Synthesis of dispiro heteroanalogs of pyrrolizidine alkaloids: crystal and molecular structure of substituted 3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide

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Abstract

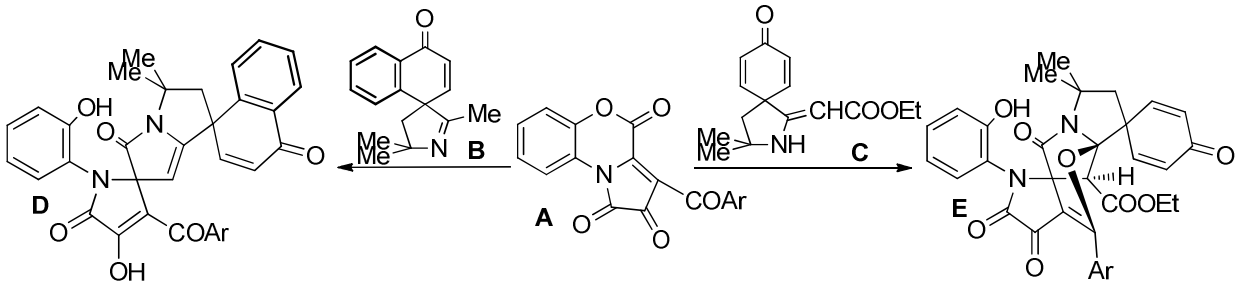
3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones react with substituted 2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamides to produce substituted 3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole] systems. The crystal and molecular structure of substituted 3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide was confirmed by X-ray analysis.

Keywords: 1*H*-Pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-trione, 2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamide, heterocyclization, analogs of pyrrolizidine alkaloids

Introduction

The annulation of a pyrrol-dione cycle with a benzoxazine fragment led to the formation of the polycarbonylic heterocyclic 1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-trione system.[1,2] Nucleophilic transformations of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones by the action of OH- and NH-mono- and NH,NH-, NH,OH-, and NH,SH-binucleophiles are convenient methods for the synthesis of carbonyl derivatives of five- and six-membered nitrogen-containing heterocycles, ensembles of such heterocycles, and fused heterocyclic systems.[1,3-5]

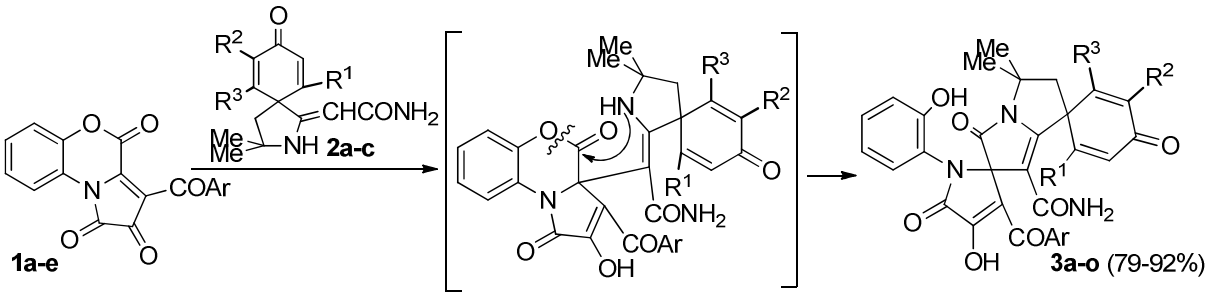
Recently, we have described the interactions of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **A** with 4′,5′-dihydro-2′,5′,5′-trimethyl-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one **B** and ethyl (2*Z*)-2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)-acetate **C** giving rise to substituted dispiro[naphthalene-1(4*H*),1′-[1*H*]pyrrolizine-6′(5′*H*),2″-[2*H*]pyrrole]-4,5′,5″(1″*H*)-triones[6] **D** and a bridged 7′-oxa-2′,12′-diazatetracyclo[6.5.1.0^{1,5}.0^{8,12}]tetradecane system[7,8] **E**, respectively (Scheme 1). During continuing studies on analogous transformations, we have now examined the reaction of pyrrolobenzoxazinetriones with a spiro heterocyclic enamine containing an additional functional amide group NH_2 – substituted 2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamides.[9] The latter possess three nucleophilic centers, β-CH and NH groups in the enamine moiety and an amide NH_2 group. Initial electrophilic attack at one of these centers should determine the structure of the final product.



