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Enantioselective Synthesis of Isoxazolecarboxamides and their Fungicidal Activity

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Abstract. A series of new 3-substituted isoxazolecarboxamides have been prepared from aldehydes. The key step was a 1,3-dipolar cycloaddition reaction of nitrile oxides to α,β-unsaturated esters and amides. The cycloadditions to amides were mediated by chiral ligands and several products displayed excellent enantioselectivities. Some of the title compounds exhibited good fungicidal activities against *Alternaria alternata*, *Botrytis cinerea*, *Fusarium culmorum*, *Phytophthora cactorum*, and *Rhizoctonia solani* strains.
Key words: cycloaddition, isoxazole derivatives, regioselectivity, enantioselectivity, fungicides.

Resumen. Una serie de nuevas isoxazolcarboxamidas 3-sustituidas se prepararon a partir de aldehídos. El paso clave fue la reacción de cicloadición dipolar-1,3 de óxidos de nitrilo con ésteres o amidas α,β-insaturados. Las cicloadiciones con amidas fueron llevadas a cabo en presencia de ligantes quirales, y varios productos mostraron excelentes enantioselectividades. Algunos de los compuestos preparados mostraron buena actividad fungicida contra las cepas de A*lternaria alternata, Botrytis cinerea, Fusarium culmorum, Phytophthora cactorum y Rhizoctonia solani.*
Palabras clave: cicloadición, derivados de isoxazol, regioselectividad, enantioselectividad, fungicidas.

Introduction

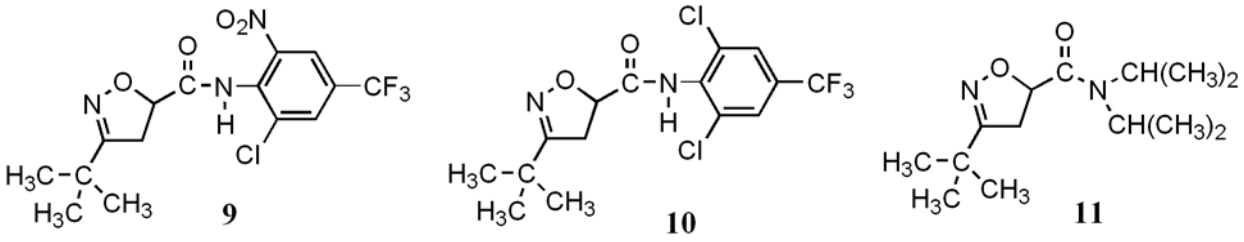
Biological activity of carboxamides is known for a long time. Fungicidal activity of some amides (pyridinecarboxamides and benzamides) results from disrupting the succinate dehydrogenase complex in the respiratory electron transport chain [1,2a], inhibition of rybosomic RNA synthesis (acylalanines such as metalaxyl, oxazolidinones such as oxadixyl) [2a] and targeting cellulose synthases [2b]. Herbicidal activity is presumably due to inhibiting phytoenone desaturase, enzyme involved in biosynthesis of carotenoids [3]. Simple derivatives of isoxazole show also biological activity: 3-hydroxy-5-methylisoxazole disturbs RNA metabolism of fungi [4]. Fast appearance of resistance in pathogenic organisms and climatic changes result in a continuous quest for new plant protective agents which would exhibit a selective activity against pests and apropriate durability in the environment. There is a growing interest in agrochemistry to use pure optical isomers since the desired biological activity occurs generally only in one of the enantiomers. Application of single enantiomers induced by legislative, environmental and commercial factors brings several benefits, such as a decrease of environmental pollution, elimination of useless or even detrimental activity of the undesired antipode and reduced costs of raw materials, labor, and effluent treatment. Those facts induced us to synthesize several 3-aryl- and 3-alkylisoxazolecarboxamides showing fungicidal activity [5,6]. In continuation of these studies we have prepared a number of new 3-aryl (alkyl)isoxazolecarboxamides and examined their activity against *Alternaria alternate, Botrytis cinerea, Rhizoctonia solani, Fusarium culmorum, and Phytophthora cactorum* fungal strains.

Results and Discussion

The title compounds have been prepared by two methods. Following the first method, fifteen 3-arylisoxazole-(3-aryl-2-isoxazoline-)-5-carboxamides **6**-**8** were synthesized from arylaldehydes **1** (Scheme 1, Table 1) via carboxylates **4**. Then three 3-*t*-butyl-2-isoxazoline-5-carboxamides **9**-**11** were similarly obtained (Fig. 1). In the second method, fourteen 3-arylcarboxamides **14**-**15** were prepared by enantioselective 1,3-dipolar cycloadditon reaction of benzonitrile oxides **12a-c** and unsaturated amides **13a**-**h** (Scheme 2).

Preparation of isoxazolecarboxamides 6a-f and 8a-i

The isoxazolecarboxamides listed at Scheme 1 and in Table **1** were prepared in a few steps starting from aldehydes which were oximated with hydroxylamine. *E*-configuration of the oximes was established based on chemical shift values of HC=N proton in ^{1}H NMR spectra above 8.0 ppm [7-9]. The next step was chlorination of oximes with NCS in DMF [10]. The key step was a 1,3-dipolar cycloaddition reaction of ethyl acrylate or a,b-unsaturated amides and nitrile oxides generated *in situ* in the presence of triethylamine (Huisgen method) [11] or on a basic Amberlyst A-21 column in the case of the cycloaddition reaction of a,b-unsaturated amides **13a**-**h**, which lead to cycloadducts **14**-**15** [12] (Scheme **2**). The reaction with ethyl acrylate showed high regioselectivity and only 3-aryl-2-isoxazoline-5-carboxylates **4** were isolated. Some 3-aryl-2-isoxazolinecarboxylates were dehydrated to give the corresponding isoxazoles 7 using



Scheme 1

N-bromosuccinimide bromination, followed by potassium acetate-promoted dehydrobromination [13]. The title amides were synthesized by reaction of acid chlorides prepared by saponification of the corresponding esters, reaction of the obtained acids with oxalyl chloride, followed by acylation of the aromatic, heterocyclic or alkyl amines in the presence of tertiary amines (Method A1 and A2, see experimental part). In the case of weakly nucleophilic aromatic amines, the amidation process was carried out by activation of amines with *n*-butyllithium in diethyl ether (Method B1, see experimental part) or by formation of lithium amides with *t*-butyllithium (Method B2, see experimental part) to avoid formation of side products due to degradation of the acid chlorides [14] and to increase yields of the amides.

2-Isoxazolinecarboxamides **9**-**11** (Fig. 1) were similarly prepared starting from trimethylacetaldehyde via a cycloaddition of the corresponding nitrile oxide with ethyl acrylate and acylation of an amine with the prepared 2-isoxazoline-5-carboxylic acid chloride (a description is provided in the experimental part).

Enantioselective cycloaddition reactions of nitrile oxides to amides

In another approach to isoxazolinecarboxamides, we examined the cycloadditon reaction of benzonitrile oxides to acrylamides

