Synthesis and Structural Characterization of Pyrrole Heterocyclic Systems Bearing Amino Acid Units: Novel Pyrrol-3-ones, Pyrrolo[1,2-*a*][3,1] benzoxazines, and Pyrrolo[2,1-*b*][1,3]oxazoles

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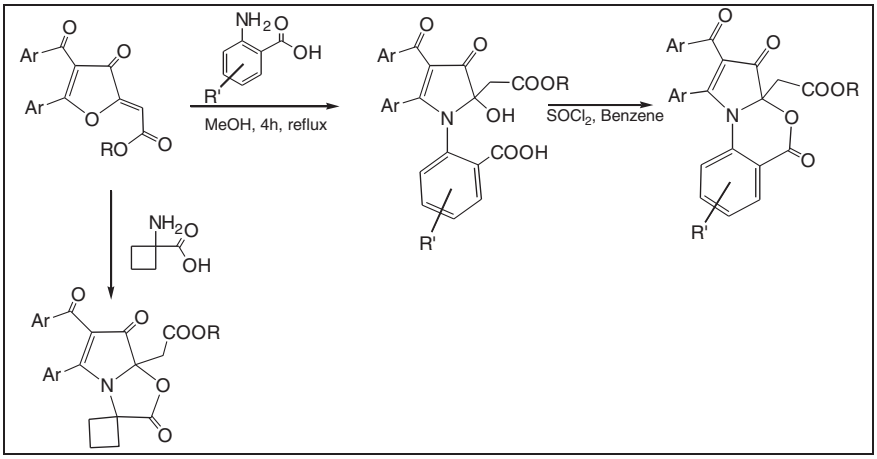

Furan-3-one derivatives **1** were converted into 2-hydroxy-pyrrole-3-ones **4** by reacting with various α- and β-amino acids. In contrast, the reaction of furan-3-ones and 1-aminocyclobutanecarboxylic acid afforded spiro-pyrrolo[2,1-*b*][1,3]oxazoles **5** via the pyrrole-3-one intermediate under the same reaction conditions. Some of 2-hydroxy-pyrrole-3-ones **3** derived from anthranilic acids were transformed to pyrrolo[1,2-*a*][3,1] benzoxazines via intramolecular esterification.

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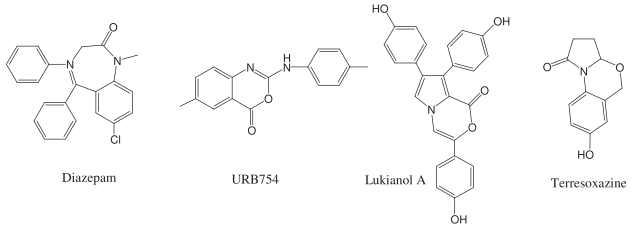
INTRODUCTION

Amino acids play crucial roles both as building blocks of proteins and as intermediates in metabolism. Moreover, some natural heterocycles and synthetic drugs contained cyclic amino acid units for instance guanin, caffeine, lukianol A, diazepam, URB754, and cetilistat. Therefore, naturally occurring or synthetically obtained heterocyclic amino acid derivatives constitute an important resource for new drugs [1–4]. Especially, synthesis of novel heterocyclic systems provides new contributions to these research topics.



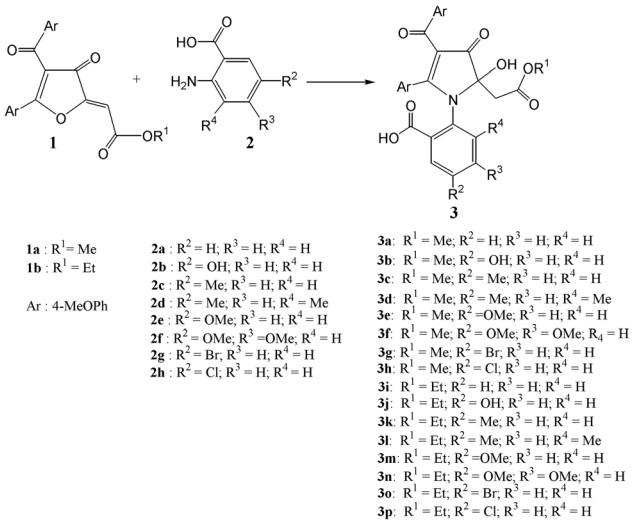
Pyrroles and their condensed compounds become increasingly important in medicinal chemistry and organic synthesis [5]. For instance, lamellarins, lukianols [6], and terresoxazine [7], which possess a pyrrole ring, are natural and bioactive products that were isolated from marine organism or plant. In the light of this, pyrroles including amino acid units are interesting compounds from the viewpoint of both their synthesis and biological applications.

In the course of our recent studies on the furan chemistry, it was shown that pyrroles including amino acid moiety could be prepared from the reactions of amino acids with 2-methylene-furan-3-ones [8]. In this work, we aimed to prepare novel pyrroles, spiro-pyrrolo-oxazoles and pyrrolo-benzoxazoles, as new amino acid heterocycles on the basis of 2-methylene-furan-3-one chemistry.

RESULTS AND DISCUSSIONS

Various anthranilic acid derivatives **2** reacted with 2-methylene-furan-3-ones **1** in methanol in the presence of pyridine to give the corresponding 2,3-dihydro-1*H*-pyrrol-3-ones (**3**) as described in Scheme 1. Although the compounds **3** have an alcohol group and an acid group at corresponding positions of the molecule, these groups did not react to give pyrrolo[1,2-*a*][3,1]benzoxazin-5-one by intramolecular esterification, spontaneously.