Scheme 1. Formation of substituted dispiro[naphthalene-1(4*H*),1′-[1*H*]pyrrolizine-6′(5′*H*),2″-[2*H*]pyrrole]-4,5′,5″(1″*H*)-triones **D** and a bridged 7′-oxa-2′,12′-diazatetracyclo [6.5.1.0^{1,5}.0^{8,12}] tetradecane system **E**.

Results and Discussion

3-Aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **1a-e** interacted with substituted 2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamides **2a-c**,[9] proceeding at a 1:1 molar ratio of reactants under reflux for 2-5 min in anhydrous acetonitrile (until the disappearance of the bright violet color typical of the initial compounds **1**) and resulted in the formation of substituted dispiro pyrrolizidines **3a-o** (Scheme 2). The structure of compound **3f** was confirmed by X-ray analysis (Figure 1).



	3a(f)	3b(g)	3c(h)	3d(i)	3e(j)	3k	3l	3m	3n	3o
R^1	Me	Me	Me	Me	Me	H	H	H	H	H
R^2	Me(OMe)	Me(OMe)	Me(OMe)	Me(OMe)	Me(OMe)	$R^2+R^3 = (CH)_4$				
R^3	H	H	H	H	H					
Ar	C_6H_5	C_6H_4Me-4	C_6H_4OMe-4	C_6H_4Cl-4	C_6H_4Br-4	C_6H_5	C_6H_4Me-4	C_6H_4OMe-4	C_6H_4Cl-4	C_6H_4Br-4

1: Ar = Ph (a), 4-MeC_6H_4 (b), 4-$MeOC_6H_4$ (c), 4-ClC_6H_4 (d), 4-BrC_6H_4 (e); **2**: R^1 = R^2 = Me, R^3 = H (a), R^1 = Me, R^2 = OMe, R^3 = H (b), R^1 = H, R^2+R^3 = $(CH)_4$ (c)

Scheme 2. Interaction of 3-aroyl-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine-1,2,4-triones **1** with substituted 2-(3,3-dimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamides **2**.

Compounds **3a-o** are light yellow crystalline substances readily soluble in dimethylsulfoxide (DMSO) and *N,N*-dimethylformamide (DMF), poorly soluble in alcohols, ethers, chlorocarbons, aromatics and insoluble in saturated hydrocarbons and water. They showed a positive color test result (cherry color) for phenolic and enolic hydroxyl group upon treatment with an alcoholic solution of $FeCl_3$.

The molecular structures of compounds **3a-o** were confirmed with the help of spectroscopic and analytical data. For example, the IR spectra of **3a-o** contained two stretching bands of an NH_2 group in the range of 3428-3496 and 3303-3383 cm^{-1}, respectively, a stretching band indicating enol OH group as broadened band in the range of 3088–3247 cm^{-1}, two stretching bands of C^5=O and $C^{3'}$=O lactam carbonyl groups in the range of 1692-1746 cm^{-1}, stretching bands of $C^{4''}$=O and $CONH_2$ carbonyl groups in the range of 1647-1671 cm^{-1} and a stretching band indicating ArC=O carbonyl group at 1620-1634 cm^{-1}.

Analysis of compounds **3a**-**o** by ^1H NMR spectra (DMSO-d_6) showed that, besides the signals inherent to the protons of aromatic rings and the substituents attached thereto, the spectra exhibited two singlets at δ 1.16–1.91 ppm due to six protons of two methyl groups at the $C^{5'}$-atom of the pyrrolidine moiety, a two doublets at δ 1.98–2.72 ppm due to the methylene protons at $C^{6'}$-atom of the pyrrolidine moiety, a broadened a singlet at δ 5.67–6.37 ppm due to two protons of group NH_2, a singlet at δ 9.89–10.34 ppm due to proton of the phenolic group OH, and a singlet at δ 11.81–12.51 ppm due to proton of the enolic group OH.

