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Functionalized 5-amino-4-cyanoxazoles, their hetero- and macrocyclic derivatives: preparation and synthetic applications

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Abstract: An approach to a series of new 5-amino-4-cyanoxazoles is described. Synthesis of the title compounds relied on a two-step sequence including heterocyclization of 2-amido-3,3-dichloroacrylonitriles with aliphatic secondary amines (dimethylamine, morpholine), primary aliphatic amines with active functional groups (2-aminoethanol and glycine ethyl ester), and aniline. An efficient and straightforward protocol introduces a carboxylate group at the C-2 position of 5-amino-4-cyanoxazoles, connected to the heterocycle directly or through an aliphatic linker. This carboxylic group is an attractive motif that can be found in a variety of drug-relevant compounds and also used for further modifications. Furthermore, efficient transformations of selected trisubstituted compounds were used to demonstrate their rich synthetic potential – e.g., as precursors to 2-(4-cyano-5-(dimethylamino)oxazol-2-yl)acetamides, oxazole-containing macrocyclic structures, 2-(oxazol-2-yl)acetamides, amino pyrazoles, 3-(4-cyano-5-aminoxazol-2-yl)coumarins, and oxazole amino acids.

Introduction

Trisubstituted oxazoles have been receiving increasing attention in both industrial and academic fields for a long time.[1–3] This interest is driven by the fact that a variety of natural and synthetic compounds with the oxazole substructure exhibit noticeable biological activities, such as antibacterial, anticancer, antiviral, antidiabetic, anti-inflammatory, etc.[4–7] Moreover, oxazole derivatives can be used as the synthetic intermediates in the synthesis of α-ketoamides,[8] macromolecular scaffolds,[9,10] and organic materials, such as corrosion inhibitors.[11] Figure 1 shows some examples of 2,4,5-trisubstituted oxazoles and their applications – selective inhibitors of human reticulocyte 12/15-lipoxygenase for anti-stroke therapies **1**,[12] inflammatory agent **2**,[13] or anticancer agent **3**.[14] Furthermore, the 2-keto-5-aminooxazole compounds are extraordinarily potent and selective inhibitors of fatty acid amide hydrolase (FAAH) – the primary *in vivo* catabolic regulator of several bioactive lipid amides.[15] Substituted oxazoles are fairly often considered as peptidomimetics due to the proposed non-classical isosterism of the oxazole ring and the amide residue.[16–20] In particular, oxazole **4** was used as the key intermediate in the synthesis of dipeptide mimics.[19]

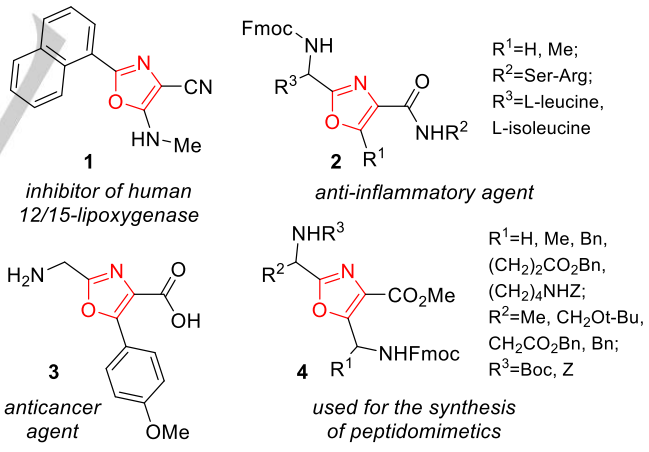
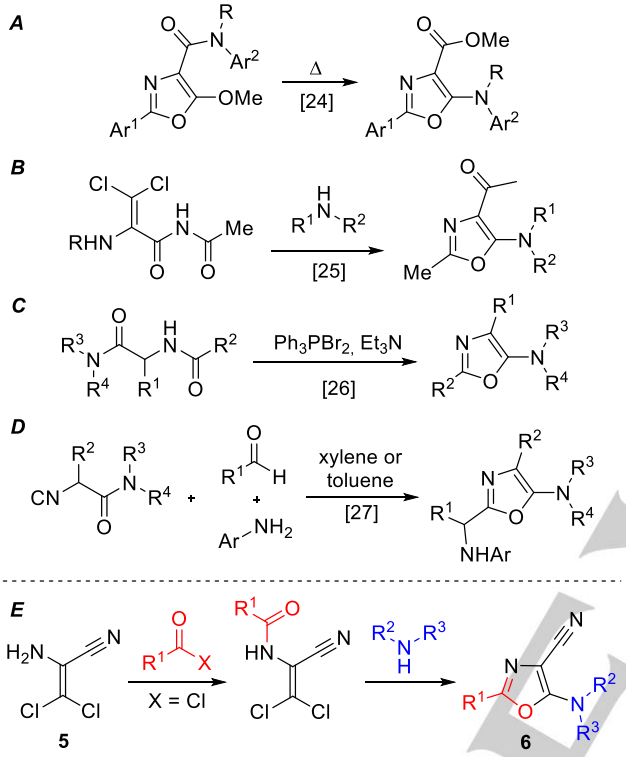


Figure 1. Examples of 2,4,5-trisubstituted oxazoles and their applications

Driven by important applications of oxazole derivatives, various synthetic methodologies for their synthesis have been developed. The classical approaches to the synthesis of trisubstituted oxazoles include dehydrative cyclization of acyclic precursors described in numerous reviews;[1–3] newer methods rely on Ni-catalyzed Suzuki–Miyaura coupling,[21] cross-coupling reactions of 2-, 4- and 5-bromooxazoles,[22] and palladium-catalyzed C–H activation.[23] Notably, direct approaches to highly functionalized oxazoles are rare, thus making a general and efficient procedure to access trisubstituted oxazoles – in

particular, those containing both amino and carboxyl groups – highly desirable.

Some of the known approaches to the synthesis of trisubstituted 5-aminooxazoles are based on the thermal Cornforth rearrangement of 2-aryl-5-methoxyoxazole-4-carboxamides (Scheme 1, ***A***),[24] heterocyclization of 2-acethylamino-3,3-dichloroacrylic-*N*-acetamide with aliphatic primary amines (***B***),[25] reaction of α-acylaminoamides with dibromotriphenylphosphorane (***C***),[26] and isocyanide-based multicomponent reactions (***D***).[27]



Scheme 1. Some known approaches to trisubstituted 5-aminooxazoles

One of the particularly efficient precursors to substituted oxazoles is 2-amino-3,3-dichloroacrylonitrile (ADAN, **5**). This reagent was introduced into the chemistry of heterocyclic compounds in 1970s.[28,29] Recent publications report the use of **5** for the preparation of imidazol-2-ones,[30] pyrazolo-[1,5-*a*]pyrimidines,[31] pyrazolo[1,5-*a*][1,3,5]triazines,[32] as well as a number of trisubstituted oxazoles.[33–35] The latter approach includes acylation of **5** at the amino group with acyl halides or anhydrides, followed by reaction with a primary or secondary aliphatic, or primary aromatic amine, resulting in the formation of the oxazole ring (Scheme 1, ***E***). In most cases, the method was applied for aromatic acyl chlorides.[34] Only a few examples with their aliphatic counterparts were reported in the literature.[34a,f] In particular, haloacetyl chlorides and acyl chlorides bearing a protected aminogroup (i.e., phtalimide moiety) were used in such heterocyclizations previously,[35] while to the best of our knowledge, acyl chlorides with an additional ester group were not studied. This leaves questions of selectivity in the reaction of **5** with such polyfunctional compounds and impact of the additional ester group at further formation of the oxazole ring unaddressed.

In this work, we present the synthesis and chemical transformations of novel 5-amino-4-cyanooxazoles **6a–c** bearing an ester function at the C-2 position of the oxazole, connected to the heterocycle directly or through an aliphatic linker (Figure 2). Acyl chlorides derived from oxalic, malonic, and succinic monoesters were necessary as the starting materials for the corresponding reaction sequences. Since target substances **6b** derived from malonate might exhibit some reactivity at the methylene group, a number of hereto unknown derivatives with benzyl moiety (R^1 = Bn; can be synthesized from α-phenylacetyl chloride) were also added to the scope of the study as the model compounds.

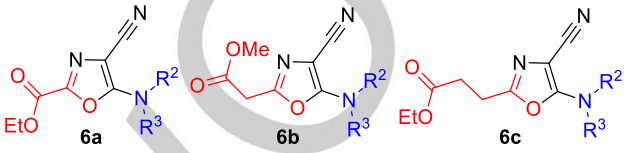
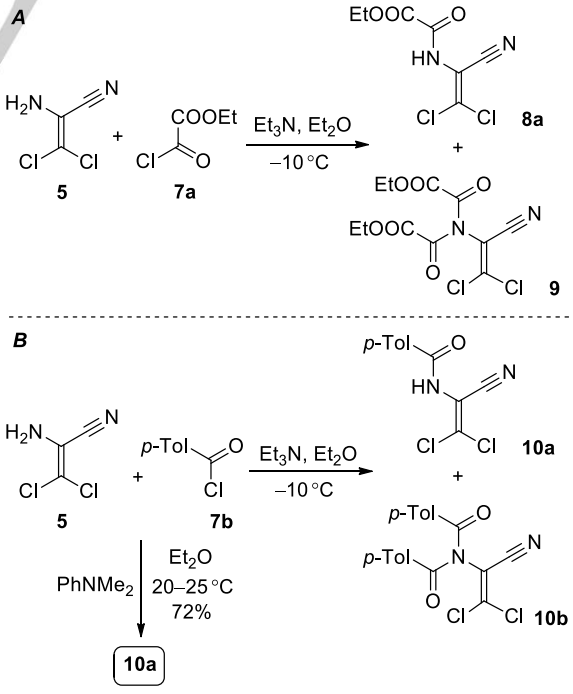


Figure 2. The key target molecules of this study

Results and Discussion

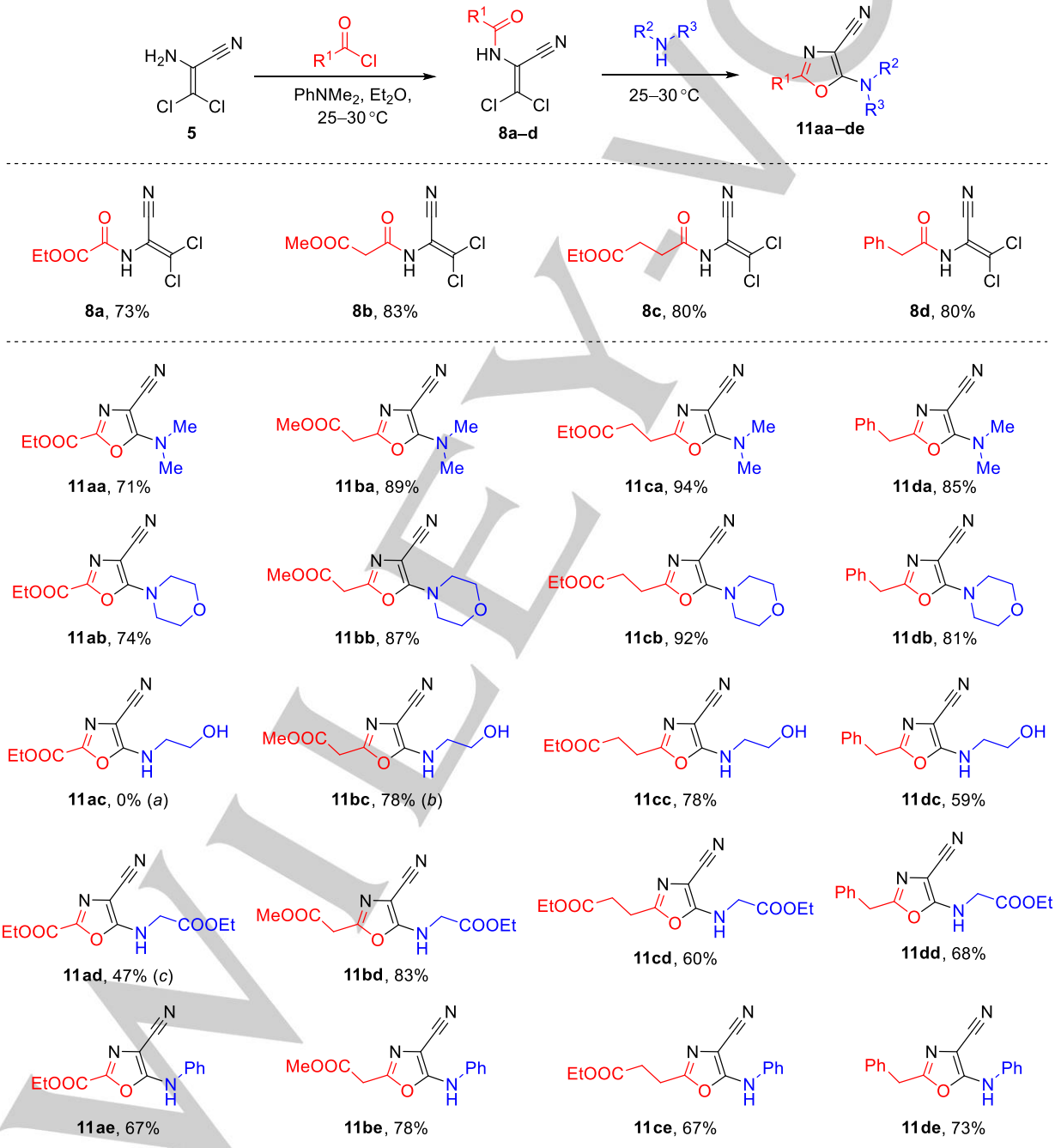
The study commenced with optimization of the reaction conditions for the acylation of 2-amino-3,3-dichloroacrylonitrile (**5**) with the aforementioned acyl chlorides. It was found that the use of Et_3N as a base in the reaction of **5** with ethyl oxalyl chloride significantly decreased the yield of the target compound due to the formation of a diacylation byproduct. Thus, ADAN reacted with ethyl oxalyl chloride (**7a**, 1 eq) in the presence of Et_3N (1.1 eq) in diethyl ether at –10 °C to give a mixture of ethyl 2-((2,2-dichloro-1-cyanovinyl)amino)-2-oxoacetate (**8a**), diacyl derivative **9**, and unreacted **5** (Scheme 2, ***A***).



