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Nitroacetic esters in the regioselective synthesis of isoxazole-3,5-dicarboxylic acids derivatives

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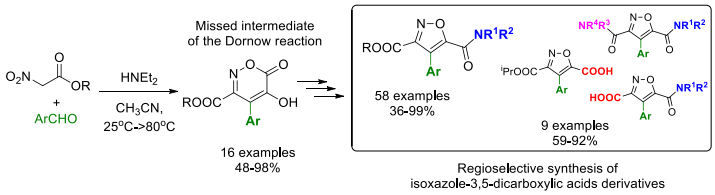


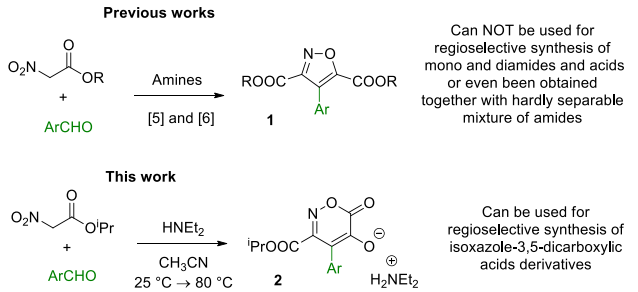
ABSTRACT: An efficient and high-yielding strategy to prepare "unsymmetrical" 4-aryl-isoxazol-3,5-dicarboxylic acids derivatives from nitroacetic esters and aromatic aldehydes has been developed. The strategy is based on the isolation and usage of the previously missed intermediate of the Dornow reaction - 5-hydroxy-6-oxo-4-aryl-6*H*-1,2-oxazine-3-carboxylates. In addition the mechanism of Dornow reaction was partially revised.

INTRODUCTION

The development of new synthetic approaches with the use of the simple and cheap reagents leading to densely functionalized heterocyclic scaffolds is highly aimed by the modern organic chemistry. Among such reagents, nitroacetic esters should be emphasized. Their condensation with esters of acetylene mono-[1] and dicarboxylic acids,[2] acrylic derivatives,[3] and other unsaturated compounds[4] is well known and leads to the formation of isoxazole and isoxazoline rings. Another example of these esters reaction is condensation with aromatic aldehydes, which leads to the formation of derivatives of isoxazole-3,5-dicarboxylic acids. This process is so-called as Dornow reaction and dates back to the 50s of the last century.[5] Application of the reaction up to date was sporadic since the proposed conditions often give a mixture of isoxazole-3,5-dicarboxylic acid esters **1** and their mono or diamides.[5,6] What's more the usage of esters **1** in the synthesis of "unsymmetrical" derivatives of isoxazole dicarboxilic acid was limited due to the similar reactivity of two ester groups (Scheme 1). To the best of our knowledge, no protocol is still known which could afford regioselective formation of such isoxazoles with different substitution pattern of carboxylic moieties at the positions 3 and 5. Development of a selective protocol would provide huge application possibilities for drug discovery and medicinal chemistry.[7]

In our previous communication, we observed that condensation of aromatic aldehydes with nitroacetic esters can also generate 5-hydroxy-6-oxo-4-aryl-6*H*-1,2-oxazine-3-carboxylate salts **2** (Scheme 1).[8] However, the synthetic procedures proposed in that work were characterized by rather low yields. Moreover, the suggested mechanism contradicted our later observations and the possible role of these compounds in the conversion of nitroacetic esters into isoxazole derivatives was not discussed.

Scheme 1. Condensation of nitroacetic esters with aromatic aldehydes

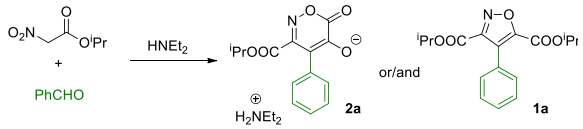


In the present work, we optimized the protocol of compounds **2** synthesis, revised the Dornow reaction mechanism (regarding intermediacy of oxazinones **2**) and demonstrated synthetic potential of these substances in the regioselective synthesis of "unsymmetrical" mono and diamides of isoxazole-3,5-dicarboxylic acids.

RESULTS AND DISCUSSION

During the optimization of the condensation reaction conditions (Table 1, SI Part 1), we showed that the highest yields of the compounds **2** are achieved in highly polar, but aprotic media (e.g. acetonitrile). It was shown that the presence of tertiary amines (DIPEA, Et_3N) instead of diethylamine, which was used in our previous communication,[8] leads to a significant deceleration of the reaction. Meanwhile the presence of less sterically hindered secondary (as well as primary) amines leads to the uncontrolled formation of amides (data is not shown in table 1).

Table 1. Examining the reaction conditions of nitroacetic esters condensation[a]



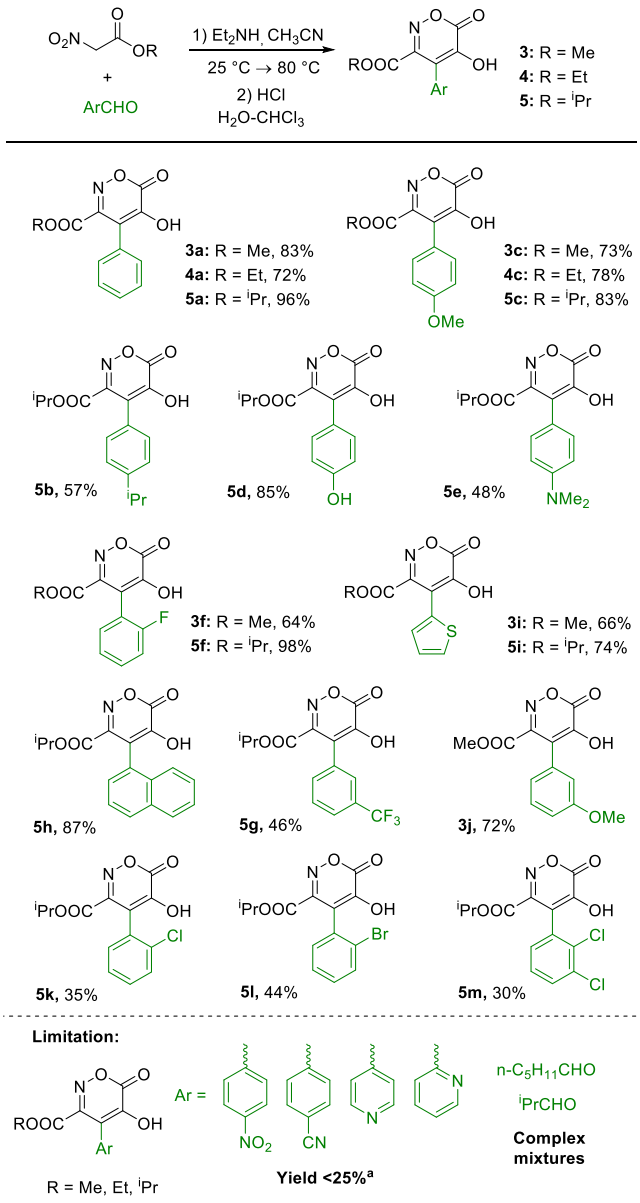
Solvent	Time	Temp.	Yield of **2a**	Yield of **1a**
^{i}PrOH	7 d	25 °C	45%[b]	~50%[c]
$CHCl_3$	7 d	25 °C	15%[b]	~35%[c,d]
THF	7 d	25 °C	11%[b]	~25%[c,d]
dioxane	7 d	25 °C	~5%[c]	~30%[c,d]
CH_3CN	2 d	25 °C	63%[b]	~5%[c]
^{i}PrOH	12 h	80 °C	~5%[c]	~80%[c]
CH_3CN	12 h	80 °C	~10%[c]	74%[b]
CH_3CN	2d at 25°C + 3h at 80 °C		89%[b]	~5%[c]

[a]Reaction conditions: 2 mmol of benzaldehyde, 4.4 mmol of isopropyl nitroacetate and 5 mmol of Et_2NH were mixed in the corresponding solvent (see SI). [b]Isolated yield. [c]Determined by ^{1}H NMR for the reaction mixtures. [d]Residual unreacted starting materials remained.

Surprisingly, we found that the temperature mode also affects the ratio of products **1** and **2**. Thus, while instant reflux of the reaction mixture leads to the almost exclusive formation of ester **1**, the combination of the introductory period at room temperature of two days and subsequent short heating gave a product **2** in the highest yield (Table 1).

We successfully transferred the developed technique on a series of aldehydes having various electronic and sterical properties along with three simple nitroacetic esters (Scheme 2). In most cases resulting diethylammonium salts **2** could be easily separated from the reaction mixture by crystallization. Afterwards, the treatment with hydrochloric acid, converted all of these salts into hydroxy derivatives **3-5**. The main limitations that were revealed were the usage of aldehydes with EWG, in which case mainly the esters **1** were formed and the usage of aliphatic aldehydes, which transformed into the complex mixtures.

Scheme 2. Scope of the reaction of nitroacetic esters with aromatic aldehydes

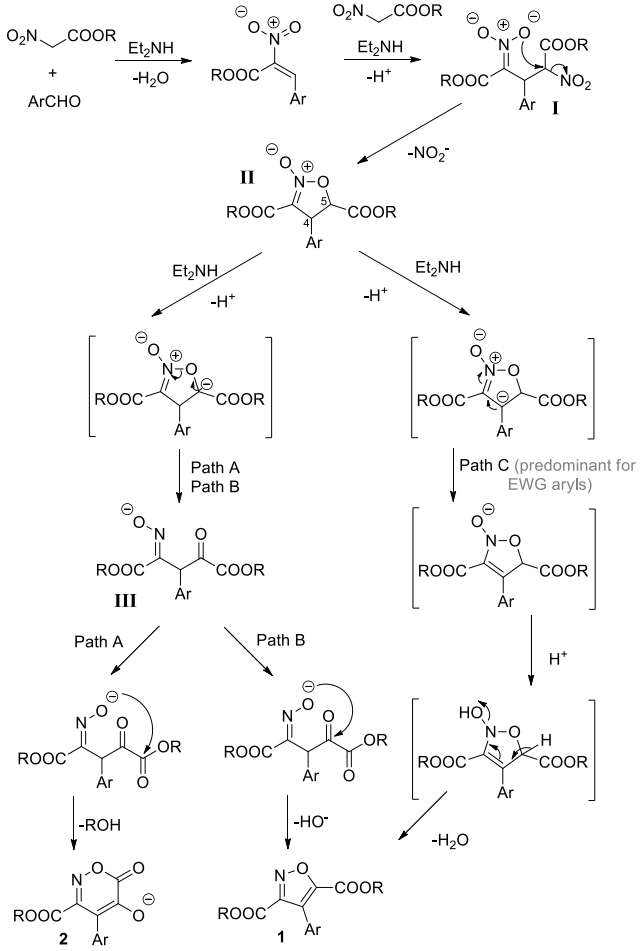


[a]Predominant formation of ester **1**, the yields were determined by ^{1}H NMR for the reaction mixtures.

The ease of formation of oxazinones **2** inspired us to reconsider the mechanism of the Dornow reaction. Based on the literature data, isoxazole formation starts from 3,5-dinitroglutaric esters **I** cyclization into isoxazoline N-oxides **II** (Scheme 3). The intermediacy of compounds **II** was confirmed in previous studies[5,6] and their isolation was also possible.[9] However, information about the following steps was contradictory. The mostly appeared in literature mechanism involves water elimination directly from the isoxazolines **II**, which occurs after deprotonation and migration of the double bond (Scheme 3,

Path C). However, in some works, the possible formation of oximes **III** (Scheme 3, Path B) was also discussed. This process also occurs after deprotonation, but at a different position of the isoxazoline cycle.[6c,10] Our results suggest that both of these processes actually take place. Thus, the predominant formation of esters **1** in the case of aldehydes with electron-withdrawing substituents (Scheme 2, bottom) can be explained by the increased acidity of the proton at the position 4, which is necessary for the passage of the reaction along the path C. At the same time, formation of oxazolinones **2** (as well as related diaryl compounds in other publications[11]), confirms the formation of oximes **III**.

Scheme 3. Processes occurred during the interaction of nitroacetic esters and aromatic aldehydes



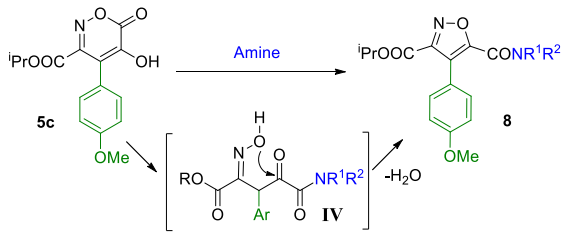
The cyclization of oximes **III** into five- or six-membered rings (Pathways A and B) can be highly sensitive to the medium properties, that explains the different ratios of products **1** and **2** in various solvents. The revealed dependence on the temperature mode can be associated with the aldehyde remained in the mixture (SI Part 2). The aldehyde may affect the properties of the medium and/or can prevent the formation of anion in position 5 and stimulate the process to proceed along the path C. The heating is probably necessary for *E*/*Z* isomerization of oxime **III**.

The structure of compounds **2**, having carbonyl groups already differentiated, has brought us to a successful idea of synthesis of monoamides simply by treatment of these oxazinones with primary and secondary amines (Table 2).