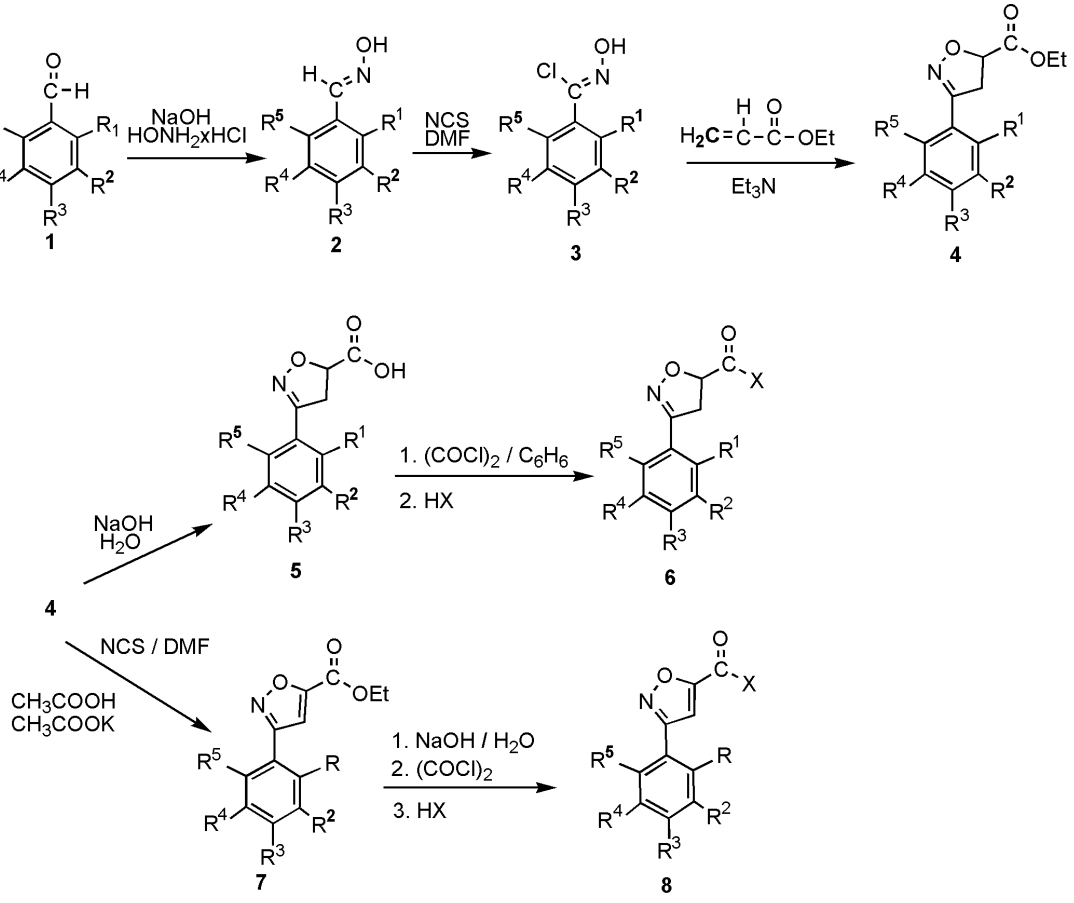
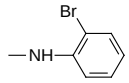
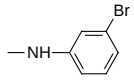
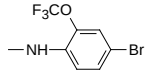
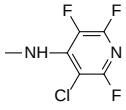
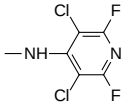
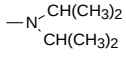
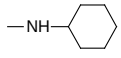
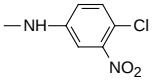
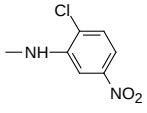
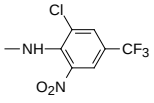
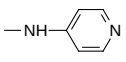
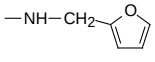
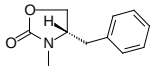
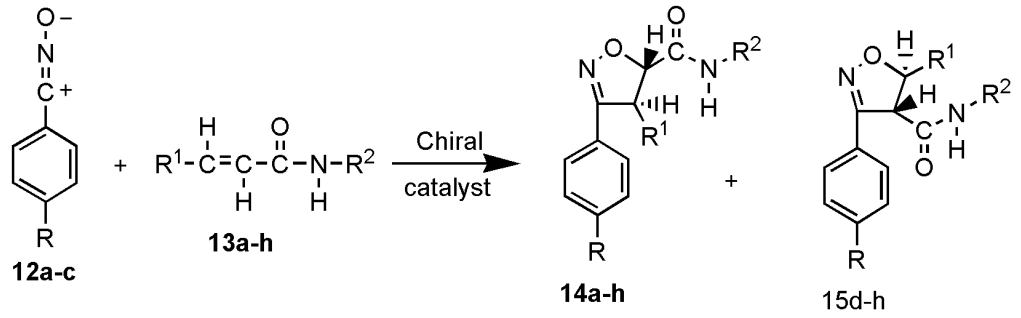


Fig. 1

Table 1. Synthesized amides **6-8**

Compd No.	NR	R¹	R²	R³	R⁴	R⁵	Yield [%]	Method
6a	—NHCH$_2$CH$_2$CH$_2$Br	Cl	Cl	H	H	Cl	15	A1
6b		Cl	Cl	H	H	Cl	38	A2
6c		Cl	Cl	H	H	Cl	75	A2
6d		Cl	Cl	H	H	Cl	27	B2
6e		Cl	Cl	H	H	Cl	44	B2
6f		F	H	F	F	H	42	B2
8a		H	H	CF_3	H	H	95	A1
8b		H	H	CF_3	H	H	30	A2
8c		H	H	CF_3	H	H	32	B2
8d		H	H	CF_3	H	H	14	B2
8e		H	H	CF_3	H	H	49	B2
8f		H	H	CF_3	H	H	44	A2
8g		H	H	CF_3	H	H	70	A2
8h		H	H	CF_3	H	H	77	B1
8i		H	H	CF_3	H	H	78	A2



12a: R = CF_3 **13a**: R^1 = H, R^2 = C_6H_5 **14a**: R = CF_3, R^1 = H, R^2 = C_6H_5
12b: R = *i*-Pr **13b**: R^1 = H, R^2 = C_6H_4-4-OMe **14b**: R = CF_3, R^1 = H, R^2 = C_6H_4-4-*sec*-Bu
12c: R = H **13c**: R^1 = H, R^2 = C_6H_4-4-*sec*-Bu **14c**: R = CF_3, R^1 = H, R^2 = C_6H_4-4-OMe
13d: R^1 = Me, R^2 = C_6H_4-4-OMe **14d, 15d**: R = CF_3, R^1 = Me, R^2 = C_6H_4-4-OMe
13e: R^1 = Me, R^2 = C_6H_4-4-*sec*-Bu **14e, 15e**: R = CF_3, R^1 = Me, R^2 = C_6H_4-4-*sec*-Bu
13f: R^1 = Me, R^2 = C_6H_4-2-OMe **14f, 15f**: R = CF_3, R^1 = Me, R^2 = C_6H_4-2-OMe
13g: R^1 = Me, R^2 = C_6H_4-3-OMe **14g, 15g**: R =*i*-Pr, R^1 = Me, R^2 = C_6H_4-4-OMe
13h: R^1 = Me, R^2 = C_6H_4-4-CF_3 **14h, 15h**: R = H, R^1 = Me, R^2 = C_6H_4-2-OMe

Scheme 2.

Table 2. Enantioselective nitrile oxide cycloaddition reactions to amides **13a–h**

Entry	**14**,**15**	R	R^1	R^2	Chiral catalyst	Yield[a] (%)	**14/15**[b]	**14** Reg.5 % ee	**15** Reg.4 % ee
1	**a**	CF_3	H	C_6H_5	-	30	100/0	-	-
2	**b**	CF_3	H	C_6H_4-4-sec-Bu	-	40	100/0	-	-
3[c]	**c**	CF_3	H	C_6H_4-4-OMe	-	71	100/0	-	-
4	**c**	CF_3	H	C_6H_4-4-OMe	Yb$(OTf)_3$-**C**	53	100/0	-	-
5	**d**	CF_3	Me	C_6H_4-4-OMe	Yb$(OTf)_3$-**B**	96	54/46	0.1	93.0
6	**e**	CF_3	Me	C_6H_4-4-sec-Bu	Yb$(OTf)_3$-**A**	43	2/1	2.0	18.0
7	**f**	CF_3	Me	C_6H_4-2-OMe	Yb2O3-**A**	61	41/59	99.9	0.0
8	**f**	CF_3	Me	C_6H_4-2-OMe	$AlCl_3$-**A**	21	20/80	7.4	0.0
9	**f**	CF_3	Me	C_6H_4-2-OMe	$RuCl_3$-**A**	31	38/62	-	0.6
10	**f**	CF_3	Me	C_6H_4-2-OMe	YbF_3-**A**	54	37/63	5.0	0.4
11	**f**	CF_3	Me	C_6H_4-2-OMe	La$(OTf)_3$-**A**	80	70/30	2.4	0.6
12	**g**	i-Pr	Me	C_6H_4-4-OMe	-	29	20/1	-	-
13	**h**	H	Me	C_6H_4-2-OMe	Yb$(OTf)_3$-**D**	65	1/1	96.0	5.0
14	**h**	H	Me	C_6H_4-2-OMe	Yb$(OTf)_3$-**A**	85	1/1	87.0	0.6
15	**h**	H	Me	C_6H_4-2-OMe	CsF-**C**	60	1/1	81	0.1
16	-	CF_3	Me	C_6H_4-3-OMe	-	0	-	-	-
17	-	CF_3	Me	C6H4-4-CF_3	-	0	-	-	-

[a] Isolated yield of amides **14** and **15**, [b] Regioisomer-5(**14**)/regioisomer-4(**15**), [c] Reaction described in [15]