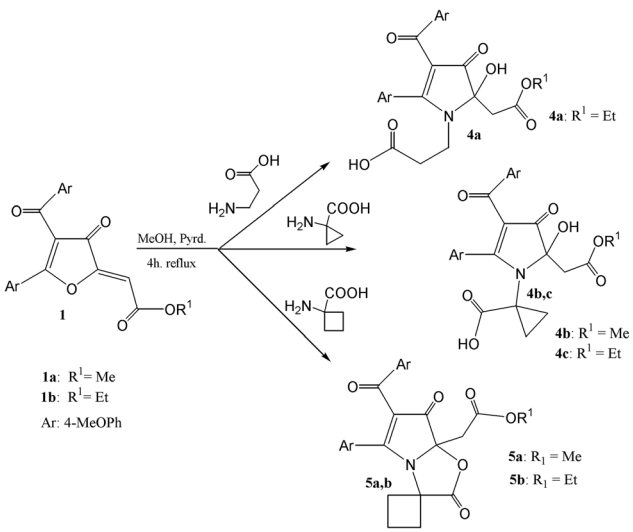
Scheme 1. Reaction of furan-3(2H)-ones with anthranilic acid derivatives.



Compounds **1** also led to the corresponding pyrrole-3-one skeleton **4** by reacting β-alanine and 1-aminocyclopropanecarboxylic acid (Scheme 2). On the other hand, spiro-pyrrolo[2,1-*b*][1,3]oxazoles **5** were obtained from the reaction of **1** with 1-aminocyclobutanecarboxylic acid via the pyrrole-3-one intermediate. In the ^{1}H NMR spectra, the methylene protons attached to an asymmetric center of a pyrrole ring show the signals of AB system as four lines. The signals of these diastereotopic protons clearly revealed the proposed pyrrole structure.

The structure of compound **5a** was determined from X-ray crystallography method [9]. The molecular structure of **5a** with the atom labeling is shown Figure 1. There are five ring systems, which are cyclobutane [Cg1: C(6)–C(7)–C(8)–C(9)], oxazole [Cg2: N(1)–C(4)–O(2)–C(5)–C(6)], pyrrole [Cg3: N(1)–C(2)–C(3)–C(4)], and two phenyl rings [Cg4: C(10)–C(11)–C(12)–C(13)–C(14)–C(15); Cg5: C(18)–C(19)–C(20)–C(21)–C(22)–C(23)] in molecular structure. C–C bond distances ranging from 1.518(3) Å [C(7)–C(8)] to 1.549(3) Å [C(6)–C(9)] and average bond angle value is 89.94° in cyclobutane ring. The bond distances are typical single-bond character in oxazole ring. The dihedral angles of the N(1)–C(4)–O(2)–C(5)–C(6) oxazole plane with the C(6)–C(7)–C(8)–C(9) cyclobutane plane and the N(1)–C(2)–C(3)–C(4) pyrrole plane are 87.21° and 48.73°, respectively.

Scheme 2. Reaction of furan-3(2H)-ones with aliphatic amino acids.



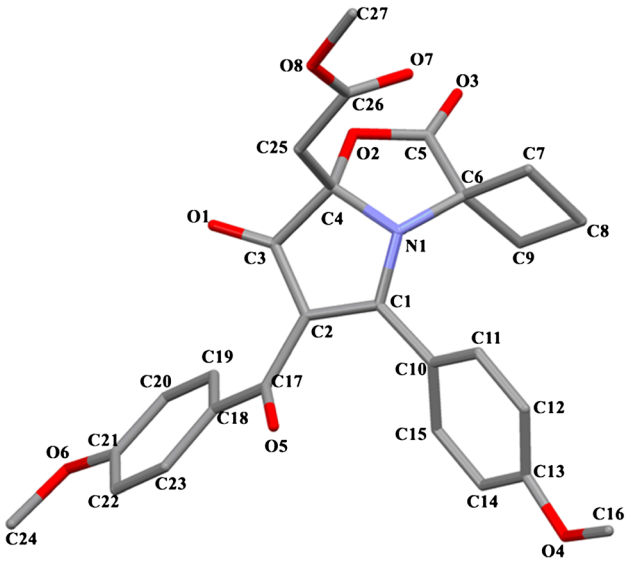


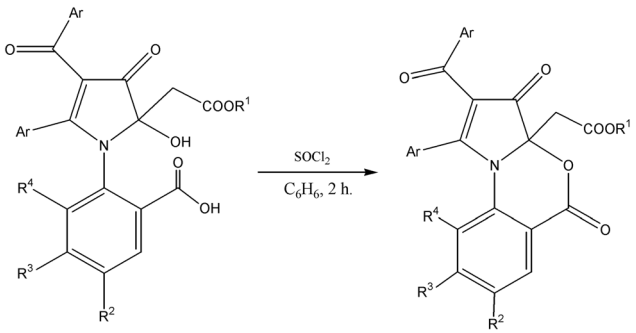
Figure 1. Molecular structure of **5a** (hydrogen atoms have been omitted for clarity). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

The crystal packing of **5a** is a composite of C–H···π and C=O···π interactions. Inter molecular C–H···π interaction occurs between C(25)–H(25B) and Cg(4). The H-ring centroid (H···Cg) distance is 2.65 Å, and the γ angle is 2.83°. C(25)–H(25B)···Cg4 angles, 142°, is below the optimal value (180°) for the strongest C–H···π interaction, which may be due to the steric constraints in the molecule. In addition, there is also C=O···π interaction between C(5)–O(3) group and pyrrole ring center [C(5)–O(3)···Cg(3) = 3.838 Å].