We hypothesized that the described reaction involves the initial addition of an activated β-CH group of **2** to the C^{3a} in molecule **1**, followed by pyrrole ring closure via intramolecular

attack by the NH group on the lactone carbonyl carbon atom C^4 in the oxazine ring and opening of the latter at C^4–O^5, as has been described previously for the reaction of the same pyrrolobenzoxazinetriones with heterocyclic enamines: 1-methyl-3,4-dihydroisoquinolines[10,11] 2′,5′,5′-trimethyl-4′,5′-dihydro-4*H*-spiro[naphthalene-1,3′-pyrrol]-4-one.[6] It should be noted that the most favorable nucleophilic reaction center is the acetamide group NH_2 ($N^{\delta-}$ -0.400 for compound **2a**, $N^{\delta-}$ -0.401 for compound **2b**, $N^{\delta-}$ -0.402 for compound **2c**), according to semiempirical AM1 quantum-chemical calculations (Hyperchem 8.0 software package), but not the β-CH group ($C^{\delta-}$ -0.040 for compound **2a**, $C^{\delta-}$ -0.061 for compound **2b**, $C^{\delta-}$ -0.040 for compound **2c**) or NH group ($N^{\delta-}$ -0.122 for compound **2a**, $N^{\delta-}$ -0.138 for compound **2b**, $N^{\delta-}$ -0.130 for compound **2c**) of the enamine fragment. However, the NH_2 group does not participate in the course of this interaction.

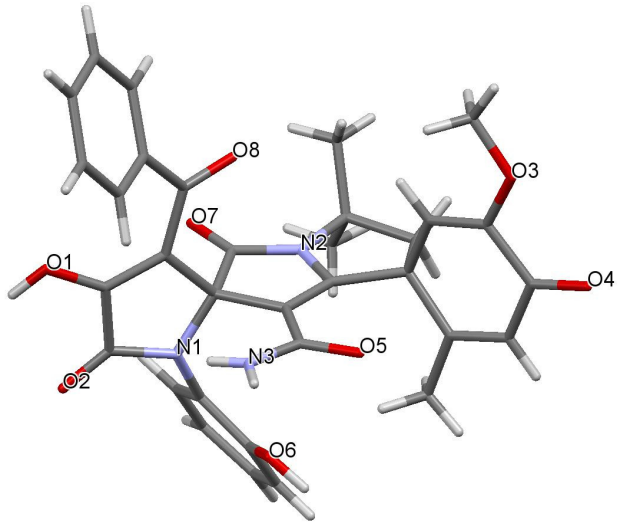


Figure 1. The molecular structure of 3-benzoyl-5',6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-2'',5',5'-trimethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]--1'-carboxamide **3f**.

Crystallographic data. According to the X-ray data, compound **3f** crystallizes in the centrosymmetric space group of a monoclinic system as a solvate with acetonitrile (1:1). The molecule has a complicated stereochemistry (Figure 1), so only heteroatoms are marked in Figure 1 for clarity. All bond distances and angles are typical for this class of compound. In the crystal packing, a system of intramolecular H-bonds with the participation of $CONH_2$, OH and C=O groups is present.

Conclusions

The described interaction may be regarded as an example of a regioselective synthetic pathway to a previously inaccessible dispiro heterocyclic system with various substituents in several positions of both heterocyclic fragments. The products may be regarded as dispiro heterocyclic analogs of pyrrolizidine alkaloids. Derivatives of pyrrolizidine alkaloids exhibit important pharmacological properties;[12] among these, the most significant are indicine *N*-oxide, platiphillin, and sarracine, which are important antitumor and spasmolytic drugs.