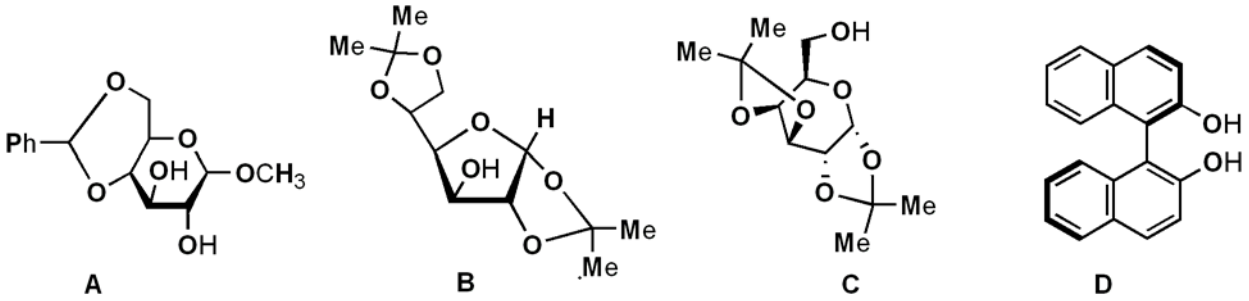
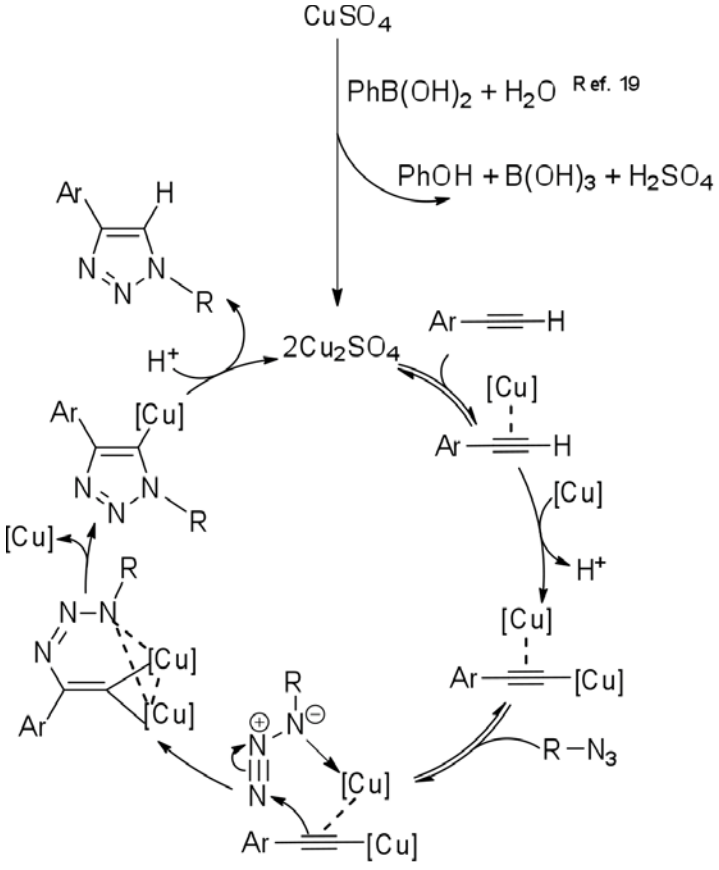


Fig. 2.

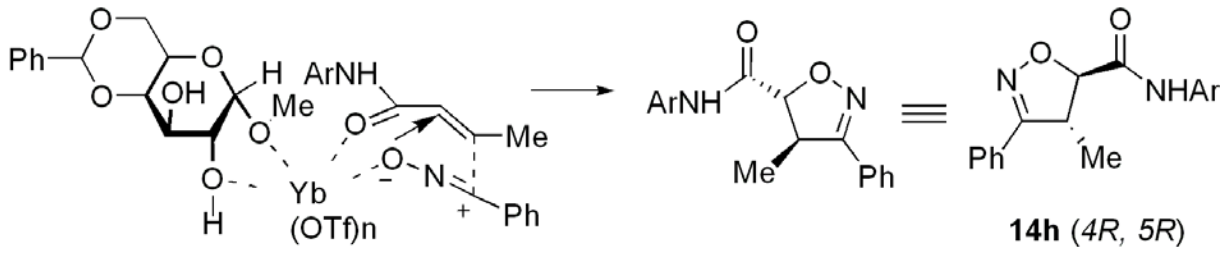
with application of chiral ligands (+)-(4,6-benzylidene)methyl-α-D-glucopyranoside (**A**), 1,2:5,6-di-*O*-isopropylidene- α-D-glucofuranose (**B**), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**C**), and *R*-(+)-1,1'-bi-2-naphthol (**D**) (Fig. 2). We have tested before application of chiral complexes to control regio- and enantioselectivity of the dipolar cycloaddition reaction of nitrile oxides to crotonamides and cinnamides [15] as well as to unsaturated esters [16]. In this approach we describe the cycloadditions of benzonitrile oxides **12a-c** to substituted acrylamides **13a-h** mediated by new complexes of chiral ligands **A-D** and Lewis acids, especially lanthanides (Table 2).

Structure-reactivity relationship

The reactivity of aromatic amides as dipolarofiles in the cycloaddition reaction of nitrile oxides depends on the nature of the substituent and its position on the aromatic ring of the amide fragment (R^2, Scheme 2). Amides with electron donating substituents (EDG) on the aromatic ring such as methoxy and *sec*-butyl in the ortho or para position are the most reactive; meta substituted amide (Table 2, entry 16) was unreactive. On the other hand amides with electron withdrawing



Scheme 3



Scheme 4

Table 3. Fungicidal activity of compounds **6b**-**15h** at 200 μg/mL.[a]

Comp. No.	*cLogP* (+/-) 0.75	Fungicidal activity				
		Alternaria alternata	*Boritis cinerea*	*Fusarium culmorum*	*Phytophtora cactorum*	*Rhizoctonia solani*
6b	4.23	-	3	5	7	9
6c	5.22	-	4	3	5	18
6d	6.24	-	5	8	19	23
6e	4.56	-	0	0	2	0
6f	4.30	-	23	27	67	19
8a	2.43	-	3	7	9	5
8d	3.81	-	0	5	8	18
8e	5.02	-	17	7	5	4
8f	2.34	-	20	5	23	7
8g	2.34	-	5	3	7	8
8h	2.50	-	6	7	4	5
8i	1.11	-	9	3	8	7
9	4.89	-	30	9	63	9
10	5.19	-	18	-	21	-
11	2.88	-	0	0	0	0
14a *RS*	2.95	-	0.0	12.9	4.2	10
14b *RS*	4.82	-	44	50	30	85
14c *RS*	2.96	58	0	19	48.3	38
14c *RR*	2.96	0.8	0	0.3	1.0	30
14d *SS*	3.46	100	100	78	100	78
14d *RS*	3.46	0.8	71	0.0	40	38
14e *RR*	5.31	6	47	25	0	3.9
15e *RS*	5.31	0	47	7	-	11
14f *SS*	3.34	100	100	100	100	100
14f *RS*	3.34	46	0.0	17	38	7
14f *RR*	3.34	51	33	12.5	12.5	44
15f *RS*	3.34	-	0.0	17	0.0	0.0
14g *RS*	4.22	6	31	9	5	7.8
14h *RR*	2.77	45	33	15	-	47
14h *SS*	2.77	0	53	41	-	55
15h *RR*	4.22	41	53	48	-	80
Chlorothalonil[b]	2.88	-	80.0	38.0	61.0	88.0

[a]Percentage of linear growth inhibition. [b]Reference compound.

substituents (EWG) on the aromatic ring, such as CF_3, did not react in the cycloaddition reactions as well.

Reactions of acrylamides **13a-c** afforded as expected only 5-substituted regioisomers **14a-c**. The rest of the cycloadditions gave mixtures of 4- and 5-substituted regioisomers (Table 2, entries 5-15). Good regioselectivity was observed in the uncatalyzed reaction of 4-isopropylbenzonitrile oxide (Table 2, entry 12), where regioisomer-5 was favored (20:1), and in the reaction mediated by a complex of aluminum chloride-carbohydrate **A**, where regioisomer-4 was favored (4:1) (entry 8).

Excellent enantioselectivities were achieved in reactions mediated by complexes of ytterbium triflate with carbohydrates **A**, **B** and binaphthol **D** (Table 2, entries 5, 13, 14). Very good enantioselectivities were also observed in cycloadditions mediated by systems Yb_2O_3-**A** and CsF-**C** (Table 2, entries 7 and 15). The observed enantioselectivity of the reaction leading to (4*S*,5*S*)-5-carbamoyl derivatives could be explained by binding of the amides to the chiral catalytic complex of e.g. ytterbium triflate with *R*-BINOL, followed by a preferential attack of nitrile oxide from lower *si*-face of the dipolarophile opposite to the chirally twisted *R*-BINOL-Yb(OTf)$_3$ complex affording isoxazolines of (4*S*,5*S*) configuration (Scheme 3). This direction of enantioselectivity was found also for cesium fluoride-carbohydrate **C** system.