The reactions of **3** with $SOCl_2$ in benzen at 50 °C are composed of complex crude products. According to the NMR data, the crude products contain both intramolecular esterification products and also β-elimination products as by-product. The compounds **6a,l** could be isolated from some crude products by using column chromatography method (Scheme 3).

The reaction products of **3a,l** with $SOCl_2$ do not show the absorptions of –OH groups. This observation is clearly revealed to intramolecular esterification of **3a,l**. In addition to this, intramolecular esterifications of **3a,l** were verified

Scheme 3. Products from the reaction of some 2,3-dihydro-1*H*-pyrrol-3-ones attached to anthranilic acids with $SOCl_2$.



3a,l **6a, 6l**

Ar = 4-MeOPh

3a: R^1 = Me, R^2 = H, R^3 = H R^4 = H
3l: R^1 = Et, R^2 = Me, R^3 = H R^4 = Me
6a: R^1 = Me, R^2 = H, R^3 = H R^4 = H
6l: R^1 = Et, R^2 = Me, R^3 = H R^4 = Me

by the detection of lacton C=O absorbtion of **6a,l**. The spectroscopic data of all synthesized compounds are in agreement with the proposed structure.

CONCLUSIONS

We have synthesized novel 2,3-dihydro-1*H*-pyrrol-3-one, pyrrolo[1,2-*a*][3,1]benzoxazin-5-one, and pyrrolo[2,1-*b*][1,3] oxazole compounds containing amino acid units in miscellaneous yields from 2-methylene-furan-3-ones. This report is the first about synthesis and crystal structure of a spiro-pyrrolo[2,1-*b*][1,3]oxazole ring system. These functionalized products with amino acid units are amenable to further transformations, and we anticipate that they may have important applications in medicinal and synthetic organic chemistry.

EXPERIMENTAL

The starting materials **1a,b** were prepared according to Saçmacı [8] and Üngören [10]. Melting points were determined on an Electrothermal 9200 apparatus and are uncorrected. We carried out elemental analyses (C, H, N) using LECO-932 CHNS-O analyzer. We recorded IR spectra on a Jasko Plus Model 460 FT-IR Spectrometer as KBr pellets and Perkin Elmer Spectrum 400 FT-IR Spectrometer by using the ATR method. We obtained ^{1}H (300.13 MHz) and ^{13}C (75.47 MHz) NMR by using Bruker Ultrashield in $CDCl_3$ and DMSO-d_6. All experiments were followed by tlc using DC Alufolien Kieselgel 60F 254 Merck and Camag TLC lamb (254/366 nm).

Crystallographic analyses: We collected diffraction data for complexes with a Bruker AXS APEX [11] CCD diffractometer equipped with a rotation anode at 100 (2) K by using graphite monochrometed Mo Kα radiation (λ = 0.71069 Å). Diffraction data were collected over the full sphere and were corrected for absorption. The data reduction was performed with the SAINT program package. We found the structure solution with the SHELXS-97 [12] package by using the direct methods, and we refined SHELXL-97 [13] against F^2 by using first isotropic. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were added to the structure model at calculated positions. Geometric calculations were performed with Platon [14]. We obtained molecular drawings by using mercury [15].

General procedure for the preparation of 2,3-dihydro-1*H*-pyrrol-3-one (3, 4) and pyrrolo[2,1-b][1,3]oxazol (5) from the α- and β-amino acid derivatives. Corresponding α- and β-amino acid derivatives (1 mmol) and **1a,b** (1 mmol) were refluxed in a mixture of 50 mL methanol and about 1 mL of pyridine for 1 h. To the crude product was added 30 mL 1 *M* HCl solution. The mixture was extracted with AcOEt (3 × 20 mL), and the solvent was removed by evaporation. The combined organic extracts were dried ($MgSO_4$). The solvent was removed on a rotary evaporator, and the residue was subjected to column chromatography on Silica gel *60 HF_{254}*. Elution with AcOEt afforded the product.

2-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3a). This compound was obtained as pale yellow crystals, 0.351 g (66%), mp 132 °C; ir (KBr): 3429 (OH, acid), 3251 (OH, alcohol), 1736, 1691, 1628, 1605 (C=O), 1576 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90–6.50 (m, 12H, Ar–H), 3.76, 3.74, 3.59 (3s, 9H, 3 MeO), 3.36 (A part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe), 3.00 (B part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 189.7, 178.7, 170.3 (4 C=O), 162.9, 161.4, 145.0, 136.3, 133.1, 132.5, 132.0, 131.8, 131.4, 131.0, 128.7, 121.1, 1113.6, 113.1, 112.8 (Ar–C=C, C=C), 91.0 (N–C–OH), 55.3, 55.1, 52.2 (3 MeO), 40.5 (CH_2). *Anal*. Calcd for $C_{29}H_{25}NO_9$ (531.5 g/mol): C, 65.53; H, 4.74; N, 2.64. Found: C, 65.18; H, 4.52; N 3.01.

5-Hydroxy-2-[2-hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3b). This compound was obtained as pale green crystals, 0.223 g (41%), mp 167 °C; ir (KBr): 3393 (OH, acid), 3247 (OH, alcohol), 1730, 1692 (C=O), 1577 cm^{-1} (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.07 (s, 1H, Ar–OH), 7.88–6.72 (m, 11H, Ar–H), 3.83, 3.68, 3.62 (3s, 9H, 3 MeO), 3.46 (s, 1H, COOH, br), 2.95 (A part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe), 2.69 (B part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.0, 188.5, 178.6, 169.1 (4 C=O), 168.5, 162.9, 161.0, 160.9, 157.4, 132.3, 132.1, 132.0, 131.6, 131.2, 126.4, 122.5, 119.1, 117.5, 113.7, 113.6 (Ar–C=C, C=C), 90.2 (N–C–OH), 55.9, 55.6, 52.3 (3 MeO), 41.0 (CH_2). *Anal*. Calcd for $C_{29}H_{25}NO_{10}$ (548.5 g/mol): C, 63.62; H, 4.60; N, 2.56. Found: C, 63.84; H, 4.51; N 2.31.

