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Synthesis of isoxazolylpyrrolones by three-component reaction of α-ketoglutaric acid or its diethyl ester with 3-amino-5-methylisoxazole and aromatic aldehydes

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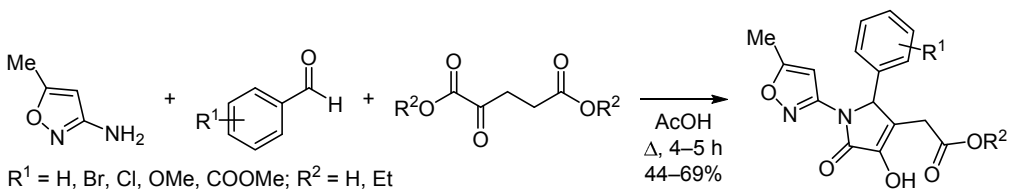


[2-Aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acids and their esters were synthesized by the three-component reaction of α-ketoglutaric acid or its diethyl ester with 3-amino-5-methylisoxazole and aromatic aldehydes.

Keywords: 3-amino-5-methylisoxazole, α-ketoglutaric acid, [1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid, multicomponent reaction.

α-Ketoglutaric acid (KGA) and its derivatives play an important role in biological processes and are a part of some pharmacologically active compounds – some of them are presented in Figure 1.[1–3] Therefore, many chemical transformations involving KGA as attractive building block for combinatorial medicinal- and diversity-oriented synthesis have been described in literature.[1–7]

However, multicomponent reactions (MCRs) based on KGA have remained scarcely reported in the literature. Only few examples of MCRs of KGA with aldehydes and aromatic amines with the formation of pyrrolone derivatives are described.[8–11] It should be additionally noted that pyrrol-2-ones containing γ-lactam in their skeleton are presented in numerous bioactive ingredients, such as the endothelin receptor antagonist oteromicyn,[12] antibiotic pyrrocides,[13] antimicrobials,[14] antipyretics,[10] and analgesics.[9]

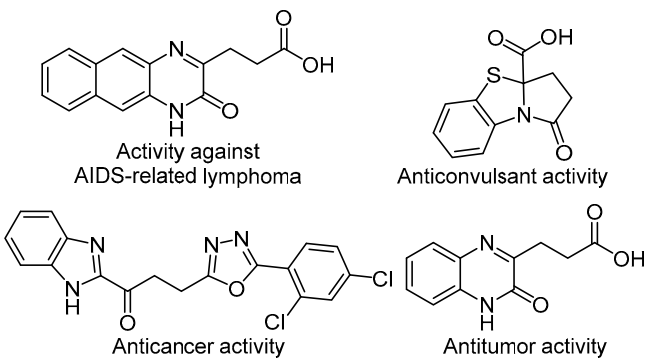


Figure 1. Some biologically active KGA derivatives.

On the other hand, an extremely wide spectrum of biological activity of isoxazole-containing compounds was discovered. Previously, the search for therapeutic agents against various forms of dementia, particularly Alzheimer's disease was conducted among full and partial agonists of muscarinic acetylcholine receptors.[15] The most common compounds containing isoxazole are its various 3,5-disubstituted derivatives. For example, 5-aryl-3-cyclopentylisoxazoles can be used for inhibiting chronic pain.[16] Among drugs that affect different receptors, 3-bromo-4-isoxazolylaminoalcohols are worth mentioning[17] and one of the most well-known drugs based on this scaffold is broxaterol. Additionally, compounds with potential analgesic activity are known among isoxazole-substituted benzimidazoles, which have revealed themselves as potential

nonsteroidal anti-inflammatory drugs (aggregate analgesic and anti-inflammatory activity) in *in vivo* studies in mice.[18]

It was found by our group that MCRs (Doebner-type reactions) of 3-amino-5-methylisoxazole with aromatic aldehydes and pyruvic acids were suitable to elaborate effective synthetic procedures for selective synthesis of furanones and pyrrolones[19,20] since 3-amino-5-methylisoxazole usually reacted as primary amine involving exocyclic amino group as reaction center in these heterocyclizations.

