

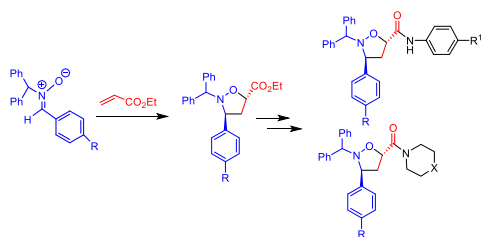
# Synthesis and fungicidal activity of 2-(diphenylmethyl)-3-arylisoxazolidine-5-carboxamides

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**Abstract** A series of new 2-(diphenylmethyl)-3-arylisoxazolidine-5-carboxamides have been prepared from aldehydes. A key step was an uncatalyzed stereoselective and regioselective 1,3-dipolar cycloaddition reaction of *N*-benzylidene-*N*-diphenylmethyl nitrones with ethyl acrylate. Some of these amides exhibited fungicidal activities against *Fusarium culmorum*, *Phytophthora cactorum*, *Alternaria alternata*, *Rhizoctonia solani*, *Botrytis cinerea*, and *Blumeria graminis*.

**Graphical abstract**



**Keywords** Cycloaddition · Nitrones · Stereoselectivity · NMR spectroscopy · Configuration · Fungicides

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## Introduction

1,3-Dipolar cycloaddition reaction of nitrones to alkenes is the most convenient method of preparation of isoxazolidines which can be easily transformed via reductive ring opening to  $\gamma$ -amino alcohols, where configuration of all carbon atoms is preserved [1]. The obtained  $\gamma$ -amino alcohols are important semi-products in synthesis of  $\beta$ -amino acids,  $\beta$ -lactam antibiotics, or piperidine and indolizidine alkaloids. Nitrones, on the contrary to most of the other dipoles, are stable compounds not requiring preparation in situ, and therefore can be used at room temperature without an inert atmosphere.

Stereospecificity is a striking feature of this reaction discovered by Huisgen—geometry of the alkene is completely preserved in the cycloadduct. However, problem of regio- and stereoselectivity of this transformation should still be solved. In reaction of nitrones with monosubstituted alkenes two regioisomeric products can be formed—5-isoxazolidines with a substituent on the carbon atom  $\alpha$  to the oxygen atom, and 4-isoxazolidines with a substituent on the carbon atom  $\beta$  to the oxygen atom, depending on the electronic character of the substituents. According to the theory of frontier molecular orbitals (FMO) reactions of the alkenes with electron-donating substituents are controlled by interactions of dipole LUMO and dipolarophile HOMO orbitals, which leads to 5-isoxazolidines. On the other hand reactions of the alkenes with strongly electron-accepting substituents are controlled by interactions of dipole HOMO and dipolarophile LUMO orbitals leading exclusively to 4-isoxazolidines. In case of alkenes with moderately electron-accepting substituents, similarly as with 1,2-disubstituted alkenes, formation of mixture of regioisomers is expected [2, 3]. This problem is approached by a

substrate control (choice of both cycloaddition reaction partners) or by application of the appropriate catalysts.

Stereochemistry of the reaction is another problem, since products can be formed via endo and exo intermediate states on routes which often cannot be easily predicted, and acyclic nitrones can undergo *E/Z* isomerization [4–7]. Problem of diastereoselectivity and enantioselectivity of the cycloaddition reaction was handled by application of chiral nitrones or alkenes or since 1994 by application of chiral catalysts [1, 8, 9].

Isoxazolidine derivatives exhibit a broad spectrum of biological activities. Isoxazolidine-based nucleoside analogs show a cytotoxic potency [10, 11]. Spiro isoxazolidine derivatives of  $\alpha$ -santonine show anticancer and antiviral activity [12]. Isoxazolidine-3,5-dione is a hypoglycemic agent [13]. A literature data analysis of the recent years concerning synthesis of new plant protection agents indicates that many new active substances were obtained by combination of the known biologically active compounds, often of a quite different mechanism of action. Favorable effect of such a combination can be a synergistic increase of efficacy of the obtained compound mixtures. An alternative approach consists in planning new chemical compounds containing in one molecule two different toxophors. The obtained new chemical compounds can easier undergo formulation than a mixture of two compounds containing each single toxophors, which can differ significantly in physicochemical properties. Carboxamides are one of the several known groups of herbicides; many examples are provided by Pesticide Manual monograph [14]. Biological activity of simple isoxazolidine derivatives is also known [15–17]. 2-Alkyl-*N*-substituted isoxazolidines show insecticidal, fungicidal, and arachnidicidal properties [18]. In light of a growing plant pathogens resistance to action of the applied pesticides and increasing registration hurdles there is a constant demand for new, more selective plant protection agents. In this work combination in one molecule of isoxazolidine and carboxamide moiety was planned. Herein, we present results of our research concerning stereoselective and regioselective 1,3-dipolar cycloaddition reaction of *N*-benzylidene-*N*-diphenylmethyl nitrones with ethyl acrylate and transformation of the obtained esters to carboxamides.

## Results and discussion

### Chemistry

Nitrones **5a–5c** were prepared starting from benzophenone by oximation [19], reduction of the oximes with sodium cyanoborohydride [20], and condensation with arylaldehydes **4a–4c**.

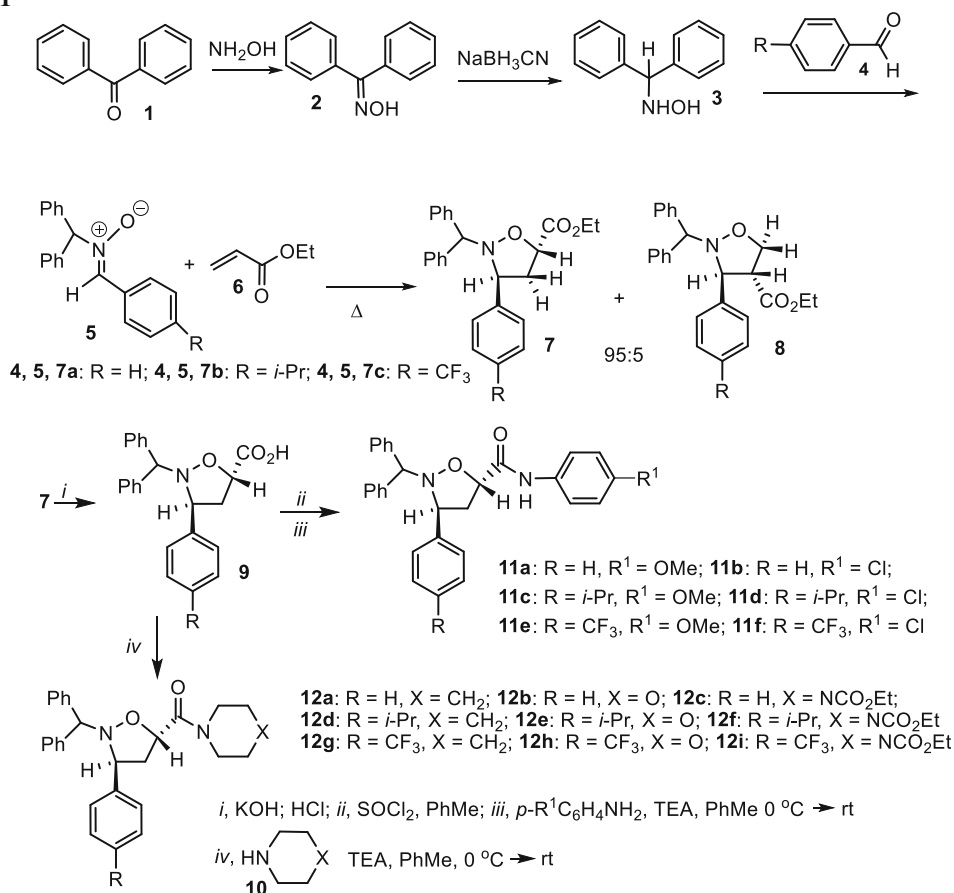
A character of the *N*-substituent was critical in the planned syntheses of nitrones. We reasoned that a bulky group, such as diphenylmethyl (DPM), would favor regio- and stereoselectivity of the cycloaddition reaction. This corollary was confirmed by our initial experiments where *N*-benzyl protective group was used and a complex mixture of cycloaddition products was obtained. Similarly mixtures of products were obtained in cycloaddition of *C*-(3-pyridyl)-*N*-alkylnitrones (*N*-Me, benzyl, and DPM protection) with methyl acrylate and with optically active *N*-(acryloyl)bornane-10,2-sultams [21]. Only in the presence of Lewis acid one major *cis*-isomer was obtained in reaction of the sultam derivative apart from the other cycloadducts. Another advantage of using DPM *N*-protection was that it could be easily removed through NBS oxidation followed by acidic hydrolysis of the formed hemiaminal [22, 23] or with Et<sub>3</sub>SiH/TFA leaving the isoxazolidine ring intact [24].

