-phenoxyphenyl)isoxazole-5-carboxylate (**4a**, $C_{18}H_{17}NO_4$)
Yield 67%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.68–7.62 (m, 2H, H-arom.), 7.42–7.31 (m, 2H, H-arom.), 7.20–7.17 (m, 1H, H-arom.), 7.07–6.96 (m, 4H, H-arom.), 5.16 (dd, J = 10.4, 8.0 Hz, 1H, H-5), 4.27 (q, J = 7.1 Hz, 2H, OCH_2), 3.63 (d, J = 10.4 Hz, 1H, H-4a), 3.62 (d, J = 8.0 Hz, 1H, H-4b), 1.33 (t, J = 7.2 Hz, 3H, CH_3) ppm.

Ethyl 4,5-dihydro-3-(2-hydroxyphenyl)isoxazole-5-carboxylate (**4c**, $C_{11}H_{13}NO_4$)
Yield 64%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.56 (1H, OH), 7.39–7.11 (m, 2H, H-4′, H-6′), 7.04 (dd, J = 8.4, 1.0 Hz, 1H, H-3′), 6.93 (m, 1H, H-5′), 5.14 (dd, J = 10.2, 8.0 Hz, 1H, H-5), 4.28 (q, J = 7.2 Hz, 2H, CH_2), 3.74 (d, J = 10.2 Hz, 1H, H-4a), 3.73 (d, J = 8.0 Hz, 1H, H-4b), 1.33 (t, J = 7.2 Hz, 3H, CH_3CH_2O) ppm; HRMS: calcd for $C_{12}H_{13}NNaO_4$ [M + Na^+] 258.0742, found 258.0751.

Ethyl 3-(2,4-dichlorophenyl)isoxazole-5-carboxylate (**4d**, $C_{12}H_{11}Cl_2NO_3$)
Yield 51%; m.p.: 154–157 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.4 Hz, 1H, H-6′), 7.45 (d, J = 2.0 Hz, 1H, H-3′), 7.42 (s, 1H, H-4), 7.38 (dd, J = 8.4, 2.0 Hz, 1H, H-5′), 4.47 (q, J = 7.2 Hz, 2H, CH_2), 1.44 (t, J = 7.2 Hz, 3H, CH_3) ppm; IR (KBr): $\bar{\nu}$ = 2,963, 2,920, 1,739, 1,584, 1,420, 1,307, 1,261, 1,215, 1,098, 803 cm^{-1}.

Methyl 4,5-dihydro-5-methyl-3-(2,3,6-trichlorophenyl) isoxazole-4-carboxylate (**4f**, $C_{12}H_{10}Cl_3NO_3$)
Yield 60%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.7 Hz, 1H, H-4′), 7.34 (d, J = 8.7 Hz, 1H, H-5′), 5.36 (quint, J = 6.7 Hz, 1H, H-5), 4.15 (d, J = 6.7 Hz, 1H, H-4), 3.64 (s, 3H, CH_3O), 1.55 (d, J = 6.7 Hz, 3H, CH_3CH) ppm; IR (neat): $\bar{\nu}$ = 2,940, 1,743, 1,560, 1,440, 1,400, 1,210, 1,190, 1,110, 1,022, 920, 820, 780, 730 cm^{-1}.

Ethyl 3-[4-(trifluoromethyl)phenyl]isoxazole-5-carboxylate (**4h**, $C_{13}H_{13}F_3NO_3$)
Yield 89%; m.p.: 124–126 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.97 (d, J = 8.4 Hz, 2H, H-3′, H-5′), 7.76 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.29 (s, 1H, H-4), 4.48 (q, J = 7.0 Hz, 2H, CH_2), 1.45 (t, J = 7.0 Hz, 3H, CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3,124, 2,997, 2,925, 1,734, 1,438, 1,329, 1,165, 1,128, 1,071, 855, 767 cm^{-1}; EIMS: *m/z* (%) = 285 (M^+, 18), 266 M^+–F, 4), 212 (M^+–CO_2Et, 100), 184 (M^+–CO_2Et–C_2H_4, 18), 145 ($C_6H_5CF_3$, 21).

Ethyl 3-[3,5-bis(trifluoromethyl)phenyl]isoxazole-5-carboxylate (**4i**, $C_{14}H_9F_6NO_3$)
Yield 73%; m.p.: 91–93 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.30 (s, 2H, H-2′, H-6′), 8.00 (d, J = 0.6 Hz, 1H, H-4′), 7.36 (s, 1H, H-4), 4.49 (q, J = 7 Hz, 2H, OCH_2), 1.46 (t, J = 7 Hz, 3H, CH_3) ppm; IR (KBr): $\bar{\nu}$ = 3,132, 3,000, 1,722, 1,622, 1,444, 1,353, 1,284, 1,191, 1,145, 1,026, 953, 914, 847, 834, 774, 707, 683 cm^{-1}.

Ethyl 4,5-dihydro-3-(2,4,5-trifluorophenyl)isoxazole-5-carboxylate (**4j**, $C_{12}H_{10}F_3NO_3$)
Yield 70%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76 (m, J = 8.7 Hz, 1H, H-6′), 7.00 (td, J = 10.0, 6.5 Hz, 1H, H-3′), 5.18 (dd, J = 9.4, 9.1 Hz, 1H, H-5), 4.28 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 3.70 (d, J = 9.1 Hz, 2H, H-4a), 3.68 (d, J = 9.4 Hz, 1H, H-4b), 1.33 (t, J = 7.2 Hz, 3H, CH_3CH_2) ppm; IR (neat): $\bar{\nu}$ = 3,080, 2,986, 1,741, 1,690, 1,627, 1,580, 1,512, 1,480, 1,440, 1,367, 1,285, 1,208, 1,162, 1,140, 1,035, 1,011, 891, 850, 809, 730 cm^{-1}; HRMS: calcd for $C_{12}H_{10}F_3NNaO_3$ [M + Na^+] 296.0505, found 296.0513.