In the present article, we describe the multicomponent treatment of 3-amino-5-methylisoxazole with KGA or 2-oxopentanedioate and aromatic aldehydes for the selective formation of pyrrolone derivatives containing a free carboxylic group and their further modification to obtain libraries of novel heterocycles with potential biological activity.

It was established that three-component reaction of 3-amino-5-methylisoxazole (**1**), aromatic aldehydes **2a**–**e**, and KGA (**3a**) in boiling AcOH for 4 h gave [2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acids **4a**–**e** in 44–62% yields (Scheme 1, Table 1). There was also the possibility of applying 2-oxopentanedioate (**3b**) instead of KGA as a starting material in the reaction with 3-amino-5-methylisoxazole and aromatic aldehydes under conventional heating at reflux in AcOH for 5 h. In this case, corresponding ethyl [2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]-acetates **4f**–**h** were isolated in 58–69% yields (Scheme 1, Table 1).

MCRs of KGA with aromatic aldehydes and 3-amino-5-methylisoxazole always gave pyrrolone derivatives and not furanone derivatives, the formation of which had earlier been described in the similar multicomponent treatments involving pyruvic acid.[19]

Scheme 1

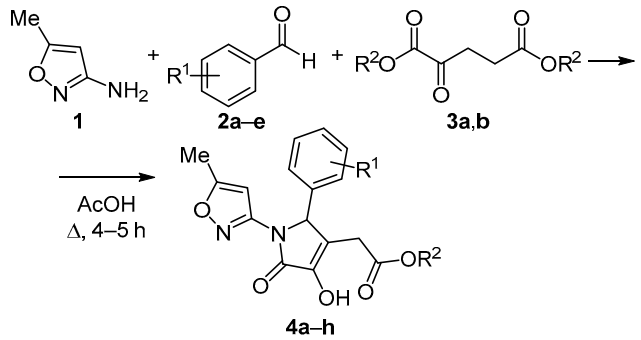


Table 1. Yields of compounds **4a**–**h**

Aldehyde	R^1	KGA or its ester	R^2	Time, h	Product	Yield, %
2a	H	**3a**	H	4	**4a**	59
2b	4-OMe	**3a**	H	4	**4b**	44
2c	4-Br	**3a**	H	4	**4c**	55
2d	4-Cl	**3a**	H	4	**4d**	62
2e	4-COOMe	**3a**	H	4	**4e**	61
2b	4-OMe	**3b**	Et	5	**4f**	69
2d	4-Cl	**3b**	Et	5	**4g**	58
2e	4-COOMe	**3b**	Et	5	**4h**	68

It should be noted, that workup procedure for compounds **4a**–**e** was very simple and consisted of filtration of the crystalline materials after cooling the reaction mixtures and further drying. No additional purification such as recrystallization or column chromatography was required for isoxazolylpyrrolones **4a**–**e**. In the case of pyrrolylacetates **4f**–**h**, cold Et_2O was added before the filtration step for better precipitation. Heterocycles **4a**–**e** were obtained as colorless or light-yellow substances, soluble in EtOH, DMSO, DMF and insoluble in PhMe and Et_2O. While compounds **4f**–**h** were soluble in Me_2CO, EtOH, CH_2Cl_2, DMSO, DMF and insoluble in Et_2O.

It has been also established that melting the mixture of [4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid (**4b**) with aromatic amines **5a**–**c** in a very small amount of DMF for 3 min led to the nucleophilic substitution of OH group and decarboxylation to give 3-arylamino-5-(4-methoxyphenyl)-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones **6a**–**c** in 71–75% yields (Scheme 2, Table 2). Decarboxylated enamines **6a**–**c** were yellow crystalline substances, insoluble in H_2O, Et_2O, soluble in DMSO, DMF, Me_2CO, and MeOH.