*Z*-geometry was ascribed to the nitrones based on steric consideration and relatively high field position in the <sup>1</sup>H NMR spectrum of the azomethine proton giving sharp signals at  $\delta = 7.44\text{--}7.57$  ppm [25]. In case of *E*-geometry absorption above 8 ppm is expected. It is well established that nitrones with the bulky groups possess *Z*-configuration with *N*-aryl (alkyl)—*C*-aryl groups in a *trans* relationship as proved by X-ray crystallography and NOE experiments. It is also assumed that this configuration is maintained in the transition state and no *Z/E* isomerization is taking place [26].

A key step in the synthesis of the title compounds was 1,3-dipolar cycloaddition reaction of nitrones **5a–5c** with ethyl acrylate functioning also as a solvent. Two new chiral centers were created in the reaction where two regioisomers and two *cis/trans* stereoisomers are possible. Analysis of the <sup>1</sup>H NMR spectra showed a high selectivity of the cycloaddition, since only one major crystalline *trans* 3,5-disubstituted isoxazolidine was obtained in each case (Scheme 1). One of the minor *trans* 3,4-disubstituted isoxazolidines **8c**, formed in about 5:95 proportion, was isolated by flash chromatography of the mother liquor obtained after crystallization of the major isomer. Neither of the two possible *cis* isomers has been detected.

Differences in the <sup>1</sup>H NMR spectra allow for a clear distinction between the two regioisomers. The 3,5 regioisomer showed characteristic signals for the C<sup>3</sup>H-C<sup>4</sup>H<sub>a</sub>H<sub>b</sub>-C<sup>5</sup>H unit, i.e., two dd for the methine protons H-3 at 4.55–4.57 ppm and for H5 at 4.29–4.41 ppm, and a multiplet at 2.90–3.02 ppm as well as a ddd at 2.64–2.66 ppm derived from non-equivalent diastereotopic protons of the C-4 methylene group. In contrast, the 3,4 regioisomer showed signals characteristic of the system C<sup>3</sup>H-C<sup>4</sup>H-C<sup>5</sup>H<sub>a</sub>H<sub>b</sub>, i.e., a doublet at 4.51 ppm for the C-3 methine proton, a dd at 4.36 and a doublet at 4.30 ppm for the non-equivalent diastereotopic protons of the C-5 methylene

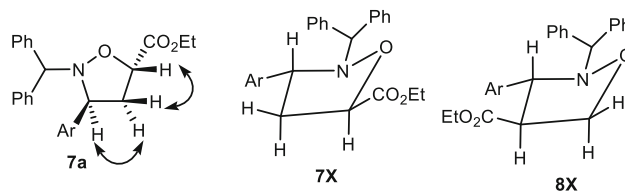
Scheme 1



group, and a ddd of the central C-4 methine group at 3.42 ppm.

The relative location of protons in positions 3 and 5 of ethyl 2-(diphenylmethyl)-3-arylisoxazolidine-5-carboxylates was determined based on the 2D NMR ROESY spectrum. This technique allows to find correlations between the proximate protons, regardless of the number of bonds separating these atoms. On the basis of this spectrum, it can be concluded that the methine protons in positions 3 and 5 interact with the different protons of the methylene group, which means that they are located on the opposite sides of the plane of the isoxazolidine ring, and that aryl and ester functions are *trans*. This is illustrated in the Figs. 1 and 2. Both regioisomers and the corresponding transition states leading to them are displayed in Scheme 2.

The major 3,5-*trans* isomer **7X** is formed via *Z-exo* TS. The minor 3,4-*trans* isomer **8X** is formed via *Z-endo* TS destabilized by steric interaction of the ester—DPM groups. The electronic effects are of minor importance, since matching between negative charge of terminal oxygen atom of the dipole and positive end of  $\beta$ -carbon atom of the acrylate would favor regioisomer **8X**.