2-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-5-methylbenzoic acid (3c). This compound was obtained as pale yellow crystals, 0.454 g (83%), mp 129 °C; ir (KBr): 3423 (OH, acid), 3224 (OH, alcohol), 1737, 1690, 1631, 1605 (C=O), 1575 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–6.49 (m, 11H, Ar–H), 3.74, 3.72, 3.57 (3s, 9H, 3 MeO), 3.33 (A part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe), 2.96 (B part of AB system, d, 1H, *J* = 15.4, $C\underline{H}_2$COOMe), 2.29 (s, 3H, Me); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 195.3, 189.7, 179.0, 170.7 (4 C=O), 162.8, 161.3, 144.8, 138.9, 133.3, 133.0, 132.3, 132.0, 131.5, 131.3, 130.7, 121.3, 113.6, 113.1, 112.7 (Ar–C=C, C=C), 90.9 (N–C–OH), 55.3, 55.1, 52.2 (3 MeO), 40.5 (CH_2), 21.0 (Me). *Anal*. Calcd for $C_{30}H_{27}NO_9$ (545.5 g/mol): C, 66.05: H, 4.99; N, 2.57. Found: C, 66.35; H, 4.95; N, 2.90.

2-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-3,5-dimethylbenzoic acid (3d). This compound was obtained as pale yellow crystals, 0.245 g (44%), mp 136 °C; ir (KBr): 3437 (OH, acid), 3282 (OH, alcohol), 1804, 1742, 1706, 1647, 1600 (C=O), 1574 cm^{-1} (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ 8.64–6.47 (m, 10H, Ar–H), 3.82, 3.67, 3.58 (3s, 9H, 3 MeO), 3.34 (s, 1H, COOH, br), 2.86 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 2.63 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe), 2.27, 2.01 (2s, 6H, 2 Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.9, 188.6, 179.0, 169.7 (4 C=O), 162.9, 161.1, 138.5, 138.2, 134.7, 132.4, 132.0, 131.0, 130.6, 129.3, 129.3, 122.9, 113.6, 113.6, 111.6 (Ar–C=C, C=C), 90.7 (N–C–OH), 55.9, 55.6, 52.1 (3 MeO), 40.0 (CH_2) 20.8, 18.1 (2 Me). *Anal*. Calcd for $C_{31}H_{29}NO_9$ (559 g/mol): C, 66.54; H, 5.22; N, 2.50. Found: C, 66.15; H, 5.19; N, 2.53.

2-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-5-methoxybenzoic acid (3e). This compound was obtained as pale yellow crystals, 0.433 g (77%), mp 105 °C; ir (KBr): 3451 (OH, acid), 3217 (OH, alcohol), 1737, 1688, 1631, 1604 (C=O), 1573 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (br, 2H, 2 OH,), 7.76–6.49 (m, 11H, Ar–H), 3.76, 3.75, 3.72, 3.59 (4s, 12H, 4 MeO), 3.32 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 2.96 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 189.6, 179.0, 170.4 (4 C=O), 162.8, 161.3, 159.1, 134.5, 132.1, 132.0, 131.4, 131.3, 128.7, 128.3, 121.3, 118.3, 116.0, 113.6, 113.1 (Ar–C=C, C=C), 90.8 (N–C–OH), 55.6, 55.3, 55.1, 52.2 (4 MeO), 40.4 (CH_2). *Anal*. Calcd for $C_{30}H_{27}NO_{10}$ (561 g/mol): C, 64.17; H, 4.85; N, 2.49. Found: C, 64.22; H, 5.00; N, 2.20.

2-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-4,5-dimethoxybenzoic acid (3f). This compound was obtained as pale yellow crystals, 0.162 g (27%), mp 107 °C; ir (KBr): 3446–3352 (OH, acid), 3135 (OH, alcohol), 1735, 1688, 1627, 1603 (C=O), 1574 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–6.22 (m, 10H, Ar–H), 4.00, 3.87, 3.83, 3.77, 3.74 (5s, 15H, 5 MeO), 3.37 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 3.00 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8, 189.5, 178.8, 169.9 (4 C=O), 162.9, 161.4, 152.3, 144.5, 131.9, 131.3, 130.9, 130.3, 128.7, 124.4, 113.7, 113.7, 113.5, 113.1, 112.7 (Ar–C=C, C=C), 90.9 (N–C–OH), 56.4, 56.1, 55.3, 55.1, 52.3 (5 MeO), 41.0 (CH_2). *Anal*. Calcd for $C_{31}H_{29}NO_{11}$ (591 g/mol): C, 62.94; H, 4.94; N, 2.37. Found: C, 62.88; H, 5.24; N, 2.52.

5-Bromo-2-[2-hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3g). This compound was obtained as pale yellow crystals, 0.452 g (74%), mp 146 °C; ir (KBr): 3452 (OH, acid), 3394 (OH, alcohol), 1736, 1704, 1608 (C=O), 1575 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 9.66 (OH, br), 7.84–6.51 (m, 11H, Ar–H), 3.77, 3.73, 3.62 (3s, 9H, 3 MeO), 3.35 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 3.00 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 189.4, 178.3, 170.1 (4 C=O), 162.9, 161.4, 145.6, 136.9, 135.2, 134.8, 134.4, 132.5, 131.9, 131.3, 122.4, 121.1, 113.7, 113.4, 113.1 (Ar–C=C, C=C), 90.9 (N–C–OH), 55.3, 55.1, 52.2 (3 MeO), 40.7 (CH_2). *Anal*. Calcd for $C_{29}H_{24}BrNO_9$ (610 g/mol): C, 57.06; H, 3.96; N, 2.29. Found: C, 57.22; H, 4.25; N, 2.26.