The most probable pathway to methylisoxazolylpyrrolylacetic acids **4** in the multicomponent reaction includes attack of the NH_2 group of aminoisoxazole on the carbonyl group of the aldehyde with the formation of azomethine, its further cyclization with KGA into the corresponding pyrrolylacetic acids **4** *via* an attack of enole fragment of KGA on imine carbon and, then, attack of the secondary amine on one of the carbonyl groups (Scheme 3). The similar pathway *via* formation of azomethines was previously described.[8,21]

The purity and structure of compounds **4a**–**h** were established by elemental analysis, mass spectrometry, ^{1}H and ^{13}C NMR spectroscopy, and X-ray diffraction study. For example, ^{1}H NMR spectra of products **4a**–**e** exhibit signals of protons of the OH group (10.27–11.53 ppm) and the 5-CH group of pyrrolone ring (5.48–5.65 ppm) which are in good accordance with chemical shifts described in the literature for similar compounds,[19,22] singlet for CH group of isoxazolyl moiety (6.72–6.77 ppm), two signals

Scheme 2

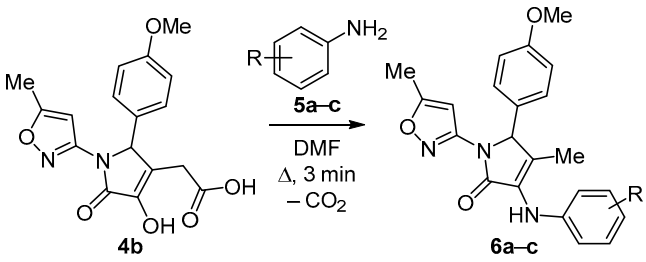
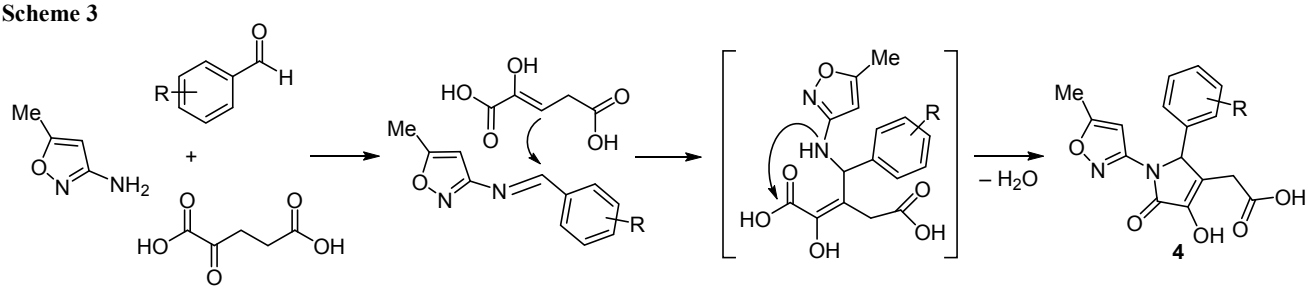


Table 2. Yields of compounds **6a**–**c**

Compound	R	Time, min	Yield, %
6a	4-OMe	3	75
6b	3-Me	3	71
6c	4-F	3	74

Scheme 3



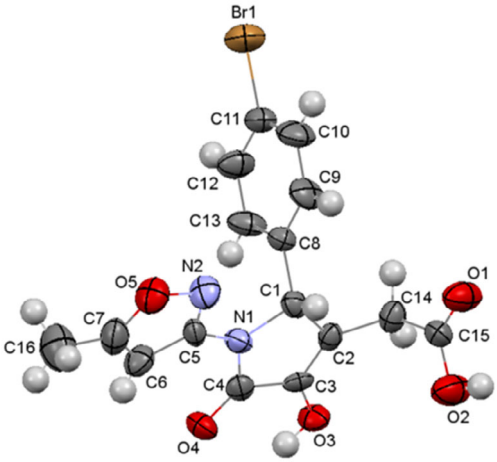


Figure 2. Molecular structure of compound **4c** with atoms represented as thermal vibration ellipsoids of 50% probability.

for diastereotopic protons of CH_2 group (about 2.55–2.66 and 3.29–3.39 ppm), signals for aromatic protons (6.82–7.98 ppm), appropriate signals for terminal substituents and for protons of CH_2CH_3 moiety (in the case of esters **4f**–**h**).

The ^{1}H NMR spectra of compounds **6a**–**c** contain singlets of CH_3 group protons in isoxazole fragment at 2.32 ppm and of methine proton in pyrrolone (5.50–5.58 ppm), singlet for enamine NH group (7.33–7.63 ppm), signals for aromatic ring and other functional group protons.