We found that interaction of oxazinones **3** and **4** with amines was always accompanied with the formation of symmetric diamides in the case of methyl and ethyl esters (in one case it was isolated and fully characterized see SI, compound **6a***). The problem can be avoided by the use of the isopropyl derivatives.

During the optimization (Table 2), we showed that this reaction takes place only in the presence of double excess of amine and requires heating. Excess of amine in some cases could be replaced by combination of 1 equivalent of amine and excess of DIPEA, but this approach was not universal (not applicable for e.g. primary amines). Finally the best results were achieved upon heating in chloroform with 2 equivalents of corresponding amine.

Table 2. Examining the reaction of oxazinones with amines at various conditions



Solvent	Amine	Temp	Time[b]	Yield[a]
^{i}PrOH	pyrrolidine (1.2 equiv)	25°C	24 h	0%[c]
^{i}PrOH	pyrrolidine (1.2 equiv)	70°C	24 h	0%[c]
^{i}PrOH	pyrrolidine (2 equiv)	70°C	5 h	71%
EtOH	pyrrolidine (2 equiv)	70°C	5 h	61%
CH_3CN	pyrrolidine (2 equiv)	70°C	8 h	66%
dioxane	pyrrolidine (2 equiv)	70°C	6 h	68%
THF	pyrrolidine (2 equiv)	70°C	6 h	65%
$CHCl_3$	pyrrolidine (2 equiv)	70°C	12 h	84%
$CHCl_3$	cyclohexylamine (2 equiv)	70°C	12 h	80%
$CHCl_3$	pyrrolidine (1 equiv), DIPEA (1.2 equiv)	70°C	12 h	90%
$CHCl_3$	cyclohexylamine (1 equiv), DIPEA (1.2 equiv)	70°C	12 h	9%[c]

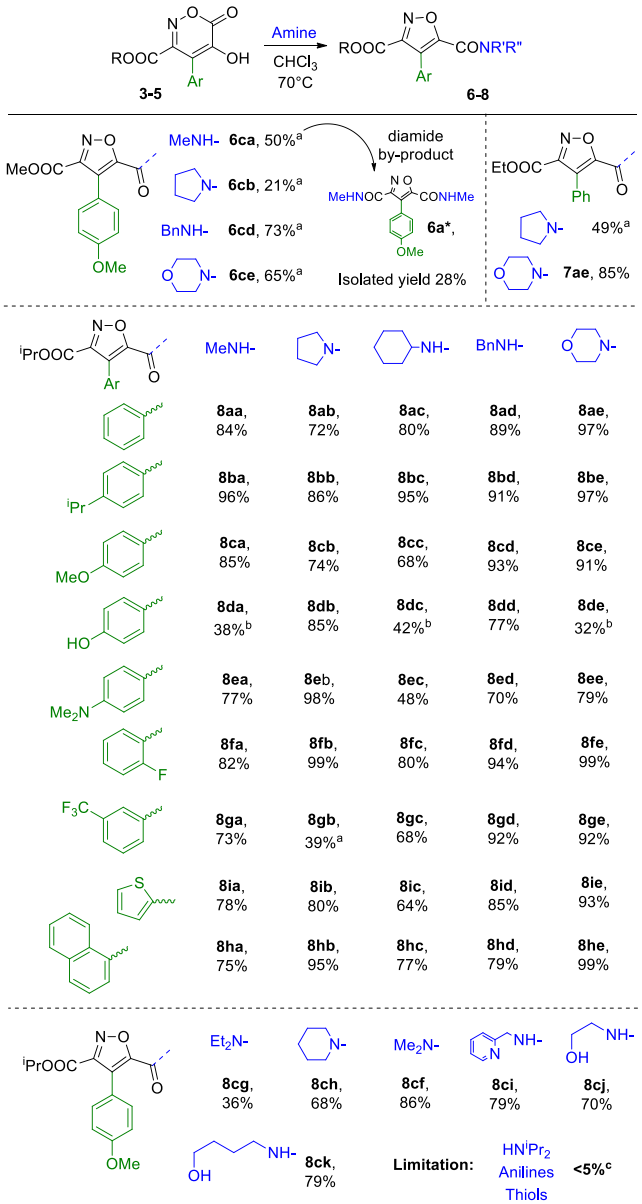
[a]Isolated yield. [b]Full conversion time, unless otherwise indicated. [c]Starting materials remain unreacted.

Apparently, this transformation (which is somewhat close to path B, because it includes the oxime **IV** formation) also occurred in many other previously described examples of nitroacetic esters condensation with aldehydes in the presence of various amines,[5,6] simultaneously with the reaction by path-

ways B and C. This fact well explains the previously observed simultaneous formation of esters **1** and mono and diamides of isoxazole-3,5-dicarboxylic acids with the predominant formation of monoamides at position 3. Therefore, isolation of products **2** is the previously "missed link" which allows to control the selectivity of the process.

According to the optimized procedure, we synthesized few amides **6** and **7**, bearing methyl and ethyl esters, with moderate yield and a library of more than five dozens of monoamides **8** in a good yields (Scheme 4). The exclusive formation of the amide in position 5 was confirmed by the single crystal X-Ray analysis (SI Part 5, compound **8ce**).

Scheme 4. Scope of the oxazinones 3-5 reaction with amines

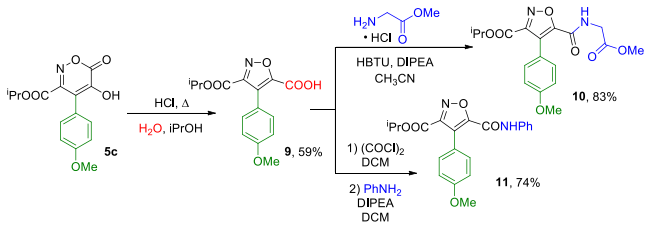


[a]Accompanied with diamide formation. [b]Unidentified by-products formation. [c]Starting materials remain.

The yield of the reaction decreases dramatically when amines with the bulky substituents were used (e.g. no reaction with diisopropyl or dicyclohexylamine). We also found that the reaction conditions are not applicable for anilines and thiols. An increase of temperature (e.g. boiling in DMF or dioxane) did not allow the corresponding derivatives to be obtained.

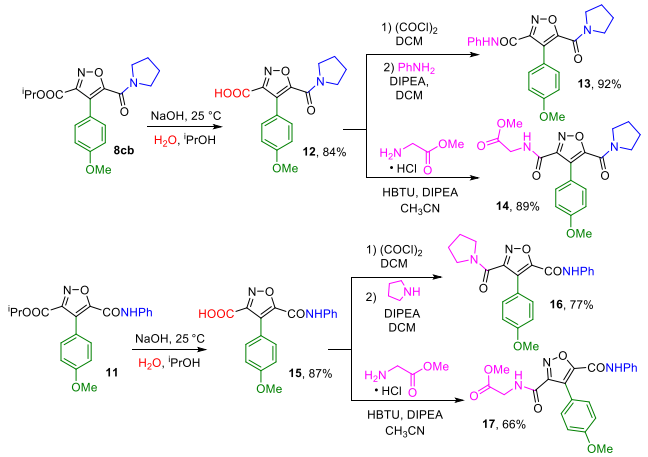
Facing this obstacle, an indirect approach was developed. Thus, we showed that the proposed oxazinones can be converted to the corresponding isoxazole-5-carboxylic acids on the example of compounds **5c** (Scheme 5). Surprisingly, the action of alkali (as well as carbonates or hydrocarbonates) led to the formation of a complex mixture, but after the treatment with acid, the necessary isoxazole-5-carboxylic acid **9** was formed. This product can be easily used in the synthesis of monoamides that were inaccessible by the above-mentioned general approach by HBTU or acyl chloride-mediated condensations (Scheme 5).

Scheme 5. Formation of izoxazole-5-carboxilic acid 9 and corresponding monoamides 10 and 11



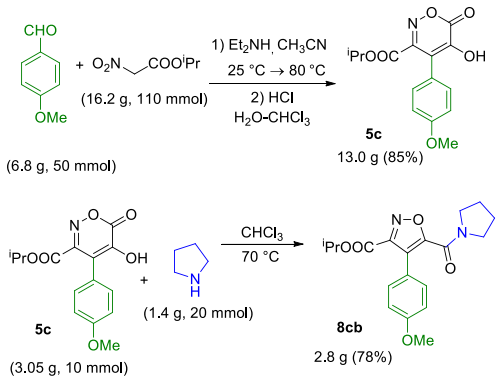
To fully establish a library of compounds, which the described method could provide, "unsymmetrical" diamides were synthesized from monoamides **8cb** and **11** *via* intermediate formation of acid at position 3 (Scheme 6).

Scheme 6. Synthesis of diamides



The scale-up experiments were also conducted. The yields of condensation and isoxazole formation even slightly increase upon increase of scale (Scheme 7).

Scheme 7. Scale-up experiments



CONCLUSIONS

Thus, in the present work, we showed that 5-hydroxy-6-oxo-4-aryl-6*H*-1,2-oxazine-3-carboxylates **2** are one of the intermediates of the Dornow reaction – the process of nitroacetic esters condensation with aldehydes, which leads to the formation of isoxazole-3,5-dicarboxylic acids derivatives. The possible simultaneous formation of various intermediates in this reaction explains the formation of complex mixtures, observed by authors of the previous works. Contrary, the proposed in this work technique of oxazinones **2** isolation allows to precede the process selectively. Based on the utilization of these oxazinones a general and high-yielding protocol for regioselective formation of "unsymmetrical" 4-aryl-isoxazol-3,5-dicarboxylic acids derivatives is developed and a library of 60+ 3,5-substituted isoxazoledicarboxylates was synthesized.

EXPERIMENTAL SECTION

General Comments. Commercially available reagents were used without additional purification. Isopropyl nitroacetate was synthesized according the literature procedure.[12] E. Merck Kieselgel 60 was used for column chromatography. Thin layer chromatography (TLC) was performed on silica gel 60 F254 glass-backed plates (MERCK). Visualization was effected by UV light (254 or 312 nm) and staining with $KMnO_4$.

NMR spectra were recorded on a 700 MHz Bruker Avance III NMR at 303 K and Bruker Fourier 300. Chemical shifts are reported relative to residue peaks of $CDCl_3$ (7.27 ppm for ^1H and 77.0 ppm for ^{13}C) or DMSO-d_6 (2.51 ppm for ^1H and 39.5 ppm for ^{13}C). Melting points were measured on a SMP 30 apparatus without correction. High-resolution mass spectra (HRMS) spectra were recorded on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were done in a positive ion mode (interface capillary voltage – 4500 V) or in a negative ion mode (3200 V); mass range from m/z 50 to m/z 3000; external or internal calibration was done with ESI Tuning Mix, Agilent. A syringe injection was used for solutions in acetonitrile, methanol, or water (flow rate 3 mL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180°C.

General procedure for synthesis of 5-hydroxy-6-oxo-4-aryl-6H-1,2-oxazine-3-carboxylates. 2 mmol (1 equiv) of arylaldehyde, 4.4 mmol (2.2 equiv) of nitroacetic ester and 365 mg (5 mmol, 2.5 equiv) of diethylamine were dissolved in 5 ml of acetonitrile. Resulted solution was stirred for 48 h at room temperature and then additionally heated in oil bath at 80°C for 3 h. All volatiles were removed in vacuo, 6-7 ml of corresponding alcohol was added and the mixture was refluxed until the complete solid dissolution (1-5 min). Resulted solution was cooled to -20°C and stored for 8 h at this temperature. The precipitated diethylammonium salt was filtered and washed with a cold (0°C) alcohol (1-2 ml, twice), washed with 2 ml of ether and dried in vacuo. To obtain neutral hydroxyoxazines the corresponding salt (2 mmol) was dissolved in 50 ml of $CHCl_3$ and washed 3 times with 20 ml of 3% aq. HCl. Organic layer was dried with anhydrous Na_2SO_4 and evaporated. For all presented compounds this procedure allowed to obtain a pure product. Anyway, if it is necessary, 5-hydroxy-6-oxo-4-aryl-6H-1,2-oxazine-3-carboxylates could be purified by column chromatography using $CHCl_3$ – EtOH mixture as eluent (~20:1, v:v).