Ethyl 3-[3-(trifluoromethyl)phenyl]isoxazole-5-carboxylate (**4k**, $C_{13}H_{13}F_3NO_3$)
Yield 82%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.09 (s, 1H, H-2′), 8.04 (d, J = 7.7 Hz, 1H, H-4′), 7.75 (d, J = 7.7 Hz, 1H, H-6′), 7.63 (t, J = 7.7 Hz, 1H, H-5′), 7.31 (s, 1H, H-4), 4.48 (q, J = 7.1 Hz, 2H, CH_2CH_3), 1.45 (t, J = 7.1 Hz, 3H, CH_2CH_3) ppm; IR (neat): $\overline{\nu}$ = 3,448, 3,120, 2,940, 2,910, 1,731, 1,620, 1,583, 1,470, 1,450, 1,390, 1,369, 1,335, 1,307, 1,227, 1,168, 1,120, 1,077, 1,017, 940, 912, 860, 809, 772, 697 cm^{-1}.

Ethyl 3-[2-(trifluoromethyl)phenyl]isoxazole-5-carboxylate (**4l**, $C_{13}H_{13}F_3NO_3$)
Yield 96%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.82 (m, 1H, H-6′), 7.68–7.57 (m, 3H, H-4′, H-5′, H-6′), 7.14 (s, 1H, H-4), 4.47 (q, J = 7.2 Hz, 2H, CH_2CH_3), 1.44 (t, J = 7.2 Hz, 3H, CH_2CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 162.8, 160.6, 156.8, 132.3, 132.3, 132.0, 130.4, 129.0 (q, J = 31.4 Hz), 126.7 (q, J = 5.2 Hz), 110.6 (q, J = 3.2 Hz) ppm; IR (neat): $\overline{\nu}$ = 2,987, 2,920, 1,740, 1,610, 1,581, 1,520, 1,470, 1,434, 1,390, 1,370, 1,316, 1,290, 1,275, 1,221, 1,180, 1,134, 1,080, 1,050, 1,035, 1,020, 950, 930, 770, 693 cm^{-1}; HRMS: calcd for $C_{13}H_{13}F_3NNaO_3$ [M + Na^+] 308.0505, found 308.0596.

Ethyl 4,5-dihydro-3-(4-isopropylphenyl)-5-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxylate (**4m**, $C_{22}H_{22}F_3NO_3$)
Yield 84%; oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.6 Hz, 2H, H-6′, H-2′), 7.65 (d, J = 8.3 Hz, 2H, H-3″, H-5″), 7.51 (d, J = 7.6 Hz, 2H, H-2″, H-6″), 7.26 (d, J = 8.3 Hz, 2H, H-3′, H-5′), 6.02 (d, J = 6.1 Hz, 1H, H-5), 4.39 (d, J = 6.1 Hz, 1H, H-4), 4.26 (q, J = 7.1 Hz, 2H, OCH_2), 2.93 (m, J = 7.1 Hz, 1H, $CH[CH_3]_2$), 1.25 (d, J = 7.0 Hz, 6H, $CH[CH_3]_2$), 1.08 (t, J = 7.1 Hz, 3H, CH_3CH_2O) ppm.

4,5-Dihydro-3-(4-phenoxyphenyl)isoxazole-5-carboxylic acid (**5a**, $C_{16}H_{13}NO_4$)
Yield 71%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.63 (dd, J = 8.8, 2.0 Hz, 2H, H-2″, H-6″), 7.35 (dd, J = 8.8, 7.9 Hz, 2H, H-3″, H-5″), 7.12 (t, J = 7.9 Hz, 1H, H-4″), 7.05 (d, J = 8.0 Hz, 2H, H-2′, H-6′), 6.99 (d, J = 8.0 Hz, 2H, H-3′, H-5′), 6.45 (s, 1H, HO), 5.23 (dd, J = 8.3, 9.2 Hz, 1H, H-5), 3.73 (d, J = 8.3 Hz, 1H, H-4), 3.69 (d, J = 9.2 Hz, 1H, H-4) ppm; IR (KBr): $\overline{\nu}$ = 3,432, 3,050, 2,940, 1,726, 1,589, 1,510, 1,490, 1,358, 1,250, 1,165, 1,094, 1,005, 875, 830, 752, 693 cm^{-1}; EIMS: *m/z* (%) = 281 (M^+, 75), 236 (M^+–HOC=O, 70), 77 (C_6H_5, 100).

3-(4-Ethylphenyl)-4,5-dihydroisoxazole-5-carboxylic acid (**5b**, $C_{12}H_{13}NO_3$)
Yield 89%; m.p.: 106–108 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 2H, H-3′, H-5′), 7.76 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.29 (s, 1H, H-4), 2.68 (q, J = 7.0 Hz, 2H, CH_2), 1.45 (t, J = 7.0 Hz, 3H, CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 175.0, 156.7, 147.7, 128.6 (2C), 127.3 (2C), 125.6, 77.4, 29.0, 15.5 ppm; IR (KBr): $\overline{\nu}$ = 3,500–2,800, 1,730 (COOH) cm^{-1}; EIMS: *m/z* (%) = 285 (M^+, 18), 266 (M^+–F, 4), 212 (M^+–CO_2Et, 100), 184 (M^+–CO_2Et–C_2H_4, 18), 145 ($C_6H_5CF_3$, 21).

4,5-Dihydro-3-(2-hydroxyphenyl)isoxazole-5-carboxylic acid (**5c**, $C_{10}H_9NO_4$)
Yield 61%; m.p.: 80–82 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.45 (s, 1H, COOH), 8.36 (s, 1H, ArOH), 7.15 (m, 4H, H-3′, H-4′, H-5′, H-6′), 5.23 (m, 1H, H-5), 3.78 (dd, J = 9.2, 8.2 Hz, 1H, H-4), 3.78 (m, 1H, H-4) ppm; IR (KBr): $\overline{\nu}$ = 3,410, 3,051, 2,680, 2,530, 1,721, 1,620, 1,598, 1,575, 1,493, 1,475, 1,438, 1,398, 1,360, 1,310, 1,259, 1,240, 1,220, 1,160, 1,100, 980, 921, 878, 823, 750 cm^{-1}.