Scheme 2. Optimization of the ADAN acylation conditions

Although diacyl derivative **9** had low hydrolytic stability and could lose one acetyl residue upon work-up of the reaction thus giving the target product **8a**, the tendency of unreacted starting material **5** to decompose after a few hours at room temperature, causing significant tar formation, prompted us to seek for an alternative procedure allowing for a quick processing of the acylation products. Further optimization of the reaction conditions was performed with *p*-toluoyl chloride (**7b**) as the acylating agent which, besides stability, has the advantage of simplified analysis of the reaction mixtures by ^{1}H NMR spectroscopy, as well as the formation of crystalline products. Again, acylation of **5** with **7b** (1 eq) in the presence of Et_3N (1 eq) in Et_2O at at –10 °C resulted in a mixture of mono- and diacyl derivatives (Scheme 2, ***B***). Nevertheless, replacing Et_3N with a weaker base – *N*,*N*-dimethylaniline – and raising the temperature to 20–25°C allowed to completely avoid the formation of undesirable by-product **10b** and obtain compound **10a** in 72% yield. The diacyl derivatives **9** and **10b** were purposely synthesized by a reaction of **5** with a two-fold excess of ethyl oxalyl chloride (**7a**) and *p*-toluoyl chloride (**7b**) in the presence of Et_3N (2.2 eq). Unlike the oxalate diacyl derivative **9** that decomposed soon after isolation, the product **10b** appeared to be quite stable.

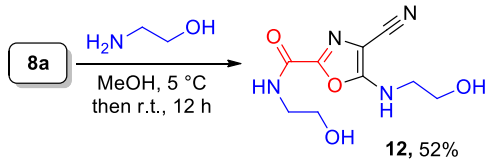
The optimized method was used to acylate **5** with all the four starting acyl chlorides to give amides **8a–d** in 68–83% yields (Scheme 3). As expected, the compound **8a** was the least stable among amides **8a–d** – it decomposed at room temperature in less than a month, but could be stored at -10 °C for about 6



Scheme 3. Synthesis of amides **8a–d** and oxazoles **11aa–de**. *(a)* amide **12** was obtained, see Scheme 4 *(b)* amide **13** and iminopyrrolidinone **14** were also obtained, see Scheme 5 *(c)* amide **15** was also obtained, see Scheme 6

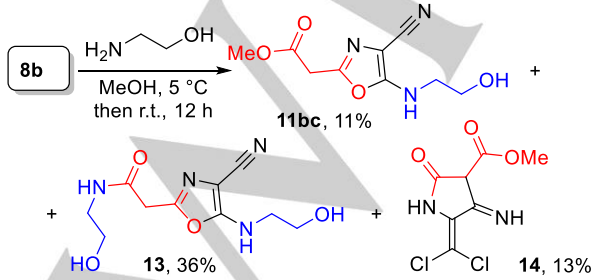
months. Compounds **8a**, **8b**, and **8d** could be stored without significant decomposition at room temperature for several months.

Target oxazoles **11aa–de** were obtained by treating amides **8a–d** with common aliphatic secondary amines (dimethylamine, morpholine), primary aliphatic amines with additional functional groups (2-aminoethanol and glycine ethyl ester), and aniline (Scheme 3). The synthetic protocol developed for preparing compounds **11aa-de** provides a highly versatile and efficient method for derivatization of positions 2, 4 and 5 of the oxazole core, allowing the introduction of diverse functional groups. Nevertheless, some of target compounds **11** could not be obtained or were formed together with by-products due to the competing reactions at the ester moiety. For example, the formation of the oxazole ring in the reaction of oxalate-derived dichloroacrylonitrile **8a** with aminoethanol was accompanied by the simultaneous amidation at the ester group to give oxazole **12** (Scheme 4). Carrying out the synthesis without affecting the ester group was unsuccessful even when lowering the reaction mixture temperature. Acrylonitriles **8** did not react even with an excess of amines at -10–0°C.



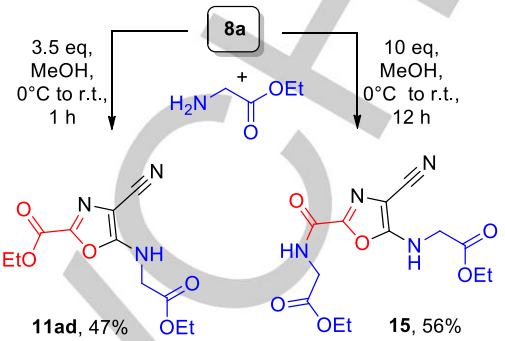
Scheme 4. Synthesis of oxazole **12**

The formation of oxazole **13** as an impurity to **11bc** was established in the reaction of aminoethanol with malonate-derived dichloroacrylonitrile **8b**. In this case, the iminopyrrolidinone **14** was also formed as a side product of the addition (Scheme 5). The presence of by-products in the reaction mixture was determined using TLC and HPLC-MS, these substances were isolated and purified using preparative HPLC. The directed synthesis of compounds **11bc** and **13** could be performed with high yields and minimal amount of impurities by using ethanolamine in the acetate form or a 10-fold excess of ethanolamine in the reaction with acrylonitrile **8b**, respectively (see the experimental section for more details). The formation of **14** can be explained by relatively high CH-acidity of the methylene group in **8b** that acts as a nucleophile towards the electrophilic CN group in basic medium. Thus, reaction of **8b** with triethylamine gave **14** in a nearly quantitative yield.



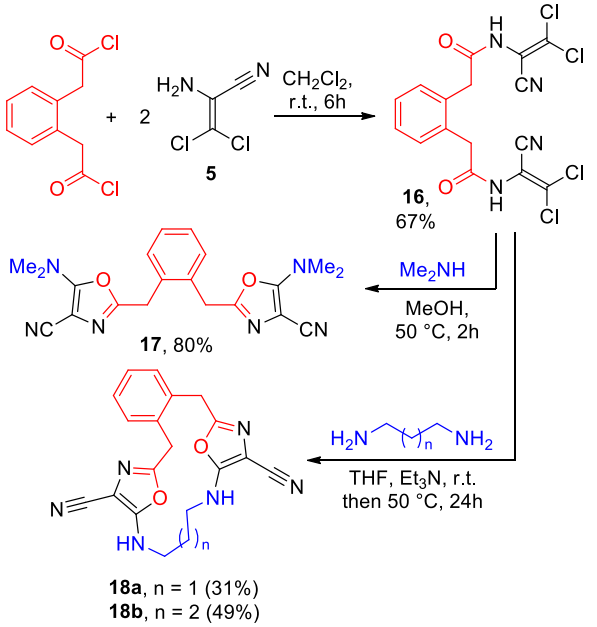
Scheme 5. Formation of by-products in the synthesis of oxazole **11bc**

Varying reagent ratios and reaction duration allowed obtaining different products in the reaction of acrylonitrile **8a** with glycine ethyl ester. Thus, target oxazole **11ad** was obtained in 47% yield using 3.5 eq of glycine ethyl ester after 1 h of the reaction time, while oxazole **15** was obtained in 56% yield with 10-fold excess of glycine ethyl ester and at longer reaction time of 12 h (Scheme 6).



Scheme 6. Synthesis of oxazoles **11ad** and **15**

Finally, macrocyclic structures with oxazole rings could be synthesized using the presented method. Thus, the use of α,α′-(*o*-phenylene)diacetyl chloride instead of α-phenylacetyl chloride in the reaction with **5** gave product **16** bearing two acrylonitrile fragments (Scheme 7). The molecular structure of **16** was confirmed by X-Ray diffraction studies (Figure 3). Compound **16** was more stable than nitriles **18a–d** and therefore, less active towards amines. The synthesis of oxazole derivatives based on **16** required higher temperatures and significantly longer reaction times. Thus, reaction of **16** with dimethylamine gave bis-oxazole derivative **17** (Scheme 7). This prompted us to use diamines – 1,3-diaminopropane and 1,4-diaminobutane – in the reaction with compound **16**, which resulted in the formation of the macrocyclic products **18a** and **18b** in 31% and 49% yields, respectively. The structure of compounds **18a** and **18b** was con-



Scheme 7. Formation of oxazoles from ADAN and α,α′-(*o*-phenylene)diacetyl chloride

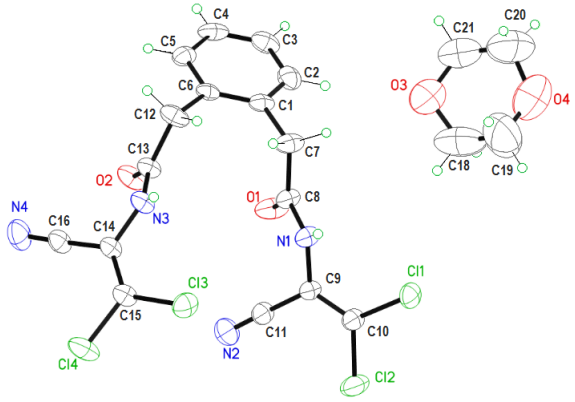
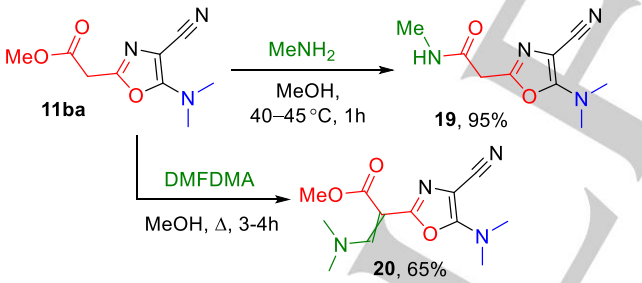


Figure 3. Molecular structure of **16**

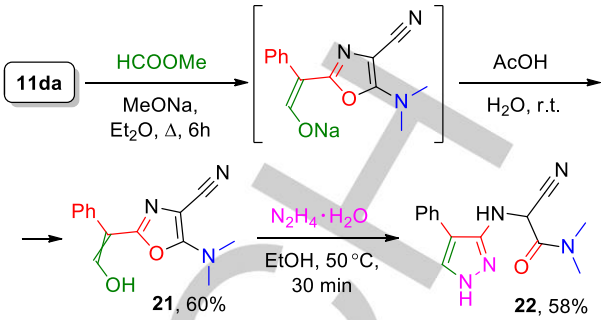
firmed by 2D NMR experiments (see the supporting information for more details).

As it was mentioned above, formation of the oxazole ring in the reaction of dichloroacrylonitriles **8a** and **8b** with aminoethanol or glycine ethyl ester was accompanied by the formation of corresponding amides **12**, **13** and **15** (Schemes 4–6)**.** Apparently, this transformation is general for similar substances and can be used successfully in the targeted synthesis of 2-(oxazol-2-yl)-acetamides. Additionally, amide **19** was obtained via the reaction of ester **11ba** and methylamine.[36] The high activity of the methylene group of 2-(oxazol-2-yl)acetates was demonstrated by the reaction of ester **11ba** with DMFDMA, which occured under mild conditions and gave enamine **20** (Scheme 8).