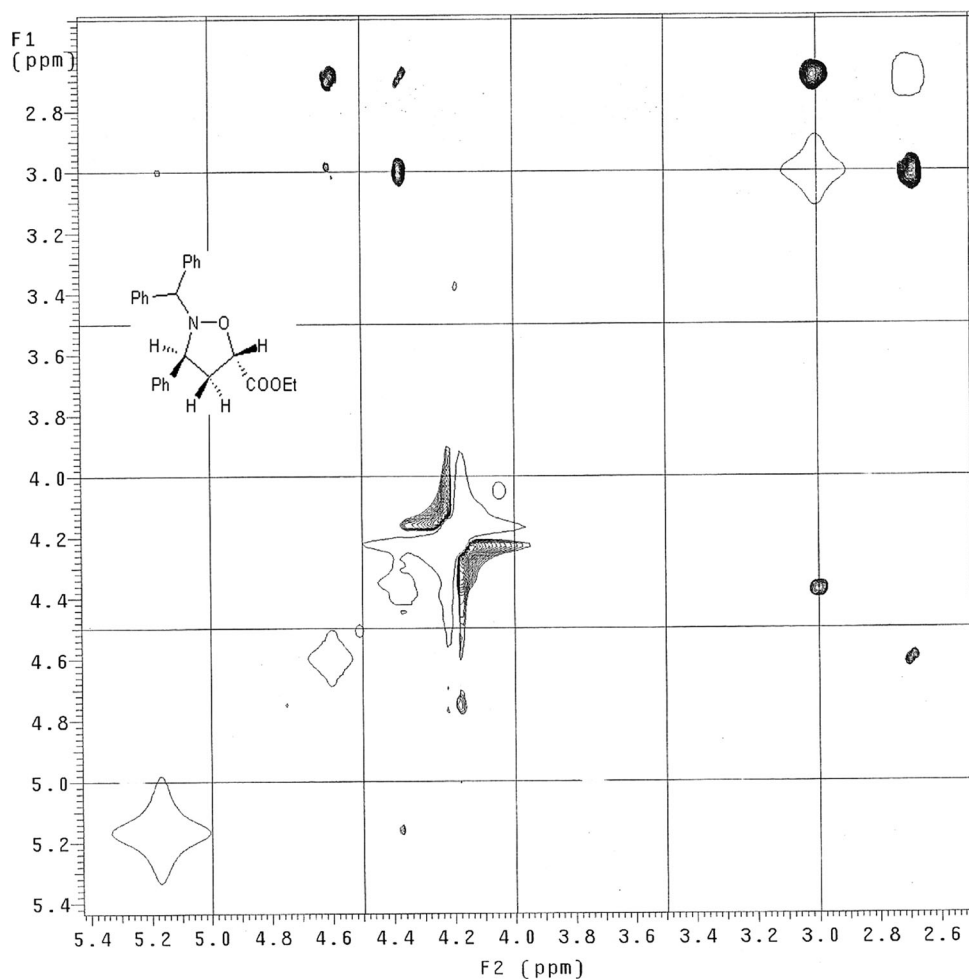


**Fig. 1** Selected ROESY spectrum for ester **7a** and preferred conformations of esters **7a–7c** and **8a–8c**

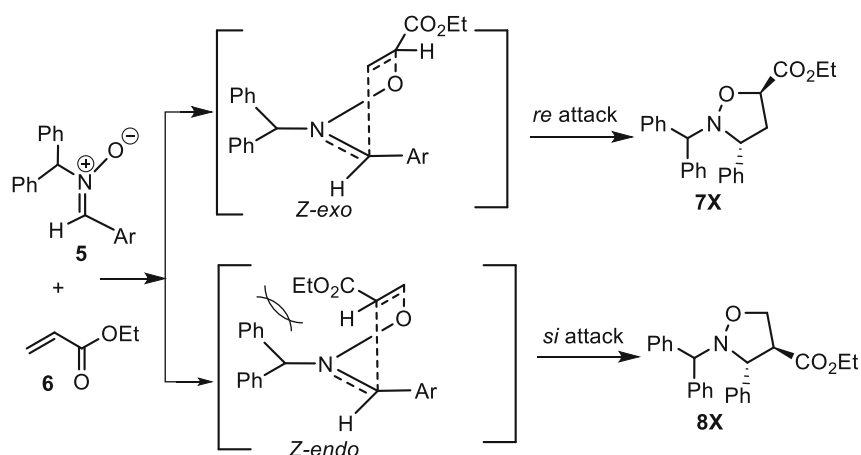
Isoxazolidines exhibit an envelope conformation of the ring with the *O* atom placed out-of-plane [27, 28]. In light of the above results a preferred all-*pseudoequatorial* conformation **7X** can be proposed to the major isomers of esters **7a–7c**. The dihedral angles from molecular modeling between H5/H<sub>4a</sub> and H3/H<sub>4a</sub> are close to 0° (19°) and 180° (161°), respectively. Thus, the observed coupling constants 7.2 and 8.4 Hz correspond to pseudoaxial positions of the relevant protons and pseudoequatorial positions of C3-aryl and C5-ester substituents [29].

The next steps were saponification of the major esters **7a–7c** and synthesis of carboxamides **11a–11f** and **12a–12i** via the intermediate acid chlorides used to acylate aniline

**Fig. 2** 2D NMR ROESY spectrum of ester **7a**



**Scheme 2**



or piperidine/piperazine/morpholine derivatives. In the secondary aryl amides **11a–11f** a signal broadening was observed. It could be explained by inversion at the nitrogen atom taking place on the  $^1\text{H}$  NMR time scale [30]. 5-Membered nitrogen heterocyclic rings are much more

flexible than saturated 6-membered rings [31]. Conformational analysis of the bicyclic isoxazolidines by  $^1\text{H}$  NMR showed two sets of peaks at low temperature spectra of some compounds, ascribed to the presence of two isomers interconverting via nitrogen atom inversion (a rate

determining step) followed by a low-energy ring flip. The free energy of activation of the process was measured (ca 55.7 kJ/mol in the temperature range up to 20 °C). For simple monocyclic 3,5,5-trisubstituted isoxazolidines this energy was estimated as 50–58 kJ/mol based on NMR measurements at variable temperatures [32]. Presence of electronegative substituents increases the nitrogen inversion barrier to the extent, that some invertomers can be separated. For 2-methoxy-*N,N'*-dimethylisoxazolidine-3,3-dicarboxamide this energy is equal to 88–100 kJ/mol [33]. 5-Methyl-2-(2-nitro-1-phenylethoxy)-3,3-dinitro-5-phenylisoxazolidines exist at room temperature as pairs of *N*-invertomers, for which free energy of activation at 353 K was measured (75 kJ/mol) [34]. Esters **7a–7c** and aliphatic amides **11a–11f** show sharp signals in the <sup>1</sup>H NMR spectrum. This result suggests either a fast inversion at the nitrogen atom and occurrence of the averaged configuration, or rather a high energy barrier to the inversion and presence of only one invertomer. Broadening of proton signals in <sup>1</sup>H NMR spectrum of the aromatic amides **11a–11f** indicates rather, that  $\Delta G$  of *N*-inversion was so lowered, that *N*-inversion/ring inversion are taking place on the <sup>1</sup>H NMR time scale. In the transition state of this process the isoxazolidine ring is planar and presence of a resonance-stabilized aromatic carbamoyl moiety should lower the energy of this TS compared to the tertiary amides.

### The biological activity

The obtained carboxamides were screened for the antifungal activity against propiconazole as a reference compound (Table 1). Analyzing generally moderate activity of the

obtained amides, compounds with electron-withdrawing groups (EWG) in the acid moiety and with electron-donating groups (EDG) in the amine moiety tend to demonstrate the best fungicidal activity. The highest potency against *B. cinerea* (89.9 %) was displayed by the aromatic amide **11a**. This compound with the EDG in the amine part was also most active against *P. cactorum*. The best activity against *R. solani* was exhibited by heterocyclic amides **12a** and **12i** with the EWG in the acid moiety. The most potent fungistatic activity against *B. cinerea* was shown also by the same compounds **12a**, **12i**, and **11b**.

### Conclusion

Several new 3-arylisoxazolidine-5-carboxamides **11a–12i** have been prepared using corresponding nitrones as basic starting materials. The obtained compounds were characterized by spectroscopic methods (IR, <sup>1</sup>H, and <sup>13</sup>C NMR as well as MS spectra). NMR methods (including 2D techniques) allowed to define the detailed stereo- and regioselectivity of the synthesized compounds. Carboxamides **12a** and **12i** showed a moderate antifungal activity against *Rhizoctonia solani* and *Botrytis cinerea* fungal strains. Based on the obtained results syntheses of new, more potent derivatives with different *N*-substituents could be envisaged.