3-(2,4-Dichlorophenyl)isoxazole-5-carboxylic acid (**5d**, $C_{10}H_5Cl_2NO_3$)
Yield 92%; m.p.: 165–167 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.2 Hz, 1H, H-6′), 7.56 (d, J = 2.0 Hz, 1H, H-3′), 7.52 (s, 1H, H-4), 7.39 (dd, J = 8.2, 2.0 Hz, 1H, H-5′) ppm; EIMS: *m/z* (%) = 257 (M^+, 32), 212 (M^+–CO_2H, 100), 184 (M^+–CO_2H–CO, 44).

4,5-Dihydro-3-(2,3,6-trichlorophenyl)isoxazole-5-carboxylic acid (**5e**, $C_{12}H_6Cl_3NO_3$)
Yield 87%; m.p.: 89–91 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.50 (d, J = 8.6 Hz, 1H, H-4′), 7.34 (d, J = 8.6 Hz, 1H, H-5′), 5.33 (dd, J = 11.2, 6.8 Hz, 1H, H-5), 4.30 (q, J = 7.2 Hz, 2H, CH_2), 3.66 (d, J = 11.2 Hz, 1H, H-4), 3.62 (d, J = 6.8 Hz, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 173.6, 154.2, 133.6, 133.3, 132.5, 132.2, 129.2, 128.9, 72.0, 41.3 ppm; IR (KBr): $\overline{\nu}$ = 3,600–2,500, 1,731 (COOH), 819, 523 cm^{-1}.

3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid (**5f**, $C_{11}H_6F_3NO_3$)
Yield 71%; m.p.: 192–195 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.99 (d, J = 8.1 Hz, 2H, H-3′, H-5′), 7.77 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.38 (s, 1H, H-4) ppm; IR (KBr): $\overline{\nu}$ = 3,400–2,900, 2,923, 1,720, 1,328, 1,136, 1,071, 842 cm^{-1}.

3-[3,5-Bis(trifluoromethyl)phenyl]isoxazole-5-carboxylic acid (**5g**, $C_{12}H_5F_6NO_3$)
Yield 83%; m.p.: 152–154 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (s, 2H, H-6′, H-2′), 8.02 (s, 1H, H-4′), 7.48 (s, 1H, H-4), 5.48 (s, OH) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 161.1, 159.1, 146.9, 132.9 (q, J = 34.2 Hz, 2C), 130.0, 127.0 (m), 124.3 (m), 108.4 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): δ = −63.5 ppm; IR (KBr): $\overline{\nu}$ = 3,429, 3,170, 2,980, 2,670, 1,720, 1,615, 1,605, 1,590, 1,500,

1,450, 1,422, 1,354, 1,282, 1,170, 1,143, 1,075, 990, 902, 846, 799, 760, 730, 706, 683 cm^{-1}.

4,5-Dihydro-3-(2,4,5-trifluorophenyl)isoxazole-5-carboxylic acid (**5h**, $C_{10}H_6F_3NO_3$)
Yield 75%; m.p.: 90–93 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.75$ (dt, $J = 10.0$, 6.5 Hz, 1H, H-6′), 7.01 (td, $J = 10.0$, 6.5 Hz, 1H, H-3′), 6.51 (s, 1H, OH), 5.25 (dd, $J = 10.5$, 7.9 Hz, 1H, H-5), 3.76 (d, $J = 10.5$ Hz, 2H, H-4a), 3.74 (d, $J = 7.9$ Hz, 1H, H-4b) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 174.3$, 151.7, 116.7 (dd, $J = 24.2$, 3.6 Hz), 114.8 (dd, $J = 21.7$, 4.3 Hz), 77.8, 40.3 (d, $J = 8.3$ Hz) ppm; IR (KBr): $\overline{\nu} = 3{,}433$, 3,080, 2,920, 2,650, 1,719, 1,628, 1,580, 1,516, 1,440, 1,367, 1,290, 1,230, 1,190, 1,140, 1,010, 980, 897, 806, 730, 645, 600 cm^{-1}.

3-[3-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid (**5i**, $C_{11}H_6F_3NO_3$)
Yield 88%; m.p.: 104–106 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.04$ (s, 1H, OH), 8.12 (s, 1H, H-2′), 8.04 (d, $J = 7.6$ Hz, 1H, H-4′), 7.77 (d, $J = 7.6$ Hz, 1H, H-6′), 7.65 (t, $J = 7.6$ Hz, 1H, H-5′), 7.43 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 170.9$, 162.1, 160.6, 130.1, 129.8, 129.7 (q, $J = 39.6$ Hz), 128.6, 127.4 (q, $J = 3.5$ Hz), 123.8 (q, $J = 3.6$ Hz), 108.6 ppm; IR (KBr): $\overline{\nu} = 3{,}440$, 3,120, 2,910, 1,730, 1,698, 1,620, 1,600, 1,585, 1,457, 1,430, 1,410, 1,380, 1,329, 1,280, 1,230, 1,180, 1,150, 1,128, 1,100, 1,071, 990, 940, 915, 860, 805, 780, 760, 698 cm^{-1}.

3-[2-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid (**5j**, $C_{11}H_6F_3NO_3$)
Yield 78%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.81$ (s, 1H, OH), 7.82 (m, 1H, H-3′), 7.68–7.58 (m, 3H, H-4′, H-5′, H-6′), 7.67 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 162.4$, 160.3, 159.9, 132.4, 132.4, 132.0, 130.6, 129.0 (q, $J = 31.4$ Hz), 126.8 (q, $J = 5.2$ Hz), 112.0 (q, $J = 3.2$ Hz) ppm; IR (KBr): $\overline{\nu} = 3{,}000$, 2,840, 1,717, 1,605, 1,595, 1,580, 1,515, 1,445, 1,400, 1,387, 1,315, 1,270, 1,232, 1,180, 1,126, 1,105, 990, 950, 938, 905, 850, 771, 690 cm^{-1}.