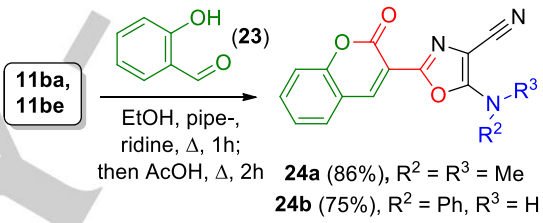
Scheme 8. Synthesis of derivatives **19** and **20**

The formylation of the methylene group in the benzyl moiety of compound **11da** required harsher reaction conditions – thus, aldehyde **21** was obtained by the Claisen condensation with methyl formate in the presence of sodium methoxide (Scheme 9). Only the enol form of compound **21** was detected predominantly in the NMR spectra recorded in DMSO-d_6. A possible synthetic use of the formylation products includes, for example, recyclizations involving the aldehyde function and the oxazole ring. For example, product **21** was converted to aminopyrazole **22** upon action of hydrazine in alcoholic solution (Scheme 9). This recyclization has few analogies in the literature; therefore, the structure of **22** was confirmed by a number of 2D NMR spectroscopic methods. In particular, the conformation of **22** in the DMSO solution corresponded to that shown in Scheme 9, as evidenced by the ROESY spectrum (see the supporting information for more details).



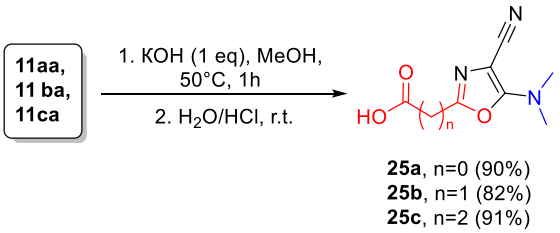
Scheme 9. Formylation of the ester **11da** and the subsequent recyclization

An additional indication of the 2-(4-cyanooxazol-2-yl)acetates reactivity was their participation in the coumarin ring formation in the condensation reaction with salicylic aldehyde, carried out by refluxing equivalent amounts of reagents in an alcohol solution in the presence of catalytic amounts of piperidine (Scheme 10).



Scheme 10. Synthesis of coumarins **24a,b**

With the possible further use of the obtained substances in the synthesis of peptidomimetics in mind, it was important to demonstrate the possibility of ester hydrolysis in the obtained products with retention of the other structural fragments. As it turned out, hydrolysis of esters **11aa**, **11ba**, and **11ca** proceeded very smoothly in a weakly alkaline medium and the yield of the corresponding acids **25a**, **25b**, and **25c** (Scheme 11) was virtually independent of the distance between the ester group and the heterocycle.



Scheme 11. Synthesis of carboxyli acids **25a–c**

Conclusions

In this work, we developed efficient and straightforward protocols for the construction of trisubstituted oxazoles found in a variety of drug-relevant compounds and useful for further derivatization. We demonstrated that the heterocyclization of 2-amido-3,3-dichloroacrylonitriles with amines (dimethylamine,

morpholine, 2-aminoethanol, glycine ethyl ester, and aniline) produced a series of 5-amino-4-cyanoxazoles with a carboxylate group at the C-2 position, connected to the heterocycle either directly or through an aliphatic linker. 2-Amido-3,3-dichloroacrylonitriles were readily obtained by the acylation of 2-amino-3,3-dichloroacrylonitrile (ADAN) with dicarboxylic acid chlorides, which were not used as the substrates in the synthesis of 2-substituted 5-amino-4-cyanoxazoles prior this work. The presented method is an attractive approach to the construction of 2,4,5-trisubstituted oxazoles, applicable to the synthesis of a broad range of 2,4,5-trisubstituted oxazole derivatives. The obtained polyfunctional compounds can be used as synthetic precursors and as potential biologically active molecules. Selected compounds were used to demonstrate their rich synthetic potential, e.g. in: a) synthesis of macrocylic structures starting from ADAN and *o*-phenyldiacetic acid chloride; b) synthesis of 2-(4-cyano-5-(dimethylamino)oxazol-2-yl)acetic acid amides; c) formylation of the methylene group of 2-(4-cyano-5-(dimethylamino)oxazol-2-yl)acetate and 2-benzyl-5-(dimethylamino)oxazol-4-carbonitrile and further recyclization of the latter into a pyrazole derivative; d) synthesis of new 3-(4-cyano-5-aminoxazol-2-yl)coumarins; e) synthesis of oxazole aminoacids via hydrolysis of corresponding esters. Further investigation of synthetic and biological potential of the obtained compounds is in progress in our laboratory.

Experimental Section

General. The solvents were purified according to the standard procedures.[37] All other starting materials were purchased from commercial sources. Analytical TLC was performed using Polychrom SI F254 plates. For flash chromatography Silica gel 230-400 mesh was used. Elemental analyses were performed at the Analytical Laboratory of the V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry NAS of Ukraine. Melting points were measured on MPA100 OptiMelt automated melting point system. NMR spectra of obtained products were recorded at Varian Unity Plus 400 spectrometer (400 MHz for ^{1}H and 101 MHz for ^{13}C), Bruker 170 spectrometer (500 MHz for ^{1}H and 126 MHz for ^{13}C), and Agilent ProPulse 600 spectrometer (600 MHz for ^{1}H, 151 MHz for ^{13}C) in $CDCl_3$ and DMSO-d_6 solution; chemical shifts are reported in ppm with solvent residual signal used as an internal standard (^{1}H, ^{13}C). IR spectra were recorded on a Vertex-70 spectrometer in KBr tablets. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General procedure for the preparation of diacyl derivatives 9 and 10b. To a solution of ADAN **5** (1 g, 7.30 mmol) in Et_2O (50 mL), Et_3N (2.23 mL, 16.06 mmol, 2.2 eq) was added under argon atmosphere. The reaction mixture was cooled to –20 °C and, while maintaining the temperature, a solution of the corresponding acyl chlorides **7a** or **7b** (14.60 mmol, 2 eq) in Et_2O (25 mL) was added slowly (over 30 min) dropwise under argon atmosphere. After the reagent was added, the reaction mixture was slowly warmed to room temperature (25 °C) and stirred for 2 h, then H_2O (30 mL) was added. The organic layer was separated, dried over Na_2SO_4. The product was extracted and purified by flash chromatography on silica gel.

Diethyl 2,2'-((2,2-dichloro-1-cyanovinyl)azanediyl)bis(2-oxoacetate) (9). Yield 1.60 g (65 %), colorless solid, mp 40–43 °C decomp. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.28 (q, J = 7.1 Hz, 4H, 2 CH_2), 1.30 (t, J = 7.1 Hz, 6H, 2 CH_3) ppm.

***N*-(2,2-dichloro-1-cyanovinyl)-4-methyl-*N*-(4-methylbenzoyl)benzamide (10b).** Yield 2.08 g (76 %), colorless solid, mp 114–116 °C. ^{1}H NMR (DMSO-d_6): δ = 7.65 (d, J = 8.0 Hz, 4H, Ar), 7.33 (d, J = 8.0 Hz, 4H, Ar), 2.35 (s, 6H, 2 CH_3) ppm. ^{13}C NMR (DMSO-d_6): δ = 168.2 × 2 (2 C=O), 142.8 × 2 (Ar), 139.7, 128.0 × 2, 127.8 × 4 (Ar), 127.2 × 4 (Ar), 111.3, 110.9, 19.4 × 2 (2 CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3046, 2960, 2923, 2229, 1708 (vs), 1691 (vs), 1664 (vs), 1606 (s), 1573, 1519, 1486, 1447, 1407, 1298, 1281 (vs), 1234 (s), 1211, 1173, 1120, 1062, 1014, 961, 931, 855, 834 (s), 763, 747 (s), 721, 680, 634, 619, 587 cm^{-1}. MS, *m/z* (I_{rel}, %): 119.0 [*p*-TolCO]$^+$ (100), 394.8 [M+Na]$^+$ (10). Found, %: C 61.33; H 3.81; Cl 18.81; N 7.64. $C_{19}H_{14}Cl_2N_2O_2$. Calculated, %: C, 61.14; H, 3.78; Cl, 19.00; N, 7.51.

General procedure for the preparation of amides 8a–8c and 10a. ADAN **5** (10 g, 0.073 mol) and *N*,*N*-dimethylaniline (10.2 mL, 0.080 mol, 1.1 eq) were dissolved in Et_2O (50 mL) at rt (25 °C), and a solution of the corresponding acyl chloride (0.073 mol, 1 eq) in Et_2O (25 mL) was added dropwise. When adding the reagent, the reaction mixture temperature had to be kept no higher than 30 °C and the reactor cooled, if necessary, with cold water, but not ice – the reaction did not proceed near 0 °C. After the acyl chloride was added, the reaction mixture was stirred at 25 °C for 6 h (in case of aliphatic acyl chlorides) or 24 h (for aromatic acyl chlorides). Hexane (50 mL) and H_2O (100 mL) were added to the reaction mixture; the residue formed in the two-phase system which was then filtered and washed sequentially with H_2O (50 mL) and a 1:2 mixture of Et_2O and hexane (30 mL). The obtained target product had purity of more than 95 % according to NMR and chromatography mass spectrometry and was used in further stages without additional purification. Analytical samples were prepared by recrystallization from $CHCl_3$ – hexane (1:1).

Ethyl 2-((2,2-dichloro-1-cyanovinyl)amino)-2-oxoacetate (8a). Yield 12.66 g (73 %), colorless solid, mp 41–43 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.13 (s, 1H, NH), 4.29 (q, J = 7.1 Hz, 2H, CH_2), 1.29 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.1 (C=O), 156.2 (C=O), 137.0, 112.8, 110.0, 63.4 (OCH_2), 14.2 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3456, 3248 (br), 3049, 2986, 2205 (vw), 1734 (vs), 1684 (vs), 1637 (vs), 1571, 1532, 1484, 1465, 1401, 1375, 1349, 1264, 1235, 1177, 1152, 1123, 1007, 929, 853, 780, 728, 639, 620, 540, 505, 475 cm^{-1}. MS, *m/z* (I_{rel}, %): 237.0 [M+H]$^+$ (90). Found, %: C 35.73; H 2.42; Cl 30.07; N 11.68. $C_7H_6Cl_2N_2O_3$. Calculated, %: C, 35.47; H, 2.55; Cl, 29.91; N, 11.82.

Methyl 3-((2,2-dichloro-1-cyanovinyl)amino)-3-oxopropanoate (8b). Yield 14.36 g (83 %), colorless solid, mp 106–108 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.48 (s, 1H,

NH), 3.66 (s, 3H, CH_3), 3.52 (s, 2H, CH_2) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.7 (C=O), 165.0 (C=O), 132.0, 112.7, 111.0, 52.6 (CH_3), 42.2 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3234 (s, br), 3176, 3008, 2961, 2915, 2229, 1718 (vs), 1684 (vs), 1596 (s), 1483 (vs, br), 1450, 1440, 1396, 1354 (vs), 1299 (s), 1227 (vs), 1170 (s), 1033, 992, 961, 940 (s), 911, 878, 841, 781, 665, 626, 610, 511, 483 cm^{-1}. MS, *m/z* (I_{rel}, %): 102.2 $[COCH_2CO_2Me]^+$ (100), 237.0 $[M+H]^+$ (90). Found, %: C 35.68; H 25.27; Cl 29.88; N 11.75. $C_7H_6Cl_2N_2O_3$. Calculated, %: C, 35.47; H, 2.55; Cl, 29.91; N, 11.82.

Ethyl 4-((2,2-dichloro-1-cyanovinyl)amino)-4-oxobutanoate (8c). Yield 15.48 g (80 %), colorless solid, mp 97–99 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.32 (s, 1H, NH), 4.05 (q, J = 7.0 Hz, 2H, $\underline{CH_2}CH_3$), 2.64 – 2.53 (m, 4H, $2CH_2$), 1.18 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 172.3 (C=O), 170.8 (C=O), 131.1, 112.9, 111.4, 60.5 (OCH_2), 30.0 (CH_2), 28.8 (CH_2), 14.5 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3266 (s, br), 3190, 2992, 2949, 2936, 2927, 2913, 2233, 1729 (vs), 1675 (vs), 1605, 1490 (vs), 1421, 1367, 1332, 1280, 1177, 1160, 1118, 1031, 999, 962, 943, 893, 868, 820, 808, 771, 649, 613, 558, 476, 435 cm^{-1}. MS, *m/z* (I_{rel}, %): 101.2 $[(CH_2)_2CO_2Et]^+$ (50), 129.2 $[CO(CH_2)_2CO_2Et]^+$ (100), 265.0 $[M+H]^+$ (40). Found, %: C 40.89; H 3.97; Cl 26.58; N 10.62. $C_9H_{10}Cl_2N_2O_3$. Calculated, %: C, 40.78; H, 3.80; Cl, 26.75; N, 10.57.