Experimental Section

General. The IR spectra were recorded in mineral oil on an IFS 66 (Bruker) spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Mercury-300BB instrument with dimethylsulfoxide (DMSO-d_6) [for compounds **3a-o**] or $CDCl_3$ [for compounds **2a,b**] as solvents and HMDS as the internal standard. The mass spectra were obtained on a Kratos MS-30 (UK) spectrometer (electron impact, 70 eV). Elemental analyses for C, H and N were obtained using a LECO CHNS-932 analyzer.

General procedure, exemplified by 2-(3,3,6,9-tetramethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamide (2a). 5.0 mmol of cyanoacetic acid amide was dissolved in 4 ml of 92% H_2SO_4, then under ice-cold water, 5.0 mmol of 2,5-dimethylanisole and 7.5 mmol of isobutyric aldehyde in 1 ml of CH_2Cl_2 were added. The mixture was stirred for 20 min at room temperature, then poured into a mixture of ice and 25 ml of aqueous ammonia. The resulting solid precipitate after neutralization was filtered off and purified by recrystallization from an ethanol-acetone mixture. **2a.** Light yellow crystals (from EtOH-$(Me)_2CO$), yield 61%, mp 197.5-198.5 °C; IR (ν_{max}, cm^{-1}): 3412, 3286, 1659, 1629. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.44 (3H, s, $C^{3}CH_3$), 1.46 (3H, s, $C^{3}CH_3$), 1.87 (3H, s, CH_3), 1.94 (3H, s, CH_3), 1.97 (1H, d, H^{4}_{A}, $^{2}J_{HH}$ 14.3 Hz), 2.15 (1H, d, H^{4}_{B}, $^{2}J_{HH}$ 14.3 Hz), 4.03 (1H, s, =CH-), 5.04 (2H, bs, NH_2), 6.14 (1H, s, H^{10}), 6.68 (1H, s, H^{7}), 8.49 (1H, bs, NH). MS, *m/z* (%): 260 $[M]^+$ (63.9), 245 $[M-Me]^+$ (17.1), 228 (19.4), 216 $[M-CO(NH_2)]^+$ (8.4), 200 (13.9), 176 $[M-NHCH=CHCO(NH_2)]^+$ (100), 161 (100), 146 (9), 134 (24.8), 121 (36.1), 103 (5.8), 91 (21.9), 85 (24.8), 77 (10). 43 (17.1). Anal. Calcd for $C_{15}H_{20}N_2O_2$ (260.33): C, 69.20; H, 7.74; N, 10.76%. Found: C, 69.27; H, 7.35; N, 10.71%.

2-(9-methoxy-3,3,6-trimethyl-8-oxo-2-azaspiro[4.5]deca-6,9-dien-1-ylidene)acetamide (2b). 2.0 mmol of cyanoacetic acid amide was dissolved in 2 ml of 92% H_2SO_4, then under ice-cold water, 5.0 mmol of 2,5-dimethylanisole and 7.5 mmol of isobutyric aldehyde were added. The mixture was stirred for 20 min at room temperature, then poured into a mixture of ice and 7 ml of aqueous ammonia, and extracted with methylene chloride (3 × 10 ml). The combined extracts

were dried over $MgSO_4$, the solvent was distilled off, and the residue was crystallized from isopropanol.

Light yellow crystals (from isopropanol), yield 44%, mp 208-210 °C; IR (ν_{max}, cm^{-1}): 3398, 3327, 3012, 1650, 1566. ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.46 (3H, s, C^3CH_3), 1.48 (3H, s, C^3CH_3), 1.96 (3H, s, C^6CH_3), 2.02 (1H, d, H^4_A, $^2J_{HH}$ 13.8 Hz), 2.23 (1H, d, H^4_B, $^2J_{HH}$ 13.8 Hz), 3.66 (3H, s, H_3CO-C^9), 4.06 (1H, s, -CH=), 4.97 (2H, br s, NH_2), 5.84 (1H, s, H^{10}), 6.18 (1H, s, H^7), 8.52 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 19.61 (CH_3-C^6), 30.84 and 32.09 ($2CH_3$-C^3), 46.68 (C^4), 54.85 (H_3CO-C^9), 56.63, 61.15 (C^3, C^5), 78.15 (-CH=), 119.78 and 127.98 (C^7, C^{10}), 148.89 and 159.36 (C^6, C^9), 161.99 (C^1), 172.49 (C=O), 180.95 (C^8). MS, *m/z* (%): 276 [M^+] (17), 259 [M^+-Me] (3), 245 [M^+-OMe] (2), 192 [M^+-NHC(CH)$CONH_2$] (83), 177 [M^+-NHC(CH)$CONH_2$-Me] (100). Anal. Calcd. for $C_{15}H_{20}N_2O_3$ (276.15): C, 65.20; H, 7.30; N, 10.14%. Found: C, 64.96; H, 7.27; N, 9.78%.