4,5-Dihydro-5-methyl-3-(2,3,6-trichlorophenyl)isoxazole-4-carboxylic acid (**5k**, $C_{11}H_8Cl_3NO_3$)
Obtained by hydrolysis of a corresponding known ester [9].
Yield 67%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.40$ (s, 1H, OH), 7.49 (d, $J = 8.8$ Hz, 1H, H-4′), 7.33 (d, $J = 8.8$ Hz, 1H, H-5′), 5.30 (quint, $J = 6.7$ Hz, 1H, H-5), 4.21 (d, $J = 6.7$ Hz, 1H, H-4), 1.55 (d, $J = 6.7$ Hz, 3H, CH_3CH) ppm; IR (neat): $\overline{\nu} = 3{,}420$, 3,080, 2,986, 2,640, 1,715, 1,635, 1,422, 1,388, 1,287, 1,230, 1,200, 1,180, 1,036, 917, 830, 818, 760, 720 cm^{-1}.

4,5-Dihydro-3-(4-isopropylphenyl)-5-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxylic acid (**5l**, $C_{20}H_{18}F_3NO_3$)
Yield 94%; glass; IR (KBr): $\overline{\nu} = 2{,}960$, 1,717, 1,610, 1,415, 1,323, 1,265, 1,160, 1,130, 1,069, 1,018, 960, 894, 836 cm^{-1}; EIMS: *m/z* (%) = 377 (M^+, 26), 362 (M^+–CH_3, 20), 334 (M^+–$CH[CH_3]_2$, 12), 333 (M^+–O=C–O, 58), 318 (M^+–O=C–OCH_2, 25), 303 (M^+–O=C–O$[CH_3]_2$, 12), 188 (M^+–O=C–$OC_6H_4CF_3$, 18), 173 (M^+–O=C–$OC_6H_4CF_3CH_3$, 31), 145 ($C_6H_4CF_3$, 28), 43 ($CH[CH_3]_2$, 71).

4,5-Dihydro-3-(4-phenoxyphenyl)isoxazole-5-carboxylic acid 2,4,6-trichlorophenylamide (**8a**, $C_{22}H_{15}Cl_3N_2O_3$)
Method A, yield 41%; m.p.: 254–257 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.90$–7.00 (m, 12H, H-3′, H-5′, H-2′, H-6′, H-3″, H-5″, H-2″, H-6″, H-4″, H-3‴, H-5‴, NH), 5.33 (dd, $J = 9.0$, 8.1 Hz, 1H, H-5), 3.78 (d, $J = 9.0$ Hz, 1H, H-4), 3.77 (d, $J = 8.1$ Hz, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 169.1$, 159.5, 158.8, 155.2, 135.3 (2C), 134.9, 129.9 (2C), 129.7 (2C), 129.1 (2C), 125.3, 124.7, 122.5, 120.5 (2C), 118.7 (2C), 76.6, 39.8 ppm; IR (KBr): $\overline{\nu} = 3{,}434$, 3,262, 3,080, 1,693, 1,580, 1,555, 1,487, 1,373, 1,243, 1,167, 1,078, 847, 804, 690 cm^{-1}; EIMS: *m/z* (%) = 462 (M^+, 2), 238 (M^+–$CONHC_6H_2Cl_3$, 5), 224 ($OCNHC_6H_2Cl_3$, 10), 195 ($NHC_6H_2Cl_3$, 45), 169 ($C_6H_5OC_6H_4$, 20).

3-(4-Ethylphenyl)-4,5-dihydroisoxazole-5-carboxylic acid 2-cyanophenylamide (**8b**, $C_{19}H_{17}N_3O_2$)
Method A, yield 25%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.12$ (s, 1H, NH), 8.31 (d, $J = 8.2$ Hz, 1H, H-3″), 7.63 (d, $J = 8.3$ Hz, 2H, H-6′, H-2′), 7.62 (d, 1H, $J = 7.8$ Hz, H-6″), 7.58 (dd, $J = 7.8$, 1.6 Hz, 1H, H-5″), 7.26 (d, $J = 8.3$ Hz, 2H, H-5′, H-3′), 7.26–7.19 (td, $J = 8.4$, 1.4 Hz, 1H, H-4″), 5.29 (dd, $J = 9.7$, 6.7 Hz, 1H, H-5), 3.79 (m, $J = 9.8$, 6.4 Hz, 2H, H-4), 2.68 (q, $J = 7.6$ Hz, 2H, CH_2), 1.24 (t, $J = 7.4$ Hz, 3H, CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 170.2$, 157.6, 147.7, 139.2, 134.1, 132.7, 128.5 (2C), 127.3 (2C), 125.5, 125.2, 121.8, 115.9, 103.9, 78.9, 40.0, 28.9, 15.4 ppm; IR (KBr): $\overline{\nu} = 3{,}366$, 1,698, 1,581, 1,523, 1,449, 1,303, 860, 829, 759 cm^{-1}; EIMS: *m/z* (%) = 319 (M^+, 7), 174 (M^+–$CONHC_6H_4CN$, 100), 118 ($NH_2C_6H_4CN$, 25), 105 ($C_6H_4C_2H_5$, 10).