The structure of heterocycles of type **4** was finally assigned based on X-ray diffraction analysis made for 2-[2-(4-bromophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid **4c** (Fig. 2).

In summary, this paper describes effective approach to the synthesis of novel [2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acids (esters) and their modification with aromatic amines which allowed to obtain 3-(arylamino)-5-(4-methoxyphenyl)-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones. Multicomponent heterocyclizations of 3-amino-5-methylisoxazole with aromatic aldehydes and KGA proceeds with participation of only one nucleophilic center of 3-amino-5-methylisoxazole (exocyclic NH_2 group).

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian MR-400 spectrometer (400 and 100 MHz, respectively) in DMSO-d_6. Mass spectra were registered on a GC-MS Varian 1200L system (ionizing voltage 70 eV) for compound **6b** and an LC/MSD Agilent instrument applying ESI (negative ion mode) for compounds **4a**,**b**,**d**,**e**,**f** and ESI (positive mode) for compounds **4c**,**g**,**h**, **6a**,**c**. Elemental analysis was performed on a Euro Vector EA-3000. Melting points of all synthesized compounds were determined with a Kofler melting point apparatus and are uncorrected.

3-Amino-5-methylisoxazole (**1**), aldehydes **2a**–**e**, KGA (**3a**) were commercially available. Diethyl 2-oxopentanedioate (**3b**) was synthesized according to the known procedure.[23,24]

Synthesis of [2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acids 4a–e (General method). 3-Amino-5-methylisoxazole (**1**) (98 mg, 1 mmol), aromatic aldehyde **2a**–**e** (1 mmol), KGA (**3a**) (146 mg, 1 mmol), and AcOH (1.5 ml) were put into a round-bottom flask. The contents were brought to reflux, and after 4 h, the reaction mixture was cooled to room temperature. The mixture was allowed to stand until a precipitate formed. The precipitate was then filtered off and dried *in vacuo*.

[4-Hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid (4a). Yield 190 mg (59%), light-yellow solid, mp 189–191°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 2.55 (1H, d, *J* = 17.2, CH_2); 3.39 (1H, d, *J* = 17.2, CH_2); 5.56 (1H, s, CH pyrrolone); 6.75 (1H, s, CH isoxazole); 7.12–7.36 (5H, m, H Ph); 11.53 (2H, br. s, OH, COOH). ^{13}C NMR spectrum, δ, ppm: 12.5; 30.1; 62.1; 95.5; 122.5; 127.4; 128.7; 129.1; 136.4; 143.0; 156.5; 165.7; 170.4; 171.1. Mass spectrum, *m*/*z* (I_{rel}, %): 313 $[M–H]^-$ (100), 314 $[M]^-$ (17). Found, %: C 61.01; H 4.57; N 8.98. $C_{16}H_{14}N_2O_5$. Calculated, %: C 61.14; H 4.49; N 8.91.

[4-Hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid (4b). Yield 150 mg (44%), light-yellow solid, mp 191–193°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3 isoxazole); 2.60 (1H, d, *J* = 18.0, CH_2); 3.29 (1H, d, *J* = 18.0, CH_2); 3.71 (3H, s, OCH_3); 5.48 (1H, s, CH pyrrolone); 6.72 (1H, s, CH isoxazole); 6.82–7.12 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 12.5; 30.1; 55.5; 61.7; 95.6; 114.5; 122.6; 127.9; 128.8; 142.9; 156.5; 159.5; 165.7; 170.3; 171.1. Mass spectrum, *m*/*z* (I_{rel}, %): 343 $[M–H]^-$ (100). Found, %: C 59.15; H 4.75; N 8.22. $C_{17}H_{16}N_2O_6$. Calculated, %: C 59.30; H 4.68; N 8.14.