On the other hand, the opposite chiral induction indicated by opposite elution order of enantiomers of the same compound, from the chiral column and opposite sign of optical rotation, was observed in the reaction mediated by the ytterbium triflate-carbohydrate **A** complex. The observed enantioselectivity could be explained by a preferred attack of the nitrile oxide from upper *re*-face of the dipolarophile opposite to the ligand alpha-1,2-substituents affording isoxazolines of (4*R*,5*R*) configuration (Scheme 4). This chirality was observed also for the catalytic systems Yb_2O_3-carbohydrate **A**.

Absolute configuration of the carboxamides was established via Li-Selectride reduction to the known isoxazoline methanol derivative [15,18].

Biological activity

The biological activity of the compounds **6b**-**15h** against several fungal strains was examined. Preliminary assays showed high fungistatic potency of cycloadducts **14d** and **14f.** Cycloadduct **14f** (*S,S* enantiomer) showed 100% growth retardation against *Alternaria alternate, Botrytis cinerea, Fusarium culmorum, Phytophtora cactorum Rhizoctonia solani* and was the most active of all the tested compounds (Table 3). The reference compound (chlorothalonil) showed smaller 38% and 88% activities against these strains. The presented data show the importance of the optical purity of the screened compounds since *R,R* antipode of **14f** was significantly less active. Similarly *S,S*-rich enantiomer of **14d** exhibited much higher biological activity than a racemic mixture.

Analyzing structure-activity relationship (SAR) some regularities were found. Compounds with a stronger electron-withdrawing character (EWG) of a C-3 aryl substituent (CF_3) and electron-donating character (EDG) of an amide group (OMe) were the most active amides, **14d** (*S,S*) and **14f** (*S,S*). Stronger EWG character of F atoms compared to Cl substituents at the C-3 moiety was reflected by a higher antifungal activity of **6f** compared to **6e**. Presence of a weaker EDG at the amide function at **14e** (*sec*-Bu) lowered the biological activity. A similar negative effect exerted by the EDG (or hydrogen atom) at the C-3 aryl group (i.e., compounds **14g** and **14h**).

The antifungal activity can be correlated with lipophilicity of the compounds measured by the logarithm of octanol-water partition coefficient *logP* [19]. Although no simple dependence between calculated c*logP* and the biological activity was found, the optimal range of c*logP* as a measure of lipophilicity was observed and for the most potent antifungal amides c*logP* fell in the range 3.5-3.3 (Table 3).

We have not examined the mechanism of action of the new antifungal compounds. However, it can be tentatively assumed that described here derivatives interact with fungal wall enzymes as was recently demonstrated for the other carboxylic acid amides. [2b]

Conclusion

We have applied new chiral complexes of carbohydrates **A**, **B**, **C,** and *R*-binaphthol, with inorganic salts of metals belonging to several groups of elements, especially lanthanides to study the 1,3-dipolar cycloaddition reaction of nitrile oxides and substituted acrylamides achieving high enantioselectivity and regioselectivity for some systems. By the appropriate choice of the chiral catalysts, both enantiomers of 3-aryl-4(5)-methyl-2-isoxazolinecarboxylates can be obtained. The use of single enantiomers is highly advisable as pure or enriched enantiomers exhibiting often a much higher fungicidal activity than racemic mixtures (compounds **14d** and **14f**, Table 3). The type and position of the substituent on the aromatic ring of the amide fragment of the dipolarophile has a decisive influence on the reactivity in the 1,3-dipolar cycloaddition reaction of nitrile oxides. We are continuing research to diminish the amount of chiral Lewis acid from equimolar to catalytic quantities.

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 13C 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

13C NMR spectra, signals of fluorine-substituted carbon atoms and some alpha carbon atoms were not observed because of strong 19F–13C coupling. In order to further characterize these compounds, 19F spectra were recorded. Flash chromatography was carried out using silica gel S 230-400 mesh (Merck) and hexanes-ethyl acetate mixtures as eluents. Hydroximinoyl acid chlorides were prepared from the corresponding aryl aldehyde oximes and NCS in DMF [10]. The enantiomeric excess of the separated regioisomers was determined by HPLC analysis (AD-H column). *LogP* was calculated using ACD/CNMR Predictor v.12 computer program of Advanced Chemistry Development (ACD/Labs), Toronto, Canada.

General procedure for the 1,3-dipolar cycloaddition reactions to obtain adducts 4a-f and 9-11.

A solution of chlorooxime (13 mmol) in anhydrous toluene (15 mL) was added dropwise over 30 min to a stirred mixture of anhydrous toluene (60 mL), anhydrous Et_3N (6 mL), $MgSO_4$ (2 g), and ethyl acrylate (8 mL, 80 mmol). The reaction mixture was stirred overnight at room temperature, diluted with toluene (50 mL), washed with water (5 x 50 ml), and evaporated *in vacuo*.

General procedure for the synthesis of isoxazoles 7.

The flask was charged with CCl_4 (50 mL), 3-(4-trifluoromethylphenyl)-5-ethoxycarbonyl-2-isoxazoline (**4**) (2.6 mmol) and a pinch of azoisobutylnitrile. NBS (5 mmole) was added portionwise with stirring over 0.5 h. The reaction was carried out for 5 h at reflux. After cooling to room temperature (rt), a mixture of CH_3COOH (1.65 mL, 27.5 mmol) and CH_3COOK (4 g, 40.8 mmol) was added, the reaction was continued for 70 min at reflux. The reaction progress was monitored by TLC. Then, after cooling, the reaction mixture was poured into ice water, containing NaOH (4.86 g, 121.5 mmol) and stirred for 5 minutes. Dichloromethane (50 mL) was added, the mixture was washed with water (3 x 50 mL). The organic phase was dried over $MgSO_4$. After filtration and evaporation the product was purified by dissolving in dichloromethane and precipitation with hexanes.

General procedure for the synthesis of amides 6a, 8a and 11 with tertiary amines (Method A1)

A solution of an amine derivative (1.2 mmol) in anhydrous dichloromethane (10 mL) was added with stirring to an acid chloride prepared from compounds **5** or **7** followed by anhydrous triethyl amine (4 mL, 30.0 mmol). The solution was stirred for 1 h at 0 °C. Water (10 mL) was added, the organic layer was washed with 3% hydrochloric acid solution and water, and was dried over magnesium sulfate. A crude amide obtained after evaporation of the solvent was purified by crystallization.

General procedure for the synthesis of amides 6b, 6c, 8b, 8f, 8g and 8i with tertiary amines (Method A2).

A solution of an aniline derivative (1.2 mmol) in anhydrous toluene (10 mL) was added with stirring to an acid chloride followed by anhydrous triethyl amine (4 mL, 30.0 mmol). The solution was stirred under reflux for 1 h and overnight at rt. Water (10 mL) was added, the organic layer was washed with 3% hydrochloric acid solution and water, and was dried over magnesium sulfate. A crude amide obtained after evaporation of the solvent was purified by crystallization.

General procedure for the synthesis of amide 8h with *n*-butyl lithium (Method B1)

A 2.5 M solution of *n*-BuLi in hexanes (0.2 mL, 0.5 mmol) was added dropwise to a stirred solution of 4-aminopyridine derivative (0.4 mmol) in anhydrous diethyl ether at -78 °C. Stirring was continued for 1 h and a solution of acid chloride (0.3 mmol) in anhydrous diethyl ether (or HMPA) was added dropwise. The mixture was stirred for 2 h at -78 °C and for 0.5 h at 0 °C. The reaction was quenched with ammonium chloride solution, product was extracted with methylene chloride and purified by flash chromatography.

General procedure for the synthesis of amides 6d, 6e, 6f, 8c, 8d, 8e, 9 and 10 with *tert*-butyl lithium (Method B2)

A 1.7 M solution of *tert*-BuLi in hexanes (0.2 mL, 0.5 mmol) was added dropwise to a stirred solution of 4-aminopyridine derivative (0.4 mmol) in anhydrous diethyl ether at 0 °C. Stirring was continued for 1 h and a solution of acid chloride (0.3 mmol) in anhydrous diethyl ether (or HMPA) was added dropwise. The mixture was stirred for 5 h at 0 °C and overnight at rt. The reaction was quenched with ammonium chloride solution, the product was extracted with methylene chloride and purified by flash chromatography.