***N*-(2,2-Dichloro-1-cyanovinyl)-2-phenylacetamide (8d).** Yield 12.63 g (68 %), colorless solid, mp 150–152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.48 (s, 1H, NH), 7.37 – 7.22 (m, 5H, Ph), 3.67 (s, 2H, CH_2) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.5 (C=O), 134.7, 131.4, 129.1 × 2 (Ar), 128.3 × 2 (Ar), 126.9, 112.6, 111.0, 41.3 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3238 (s, br), 3171, 3070, 3032, 2953, 2920, 2229, 1669 (vs), 1597, 1486 (vs), 1455, 1402, 1343, 1281 (s), 1214, 1176, 1076, 993, 956, 895, 857, 790, 729, 701, 669, 645, 611, 556, 546, 479 cm^{-1}. MS, *m/z* (I_{rel}, %): 255.0 $[M+H]^+$ (100). Found, %: C 51.70; H 3.17; Cl 28.07; N 10.70. $C_{11}H_8Cl_2N_2O$. Calculated, %: C, 51.79; H, 3.16; Cl, 27.79; N, 10.98.

***N*-(2,2-dichloro-1-cyanovinyl)-4-methylbenzamide (10a).** Yield 13.41 g (72 %), colorless solid, mp 145–147 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.56 (s, 1H, NH), 7.84 (d, J = 8.0 Hz, 2H, Ar), 7.35 (d, J = 8.0 Hz, 2H, Ar), 2.38 (s, 3H, CH_3) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.4 (C=O), 141.4, 132.6, 127.4 × 2 (Ar), 127.1, 126.2 × 2 (Ar), 111.2, 109.3, 19.3 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3242 (br), 3176, 3068, 2958, 2916, 2233 (w), 1663 (vs), 1612, 1596, 1521, 1485 (s), 1301 (s), 1271, 1255, 1210, 1187, 1119, 1018, 966, 922, 883, 836, 749, 677, 604, 582, 503 cm^{-1}. MS, *m/z* (I_{rel}, %): 255.0 $[M+H]^+$ (100). Found, %: C 52.05; H 3.14; Cl 27.67; N 11.03. $C_{11}H_8Cl_2N_2O$. Calculated, %: C, 51.79; H, 3.16; Cl, 27.79; N, 10.98.

General procedure for synthesis of oxazoles 11aa-ac, 11ba-bc, 11ca-cc, 11da-dc. Dimethylamine was used as a 10% solution in 1,4-dioxane. Ethyl ester of glycine was used as a freshly prepared base: commercially available hydrochloride of ethyl ester of glycine was dissolved in water (5 mL per 1 g), 1.1 eq 20 % NaOH was added and the base extracted with diethyl ether (thrice with 20 mL); after evaporating the ether, the aminoester was distilled in vacuum of an oil pump (1 Torr).

To the solution of corresponding acrylonitrile **8a–d** (4 mmol) in MeOH (10 mL), cooled to 0 °C, a corresponding amine - dimethylamine, morpholine, and ethyl ester of glycine (14 mmol, 3.5 eq) were added. The temperature was slowly raised to room temperature (25 °C) and the reaction mixture was stirred for about 1 h until the full conversion of the source compound (monitored with TLC).

General procedure for synthesis of oxazoles 11ac, 11bc, 11cc, 11dc. A solution of ethanolamine acetate was prepared be forehand by mixing of ethanolamine (1.21 mL, 20 mmol, 5 eq.) and glacial acetic acid (1.15 mL, 20 mmol, 5 eq.) in methanol (15 mL). The corresponding acrylonitrile **8a–d** (4 mmol) was added to the prepared mixture in one go at rt (25 °C) and the mixture was stirred for about 48 h until the full conversion of the source compound (monitored with TLC). The exothermic effect was not observed because the reaction proceeded slowly in this system.

General procedure for synthesis of oxazoles 11ae, 11be, 11ce, 11de.

The corresponding acrylonitrile **8a–d** (4 mmol) and aniline (1.83 mL, 20 mmol, 5 eq.) were mixed and stirred at room temperature (25 °C) for 24 h. Crystallization of aniline hydrochloride from the reaction mixture could be observed.

General procedure for the extraction and purification of oxazoles 11aa-de. The solvent was evaporated from the reaction mixture in diaphragm pump vacuum (10 Torr) at 30 °C. The residue was diluted with water (15 mL) and extracted with CH_2Cl_2 (2×15 mL), the organic layer was separated, dried over Na_2SO_4, and purified with flash chromatography on silica gel (the eluent is CH_2Cl_2 – methanol (95:5 or 90:10, 85:15) in the case of aminoethanol derivatives and CH_2Cl_2 in other cases). After chromatography, the solvent was evaporated in the water jet pump vacuum, the residue was treated with hexane, and the residue of the target product filtered.

Ethyl 4-cyano-5-(dimethylamino)oxazole-2-carboxylate (11aa). Yield 594 mg (71 %), colorless solid, mp 57–58 °C; R_f = 0.8 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.31 (q, J = 7.0 Hz, 2H, CH_2), 3.16 (s, 6H, $N(CH_3)_2$), 1.29 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.0, 153.9, 140.3, 115.4 (C≡N), 85.6 (C-4 oxazole), 62.0 (OCH_2), 38.3 × 2 (2 NCH_2), 13.9 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3006, 2990, 2945, 2911, 2886, 2810, 2217 (s), 1732 (vs), 1653 (vs), 1556 (s), 1476, 1441, 1420, 1402, 1368, 1335, 1264, 1244, 1179 (s), 1144, 1123, 1101, 1062, 1009, 959, 934, 838, 800, 762, 700, 660, 633, 510 cm^{-1}. MS, *m/z* (I_{rel}, %): 164.0 $[M - OEt]^+$ (100), 210.2 $[M+H]^+$ (80). Found, %: C 51.74; H 5.43; N 19.98. $C_9H_{11}N_3O_3$. Calculated, %: C, 51.67; H, 5.30; N, 20.09.

Ethyl 4-cyano-5-morpholinooxazole-2-carboxylate (11ab). Yield 742 mg (74 %), colorless solid, mp 64–66 °C; R_f = 0.4 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.32 (q, J = 6.9 Hz, 2H, $\underline{CH_2}CH_3$), 3.80 – 3.67 (m, 4H, $O(CH_2)_2$), 3.62 – 3.49 (m, 4H, $N(CH_2)_2$), 1.29 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 160.9, 154.3, 141.3, 115.3 (C≡N), 87.3 (C-4 oxazole), 65.3 × 2 (2 OCH_2), 62.6 (OCH_2), 46.3 × 2 (2 NCH_2), 14.4 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2932, 2867, 2211 (s), 1735 (vs), 1628 (vs), 1560, 1437, 1398, 1374,

1340, 1303, 1283, 1267, 1221, 1205, 1188, 1148, 1129, 1113 (s), 1062, 1038, 1015, 961, 928, 846, 765, 700, 658, 632, 613, 553, 514 cm^{-1}. MS, *m/z* (I_{rel}, %): 252.2 $[M+H]^+$ (100). Found, %: C 52.93; H 5.17; N 16.84. $C_{11}H_{13}N_3O_4$. Calculated, %: C, 52.59; H, 5.22; N, 16.73.

Ethyl 4-cyano-5-((2-ethoxy-2-oxoethyl)amino)oxazole-2-carboxylate (11ad). Yield 504 mg (47 %), colorless solid, mp 78–80 °C; R_f = 0.2 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.38 (br. s, 1H, NH), 4.30 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.20 – 4.13 (m, 4H, 2 CH_2), 1.28 (t, J = 7.1 Hz, 3H, CH_3), 1.21 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 167.1 (C=O), 160.0, 152.0, 139.1, 112.2 (C≡N), 84.3 (C-4 oxazole), 60.3 (OCH_2), 59.4 (OCH_2), 42.0 (NCH_2), 12.2 (CH_3), 12.1 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3291, 3236, 3110, 3075, 2983, 2939, 2236 (s), 1751 (s), 1728 (s), 1648 (vs), 1550 (s), 1487, 1475, 1446, 1418, 1373, 1334, 1276, 1214 (vs), 1181 (s), 1129, 1094, 1013, 846, 763, 717, 665, 632, 565 cm^{-1}. MS, *m/z* (I_{rel}, %): 268.2 $[M+H]^+$ (100). Found, %: C 49.20; H 4.83; N 15.58. $C_{11}H_{13}N_3O_5$. Calculated, %: C, 49.44; H, 4.90; N, 15.72.

Ethyl 4-cyano-5-(phenylamino)oxazole-2-carboxylate (11ae). Yield 687 mg (67 %), colorless solid, mp 158–160 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.07 (s, 1H, NH), 7.40 (t, J = 7.7 Hz, 2H, Ph), 7.34 (d, J = 7.7 Hz, 2H, Ph), 7.16 (t, J = 7.2 Hz, 1H, Ph), 4.33 (q, J = 7.0 Hz, 2H, CH_2), 1.30 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 158.2, 154.0, 141.7, 137.1, 129.3 × 2 (Ph), 124.5, 120.0 × 2 (Ph), 113.4 (C≡N), 89.2 (C-4 oxazole), 62.1 (OCH_2), 13.9 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3281, 3209 (br), 3099, 3048, 2979, 2936, 2900, 2228 (s), 1732 (s), 1648 (vs), 1590, 1554 (s), 1500, 1483, 1448, 1398, 1372, 1332, 1246, 1203 (s), 1157, 1122, 1012, 842, 747, 690, 668, 634, 514, 494 cm^{-1}. MS, *m/z* (I_{rel}, %): 258.0 $[M+H]^+$ (100). Found, %: C 60.67; H 4.43; N 16.26. $C_{13}H_{11}N_3O_3$. Calculated, %: C, 60.70; H, 4.31; N, 16.33.

Methyl 2-(4-cyano-5-(dimethylamino)oxazol-2-yl)acetate (11ba). Yield 743 mg (89 %), colorless solid, mp 94–96 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.86 (s, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.08 (s, 6H, $N(CH_3)_2$) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.3 (C=O), 161.6 (C-5 oxazole), 147.1 (C-2 oxazole), 116.9 (C≡N), 83.3 (C-4 oxazole), 52.9 (OCH_3), 38.8 × 2 ($N(CH_3)_2$), 33.8 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3012, 2979, 2955, 2937, 2885, 2206 (vs), 1731 (vs), 1654 (vs), 1612, 1435, 1413, 1355, 1291, 1212, 1177, 1143, 1111, 1068, 1002, 967, 942, 917, 895, 802, 731, 693, 652, 570, 517 cm^{-1}. MS, *m/z* (I_{rel}, %): 210.2 $[M+H]^+$ (100). Found, %: C 51.82; H 5.25; N 20.13. $C_9H_{11}N_3O_3$. Calculated, %: C, 51.67; H, 5.30; N, 20.09.

Methyl 2-(4-cyano-5-morpholinooxazol-2-yl)acetate (11bb). Yield 877 mg (87 %), colorless solid, mp 69–71 °C; R_f = 0.2 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 – 3.76 (m, 4H, $O(CH_2)_2$), 3.74 (s, 3H, OCH_3), 3.69 (s, 2H, $COCH_2$), 3.55 – 3.49 (m, 4H, $N(CH_2)_2$) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.1 (C=O), 161.1 (C-5 oxazole), 148.1 (C-2 oxazole), 116.1 (C≡N), 85.3 (C-4 oxazole), 65.4 × 2 (2 OCH_2), 52.8 (OCH_3), 46.4 × 2 (2 NCH_2), 33.8 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3027, 2987, 2959, 2924, 2909, 2865, 2217 (s), 1751 (vs), 1640 (vs), 1602 (s), 1450, 1435, 1404, 1391, 1378, 1356, 1286, 1209 (s), 1155, 1126, 1114 (s), 1044, 1000, 935, 923, 897, 849, 798, 694, 667, 649, 587, 565, 532, 511 cm^{-1}. MS, *m/z* (I_{rel}, %): 252.0 $[M+H]^+$ (100). Found, %: C 52.55; H 5.28; N 16.71. $C_{11}H_{13}N_3O_4$. Calculated, %: C, 52.59; H, 5.22; N, 16.73.