5-Chloro-2-[2-hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3h). This compound was obtained as pale yellow crystals, 0.368 g (65%), mp 127 °C; ir (KBr): 3428 (OH, acid), 3234 (OH, alcohol), 1736, 1692, 1633, 1604 (C=O), 1575 cm^{-1} (C=C); ^1H NMR (300 MHz, $CDCl_3$): δ 8.47 (OH, br), 7.73–6.51 (m, 11H, Ar–H), 3.75, 3.72, 3.60 (3s, 9H, 3 MeO), 3.34 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 2.95 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 189.6, 178.5, 169.6 (4 C=O), 162.9, 161.5, 144.2, 135.9, 134.6, 134.5, 132.2, 132.0, 131.7, 131.3, 131.2, 126.2, 121.0, 113.7, 113.1 (Ar–C=C, C=C), 91.0 (N–C–OH), 55.3, 55.1, 52.2 (3 MeO), 40.6 (CH_2). *Anal*. Calcd for $C_{29}H_{24}ClNO_9$ (566 g/mol): C, 61.54; H, 4.27; N, 2.47. Found: C, 61.24; H, 4.16; N, 2.36.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3i). This compound was obtained as pale yellow crystals, 0.197 g (36%), mp 111 °C; ir (KBr): 3429 (OH, acid), 3378 (OH, alcohol), 1732, 1691, 1631, 1602 (C=O), 1575 (C=C). ^1H NMR (300 MHz, $CDCl_3$): 7.79–6.51 (m, 12H, Ar–H), 4.21 (q, ^3J = 6.9, 2H, OCH_2), 3.77, 3.60 (2s, 6H, 2 MeO), 3.35 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.98 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 1.25 (*t*, ^3J = 6.9, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 189.6, 178.9, 170.7 (4 C=O), 162.9, 161.3, 144.5, 136.2, 133.6, 132.4, 132.0, 131.5, 131.3, 131.0, 128.6, 121.1, 113.58, 113.6, 113.1, 112.9 (Ar–C=C, C=C), 91.0 (N–C–OH), 61.2 (OCH_2CH_3), 55.3, 55.1 (2 MeO), 40.8 (C–CH_2COEt), 14.1 (OCH_2CH_3). *Anal*. Calcd for: $C_{30}H_{27}NO_9$ (545 g/mol): C, 66.05; H, 4.99; N, 2.57. Found: C, 65.97; H, 5.14; N, 2.84.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-5-hydroxybenzoic acid (3j). This compound was obtained as pale green crystals, 0.320 g (57%), mp 155 °C; ir (KBr): 3380 (OH, acid), 3208 (OH, alcohol), 1729, 1692, 1604 (C=O), 1573 cm^{-1} (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ 7.97–6.61 (m, 11H, Ar–H), 4.09 (q, ^3J = 7.1, 2H, OCH_2), 3.83, 3.68 (2s, 6H, 2 MeO), 3.40 (OH, alcohol, br), 2.94 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.68 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 1.15 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.0, 188.5, 178.7, 168.6 (4 C=O), 163.0, 161.0, 157.4, 132.9, 132.4, 132.0, 131.3, 129.2, 122. 5, 119.2, 118,2, 117.6, 115.7, 113.7, 113.6 (Ar–C=C, C=C), 90.3 (N–C–OH), 61.1 (OCH_2CH_3), 55.9, 55.6 (2 MeO), 41.4 (C–CH_2COEt), 14.4 (OCH_2CH_3). *Anal*. Calcd for $C_{30}H_{27}NO_{10}$ (561 g/mol): C, 64.17; H, 4.85; N, 2.49. Found: C, 64.22; H, 5.00; N, 2.20.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-5-methylbenzoic acid (3k). This compound was obtained as pale yellow crystals 0.419 g (75%), mp 135 °C; ir (KBr): 3428 (OH, acid), 3378 (OH, alcohol), 1732, 1690, 1631, 1605 (C=O), 1575 cm^{-1} (C=C); ^1H NMR (300 MHz, DMSO-d_6): δ 7.80–6.71 (m, 11H, Ar–H), 4.09 (q, ^3J = 7.1, 2H, OCH_2), 3.83, 3.67 (2s, 6H, 2 MeO), 2.97 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.63 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.31 (s, 3H, Me), 1.15 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz,