3-(isopropoxycarbonyl)-6-oxo-4-phenyl-6H-1,2-oxazin-5-olate diethylammonium salt (**2a**). ^1H NMR (700 MHz, $CDCl_3$): δ 0.91 - 1.01 (m, 12 H), 2.22 (q, *J*=7.1 Hz, 4 H), 4.86 (spt, *J*=6.3 Hz, 1 H), 7.26 - 7.29 (m, 2 H), 7.29 - 7.33 (m, 1 H), 7.34 - 7.38 (m, 2 H), 9.12 (br. s., 2 H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 11.8, 21.2, 43.0, 70.0, 110.8, 127.7, 130.0, 128.6, 134.6, 154.5, 156.7, 162.6, 170.2. The ^1H and ^{13}C spectra are identical to the previously reported in the literature.[8]

diisopropyl 4-phenylisoxazole-3,5-dicarboxylate (**1a**). White solid, m.p. 77-78°C. ^1H NMR (700 MHz, DMSO-d_6): δ 1.12 (d, J=6.3 Hz, 6 H), 1.14 (d, J=6.1 Hz, 6 H), 4.99 - 5.10 (m, 2 H), 7.37 - 7.48 (m, 5 H); $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d6): δ 21.1 (2 C), 70.2 (2 C), 124.3, 127.0, 127.5, 128.5, 130.0, 155.3, 155.8, 156.8, 158.1; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{20}NO_5$ 318.1336; Found 318.1338.

methyl 5-hydroxy-6-oxo-4-phenyl-6H-1,2-oxazine-3-carboxylate (**3a**). Yield 410 mg (83%), white solid, m.p. 148-149°C; ^1H NMR (700 MHz, $CDCl_3$): δ 3.74 (s, 3H), 7.32 - 7.40 (m, 2H), 7.42 - 7.50 (m, 3H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 53.5, 116.2, 128.5, 128.7, 129.7, 144.1, 153.0, 161.4, 163.6; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{12}H_8NO_5$ 246.0408; Found 246.0405.

methyl 5-hydroxy-4-(4-methoxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**3c**). Yield 405mg (73%), white solid, m.p. 105-107°C; ^1H NMR (700 MHz, DMSO-d_6): δ 3.67 (s, 3H), 3.79 (s, 3H), 7.00 (d, *J*=9.0 Hz, 2H), 7.24 (d, *J*=9.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 53.4, 55.2, 113.9, 114.9, 121.7, 130.1, 146.4, 153.1, 159.5, 162.0, 162.7; HRMS (ESI-TOF) *m/z*: $[M-H]^-$. $C_{13}H_{10}NO_6$ Calcd for 276.0514; Found 276.0511.

methyl 4-(2-fluorophenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**3f**). Yield 339 mg (64%), white solid, m.p. 107-109°C; ^1H NMR (700 MHz, $CDCl_3$): δ 3.83 (s, 3H), 7.18 (t, *J*=9.1 Hz, 1H), 7.29 (d, *J*=7.9 Hz, 1H), 7.42 (t, *J*=7.3 Hz, 1H), 7.48 (q, *J*=6.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 53.5, 111.3, 115.7 (d, *J*=21.4 Hz), 116.6 (d, *J*=15.4 Hz), 124.4 (d, *J*=3.3 Hz), 130.7 (d, *J*=2.3 Hz), 131.8 (d, *J*=8.4 Hz), 145.2, 151.5, 159.4 (d, *J*=248.6 Hz), 161.1, 163.3; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{12}H_7FNO_5$ 264.0314; Found 264.0312.

methyl 5-hydroxy-6-oxo-4-(thiophen-2-yl)-6H-1,2-oxazine-3-carboxylate (**3i**). Yield 334 mg (66%), white solid, m.p.

165°C with decomposition; ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.15 (t, *J*=4.4 Hz, 1H), 7.33 (d, *J*=3.3 Hz, 1H), 7.59 (d, *J*=4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 53.8, 109.9, 127.5, 128.4, 129.8, 130.2, 142.6, 152.3, 161.6, 163.3; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{10}H_6NO_5S$ 251.9972; Found 251.9969.

methyl 5-hydroxy-4-(3-methoxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**3j**). Yield 398 mg (72%), white solid, m.p. 96-97°C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 3.76 (s, 3H), 3.83 (s, 3H), 6.90 - 6.94 (m, 2H), 6.98 (dd, *J*=8.2, 1.6 Hz, 1H), 7.37 (t, *J*=7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$): δ 53.6, 55.4, 114.4, 115.4, 115.9, 120.7, 129.8, 129.9, 144.4, 153.1, 159.8, 161.5, 163.9; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{13}H_{10}NO_6$ 276.0514; Found 276.0509.

ethyl 5-hydroxy-6-oxo-4-phenyl-6H-1,2-oxazine-3-carboxylate (**4a**). Yield 376 mg (72%), white solid, m.p. 117-118°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.95 (t, *J*=7.1 Hz, 3H), 4.07 (q, *J*=7.2 Hz, 2H), 7.27 - 7.33 (m, 2H), 7.38 - 7.47 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 13.6, 63.2, 116.0, 128.5, 128.8, 129.8, 143.7, 153.3, 160.8, 163.8; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{13}H_{10}NO_5$ 260.0564; Found 260.0566.

ethyl 5-hydroxy-4-(4-methoxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**4c**). Yield 535 mg (78%), white solid, m.p. 103-105°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.01 (t, *J*=7.1 Hz, 3H), 3.78 (s, 3H), 4.11 (q, *J*=7.1 Hz, 2H), 7.00 (d, *J*=8.6 Hz, 2H), 7.24 (d, *J*=8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 13.7, 55.3, 63.2, 114.2, 115.8, 120.4, 130.0, 143.4, 153.5, 160.6, 161.0, 163.8; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{14}H_{12}NO_6$ 290.0670; Found 290.0668.

isopropyl 5-hydroxy-6-oxo-4-phenyl-6H-1,2-oxazine-3-carboxylate (**5a**). Yield 425 mg (86%), white solid, m.p. 133-135°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.97 (d, *J*=6.3 Hz, 6H), 4.85 (spt, *J*=6.3 Hz, 1H), 7.28 - 7.32 (m, 2H), 7.39 - 7.47 (m, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 20.78, 70.78, 115.04, 128.35, 128.78, 128.83, 129.98, 146.78, 153.28, 160.74, 162.72; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{12}H_8NO_5$ 246.0408; Found 246.0405.

isopropyl 5-hydroxy-4-(4-isopropylphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**5b**). Yield 361 mg (57%), white solid, m.p. 128-130°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.94 (d, *J*=6.3 Hz, 6H), 1.20 (d, *J*=7.0 Hz, 6H), 2.91 (spt, *J*=6.9 Hz, 1H), 4.85 (spt, *J*=6.2 Hz, 1H), 7.22 (d, *J*=8.2 Hz, 2H), 7.32 (d, *J*=8.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 20.7, 23.8, 33.3, 70.7, 115.1, 126.3, 127.4, 128.8, 146.6, 149.3, 153.5, 160.8, 162.7; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{17}H_{18}NO_5$ 316.1190; Found 316.1188.

isopropyl 5-hydroxy-4-(4-methoxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**5c**). Yield 506 mg (83%), white solid, m.p. 120-122°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.03 (d, *J*=6.3 Hz, 6H), 3.78 (s, 3H), 4.89 (spt, *J*=6.2 Hz, 1H), 7.00 (d, *J*=8.8 Hz, 2H), 7.24 (d, *J*=8.8 Hz, 2H); ^{13}C NMR$\{^1H\}$ (75 MHz, DMSO-d_6): δ 20.9, 55.3, 70.8, 113.8, 114.8, 121.9, 130.3, 146.6, 153.5, 159.6, 160.9, 162.8; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{15}H_{14}NO_6$ 304.0826; Found 304.0834.

isopropyl 5-hydroxy-4-(4-hydroxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**5d**). Yield 495 mg (85%), white solid, m.p. 180-181°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.03 (d, *J*=6.3 Hz, 6H), 4.89 (spt, *J*=6.2 Hz, 1H), 6.81 (d, *J*=8.6 Hz, 2H), 7.12 (d, *J*=8.5 Hz, 2H), 9.74 (br. s., 1H), 12.20 (br. s., 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 20.9, 70.8, 79.2, 115.2, 115.3, 120.1, 130.2, 146.2, 153.8, 158.0, 161.0, 162.8; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{14}H_{12}NO_6$ 290.0670; Found 290.0666.

isopropyl 4-(4-(dimethylamino)phenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**5e**). Yield 288 mg (45%), orange solid, m.p. 130-132°C with decomposition; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.07 (d, *J*=6.3 Hz, 6H), 2.93 (s, 6H), 4.92 (spt, *J*=6.2 Hz, 1H), 6.75 (d, *J*=8.9 Hz, 2H), 7.15 (d, *J*=8.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.0, 70.7, 111.5, 115.5, 116.5, 129.6, 145.7, 150.4, 153.9, 161.2, 162.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_5$ 319.1288; Found 319.1286.

isopropyl 4-(2-fluorophenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**5f**). Yield 516 mg (88%), white solid, m.p. 133-134°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.00 (br. s., 6H), 4.87 (spt, *J*=6.2 Hz, 1H), 7.25 - 7.31 (m, 2H), 7.35 (td, *J*=7.5, 1.6 Hz, 1H), 7.46 - 7.50 (m, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d_6): δ 20.8, 70.7, 109.6, 115.5 (d, *J*=21.6 Hz), 117.9 (d, *J*=16.4 Hz), 124.5 (s, *J*=3.0 Hz), 131.1 - 131.2 (m, 2 C), 148.0, 152.3, 159.2 (d, *J*=246.6 Hz), 160.3, 162.3; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{14}H_{11}FNO_5$ 292.0627; Found 292.0621.

isopropyl 5-hydroxy-6-oxo-4-(3-(trifluoromethyl)phenyl)-6H-1,2-oxazine-3-carboxylate (**5g**). Yield 384 mg (56%), white solid, m.p. 158-160°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.97 (d, *J*=6.3 Hz, 6H), 4.85 (spt, *J*=6.2 Hz, 1H), 7.63 (d, *J*=7.7 Hz, 1H), 7.65 (s, 1H), 7.70 (t, *J*=7.7 Hz, 1H), 7.79 (d, *J*=7.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, DMSO-d_6): δ 20.7, 70.8, 113.6, 123.9 (q, 272.2 Hz), 125.3 (q, *J*=3.5 Hz), 125.5 (q, *J*=3.7 Hz), 129.2 (q, *J*=31.9 Hz), 129.6, 131.5, 133.2, 147.6, 152.5, 160.5, 162.6; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{15}H_{11}F_3NO_5$ 342.0595; Found 342.0605.

isopropyl 5-hydroxy-4-(naphthalen-1-yl)-6-oxo-6H-1,2-oxazine-3-carboxylate (**5h**) .Yield 566 mg (87%), white solid, m.p. 148-150°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.44 (d, *J*=6.3 Hz, 3H), 0.70 (d, *J*=6.3 Hz, 3H), 4.57 (spt, *J*=6.2 Hz, 1H), 7.37 (dd, *J*=7.0, 0.9 Hz, 1H), 7.50 - 7.53 (m, 1H), 7.53 - 7.58 (m, 2H), 7.79 (d, *J*=8.3 Hz, 1H), 7.96 - 8.01 (m, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 20.1, 20.6, 70.2, 113.9, 125.3, 125.8, 126.3, 126.5, 127.1, 128.0, 128.1, 129.1, 130.9, 133.0, 148.0, 153.6, 160.4, 162.6; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{18}H_{14}NO_5$ 324.0877; Found 324.0882.

isopropyl 5-hydroxy-6-oxo-4-(thiophen-2-yl)-6H-1,2-oxazine-3-carboxylate (**5i**). Yield 371 mg (66%), green solid, m.p. 128-130°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.14 (d, *J*=6.3 Hz, 6H), 5.03 (spt, *J*=6.2 Hz, 1H), 7.11 - 7.13 (m, 1H), 7.13 - 7.16 (m, 1H), 7.75 (dd, *J*=5.1, 1.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.0, 71.2, 108.2, 127.0, 128.5, 129.1, 129.8, 146.7, 152.5, 161.1, 162.3; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{12}H_{10}NO_5S$ 280.0285; Found 280.0285.

isopropyl 4-(2-chlorophenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**5k**). Yield 216 mg (35%), white solid, m.p. 170-171°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.91 (d, J=6.3 Hz, 3 H), 1.00 (d, J=6.3 Hz, 3 H), 4.83 (spt, J=6.2 Hz, 1 H), 7.35 (d, J=7.6 Hz, 1 H), 7.41 (t, J=7.5 Hz, 1 H), 7.43 - 7.47 (m, 1 H), 7.55 (d, J=7.8 Hz, 1 H); $^{13}C\{^1H\}$ NMR (176 MHz,

DMSO-d_6): δ 20.6, 20.7, 70.5, 113.3, 127.1, 129.1, 129.4, 130.6, 131.2, 132.7, 147.6, 152.1, 160.0, 162.4; HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_{11}ClNO_5$ 308.0331; Found 308.0328.

isopropyl 4-(2-bromophenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**5l**). Yield 311 mg (44%), white solid, m.p. 164-166°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.90 (d, J=6.3 Hz, 3 H), 0.99 (d, J=6.1 Hz, 3 H), 4.83 (spt, J=6.2 Hz, 1 H), 7.33 (dd, J=7.5, 1.6 Hz, 1 H), 7.36 (td, J=7.8, 1.7 Hz, 1 H), 7.45 (td, J=7.5, 1.1 Hz, 1 H), 7.71 (dd, J=8.0, 1.0 Hz, 1 H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 20.6, 20.7, 70.5, 115.1, 123.1, 127.6, 130.7, 131.3, 131.5, 132.2, 147.3, 152.1, 159.9, 162.5; HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_{11}BrNO_5$ 351.9826; Found 351.9828.

isopropyl 4-(2,3-dichlorophenyl)-5-hydroxy-6-oxo-6H-1,2-oxazine-3-carboxylate (**5m**). Yield 206 mg (30%), white solid, m.p. 161-162°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.90 (d, J=6.1 Hz, 3 H), 1.02 (d, J=6.3 Hz, 3 H), 4.84 (spt, J=6.2 Hz, 1 H), 7.32 (dd, J=7.6, 1.5 Hz, 1 H), 7.43 (t, J=7.9 Hz, 1 H), 7.69 (dd, J=8.1, 1.4 Hz, 1 H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 20.6, 20.8, 70.5, 112.9, 128.3, 129.8, 130.8, 131.1, 131.8, 132.1, 147.8, 151.5, 159.9, 162.4; HRMS (ESI-TOF) m/z: $[M-H]^-$ Calcd for $C_{14}H_{10}Cl_2NO_5$ 341.9942; Found 341.9940.