Methyl 2-(4-cyano-5-((2-hydroxyethyl)amino)oxazol-2-yl)acetate (11bc). Yield 705 mg (78 %), colorless solid, mp 57–59 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 85:15). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.25 (t, J = 5.6 Hz, 1H, NH), 4.87 (br. s, 1H, OH), 3.85 (s, 2H, $COCH_2$), 3.66 (s, 3H, OCH_3), 3.53 (br. s, 2H, OCH_2), 3.32 – 3.26 (m, 2H, NCH_2). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.3 (C=O), 162.0 (C-5 oxazole), 146.7 (C-2 oxazole), 116.3 (C≡N), 82.1 (C-4 oxazole), 59.9 (OCH_3), 52.8 (OCH_2), 45.8 (NCH_2), 33.8 (CH_2). IR (KBr): $\tilde{\nu}$ = 3448 (br), 3239 (br), 3060, 2979, 2954, 2920, 2881, 2207 (s), 1748, 1723 (vs), 1643 (vs), 1597, 1551, 1448, 1387, 1370, 1353, 1340, 1292, 1258, 1227, 1210, 1179, 1139, 1067, 998, 976, 909, 880, 807, 692, 588 (br), 508 cm^{-1}. MS, *m/z* (I_{rel}, %): 226.2 $[M+H]^+$ (100). Found, %: C 47.86; H 5.03; N 18.60. $C_9H_{11}N_3O_4$. Calculated, %: C, 48.00; H, 4.92; N, 18.66.

Ethyl (4-cyano-2-(2-methoxy-2-oxoethyl)oxazol-5-yl)glycinate (11bd). Yield 890 mg (83 %), colorless solid, mp 42–44 °C; R_f = 0.1 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.64 (t, J = 6.0 Hz, 1H, NH), 4.15 (q, J = 7.0 Hz, 2H, OCH_2), 4.07 (d, J = 6.0 Hz, 2H, NCH_2), 3.87 (s, 2H, $COCH_2$), 3.65 (s, J = 12.7 Hz, 3H, OCH_3), 1.20 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.8 (C=O), 168.2 (C=O), 161.9 (C-5 oxazole), 147.4 (C-2 oxazole), 115.5 (C≡N), 83.5 (C-4 oxazole), 61.5 (OCH_2), 52.8 (OCH_3), 44.3 (NCH_2), 33.8 (CH_2), 14.4 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3306 (s, br), 3019, 2990, 2964, 2940, 2908, 2213 (s), 1749 (vs), 1645 (vs), 1602 (s), 1517, 1475, 1435, 1412, 1387, 1350, 1323, 1281, 1231 (s), 1203 (s), 1169, 1140, 1021, 996, 961, 918, 897, 874, 827, 788, 728, 699, 671, 628, 588, 553, 511 cm^{-1}. MS, *m/z* (I_{rel}, %): 268.2 $[M+H]^+$ (100). Found, %: C 49.39; H 4.94; N 15.51. $C_{11}H_{13}N_3O_5$. Calculated, %: C, 49.44; H, 4.90; N, 15.72.

Methyl 2-(4-cyano-5-(phenylamino)oxazol-2-yl)acetate (11be). Yield 798 mg (78 %), colorless solid, mp 79–81 °C; R_f = 0.25 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.37 (s, 1H, NH), 7.34 (t, J = 7.6 Hz, 2H, Ph), 7.22 (d, J = 7.6 Hz, 2H, Ph), 7.06 (t, J = 6.8 Hz, 1H, Ph), 3.98 (s, 2H, CH_2), 3.69 (d, J = 4.7 Hz, 3H, OCH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.2 (C=O), 157.6 (C-5 oxazole), 149.1 (C-2 oxazole), 138.8, 129.7 × 2 (Ph), 123.7, 119.0 × 2 (Ph), 114.6 (C≡N), 88.4 (C-4 oxazole), 52.9 (OCH_3), 34.0 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3282 (s), 3131, 3063, 3017, 2979, 2938, 2888, 2220, 1718 (vs), 1632 (s), 1599 (s), 1583, 1540, 1496, 1449, 1436, 1409, 1352, 1291, 1245, 1226, 1177, 1158, 1127, 1076, 1001, 975, 903, 807, 779, 747, 724, 691, 650, 548, 508, 489 cm^{-1}. MS, *m/z* (I_{rel}, %): 258.2 $[M+H]^+$ (100). Found, %: C 60.45; H 4.41; N 16.25. $C_{13}H_{11}N_3O_3$. Calculated, %: C, 60.70; H, 4.31; N, 16.33.

Ethyl 3-(4-cyano-5-(dimethylamino)oxazol-2-yl)-propanoate (11ca). Yield 892 mg (94 %), colorless solid, mp 53–55 °C; R_f = 0.4 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR

(400 MHz, DMSO-d_6): δ = 4.07 (q, J = 7.0 Hz, 2H, OCH_2), 3.05 (s, 6H, $N(CH_3)_2$), 2.85 (t, J = 6.8 Hz, 2H, CH_2), 2.68 (t, J = 6.8 Hz, 2H, CH_2), 1.17 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (DMSO-d_6): δ = (126 MHz, DMSO) δ 171.4 (C=O), 160.9 (C-5 oxazole), 152.1 (C-2 oxazole), 116.7 (C≡N), 82.4 (C-4 oxazole), 60.1 (OCH_2), 38.2 × 2 ($N(CH_3)_2$), 29.7 (CH_2), 22.3 (CH_2), 14.0 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3007, 2988, 2966, 2939, 2807, 2201 (vs), 1730 (s), 1655 (vs, br), 1605, 1462, 1430, 1414, 1393, 1371, 1352, 1300, 1271, 1225, 1199, 1171, 1148, 1108, 1093, 1053, 1015, 994, 968, 936, 880, 857, 792, 744, 690, 663, 639, 621, 594, 511, 489 cm^{-1}. MS, *m/z* (I_{rel}, %): 238.2 $[M+H]^+$ (100). Found, %: C 55.80; H 6.33; N 17.69. $C_{11}H_{15}N_3O_3$. Calculated, %: C, 55.69; H, 6.37; N, 17.71.

Ethyl 3-(4-cyano-5-morpholinooxazol-2-yl)propanoate (11cb). Yield 1032 mg (92 %), colorless solid, mp 41–43 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.07 (q, J = 7.1 Hz, 2H, OCH_2), 3.74 – 3.67 (m, 4H, $O(CH_2)_2$), 3.46 – 3.39 (m, 4H, $N(CH_2)_2$), 2.87 (t, J = 6.9 Hz, 2H, CH_2), 2.70 (t, J = 7.0 Hz, 2H, CH_2), 1.17 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.4 (C=O), 160.4 (C-5 oxazole), 153.2 (C-2 oxazole), 115.9 (C≡N), 84.5 (C-4 oxazole), 65.0 × 2 (2 OCH_2), 60.2 (OCH_2), 46.0 × 2 (2 NCH_2), 29.7 (CH_2), 22.4 (CH_2), 14.0 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2989, 2925, 2870, 2208 (s), 1722 (vs), 1636 (vs), 1589 (vs), 1454, 1427, 1404, 1375, 1337, 1277 (s), 1233, 1206, 1187, 1157, 1117 (s), 1068, 1045, 1022, 966, 921, 870, 851, 804, 780, 695, 658, 570, 537, 516 cm^{-1}. MS, *m/z* (I_{rel}, %): 280.0 $[M+H]^+$ (100). Found, %: C 56.03; H 6.18; N 15.05. $C_{13}H_{17}N_3O_4$. Calculated, %: C, 55.91; H, 6.14; N, 15.05.

Ethyl 3-(4-cyano-5-((2-hydroxyethyl)amino)oxazol-2-yl)propanoate (11cc). Yield 786 mg (78 %), colorless solid, mp 39–41 °C; R_f = 0.15 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.08 (t, J = 5.6 Hz, 1H, NH), 4.83 (t, J = 5.2 Hz, 1H, OH), 4.07 (q, J = 7.0 Hz, 2H, OCH_2), 3.55 – 3.48 (m, 2H), 3.30 – 3.24 (m, 2H, partially in water), 2.82 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H), 1.17 (t, J = 7.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.4 (C=O), 161.2 (C-5 oxazole), 151.7 (C-2 oxazole), 116.1 (C≡N), 81.2 (C-4 oxazole), 60.1 (OCH_2), 59.5 (OCH_2), 45.3 (NCH_2), 29.8 (CH_2), 22.3 (CH_2), 14.0 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3401 (br), 3215, 3136, 3093, 2980, 2948, 2936, 2881, 2222 (s), 1735 (s), 1669 (vs), 1605, 1503, 1472, 1452, 1430, 1403, 1378, 1345, 1317, 1221, 1200, 1183, 1157, 1132, 1088, 1071, 1061, 1050, 1044, 1020, 964, 940, 872, 866, 789, 696, 636, 599, 507, 481 cm^{-1}. MS, *m/z* (I_{rel}, %): 254.2 $[M+H]^+$ (100). Found, %: C 52.31; H 5.92; N 16.61. $C_{11}H_{15}N_3O_4$. Calculated, %: C, 52.17; H, 5.97; N, 16.59.

Ethyl 3-(4-cyano-5-((2-ethoxy-2-oxoethyl)amino)oxazol-2-yl)propanoate (11cd). Yield 712 mg (60 %), orange oil; R_f = 0.2 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.50 (t, J = 6.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 4.09 – 4.03 (m, 4H), 2.84 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 6.9 Hz, 2H), 1.23 – 1.14 (m, 6H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 171.6 (C=O), 169.4 (C=O), 161.4 (C-5 oxazole), 152.6 (C-2 oxazole), 115.5 (C≡N), 82.8 (C-4 oxazole), 61.0 (OCH_2), 60.3 (OCH_2), 44.0 (NCH_2), 29.9 (CH_2), 22.6 (CH_2), 14.2 (CH_3), 14.1 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 2984, 2938, 2909, 2214, 1731 (s), 1643 (vs), 1600, 1442, 1421, 1396, 1374, 1352, 1193 (vs), 1163 (s), 1139, 1096, 1019, 997, 935, 860, 791, 699, 582, 569, 511 cm^{-1}. MS, *m/z* (I_{rel}, %): 296.2 $[M+H]^+$ (100). Found, %: C 52.99; H 5.82; N 14.18. $C_{13}H_{17}N_3O_5$. Calculated, %: C, 52.88; H, 5.80; N, 14.23.

Ethyl 3-(4-cyano-5-(phenylamino)oxazol-2-yl)propanoate (11ce). Yield 767 mg (67 %), brown solid, mp 118–120 °C; R_f = 0.35 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.24 (s, 1H, NH), 7.34 (t, J = 7.9 Hz, 2H, H-3,5 Ph), 7.21 (d, J = 7.7 Hz, 2H, H-2,6 Ph), 7.05 (t, J = 7.4 Hz, 1H, H-4 Ph), 4.08 (q, J = 7.4 Hz, 2H, OCH_2), 2.95 (t, J = 7.0 Hz, 2H, CH_2), 2.73 (t, J = 7.1 Hz, 2H, CH_2), 1.17 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 171.5 (C=O), 156.8 (C-5 oxazole), 154.4 (C-2 oxazole), 138.8, 129.4 × 2 (Ph), 123.1, 118.4 × 2 (Ph), 114.6 (C≡N), 88.1 (C-4 oxazole), 60.3 (OCH_2), 30.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3329, 3280, 3226, 3152, 3109, 3077, 3017, 2982, 2934, 2224 (s), 1726 (s), 1677 (vs), 1604, 1588, 1516, 1502, 1440, 1423, 1400, 1387, 1325, 1256, 1221, 1193, 1156, 1117, 1067, 1018, 955, 932, 894, 884, 876, 864, 798, 753, 688, 652, 495 cm^{-1}. MS, *m/z* (I_{rel}, %): 286.0 $[M+H]^+$ (100). Found, %: C 63.27; H 5.24; N 14.77. $C_{15}H_{15}N_3O_3$. Calculated, %: C, 63.15; H, 5.30; N, 14.73.

2-Benzyl-5-(dimethylamino)oxazole-4-carbonitrile (11da). Yield 770 mg (85 %), yellow solid, mp 43–45 °C; R_f = 0.7 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.33 (t, J = 7.4 Hz, 2H, Ph), 7.30 – 7.23 (m, 3H, Ph), 3.98 (s, 2H, CH_2), 3.02 (s, 6H, $N(CH_3)_2$). ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 161.5 (C-5 oxazole), 152.1 (C-2 oxazole), 135.5, 129.1 × 2 (Ph), 129.0 × 2 (Ph), 127.4, 117.1 (C≡N), 83.1 (C-4 oxazole), 38.7 × 2 ($N(CH_3)_2$), 33.6 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3083, 3065, 3035, 3009, 2919 (br), 2811, 2206 (s), 1655 (vs), 1599 (s), 1495, 1451, 1443, 1413, 1279, 1236, 1175, 1144 (s), 1109, 1066, 1029, 960, 933, 903, 848, 794, 736 (vs), 705 (s), 691 (s), 647, 597, 571, 512 cm^{-1}. MS, *m/z* (I_{rel}, %): 228.0 $[M+H]^+$ (100). Found, %: C 68.38; H 5.65; N 18.60. $C_{13}H_{13}N_3O$. Calculated, %: C, 68.70; H, 5.77; N, 18.49.