DMSO-d_6): δ 193.9, 188.5, 178.3, 168.6 (4 C=O), 163.0, 161.1, 149.9, 138.6, 133.2, 133.2, 132.3, 132.0, 131.7, 131.3, 129.2, 122.3, 113.9, 113.6, 112.2 (Ar–C=C, C=C), 90.4 (N–C–OH), 61.1 ($O\underline{C}H_2CH_3$), 55.9, 55.6 (2 MeO), 41.5 (C–$\underline{C}H_2CO_2Et$), 20.9 (Ar–CH_3), 14.4 ($OCH_2\underline{C}H_3$). *Anal*. Calcd for $C_{31}H_{29}NO_9$ (559 g/mol): C, 66.54; H, 5.22; N, 2.50. Found: C, 66.15; H, 5.19; N, 2.53.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-3,5-dimethylbenzoic acid (3l). This compound was obtained as pale yellow crystals, 0.253 g (44%), mp 120 °C; ir (KBr): 3425 (OH, acid), 3240 (OH, alcohol), 1734, 1691, 1631, 1604 (C=O), 1575 cm^{-1} (C=C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.82–6.73 (m, 10H, Ar–H), 4.04 (q, ^3J = 7.1, 2H, –OCH_2), 3.82, 3.66 (2s, 6H, 2 MeO), 2.63 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.17 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.27 (2s, 6H, 2 Me), 1.16 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.7, 188.6, 179.2, 169.7 (4 C=O), 162.9, 161.2, 138.8, 138.4, 136.9, 132.4, 132.0, 131.0, 130.7, 129.5, 129.2, 122.8, 113.7, 113.6, 111.6 (Ar–C=C, C=C), 90.6 (N–C–OH), 60.9 ($O\underline{C}H_2CH_3$), 55.9, 55.6 (2 MeO), 20.8, 18.1 (2 Ar–CH_3), 14.4 ($OCH_2\underline{C}H_3$). *Anal*. Calcd for $C_{32}H_{31}NO_9$ (573 g/mol): C, 67.01; H, 5.45; N, 2.44. Found: C, 66.98; H, 5.40; N, 2.70.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-5-methoxybenzoic acid (3m). This compound was obtained as pale yellow crystals, 0.317 g (55%), mp 120 °C, ir (KBr): 3433 (OH, acid), 3256 (OH, alcohol), 1732, 1687, 1627, 1606 (C=O), 1577 cm^{-1} (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.79–6.72 (m, 11H, Ar–H), 4.08 (q, ^3J = 7.1, 2H, OCH_2), 3.84, 3.77, 3.68 (3s, 9H, 3 MeO), 2.95 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.61 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 1.15 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.9, 188.5, 178.6, 168.6 (4 C=O), 163.0, 161.1, 158.8, 136.9, 133.0, 132.3, 132.1, 132.0, 129.2, 128.0, 122.4, 117.9, 115.9, 113.8, 113.6 (Ar–C=C, C=C), 90.4 (N–C–OH), 61.1 ($O\underline{C}H_2CH_3$), 56.0, 55.9, 55.6 (3 MeO), 41.5 (C–$\underline{C}H_2$COEt), 14.4 ($OCH_2\underline{C}H_3$). *Anal*. Calcd for $C_{31}H_{29}NO_{10}$ (575 g/mol): C, 64.69; H, 5.08; N, 2.43. Found: C, 64.85; H, 5.16; N, 2.82.

2-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]-4,5-dimethoxybenzoic acid (3n). This compound was obtained as pale yellow crystals, 0.162 g (27%), mp 118 °C, ir (KBr): 3437 (OH, acid), 3258 (OH, alcohol), 1730, 1691, 1636, 1604 (C=O), 1577 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–6.54 (m, 10H, Ar–H), 4.19 (q, ^3J = 7.1, 2H, OCH_2), 4.00, 3.84, 3.77, 3.63 (4s, 12H, 4 MeO), 3.35 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.97 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 1.23 (*t*, ^3J = 7.1 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7, 189.4, 179.2, 169.7 (4 C=O), 162.9, 161.4, 152.2, 145.3, 132.0, 131.5, 130.9, 130.2, 128.6, 124.5, 121.3, 113.7, 113.5, 113.1, 112.7 (Ar–C=C, C=C), 91.1 (N–C–OH), 61.4 ($O\underline{C}H_2CH_3$), 56.4, 56.1, 55.3, 55.1 (4 MeO), 41.3 (C–$\underline{C}H_2$COEt), 14.1 ($OCH_2\underline{C}H_3$). *Anal*. Calcd for $C_{32}H_{31}NO_{11}$ (605 g/mol): C, 63.47; H, 5.16; N, 2.31. Found: C, 63.20; H, 4.90; N, 2.60.

5-Bromo-2-[2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3o). This compound was obtained as pale yellow crystals, 0.270 g (43%), mp 124 °C, ir (KBr): 3414 (OH, acid), 3232 (OH, alcohol), 1731, 1692, 1631, 1603 (C=O), 1575 cm^{-1} (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.99–6.75 (m, 11H, Ar–H), 4.08 (q, ^3J = 7.1, 2H, OCH_2), 3.84, 3.68 (2s, 6H, 2 MeO), 2.98 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.67 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 1.14 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.9, 188.6, 178.0, 168.6 (4 C=O), 163.1, 161.3, 149.5, 137.4, 135.7, 135.2, 133.8, 132.1, 132.0, 131.4, 122.0, 121.7, 114.0, 113.9, 113.7 (Ar–C=C, C=C), 90.6 (N–C–OH), 61.2 ($O\underline{C}H_2CH_3$), 55.9, 55.7 (2 MeO), 41.7 (C–$\underline{C}H_2$COEt), 14.3 ($OCH_2\underline{C}H_3$). *Anal*. Calcd fo $C_{30}H_{26}BrNO_9$ (624 g/mol): C, 57.70; H, 4.20; N, 2.24. Found: C, 57.76; H, 4.21; N, 2.18.