3-(4-Ethylphenyl)isoxazole-5-carboxylic acid (4-trifluoromethyl)phenylamide (**8c**, $C_{19}H_{15}F_3N_2O_2$)
Method A, yield 95%; m.p.: 154–156 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.70$ (s, 1H, NH), 7.72 (d, $J = 8.8$ Hz, 2H, H-3″, H-5″), 7.60 (d, $J = 8.4$ Hz, 2H, H-2′, H-6′), 7.59 (d, 2H, $J = 8.8$ Hz, H-2″), 7.26

(d, $J = 8.4$ Hz, H-3′, H-5′), 5.25 (dd, $J = 10.2$, 6.6 Hz, 1H, H-5), 3.80 (d, $J = 6.6$ Hz, 1H, H-4a), 3.78 (d, $J = 10.2$ Hz, 1H, H-4b), 2.85 (q, $J = 7.6$ Hz, 2H, CH_2Ph), 1.24 (t, $J = 7.6$ Hz, 3H, C–CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 169.6$, 157.0, 148.4, 145.5, 129.6 (2C), 128.4 (2C), 127.3 (q, $J = 4.0$ Hz, 2C), 121.7, 121.3 (2C), 80.6, 40.4, 29.5, 16.3 ppm; IR (KBr): $\overline{\nu} = 3{,}320$, 2,962, 2,925, 1,681, 1,620, 1,530, 1,411, 1,327, 1,160, 1,123, 1,072, 836 cm^{-1}.

4,5-Dihydro-3-(2-hydroxyphenyl)isoxazole-5-carboxylic acid 4-(sec-butyl)phenylamide (**8d**, $C_{20}H_{22}N_2O_3$)
Method A, yield 55%; glass; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 9.47$ (s, 1H, NH), 8.41(s, 1H, HO), 7.48 (d, $J = 8.6$ Hz, 2H, H-6″, H-2″), 7.16 (m, 4H, H-3′, H-4′, H-5′, H-6′), 7.15 (d, $J = 8.6$ Hz, 2H, H-3″, H-5″), 5.23 (dd, $J = 11.2$, 5.6 Hz, 1H, H-5), 3.90 (d, $J = 5.6$ Hz, 1H, H-4), 3.86 (d, $J = 11.2$ Hz, 1H, H-4), 2.57 (m, 1H, CH), 1.56 (m, 2H, CH_2), 1.20 (d, $J = 5.6$ Hz, 3H, CH_3), 0.79 (t, $J = 7.4$ Hz, 3H, CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 168.4$, 159.6, 157.6, 144.9, 134.4, 132.8, 129.2, 127.8 (2C), 120.3 (2C), 120.1, 117.3, 113.0, 77.9, 41.4, 40.2, 31.3, 22.0, 12.4 ppm; IR (KBr): $\overline{\nu} = 3{,}300$, 3,060, 2,961, 1,683, 1,600, 1,525, 1,495, 1,417, 1,310, 1,258, 918, 870, 824, 754 cm^{-1}.

3-(2,4-Dichlorophenyl)isoxazole-5-carboxylic acid 4-bromophenylamide (**8e**, $C_{16}H_9BrCl_2N_2O_2$)
Method A, yield 75%; glass; ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 8.26$ (s, 1H, NH), 7.72 (d, $J = 8.2$ Hz, 1H, H-6′), 7.56 (m, 4H, H-2″, H-3″, H-5″, H-6″), 7.49 (s, 1H, H-4), 7.39 (dd, $J = 8.2$, 1.9 Hz, 1H, H-5′) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 163.2$, 161.8, 153.6, 137.4, 135.8, 134.1, 132.6 (2C), 131.9, 131.0, 130.8, 128.0, 122.1 (2C), 109.2 ppm; IR (KBr): $\overline{\nu} = 3{,}340$, 2,340, 1,670, 1,596, 1,532, 1,395, 819 cm^{-1}; EIMS: *m/z* (%) = 410 (M^+, 27), 214 (M^+–O=C–NHC_6H_4Br, 68), 172 ($NH_2C_6H_4Br$, 15), 171 (NHC_6H_4Br, 7), 157 (C_6H_4Br, 16), 75 (C_6H_3, 16).

3-(2,4-Dichlorophenyl)isoxazole-5-carboxylic acid 4-methoxyphenylamide (**8f**, $C_{17}H_{12}Cl_2N_2O_3$)
Method A, yield 69%; m.p.: 154–157 °C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.39$ (s, 1H, NH), 7.71 (d, $J = 8.6$ Hz, 1H, H-6′), 7.57 (d, $J = 8.8$ Hz, 2H, H-2″, H-6″), 7.47 (d, $J = 2.0$ Hz, 1H, H-3′), 7.46 (s, 1H, H-4), 7.30 (dd, $J = 8.6$, 2.0 Hz, 1H, H-5′), 3.80 (s, 3H, OCH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 163.7$, 161.7, 157.6, 153.5, 137.3, 134.1, 131.9, 130.7, 129.8, 127.9, 126.0, 122.3 (2C), 114.7 (2C), 108.8, 55.7 ppm; IR (KBr): $\overline{\nu} = 3{,}382$, 2,922, 1,684, 1,540, 1,510, 1,423, 1,250, 1,034, 825 cm^{-1}; EIMS: *m/z* (%) = 362 (M^+, 53), 212 (M^+–$C_8H_8NO_2$, 100), 184 (M^+–$C_8H_8NO_2$–CO, 27), 149 (M^+–$C_8H_8NO_2$–CO–Cl, 34), 123 ($C_4H_3Cl_2$, 85).

4,5-Dihydro-3-(2,3,6-trichlorophenyl)isoxazole-5-carboxylic acid 4-(trifluoromethoxy)phenylamide (**8g**, $C_{17}H_{10}Cl_3F_3N_2O_3$)
Method B, yield 37%; glass; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.60$ (s, 1H, NH), 7.63 (d, $J = 8.8$ Hz, 1H, H-6″), 7.51 (d, $J = 8.8$ Hz, 1H, H-4′), 7.34 (d, $J = 8.8$ Hz, 1H, H-3′), 7.22 (d, $J = 8.8$ Hz, 2H, H-3″, H-5″), 5.35 (dd, $J = 10.8$, 5.4 Hz, 1H, H-5), 3.74 (d, $J = 10.8$ Hz, 1H, H-4), 3.69 (d, $J = 5.4$ Hz, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 167.9$, 158.1, 151.3 (q, $J = 4.8$ Hz), 139.9, 134.1, 133.8, 133.6, 132.5, 132.4, 129.0, 122.5 (2C), 121.3 (2C), 78.9, 38.4 ppm; IR (KBr): $\overline{\nu} = 3{,}300$, 3,080, 2,932, 1,684, 1,610, 1,530, 1,510, 1,450, 1,420, 1,305, 1,262, 1,220, 1,165, 1,107, 1,040, 850, 817, 750 cm^{-1}; EIMS: *m/z* (%) = 477 (M^+, 65).