2-Benzyl-5-morpholinooxazole-4-carbonitrile (11db). Yield 874 mg (81 %), white solid, mp 92–94 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 – 7.28 (m, 2H, Ph), 7.28 – 7.20 (m, 3H, Ph), 3.92 (s, 2H, Ph$\underline{CH_2}$), 3.78 – 3.70 (m, 4H, $O(CH_2)_2$), 3.50 – 3.41 (m, 4H, $O(CH_2)_2$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ = 160.77 (C-5 oxazole), 153.0 (C-2 oxazole), 134.4, 128.9 × 2 (Ph), 128.7 × 2 (Ph), 127.4, 115.6 (C≡N), 86.4 (C-4 oxazole), 65.7 × 2 (2 OCH_2), 46.4 × 2 (2 NCH_2), 34.3 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3066, 3032, 2979, 2931, 2908, 2873, 2851, 2205 (vs), 1635 (vs), 1580, 1493, 1448, 1431, 1371, 1278, 1205, 1192, 1112 (vs), 1069, 1043, 1025, 920, 849, 735, 707, 695, 657, 627, 580 cm^{-1}. MS, *m/z* (I_{rel}, %): 270.2 $[M+H]^+$ (100). Found, %: C 66.77; H 5.69; N 15.54. $C_{15}H_{15}N_3O_2$. Calculated, %: C, 66.90; H, 5.61; N, 15.60.

2-Benzyl-5-((2-hydroxyethyl)amino)oxazole-4-carbonitrile (11dc). Yield 573 mg (59 %), light-brown solid, mp 66–68 °C; R_f = 0.15 (CH_2Cl_2–MeOH, 95:5). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.12 (t, J = 5.7 Hz, 1H, NH), 7.34 (t, J = 7.4 Hz, 2H, Ph), 7.29 – 7.23 (m, 3H, Ph), 4.82 (t, J = 5.4 Hz, 1H, OH), 3.96 (s, 2H, Ph$\underline{CH_2}$), 3.50 (q, J = 5.6

Hz, 2H, OCH_2), 3.26 (q, J = 5.7 Hz, 2H, NCH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.6 (C-5 oxazole), 151.7 (C-2 oxazole), 135.5, 129.0 × 2 (Ph), 128.9 × 2 (Ph), 127.2, 116.4 (C≡N), 81.4 (C-4 oxazole), 59.6 (OCH_2), 45.6 (NCH_2), 33.4 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3324, 3279 (br), 3069, 2950, 2923, 2866, 2205 (vs), 1664 (vs), 1644 (vs), 1595, 1547, 1496, 1444, 1422, 1380, 1344, 1268, 1235, 1166, 1143, 1070 (vs), 1056, 970, 865, 812, 753, 730, 696, 681, 582, 510 cm^{-1}. MS, *m/z* (I_{rel}, %): 244.0 $[M+H]^+$ (100). Found, %: C 64.32; H 5.37; N 17.18. $C_{13}H_{13}N_3O_2$. Calculated, %: C, 64.19; H, 5.39; N, 17.27.

Ethyl (2-benzyl-4-cyanooxazol-5-yl)glycinate (11dd). Yield 773 mg (68 %), colorless solid, mp 34–36 °C; R_f = 0.3 (CH_2Cl_2–MeOH, 95:5). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.17 (m, 5H, Ph), 5.75 – 5.65 (m, 1H, NH), 4.21 (q, J = 7.1 Hz, 2H, $\underline{CH_2}CH_3$), 4.06 (d, J = 5.6 Hz, 2H, NCH_2), 3.91 (s, 2H, Ph$\underline{CH_2}$), 1.25 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.0 (C=O), 160.2 (C-5 oxazole), 153.0 (C-2 oxazole), 134.4, 128.8 × 2 (Ph), 128.7 × 2 (Ph), 127.4, 114.6 (C≡N), 85.6 (C-4 oxazole), 62.2 (OCH_2), 44.6 (NCH_2), 34.2 (CH_2), 14.1 (CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3312, 3277, 3235, 3124, 3068, 2982, 2964, 2938, 2217 (vs), 1743 (vs), 1667 (vs), 1596, 1492, 1459, 1444, 1409, 1390, 1368, 1350, 1296, 1282, 1221, 1201, 1173, 1142, 1096, 1075, 1018, 999, 944, 862, 825, 752, 703, 665, 590, 512 cm^{-1}. MS, *m/z* (I_{rel}, %): 286.2 $[M+H]^+$ (100). Found, %: C 63.18; H 5.22; N 14.64. $C_{15}H_{15}N_3O_3$. Calculated, %: C, 63.15; H, 5.30; N, 14.73.

2-Benzyl-5-(phenylamino)oxazole-4-carbonitrile (11de). Yield 802 mg (73 %), colorless solid, mp 98–100 °C; R_f = 0.5 (CH_2Cl_2–MeOH, 95:5). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.33 (s, 1H, NH), 7.40 – 7.24 (m, 7H, Ph), 7.18 (d, J = 8.0 Hz, 2H, Ph), 7.04 (t, J = 7.2 Hz, 1H, Ph), 4.09 (s, 2H, CH_2) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 156.9 (C-5 oxazole), 153.9 (C-2 oxazole), 138.4, 135.0, 129.2 × 2 (Ph), 128.9 × 2 (Ph), 128.7 × 2 (Ph), 127.1, 123.0, 118.4 × 2 (Ph), 114.4 (C≡N), 87.8 (C-4 oxazole), 33.3 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3318, 3261, 3221, 3137, 3098, 3062, 3028, 2994, 2219 (s), 1665 (vs), 1603, 1583, 1499, 1453, 1418, 1245, 1190, 1156, 1116, 1030, 948, 891, 746, 690, 644, 509, 496 cm^{-1}. MS, *m/z* (I_{rel}, %): 276.2 $[M+H]^+$ (100). Found, %: C 74.30; H 4.64; N 15.16. $C_{17}H_{13}N_3O$. Calculated, %: C, 74.17; H, 4.76; N, 15.26.

General procedure for synthesis of oxazoles 12 and 13. To a cooled (5 °C) solution of the corresponding acrylonitrile **8a,b** (2 mmol) in MeOH (20 mL), ethanolamine (1.21 mL, 20 mmol, 10 eq.) was added. The resulting mixture was stirred at rt (25 °C) for 12 h. The extraction and purification of the product was performed according to the procedure for oxazoles **11** given above.

4-Cyano-*N*-(2-hydroxyethyl)-5-((2-hydroxyethyl)amino)-oxazole-2-carboxamide (12). Yield 251 mg (52 %), colorless solid, mp 120–122 °C R_f = 0.1 (CH_2Cl_2–MeOH, 90:10). ^1H NMR (500 MHz, DMSO-d_6): δ = 8.72 (br. s, 1H, NH), 8.55 (t, J = 5.5 Hz, 1H, NH), 4.90 (t, J = 5.2 Hz, 1H, OH), 4.73 (t, J = 5.5 Hz, 1H, OH), 3.55 (q, J = 5.4 Hz, 2H), 3.45 (q, J = 5.8 Hz, 2H), 3.37 (br. q, J = 5.0 Hz, 2H), 3.24 (q, J = 5.8 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.2 (C-5 oxazole), 154.3, 143.9, 115.5 (C≡N), 83.6 (C-4 oxazole), 59.9 (OCH_2), 59.8 (OCH_2), 45.8 (NCH_2), 42.1 (NCH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3484 (br), 3408 (br), 3296, 3253 (s), 3204 (br), 3100, 2944, 2927, 2892, 2218 (s), 1664 (vs), 1635, 1567 (s), 1474 (s), 1431, 1366, 1345, 1280, 1245, 1215, 1202, 1083, 1056 (s), 954, 886, 868, 812, 708, 674, 658, 629, 560, 506 cm^{-1}. MS, *m/z* (I_{rel}, %): 241 $[M+H]^+$ (100). Found, %: C 45.80; H 5.12; N 23.24. $C_9H_{12}N_4O_4$. Calculated, %: C, 45.00; H, 5.04; N, 23.32.

2-(4-Cyano-5-((2-hydroxyethyl)amino)oxazol-2-yl)-*N*-(2-hydroxyethyl)acetamide (13). Yield 293 mg (58 %), colorless oil; R_f = 0.3 (CH_2Cl_2–MeOH, 85:15). ^1H NMR (400 MHz, DMSO-d_6): δ = 8.28 – 8.00 (m, 2H), 4.93 – 4.78 (m, 1H, OH), 4.78 – 4.61 (m, 1H, OH), 3.52 (br. s, 4H), 3.47 – 3.38 (m, 2H), 3.32 – 3.23 (m, 2H), 3.20 – 3.06 (m, 2H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.25 (C=O), 161.9 (C-5 oxazole), 148.5 (C-2 oxazole), 116.4 (C≡N), 82.0 (C-4 oxazole), 60.1 (OCH_2), 59.9 (OCH_2), 45.8 (NCH_2), 42.2 (NCH_2), 35.3 (CH_2) ppm. IR (ATR): $\tilde{\nu}$ = 3600 – 3150 (br), 2956, 2882, 2211, 1741, 1642 (vs), 1601, 1530, 1438, 1405, 1351, 1261, 1205, 1177, 1135, 1062, 1003, 899, 868, 805, 735, 698, 648, 633, 576, 549, 511 cm^{-1}. MS, *m/z* (I_{rel}, %): 255.2 $[M+H]^+$ (100). Found, %: C 47.53; H 5.42; N 21.95. $C_{10}H_{14}N_4O_4$. Calculated, %: C, 47.24; H, 5.55; N, 22.04.

Methyl 4-amino-5-(dichloromethylene)-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate (14). To a solution of acrylonitrile **8b** (0.474 g, 2 mmol) in MeOH (10 mL), Et_3N (0.56 mL, 4 mmol, 2 eq.) was added and the resulting mixture was stirred for 12 h at rt (25 °C). MeOH was evaporated in water jet pump vacuum, and the residue was treated with glacial acetic acid (0.23 mL, 4 mmol, 2 eq.) and brine (10 mL). The formed precipitated was filtered and recrystallized from EtOH. Yield 447 mg (94 %), light-brown solid, mp 205–207 °C; R_f = 0.45 (CH_2Cl_2–MeOH, 85:15). ^1H NMR (500 MHz, DMSO-d_6): δ = 9.81 (s, 1H), 8.24 (br. s, 1H), 7.70 (br. s, 1H), 3.68 (s, 3H, OCH_3) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 165.5, 165.4, 158.8, 130.9, 104.0, 90.3, 50.8 ppm. IR (KBr): $\tilde{\nu}$ = 3489 (s, br), 3415 (s, br), 3318 (s, br), 3299 (s, br), 2957, 1708 (vs), 1674 (vs), 1610 (vs), 1537 (vs), 1471, 1369, 1340, 1273, 1216, 1190, 1104 (vs), 977, 955, 893, 801, 748, 720, 666, 596, 517, 485 cm^{-1}. MS, *m/z* (I_{rel}, %): 205.0 $[M - OMe]^+$ (100), 237.0 $[M+H]^+$ (65). Found, %: C 35.56; H 2.53; Cl 30.04; N 11.80. $C_7H_6Cl_2N_2O_3$. Calculated, %: C, 35.47; H, 2.55; Cl, 29.91; N, 11.82.

Ethyl (4-cyano-2-((2-ethoxy-2-oxoethyl)carbamoyl)-oxazol-5-yl)glycinate (15). The base of ethyl ester of glycine was prepared as per above. To a solution of acrylonitrile **8a** (0.474 g, 2 mmol) in MeOH (10 mL), cooled up to +5 °C, a methanol solution of ethyl ester of glycine (20 mmol, 10 eq.) was added dropwise. The reaction mixture was stirred at rt (25 °C) for 12 h. The extraction and purification of the product was performed according to the procedure for oxazoles **11**, given above. Yield 362 mg (56 %), colorless solid, mp 160–162 °C; R_f = 0.1 (CH_2Cl_2–MeOH, 95:5). ^1H NMR (500 MHz, DMSO-d_6): δ = 9.22 (br. s, 1H), 9.12 (t, J = 5.7 Hz, 1H), 4.21 – 4.14 (m, 4H), 4.11 (qd, J = 7.0 Hz, J = 1.7 Hz, 2H), 3.93 (d, J = 5.6 Hz, 2H), 1.25 – 1.15 (m, 6H) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 169.0 (C=O), 168.9 (C=O), 161.6 (C-5 oxazole), 153.8, 143.4, 114.1 (C≡N), 84.5 (C-4 oxazole),

61.1 (OCH_2), 60.5 (OCH_2), 43.7 (NCH_2), 40.8 (NCH_2), 13.9 (CH_3), 13.8 (CH_3) ppm. IR (KBr): ṽ = 3350 (s), 3235 (s, br), 3050, 2987, 2907, 2216 (s), 1745 (vs), 1727 (vs), 1685 (vs), 1636 (vs), 1563 (vs), 1530, 1472, 1426, 1395, 1378, 1358, 1346, 1302, 1266, 1235, 1213 (vs, br), 1195, 1118, 1096, 1020, 991, 864, 834, 720, 676, 659, 616, 574, 513 cm^{-1}. MS, *m/z* (I_{rel}, %): 325.2 $[M+H]^+$ (100). Found, %: C 48.02; H 5.03; N 17.21. $C_{13}H_{16}N_4O_6$. Calculated, %: C, 48.15; H, 4.97; N, 17.28.