5-Chloro-2-[2-(2-ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]benzoic acid (3p). This compound was obtained as pale yellow crystals, 0.161 g (28%), mp 101 °C, ir (KBr): 3413 (OH, acid), 3234 (OH, alcohol), 1732, 1692, 1631, 1604 (C=O), 1575 cm^{-1} (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75–6.53 (m, 11H, Ar–H), 4.19 (q, ^3J = 7.1, 2H, OCH_2), 3.76, 3.62 (2s, 6H, 2 MeO), 3.32 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.92 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 1.24 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 189.6, 178.8, 169.1 (4 C=O), 132.9, 161.5, 143.8, 135.1, 134.8, 134.5, 132.2, 132.0, 131.7, 131.34, 131.3, 126.4, 120.9, 113.8, 113.1 (Ar–C=C, C=C), 91.1 (N–C–OH), 61.3 ($O\underline{C}H_2CH_3$), 55.3, 55.1 (2 MeO), 40.8 (C–$\underline{C}H_2$COEt), 14.1 ($OCH_2\underline{C}H_3$). *Anal*. Calcd for $C_{30}H_{26}ClNO_9$ (580 g/mol): C, 62.13; H, 4.52; N, 2.42. Found: C, 62.40; H, 4.25; N, 2.60.

3-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]propanoic acid (4a). This compound was obtained as white crystals, 0.227 g (46%), mp 152 °C; ir (KBr): 3384 (OH, acid), 3178 (OH, alcohol), 1735, 1713, 1692, 1608 (C=O), 1571 cm^{-1} (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.36 (s, 1H, COOH), 7.66–6.90 (m, 8H, Ar–H), 4.08 (q, ^3J = 7.1, 2H, OCH_2), 3.81 (2s, 6H, 2 MeO), 3.69–3.47 (m, 2H, CH_2N), 3.12 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.93 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOEt), 2.64–2.35 (m, 2H, $C\underline{H}_2CO_2H$), 1.16 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 193.7, 187.3, 179.6, 172.4 (4 C=O), 162.8, 161.1, 132.2, 131.8, 129.6, 122.5, 114.5, 113.4, 110.6 (Ar–C=C, C=C), 89.0 (N–C–OH), 61.0 ($O\underline{C}H_2CH_3$), 55.9, 55.7 (2 MeO), 34.5 ($\underline{C}H_2$COOH) 14.4 ($OCH_2\underline{C}H_3$). *Anal.* Calcd for $C_{26}H_{27}NO_9$ (497 g/mol): C, 62.77; H, 5.47; N, 2.82. Found: C, 62.61; H, 5.40; N, 3.00.

1-[2-Hydroxy-4-(4-methoxybenzoyl)-2-(2-methoxy-2-oxoethyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl] cyclopropanecarboxylic acid (4b). This compound was obtained as white crystals, 0.312 g (63%), mp 137 °C; ir (KBr): 3393, 3154 (OH, alcohol, and acid), 1738, 1698, 1631 cm^{-1} (C=O). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.66 (b, 1H, OH), 7.80–6.91 (m, 8H, Ar–H), 3.82, 3.78 (2s, 6H, 2 MeO), 3.44 (b, 1H, OH), 3.08 (A part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOMe), 2.99 (B part of AB system, d, 1H, J = 15.4, $C\underline{H}_2$COOMe), 1.39–0.84 (m, 2× CH_2, cyclopropane); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.4, 187.8, 181.0, 174.0 (4 C=O), 163.1, 162.9, 132.2, 132.0, 131.9, 130.1, 123.4, 113.7, 113.5, 111.7 (Ar–C=C, C=C), 89.6 (N–C–OH), 55.9, 55.6, 51.9 (3 MeO), 37.2 (CH_2), 20.5 (CH_2, cyclopropane). *Anal*. Calcd for $C_{26}H_{25}NO_9$ (495 g/mol): C, 63.03; H, 5.09; N, 2.83. Found: C, 63.19; H, 5.00; N, 2.86.

1-[2-(2-Ethoxy-2-oxoethyl)-2-hydroxy-4-(4-methoxybenzoyl)-5-(4-methoxyphenyl)-3-oxo-2,3-dihydro-1H-pyrrol-1-yl]

cyclopropanecarboxylic acid (4c). This compound was obtained as white crystals, 0.295 g (58%), mp 105 °C; ir (KBr): 3421 (OH, alcohol, and acid), 1733, 1698, 1633 cm^{-1} (C=O); ^1H NMR (300 MHz, DMSO-d_6): δ 12.82 (b, 1H, OH), 7.80–6.91 (m, 8H, Ar–H), 4.21–3.99 (m, 2H, OCH_2), 3.82, 3.78 (2s, 6H, 2 MeO), 3.38 (b, 1H, OH), 3.06 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.97 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.40–2.30, 0.99–0.85 (m, 4H, 2× CH_2, cyclopropane), 1.20 (*t*, ^3J = 7.1, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): δ 194.4, 187.8, 181.1, 174.0 (4 C=O), 162. 9, 160.6, 132.2, 132.0, 130.0, 123.5, 115.1, 113.7, 113.4, 111.6 (Ar–C=C, C=C), 89.6 (N–C–OH), 60.6 (OCH_2), 55.9, 55.6 (2 MeO), 37.3 (CH_2), 15.4 (Me), 14.4 (CH_2, cyclopropane). *Anal*. Calcd for $C_{27}H_{27}NO_9$ (509 g/mol): C, 63.65; H, 5.34; N, 2.75. Found: C, 63.56; H, 5.39; N, 2.81.