General procedure of synthesis of isoxazole-3,5-bis-carboxylic acid amides. 0.2 mmol (1 equiv) of corresponding oxazinone and 0.4 mmol (2 equiv) of amine were dissolved in 0.5 ml of $CHCl_3$. Resulted solution was stirred for 12 h in oil bath at 70°C. All volatiles were removed in vacuo and the residue was purified by column chromatography using $CHCl_3$ – EtOH mixture as eluent (100:1, v:v for all compounds except **8da-8de** when 20:1, v:v mixture was used).

methyl 4-(4-methoxyphenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**6ca**). Yield 29 mg (50%), white solid, m.p. 120-122°C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.95 (d, *J*=4.8 Hz, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 6.35 (br. s., 1H), 6.98 (m, 2H), 7.38 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 25.8, 52.9, 55.1, 113.2, 118.6, 120.8, 131.5, 154.9, 156.1, 159.4, 159.7, 159.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O_5$ 291.0975; Found 291.0976.

4-(4-methoxyphenyl)-N^3,N^5-dimethylisoxazole-3,5-dicarboxamide (**6a***). Yield 16 mg (28%), white solid, m.p. 118-120°C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 2.92 (d, *J*=5.0 Hz, 3H), 2.95 (d, *J*=5.0 Hz, 3H), 3.85 (s, 3H), 6.22 (br. s., 1H), 6.64 (br. s., 1H), 6.98 (m, 2H), 7.42 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 25.9 (2 C), 55.2, 113.4, 119.1, 119.4, 131.1, 156.6, 158.3, 158.7, 159.3, 159.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{14}H_{16}N_3O_4$ 290.1135; Found 290.1128.

methyl 4-(4-methoxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**6cb**). Yield 14 mg (21%), white solid, m.p. 114-115°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.71 - 1.81 (m, 4H), 3.18 (t, *J*=6.7 Hz, 2H), 3.42 (t, *J*=6.9 Hz, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 6.98 (d, *J*=8.8 Hz, 2H), 7.33 (d, *J*=8.6 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 23.4, 25.2, 45.9, 46.9, 52.9, 55.1, 113.7, 118.5, 119.0, 130.6, 153.8, 155.8, 159.5, 159.7, 161.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_5$ 331.1288; Found 331.1292.

methyl 5-(benzylcarbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**6cd**). Yield 53 mg (73%), white solid, m.p. 68-69°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.79 (s, 3H), 3.82 (s, 3H), 4.40 (d, *J*=6.1 Hz, 2H), 6.94 (d, *J*=8.8 Hz, 2H), 7.25 (d, *J*=7.6 Hz, 3H), 7.31 (d, *J*=7.1 Hz, 2H), 7.34 (d, *J*=8.8 Hz, 2H), 9.49 (t, *J*=6.1 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 42.3, 52.9, 55.1, 113.2, 118.6, 121.0, 127.0, 127.4, 128.3, 131.5, 138.4, 154.9, 155.8, 159.4, 159.6, 159.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{19}N_2O_5$ 367.1288; Found 367.1290.

methyl 4-(4-methoxyphenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**6ce**). Yield 38 mg (51%), white solid, m.p. 137-139°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.11 (dd, *J*=16.8, 4.5 Hz, 4H), 3.48 - 3.53 (m, 2H), 3.53 - 3.58 (m, 2H), 3.80 (s, 3H), 3.85 (s, 3H), 7.03 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=8.6 Hz, 2H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 42.1, 46.4, 52.9, 55.2, 65.5, 65.6, 114.0, 118.2, 119.0, 130.7, 153.5, 156.6, 159.5, 159.7, 160.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_6$ 347.1238; Found 347.1239.

ethyl 5-(morpholine-4-carbonyl)-4-phenylisoxazole-3-carboxylate (**7ae**). Yield 56 mg (85%), white solid, m.p. 88-90°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.20 (t, *J*=7.1 Hz, 3H), 3.05 (t, *J*=4.3 Hz, 2H), 3.12 - 3.17 (m, 2H), 3.46 - 3.51 (m, 2H), 3.53 - 3.56 (m, 2H), 4.31 (q, *J*=7.1 Hz, 2H), 7.33 - 7.41 (m, 2H), 7.43 - 7.52 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 13.7, 42.2, 46.5, 62.1, 65.5, 65.6, 119.3, 126.4, 128.5, 129.0, 129.5, 153.8, 156.5, 158.9, 160.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{19}N_2O_5$ 331.1288; Found 331.1288.

isopropyl 5-(methylcarbamoyl)-4-phenylisoxazole-3-carboxylate (**8aa**). Yield 48 mg (84%), white solid, m.p. 150-152°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.13 (d, *J*=6.3 Hz, 6H), 2.73 (d, *J*=4.6 Hz, 3H), 5.06 (dt, *J*=12.4, 6.2 Hz, 1H), 7.34 - 7.47 (m, 5H), 8.92 (d, *J*=4.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 25.8, 70.2, 120.9, 127.1, 127.7, 128.3, 130.0, 155.7, 155.9, 158.6, 160.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_4$ 289.1183; Found 289.1182.

isopropyl 4-phenyl-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8ab**). Yield 47 mg (72%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 1.69 - 1.83 (m, 4H), 3.23 (t, *J*=6.7 Hz, 2H), 3.41 (t, *J*=6.9 Hz, 2H), 5.1 (spt, *J*=6.2 Hz, 1H), 7.35 - 7.43 (m, 2H), 7.45 - 7.47 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 23.4, 25.2, 45.9, 47.0, 70.2, 119.3, 126.8, 128.2, 128.6, 129.4, 154.5, 155.6, 158.6, 161.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_4$ 329.1496; Found 329.1495.

isopropyl 5-(cyclohexylcarbamoyl)-4-phenylisoxazole-3-carboxylate (**8ac**). Yield 57 mg (80%), white solid, m.p. 90-91°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.05 - 1.12 (m, 1H), 1.14 (d, *J*=6.3 Hz, 6H), 1.20 - 1.31 (m, 4H), 1.55 (d, *J*=12.8 Hz, 1H), 1.66 (dd, *J*=9.4, 3.3 Hz, 2H), 1.73 (d, *J*=9.2 Hz, 2H), 3.59 - 3.72 (m, 1H), 5.07 (spt, *J*=6.3 Hz, 1H), 7.36 - 7.42 (m, 5H), 8.74 (d, *J*=8.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 24.6, 25.0, 31.8, 48.3, 70.2, 120.4, 127.1, 127.8, 128.4, 129.9, 154.8, 155.4, 158.6, 160.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_4$ 357.1809; Found 357.1806.

isopropyl 5-(benzylcarbamoyl)-4-phenylisoxazole-3-carboxylate (**8ad**). Yield 65 mg (89%), white solid, m.p. 136-137°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.14 (d, *J*=6.3 Hz, 6H), 4.40 (d, *J*=6.1 Hz, 2H), 5.07 (spt, *J*=6.2 Hz, 1H), 7.22 - 7.27 (m, 3H), 7.31 (t, *J*=7.5 Hz, 2H), 7.36 - 7.42 (m, 5H), 9.53 (t, *J*=6.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 42.3, 70.2, 121.1, 127.0, 127.0, 127.4, 127.7, 128.3, 128.4, 130.0, 138.4, 155.6, 158.5, 160.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}N_2O_4$ 365.1496; Found 365.1496.

isopropyl 5-(morpholine-4-carbonyl)-4-phenylisoxazole-3-carboxylate (**8ae**). Yield 67 mg (97%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.20 (d, *J*=6.3 Hz, 6H), 3.06 (t, *J*=4.2 Hz, 2H), 3.12 - 3.18 (m, 2H), 3.45 - 3.52 (m, 2H), 3.52 - 3.57 (m, 2H), 5.13 (spt, *J*=6.2 Hz, 1H), 7.35 - 7.40 (m, 2H), 7.44 - 7.49 (m, 3H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.2, 42.2, 46.5, 65.5, 65.6, 70.3, 119.2, 126.5, 128.5, 128.9, 129.4, 154.1, 156.5, 158.5, 160.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_5$ 345.1445; Found 345.1443.

isopropyl 4-(4-isopropylphenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**8ba**). Yield 63 mg (96%), white solid, m.p. 101-102°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.13 (d, *J*=6.3 Hz, 6H), 1.23 (d, *J*=6.9 Hz, 6H), 2.73 (d, *J*=4.6 Hz, 3H), 2.93 (quin, *J*=6.8 Hz, 1H), 5.06 (quin, *J*=6.2 Hz, 1H), 7.27 (m, 2H), 7.30 (m, 2H), 8.92 (d, *J*=5.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 23.8, 25.8, 33.3, 70.2, 120.8, 124.4, 125.6, 130.0, 148.6, 155.8, 156.0, 158.7, 159.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{23}N_2O_4$ 331.1652; Found 331.1653.

isopropyl 4-(4-isopropylphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8bb**). Yield 64 mg (86%), white solid, m.p. 89-90°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.19 (d, *J*=6.3 Hz, 6H) 1.22 (d, *J*=6.9 Hz, 6H) 1.72 - 1.82 (m, 4H) 2.92 (spt, *J*=6.9 Hz, 1H) 3.25 (t, *J*=6.7 Hz, 2H) 3.42 (t, *J*=6.9 Hz, 2H) 5.11 (spt, *J*=6.2 Hz, 1H) 7.24 - 7.34 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.2, 23.5, 23.8, 25.3, 33.2, 46.0, 47.1, 70.3, 119.3, 124.1, 126.2, 129.4, 149.0, 154.6, 155.7, 158.7, 161.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_4$ 371.1965; Found 371.1966.

isopropyl 5-(cyclohexylcarbamoyl)-4-(4-isopropylphenyl)isoxazole-3-carboxylate (**8bc**). Yield 76 mg (95%), viscous oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.10 (dd, *J*=12.1, 2.8 Hz, 1H), 1.14 (d, *J*=6.1 Hz, 6H), 1.22 (d, *J*=6.9 Hz, 6H), 1.23 - 1.29 (m, 4H), 1.51 - 1.57 (m, 1H), 1.61 - 1.67 (m, 2H), 1.70 - 1.76 (m, 2H), 2.93 (spt, *J*=6.9 Hz, 1H), 3.62 - 3.70 (m, 1H), 5.07 (spt, *J*=6.2 Hz, 1H), 7.27 (m, 2H), 7.30 (m, 2H), 8.69 (d, *J*=8.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 23.8, 24.5, 25.0, 31.8, 33.3, 48.2, 70.2, 120.4, 124.4, 125.7, 129.8, 148.7, 154.8, 155.5, 158.7, 160.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{31}N_2O_4$ 399.2278; Found 399.2276.

isopropyl 5-(benzylcarbamoyl)-4-(4-isopropylphenyl)isoxazole-3-carboxylate (**8bd**). Yield 74 mg (91%), white solid, m.p. 64-66°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.14 (d, *J*=6.1 Hz, 6H), 1.22 (d, *J*=7.0 Hz, 6H), 2.92 (spt, *J*=6.9 Hz, 1H), 4.40 (d, *J*=6.1 Hz, 2H), 5.07 (spt, *J*=6.2 Hz, 1H), 7.22 - 7.28 (m, 5H), 7.28 - 7.34 (m, 4H), 9.50 (t, *J*=6.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 23.8, 33.3, 42.3, 70.2, 121.0, 124.3, 125.7, 127.0, 127.4, 128.3, 130.0, 138.4, 148.7, 155.7, 158.6, 159.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_4$ 407.1965; Found 407.1963.

isopropyl 4-(4-isopropylphenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**8be**). Yield 75 mg (97%), white solid, m.p. 121-122°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.21 (d, *J*=6.3 Hz, 6H), 1.22 (d, *J*=6.9 Hz, 6H), 2.94 (dt, *J*=13.8, 6.9 Hz, 1H), 3.03 - 3.09 (m, 2H), 3.13 - 3.19 (m, 2H), 3.47 - 3.52 (m, 2H), 3.52 - 3.57 (m, 2H), 5.12 (spt, *J*=6.3 Hz, 1H), 7.29 (m, 2H), 7.34 (m, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.2, 23.8, 33.2, 42.2, 46.5, 65.5, 65.6, 70.2, 119.2, 123.8, 126.4, 129.4, 149.4, 154.1, 156.6, 158.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_5$ 387.1914; Found 387.1911.

isopropyl 4-(4-methoxyphenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**8ca**). Yield 54 mg (85%), white solid, m.p. 91-93°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 2.73 (d, *J*=4.8 Hz, 3H), 3.79 (s, 3H), 5.09 (dt, *J*=12.4, 6.2 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 2H), 7.32 (d, *J*=8.8 Hz, 2H), 8.87 (d, *J*=4.3 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.2, 25.8, 55.2, 70.2, 113.2, 118.9, 120.6, 131.4, 155.7, 156.1, 158.8, 159.4, 159.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_5$ 319.1288; Found 319.1289.