### Experimental

Reagent grade chemicals were used without further purification unless otherwise noted. Spectra were recorded as follows: IR spectra on a JASCO FTIR-420

**Table 1** Fungicide activity of amides against 5 species of pathogenic fungi (in vitro, on PDAs and in vivo), % inhibition of mycelial growth

Comp	<i>Botrytis cinerea</i> 200 ppm	<i>Fusarium culmorum</i>	<i>Phytophthora cactorum</i>	<i>Rhizoctonia solani</i>	<i>Blumeria graminis</i> 1000 ppm
<b>11a</b>	14.0	0	72	0	89.9
<b>11b</b>	57.5	30	0	37.5	17.8
<b>11c</b>	11.9	0	0	0	5.0
<b>11e</b>	19.0	0	0	0	9.7
<b>11f</b>	38.1	0	0	0	12.8
<b>12a</b>	54.5	33	40	88.5	40.7
<b>12c</b>	61.0	50	0	0	46.6
<b>12d</b>	33.3	0	0	36.0	3.5
<b>12e</b>	0	0	0	0	28.7
<b>12f</b>	0	0	–	0	45.5
<b>12h</b>	23.1	0	9.5	0	7.6
<b>12i</b>	75	42	36	73	16.9
Propiconazole <sup>a</sup>	100	100	74	86	100

<sup>a</sup> Reference compound

spectrometer,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR, and ROESY spectra on a Varian 500 UNITY plus-500, and a Varian 200 UNITY plus-200 spectrometers in deuterated chloroform. Chemical shifts are given in ppm ( $\delta$ ) relative to TMS as an internal standard, coupling constants are reported in Hz. EI mass spectra were run on an AMD M-40 instrument, ESI mass spectra on a LCT (Micromass) apparatus. Flash chromatography was carried out using silica gel S 230–400 mesh (Merck) using hexane–ethyl acetate mixtures as an eluent. Molecular Mechanics calculations were performed with the computer program Hyperchem 7.5.

#### Synthesis of nitrones—typical procedure: *N*-Benzylidenediphenylmethanamine, *N*-oxide (5a)

In a dry 150 cm<sup>3</sup> flask equipped with a calcium chloride tube were placed 1.79 g *N*-(diphenylmethyl)hydroxylamine (9 mmol), 130 cm<sup>3</sup> toluene, and 1.2 g magnesium sulfate (10 mmol, 1.1 eq). Benzaldehyde (1.4 cm<sup>3</sup>, 13.5 mmol, 1.5 eq) was added dropwise to the suspension. The mixture was stirred at room temperature for 26 h, was filtered and concentrated in vacuo. The solid residue was recrystallized from 35 cm<sup>3</sup> methanol to afford 2.0 g of a colorless product (77 %). *m.p.*: 152–153 °C (Ref. [35] 163–165 °C);  $R_f$  = 0.27 (cyclohexane:ethyl acetate 4:1).

#### *N*-[4-(1-Methylethyl)benzylidene]diphenylmethanamine, *N*-oxide (5b, C<sub>23</sub>H<sub>23</sub>NO)

Yield: 1.35 g (81 %) of a colorless product; *m.p.*: 138–140 °C;  $R_f$  = 0.47 (cyclohexane:ethyl acetate 4:1); IR (KBr):  $\bar{\nu}$  = 3063, 2926, 1555, 1495, 1454, 1325, 1268, 1167, 1135, 1066, 845, 722 cm<sup>-1</sup>;  $^1\text{H}$  NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.20–8.16 (m, 2H), 7.44 (s, 1H), 7.37–7.24 (m, 12H), 6.35 (s, 1H), 2.92 (septet,  $J$  = 6.8 Hz, 1H), 1.24 (d,  $J$  = 6.8 Hz, 6H) ppm;  $^{13}\text{C}$  NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 23.9, 34.4, 83.6, 126.8, 128.2, 128.7, 128.9, 129.2, 135.1, 137.4, 152.1 ppm; HRMS (ESI):  $m/z$  calcd for C<sub>23</sub>H<sub>23</sub>NONa 352.1677, found 352.1672.

#### *N*-[4-(Trifluoromethyl)benzylidene]diphenylmethanamine, *N*-oxide (5c, C<sub>21</sub>H<sub>16</sub>F<sub>3</sub>NO)

Yield: 1.57 g (85 %) of a colorless product; *m.p.*: 150–153 °C;  $R_f$  = 0.34 (cyclohexane:ethyl acetate 4:1); IR (KBr):  $\bar{\nu}$  = 3063, 3021, 3000, 2956, 2926, 1605, 1496, 1463, 1294, 1138, 868, 724 cm<sup>-1</sup>;  $^1\text{H}$  NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.36 (d,  $J$  = 8.2 Hz, 2H), 7.65 (d,  $J$  = 8.2 Hz, 2H), 7.57 (s, 1H), 7.45–7.30 (m, 10H), 6.40 (s, 1H) ppm;  $^{13}\text{C}$  NMR (50 MHz, CD<sub>3</sub>OD):  $\delta$  = 84.2, 126.5 (q,  $J$  = 3.5 Hz), 129.7, 129.9, 130.5, 131.0, 133.9, 136.8, 138.5 ppm; HRMS (ESI):  $m/z$  calcd for C<sub>21</sub>H<sub>16</sub>F<sub>3</sub>NONa 378.1082, found 378.1073.

#### Synthesis of ethyl esters of 2-(diphenylmethyl)-3-arylisoxazolidine-5-carboxylic acid—typical procedure

##### *Ethyl 2-(diphenylmethyl)-3-phenylisoxazolidine-5-carboxylate (7a, C<sub>25</sub>H<sub>25</sub>NO<sub>3</sub>)*

In a dry 25 cm<sup>3</sup> flask equipped with a magnetic stirrer, reflux condenser provided with a calcium chloride tube were placed 1.92 g 5a (6.7 mmol) and 7.4 cm<sup>3</sup> ethyl acrylate (67 mmol). The flask was placed in an oil bath heated to 100 °C and reaction mixture was stirred for 19.5 h. The solution turned clear yellow during the reaction. After cooling to ambient temperature the reaction mixture was concentrated under reduced pressure (water pump) using a short set for distillation. The resulting pale yellow oil was placed in the refrigerator for about 2 h. The precipitate was suspended in 20 cm<sup>3</sup> hexane, filtered, and was washed with hexane (2 × 10 cm<sup>3</sup>). The precipitate was recrystallized from 40 cm<sup>3</sup> ethanol to afford 1.78 g (69 %) of a colorless solid. *m.p.*: 116–117 °C;  $R_f$  = 0.44 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3063, 3031, 2979, 1729, 1492, 1451, 1279, 1211, 743 cm<sup>-1</sup>;  $^1\text{H}$  NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53 (bs, 2H), 7.36–7.07 (m, 13H, aryl), 5.12 (bs, 1H), 4.56 (dd,  $J$  = 6.9, 8.4 Hz, 1H, H3), 4.34 (dd,  $J$  = 4.6, 7.2 Hz, 1H, H5), 4.16 (q,  $J$  = 7.2 Hz, 2H), 2.97 (app. quintet,  $J$  = 6.5 Hz, 1H, H4a), 2.66 (ddd,  $J$  = 4.4, 8.4, 12.5 Hz, 1H, H4b), 1.22 (t,  $J$  = 7.2 Hz, 3H) ppm;  $^{13}\text{C}$  NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.1, 41.4, 61.3, 65.6, 73.8, 127.0, 127.1, 127.2, 127.9, 128.2, 128.2, 128.3, 128.4, 140.8, 141.6, 141.8, 172.2 ppm; HRMS (ESI):  $m/z$  calcd for C<sub>25</sub>H<sub>25</sub>NO<sub>3</sub>Na 410.1732; found: 410.1736.