Methyl [6′-(4-methoxybenzoyl)-5′-(4-methoxyphenyl)-2′,7′-dioxospiro[cyclobutane-1,3′-pyrrolo[2,1-b][1,3]oxazol]-7a′(7′H)-yl]acetate (5a). This compound was obtained as yellow crystals, recrystallized from acetic acid, 0.285 g (58%), mp 91 °C; ir (KBr): 1797, 1744, 1690, 1637 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.82–6.85 (m, 8H, Ar–H), 3.86, 3.75 (3s, 9H, 3 MeO), 3.13 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 3.06 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe), 2.89–1.54 (m, 6H, 3× CH_2, cyclobutane); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.5, 188.7, 179.2, 175.4 (4 C=O), 163.9, 163.3, 132.1, 130.7, 130.0, 123.3, 120.9, 114.7, 113.6 (Ar–C=C, C=C), 93.9 (N–C–O), 64.5 (N–C–COOH), 55.6, 55.5, 52.3 (3 MeO), 39.6 (CH_2COOMe), 36.3, 30.3, 13.9 (CH_2, cyclobutane). *Anal*. Calcd for $C_{27}H_{25}NO_8$ (491 g/mol): C, 65.98; H, 5.13; N, 2.85. Found: C, 65.76; H, 5.29; N, 2.91.

Ethyl [6′-(4-methoxybenzoyl)-5′-(4-methoxyphenyl)-2′,7′-dioxospiro[cyclobutane-1,3′-pyrrolo[2,1-b][1,3]oxazol]-7a′(7′H)-yl] acetate (5b). This compound was obtained as yellow crystals, recrystallized from acetic acid, 0.320 g (63%), mp 180 °C; ir (KBr): 1797, 1739, 1693, 1637 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.84–6.86 (m, 8H, Ar–H), 4.19 (q, ^3J = 7.1, 2H, OCH_2), 3.87 (2s, 6H, 2 MeO), 3.13 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 3.03 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.89–1.57 (m, 6H, 3× CH_2, cyclobutane), 1.28 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 188.7, 179.3, 175.4 (4 C=O), 163.9, 163.3, 132.1, 130.7, 130.1, 123.3, 120.8, 114.7, 113.6 (Ar–C=C, C=C), 94.0 (N–C–O), 64.5 (N–C–COOH), 61.5 (OCH_2), 55.5, 55.4 (2 MeO), 39.8 (CH_2), 36.3, 36.2 (2 CH_2, cyclobutane), 14.1 (Me). *Anal*. Calcd for $C_{28}H_{27}NO_8$ (505 g/mol): C, 66.53; H, 5.38; N, 2.77. Found: C, 66.22; H, 5.50; N, 2.52.

General procedure for preparation of pyrrolo[1,2-*a*][3,1] benzoxazin (6) and 2-methylene pyrrol-3-one (7). Corresponding pyrrol-3-one derivatives (**3a,l,n**) (1 mmol) and excess of equivalent amount of $SOCl_2$ (about three to four drops) were stirred at RT in 50 mL benzene for 15 min. Then, the solution was refluxed for 45 min. The solvent was removed by evaporation. The oily residue was subjected to column chromatography on Silica gel *60 HF_{254}*. Elution with AcOEt/hexane (5:1) afforded the product.

***Methyl [2-(4-methoxybenzoyl)-1-(4-methoxyphenyl)-3,5-dioxo-5H*-pyrrolo[1,2-*a*][3,1]benzoxazin-3a(3H)-yl]acetate (6a).** This compound was obtained as pale yellow crystals, recrystallized from AcOEt, 0.210 g (41%), mp 180 °C; ir (KBr): 1734, 1705, 1645 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 8.13–6.46 (m, 12H, Ar–H), 3.86, 3.83, 3.67 (3s, 9H, 3 MeO), 3.48 (A part of AB system, d, 1H, J = 15.4, CH_2COOMe), 3.14 (B part of AB system, d, 1H, J = 15.4, CH_2COOMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.4, 187.1, 176.5, 167.2 (4 C=O), 163.7, 161.7, 160.4, 136.1, 135.1, 132.1, 131.2, 130.8, 130.4, 130.0, 126.5, 122.6, 119.7, 116.0, 114.1, 113.5 (Ar–C=C, C=C), 88.5 (N–C–O), 55.5, 55.4, 52.3 (3 MeO), 38.3 (CH_2). *Anal*. Calcd for $C_{29}H_{23}NO_8$ (513 g/mol): C, 67.83; H, 4.51; N, 2.73. Found: C, 67.80; H, 4.50; N, 2.62.

Ethyl [2-(4-methoxybenzoyl)-1-(4-methoxyphenyl)-7,9-dimethyl-3,5-dioxo-5H-pyrrolo[1,2-a][3,1]benzoxazin-3a(3H)-yl] acetate (6l). This compound was obtained as pale yellow crystals, recrystallized from AcOEt, 0.263 g (47%), mp 95 °C; ir (KBr): 1741, 1711, 1645 cm^{-1} (C=O); ^1H NMR (300 MHz, $CDCl_3$): δ 7.96–6.78 (m, 10H, Ar–H), 4.14 (q, ^3J = 7.1, 2H, OCH_2), 3.88, 3.81 (2s, 6H, 2 MeO), 3.50 (A part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.95 (B part of AB system, d, 1H, J = 15.4, CH_2COOEt), 2.42, 1.45 (2s, 6H, 2 Ar–CH_3), 1.26 (*t*, ^3J = 7.1, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.8, 187.7, 176.7, 167.1 (4 C=O), 163.7, 161.9, 160.9, 138.5, 138.0, 134.1, 132.5, 132.2, 131.0, 130.3, 129.3, 120.8, 120.5, 114.1, 113.9, 113.5 (Ar–C=C, C=C), 89.1 (N–C–O), 61.5 (OCH_2) 55.5, 55.4 (2 MeO), 37.2 (CH_2), 21.0, 17.1 (2 Ar–CH_3), 14.1 (Me). *Anal*. Calcd for $C_{32}H_{29}NO_8$ (555 g/mol): C, 69.18; H, 5.26; N, 2.52. Found: C, 69.33; H, 5.21; N, 2.71.

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