General procedure, exemplified by 3-benzoyl-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-2'',5',5',5''-tetramethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3a). A solution of compounds **1a** (1 mmol) and **2a** (1 mmol) in dry acetonitrile (20 ml) was heated under reflux for 2 min and then allowed to cool. The resulting solid precipitate was filtered off and purified by recrystallization from ethylacetate. **3a.** Light yellow crystals (from EtOAc), yield 89%, mp 253-254 °C; IR (ν_{max}, cm^{-1}): 3457, 3350 (NH_2), 3162 w (OH), 1740, 1717 (C^5=O, $C^{3'}$=O), 1663 ($C^{4''}$=O, $CONH_2$), 1627 (COPh). ^1H NMR (300.1 MHz, DMSO-d_6): δ_H 1.27 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.69, 1.75 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 14.4 Hz), 2.48 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 14.4 Hz), 5.85 (2H, bs, NH_2), 6.02 (1H, s, CH), 6.79 (1H, s, CH), 6.86-7.85 ($9H_{arom}$, m, 9CH), 9.92 (1H, s, OH, phenol), 12.44 (1H, bs, OH enol). Anal. Calcd for $C_{33}H_{29}N_3O_7$ (579.60): C, 68.38; H, 5.04; N, 7.25%. Found: C, 68.24; H, 5.17; N, 7.25%.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-2'',5',5',5''-tetramethyl-3-(4-methylbenzoyl)-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3b). Light yellow crystals (from EtOAc), yield 92%, mp 259-260 °C; IR (ν_{max}, cm^{-1}): 3496, 3377 (NH_2), 3153 w (OH), 1742, 1695 (C^5=O, $C^{3'}$=O), 1671 ($C^{4''}$=O, $CONH_2$), 1627 ($COC_6H_4CH_3$-4). ^1H NMR (300.1 MHz, DMSO-d_6): δ_H 1.27 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.69, 1.75 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 13.8 Hz), 2.47 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 14.4 Hz), 2.54 (3H, s, $C_6H_4CH_3$-4), 5.83 (2H, bs, NH_2), 6.01 (1H, s, CH), 6.77 (1H, s, CH), 6.85-7.76 ($8H_{arom}$, m, 8CH), 9.89 (1H, s, OH, phenol), 12.45 (1H, bs, OH enol). Anal. Calcd for $C_{34}H_{31}N_3O_7$ (593.63): C, 68.79; H, 5.26; N, 7.08%. Found: C, 68.72 ; H, 5.34; N, 6.97%.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxybenzoyl)-2'',5',5',5''-tetramethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3c). Light yellow crystals (from EtOAc), yield 86%, mp 270-271 °C; IR (ν_{max}, cm^{-1}): 3465, 3371 (NH_2), 3088 w (OH), 1746, 1713 (C^5=O, $C^{3'}$=O), 1665 ($C^{4''}$=O, $CONH_2$), 1620 ($COC_6H_4OCH_3$-4). ^1H NMR (300.1 MHz, DMSO-d_6): δ_H 1.27 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.69, 1.76 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 14.4 Hz), 2.47

(1H, d, $H^{6'}_{B}$, $^{2}J_{HH}$ 13.8 Hz), 3.89 (3H, s, $C_6H_4OCH_3$-4), 5.83 (2H, bs, NH_2), 6.01 (1H, s, CH), 6.77 (1H, s, CH), 6.86-7.87 ($8H_{arom}$, m, 8CH), 9.89 (1H, s, OH, phenol), 12.40 (1H, bs OH enol). Anal. Calcd for $C_{34}H_{31}N_3O_8$ (609.63): C, 66.99; H, 5.13; N, 6.89%. Found: C, 66.92; H, 5.15; N, 6.74%.