##### *Ethyl 2-(diphenylmethyl)-3-[4-(1-methylethyl)phenyl]isoxazolidine-5-carboxylate (7b, C<sub>28</sub>H<sub>31</sub>NO<sub>3</sub>)*

Yield: 1.39 g (63 %) of a colorless solid; *m.p.*: 134–136 °C (ethanol);  $R_f$  = 0.47 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3063, 3031, 2960, 2905, 1732, 1453, 1205, 1159, 1053, 803, 744 cm<sup>-1</sup>;  $^1\text{H}$  NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.08–7.55 (m, 14H, Ar), 5.11 (s, 1H), 4.57 (dd,  $J$  = 6.9, 8.4 Hz, 1H, H3), 4.29 (dd,  $J$  = 4.6, 7.0 Hz, 1H, H5), 4.15 (q,  $J$  = 7.2 Hz, 2H), 2.90 (m, 1H, H4a), 2.66 (ddd,  $J$  = 4.6, 8.4, 12.9 Hz, 1H, H4b), 1.23 (d,  $J$  = 6.8 Hz, 6H), 1.22 (t,  $J$  = 7.2 Hz, 3H) ppm;  $^{13}\text{C}$  NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.1, 24.0, 33.8, 41.3, 61.3, 65.4, 73.7, 126.3, 127.0, 127.1, 127.2, 127.9, 128.1, 128.3, 137.9, 141.6, 141.8, 147.7, 172.3 ppm; HRMS (ESI):  $m/z$  calcd for C<sub>28</sub>H<sub>31</sub>NO<sub>3</sub>Na 452.2202, found 452.2198.

##### *Ethyl 2-(diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]isoxazolidine-5-carboxylate (7c, C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>3</sub>) and ethyl 2-(diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]isoxazolidine-4-carboxylate (8c, C<sub>26</sub>H<sub>24</sub>F<sub>3</sub>NO<sub>3</sub>)*

Yield: 1.45 g (74 %) of a colorless solid; *m.p.*: 131–132 °C;  $R_f$  = 0.31 (cyclohexane:ethyl acetate 4:1); IR (KBr)



$\bar{\nu}$  = 3031, 2979, 1731, 1454, 1324, 1212, 1158, 1129, 1067, 1018, 745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.57–7.09 (m, 14H, Ar), 5.16 (s, 1H), 4.55 (dd,  $J$  = 6.6, 8.5 Hz, 1H, H3), 4.41 (dd,  $J$  = 4.6, 7.2 Hz, 1H, H5), 4.17 (q,  $J$  = 7.3 Hz, 2H), 3.02 (app. quintet,  $J$  = 6.8 Hz, 1H, H4a), 2.64 (ddd,  $J$  = 4.7, 8.5, 13.0 Hz, 1H, H4b), 1.23 (t,  $J$  = 7.3 Hz, 3H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 14.1, 41.4, 61.5, 65.5, 74.4, 76.6, 125.3 (q,  $J$  = 3.9 Hz), 127.1, 127.4, 127.5, 127.8, 128.0, 128.3, 128.4, 141.0, 141.9, 145.0, 172.0 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{26}\text{H}_{24}\text{F}_3\text{NO}_3\text{Na}$  478.1606, found 478.1591.

The crystallization mother liquor was concentrated to afford 0.41 g of a yellow oil, 0.14 g of which was subjected to flash chromatography on silica gel to give 23.1 mg of a yellow oil which was identified by  $^1\text{H}$  NMR spectrum as the other regioisomer, ethyl 2-(diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]isoxazolidine-4-carboxylate (**8c**). The overall yield was 4 %;  $R_f$  = 0.38 (cyclohexane:ethyl acetate 4:1);  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.54–7.07 (m, 14H, Ar), 5.16 (s, 1H), 4.51 (d,  $J$  = 5.1 Hz, 1H, H3), 4.36 (dd,  $J$  = 6.8, 8.4 Hz, 1H, H5a), 4.30 (d,  $J$  = 8.4 Hz, 1H, H5b), 4.21 (q,  $J$  = 7.2 Hz, 2H), 3.42 (ddd,  $J$  = 5.1, 6.8, 8.4 Hz, 1H, H4), 1.26 (t,  $J$  = 7.2 Hz, 3H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 14.4, 58.0, 61.8, 68.7, 69.6, 72.8, 125.5 (q,  $J$  = 3.7 Hz), 127.5, 127.6, 127.8, 128.0, 128.4, 128.6, 128.6, 141.0, 141.6, 146.3, 172.3.

### Hydrolysis of ethyl 2-(diphenylmethyl)-3-arylisoxazolidine-5-carboxylates—typical procedure

#### 2-(Diphenylmethyl)-3-phenylisoxazolidine-5-carboxylic acid (**9a**)

To a suspension of 1.39 g ethyl 2-(diphenylmethyl)-3-phenylisoxazolidine-5-carboxylate (**7a**, 3.6 mmol) in 7.2  $\text{cm}^3$  ethanol was added 17.6 g of 2 % sodium hydroxide. The mixture was heated under reflux with stirring for 3 h. After cooling 5  $\text{cm}^3$  of 2 N hydrochloric acid was added and the mixture was extracted with dichloromethane ( $3 \times 30 \text{ cm}^3$ ). The organic phase was dried over sodium sulfate. After filtration and concentration, the precipitate was recrystallized from dichloromethane-hexane (1:6) to afford 1.19 g of the product (92 %).

### Synthesis of amides **11a–11f**, **12a–12i**—typical procedure

#### 2-(Diphenylmethyl)-*N*-(4-methoxyphenyl)-3-phenylisoxazolidine-5-carboxamide (**11a**, $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_3$ )

To a solution of 0.15 g 2-(diphenylmethyl)-3-phenylisoxazolidine-5-carboxylic acid (0.42 mmol) in 5  $\text{cm}^3$  toluene was added dropwise 62  $\text{cm}^3$  thionyl chloride (0.85 mmol, 2 eq). The mixture was stirred at room temperature for 18 h.

The solution was concentrated under reduced pressure. The resulting oil was dissolved in 5  $\text{cm}^3$  toluene, cooled in ice-water bath to a temperature of about 0 °C and a solution of 0.057 g 4-methoxyaniline (0.47 mmol, 1.1 eq) in 2  $\text{cm}^3$  toluene was added dropwise followed by 0.12  $\text{cm}^3$  triethylamine (0.87 mmol, 2 eq). The mixture was stirred at about 0 °C for 30 min, and then at room temperature for 3 h. The reaction mixture was diluted with 15  $\text{cm}^3$  toluene and washed successively with 10  $\text{cm}^3$  water, 10  $\text{cm}^3$  5 % HCl, and 10  $\text{cm}^3$  water. The organic phase was dried over sodium sulfate. After filtration and concentration, the resulting oil was recrystallized from ethyl acetate:hexane mixture (1:19) to afford 0.14 g (73 %) of a colorless product. *m.p.*: 137–138 °C;  $R_f$  = 0.23 (cyclohexane: ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3375, 3063, 3031, 3000, 2937, 1675, 1523, 1453, 1231, 1039, 833, 751  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.78 (bs, 1H, NH), 7.46–6.80 (m, 19H, Ar), 4.93 (bs, 1H), 4.65 (t,  $J$  = 8.1 Hz, 1H, H3), 4.35 (m, 1H, H5), 3.79 (s, 3H), 3.01 (m, 1H, H4a), 2.93–2.81 (m, 1H, H4b) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 41.0, 55.7, 65.2, 114.2, 121.3, 127.6, 127.8, 127.9, 128.7, 128.9, 129.0, 130.4, 140.5, 156.6 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{30}\text{H}_{28}\text{N}_2\text{O}_3\text{Na}$  487.1998, found 487.2011.