General procedure for the synthesis of dipolarophile amides 13a-h

A solution of an aniline derivative (1.2 mmol) in anhydrous toluene (or anhydrous dichloromethane) (10 mL) was added with stirring to an acid chloride (1.0 mmol) followed by an anhydrous triethylamine (30 mmol) at rt. The obtained solution was stirred under reflux for 1 h and overnight at rt. Water (10 mL) was added, the organic layer was separated, washed with 3% hydrochloric acid solution and water, and was dried over magnesium sulfate. Product was extracted with dichloromethane and purified by flash chromatography.

General procedure for the enantioselective cycloaddition to carboxamides 14a, 14b, 14c-h, and 15c-h.

A mixture of carbohydrate **A** (1.0 mmol) and $Yb(OTf)_3$ (1.0 mmol) in dry dichloromethane was stirred at rt for 30 min. Dipolarophile (1 mmol) was added dropwise followed by a solution of dipole in the same solvent generated by passing a hydroximinoyl chloride solution through a column of Amberlyst A-21 over 20–30 min. The solution was stirred at rt for ca. 20 h, and water was added to quench the reaction followed

by the usual work-up. The crude product was purified by flash column chromatography over silica gel and the enantiomeric excess of the separated regioisomers was determined by HPLC analysis (AD-H column).

***N*-(3-Bromopropyl)-3-(2,3,6-trichlorophenyl)-4,5-dihydro-1,2-oxazole-5-carboxamide (6a).** A greenish oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.65 (m, 3H, NH, H-4", H-5"), 5.26-5.18 (m, 1H, H-5), 3.76-3.36 (m, 6H, H-4, -CH_2Br, -CH_2NH], 2.11 (sept. *J* = 6.5 Hz, 2H, BrCH_2**CH_2**CH_2NH). Anal. Calcd for $C_{13}H_{12}BrCl_3N_2O_2$: C 37.67: H 2.92. Found: C 37.98; H .2.97.

***N*-(2-Bromophenyl)-3-(2,3,6-trichlorophenyl)-4,5-dihydroisoxazole-5-carboxamide (6b). A** colorless glass. IR (KBr) ν_{max} 3357, 3080, 2920, 2840, 1699, 1650, 1591, 1521, 1438, 1400, 1304, 1180, 1150, 1040, 1020, 950, 870, 817, 735 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.16 (s, 1H, NH), 8.33 (dd, *J* = 8.3; 1.6 Hz, 1H, H-3"), 7.58 (dd, *J* = 8.2; 1.6 Hz, 1H, H-6"), 7.50 (d, *J* = 8.8 Hz, 1H, H-4'), 7.36 (td, *J* = 8.3; 1.6 Hz, 1H, H-4"), 7.33 (d, *J* = 8.8 Hz, 1H, H-3'), 7.04 (td, *J* = 8.3; 1.6 Hz, 1H, H-5"), 5.38 (dd, *J* = 11.0; 5.3 Hz, 1H, H-5), 3.74 (d, *J* = 11.0 Hz, 1H, H-4), 3.69 (d, *J* = 5.3 Hz, 1H, H-4). Anal. Calcd for $C_{16}H_{10}BrCl_3N_2O_2$: C 42.85: H 2.25. Found: C 42.63; H .2.56.

***N*-(3-Bromophenyl)-3-(2,3,6-trichlorophenyl)-4,5-dihydroisoxazole-5-carboxamide (6c).** A greenish pulp. IR (KBr) ν_{max} 3480, 3373, 3080, 2920, 1685, 1620, 1591, 1530, 1480, 1450, 1400, 1303, 1280, 1180, 1140, 1070, 1040, 990, 870, 820, 774, 680 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.54 (s, 1H, NH), 7.89 (t, *J* = 2.0 Hz, 1H, H-2"), 7.51 (d, *J* = 8.7 Hz, 1H, H-4'), 7.34 (d, *J* = 8.7 Hz, 1H, H-5'), 7.24 (d, *J* = 8.1 Hz, 1H, H-4"), 7.00 (td, *J* = 8.1; 0.7 Hz, 1H, H-5"), 6.86 (dm, *J* = 8.1 Hz, 1H, H-6"), 5.34 (dd, *J* = 10.9; 5.5 Hz, 1H, H-5), 3.73 (d, *J* = 10.9 Hz, 1H, H-4), 3.68 (d, *J* = 5.5 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.92, 155.70, 138.06, 132.33, 130.60, 128.91, 128.31, 123.23, 118.74, 79.34 (C-5), 42.21 (C-4). Anal. Calcd for $C_{16}H_{10}BrCl_3N_2O_2$: C 42.85: H 2.25. Found: C 42.68; H .2.48.

3-(2,3,6-Trichlorophenyl)-4,5-dihydroisoxazole-5-carboxylic acid 2-trifluorometoxy-4-bromophenylamide (6d). A greenish wax. IR (KBr) ν_{max} 3395, 3120, 2960, 2928, 2850, 1702, 1640, 1519, 1519, 1440, 1400, 1303, 1250, 1211, 1190, 1150, 1080, 1044, 941, 879, 818, 753, 730, 670 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.94 (s, 1H, NH), 8.33 (d, *J* = 9.2 Hz, 1H, H-6"), 7.94 (d, *J* = 8.8 Hz, 1H, H-5'), 7.53-7.43 (m, 3H, H-4', H-3", H-5"), 5.35 (dd, *J* = 10.8; 5.8 Hz, 1H, H-5), 3.72 (d, *J* = 10.8 Hz, 1H, H-4), 3.68 (d, *J* = 5.8 Hz, 1H, H-4). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.95, 155.33, 138.81, 133.32, 132.91, 132.44, 132.15, 131.83, 130.74, 128.93, 128.78, 128.72, 124.73, 124.05, 122.78, 122.07, 117.793, 116.94, 79.17, 41.91. ESI MS *m/z* (rel. int.) 532 [M^+] (95). Anal. Calcd for $C_{17}H_9BrCl_3F_3N_2O_3$: C 38.34: H 1.70. Found: C 38.09; H .1.56.

***N*-(5-Chloro-2,3,6-trifluoropyridin-4-yl)-3-(2,3,6-trichlorophenyl)-4,5-dihydroisoxazole-5-carboxamide (6e).** A white-brownish semisolid. IR (KBr) ν_{max} 3490, 3350, 3256, 3080, 2925, 2850, 1715, 1623, 1500, 1474, 1440, 1400, 1320, 1270, 1240, 1203, 1182, 1150, 1100, 1067, 1042, 1021, 869, 818, 760, 703, 675 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) d 8.81 (s, 1H, NH), 7.53 (d, *J* = 8.7 Hz, 1H, H-4'), 7.35 (d, *J* = 8.7 Hz, 1H, H-5'), 5.46 (dd, *J* = 10.8; 5.5 Hz, 1H, H-5), 3.77 (d, *J* = 10.8 Hz, 1H, H-4a), 3.73 (d, *J* = 5.5 Hz, 1H, H-4b). ESI MS *m/z* calcd for $C_{15}H_6N_3O_2F_3Cl_4Na$: 479.9064. Found: 479.9026. Anal. Calcd for $C_{15}H_6Cl_4F_3N_3O_3$: C 39.25; H 1.32. Found: C 39.09; H .1.46.

***N*-(2,6-Difluoro-3,5-dichloropyridin-4-yl)-3-(2,4,5-trifluorophenyl)-4,5-dihydroisoxazole-5-carboxamide (6f).** A white-brownish semisolid. IR (KBr) ν_{max} 3360, 3280, 3080, 2915, 2850, 1709, 1630, 1597, 1540, 1512, 1485, 1437, 1409, 1373, 1260, 1230, 1191, 1140, 1060, 1040, 1005, 916, 890, 804, 781, 735 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) d: 8.59 (1H, NH), 7.72 (m, 1H, H-6'), 7.05 (td, *J* = 10.2; 6.3 Hz, 1H, H-3'), 5.36 (t, *J* = 8.4 Hz, 1H, H-5), 3.87 (d, *J* = 8.4 Hz, 1H, H-4a), 3.86 (d, *J* = 8.4 Hz, 1H, H-4b). ESI-MS *m/z* calcd for $C_{15}H_6O_2N_3F_5Cl_2Na$: 447.9655. Found: 447.9655. Anal. Calcd for $C_{15}H_6Cl_2F_5N_3O_2$: C 42.28; H 1.42. Found: C 42.07; H .1.59.