[2-(4-Bromophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid (4c). Yield 220 mg (55%), colorless solid, mp 203–205°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d,

J = 0.7, CH_3 isoxazole); 2.64 (1H, d, J = 17.2, CH_2); 3.36 (1H, d, J = 17.2, CH_2); 5.56 (1H, s, CH pyrrolone); 6.76 (1H, d, J = 0.7, CH isoxazole); 7.08–7.60 (4H, m, H Ar); 11.48 (2H, br. s, OH, COOH). ^{13}C NMR spectrum, δ, ppm: 12.5; 29.9; 61.5; 95.4; 121.7; 121.9; 129.7; 132.0; 135.9; 143.2; 156.4; 165.5; 170.6; 170.9. Mass spectrum, *m*/*z* (I_{rel}, %): 393 $[M+H]^+$ (100). Found, %: C 48.70; H 3.44; N 7.23. $C_{16}H_{13}BrN_2O_5$. Calculated, %: C 48.88; H 3.33; N 7.12.

[2-(4-Chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetic acid (4d). Yield 225 mg (62%), light-yellow solid, mp 193–195°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, d, J = 0.6, CH_3 isoxazole); 2.66 (1H, d, J = 17.1, CH_2); 3.38 (1H, d, J = 17.1, CH_2); 5.57 (1H, s, CH pyrrolone); 6.76 (1H, d, J = 0.6, CH isoxazole); 7.16–7.42 (4H, m, H Ar); 10.27 (1H, br. s, OH); 12.47 (1H, br. s, COOH). ^{13}C NMR spectrum, δ, ppm: 12.4; 30.1; 61.6; 95.4; 122.1; 129.1; 129.5; 133.2; 135.5; 143.3; 156.6; 165.6; 170.5; 170.9. Mass spectrum, *m*/*z* (I_{rel}, %): 347 $[M–H]^-$ (100). Found, %: C 55.02; H 3.89; N 8.11. $C_{16}H_{13}ClN_2O_5$. Calculated, %: C 55.11; H 3.76; N 8.03.

{4-Hydroxy-2-[4-(methoxycarbonyl)phenyl]-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl}acetic acid (4e). Yield 220 mg (61%), colorless solid, mp 195–197°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3 isoxazole); 2.64 (1H, d, J = 17.1, CH_2); 3.36 (1H, d, J = 17.1, CH_2); 3.83 (3H, s, OCH_3); 5.65 (1H, s, CH pyrrolone); 6.77 (1H, s, CH isoxazole); 7.28–7.98 (4H, m, H Ar); 11.36 (2H, br. s, OH, COOH). ^{13}C NMR spectrum, δ, ppm: 12.5; 30.1; 52.6; 61.8; 95.4; 122.8; 127.8; 129.9; 130.0; 142.1; 143.3; 156.5; 165.6; 166.3; 170.6; 171.0. Mass spectrum, *m*/*z* (I_{rel}, %): 371 $[M–H]^-$ (100), 372 $[M]^-$ (22). Found, %: C 57.92; H 4.44; 7.48. $C_{18}H_{16}N_2O_7$. Calculated, %: C 58.07; H 4.33; N 7.52.

Synthesis of ethyl [2-aryl-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetates 4f–h. A mixture of 3-amino-5-methylisoxazole (**1**) (98 mg, 1 mmol) aromatic aldehyde **2b**,**d**,**e** (1 mmol), and diethyl 2-oxopentanedioate (**3b**) (200 mg, 1 mmol) in AcOH (1.5 ml) was refluxed for 5 h. Cold Et_2O was added to the mixture, and precipitate formed. The precipitate was then filtered off and dried *in vacuo*. An additional amount of reaction product from mother liquor was obtained. The reaction mixture was concentrated under reduced pressure, and the crude material was then diluted with EtOAc (2 ml) and washed with H_2O and brine. The organic layer was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The product was purified by column chromatography (eluent 2% of MeOH in CH_2Cl_2).

Ethyl [4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetate (4f). Yield 260 mg (69%), colorless solid, mp 144–146°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.13 (3H, t, J = 7.0, $OCH_2C\underline{H}_3$); 2.32 (3H, s, CH_3 isoxazole); 2.75 (1H, d, J = 17.4, CH_2); 3.40 (1H, d, J = 17.4, CH_2); 3.71 (3H, s, OCH_3); 3.99 (2H, q, J = 7.0, $OC\underline{H}_2CH_3$); 5.50 (1H, s, CH pyrrolone); 6.72 (1H, s, CH isoxazole); 6.85–7.11 (4H, m, H Ar); 10.19 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 12.1; 13.9; 29.6; 55.1; 60.6; 61.3; 95.2; 114.1; 121.4; 127.3; 128.5; 142.8; 156.1; 159.2; 165.2; 169.0; 169.9. Mass spectrum, *m*/*z* (I_{rel}, %): 371 $[M–H]^-$ (100), 372 $[M]^-$ (44). Found, %: C 61.16; H 5.51; N 7.55. $C_{19}H_{20}N_2O_6$. Calculated, %: C 61.28; H 5.41; N 7.52.