#### *N*-(4-Chlorophenyl)-2-(diphenylmethyl)-3-phenylisoxazolidine-5-carboxamide (**11b**, $\text{C}_{29}\text{H}_{25}\text{ClN}_2\text{O}_2$ )

Yield: 0.13 g of a colorless product (64 %); *m.p.*: 195–196 °C (ethyl acetate:hexane 1:13);  $R_f$  = 0.39 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3364, 3063, 3031, 2916, 1683, 1590, 1519, 1401, 1027, 829, 745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.88 (bs, NH), 7.45–7.22 (m, 19H, Ar), 4.91 (bs, 1H), 4.64 (t,  $J$  = 8.2 Hz, 1H, H3), 4.38 (m, 1H, H5), 3.02 (m, 1H, H4a), 2.94–2.81 (m, 1H, H4b) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 40.6, 65.0, 72.3, 120.8, 127.4, 127.6, 127.7, 128.5, 128.7, 128.8, 129.3, 135.6, 140.3, 141.8, 170.4 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{29}\text{H}_{25}\text{ClN}_2\text{O}_2\text{Na}$  491.1502, found 491.1518.

#### 2-(Diphenylmethyl)-*N*-(4-methoxyphenyl)-3-[4-(1-methylethyl)phenyl]isoxazolidine-5-carboxamide (**11c**, $\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_3$ )

Yield: 0.12 g (62 %) of a colorless product; *m.p.*: 80–81 °C (toluene-hexane);  $R_f$  = 0.26 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3354, 3063, 3031, 2960, 1672, 1512, 1453, 1413, 1248, 1032, 832, 746  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.77 (bs, NH), 7.45–6.79 (m, 19H, Ar), 4.95 (bs, 1H), 4.65 (t,  $J$  = 8.0 Hz, 1H, H5), 4.29 (bs, 1H, H3), 3.78 (s, 3H), 3.01–2.80 (m, 3H), 1.26 (d,  $J$  = 6.8 Hz, 6H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 24.2, 27.1, 34.0, 55.6, 64.9, 72.1, 114.1, 121.4, 126.7, 127.7, 127.8, 128.8, 128.9, 130.4, 140.5, 148.5, 156.6, 170.3 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{33}\text{H}_{34}\text{N}_2\text{O}_3\text{Na}$  529.2467, found 529.2471.

*N*-(4-Chlorophenyl)-2-(diphenylmethyl)-3-[4-(1-methylethyl)phenyl]isoxazolidine-5-carboxamide (**11d**, C<sub>32</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>)

Yield: 0.12 g (67 %) of a colorless product; *m.p.*: 134–135 °C (ethyl acetate:hexane 1:30); *R<sub>f</sub>* = 0.45 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3378, 3063, 3021, 2958, 1692, 1516, 1400, 831, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.86 (bs, NH), 7.45–7.17 (m, 18H, Ar), 4.93 (bs, 1H), 4.65 (t, *J* = 8.1 Hz, 1H), 4.32 (bs, 1H), 2.98–2.81 (m, 3H), 1.26 (d, *J* = 6.8 Hz, 6H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 24.0, 33.8, 40.6, 64.8, 72.0, 120.8, 126.6, 127.5, 127.6, 127.7, 128.7, 128.8, 128.8, 129.3, 135.6, 140.3, 148.38 ppm; HRMS (ESI): *m/z* calcd for C<sub>32</sub>H<sub>31</sub>ClN<sub>2</sub>O<sub>2</sub>Na 533.1972, found 533.1993.

2-(Diphenylmethyl)-*N*-(4-methoxyphenyl)-3-[4-(trifluoromethyl)phenyl]isoxazolidine-5-carboxamide (**11e**, C<sub>31</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>)

Yield: 0.12 g (66 %) of a colorless product; *m.p.*: 158–160 °C (ethyl acetate:hexane 1:10); *R<sub>f</sub>* = 0.15 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3360, 3063, 3000, 2937, 2386, 1675, 1529, 1413, 1325, 1247, 1158, 1123, 1067, 828, 746 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.77 (bs, NH), 7.59 (d, *J* = 7.8 Hz, 1H), 7.45–7.15 (m, 14H, Ar), 6.82 (d, *J* = 9.0 Hz, 2H), 4.92 (bs, 1H), 4.65 (t, *J* = 8.0 Hz, 1H, H5), 4.45 (m, 1H, H3), 3.79 (s, 3H), 3.16–3.09 (m, 1H, H4a), 2.91–2.79 (m, 1H, H4b) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 40.6, 55.7, 65.0, 73.1, 75.9, 114.2, 121.3, 125.6 (q, *J* = 5.7 Hz), 127.6, 128.0, 128.0, 128.3, 129.0, 129.1, 130.3, 140.6, 156.6, 169.7 ppm; HRMS (ESI): *m/z* calcd for C<sub>31</sub>H<sub>27</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>Na 555.1871, found 555.1891.

*N*-(4-Chlorophenyl)-2-(diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]isoxazolidine-5-carboxamide (**11f**, C<sub>30</sub>H<sub>24</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>)

Yield: 0.14 g (70 %) of a colorless product; *m.p.*: 158–159 °C (ethyl acetate:hexane 1:15); *R<sub>f</sub>* = 0.36 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3376, 3063, 3031, 2926, 2368, 1690, 1594, 1528, 1493, 1384, 1326, 1170, 1124, 1069, 1017, 815 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.85 (bs, NH), 7.61–7.17 (m, 18H, Ar), 4.91 (s, 1H), 4.62 (t, *J* = 8.0 Hz, 1H, H5), 4.52 (dd, *J* = 1.3, 7.9 Hz, 1H, H3), 3.17–3.11 (m, 1H, H4a), 2.92–2.80 (m, 1H, H4b) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 40.1, 64.8, 120.7, 125.5 (q, *J* = 3.5 Hz), 127.4, 127.8, 127.9, 128.0, 128.9, 129.0, 129.4, 135.4 ppm; HRMS (ESI): *m/z* calcd for C<sub>30</sub>H<sub>24</sub>ClF<sub>3</sub>N<sub>2</sub>O<sub>2</sub>Na 559.1376, found 559.1375.

[2-(Diphenylmethyl)-3-phenyl-5-isoxazolidinyl]-(1-piperidinyl)methanone (**12a**, C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>)

Yield: 0.13 g (81 %) of a colorless product; *m.p.*: 169–170 °C (ethyl acetate:hexane 1:13); *R<sub>f</sub>* = 0.22 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3063, 3031, 2931,

2853, 1639, 1492, 1453, 1254, 1228, 1016, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.54–7.11 (m, 15H, Ar), 5.01 (s, 1H), 4.68 (t, *J* = 7.9 Hz, 1H, H5), 4.52 (dd, *J* = 1.6, 7.8 Hz, 1H, H3), 3.79–3.65 (m, 2H), 3.25–3.00 (m, 3H), 2.46 (ddd, *J* = 2.2, 8.5, 13.0 Hz, 1H, H4b), 1.62–1.17 (m, 6H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 24.5, 25.3, 25.7, 36.8, 43.6, 46.6, 66.3, 74.2, 76.5, 126.8, 126.9, 127.0, 127.6, 127.8, 128.2, 128.3, 128.5, 128.8, 142.2, 142.6, 142.8, 168.2 ppm; HRMS (ESI): *m/z* calcd for C<sub>28</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub>Na 449.2205, found 449.2185.