***N,N*-Diisopropyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxamide (8a).** A colorless glass. IR (KBr) ν_{max} 3440, 3121, 2974, 2910, 1645, 1478, 1437, 1380, 1323, 1175, 1120, 1063, 1040, 1020, 990, 951, 920, 846, 820, 760, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) d 7.95 (d, *J* = 8.2 Hz, 1H, H-3', H-5'), 7.75 (d, *J* = 8.2 Hz, 2H, H-2', H-6'), 4.11 (m, 1H, CH, C**H**$(CH_3)_2$), 3.63 (m, 1H, CH, CH(CH3)2), 1.54 (d, *J* = 6.2 Hz, 6H, HC(C**H$_3$**)$_2$), 1.31 (d, *J* = 6.2 Hz, 6H, HC(C**H3**)2). 13C NMR ($CDCl_3$, 50 MHz) d 167.27 (C=O), 161.33 (C-3), 157.94 (C-5), 132.66 (C-1'), 131.97 (m, C-4'), 127.40 (2C, C-2', C-6'), 126.23 (q, *J* = 3.6 Hz, 2C, C-3', C-5'), 104.10 (C-4), 50.93 (H**C**$(CH_3)_3$), 47.07 (H**C**$(CH_3)_3$), 21.17 (2C, **C**H, HC(**C**$H_3)_2$), 20.39 (2C, HC(**C**$H_3)_2$). 19F NMR ($CDCl_3$, 471 MHz) d -63.35 (s, 3F, **F$_3$**C-Ar). ESI MS *m/z* calcd for $C_{17}H_{19}O_2N_2F_3Na$: 363.1296. Found: 363.1262.

***N*-Cyclohexyl-3-(4-trifluoromethylphenyl)isoxazole-5-carboxamide (8b).** A yellowish semisolid. IR (KBr) ν^{max} 3460, 3318, 3287, 3160, 2936, 2854, 1650, 1536, 1521, 1450, 1438, 1326, 1283, 1260, 1240, 1181, 1135, 1115, 1095, 1070, 1020, 950, 832, 782, 761, 670 cm-1. 1H NMR ($CDCl_3$, 200 MHz) d 7.96 (d, *J* = 8.4 Hz, 2H, H-5', H-3'), 7.75 (d, *J* = 8.4 Hz, 2H, H-6', H-2'), 7.28 (s, 1H, H-4), 6.53 (s, 1H, NH), 3.99 (m, 1H, -CH, NHC**H**$(CH)_2$, H-1"), 2.07-1.08 (m, 10H, -CH2, H-2", H-3", H-4", H-5", H-6"). Anal. Calcd for $C_{17}H_{17}F_3N_2O_2$: C 60.35; H 5.06. Found: C 60.07; H .5.27.

***N*-(4-Chloro-3-nitrofenyl)-3-(4-trifluoromethylphenyl)isoxazole-5-carboxamide (8c).** A white-brownish solid. mp. 217-219 oC. IR (KBr) ν_{max} 3416, 3100, 2920, 2880, 1696, 1615, 1595, 1534, 1480, 1438, 1350, 1325, 1245, 1175, 1132, 1067,1019, 950, 850, 828, 755, 680 cm^{-1}. ^{1}H NMR ($CDCl_3$,, 200 MHz) d 8.48 (s, 1H, NH), 8.40 (d, *J* = 2.6 Hz, 1H, H-2"), 7.99 (d, *J* = 8.1 Hz, 2H, H-5', H-3'), 7.83 (dd, *J* = 8.7; 2.6 Hz, 1H, H-6"), 7.79 (d, *J* = 8.1 Hz, 2H, H-6', H-2'), 7.59 (d, *J* = 8.7 Hz, 1H, H-5"), 7.44 (s, 1H, H-4). Anal. Calcd for $C_{17}H_9ClF_3N_3O_4$: C 49.59; H 2.20. Found: C 49.41; H .2.38.

***N*-(2-Chloro-5-nitrofenyl)-3-(4-trifluoromethylphenyl) isoxazole-5-carboxamide (8d)**. A white semisolid. IR (KBr)

ν_{max} 3376, 3300, 3150, 2925, 2850, 1703, 1678, 1618, 1595, 1536, 1460, 1440, 1421, 1348, 1327, 1275, 1241, 1163, 1128, 1069,1018, 950, 870, 848, 740 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) d 9.44 (d, *J* = 2.5 Hz, 1H, H-6"), 8.97 (s, 1H, NH), 8.05 (dd, *J* = 8.8; 2.5 Hz, 1H, H-4"), 8.01 (d, *J* = 8.2 Hz, 2H, H-5', H-3'), 7.79 (d, *J* = 8.2 Hz, 2H, H-6', H-2'), 7.66 (d, *J* = 8.8 Hz, 1H, H-3"), 7.47 (s, 1H, H-4). Anal. Calcd for $C_{16}H_{10}BrCl_3N_2O_2$: C 42.85; H 2.25. Found: C 42.99; H .2.41.

***N*-(2-Chloro-4-trifluoromethyl-6-nitrophenyl)-3-(4-(trifluoromethylphenyl)isoxazole-5-carboxamide (8e).** A white-brownish semisolid. IR (KBr) ν_{max} 3444, 3280, 3080, 2920, 1687, 1618, 1549, 1510, 1440, 1400, 1360, 1326, 1270, 1240, 1170, 1133, 1071,1020, 950, 900, 830, 751, 680 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) d 9.01 (s, 1H, NH), 8.25 (d, *J* = 2.0 Hz, 1H, H-5"), 8.06 (d, *J* = 2.0 Hz, 1H, H-3"), 7.99 (d, *J* = 8.3 Hz, 2H, H-3', H-5'), 7.79 (d, *J* = 8.3 Hz, 1H, H-2', H-6'), 7.45 (s, 1H, H-4). Anal. Calcd for $C_{18}H_8ClF_6N_3O_4$: C 45.07; H 1.68. Found: C 45.31; H .1.51.

***N*-(Pyridin-4-yl)-3-(4-trifluoromethylphenyl)isoxazole-5-carboxamide (8f).** A grey wax. Mp. 247-249 ºC. IR (KBr) ν_{max} 3418, 3360, 3120, 2940, 2830, 1686, 1591, 1514, 1440, 1417, 1334, 1293, 1240, 1170, 1114, 1071, 1020, 1000, 950, 890, 822, 750 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) d 8.63 (m, 2H, H-3", H-5"), 8.49 (s, 1H, -NH), 7.99 (d, *J* = 7.7 Hz, 2H, H-3', H-5'), 7.78 (d, *J* = 7.7 Hz, 2H, H-2', H-6'), 7.68 (m, 2H, H-2", H-6"), 7.47 (s, 1H, H-4). 13C NMR (CDCl3, 50 MHz) d 163.75 (C=O), 161.71 (C-3), 154.55 (C-5), 150.46 (2C, C-2", C-6"), 144.63 (C-4"), 131.41 (C-1'), 130.68 (q, *J* = 31.6 Hz, C-4'), 127.61 (2C, C-2', C-6'), 126.17 (q, *J* = 4.0 Hz, 2C, C-3', C-5'), 114.28 (2C, C-3", C-5"), 106.53 (C-4). ^{19}F NMR (CDC_{l3}, 471 MHz) d -61.85 (s, 3F, **F$_3$**C-Ar). Anal. Calcd for $C_{16}H_{10}F_3N_3O_2$: C 57.66; H 3.02. Found: C 57.49; H .2.89.

***N*-(Furan-2-yl-methyl)-3-(4-trifluoromethylphenyl)isoxazole-5-carboxamide (8g).** A white-brownish solid: mp. 188-190 ºC. IR (KBr) ν_{max} 3437, 3296, 3052, 2937, 1670, 1622, 1538, 1525, 1502, 1435, 1418, 1384, 1332, 1297, 1269, 1253, 1197, 1122, 1076, 1066, 1032, 1019, 997, 953, 937, 924, 848, 771, 747, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, *J* = 8.1 Hz, 2H, H-5', H-3'), 7.75 (d, *J* = 8.1 Hz, 2H, H-6', H-2'), 7.41 (dd, *J* = 10.0; 1.8 Hz, 1H, -OCH=), 7.29 (s, 1H, H-4), 6.92 (s, 1H, NH), 6.36 (m, 2H, C=C**H**-C**H**=C), 4.67 (d, *J* = 5.6 Hz, 2H, CH_2, CH_2NH). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.26 (C=O), 162.48, 155.55, 150.02, 142.96, 127.51 (s, 2C, C-2', C-6'), 126.5 (q, *J* = 3.6 Hz, 2C, C-3', C-5'), 110.83, 108.58, 105.63, 36.67. ^{19}F NMR ($CDCl_3$, 471 MHz) δ -63.39 (s, 3F, F_3C-Ar). ESI-MS *m/z* calcd for $C_{16}H_{11}O_3N_2F_3Na$: 359.0620. Found: 359.0625.