Ethyl [2-(4-chlorophenyl)-4-hydroxy-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]acetate (4g). Yield 220 mg (58%), colorless solid, mp 169–171°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.11 (3H, t, J = 7.0, $OCH_2C\underline{H}_3$); 2.32 (3H, s, CH_3 isoxazole); 2.84 (1H, d, J = 17.1, CH_2); 3.38 (1H, d, J = 17.1, CH_2); 3.95 (2H, q, J = 7.0, $OC\underline{H}_2CH_3$); 5.57 (1H, s, CH pyrrolone); 6.75 (1H, s, CH isoxazole); 7.17–7.41 (4H, m, H Ar); 10.36 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 12.1; 13.9; 29.6; 60.7; 61.4; 95.0; 120.9; 128.7; 129.1; 132.8; 135.0; 143.1; 156.0; 165.1; 168.9; 170.2. Mass spectrum, *m*/*z* (I_{rel}, %): 377 $[M+H]^+$ (100). Found, %: C 57.26; H 4.65; N 7.49. $C_{18}H_{17}ClN_2O_5$. Calculated, %: C 57.38; H 4.55; N 7.43.

Methyl 4-[3-(2-ethoxy-4-hydroxy-2-oxoethyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl]benzoate (4h). Yield 270 mg (68%), colorless solid, mp 157–159°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.10 (3H, t, J = 7.1, $OCH_2C\underline{H}_3$); 2.32 (3H, s, CH_3 isoxazole); 2.82 (1H, d, J = 16.4, CH_2); 3.39 (1H, d, J = 16.4, CH_2); 3.83 (3H, s, OCH_3); 3.93 (2H, q, J = 7.1, $OC\underline{H}_2CH_3$); 5.65 (1H, s, CH pyrrolone); 6.78 (1H, s, CH isoxazole); 7.80–7.93 (4H, m, H Ar); 10.38 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 12.1; 13.9; 29.6; 52.2; 60.6; 61.4; 95.0; 120.7; 127.5; 129.2; 129.6; 141.5; 143.2; 156.0; 165.1; 165.9; 168.8; 170.2. Mass spectrum, *m*/*z* (I_{rel}, %): 401 $[M+H]^+$ (100). Found, %: C 59.87; H 5.15; N 7.11. $C_{20}H_{20}N_2O_7$. Calculated, %: C 60.00; H 5.04; N 7.00.

Synthesis of 3-arylamino-5-(4-methoxyphenyl)-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-ones 6a–c. A mixture of [4-hydroxy-2-(4-methoxyphenyl)-1-(5-methylisoxazol-3-yl)-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl]-acetic acid (**4b**) (340 mg, 1 mmol), corresponding aromatic amine **5a–c** (1 mmol), and DMF (2 drops) was allowed to react in reaction vessel placed in an oil bath at 215–220°C for 3 min. The reaction mixture was cooled down to room temperature and 3 ml of EtOH–H_2O, 1:1 was then added. The mixture was kept until a precipitate formed. The precipitate was then filtered off and dried *in vacuo*.

5-(4-Methoxyphenyl)-3-[(4-methoxyphenyl)amino]-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (6a). Yield 300 mg (75%), yellow solid, mp 140–142°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50 (3H, s, CH_3); 2.32 (3H, s, CH_3 isoxazole); 3.67 (3H, s, OCH_3); 3.73 (3H, s, OCH_3); 5.50 (1H, s, CH pyrrolone); 6.72 (1H, s, CH isoxazole); 6.70–7.20 (8H, m, H Ar); 7.33 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.1; 12.6; 55.1; 55.2; 64.0; 95.1; 114.1; 118.2; 128.0; 128.3; 128.4; 129.3; 134.3; 136.9; 153.1; 156.2; 159.0; 167.0; 169.7. Mass spectrum, *m*/*z* (I_{rel}, %): 406 $[M+H]^+$ (100). Found, %: C 67.98; H 5.79; N 10.47. $C_{23}H_{23}N_3O_4$. Calculated, %: C 68.13; H 5.72; N 10.36.