2,2'-(1,2-Phenylene)bis(*N*-(2,2-dichloro-1-cyanovinyl)-acetamide) (16). ADAN (5 g, 0.0365 mol) and *N,N*-dimethylaniline (13.88 mL, 0.110 mol, 3 eq.) were dissolved in CH_2Cl_2 (50 mL) at rt (25 °C), then 2,2'-(1,2-phenylene)diacetyl chloride (4.22 g, 0.0183 mol, 0.5 eq.) was added and the mixture stirred for 6 h. The formed precipitate was filtered and washed sequentially with CH_2Cl_2 (30 mL) and water (30 mL). The product obtained in this way was usually pure enough to be used in further reactions. If necessary, the compound **16** could be recrystallized from THF. Yield 5.30 g (67 %), colorless solid, mp >250 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.54 (s, 2H, 2NH), 7.32– 7.17 (m, 4H, Ar), 3.78 (s, 4H, $2CH_2$). ^{13}C NMR (151 MHz, DMSO-d_6): δ = 169.3 × 2 (2 C=O), 134.0 × 2, 131.2 × 2, 130.4 × 2, 127.1 × 2, 112.5 × 2, 110.9 × 2, 38.8 × 2 (2 CH_3) ppm. IR (KBr): ṽ = 3249 (s, br), 3082, 2961, 2920, 2233, 1774, 1676 (vs), 1601, 1495 (vs), 1438, 1344, 1288 (s), 1231, 1158, 1119, 998, 962, 895, 778, 743, 662, 642, 559 cm^{-1}. MS, *m/z* (I_{rel}, %): 433.0 $[M+H]^+$ (100). Found, %: C 48.03; H 2.26; Cl 33.02; N 12.81. $C_{16}H_{10}Cl_4N_4O_2$. Calculated, %: C, 44.48; H, 2.33; Cl, 32.82; N, 12.97. Crystal data for **16** (CCDC 2072868): $C_{16}H_{10}Cl4\ N_4O2$ x C4 H8 O2, M= 520.18, triclinic, space group P 1, *a* = 4.8163(5), *b* = 11.2820(12), *c* = 12.2283(11)Å, α =62.899(6), β =85.957(6) γ = 83.176(7)°, V = 587.21(11)Å^3, Z = 1, d_c = 1.471, μ 0.538 мм$^{-1}$, F(000) 266, crystal size ca. 0.08 x 0.22 x 0.43mm.

2,2'-(1,2-Phenylenebis(methylene))bis(5-(dimethyl-amino)oxazole-4-carbonitrile) (17). The corresponding dinitrile **16** (1 g, 2.31 mmol) was added to 20% methanol solution of dimethylamine (30 mL) and the mixture was heated at 50 °C with stirring for 2 h. The reaction mixture was evaporated in water jet pump vacuum, the residue suspended in water (20 mL), the target product precipitate was filtered and recrystallized from MeOH. Yield 693 mg (80 %), colorless solid, mp 153–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.28 (s, 4H, Ar), 4.04 (s, 4H, 2 CH_2), 3.02 (s, 6H, 2 $N(CH_3)_2$) ppm. ^{13}C NMR (151 MHz, DMSO-d_6): δ = 161.3 × 2 (2 C-5 oxazole), 151.7 × 2 (2 C-2 oxazole), 134.2 × 2, 131.2 × 2, 128.1 × 2, 117.0 × 2 (2 C≡N), 83.1 × 2 (2 C-4 oxazole), 38.7 × 4 (2 $N(CH_3)_2$), 31.7 × 2 (2 CH_2) ppm. IR (KBr): ṽ = 3023, 2912 (br), 2812, 2203 (vs), 1645 (vs), 1597 (s), 1494, 1446, 1411, 1269, 1239, 1155, 1143, 1111, 1066, 936, 909, 775, 747 (s), 694, 647, 624, 602, 570, 514 cm^{-1}. MS, *m/z* (I_{rel}, %): 377.2 $[M+H]^+$ (100). Found, %: C 63.79; H 5.42; N 22.26. $C_{20}H_{20}N_6O_2$. Calculated, %: C, 63.82; H, 5.36; N, 22.33.

General procedure for synthesis of macrocycles 18a, b. The corresponding dinitrile **16** (1 g, 2.31 mmol) was dissolved in THF (200 mL) at rt (25 °C), and a solution of the corresponding diamine (6.94 mmol, 3 eq.) with triethylamine (1.94 mL, 13.9 mmol, 6 eq.) in MeOH (100 mL) was added dropwise while stirring. The resulting mixture was heated at 50 °C with stirring for 24 h, then cooled, evaporated in water jet pump vacuum, the residue suspended with water (40 mL) and the target product precipitate filtered and purified with flash chromatography on silica gel, using THF as eluent.

6,10-Diaza-1,5(2,5)-dioxazola-3(1,2)-benzenacyclo-decaphane-1^4,5^4-dicarbonitrile (18a). Yield 256 mg (31 %), orange solid, mp 188–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.06 – 7.98 (m, 0.4H), 7.83 (br. t, *J* = 5.3 Hz, 1.6H), 7.33 – 7.22 (m, 4H), 4.00 (s, 4H), 3.28 – 3.20 (m, 4H), 1.78 – 1.74 (m, 0.4H), 1.74 – 1.66 (m, 1.6H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.3 × 2 (2 C-5 oxazole), 151.2 × 2 (2 C-2 oxazole), 134.0 × 2, 131.3 × 2, 127.8 × 2, 115.5 × 2 (2 C≡N), 82.7 × 2 (2 C-4 oxazole), 39.5 × 2 (2 NCH_2), 31.2 × 2 (2 Ar$\underline{CH_2}$), 28.0 (CH_2) ppm. IR (KBr): ṽ = 3640, 3297 (br), 3273 (br), 2953 (br), 2874 (br), 2209 (s), 1645 (vs), 1599, 1494, 1427, 1362, 1222, 1196, 1160, 1128, 1085, 1056, 953, 939, 790, 745, 694, 625, 599, 513 cm^{-1}. MS, *m/z* (I_{rel}, %): 361.2 $[M+H]^+$ (100). Found, %: C 63.11; H 4.59; N 23.15. $C_{19}H_{16}N_6O_2$. Calculated, %: C, 63.33; H, 4.48; N, 23.32.

6,11-Diaza-1,5(2,5)-dioxazola-3(1,2)-benzenacyclo-undecaphane-1^4,5^4-dicarbonitrile (18b). Yield 425 mg (49 %), green solid, mp 248–250 °C. ^{1}H NMR (DMSO-d_6): δ = 1.55 (4H, br. s, 2 $NHCH_2\underline{CH_2}$), 3.15 (4H, d, *J* = 5.8 Hz, 2 NH). ^{13}C NMR (DMSO-d_6): δ = 161.5 × 2 (2 C-5 oxazole), 151.5 × 2 (2 C-2 oxazole), 134.2 × 2, 131.3 × 2, 128.2 × 2, 116.3 × 2 (C≡N), 82.1 × 2 (C-4 oxazole), 42.6 × 2 (2 NCH_2), 31.3 × 2 (2 Ar$\underline{CH_2}$), 25.3 × 2 (2 CH_2) ppm. IR (KBr): ṽ = 3235 (s, br), 3076, 2953, 2921, 2853, 2233, 1677 (vs), 1601, 1494 (s), 1435, 1406, 1355, 1343, 1286 (s), 1204, 1171, 1157, 997, 962, 947, 931, 893, 778, 741, 661, 643, 615, 580, 560 cm^{-1}. MS, *m/z* (I_{rel}, %): 375 $[M+H]^+$ (100). Found, %: C 64.09; H 4.97; N 22.31. $C_{20}H_{18}N_6O_2$. Calculated, %: C, 64.16; H, 4.85; N, 22.45.

2-(4-Cyano-5-(dimethylamino)oxazol-2-yl)-*N*-methyl-acetamide (19). To a 20 % methanol solution of methylamine (5 mL) the corresponding ester **11ba** (0.209 g, 1 mmol) was added and the mixture was heated at 40–45 °C while stirring for 1 h. Evaporating the resulting mixture in water jet pump vacuum gave the spectrally pure target product. Yield 197 mg (95 %), colorless solid, mp 141–143 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.01 (br. s, 1H), 3.52 (s, 2H, CH_2), 3.06 (s, 6H, $N(CH_3)_2$), 2.60 (d, *J* = 4.6 Hz, 3H, $NH\underline{CH_3}$) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 166.0 (C=O), 161.2 (C-5 oxazole), 148.4 (C-2 oxazole), 116.6 (C≡N), 82.8 (C-4 oxazole), 38.3 × 2 ($N(CH_3)_2$), 34.8 ($NHCH_3$), 25.7 (CH_2) ppm. IR (KBr): ṽ = 3266 (vs, br), 3084, 2992, 2949, 2930, 2233, 1728 (vs), 1675 (vs), 1605, 1490 (vs), 1417, 1367, 1331 (s), 1281 (s), 1204, 1177 (s), 1160 (s), 1117, 1030, 998, 962, 943, 893, 868, 819, 809, 771, 649, 613, 559, 476 cm^{-1}. MS, *m/z* (I_{rel}, %): 209.1 $[M+H]^+$ (100). Found, %: C 51.85; H 5.76; N 27.05. $C_9H_{12}N_4O_2$. Calculated, %: C, 51.92; H, 5.81; N, 26.91.

Methyl 2-(4-cyano-5-(dimethylamino)oxazol-2-yl)-3-(dimethylamino)acrylate (20). To a solution of oxazole **11ba** (3 g, 14.3 mmol) in MeOH (10 mL), DMFDMA (5.74 mL, 43.0 mmol, 3 eq.) was added, and the reaction

mixture was refluxed for 3–4 h until the full conversion of the source compound (monitored with TLC). The reaction mixture was cooled, the formed precipitate was filtered and washed with cold MeOH (10 mL), resulting in the spectrally clear target product. Yield 2.47 g (65 %), colorless solid, mp 169–171 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.64 (s, 1H, =CH), 3.55 (s, 3H, CH_3), 3.34 (s, 3H, CH_3), 3.14 (br. s, 3H, CH_3), 3.07 (s, 6H, $N(CH_3)_2$) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 167.5 (C=O), 161.0 (C-5 oxazole), 153.8, 147.4, 116.9 (C≡N), 83.0, 82.7, 50.9, 46.6 (br), 38.3 × 2 ($N(CH_3)_2$) ppm. IR (KBr): $\tilde{\nu}$ = 2982, 2943, 2923, 2907, 2819, 2205 (s), 1703 (s), 1641 (s), 1609 (vs), 1474, 1429, 1414, 1377, 1291 (s), 1266, 1218 (s), 1185, 1151, 1097 (s), 1041, 964, 937, 919, 842, 769, 748, 697, 670, 520 cm^{-1}. MS, *m/z* (I_{rel}, %): 233.0 [M - OMe]$^+$ (70), 265.2 [M+H]$^+$ (100). Found, %: C 54.34; H 6.02; N 21.23. $C_{12}H_{16}N_4O_3$. Calculated, %: C, 54.54; H, 6.10; N, 21.20.