3-(4-Chlorobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-2'',5',5',5''-tetramethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3d). Light yellow crystals (from EtOAc), yield 88%, mp 281-282 °C; IR (ν_{max}, cm^{-1}): 3476, 3376 (NH_2), 3247 w (OH), 1743, 1715 (C^{5}=O, $C^{3'}$=O), 1658 ($C^{4''}$=O, $CONH_2$), 1634 (COC_6H_4Cl-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.27 (3H, s, CH_3), 1.54 (3H, s, CH_3), 1.68, 1.75 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_{A}$, $^{2}J_{HH}$ 13.8 Hz), 2.47 (1H, d, $H^{6'}_{B}$, $^{2}J_{HH}$ 14.4 Hz), 5.87 (2H, bs, NH_2), 6.01 (1H, s, CH), 6.78 (1H, s, CH), 6.85-7.88 ($8H_{arom}$, m, 8CH), 9.91 (1H, s, OH, phenol), 12.49 (1H, bs OH enol). Anal. Calcd for $C_{33}H_{28}ClN_3O_7$ (614.04): C, 64.55; H, 4.60; N, 6.84%. Found: C, 64.45; H, 4.68; N, 6.74%.

3-(4-Bromobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-2'',5',5',5''-tetramethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3e). Light yellow crystals (from EtOAc), yield 92%, mp 280-281 °C; IR (ν_{max}, cm^{-1}): 3428, 3302 (NH_2), 3242 w (OH), 1743, 1713 (C^{5}=O, $C^{3'}$=O), 1665 ($C^{4''}$=O, $CONH_2$), 1633 (COC_6H_4Br-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.28 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.68, 1.75 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_{A}$, $^{2}J_{HH}$ 14.1 Hz), 2.47 (1H, d, $H^{6'}_{B}$, $^{2}J_{HH}$ 14.1 Hz),5.83 (2H, bs, NH_2), 6.01 (1H, s, CH), 6.78 (1H, s, CH), 6.85-7.80 ($8H_{arom}$, m, 8CH), 9.91 (1H, s, OH, phenol), 12.51 (1H, bs OH enol). Anal. Calcd for $C_{33}H_{28}BrN_3O_7$ (658.50): C, 60.19; H, 4.29; N, 6.38%. Found: C, 60.02; H, 4.35; N, 6.27%.

3-Benzoyl-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-2'',5',5'-trimethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3f). Light yellow crystals (from EtOAc), yield 90%, mp 220-222 °C; IR (ν_{max}, cm^{-1}): 3465, 3361 (NH_2), 3175 w (OH), 1744, 1713 (C^{5}=O, $C^{3'}$=O), 1662 ($C^{4''}$=O, $CONH_2$), 1625 (COPh). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.38 (3H, s, CH_3), 1.68, 1.91 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_{A}$, $^{2}J_{HH}$ 13.8 Hz), 2.72 (1H, d, $H^{6'}_{B}$, $^{2}J_{HH}$ 14.1 Hz), 3.48 (3H, s, OCH_3), 5.20 (1H, s, CH), 5.82 (2H, bs, NH_2), 6.03 (1H, s, CH), 6.90-7.89 ($9H_{arom}$, m, 9CH), 9.92 (1H, s, OH, phenol), 12.42 (1H, bs, OH enol). Anal. Calcd for $C_{33}H_{29}N_3O_8$ (595.60): C, 66.55; H, 4.91; N, 7.06%. Found: C, 66.54; H, 5.02; N, 6.95%.