5-(3-Ethylphenyl)-3-[(4-methoxyphenyl)amino]-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (6b). Yield 270 mg (71%), yellow solid, mp 125–127°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.56 (3H, s, CH_3); 2.19 (3H, s, CH_3); 2.32 (3H, s, CH_3 isoxazole); 3.73 (3H, s,

OCH_3); 5.58 (1H, s, CH pyrrolone); 6.72 (1H, s, CH isoxazole); 6.47–7.23 (8H, m, H Ar); 7.58 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 12.1; 12.8; 21.3; 55.1; 64.0; 95.2; 112.6; 114.2; 116.1; 119.6; 128.2; 128.3; 128.6; 128.7; 138.7; 139.8; 144.0; 156.3; 159.1; 167.0; 169.8. Mass spectrum, *m*/*z* (I_{rel}, %) 389 $[M]^+$ (100), 264 (42). Found, %: C 70.81; H 6.08; N 10.87. $C_{23}H_{23}N_3O_3$. Calculated, %: C 70.93; H 5.95; N 10.79.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)amino]-4-methyl-1-(5-methylisoxazol-3-yl)-1,5-dihydro-2*H*-pyrrol-2-one (6c). Yield 290 mg (74%), yellow solid, mp 135–137°C (AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.56 (3H, s, CH_3); 2.32 (3H, s, CH_3 isoxazole); 3.73 (3H, s, OCH_3); 5.55 (1H, s, CH pyrrolone); 6.73 (1H, s, CH isoxazole); 6.70–7.22 (8H, m, H Ar); 7.63 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 12.1; 12.6; 55.1; 64.0; 95.1; 114.2; 115.2 (d, J_{CF} = 22.5); 117.0 (d, J_{CF} = 7.2); 128.2; 128.3; 128.9; 138.3; 140.3; 155.5 (d, J_{CF} = 234.6); 156.2; 159.1; 166.8; 169.8. Mass spectrum, *m*/*z* (I_{rel}, %): 394 $[M+H]^+$ (100). Found, %: C 67.09; H 5.03; N 10.76. $C_{22}H_{20}FN_3O_3$. Calculated, %: C 67.17; H 5.12; N 10.68.

X-ray structural investigation of compound 4c. The crystals of acid **4c** ($C_{16}H_{13}N_2O_5Br \cdot 0.5CH_3CN$) were monoclinic. Compound **4c** was found in the crystal phase as hemisolvate with acetonitrile. The acetonitrile molecule was in a special position on the 2nd order rotation axis. At 293K, *a* 24.496(2), *b* 5.5100(5), *c* 26.753(2) Å; β 101.121(7)°; *V* 3543.1(5) Å^3; M_r 827.44; *Z* 4; space group *C*2/*c*; d_{calc} 1.551 g/cm^3; μ(MoKα) 2.352 mm^{-1}; *F*(000) 1672. Parameters of the unit cell and intensities of 15218 reflections (3119 independent, R_{int} 0.114) were measured on an X-callibur diffractometer (graphite monochromated MoKα radiation, CCD-detector, ω scanning, $2\Theta_{max}$ 50°). The structures were solved by the direct method using the SHELXTL package.[25] The absorption correction was done using multiscan method (T_{min} 0.539, T_{max} 0.891). Positions of hydrogen atoms were located from electron density difference maps and refined using riding model with $U_{iso} = nU_{eq}$ (n = 1.5 for methyl groups and n = 1.2 for other hydrogen atoms). The hydrogen atoms of the hydroxy groups taking part in intermolecular hydrogen bonding were refined using isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms was converged to wR_2 0.144 for 3119 reflections (R_1 0.079 for 1464 reflections with $F>4\sigma(F)$, *S* 0.942). The final atomic coordinates and crystallographic data for molecule **4c** have been deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2018279).

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