isopropyl 4-(4-methoxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8cb**). Yield 53 mg (74%), white solid, m.p. 87-89°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.22 (d, *J*=6.3 Hz, 6H), 1.71 - 1.77 (m, 2H), 1.77 - 1.82 (m, 2H), 3.21 (t, *J*=6.6 Hz, 2H), 3.42 (t, *J*=6.9 Hz, 2H), 3.79 (s, 3H), 5.13 (spt, *J*=6.2 Hz, 1H), 6.99 (d, *J*=8.8 Hz, 2H), 7.32 (d, *J*=8.9 Hz, 2H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 21.2, 23.4, 25.2, 45.9, 46.9, 55.1, 70.2, 113.7, 118.6, 118.9, 130.7, 154.4, 155.8, 158.7, 159.5, 161.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_5$ 359.1601; Found 359.1605.

isopropyl 5-(cyclohexylcarbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8cc**). Yield 52 mg (68%), white solid, m.p. 124-126°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.04 - 1.15 (m, 1H), 1.18 (d, *J*=6.3 Hz, 6H), 1.20 - 1.32 (m, 4H), 1.55 (d, *J*=12.8 Hz, 1H), 1.67 (dd, *J*=9.3, 3.3 Hz, 2H), 1.69 - 1.78 (m, 2H), 3.62 - 3.72 (m, 1H), 3.79 (s, 3H), 5.09 (spt, *J*=6.2 Hz, 1H), 6.90 - 7.00 (m, 2H), 7.28 - 7.37 (m, 2H), 8.70 (d, *J*=7.8 Hz, 1H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 21.2, 24.6, 25.0, 31.8, 48.3, 55.2, 70.2, 113.3, 118.9, 120.1, 131.3, 155.0, 155.4, 158.8, 159.4, 160.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{27}N_2O_5$ 387.1914; Found 387.1919.

isopropyl 5-(benzylcarbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8cd**). Yield 73 mg (93%), white solid, m.p. 91-93°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 3.79 (s, 3H), 4.40 (d, *J*=6.1 Hz, 2H), 5.09 (spt, *J*=6.3 Hz, 1H), 6.93 - 6.96 (m, 2H), 7.23 - 7.27 (m, 3H), 7.29 - 7.34 (m, 4H), 9.46 (t, *J*=6.1 Hz, 1H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 21.15, 42.28, 55.12, 70.18, 113.18, 118.76, 120.70, 126.94, 127.31, 128.26, 131.34, 138.38, 155.61, 155.74, 158.68, 159.41, 159.69; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{23}N_2O_5$ 395.1601; Found 395.1604.

isopropyl 4-(4-methoxyphenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**8ce**). Yield 68 mg (91%), white solid, m.p. 129-130°C; ^{1}H NMR (700 MHz, DMSO-d_6):

δ 1.22 (d, *J*=6.3 Hz, 6H), 3.12 (d, *J*=4.8 Hz, 2H), 3.15 (d, *J*=4.8 Hz, 2H), 3.51 (t, *J*=4.2 Hz, 2H), 3.55 (t, *J*=4.3 Hz, 2H), 3.80 (s, 3H), 5.14 (spt, *J*=6.3 Hz, 1H), 7.01-7.04 (m, 2H), 7.28-7.32 (m, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.3, 42.1, 46.5, 55.3, 65.7, 70.2, 113.9, 118.3, 118.9, 130.8, 154.1, 156.7, 158.6, 159.7, 160.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_6$ 375.1551; Found 375.1554.

isopropyl 5-(dimethylcarbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8cf**). Yield 57 mg (86%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.22 (d, *J*=6.3 Hz, 6H), 2.74 (s, 3H), 2.94 (s, 3H), 3.79 (s, 3H), 5.14 (quin, *J*=6.3 Hz, 1H), 7.00 (d, *J*=8.8 Hz, 2H), 7.30 (d, *J*=8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.3, 34.5, 37.2, 55.2, 70.2, 113.9, 118.5, 130.6, 154.2, 158.0, 158.7, 159.6, 160.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}N_2O_5$ 333.1445; Found 333.1443.

isopropyl 5-(diethylcarbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8cg**). Yield 26 mg (36%), white solid, m.p. 80-81°C; ^{1}H NMR (700 MHz, $CDCl_3$): δ 1.01 (t, *J*=7.1 Hz, 3H), 1.17 (t, *J*=7.1 Hz, 3H), 1.33 (d, *J*=6.1 Hz, 6H), 3.12 (q, *J*=7.2 Hz, 2H), 3.49 (q, *J*=7.0 Hz, 2H), 3.83 (s, 3H), 5.26 (spt, *J*=6.3 Hz, 1H), 6.92 (m, *J*=8.8 Hz, 2H), 7.37 (m, *J*=8.8 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 12.2, 13.9, 21.2, 42.4, 55.1, 70.2, 113.8, 117.6, 118.3, 130.4, 154.0, 157.6, 158.7, 159.6, 161.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_5$ 361.1758; Found 361.1761.

isopropyl 4-(4-methoxyphenyl)-5-(piperidine-1-carbonyl)isoxazole-3-carboxylate (**8ch**). Yield 50 mg (67%), white solid, m.p. 98-99°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.05 - 1.12 (m, 2H), 1.23 (d, *J*=6.3 Hz, 6H), 1.44 (d, *J*=4.2 Hz, 2H), 1.49 (d, *J*=4.8 Hz, 2H), 3.05 - 3.12 (m, 2H), 3.52 (t, *J*=5.4 Hz, 2H), 3.79 (s, 3H), 5.14 (quin, *J*=6.3 Hz, 1H), 7.01 (d, *J*=8.6 Hz, 2H), 7.30 (d, *J*=8.6 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 23.5, 24.9, 25.6, 42.3, 47.0, 55.2, 70.2, 113.9, 118.1, 118.4, 130.6, 154.0, 156.4, 158.7, 159.6, 161.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_5$ 373.1758; Found 373.1754.

isopropyl 4-(4-methoxyphenyl)-5-((pyridin-2-ylmethyl)carbamoyl)isoxazole-3-carboxylate (**8ci**). Yield 62 mg (79%), white solid, m.p. 143-145°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 3.78 (s, 3H), 4.51 (d, *J*=6.0 Hz, 2H), 5.10 (quin, *J*=6.2 Hz, 1H), 6.95 (d, *J*=8.8 Hz, 2H), 7.25 - 7.29 (m, 2H), 7.35 (d, *J*=8.8 Hz, 2H), 7.74 (td, *J*=7.7, 1.8 Hz, 1H), 8.47 - 8.50 (m, 1H), 9.43 (t, *J*=5.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 44.2, 55.2, 70.2, 113.2, 118.7, 121.0, 121.1, 122.3, 131.5, 136.8, 148.9, 155.7, 155.9, 157.3, 158.7, 159.5, 159.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{22}N_3O_5$ 396.1554; Found 396.1550.

isopropyl 5-((2-hydroxyethyl)carbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8cj**). Yield 49 mg (70%), yellow oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 3.27 (q, *J*=6.1 Hz, 2H), 3.47 (q, *J*=6.0 Hz, 2H), 3.79 (s, 3H), 4.71 (t, *J*=5.6 Hz, 1H), 5.09 (quin, *J*=6.3 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 2H), 7.33 (d, *J*=8.8 Hz, 2H), 8.82 (t, *J*=5.4 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 41.7, 55.2, 59.2, 70.2, 113.2, 118.9, 120.6, 131.4, 155.7, 155.8, 158.8, 159.4, 159.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}N_2O_6$ 349.1394; Found 349.1392.

isopropyl 5-((4-hydroxybutyl)carbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**8ck**). Yield 67 mg (89%), yellow oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 1.36 - 1.42 (m, 2H), 1.49 (quin, *J*=7.3 Hz, 2H), 3.15 - 3.22 (m, 2H), 3.34 - 3.41 (m, 2H), 3.79 (s, 3H), 4.37 (t, *J*=5.1 Hz, 1H), 5.09 (quin, *J*=6.3 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 2H), 7.32 (d, *J*=8.8 Hz, 2H), 8.90 (t, *J*=5.7 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 25.4, 29.8, 55.2, 60.3, 70.2, 113.2, 118.9, 120.4, 131.4, 155.6, 155.6, 158.8, 159.4, 160.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{25}N_2O_6$ 377.1707; Found 377.1704.

isopropyl 4-(4-hydroxyphenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**8da**). Yield 23 mg (38%), yellow solid, m.p. 168-170°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 2.74 (d, *J*=4.8 Hz, 3H), 5.10 (spt, *J*=6.2 Hz, 1H), 6.78 (m, 2H), 7.21 (m, 2H), 8.83 (d, *J*=4.6 Hz, 1H), 9.63 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 25.8, 70.2, 114.6, 117.0, 120.8, 131.3, 155.8, 156.2, 157.7, 158.9, 159.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_5$ 305.1132; Found 305.1132.

isopropyl 4-(4-hydroxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8db**). Yield 58 mg (85%), white solid, m.p. 173-175°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.22 (d, *J*=6.3 Hz, 6H), 1.70 - 1.75 (m, 2H), 1.75 - 1.81 (m, 2H), 3.16 (t, *J*=6.7 Hz, 2H), 3.42 (t, *J*=7.0 Hz, 2H), 5.13 (spt, *J*=6.3 Hz, 1H), 6.80 (m, 2H), 7.18 (m, 2H), 9.70 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 23.5, 25.3, 45.9, 47.0, 70.3, 115.2, 116.8, 119.1, 130.6, 154.5, 156.0, 157.9, 158.9, 161.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_5$ 345.1445; Found 345.1443.

isopropyl 5-(cyclohexylcarbamoyl)-4-(4-hydroxyphenyl)isoxazole-3-carboxylate (**8dc**). Yield 31 mg (42%), yellow solid, m.p. 157-159°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.07 - 1.12 (m, 1H), 1.18 (d, *J*=6.3 Hz, 6H), 1.23 - 1.27 (m, 4H), 1.55 (d, *J*=12.6 Hz, 1H), 1.66 (dd, *J*=8.2, 4.2 Hz, 2H), 1.69 - 1.76 (m, 2H), 3.61 - 3.72 (m, 1H), 5.10 (spt, *J*=6.3 Hz, 1H), 6.78 (m, 2H), 7.20 (m, 2H), 8.62 (d, *J*=8.0 Hz, 1H), 9.64 (br. s., 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 24.5, 25.0, 31.8, 48.2, 70.2, 114.7, 117.0, 120.2, 131.2, 155.1, 155.5, 157.7, 159.0, 160.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{25}N_2O_5$ 373.1758; Found 373.1759.

isopropyl 5-(benzylcarbamoyl)-4-(4-hydroxyphenyl)isoxazole-3-carboxylate (**8dd**).Yield 59 mg (77%), white solid, m.p. 169-170°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 4.40 (d, *J*=6.1 Hz, 2H), 5.09 (spt, *J*=6.3 Hz, 1H), 6.76 (m, 2H), 7.20 (m, 2H), 7.22 - 7.27 (m, 3H), 7.28 - 7.34 (m, 2H), 9.42 (t, *J*=6.0 Hz, 1H), 9.63 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 42.3, 70.2, 114.6, 117.0, 121.0, 127.0, 127.3, 128.3, 131.3, 138.5, 155.8, 155.9, 157.8, 158.9, 159.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}N_2O_5$ 381.1445; Found 381.1441.

isopropyl 4-(4-hydroxyphenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**8de**). Yield 23 mg (32%), white solid, m.p. 203-204°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.22 (d, *J*=6.3 Hz, 6H), 3.05 - 3.15 (m, 4H), 3.47 - 3.57 (m, 2H), 5.14 (spt, *J*=6.2 Hz, 1H), 6.82-6.85 (m, 2H), 7.15-7.19 (m, 2H), 9.76 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ

21.3, 42.1, 46.5, 65.5, 65.6, 70.2, 115.4, 116.5, 119.1, 130.7, 154.1, 156.8, 158.1, 158.7, 159.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_6$ 361.1394; Found 361.1392.

isopropyl 4-(4-(dimethylamino)phenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**8ea**). Yield 51 mg (77%), orange solid, m.p. 122-124°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.21 (d, *J*=6.3 Hz, 6H), 2.73 (d, *J*=4.8 Hz, 3H), 2.93 (s, 6H), 5.11 (spt, *J*=6.2 Hz, 1H), 6.71 (d, *J*=8.8 Hz, 2H), 7.22 (d, *J*=8.8 Hz, 2H), 8.79 (d, *J*=4.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.3, 25.8, 39.9, 70.3, 111.3, 113.4, 120.8, 130.7, 155.8, 156.4, 159.0, 159.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{22}N_3O_4$ 332.1605; Found 332.1605.

isopropyl 4-(4-(dimethylamino)phenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8eb**). Yield 73 mg (98%), orange solid, m.p. 98-100°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.25 (d, *J*=6.3 Hz, 6H), 1.69 - 1.76 (m, 2H), 1.76 - 1.82 (m, 2H), 2.93 (s, 6H), 3.15 (t, *J*=6.7 Hz, 2H), 3.43 (t, *J*=7.0 Hz, 2H), 5.15 (spt, *J*=6.2 Hz, 1H), 6.74 (d, *J*=8.8 Hz, 2H), 7.18 (d, *J*=8.8 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.3, 23.5, 25.3, 45.9, 46.9, 70.3, 111.7, 113.1, 119.1, 129.8, 150.4, 154.5, 156.3, 159.2, 160.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{26}N_3O_4$ 372.1918; Found 372.1914.