4-Benzyloxazolidinone-2-3-(4-trifluoromethylphenyl) isoxazole-5-carboxamide (8h). It was obtained as a white-brownish solid from 4-benzyloxazolidinone-2 derivative [17]: mp: 156-159 ºC. IR (KBr) ν_{max} 3122, 3040, 3000, 1802, 1777, 1690, 1571, 1490, 1456, 1434, 1389, 1357, 1323, 1244, 1210, 1168, 1120, 1063, 1020, 952, 843, 770, 720, 701, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2H, H-5', H-3'), 7.76 (d, *J* = 8.1 Hz, 2H, H-6', H-2'), 7.37 (s, 1H, H-4), 7.29 (m, 5H, H-2", H-3", H-4", H-5", H-6"), 4.90 (m, 1H, H-11, CH, $CH_2C\mathbf{H}CH_2$), 4.37 (d, *J* = 10.8 Hz, 1H, H-10a, CH_2, OCH_2CH), 4.34 (d, *J* = 7.5 Hz, 1H, H-10b, CH_2, OCH_2CH), 3.47 (dd, *J* = 13.4; 3.5 Hz, H-12b, CH_2, $ArCH_2CH$), 2.95 (dd, *J* = 13.4; 9.2 Hz, 1H, H-12a). ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 161.81 (C=O), 161.67, 156.64, 152.19, 134.65, 131.60, 129.63, 129.34, 127.88, 127.51 (s, 2C, C-2', C-6'), 126.3 (q, *J* = 3.6 Hz, 2C, C-3', C-5'), 107.73, 67.23, 56.27, 37.68. ^{19}F NMR ($CDCl_3$, 471 MHz) δ -63.32 (s, 3F, F_3C-Ar). ESI MS *m/z* calcd for $C_{21}H_{15}O_4N_2F_3Na$: 439.0882. Found: 439.0860.

Pyrrolidine-3-(4-trifluoromethylphenyl)isoxazole-5-carboxamide (8i). A white-brownish solid: mp. 164-166 ºC. IR (KBr) ν_{max} 3116, 2977, 2887, 1626, 1595, 1467, 1438, 1413, 1383, 1326, 1320, 1228, 1157, 1125, 1114, 1064, 1016, 950, 933, 884, 850, 756, 694 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 2H, H-5', H-3'), 7.75 (d, *J* = 8.6 Hz, 2H, H-2', H-6'), 7.25 (s, 1H, H-4), 3.95 (t, *J* = 6.6 Hz, 2H, H-5a, H-8a), 3.70 (t, *J* = 6.6 Hz, 2H, H-5a, H-8b), 2.02 (m, 4H, H-6, H-7). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.27, 161.47, 155.56, 131.98, 131.84, 127.37 (s, 2C, C-2', C-6'), 126.2 (q, *J* = 3.6 Hz, 2C, C-3', C-5'), 106.68, 47.98, 47.44, 26.51, 23.84. ^{19}F NMR ($CDCl_3$, 471 MHz) δ -63.39 (s, 3F, F_3C-Ar). ESI MS *m/z* Calcd for $C_{15}H_{13}O_2N_2F_3Na$: 333.0827. Found: 333.0828.

***N*-(4-Trifluoromethyl-2-chloro-6-nitrophenyl)-3-(*tert*-butyl)-4,5-dihydroisoxazole-5-carboxamide (9).** A greyish semisolid by method **B2,** 12%. ^1H NMR ($CDCl_3$, 200 MHz) δ 9.14 (s, 1H, NH), 8.14 (d, *J* = 1.4 Hz, 1H, H-5'), 7.97 (d, *J* = 1.4 Hz, 1H, H-3'), 5.13 (dd, *J* = 9.7; 6.5 Hz, 1H, H-5), 3.40 (d, *J* = 9.7 Hz, 1H, H-4), 3.39 (d, *J* = 6.5 Hz, 1H, H-4), 1.26 (s, 9H, $C(C\mathbf{H_3})_3$)). Anal. Calcd for $C_{15}H_{15}ClF_3N_3O_4$: C 45.76; H 3.84. Found: C 46.00; H .3.61.

***N*-(4-Trifluoromethyl-2,6-dichlorophenyl)-3-(*tert*-butyl)-4,5-dihydroisoxazole-5-carboxamide (10).** A yellowish solid, method **B2**, 15%: mp. 98-103 ºC. IR (KBr) ν_{max} 3437, 2970, 1691, 1497, 1391, 1323, 1170, 1133, 880, 813 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.44 (s, 1H, NH), 7.65 (s, 2H, H-3', H-5'), 5.17 (t, *J* = 7.9 Hz, 1H, H-5), 3.42 (d, *J* = 7.9 Hz, 2H, H-4) 1.24 (s, 9H, $(C\mathbf{H_3})_3C$). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.92 (C=O), 167.28 (C-3), 134.54 (C-1'), 134.22 (C-4'), 131.50 (2C, C-2', C-6'), 130.82, 125.68 (C-3'), 125.60 (C-5'), 78.22 (C-5), 39.62 (C-4), 33.23 (**C**$(CH_3)_3$), 28.06 (3C, $(\mathbf{C}H_3)_3C$). ^{19}F NMR ($CDCl_3$, 471 MHz) δ -63.39 (3F, F_3C-Ar). Anal. Calcd for $C_{15}H_{15}Cl_2F_3N_2O_2$: C 47.02; H 3.95. Found: C 47.32; H 4.02.

***N,N*-Diisopropyl-3-(*tert*-butyl)-4,5-dihydroisoxazole-5-carboxamide (11).** A greyish semisolid, method **A1,** 98%. IR (KBr) ν_{max} 2969, 1647, 1446, 1368, 1300, 1212, 1160, 1136, 1043, 874, 818, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 5.11 (dd, *J* = 10.9; 8.8 Hz, 1H, H-5), 4.30 (sept., *J* = 6.6 Hz, 1H), 3.80 (dd, *J* = 16.9; 10.9 Hz, 1H, H-4), 3.47 (sept., *J* = 6.7 Hz, 1H, C**H**$(CH_3)_2$), 3.44 (m, *J* = 6.7 Hz, 1H, C**H**$(CH_3)_2$), 2.92 (dd, *J* = 16.9; 10.9 Hz, 1H, H-4), 1.47 (d, *J* = 6.7 Hz, 6H, $CH(\mathbf{CH_3})_2$), 1.41 (d, *J* = 6.7 Hz, 3H, $HCC\mathbf{H_3}$) 1.40 (d, *J* = 6.7 Hz, 3H, $HCC\mathbf{H_3}$), 1.23 (s, 9H, $C(C\mathbf{H_3})_3$). EI MS *m/z* (rel. int.) 254 [M^+] (9), 224 (M^+ - 2xCH_3, 5), 126 (M^+ - (O=C-N(CH(-$CH_3)_2$), 50). Anal. Calcd for $C_{14}H_{26}N_2O_2$: C 66.10; H 10.30. Found: C 66.40; H 10.11.

***N*-Phenylacrylamide (13a).** A yellowish semisolid, 35 %. IR (neat) ν_{max} 3430, 3307, 3295, 3200, 3144, 3100, 3060,

1666, 1640, 1607, 1552, 1497, 1443, 1408, 1333, 1298, 1254, 1202, 1067, 986, 960, 940, 900, 840, 800, 755, 688 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.85 (s, 1H**, HN**C=O), 7,59 (d, *J* = 7.8 Hz, 2H, H-2‘, H-6‘), 7.30 (m, 2H, H-3‘, H-5‘), 7,11 (t, *J* = 7.4 Hz, 1H, H-4‘), 6.42 (dd, *J* = 16.8; 2.1 Hz, 1H, H-3a, **H_2C**=CC=O), 6.30 (dd, *J* = 16.8; 9.4 Hz, 1H, H-3b, **H_2C**=CC=O), 5.73 (dd, *J* = 9.4; 2.1 Hz, 1H, -C=**CH**C=O). EI MS *m/z* (rel. int.) 147 [M^+], 93 (HNC_6H_5 + H), 77 (C_6H_5), 55 (O=CCH=CH_2). Anal. Calcd for C_9H_9NO: C 73.45; H 6.16. Found: C 73.1; H .6.11.