3-(2,3,6-Trichlorophenyl)isoxazole-5-carboxylic acid 4-bromophenylamide (**8h**, $C_{16}H_8BrCl_3N_2O_2$)
Method A, yield 39%; glass; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.38$ (s, 1H, NH), 7.59 (d, $J = 8.6$ Hz, 2H, H-2″, H-6″), 7.51 (d, $J = 8.7$ Hz, 1H, H-4′), 7.45 (d, $J = 8.7$ Hz, 1H, H-5′), 7.40 (d, $J = 8.6$ Hz, 2H, H-3″, H-5″), 7.12 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 163.5$, 160.2, 153.2, 135.5, 134.0, 133.6, 132.6, 132.3, 132.2 (3C), 128.8, 121.9 (2C), 118.4, 109.4 ppm; IR (KBr): $\overline{\nu} = 3{,}341$, 3,292, 3,110, 2,920, 1,695, 1,663, 1,620, 1,590, 1,539, 1,490, 1,420, 1,395, 1,350, 1,313, 1,250, 1,181, 1,099, 1,073, 1,009, 880, 820, 759 cm^{-1}.

3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 2,6-dichloro-4-nitrophenylamide (**8i**, $C_{17}H_8Cl_2F_3N_3O_4$)
Method C, yield 49%; m.p.: 129–131 °C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.39$ (s, 1H, NH), 8.17 (s, 2H, H-3″, H-5″), 7.92 (d, $J = 8.2$ Hz, 2H, H-3′, H-5′), 7.75 (d, $J = 8.2$ Hz, 2H, H-2′, H-6′), 7.47 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 162.6$, 161.7, 152.3, 144.5, 142.1, 136.4 (2C), 128.9, 127.6 (2C), 126.6 (2C), 126.1 (2C, q, $J = 3.9$ Hz), 107.9 ppm; IR (KBr): $\overline{\nu} = 3{,}364$, 1,700, 1,623, 1,496, 1,325, 1,131, 1,065, 950, 900, 816, 741 cm^{-1}; EIMS: *m/z* (%) = 446 (M^+, 1), 410 (M^+–Cl, 35), 240 (M^+–$NHC_6H_2Cl_2NO_2$, 63), 212 (M^+–$NHC_6H_2Cl_2NO_2C$=O, 100), 145 ($C_6H_5CF_3$, 51), 69 (CF_3, 10).

3-[3,5-Bis(trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 2,6-dichloro-4-nitrophenylamide (**8j**, $C_{18}H_7Cl_2F_6N_3O_4$)
Method C, yield 31%; glass; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.35$ (s, 2H, H-5″, H-3″), 8.32 (s, 2H, H-2′, H-6′), 8.21 (s, 1H, NH), 8.04 (s, 1H, H-4′), 7.52 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 162.1$, 159.6, 152.2, 144.7, 142.0, 136.3 (2C), 129.4, 128.3 (2C, q, $J = 4.3$ Hz), 107.2 ppm; IR (KBr): $\overline{\nu} = 3{,}438$, 3,100, 1,689, 1,630, 1,541, 1,520, 1,352, 1,281, 1,185, 1,137, 904, 815, 740, 706 cm^{-1}.

3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 3,5-dichloro-2,6-difluoropyridin-4-ylamide
(**9a**, $C_{16}H_6Cl_2F_5N_3O_2$)
Yield 51%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.32$ (s, 1H, NH), 8.0 (d, $J = 8.2$ Hz, 2H, H-5′, H-3′), 7.80 (d, $J = 8.2$ Hz, 2H, H-6′, H-2′), 7.50 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 162.5$, 161.7, 152.6, 128.9, 127.4 (2C), 126.4 (2C, t, $J = 3.9$ Hz), 107.6 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -63.4$ (s, 3F), −69.3 (s, 2F) ppm; IR (KBr): $\overline{\nu} = 3{,}240$, 3,000, 1,695, 1,603, 1,501, 1,435, 1,411, 1,326, 1,280, 1,160, 1,138, 1,073, 1,020, 952, 891, 849, 788, 739 cm^{-1}.

4,5-Dihydro-3-[4-(trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 3,5-dichloro-2,6-difluoropyridin-4-ylamide (**9b**, $C_{16}H_8Cl_2F_5N_3O_2$)
Method B, yield 25%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.65$ (s, 1H, NH), 7.83 (d, $J = 8.3$ Hz, 2H, H-5′, H-3′), 7.72 (d, $J = 8.3$ Hz, 2H, H-6′, H-2′), 5.43 (t, $J = 8.4$ Hz, 1H, H-5), 3.83 (d, $J = 8.4$ Hz, 2H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 168.2$, 156.8, 145.4, 131.1, 127.5 (2C), 126.1 (q, $J = 3.6$ Hz, 2C), 79.3, 39.5 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -63.8$ (s, 3F), −88.8 (s, 2F) ppm; IR (KBr): $\overline{\nu} = 3{,}220$, 2,920, 2,850, 1,705, 1,602, 1,490, 1,405, 1,327, 1,175, 1,125, 1,070, 1,040, 919, 878, 840, 788 cm^{-1}.