isopropyl 5-(cyclohexylcarbamoyl)-4-(4-(dimethylamino)phenyl)isoxazole-3-carboxylate (**8ec**). Yield 38 mg (48%), orange solid, m.p. 129-130°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.11 (dd, *J*=12.6, 3.5 Hz, 1H), 1.21 (d, *J*=6.3 Hz, 6H), 1.23 - 1.29 (m, 4H), 1.55 (dd, *J*=13.6, 3.9 Hz, 1H), 1.63 - 1.70 (m, 2H), 1.71 - 1.79 (m, 2H), 2.93 (s, 6H), 3.64 - 3.72 (m, 1H), 5.12 (quin, *J*=6.3 Hz, 1H), 6.72 (d, *J*=8.9 Hz, 2H), 7.21 (d, *J*=8.8 Hz, 2H), 8.62 (d, *J*=7.7 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.3, 24.5, 25.0, 31.8, 39.9, 48.2, 70.3, 111.4, 113.4, 120.3, 130.5, 150.3, 155.3, 155.5, 159.3, 159.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{30}N_3O_4$ 400.2231; Found 400.2230.

isopropyl 5-(benzylcarbamoyl)-4-(4-(dimethylamino)phenyl)isoxazole-3-carboxylate (**8ed**). Yield 57 mg (70%), orange solid, m.p. 93-95°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.21 (d, *J*=6.3 Hz, 6H), 2.93 (s, 6H), 4.41 (d, *J*=6.1 Hz, 2H), 5.12 (spt, *J*=6.3 Hz, 1H), 6.70 (d, *J*=8.8 Hz, 2H), 7.20 - 7.27 (m, 5H), 7.31 (t, *J*=7.5 Hz, 2H), 9.38 (t, *J*=6.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.3, 39.9, 42.3, 70.3, 111.3, 113.3, 121.1, 127.0, 127.4, 128.3, 130.7, 138.5, 150.3, 155.8, 156.1, 159.0, 159.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{23}H_{26}N_3O_4$ 408.1918; Found 408.1914.

isopropyl 4-(4-(dimethylamino)phenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**8ee**). Yield 61 mg (79%), orange oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.25 (d, *J*=6.3 Hz, 6H), 2.94 (s, 6H), 3.11 (s, 4H), 3.52 (t, *J*=4.5 Hz, 2H), 3.56 (t, *J*=4.5 Hz, 2H), 5.15 (spt, *J*=6.2 Hz, 1H), 6.77 (d, *J*=8.8 Hz, 2H), 7.16 (d, *J*=8.6 Hz, 2H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.3, 39.8, 42.1, 46.5, 65.5, 65.6, 70.2, 111.8, 112.8, 119.3, 129.9, 150.5, 154.1, 157.0, 159.0, 159.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{26}N_3O_5$ 388.1867; Found 388.1864.

isopropyl 4-(2-fluorophenyl)-5-(methylcarbamoyl)isoxazole-3-carboxylate (**8fa**). Yield 50 mg (82%), white solid, m.p. 134-136°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.12 (d, *J*=6.3 Hz, 6H), 2.73 (d, *J*=4.8 Hz, 3H), 5.06 (spt, *J*=6.2 Hz, 1H), 7.22 - 7.28 (m, 2H), 7.46 - 7.50 (m, 2H), 9.04 (q, *J*=4.5 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 25.8, 70.2, 114.8 (d, *J*=6.7 Hz), 115.1, 115.5 (d, *J*=14.9 Hz), 123.9 (d, *J*=3.0 Hz), 130. 9 (d, *J*=8.2 Hz), 132.4 (d, *J*=2.2 Hz), 155.4, 155.7, 159.4 (d, *J*=245.9 Hz), 158.1, 160.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{16}FN_2O_4$ 307.1089; Found 307.1086.

isopropyl 4-(2-fluorophenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8fb**). Yield 69 mg (99%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.15 (d, *J*=6.3 Hz, 6H), 1.80 - 1.84 (m, 4H), 3.38 - 3.44 (m, 4H), 5.10 (spt, *J*=6.2 Hz, 1H), 7.27 (td, *J*=7.5, 0.9 Hz, 1H), 7.29 - 7.33 (m, 1H), 7.46 (td, *J*=7.6, 1.6 Hz, 1H), 7.48 - 7.52 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 23.4, 25.5, 46.2, 47.2, 70.3, 114.0, 115.1 - 115.6, (m, 2C), 124.4 (d, *J*=3.7 Hz), 131.2 (d, *J*=8.2 Hz), 131. 8 (d, *J*=2.2 Hz), 155.0 (d, *J*=8.2 Hz), 157. 7 (d, *J*=245.9 Hz), 158.2, 162.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}FN_2O_4$ 347.1402; Found 347.1397.

isopropyl 5-(cyclohexylcarbamoyl)-4-(2-fluorophenyl)isoxazole-3-carboxylate (**8fc**). Yield 60 mg (80%), white solid, m.p. 121-122°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.09 (dt, *J*=12.4, 3.3 Hz, 1H), 1.13 (d, *J*=6.3 Hz, 6H), 1.20 - 1.33 (m, 4H), 1.56 (dd, *J*=9.8, 3.2 Hz, 1H), 1.65 - 1.77 (m, 4H), 3.62 - 3.69 (m, 1H), 5.07 (spt, *J*=6.2 Hz, 1H), 7.22 - 7.29 (m, 2H), 7.44 - 7.50 (m, 2H), 8.90 (d, *J*=7.9 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 24.7, 25.0, 31.8, 48.4, 70.2, 114.6, 115.0 (d, *J*=20.9 Hz), 115.5 (d, *J*=14.9 Hz), 123.9 (d, *J*=3.7 Hz), 130.9 (d, *J*=8.2 Hz), 132.2 (d, *J*=1.5 Hz), 154.3, 155.6, 159.4 (d, *J*=245.1 Hz), 158.2, 161.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{20}H_{24}FN_2O_4$ 375.1715; Found 375.1711.

isopropyl 5-(benzylcarbamoyl)-4-(2-fluorophenyl)isoxazole-3-carboxylate (**8fd**). Yield 72 mg (94%), white solid, m.p. 143-145°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.13 (d, *J*=6.3 Hz, 6H), 4.40 (d, *J*=6.1 Hz, 2H), 5.07 (spt, *J*=6.2 Hz, 1H), 7.22 - 7.28 (m, 5H), 7.29 - 7.34 (m, 2H), 7.45 - 7.51 (m, 2H), 9.66 (t, *J*=6.0 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.0, 42.3, 70.2, 114.9, 115.0 (d, *J*=13.0 Hz), 115.4 (d, *J*=15.4 Hz), 123.8 (d, *J*=3.3 Hz), 127.0, 127.3, 128.3, 130.9 (d, *J*=8.4 Hz), 132.3 (d, *J*=2.0 Hz), 138.3, 155.1, 155.7, 158.0, 159.4 (d, *J*=245.6 Hz), 160.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{20}FN_2O_4$ 383.1402; Found 383.1400.

isopropyl 4-(2-fluorophenyl)-5-(morpholine-4-carbonyl)isoxazole-3-carboxylate (**8fe**). Yield 72 mg (99%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.17 (d, *J*=6.3 Hz, 6H), 3.25 (br. s., 4H), 3.55 (d, *J*=3.3 Hz, 4H), 5.11 (spt, *J*=6.2 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.44 (td, *J*=7.6, 1.6 Hz, 1H), 7.51 - 7.56 (m, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 21.1, 42.2, 46.6, 65.6, 65.8, 70.3, 113.5, 114.7 (d, *J*=14.9 Hz), 115.6 (d, *J*=20.9 Hz), 124.7 (d, *J*=3.7 Hz), 131.4 - 131.7 (m), 154.6, 156.0, 159.3 (d, *J*=246.6 Hz), 158.1, 161.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{20}FN_2O_5$ 363.1351; Found 363.1350.

isopropyl 5-(methylcarbamoyl)-4-(3-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**8ga**). Yield 52 mg (73%), white solid, m.p. 129-131°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.10 (d, *J*=6.3 Hz, 6H), 2.73 (d, *J*=4.8 Hz, 3H), 5.04 (spt, *J*=6.3 Hz, 1H), 7.63 (t, *J*=7.7 Hz, 1H), 7.71 (d,

J=7.8 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.82 (s, 1H), 9.02 (d, *J*=4.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d_6): δ 21.0, 25.7, 70.0, 120.0, 123.9 (q, *J*=190.1 Hz), 124.8 - 125.0 (m), 127.0 (q, *J*=4.0 Hz), 128.3 (q, *J*=31.8 Hz), 128.5, 128.7, 134.4, 155.4, 155.5, 158.1, 160.3; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{16}F_3N_2O_4$ 357.1057; Found 357.1059.

isopropyl 5-(pyrrolidine-1-carbonyl)-4-(3-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**8gb**). Yield 31 mg (39%), viscous oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.14 (d, *J*=6.3 Hz, 6H), 1.78 - 1.84 (m, 4H), 3.39 - 3.44 (m, 4H), 5.09 (spt, *J*=6.2, 1H), 7.66 (t, *J*=7.8 Hz, 1H), 7.72 (d, *J*=7.6 Hz, 1H), 7.79 (d, *J*=8.6 Hz, 1H), 7.83 (s, 1H); $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d_6): δ 21.0, 23.3, 25.4, 46.2, 47.2, 70.1, 119.1, 124.0 (q, *J*=272.4 Hz), 125.1 (q, *J*=3.3 Hz), 126.5 (d, *J*=4.0 Hz), 128.5, 128.7 (q, *J*=31.8 Hz), 129.0, 133.9, 154.5, 155.1, 158.1, 162.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_4$ 397.1370; Found 397.1370.

isopropyl 5-(cyclohexylcarbamoyl)-4-(3-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**8gc**). Yield 58 mg (68%), white solid, m.p. 120-122°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.04 - 1.10 (m, 1H), 1.11 (d, *J*=6.3 Hz, 6H), 1.19 - 1.34 (m, 4H), 1.55 (d, *J*=13.0 Hz, 1H), 1.67 (d, *J*=13.0 Hz, 2H), 1.72 (d, *J*=10.3 Hz, 2H), 3.61 - 3.69 (m, 1H), 5.05 (spt, *J*=6.2 Hz, 1H), 7.64 (t, *J*=7.7 Hz, 1H), 7.70 (d, *J*=7.6 Hz, 1H), 7.77 (d, *J*=7.8 Hz, 1H), 7.81 (s, 1H), 8.89 (d, *J*=8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d_6): δ 21.0, 24.6, 24.9, 31.7, 48.3, 70.1, 119.7, 124.9 (q, *J*=272.4 Hz), 124.9 - 125.0 (m), 126.7 - 126.9 (m), 128.3 (q, *J*=31.8 Hz) 128.6, 128.7, 134.3, 154.4, 155.1, 158.1, 161.0; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{24}F_3N_2O_4$ 425.1683; Found 425.1682.

isopropyl 5-(benzylcarbamoyl)-4-(3-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**8gd**) Yield 79 mg (92%), white solid, m.p. 126-128°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.10 (d, *J*=6.1 Hz, 6H), 4.40 (d, *J*=6.1 Hz, 2H), 5.05 (spt, *J*=6.2 Hz, 1H), 7.21 - 7.28 (m, 3H), 7.30 (t, *J*=7.4 Hz, 2H), 7.63 (t, *J*=7.8 Hz, 1H), 7.71 (d, *J*=7.7 Hz, 1H), 7.77 (d, *J*=7.9 Hz, 1H), 7.82 (s, 1H), 9.63 (t, *J*=6.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d_6): δ 21.0, 42.3, 70.1, 120.3, 124.1 (q, *J*=272.0 Hz), 125.0 (q, *J*=3.7 Hz), 126.9 (d, J=4.0 Hz), 127.0, 127.3, 128.3, 128.6, 128.7, 134.4, 138.3, 155.3, 155.4, 158.0, 160.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{20}F_3N_2O_4$ 433.1370; Found 433.1367.

isopropyl 5-(morpholine-4-carbonyl)-4-(3-(trifluoromethyl)phenyl)isoxazole-3-carboxylate (**8ge**). Yield 76 mg (92%), white solid, m.p. 94-95°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.17 (d, *J*=6.3 Hz, 6H), 3.16 (br. s., 2H), 3.26 (br. s., 2H), 3.49 (br. s., 2H), 3.54 (br. s., 2H), 5.11 (spt, *J*=6.2 Hz, 1H), 7.69 - 7.73 (m, 2H), 7.81 - 7.85 (m, 2H); $^{13}C\{^{1}H\}$ NMR (176 MHz, DMSO-d_6): δ 21.1, 42.2, 46.5, 65.5, 65.8, 70.2, 118.4, 123.9 (q, *J*=272.1 Hz), 125.5 (q, *J*=3.5 Hz), 126.4 - 126.5 (m), 128.0, 129.0 (q, *J*=31.8 Hz), 129.5, 133.8, 154.0, 156.1, 158.0, 161.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{20}F_3N_2O_5$ 413.1319; Found 413.1314.