[2-(Diphenylmethyl)-3-phenyl-5-isoxazolidinyl]-(4-morpholinyl)methanone (**12b**, C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>)

Yield: 0.14 g (84 %) of a colorless product; *m.p.*: 152–153 °C (ethyl acetate:hexane 1:25); *R<sub>f</sub>* = 0.31 (cyclohexane:ethyl acetate 1:1); IR (KBr)  $\bar{\nu}$  = 3063, 3031, 2926, 2863, 1642, 1454, 1232, 1113, 1027, 749 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53–7.14 (m, 15H, Ar), 4.99 (s, 1H), 4.64 (t, *J* = 7.8 Hz, 1H, H5), 4.56 (bd, *J* = 6.8 Hz, 1H, H3), 3.82–3.68 (m, 2H), 3.64–3.52 (m, 1H), 3.40–3.24 (m, 3H), 3.18 (t, *J* = 4.8 Hz, 2H), 2.69 (app. quintet, *J* = 5.4 Hz, 1H), 2.51 (ddd, *J* = 2.0, 8.7, 13.1 Hz, 1H, H4b) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 36.1, 42.6, 45.8, 66.1, 66.2, 74.0, 76.2, 126.6, 127.0, 127.6, 127.8, 128.3, 128.4, 128.7, 141.8, 142.1, 142.4, 168.5 ppm; HRMS (ESI): *m/z* calcd for C<sub>27</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>Na 451.1998, found 451.1999.

Ethyl 4-[[2-(diphenylmethyl)-3-phenyl-5-isoxazolidinyl]-carbonyl]piperazine-1-carboxylate (**12c**, C<sub>30</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>)

Yield: 0.16 g (77 %) of a colorless product; *m.p.*: 161–162 °C (ethyl acetate:hexane 1:20); *R<sub>f</sub>* = 0.26 (cyclohexane:ethyl acetate 1:1); IR (KBr)  $\bar{\nu}$  = 3063, 3021, 2979, 2926, 1707, 1640, 1452, 1288, 1227, 1092, 748 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53–7.10 (m, 15H, Ar), 4.97 (s, 1H), 4.64 (t, *J* = 7.8 Hz, 1H, H5), 4.56 (bd, *J* = 7.6 Hz, 1H, H3), 4.12 (q, *J* = 7.1 Hz, 2H), 3.90–3.55 (m, 3H), 3.31–3.26 (m, 2H), 3.18–2.89 (m, 3H), 2.51 (ddd, *J* = 1.6, 8.7, 13.1 Hz, 1H, H4b), 2.22–2.13 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm; <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>):  $\delta$  = 14.8, 36.2, 42.3, 43.4, 45.3, 61.7, 66.2, 74.3, 76.5, 126.8, 127.2, 127.7, 127.9, 128.4, 128.6, 128.9, 141.9, 142.3, 142.6, 155.5, 168.8 ppm; HRMS (ESI): *m/z* calcd for C<sub>30</sub>H<sub>33</sub>N<sub>3</sub>O<sub>4</sub>Na 522.2369, found 522.2387.

[2-(Diphenylmethyl)-3-[4-(1-methylethyl)phenyl]-5-isoxazolidinyl]-(1-piperidinyl)methanone (**12d**, C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>)

Yield: 0.14 g (78 %) of a colorless product; *m.p.*: 163–164 °C (ethyl acetate:hexane 1:10); *R<sub>f</sub>* = 0.22 (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu}$  = 3063, 3031, 2931, 2852, 1640, 1452, 1384, 1229, 747 cm<sup>-1</sup>; <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.53–7.42 (m, 4H, Ar), 7.33–7.12 (m, 10H, Ar), 5.00 (s, 1H), 4.69 (t, *J* = 8.0 Hz, 1H, H5), 4.49 (bd, *J* = 8.0 Hz, 1H, H3), 3.76–3.62 (m, 2H),



3.22–3.00 (m, 3H), 2.88 (sept.,  $J = 6.8$  Hz, 1H), 2.48 (ddd,  $J = 2.2, 8.6, 13.0$  Hz, 1H, H4b), 1.40–1.36 (m, 4H), 1.24 (d,  $J = 6.8$  Hz, 6H), 1.17 (m, 2H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 24.0, 24.4, 25.1, 25.6, 33.7, 36.2, 43.4, 46.4, 65.9, 74.0, 126.4, 126.7, 127.3, 127.7, 128.0, 128.1, 128.6, 139.6, 142.0, 142.6, 147.4, 168.1$  ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{31}\text{H}_{36}\text{N}_2\text{O}_2\text{Na}$  491.2674, found 491.2674.

[2-(Diphenylmethyl)-3-[4-(1-methylethyl)phenyl]-5-isoxazolidinyl](4-morpholinyl)methanone (**12e**,  $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3$ )

Yield: 0.12 g (70 %) of a colorless product;  $m.p.$ : 154–155 °C (ethyl acetate:hexane 1:20); IR (KBr)  $\bar{\nu} = 3063, 3031, 2964, 2863, 1640, 1454, 1274, 1232, 1113, 1027, 747$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.50$ – $7.42$  (m, 4H, Ar), 7.32–7.14 (m, 10H, Ar), 4.97 (s, 1H), 4.65 (t,  $J = 8.0$  Hz, 1H, H5), 4.52 (bd,  $J = 8.0$  Hz, 1H, H3), 3.81–3.69 (m, 2H), 3.65–3.52 (m, 1H), 3.39–3.27 (m, 3H), 3.24–3.16 (m, 2H), 2.89 (septet,  $J = 6.9$  Hz, 1H), 2.74–2.63 (m, 1H), 2.52 (ddd,  $J = 1.7, 8.6, 13.0$  Hz, 1H, H4b), 1.24 (d,  $J = 7.0$  Hz, 6H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 24.2, 33.9, 36.0, 42.8, 46.0, 66.1, 66.4, 74.2, 76.5, 126.6, 126.8, 127.1, 127.7, 127.8, 128.0, 128.4, 128.9, 139.6, 142.0, 142.6, 147.7, 168.8$  ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_3\text{Na}$  493.2467, found 493.2465.

Ethyl 4-[[2-(diphenylmethyl)-3-[4-(1-methylethyl)phenyl]-5-isoxazolidinyl]carbonyl]piperazine-1-carboxylate

(**12f**,  $\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_4$ )

Yield: 0.15 g (75 %) of a colorless product;  $m.p.$ : 158–159 °C (ethyl acetate:hexane 1:13);  $R_f = 0.33$  (cyclohexane:ethyl acetate 1:1); IR (KBr)  $\bar{\nu} = 3063, 3031, 2961, 1694, 1641, 1436, 1242, 998, 748$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.52$ – $7.42$  (m, 4H, Ar), 7.33–7.13 (m, 10H, Ar), 4.96 (s, 1H), 4.65 (t,  $J = 8.0$  Hz, 1H, H5), 4.52 (bd,  $J = 7.4$  Hz, 1H, H3), 4.11 (q,  $J = 7.1$  Hz, 2H), 3.90–3.54 (m, 3H), 3.31–3.24 (m, 2H), 3.17–3.00 (m, 2H), 3.00–2.82 (m, 2H), 2.52 (ddd,  $J = 1.4, 8.5, 13.1$  Hz, 1H, H4b), 2.22–2.12 (m, 1H), 1.25 (t,  $J = 7.1$  Hz, 3H), 1.24 (d,  $J = 6.8$  Hz, 6H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 14.8, 24.2, 33.9, 35.9, 42.3, 43.1, 43.4, 45.3, 61.7, 66.0, 74.3, 76.5, 126.6, 126.8, 127.1, 127.7, 127.8, 128.0, 128.4, 128.9, 139.5, 142.0, 142.7, 147.7, 155.5, 168.8$  ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{33}\text{H}_{39}\text{N}_3\text{O}_4\text{Na}$  564.2838, found 564.2838.