3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 5-chloro-2,3,6-trifluoropyridin-4-ylamide
(**9c**, $C_{16}H_6ClF_6N_3O_2$)
Method C, yield 65%; m.p.: 211–214 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.32$ (s, 1H, NH), 8.00 (d, $J = 8.1$ Hz, 2H, H-3′, H-5′), 7.80 (d, $J = 8.1$ Hz, 2H, H-2′, H-6′), 7.50 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 162.8$, 162.0, 152.0, 128.5, 127.4 (2C), 126.3 (q, $J = 3.8$ Hz, 2C), 107.6 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -63.6$ (s, 3F), −72.4 (dd, $J = 25.9$, 13.7 Hz, 1F), −86.2 (dd, $J = 20.7$, 13.2 Hz, 1F), −140.9 (dd, $J = 27.3$, 20.7 Hz, 1F) ppm; IR (KBr): $\overline{\nu} = 3{,}420$, 3,252, 3,130, 2,910, 2,840, 1,697, 1,625, 1,538, 1,481, 1,430, 1,400, 1,327, 1,278, 1,250, 1,170, 1,139, 1,118, 1,074, 1,050, 950, 905, 870, 850, 838, 760, 740 cm^{-1}.

4,5-Dihydro-3-(2,4,5-trifluorophenyl)isoxazole-5-carboxylic acid 5-chloro-2,3,6-trifluoropyridin-4-ylamide
(**9d**, $C_{15}H_6ClF_6N_3O_2$)
Method C, yield 85%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.59$ (s, 1H, NH), 7.78–7.66 (dt, $J = 10.5$, 6.6 Hz, 1H, H-3′), 7.12–6.98 (td, $J = 10.0$, 6.4 Hz, 1H, H-6′), 5.18 (dd, $J = 8.9$, 8.5 Hz, 1H, H-5), 3.87 (d, $J = 8.5$ Hz, 1H, H-4), 3.86 (d, $J = 8.9$ Hz, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 168.5$, 153.4, 116.8 (ddd, $J = 21.2$, 6.4, 2.0 Hz), 107.1 (dd, $J = 28.2$, 21.2 Hz), 79.4, 41.1 (d, $J = 8.3$ Hz) ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -72.9$ (dd, $J = 26.4$, 13.2 Hz, 1F), −86.8 (dd, $J = 21,7$, 13.2 Hz, 1F), −113.4 (m, 1F), −127.3 (dtd, $J = 22.2$, 8.5, 5.7 Hz, 1F), −140.5 (m, 1F), −141.8 (dd, $J = 26.4$, 20.7 Hz, 1F) ppm; IR (KBr): $\overline{\nu} = 3{,}380$, 3,253, 3,120, 3,020, 2,900, 1,701, 1,624, 1,580, 1,520, 1,477, 1,440, 1,400, 1,360, 1,270, 1,240, 1,193, 1,140, 1,095, 1,073, 1,030, 1,005, 925, 895, 875, 800, 730 cm^{-1}.

3-[4-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 2,3,5,6-tetrafluoropyridin-4-ylamide (**9e**, $C_{16}H_6F_7N_3O_2$)
Method C, yield 66%; m.p.: 209–211 °C, ^{1}H NMR (200 MHz, $(CD_3)_2CO$): $\delta = 8.32$ (s, 1H, NH), 8.00 (d, $J = 8.3$ Hz, 2H, H-3′, H-5′), 7.80 (d, $J = 8.3$ Hz, 2H, H-2′, H-6′), 7.50 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $(CD_3)_2CO$): $\delta = 163.5$, 162.5, 154.1, 132.1, 127.9 (2C), 126.3 (2C, q, $J = 4.0$ Hz), 106.7 ppm; ^{19}F NMR (471 MHz, $(CD_3)_2CO$): $\delta = -63.9$ (3F), −93.1 (m, 1F), −141.5 (m, 1F), −146.1 (m, 1F), −146.5 (m, 1F) ppm; IR (KBr): $\overline{\nu} = 3{,}450$, 3,297, 3,130, 2,920, 2,840, 1,698, 1,650, 1,620, 1,522, 1,490, 1,436, 1,420, 1,328, 1,285, 1,240, 1,171, 1,131, 1,118, 1,077, 1,050, 1,000, 960, 910, 870, 840, 760 cm^{-1}.

3-[3-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 2,3,5,6-tetrafluoropyridin-4-ylamide (**9f**, $C_{16}H_6F_7N_3O_2$)
Method C, yield 69%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.51$ (s, 1H, NH), 8.12 (s, 1H, H-2′), 8.04 (d, $J = 7.8$ Hz, 1H, H-4′), 7.80 (d, $J = 7.8$ Hz, 1H, H-6′), 7.66 (t, $J = 7.8$ Hz, 1H, H-5′), 7.52 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 163.1$, 162.2, 152.4, 132.2 (q, $J = 32.9$ Hz), 130.4, 130.1, 128.5, 127.9 (q, $J = 3.6$ Hz), 124.1 (q, $J = 4.0$ Hz), 107.8 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -63.4$ (s, 3F), −88.8 (m, 1F), −144.6 (m, 1F) ppm; IR (KBr): $\overline{\nu} = 3{,}410$, 3,245, 2,920, 2,850, 1,699, 1,644, 1,618, 1,523, 1,464, 1,420, 1,327, 1,282, 1,240, 1,170, 1,150, 1,118, 1,076, 1,050, 1,000, 966, 920, 874, 810, 760, 696 cm^{-1}.

3-[3-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 5-chloro-2,3,6-trifluoropyridin-4-ylamide
(**9g**, $C_{16}H_6ClF_6N_3O_2$)
Method C, yield 28%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.11$ (s, 1H, H-2′), 8.01 (dm, $J = 7.6$ Hz, 1H, H-4′), 7.76 (dm, $J = 7.6$ Hz, 1H, H-6′), 7.64 (m, 1H, H-5′), 7.32 (s, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $(CD_3)_2CO$): $\delta = 163.4$, 157.4, 154.1, 131.7, 131.4, 128.4 (q, $J = 3.6$ Hz), 124.6 (q, $J = 3.5$ Hz), 108.1 ppm; ^{19}F NMR (471 MHz, $(CD_3)_2CO$): $\delta = -63.7$ (3F), −75.6 (dd, $J = 25.4$, 14.0 Hz, 1F), −90.9 (dd, $J = 25.9$, 21.7 Hz, 1F), −145.1 (dd, $J = 25.9$, 21.7 Hz, 1F) ppm; IR (KBr): $\overline{\nu} = 3{,}408$, 3,200, 2,925, 2,860, 1,715, 1,662, 1,620, 1,500, 1,475, 1,400, 1,380, 1,328, 1,270, 1,171, 1,130, 1,074, 905, 895, 805, 696 cm^{-1}.