isopropyl 5-(methylcarbamoyl)-4-(naphthalen-1-yl)isoxazole-3-carboxylate (**8ha**). Yield 51 mg (75%), white solid, m.p. 160-162°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.64 (d, *J*=6.3 Hz, 3H), 0.79 (d, *J*=6.3 Hz, 3H), 2.68 (d, *J*=4.8 Hz, 3H), 4.77 (spt, *J*=6.2 Hz, 1H), 7.41 - 7.48 (m, 3H), 7.50 - 7.57 (m, 2H), 7.99 (m, 2H), 8.98 (d, *J*=4.6 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 20.4, 20.8, 25.7, 69.6, 119.3, 124.9, 125.1, 125.6, 125.8, 126.4, 128.2, 128.3, 128.6, 131.9, 132.8, 155.5, 156.6, 158.0, 161.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_4$ 339.1339; Found 339.1337.

isopropyl 4-(naphthalen-1-yl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8hb**). Yield 72 mg (95%), white solid, m.p. 93-94°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.65 (d, *J*=5.1 Hz, 3H), 0.83 (d, *J*=5.1 Hz, 3H), 1.67-1.83 (m, 4H), 3.28 - 3.35 (m, 3H), 3.51 (br. s., 1H), 4.79 (spt, *J*=6.2 Hz, 1H), 7.46 - 7.51 (m, 2H), 7.51 - 7.57 (m, 3H), 8.01 (t, *J*=8.7 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 20.4, 20.9, 23.3, 25.4, 46.1, 47.2, 69.6, 118.3, 124.7, 125.1, 125.2, 126.0, 126.6, 128.3, 129.0, 131.7, 132.9, 155.2, 155.8, 158.0, 162.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{23}N_2O_4$ 379.1652; Found 379.1653.

isopropyl 5-(cyclohexylcarbamoyl)-4-(naphthalen-1-yl)isoxazole-3-carboxylate (**8hc**). Yield 62 mg (77%), white solid, m.p. 146-148°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.66 (d, *J*=6.1 Hz, 3H), 0.80 (d, *J*=6.1 Hz, 3H), 1.01 - 1.10 (m, 1H), 1.13 - 1.21 (m, *J*=12.5, 12.5, 12.4, 3.3, 3.3 Hz, 2H), 1.24 - 1.29 (m, 2H), 1.48 - 1.54 (m, 1H), 1.59 (d, *J*=6.9 Hz, 2H), 1.65 (d, *J*=12.0 Hz, 2H), 3.52 - 3.60 (m, 1H), 4.79 (spt, *J*=6.2 Hz, 1H), 7.42 - 7.50 (m, 3H), 7.50 - 7.57 (m, 2H), 8.00 (dd, *J*=8.2, 5.1 Hz, 2H), 8.72 (d, *J*=8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 20.5, 20.8, 24.5, 25.0, 31.8, 48.2, 69.6, 119.1, 124.8, 125.1, 125.5, 125.9, 126.4, 128.2, 128.3, 128.7, 131.8, 132.9, 154.3, 156.4, 158.0, 161.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_4$ 407.1965; Found 407.1960.

isopropyl 5-(benzylcarbamoyl)-4-(naphthalen-1-yl)isoxazole-3-carboxylate (**8hd**). Yield 65 mg (79%), white solid, m.p. 158-160°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.66 (d, *J*=6.1 Hz, 3H), 0.80 (d, *J*=6.1 Hz, 3H), 4.33 (d, *J*=6.3 Hz, 2H), 4.79 (spt, *J*=6.2 Hz, 1H), 7.17 (d, *J*=7.2 Hz, 2H), 7.19 - 7.23 (m, 1H), 7.24 - 7.29 (m, 2H), 7.45 (d, *J*=3.6 Hz, 2H), 7.48 (dd, *J*=7.0, 1.0 Hz, 1H), 7.51 - 7.56 (m, 2H), 8.00 (dd, *J*=8.0, 5.1 Hz, 2H), 9.54 (t, *J*=6.1 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 42.3, 70.3, 114.6, 117.0, 121.0, 127.0, 127.3, 128.3, 131.4, 138.5, 155.8, 155.9, 157.8, 158.9, 159.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{23}N_2O_4$ 415.1652; Found 415.1654.

isopropyl 5-(morpholine-4-carbonyl)-4-(naphthalen-1-yl)isoxazole-3-carboxylate (**8he**). Yield 78 mg (99%), white solid, m.p. 95-97°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 0.72 (d, *J*=5.5 Hz, 3H), 0.88 (d, *J*=5.5 Hz, 3H), 2.88 (br. s., 1H), 2.99 (br. s., 1H), 3.22 (br. s., 1H), 3.32 (br. s., 3H), 3.40 (br. s., 1H), 3.43 (br. s., 1H), 4.80 - 4.87 (spt, *J*=6.3, 1H), 7.48 (d, *J*=6.3 Hz, 1H), 7.49 - 7.53 (m, 1H), 7.55 - 7.61 (m, 3H), 8.02 (d, *J*=7.9 Hz, 1H), 8.05 (d, *J*=8.2 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 20.5, 20.9, 42.1, 46.5, 65.5, 65.7, 69.7, 117.6, 124.3, 124.5, 125.2, 126.2, 126.7, 128.4, 129.3, 131.5, 132.9, 155.4, 156.2, 157.9, 161.7; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{23}N_2O_5$ 395.1601; Found 395.1598.

isopropyl 5-(methylcarbamoyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (**8ia**). Yield 46 mg (78%), white solid, m.p. 123-125°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.23 (d, *J*=6.3 Hz, 6H), 2.76 (d, *J*=4.6 Hz, 3H), 5.15 (spt, *J*=6.3 Hz, 1H), 7.12 (dd, *J*=5.1, 3.6 Hz, 1H), 7.31 (dd, *J*=3.6, 1.2 Hz, 1H),

7.69 (dd, *J*=5.1, 1.2 Hz, 1H), 8.99 (d, *J*=4.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 25.9, 70.7, 113.8, 125.9, 126.9, 128.4, 130.2, 155.5, 155.8, 158.7, 160.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{13}H_{15}N_2O_4S$ 295.0747; Found 295.0746.

isopropyl 5-(pyrrolidine-1-carbonyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (**8ib**). Yield 53 mg (80%), colorless oil; ^1H NMR (700 MHz, DMSO-d_6): δ 1.27 (d, *J*=6.3 Hz, 6H), 1.76 - 1.81 (m, 2H), 1.81 - 1.86 (m, 2H), 3.25 (t, *J*=6.6 Hz, 2H), 3.46 (t, *J*=6.9 Hz, 2H), 5.19 (spt, *J*=6.2 Hz, 1H), 7.15 (dd, *J*=5.1, 3.6 Hz, 1H), 7.31 (dd, *J*=3.6, 1.2 Hz, 1H), 7.71 (dd, *J*=5.1, 1.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.3, 23.5, 25.3, 46.1, 47.0, 70.7, 112.5, 125.8, 127.5, 128.6, 129.7, 154.1, 155.4, 158.6, 161.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_4S$ 335.1060; Found 335.1059.

isopropyl 5-(cyclohexylcarbamoyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (**8ic**). Yield 46 mg (64%), white solid, m.p. 102-103°C; ^1H NMR (700 MHz, DMSO-d_6): δ 1.08 - 1.16 (m, 1H), 1.24 (d, *J*=6.1 Hz, 6H), 1.27 (t, *J*=10.4 Hz, 4H), 1.56 (d, *J*=12.2 Hz, 1H), 1.64 - 1.73 (m, 2H), 1.73 - 1.81 (m, 2H), 3.66 - 3.74 (m, 1H), 5.07 - 5.21 (m, *J*=6.4, 6.3, 6.3, 6.3, 6.3, 6.3 Hz, 1H), 7.12 (dd, *J*=5.1, 3.6 Hz, 1H), 7.30 (dd, *J*=3.6, 1.2 Hz, 1H), 7.69 (dd, *J*=5.1, 1.0 Hz, 1H), 8.86 (d, *J*=7.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 24.5, 25.0, 31.8, 48.4, 70.7, 113.2, 126.0, 127.0, 128.4, 130.0, 154.8, 155.2, 158.7, 160.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{23}N_2O_4S$ 363.1373; Found 363.1368.

isopropyl 5-(benzylcarbamoyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (**8id**). Yield 63 mg (85%), white solid, m.p. 128-130°C; ^1H NMR (700 MHz, DMSO-d_6): δ 1.23 (d, *J*=6.3 Hz, 6H), 4.43 (d, *J*=6.0 Hz, 2H), 5.15 (spt, *J*=6.2 Hz, 1H), 7.11 (dd, *J*=5.1, 3.7 Hz, 1H), 7.23 - 7.29 (m, 3H), 7.30 (dd, *J*=3.6, 1.2 Hz, 1H), 7.32 (t, *J*=7.5 Hz, 2H), 7.70 (dd, *J*=5.1, 1.1 Hz, 1H), 9.59 (t, *J*=6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 42.4, 70.7, 114.1, 125.9, 127.0, 127.1, 127.4, 128.4, 128.5, 130.3, 138.3, 155.6, 158.6, 160.1; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_4S$ 371.1060; Found 371.1059.

isopropyl 5-(morpholine-4-carbonyl)-4-(thiophen-2-yl)isoxazole-3-carboxylate (**8ie**). Yield 65 mg (93%), colorless oil; ^1H NMR (700 MHz, DMSO-d_6): δ 1.27 (d, *J*=6.3 Hz, 6H), 3.21 (t, *J*=4.3 Hz, 2H), 3.25 (t, *J*=4.4 Hz, 2H), 3.59 (dd, *J*=16.1, 4.9 Hz, 4H), 5.19 (spt, *J*=6.3 Hz, 1H), 7.17 (dd, *J*=5.1, 3.7 Hz, 1H), 7.29 (dd, *J*=3.6, 1.2 Hz, 1H), 7.73 (dd, *J*=5.1, 1.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.3, 42.2, 46.5, 65.5, 65.8, 70.6, 112.6, 125.4, 127.7, 128.7, 129.8, 153.8, 156.3, 158.4, 160.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}N_2O_5S$ 351.1009; Found 351.1008.

3-(isopropoxycarbonyl)-4-(4-methoxyphenyl)isoxazole-5-carboxylic acid (**9**). 305 mg (1 mmol) of **5c** was dissolved in mixture of 30 ml of water and 30 ml of iPrOH, then 4.5 ml of conc. aq. HCl was added. Resulted mixture was refluxed for 4 h on a hot plate magnetic stirrer and cooled to room temperature. All volatiles were removed in vacuo and the residue was purified with column chromatography using $CHCl_3$ – EtOH mixture as eluent (9:1, v:v). Yield 199 mg (59%), colorless viscous oil; ^1H NMR (700 MHz, DMSO-d_6): δ 1.17 (d, *J*=6.3 Hz, 6H), 3.76 (s, 3H), 5.06 (spt, *J*=6.2 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 2H), 7.31 (d, *J*=8.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.3, 55.1, 69.6, 112.9, 116.9, 121.1, 131.3, 155.0, 158.7, 159.3, 159.9, 165.9; HRMS (ESI-TOF) *m/z*: $[M-H]^-$ Calcd for $C_{15}H_{14}NO_6$ 304.0827; Found 304.0828.

isopropyl 5-((2-methoxy-2-oxoethyl)carbamoyl)-4-(4-methoxyphenyl)isoxazole-3-carboxylate (**10**). 31 mg (0.1 mmol) of **9** was dissolved in 10 ml of CH_3CN, then 49 mg (0.13 mmol) of HBTU, 17.5 mg (0.14 mmol) of methyl glycinate hydrochloride and 39 mg (0.3 mmol) of DIPEA were added and the resulted mixture was stirred for 24 h. Then the solution was evaporated to one quarter of the original volume, 100 ml of EtOAc was added, the resulted organic solution was washed with 30 ml of water, 35 ml of 3% HCl, 30 ml of water, 2 times with 35 ml of saturated aqueous $NaHCO_3$, 30 ml of water and 3 times with 30 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. The residue was purified with column chromatography using $CHCl_3$ – EtOH mixture as eluent (20:1, v:v). Yield 31 mg (83%), colorless oil; ^1H NMR (700 MHz, DMSO-d_6): δ 1.18 (d, *J*=6.3 Hz, 6H), 3.64 (s, 3H), 3.79 (s, 3H), 3.98 (d, *J*=5.7 Hz, 2H), 5.10 (spt, *J*=6.2 Hz, 1H), 6.96 (d, *J*=8.6 Hz, 2H), 7.34 (d, *J*=8.8 Hz, 2H), 9.37 (t, *J*=5.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 40.7, 51.9, 55.2, 70.3, 113.2, 118.6, 121.5, 131.5, 155.8, 156.0, 158.6, 158.8, 159.5, 169.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{21}N_2O_7$ 377.1343; Found 377.1342.

isopropyl 4-(4-methoxyphenyl)-5-(phenylcarbamoyl)isoxazole-3-carboxylate (**11**). 152 mg (0.5 mmol) of **9** was dissolved in 30 ml of CH_2Cl_2, then 190 mg (1.5 mmol) of oxalyl chloride and one drop of DMF were added. Resulted solution was stirred at RT for 3 h, and then all volatiles were removed in vacuo. Residue was dissolved in 30 ml of CH_2Cl_2, 70 mg of aniline (0.75 mmol) and 129 mg (1 mmol) of DIPEA were added and resulted mixture was stirred for 18 h. 200 ml of EtOAc was added, resulted organic solution was washed with 40 ml of water, 50 ml of 3% HCl, 40 ml of water, 2 times with 50 ml of saturated aqueous $NaHCO_3$, 40 ml of water and 3 times with 40 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. The residue was purified with column chromatography using hexane – EtOAc mixture as eluent (3:1, v:v). Yield 141 mg (74%), viscous oil; ^1H NMR (700 MHz, DMSO-d_6): δ 1.20 (d, *J*=6.3 Hz, 6H), 3.80 (s, 3H), 5.12 (spt, *J*=6.3, 1H), 6.99 (d, *J*=8.6 Hz, 2H), 7.15 (t, *J*=7.4 Hz, 1H), 7.33 - 7.42 (m, 4H), 7.69 (d, *J*=8.0 Hz, 2H), 10.86 (s, 1H); $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 21.2, 55.2, 70.4, 113.3, 118.7, 120.5, 121.4, 124.7, 128.8, 131.3, 137.7, 154.2, 155.7, 158.7, 159.5, 159.6; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{21}N_2O_5$ 381.1445; Found 381.1444.