[2-(Diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolidinyl](1-piperidinyl)methanone

(**12g**,  $\text{C}_{29}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_2$ )

Yield: 0.13 g (75 %) of a colorless product;  $m.p.$ : 174–175 °C (ethyl acetate:hexane 1:12);  $R_f = 0.22$  (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu} = 3063, 3031, 2932,$

2852, 1641, 1453, 1329, 1230, 1123, 1070, 1018, 850, 749  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.58$ – $7.46$  (m, 6H), 7.40 (dd,  $J = 1.7, 7.6$  Hz, 2H), 7–32–7.12 (m, 6H, Ar), 5.03 (s, 1H), 4.66 (t,  $J = 7.8$  Hz, 1H, H5), 4.50 (bd,  $J = 7.4$  Hz, 1H, H3), 3.85–3.66 (m, 2H), 3.26–3.00 (m, 3H), 2.42 (ddd,  $J = 2.3, 8.4, 13.0$  Hz, 1H, H4b), 1.41–1.17 (m, 6H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 24.3, 25.1, 25.5, 36.9, 43.5, 46.4, 66.0, 74.2, 76.3, 125.2$  (q,  $J = 3.6$  Hz), 126.8, 127.1, 127.6, 127.8, 128.2, 128.7, 141.6, 142.4, 146.5, 167.7 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{29}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_2\text{Na}$  517.2079, found 517.2080.

[2-(Diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolidinyl](4-morpholinyl)methanone

(**12h**,  $\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_3$ )

Yield: 0.12 g (71 %) of a colorless product;  $m.p.$ : 164–165 °C (ethyl acetate:hexane 1:25);  $R_f = 0.24$  (cyclohexane:ethyl acetate 4:1); IR (KBr)  $\bar{\nu} = 3063, 3021, 2905, 2859, 1639, 1455, 1329, 1232, 1113, 1069, 1018, 850, 750$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.59$ – $7.48$  (m, 6H), 7.40 (dd,  $J = 1.7, 8.0$  Hz, 2H), 7.35–7.13 (m, 6H, Ar), 5.00 (s, 1H), 4.66 (t,  $J = 8.0$  Hz, 1H, H5), 4.60 (d,  $J = 7.0$  Hz, 1H, H3), 3.88–3.70 (m, 2H), 3.64–3.53 (m, 1H), 3.40–3.25 (m, 3H), 3.19–3.15 (m, 2H), 2.75–2.64 (m, 1H, H4a), 2.46 (ddd,  $J = 2.1, 8.5, 13.1$  Hz, 1H, H4b) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 36.6, 42.9, 46.1, 66.1, 66.4, 74.4, 76.4, 125.5$  (q,  $J = 3.6$  Hz), 127.2, 127.3, 127.6 (q,  $J = 32.0$  Hz), 127.7, 127.8, 128.5, 129.0, 141.6, 142.4, 146.5, 168.4 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_2\text{O}_3\text{Na}$  519.1871, found 519.1852.

Ethyl 4-[[2-(diphenylmethyl)-3-[4-(trifluoromethyl)phenyl]-5-isoxazolidinyl]carbonyl]piperazine-1-carboxylate (**12i**,  $\text{C}_{31}\text{H}_{32}\text{N}_3\text{O}_4\text{F}_3$ )

Yield: 0.14 g (69 %) of a colorless product;  $m.p.$ : 183–184 °C (ethyl acetate:hexane 1:9);  $R_f = 0.4$  (cyclohexane:ethyl acetate 1:1); IR (KBr)  $\bar{\nu} = 3031, 3973, 2989, 2905, 1688, 1653, 1430, 1325, 1228, 1116, 747$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ ):  $\delta = 7.55$ – $7.17$  (m, 14H, Ar), 4.99 (s, 1H), 4.66–4.59 (m, 2H), 4.12 (q,  $J = 7.2$  Hz, 2H), 3.99–3.73 (m, 2H), 3.62–3.55 (m, 1H), 3.35–2.90 (m, 5H), 2.47 (ddd,  $J = 1.9, 8.5, 13.1$  Hz, 1H), 2.23–2.14 (m, 1H), 1.25 (t,  $J = 7.2$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ ):  $\delta = 14.8, 36.6, 42.4, 43.3, 45.3, 61.7, 66.1, 74.4, 76.4, 125.5$  (q,  $J = 4.2$  Hz), 127.2, 127.7, 127.8, 127.9, 128.5, 129.0, 141.6, 142.4, 146.4, 155.5, 168.5 ppm; HRMS (ESI):  $m/z$  calcd for  $\text{C}_{31}\text{H}_{32}\text{F}_3\text{N}_3\text{O}_4\text{Na}$  590.2243, found 590.2227.

## Fungicidal testing

### In vitro test

The compounds were screened in vitro for antifungal activity against the following five plant pathogens:

*Fusarium culmorum* Sacc., *Phytophthora cactorum* Schroek, *Alternaria alternata* Keissl.(Fr.), *Rhizoctonia solani* Kuhn, and *Botrytis cinerea* Pers. Ex Fr.

The test involved determination of mycelial growth retardation in potato glucose agar (PGA; Difco). Stock solutions of test chemicals in acetone (2 cm<sup>3</sup>) were added to agar medium to give a concentration of 200 mg/cm<sup>3</sup> and dispersed into sterile Petri dishes. Plates were inoculated within 24 h after they were poured. Four discs (5 mm diameter) were cut from the margins of actively growing 2-week-old colony and were placed in equal distances from each other on the surface of the solidified agar. PGA with addition of acetone was used for the control. The plates were incubated in the growth chamber at 25 ± 1 °C.

The radial growth of the fungal colonies was measured after 4–5 days depending on the growth rate of the control samples. The growth was determined by calculating the mean of two colony diameters of four replicate colonies. The fungicidal activity was expressed as the percentage of fungi growth inhibition compared to that of the untreated control. The relative growth inhibition of the treatment compared to the control was calculated as percentage, using the following formula:

$$\text{Percent inhibition} = [(x - y)/x]100,$$

where  $x$  = fungal colony diameter in control (mm);  
 $y$  = fungal colony diameter in treatment.

#### In vivo test

Control efficacy against wheat powdery mildew *Blumeria graminis* f.sp. tritici was conducted under greenhouse conditions. Ten seeds of winter wheat cultivar Kobra (*Triticum aestivum*, L.) were planted in small square plastic pots (10 × 10 cm) with a soil and peat mixture (3:1 peat/soil) and germinated in the greenhouse at 25 ± 5 °C for 10 days, when approximately 90 % of the seedlings were at the first leaf development stage.

The wheat seedlings were sprayed (cabin sprayers) with a solution (1:10 acetone:water) of the test chemicals at the concentration of 1000 mg/cm<sup>3</sup> with addition of Tween 20 (0.1 % v/v). After 2 h, the treated seedlings were inoculated with spores of the *Blumeria graminis* by shaking conidia from inoculated pots of wheat. Pots were arranged as a randomized complete block with three replicates per treatment. Further vegetation proceeded in a controlled-environment chamber under the following conditions: 14 h photoperiod of daylight, the air temperature 20 ± 1 °C/day, 16 ± 1 °C/night, relative humidity 80 ± 5 %.

The incidence of powdery mildew was visually evaluated on individual leaflets as percentage of infected area by standard methods (visual scoring of the percentage of leaf area infected according to assessment keys presented in the EPPO Standard PP 1/26), and efficacy for *B. graminis*

control was calculated according to the Abbot formula [36].

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