5-(Dimethylamino)-2-(2-oxo-1-phenylethyl)oxazole-4-carbonitrile (21). To a solution of oxazole **11da** (3 g, 13.2 mmol) in diethyl ether (30 mL), methyl formate (3 mL, 49.0 mmol, 3.7 eq.) and MeONa (0.784 g, 14.5 mmol, 1.1 eq.) were added and the reaction mixture was refluxed in argon atmosphere while stirring for 6 h. After the reaction mixture was cooled, the sodium enolate of the formylation product precipitated. The precipitate was filtered, washed with diethyl ether (to remove the nonreacted source oxazole), dissolved in water (50 mL) and treated with glacial acetic acid (5 mL). The formed precipitate of the target product was filtered, washed with water and recrystallized from the mixture of acetonitrile-water 1:1. Yield 2.02 g (60 %), colorless solid, mp 121–123 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.97 (br. s, 1H, OH), 7.45 – 7.28 (m, 5H, Ph), 7.08 (s, 1H, =CH), 3.12 (s, 6H, $N(CH_3)_2$) ppm. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.55 (br. s, 1H, OH), 7.51 (s, 1H, =CH), 7.43 (d, *J* = 7.4 Hz, 2H, Ph), 7.34 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H, Ph), 3.07 (s, 6H, $N(CH_3)_2$) ppm (the spectra shows two main signal groups of *E*- and *Z*-diastereomers; the chemical shifts of the the dominating form are given). ^{13}C NMR APT (126 MHz, $CDCl_3$): δ = 159.0 (C), 153.2 (CH), 152.1 (C), 133.4 (C), 128.7 × 2 (CH, Ph), 128.4 × 2 (CH, Ph), 127.4 (CH), 116.0 (C≡N), 104.5 (C), 83.5 (C-4 oxazole), 39.0 × 2 ($N(CH_3)_2$) ppm. ^{13}C NMR APT (126 MHz, DMSO-d_6): δ = 159.9 (C), 151.4 (C), 147.9 (CH), 132.7 (C), 129.5 × 2 (CH, Ph), 127.5 × 2 (CH, Ph), 126.4 (CH), 116.9 (C≡N), 104.9 (C), 83.0 (C-4 oxazole), 38.2 × 2 ($N(CH_3)_2$) ppm (the spectra shows two main signal groups of *E*- and *Z*-diastereomers; the chemical shifts of the the dominating form are given). IR (KBr): $\tilde{\nu}$ = 2931, 2814, 2205 (s), 1652 (vs), 1621 (s), 1550, 1493, 1442, 1419, 1368, 1315, 1272, 1254, 1229, 1154 (s), 1074, 984, 944, 901, 776, 736, 708, 683, 646, 512 cm^{-1}. MS, *m/z* (I_{rel}, %): 256.2 [M+H]$^+$ (100). Found, %: C 65.75; H 4.98; N 16.54. $C_{14}H_{13}N_3O_2$. Calculated, %: C, 65.87; H, 5.13; N, 16.46.

2-Cyano-*N*,*N*-dimethyl-2-((4-phenyl-1*H*-pyrazol-3-yl)-amino)acetamide (22). To a solution of product **21** (1 g, 3.92 mmol) in EtOH (10 mL), 80% water solution of hydrazine hydrate (0.48 mL, 7.84 mmol, 2 eq.) was added, and the mixture was heated at 50 °C with stirring for 30 minutes (overheating the reaction mixture must be avoided – the prolonged reflux results in a non-identified polycomponent mixture). The obtained mixture was evaporated in water jet pump vacuum, the remaining product **22** was dissolved in CH_2Cl_2 (30 mL) and purified by flash chromatography in the CH_2Cl_2 – methanol 90:10 system; R_f = 0.3. Yield 614 mg (58 %), colorless solid, mp 73–75 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56 (s, 1H, H-5 pyrazole), 7.50 – 7.36 (m, 4H, H-2,3,5,6 Ph), 7.28 (t, *J* = 6.7 Hz, 1H, H-4 Ph), 5.51 (d, *J* = 7.4 Hz, 1H, COCH), 5.38 (br. d, *J* = 7.4 Hz, 1H, NH), 3.21 (s, 3H, CH_3), 3.08 (s, 3H, CH_3) ppm; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.16 (s, 1H, NH pyrazole), 7.87 (s, 1H, H-5 pyrazole), 7.48 (d, *J* = 7.4 Hz, 2H, H-2,6 Ph), 7.35 (t, *J* = 7.7 Hz, 2H, H-3,5 Ph), 7.18 (t, *J* = 7.4 Hz, 1H, H-4 Ph), 6.00 (d, *J* = 8.7 Hz, 1H, NH), 5.71 (d, *J* = 8.8 Hz, 1H, COCH), 3.05 (s, 3H, CH_3), 2.90 (s, 3H, CH_3) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.9 (C=O), 149.9 (C-3 pyrazole), 133.3 (C-1 Ph), 129.1 × 2 (C-3,5 Ph), 128.7 (C-5 pyrazole), 126.6 × 2 (C-2,6 Ph), 125.9 (C-4 Ph), 117.7 (C≡N), 107.8 (C-4 pyrazole), 48.1 (COCH), 37.1 (CH_3), 36.4 (CH_3). MS, *m/z* (I_{rel}, %): 270.2 [M+H]$^+$ (100). Found, %: C 62.66; H 5.54; N 25.89. $C_{14}H_{15}N_5O$. Calculated, %: C, 62.44; H, 5.61; N, 26.01.

General procedure for synthesis of coumarins 24a,b. The corresponding oxazole **11ba** or **11be** (2 mmol) was dissolved in EtOH (15 mL), and salicylic aldehyde (**23**, 0.25 mL, 2.4 mmol, 1.2 eq.) with 1–2 drops of piperidine were added, and the mixture refluxed with stirring for 1 h. Then glacial acetic acid (1 mL) was added and the mixture refluxed for 2 h. After cooling the mixture, the formed precipitate was filtered and washed with cold EtOH (10 mL), giving the spectrally pure target product.

5-(Dimethylamino)-2-(2-oxo-2*H*-chromen-3-yl)oxazole-4-carbonitrile (24a). Yield 483 mg (86 %), light green solid, mp 218–220 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.62 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.47 – 7.36 (m, 2H), 3.20 (s, 6H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.1 (C-5 oxazole), 156.0, 153.7, 145.5, 142.0, 133.6, 129.8, 125.4, 118.9, 116.8, 116.5, 113.6, 85.3 (C-4 oxazole), 38.8 × 2 ($N(CH_3)_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3056, 3042, 2930, 2884, 2816, 2200 (s), 1743 (vs), 1642 (vs), 1603, 1545, 1489, 1449, 1420, 1384, 1256, 1237, 1215, 1159, 1127, 1071, 970, 939, 919, 824, 768, 738, 695, 669, 619, 591, 464 cm^{-1}. MS, *m/z* (I_{rel}, %): 282.2 [M+H]$^+$ (100). Found, %: C 63.88; H 3.82; N 14.96. $C_{15}H_{11}N_3O_3$. Calculated, %: C, 64.05; H, 3.94; N, 14.94.

2-(2-Oxo-2*H*-chromen-3-yl)-5-(phenylamino)oxazole-4-carbonitrile (24b). Yield 495 mg (75 %), yellow solid, mp 237–239 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.80 (s, 1H), 8.64 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.48 – 7.33 (m, 6H), 7.10 (t, *J* = 6.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.3, 156.4, 154.0, 147.5, 142.9, 138.5, 133.8, 130.1, 129.8 × 2, 125.4, 123.9, 119.2 × 2, 118.8, 116.6, 114.6, 113.9, 89.5 (C-4 oxazole) ppm. IR (KBr): $\tilde{\nu}$ = 3297, 3211, 3121, 3093, 3048, 2993, 2216 (s), 1747 (vs), 1648 (vs), 1603, 1584 (s), 1549, 1497 (s), 1454, 1418, 1383, 1313, 1254, 1216, 1186, 1154, 1135, 1109, 1029, 963, 922, 831, 766, 745, 691, 651, 625, 569, 497, 458 cm^{-1}. MS, *m/z* (I_{rel}, %): 330.2 [M+H]$^+$ (100). Found, %: C 68.98; H 3.38; N 12.49. $C_{19}H_{11}N_3O_3$. Calculated, %: C, 69.30; H, 3.37; N, 12.76.

General procedure for synthesis of acids 25a-c. To a solution of the corresponding ester **11aa, 11ba** or **11ca**

(2 mmol) in MeOH (15 mL), a solution of potassium hydroxide (0.112 g, 2.0 mmol, 1 eq.) in MeOH (5 mL) was added and the mixture heated at 50 °C with stirring for 1 h. The reaction mixture was cooled and evaporated, the residue (potassium salt of an acid) was suspended in Et_2O (30 mL), filtered and dissolved in H_2O (20 mL). The solution was acidified to pH 4–5 with 10 % HCl, the precipitate of the target acids **25** was filtered and washed with a small amount of cold H_2O.

4-Cyano-5-(dimethylamino)oxazole-2-carboxylic acid (25a). Yield 327 mg (90 %), colorless solid, mp 130–132 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.14 (s, 6H, 2 CH_3) ppm; COOH exchanged with water. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.5, 155.7, 141.8, 116.1 (C≡N), 85.9 (C-4 oxazole), 38.8 × 2 ($N(CH_3)_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3436 (s, br), 3391 (s, br), 3203, 2944, 2885, 2809, 2669, 2431 (br), 2230 (s), 1895, 1732 (s), 1651 (s, br), 1558 (s), 1438, 1413, 1328 (s), 1246, 1201 (s), 1152, 1109, 1067, 983, 945, 778, 703, 673, 632, 586, 491 cm^{-1}. MS, *m/z* (I_{rel}, %): 136.2 [M - COOH]$^+$ (90), 164.0 [M - OH]$^+$ (100). Found, %: C 46.13; H 4.05; N 23.03. $C_7H_7N_3O_3$. Calculated, %: C, 46.41; H, 3.90; N, 23.20.

2-(4-Cyano-5-(dimethylamino)oxazol-2-yl)acetic acid (25b). Yield 320 mg (82 %), colorless solid, mp 123–125 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.73 (s, 2H), 3.06 (s, 6H) ppm; COOH exchanged with water. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.5 (C=O), 161.6 (C-5 oxazole), 147.8 (C-2 oxazole), 117.0 (C≡N), 83.2 (C-4 oxazole), 38.8 × 2 ($N(CH_3)_2$), 34.3 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3200 – 2750 (br), 3011, 2818, 2717, 2588, 2546, 2507, 2212 (s), 1742, 1720, 1643 (vs), 1601, 1435, 1419, 1344, 1310, 1227, 1205, 1158, 1112, 1067, 942, 895, 822, 717, 692, 660, 636, 568, 511, 442 cm^{-1}. MS, *m/z* (I_{rel}, %): 150.2 [M - COOH]$^+$ (40), 196.2 [M+H]$^+$ (100). Found, %: C 49.37; H 4.54; N 21.20. $C_8H_9N_3O_3$. Calculated, %: C, 49.23; H, 4.65; N, 21.53.

3-(4-Cyano-5-(dimethylamino)oxazol-2-yl)propanoic acid (25c). Yield 382 mg (91 %), colorless solid, mp 132–134°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.30 (br. s, 1H), 3.05 (s, 6H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.61 (t, *J* = 6.9 Hz, 2H) ppm. ^{13}C NMR (126 MHz, DMSO-d_6): δ = 173.2 (C=O), 161.3 (C-5 oxazole), 152.8 (C-2 oxazole), 117.2 (C≡N), 82.8 (C-4 oxazole), 38.7 × 2 ($N(CH_3)_2$), 30.2 (CH_2), 22.9 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3300–2500 (br), 3051, 2964, 2813, 2779, 2764, 2701, 2600, 2576, 2207 (s), 1714 (vs), 1649 (vs), 1605 (vs), 1434 (s), 1388 (s), 1353, 1258 (s), 1236 (s), 1150 (s), 1111, 1066, 991, 936, 843, 746, 691, 677, 635, 614, 546, 511 cm^{-1}. MS, *m/z* (I_{rel}, %): 150.2 [M - CH_2COOH]$^+$ (30), 192.0 [M - OH]$^+$ (50), 210.2 [M+H]$^+$ (100). Found, %: C 51.52; H 5.21; N 20.28. $C_9H_{11}N_3O_3$. Calculated, %: C, 51.67; H, 5.30; N, 20.09.

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Keywords: 2-amino-3,3-dichloroacrylonitrile • heterocyclization • oxazole synthesis • macrocycle• recyclization

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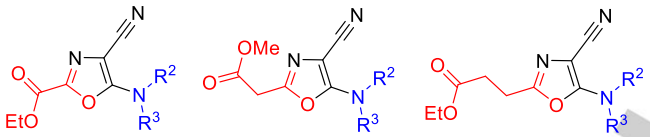
Entry for the Table of Contents



20 examples; up to 94% yield

mild reaction conditions; straighforward access; wide synthetic applications

An approach to the synthesis of new 5-amino-4-cyanoxazoles with carboxylate group at the C-2 position, connected to the heterocycle directly or through an aliphatic linker, was developed. This process features readily available starting materials, simple operations, and good to high yields of products. Wide synthetic applicability of the obtained compounds was also successfully demonstrated by further modifications.

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