4-(4-methoxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylic acid (**12**). 358 mg (1 mmol) of **8cb** was dissolved in 10 ml of iPrOH, then solution of 160 mg (4 mmol) of NaOH in 10 ml of water was added. Resulted mixture was stirred for 18 h. All volatiles were removed in vacuo, the residue was dissolved in 20 ml of water. 1 ml of conc. aqueous HCl was added and the resulted solution was extracted 3 times with 75 ml of EtOAc. Combined organic layers were washed 3 times with 15 ml of brine, dried over anhydrous Na_2SO_4 and then all volatiles were removed in vacuo. Resulted white solid was washed with 5 ml of Et_2O and dried in vacuo. Yield 265

mg (84%), white solid, m.p. 260°C with decomposition; Major form (~75%): ^{1}H NMR (700 MHz, DMSO-d_6), δ ppm: 1.84 - 1.93 (m, 4H), 3.40 (t, *J*=6.4 Hz, 2H), 3.45 (t, *J*=6.4 Hz, 2H), 3.76 (s, 3H), 6.97 (d, *J*=9.0 Hz, 2H), 7.59 (d, *J*=8.8 Hz, 2H); Minor form (~25%): ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.59 - 1.70 (m, 4H), 3.08 (t, *J*=6.7 Hz, 2H), 3.23 (t, *J*=7.0 Hz, 2H), 3.74 (s, 3H), 6.93 (d, *J*=8.8 Hz, 2H), 7.17 (d, *J*=8.8 Hz, 2H); ^{13}C{^{1}H} NMR (both forms) (176 MHz, DMSO-d_6): δ 23.5, 23.8, 25.0, 25.3, 44.9, 45.1, 46.2, 46.7, 55.1, 114.0, 114.3, 118.9, 123.0, 123.4, 124.2, 128.3, 128.4, 158.2, 158.7, 159.2, 159.4, 159.7, 161.1, 161.3, 161.4, 161.8, 162.2; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}N_2O_5$ 317.1132; Found 317.1136.

4-(4-methoxyphenyl)-N-phenyl-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxamide (**13**). 32 mg (0.1 mmol) of **12** was dissolved in 10 ml of CH_2Cl_2, then 38 mg (0.3 mmol) of oxalyl chloride and one drop of DMF were added. Resulted solution was stirred at RT for 3 h, and then all volatiles were removed in vacuo. Residue was dissolved in 10 ml of CH_2Cl_2, 14 mg of aniline (0.15 mmol) and 148 mg (1.15 mmol) of DIPEA were added and resulted mixture was stirred for 18 h. 100 ml of EtOAc was added, resulted organic solution was washed with 30 ml of water, 35 ml of 3% HCl, 30 ml of water, 2 times with 35 ml of saturated aqueous $NaHCO_3$, 30 ml of water and 3 times with 30 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. Residue was washed with 5 ml of Et_2O and dried in vacuo. Yield mg (92%), white solid, m.p. 198-199°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.73 - 1.86 (m, 4H), 3.24 (t, *J*=6.7 Hz, 2H), 3.47 (t, *J*=6.9 Hz, 2H), 3.76 (s, 3H), 6.99 (d, *J*=9.0 Hz, 2H), 7.15 (t, *J*=7.4 Hz, 1H), 7.33 - 7.41 (m, 4H), 7.68 (d, *J*=7.6 Hz, 2H), 11.00 (s, 1H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 23.5, 25.2, 45.9, 47.0, 55.1, 114.2, 117.6, 118.8, 120.0, 124.6, 128.9, 129.9, 137.9, 156.3, 157.5, 157.6, 159.5, 159.9; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}N_3O_4$ 392.1605; Found 392.1604.

methyl (4-(4-methoxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carbonyl)glycinate (**14**). 32 mg (0.1 mmol) of **12** was dissolved in 10 ml of CH_3CN, then 49 mg (0.13 mmol) of HBTU, 17.5 mg (0.14 mmol) of methyl glycinate hydrochloride and 39 mg (0.3 mmol) of DIPEA were added and the resulted mixture was stirred for 24 h. Then the solution was evaporated to one quarter of the original volume, 100 ml of EtOAc was added, the resulted organic solution was washed with 30 ml of water, 35 ml of 3% HCl, 30 ml of water, 2 times with 35 ml of saturated aqueous $NaHCO_3$, 30 ml of water and 3 times with 30 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. The residue was purified with column chromatography using $CHCl_3$ – EtOH mixture as eluent (20:1, v:v). Yield 34 mg (89%), colorless oil; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.72 - 1.84 (m, 4H), 3.19 (t, *J*=6.7 Hz, 2H), 3.45 (t, *J*=7.0 Hz, 2H), 3.67 (s, 3H), 3.78 (s, 3H), 4.02 (d, *J*=6.1 Hz, 2H), 6.97 (d, *J*=8.8 Hz, 2H), 7.36 (d, *J*=9.0 Hz, 2H), 9.39 (t, *J*=5.9 Hz, 1H); ^{13}C{^{1}H} NMR (176 MHz, DMSO-d_6): δ 23.5, 25.2, 40.9, 45.9, 47.0, 51.9, 55.2, 113.9, 117.7, 118.7, 130.1, 156.4, 156.5, 159.4, 159.6, 160.1, 169.4; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{22}N_3O_6$ 388.1503; Found 388.1504.

4-(4-methoxyphenyl)-5-(phenylcarbamoyl)isoxazole-3-carboxylic acid (**15**). 76 mg (0.2 mmol) of **11** was dissolved in the mixture of 1 ml of water and 1 ml of iPrOH. 32 mg (0.8 mmol) of NaOH was added and the resulted mixture was stirred for 1 h. Then 20 ml of water was added and the solution was acidified to pH=1 with 3% HCl. Mixture was extracted 3 times with 50 ml of EtOAc, combined organic layers were washed 3 times with 30 ml of brine, dried over Na_2SO_4. All volatiles were removed in vacuo. Yield 59 mg (87%), colorless oil; Major form: ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.78 (s, 3H), 6.95 - 7.03 (m, 2H), 7.15 (t, *J*=7.4 Hz, 1H), 7.32 - 7.41 (m, 3H), 7.66 - 7.72 (m, 3H), 10.83 (br. s., 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 55.2, 114.0, 114.2, 119.2, 119.8, 119.9, 123.9, 124.4, 128.7, 128.9, 138.1, 158.3, 160.4, 161.8; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{18}H_{15}N_2O_5$ 339.0975; Found 339.0977.

4-(4-methoxyphenyl)-N-phenyl-3-(pyrrolidine-1-carbonyl)isoxazole-5-carboxamide (**16**). 34 mg (0.1 mmol) of **15** was dissolved in 10 ml of CH_2Cl_2, and then 38 mg (0.3 mmol) of oxalyl chloride and one drop of DMF were added. Resulted solution was stirred at RT for 3 h, and then all volatiles were removed in vacuo. Residue was dissolved in 10 ml of CH_2Cl_2, 53 mg (0.75 mmol) of pyrrolidine and 26 mg (0.2 mmol) of DIPEA were added and resulted mixture was stirred for 18 h. 100 ml of EtOAc was added, resulted organic solution was washed with 20 ml of water, 30 ml of 3% HCl, 20 ml of water, 2 times with 30 ml of saturated aqueous $NaHCO_3$, 20 ml of water and 3 times with 30 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. The residue was purified with column chromatography using hexane – EtOAc mixture as eluent (3:2, v:v). Yield 30 mg (77%), white solid, m.p. = 188-190°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 1.75 - 1.81 (m, 2H), 1.81 - 1.85 (m, 2H), 3.27 - 3.29 (m, 2H), 3.44 (t, *J*=7.1 Hz, 2H), 3.78 (s, 3H), 6.99 (d, *J*=8.8 Hz, 2H), 7.15 (t, *J*=7.3 Hz, 1H), 7.36 (t, *J*=7.9 Hz, 2H), 7.42 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=7.8 Hz, 2H), 10.88 (s, 1H); ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 23.8, 25.3, 45.6, 47.7, 55.2, 113.9, 118.8, 119.7, 120.5, 124.7, 128.8, 130.5, 137.8, 154.7, 157.9, 158.1, 159.1, 159.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{22}H_{22}N_3O_4$ 392.1605; Found 392.1610.

methyl (4-(4-methoxyphenyl)-5-(phenylcarbamoyl)isoxazole-3-carbonyl)glycinate (**17**). 34 mg (0.1 mmol) of **15** was dissolved in 10 ml of CH_3CN, then 49 mg (0.13 mmol) of HBTU, 17.5 mg (0.14 mmol) of methyl glycinate hydrochloride and 39 mg (0.3 mmol) of DIPEA were added and the resulted mixture was stirred for 24 h. Then the solution was evaporated to one quarter of the original volume, 100 ml of EtOAc was added, the resulted organic solution was washed with 20 ml of water, 30 ml of 3% HCl, 20 ml of water, 2 times with 30 ml of saturated aqueous $NaHCO_3$, 20 ml of water and 3 times with 30 ml of brine. Organic layer was dried over anhydrous Na_2SO_4, all volatiles were removed in vacuo. The residue was purified with column chromatography using $CHCl_3$ - EtOH mixture as eluent (20:1, v:v). Yield 27 mg (66%), white solid, m.p. = 69-71°C; ^{1}H NMR (700 MHz, DMSO-d_6): δ 3.67 (s, 3H), 3.78 (s, 3H), 4.03 (d, *J*=6.1 Hz, 2H), 6.95 (m, *J*=8.8 Hz, 2H), 7.15 (t, *J*=7.3 Hz, 1H), 7.36 (t, *J*=7.8 Hz, 2H), 7.44 (m, *J*=8.8 Hz, 2H), 7.70 (d, *J*=8.0 Hz,

2H), 9.41 (t, *J*=5.9 Hz, 1H), 10.87 (s, 1H); $^{13}C\{^{1}H\}$ NMR (75 MHz, DMSO-d_6): δ 40.9, 52.0, 55.2, 113.5, 118.7, 120.4, 120.5, 124.7, 128.8, 131.1, 137.7, 154.7, 157.8, 158.5, 159.4, 159.5, 169.5; HRMS (ESI-TOF) *m/z*: $[M+H]^+$ Calcd for $C_{21}H_{20}N_3O_6$ 410.1347; Found 410.1352.

Gram-scale synthesis. *isopropyl 5-hydroxy-4-(4-methoxyphenyl)-6-oxo-6H-1,2-oxazine-3-carboxylate* (**5c**). P-Anisaldehyde (6.8 g, 50 mmol), isopropyl nitroacetate (16.2 g, 110 mmol) and diethylamine (9.1 g, 125 mmol) were dissolved in 130 ml of acetonitrile. Resulted solution was stirred for 48 h at room temperature and then additionally heated at 80°C for 3 h. All volatiles were removed in vacuo, 160 ml of isopropanol was added and the mixture was refluxed until the complete solid dissolution (5 min). Resulted solution was cooled to -20°C and stored for 2 h at this temperature. The precipitated diethylammonium salt was filtered and washed with a cold (0°C) alcohol (20 ml, twice), washed with 20 ml of ether and dried in vacuo. The diethylammonium salt was dissolved in 500 ml of $CHCl_3$ and washed 3 times with 200 ml of 3% aq. HCl. Organic layer was dried with anhydrous Na_2SO_4 and evaporated to obtain pure **5c**. Yield 13.0 g (85%).

isopropyl 4-(4-methoxyphenyl)-5-(pyrrolidine-1-carbonyl)isoxazole-3-carboxylate (**8cb**). Oxazinone **5c** (3.05 g, 10 mmol) and pyrrolidine (1.4 g, 20 mmol) were dissolved in 25 ml of $CHCl_3$. Resulted solution was stirred for 12 h at 70°C. All volatiles were removed in vacuo and the residue was purified by column chromatography using $CHCl_3$ – EtOH mixture as eluent (100:1, v:v). Yield 2.8 g (78%).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Reaction optimization, X-ray crystallography data, NMR spectra (PDF) and CIF file.

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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