Carboxamides **13b** and **13d** were described [15].

***N*-(4-*sec*-Butylphenyl)acrylamide (13c).** A yellowish semisolid**,** 30 %. ^1H NMR ($CDCl_3$, 500 MHz) δ 7.51 (d, *J* = 8.3 Hz, 2H, H-2‘, H-6‘), 7.12 (d, *J* = 8.3 Hz, 2H, H-3‘, H-5‘), 6.40 (d, *J* = 17.0 Hz 1H, H-3a, **H_2C**=CC=O), 6.27 (dd, *J* = 17.0; 10.5 Hz, 1H, H-3b, **H_2C**=CC=O), 5.70 (dd, *J* = 10.5; 1.5 Hz, 1H, H-2, C=**CH**C=O), 2.58 (m, *J* = 7.0 Hz, 1H, H_3C**CH**CH_2), 1.58 (quint., *J* = 7.0 Hz, 2H, H_3C**H**-$_2$**C**CH), 1.20 (d, *J* = 7.0 Hz, 3H, **H_3C**CH), 0.81 (t, *J* = 7.0 Hz, 3H, **H_3C**CH_2). HR ESI MS *m/z* Calcd for $C_{13}H_{17}NONa$: 226.1208. Found: 226.1214. Anal. Calcd for $C_{13}H_{17}NO$: C 76.81; H 8.43. Found: C 76.50: H .8.21.

***N*-(3-Methoxyphenyl)crotonamide (13g)**. A yellowish wax, 12 %, method **A2**. IR (KBr) ν_{max} 3420, 3285, 2960, 2910, 2830, 1665, 1605, 1524, 1485, 1450, 1434, 1320, 1271, 1214, 1150, 1035, 960, 870, 830, 777, 750, 720, 680 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 9.33 (s, 1H, NH), 7.40-6.65 (m, 5H, H-2‘, H-4‘, H-5‘, H-6‘, H_3C-**CH**=C), 5.94 (d, *J* = 15.2 Hz, 1H, CH, O=C**HC**=C), 3.81 (s, 3H, **H_3C**O), 1.82 (d, *J* = 6.8 Hz, 3H, **H_3C**-CH=C). Anal. Calcd for $C_{11}H_{13}NO_2$: C 69.09: H 6.85. Found: C 69.19: H .6.61.

***N*-(4-Trifluoromethylphenyl)crotonamide (13h)**. A yellowish semisolid, 10 %, method **A2**. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.70 (m, 1H, -NH), 7.69 (d, *J* = 8.0 Hz, 2H, H-5‘, H-3‘), 7.56 (d, *J* = 8.0 Hz, 2H, H-2‘, H-6‘), 7.03 (m, *J* = 14.9; 6.5 Hz, 1H, H-3, H_3C-**CH**=C), 5.97 (d, *J* = 14.9 Hz, 1H, H-2, O=C**HC**=C), 1.91 (d, *J* = 6.5 Hz, 3H, **H_3C**-CH=C). Anal. Calcd for $C_{11}H_{10}F_3NO$: C 57.64: H 4.40. Found: C 57.89: H .4.57.

***N*-Phenyl-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxamide (14a).**

A yellowish semisolid, 30 %. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.48 (s, 1H**, HN**-C=O), 7.81 (d, *J* = 8.2 Hz, 2H, H-2‘, H-6‘), 7.69 (d, *J* = 8.2 Hz, 2H, H-3‘, H-5‘), 7.57 (d, *J* = 8.0; 1.7 Hz, 2H, H-2“, H-6“), 7.34 (td, *J* = 8.0; 1.7 Hz, 2H, H-3“, H-5“), 7.15 (td, *J* = 8.0; 1.7 Hz, 1H, H-4“), 5.32 (dd, *J* = 10.9; 6.4 Hz 1H, H-5), 3.82 (d, *J* = 6.2 Hz, 1H, H-4a), 3.79 (d, *J* = 10.9 Hz, 1H, H-4b). EI-MS m/z (%) 334 (M^+), 315 (M^+-F), 214 [M^+-C=ONHC_6H_5], 145 ($F_3CC_6H_4$), 93 (M^+-HNC_6H_5), 77 (C_6H_5). Anal. Calcd for $C_{17}H_{13}F_3N_2O_2$: C 61.08; H 3.92. Found: C 60.80: H .4.17.

***N*-(4-*sec*-Butylphenyl)-3-(4-trifluoromethylphenyl)-4,5-dihydroisoxazole-5-carboxamide (14b).** A colorless glass, 40 %. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.48 (s, 1H, **HN**C=O), 7.78 (d, *J* = 8.0 Hz, 2H, H-2‘, H-6‘), 7.67 (d, *J* = 8.0 Hz, 2H, H-3‘, H-5‘), 7.48 (d, *J* = 8.3 Hz, 2H, H-2“, H-6“), 7.14 (d, *J* = 8.3 Hz, 2H, H-3“, H-5“), 5.30 (dd, *J* = 11.8; 5.2 Hz 1H, H-5), 3.83 (dd, *J* = 17.3; 5.2 Hz, 1H, H-4a), 3.73 (dd, *J* = 17.3; 11.8 Hz, 1H, H-4b), 2.56 (quint., *J* = 7.0 Hz, 1H, H_3C**CH**CH_2), 1.58 (m, 2H, H_3C**CH_2**CH), 1.20 (d, *J* = 7.0 Hz, 3H, **H_3C**CH), 0.79 (t, *J* = 7.5 Hz, 3H, **H_3C**CH_2). HR ESI MS *m/z* Calcd for $C_{21}H_{21}F_3N_2O_2Na$: 413.1453. Found: 413.1434. Anal. Calcd for $C_{21}H_{21}F_3N_2O_2$: C 64.61; H 5.42. Found: C 64.78; H 5.37.

Compounds **14c-g** and **15c-g** were described [15].

N*-(2-Methoxyphenyl)-4-methyl-3-phenyl-4,5-dihydroisoxazole-5-carboxamide (14h).** A colorless glass. {$[\alpha]_D$ – 45°, (c 0.9. in acetone) [87.0% ee, (R,R***) rich]}, {$[\alpha]_D$ + 40°, (c 0.76 in acetone) [96.0% ee, (***S,S***) rich]}. IR (KBr) ν_{max} 3398, 3380, 3080, 3040, 2910, 2860, 1687, 1603, 1536, 1490, 1463, 1440, 1328, 1295, 1254, 1115, 1024, 874, 760, 743, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 9.16 (s, 1H, NH), 8.4-6.8 (m, 9H, H-6’, H-2’, H-5’, H-3’, H-4‘, H-6”, H-4”, H-5”, H-3”), 4.84 (d, *J* = 3.4 Hz, 1H, H-5), 4.18 (dq, *J* = 7.3; 3.4 Hz, 1H, H-4), 3.88 (s, 3H, H_3CO), 1.48 (d, *J* = 7.3 Hz, 3H, H_3CCH). HR ESI MS *m/z* Calcd for $C_{18}H_{18}N_2O_3Na$: 333.1215. Found: 333.1219.

***N*-(2-Methoxyphenyl)-5-methyl-3-phenyl-4,5-dihydroisoxazole-4-carboxamide (15h)**. A colorless glass. IR (KBr) ν_{max} 3446, 3080, 3005, 2980, 2910, 2840, 1687, 1600, 1533, 1490, 1460, 1440, 1380, 1340, 1290, 1255, 1220, 1180, 1120, 1024, 920, 950, 805, 757, 697 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ 8.3-6.8 (m, 9H, H-6“, H-5’, H-4‘, H-3’, H-2’, H-6’, H-5”, H-4”, H-3”), 5.19 (qd, *J* = 6.4; 4.4 Hz, 1H, H-5), 4.09 (d, *J* = 4.4 Hz, 1H, H-4), 3.72 (s, 3H, H_3CO), 1.48 (d, *J* = 6.4 Hz, 3H, H_3CCH). HR ESI MS *m/z* Calcd for $C_{18}H_{18}N_2O_3Na$: 333.1215. Found: 333.1214.

Fungicidal testing

The compounds were screened for fungicidal activity *in vitro* test carried out for *Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl.(Fr.), *Rhizoctonia solani* Kuhn, *Botrytis cinerea* Pers. Ex Fr, which 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 μg mL^{-1} 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. The fungicidal activity was expressed as the percentage of plant infection compared to that on the control. The results of the screening are given in Table 3.

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