3-[2-(Trifluoromethyl)phenyl]isoxazole-5-carboxylic acid 2,3,5,6-tetrafluoropyridin-4-ylamide (**9h**, $C_{16}H_6F_7N_3O_2$)
Method C, yield 53%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 8.51$ (s, 1H, NH), 7.86 (m, 1H, H-3′), 7.68 (m, 3H, H-4′, H-5′, H-6′), 7.34 (d, $J = 0.8$ Hz, 1H, H-4) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 163.0$, 160.9, 152.2, 132.2, 131.7, 130.7, 126.8 (q, $J = 5.2$ Hz), 110.8 (q, $J = 4.8$ Hz) ppm; IR (KBr): $\overline{\nu} = 3{,}420$, 3,207, 3,100, 3,000, 2,900, 2,840, 1,720, 1,641, 1,604, 1,537, 1,470, 1,420, 1,400, 1,316, 1,280, 1,227, 1,192, 1,124, 1,060, 1,039, 1,005, 968, 865, 775, 700 cm^{-1}.

4,5-Dihydro-5-methyl-3-(2,3,6-trichlorophenyl)isoxazole-4-carboxylic acid 4-bromophenyl amide
(**10**, $C_{17}H_{12}BrCl_3N_2O_2$)
Method B, yield 19%; glass; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.50$ (d, $J = 8.7$ Hz, 1H, H-4′), 7.40 (d, $J = 8.7$ Hz, 2H, H-2″, H-6″), 7.34 (d, $J = 8.7$ Hz, 1H, H-5′), 7.24 (d, $J = 8.7$ Hz, 2H, H-3″, H-5″), 5.39 (quint, $J = 6.2$ Hz, 1H, H-5), 4.17 (d, $J = 6.2$ Hz, 1H, H-4), 1.59 (d, $J = 6.2$ Hz, 3H, CH_3) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 170.9$, 155.2, 135.9, 135.7, 133.9, 133.7, 132.9 (2C), 132.7, 132.5, 132.4, 129.9, 121.7 (2C), 72.6, 68.1, 14.1 ppm; IR (KBr): $\overline{\nu} = 3{,}370$, 3,292, 3,080, 2,980, 1,663, 1,595, 1,515, 1,489, 1,441, 1,396, 1,305, 1,287, 1,240, 1,179, 1,072, 1,009, 920, 819, 780, 725 cm^{-1}; EIMS: *m/z* (%) = 461 (M^+, 40).

4,5-Dihydro-3-(4-isopropylphenyl)-5-[4-(trifluoromethyl)phenyl]isoxazole-4-carboxylic acid 4-bromophenylamide (**11**, $C_{26}H_{22}BrF_3N_2O_2$)
Method A, yield 48%; m.p.: 247–250 °C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.70$ (d, $J = 8.6$ Hz, 2H, H-5″, H-3″), 7.65 (d, $J = 8.4$ Hz, 2H, H-2′, H-6′), 7.54 (d, $J = 8.6$ Hz, 2H, H-2″, H-6″), 7.43 (d, $J = 9.0$ Hz, 2H, H-3‴, H-5‴), 7.34 (d, $J = 9$ Hz, 2H, H-2‴, H-6‴), 7.33 (d, $J = 8.4$ Hz, 2H, H-5′, H-3′), 6.08 (d, $J = 3.8$ Hz, 1H, H-5), 4.37 (d, $J = 3.8$ Hz, 1H, H-4), 2.93 (sept, $J = 6.9$ Hz, 1H, $CHCH[CH_3]_2$), 1.24 (d, $J = 6.9$ Hz, 6H, $CH[CH_3]_2$) ppm; ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 167.2$, 154.6, 151.5, 145.1, 138.2, 132.0 (2C), 128.2, 127.1 (2C), 127.1 (2C), 127.0 (2C), 125.9 (2C, q, $J = 3.6$ Hz), 121.7 (2C), 87.0, 64.2, 34.0, 23.3 ppm; ^{19}F NMR (471 MHz, $CDCl_3$): $\delta = -63.1$ (3F) ppm; IR (KBr): $\overline{\nu} = 3{,}443$, 2,965, 1,658, 1,539, 1,489, 1,398, 1,327, 1,167, 1,125, 1,068, 1,010, 900, 830 cm^{-1}; EIMS: *m/z* (%) = 532, 530 (M^+, 2), 215 (M^+–$NHC_6H_4BrC_6H_4CF_3$, 20), 188 (M^+–$NHC_6H_4BrC_6H_4CF_3CO$, 24), 172 (NHC_6H_4Br, 82), 173 ($NH_2C_6H_4Br$, 100), 145 ($C_6H_4CF_3$, 15), 69 (CF_3, 12), 43 ($CH[CH_3]_2$, 10).

Biological assay

The compounds were screened for fungicidal activity in two types of tests. The in vitro test carried out for *Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl. (Fr.), *Rhizoctonia solani* Kuhn, and *Botrytis cinerea* Pers. Ex Fr involved determination of mycelial growth retardation in potato-glucose agar (PGA). Stock solutions of test chemicals in acetone were added to agar medium to give a concentration of 200 or 20 μg cm^{-3} and dispersed into Petri dishes. Four discs containing test fungus were placed at intervals on the surface of the solidified agar, and the dishes were then inoculated for 4–8 days depending on the growth rate of the control samples, after which fungal growth was compared with that in untreated control samples. An in vivo test assayed the retarding effect of the compounds on germination of *Erysiphe graminis* Tritici spores. The wheat seedlings were sprayed with a solution of the test chemical at 1,000 μg cm^{-3}, and the plants were infected with spores of the fungus 24 h later. The fungicidal activity was expressed as the percentage of plant infection compared to that on the control.

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