X-ray diffraction study of the compound (3f). X-ray analysis of **3f** including data collection, cell refinement and data reduction was carried out with an Oxford Diffraction Xcalibur SCCD diffractometer using CrysAlisPro software package[13]. Analysis was accomplished on standard procedure (monochromatic MoKα-irradiation, ω-scanning with steps 1°, 295(5) K). Absorption correction was not applied (μ= 0.094 mm^{-1}). According to X-Ray data the crystal is monoclinic, the space group C2/c, a = 29.4226(8) Å, b = 16.8116(11) Å, c = 14.2177(13) Å, β = 113.527(19)°. θ range for data collection: 2.86 to 26.38°. 6587 Reflections were collected, 2369 reflections with I>2σ(I), completeness 99.7 %. The structure was solved by the direct method

and refined by full-matrix least-squares on F^2 method using SHELXTL program package[14]. Results of refinement: R_1 = 0.0531, wR_2 = 0. 1239 (for I>2σ(I)), R_1 = 0.1253, wR_2 = 0.1288 (for all data), S = 1.003, largest diff. peak and hole 0.248 and -0.457 ēÅ^{-3}.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-2'',5',5'-trimethyl-3-(4-methylbenzoyl)-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3g). Light yellow crystals (from EtOAc), yield 87%, mp 228-230 °C; IR (ν_{max}, cm^{-1}): 3479, 3356 (NH_2), 3168 w (OH), 1740, 1701 (C^5=O, $C^{3'}$=O), 1663 ($C^{4''}$=O, $CONH_2$), 1626 ($COC_6H_4CH_3$-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.35 (3H, s, CH_3), 1.55, 1.73 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 13.8 Hz), 2.71 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 14.4 Hz), 2.42 (3H, s, $C_6H_4CH_3$-4), 3.48 (3H, s, OCH_3), 5.90 (2H, bs, NH_2), 5.95 (1H, s, CH), 6.03 (1H, s, CH), 6.85-7.80 ($8H_{arom}$, m, 8CH), 9.90 (1H, s, OH, phenol), 12.44 (1H, bs, OH enol). Anal. Calcd for $C_{34}H_{31}N_3O_8$ (609.63): C, 66.99; H, 5.13; N, 6.89%. Found: C, 66.91 ; H, 5.21; N, 6.88%.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-3-(4-methoxybenzoyl)-2'',5',5'-trimethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3h). Light yellow crystals (from EtOAc), yield 82%, mp 216-218 °C; IR (ν_{max}, cm^{-1}): 3482, 3354 (NH_2), 3157 w (OH), 1740, 1713 (C^5=O, $C^{3'}$=O), 1665 ($C^{4''}$=O, $CONH_2$), 1625 ($COC_6H_4OCH_3$-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.35 (3H, s, CH_3), 1.55, 1.73 (6H, s, $2CH_3$), 2.31 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 14.1 Hz), 2.54 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 14.1 Hz), 3.48 (3H, s, OCH_3), 3.89 (3H, s, $C_6H_4OCH_3$-4), 5.94 (1H, s, CH), 5.97 (2H, bs, NH_2), 6.02 (1H, s, CH), 6.85-7.88 ($8H_{arom}$, m, 8CH), 9.90 (1H, s, OH, phenol), 12.47 (1H, bs, OH enol). Anal. Calcd for $C_{34}H_{31}N_3O_9$ (625.62): C, 65.27; H, 4.99; N, 6.72%. Found: C, 65.15; H, 5.19; N, 6.70%.

3-(4-Chlorobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-2'',5',5'-trimethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3i). Light yellow crystals (from EtOAc), yield 88%, mp 225-227 °C; IR (ν_{max}, cm^{-1}): 3467, 3350 (NH_2), 3242 w (OH), 1740, 1718 (C^5=O, $C^{3'}$=O), 1665 ($C^{4''}$=O, $CONH_2$), 1630 (COC_6H_4Cl-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.37 (3H, s, CH_3), 1.67, 1.91 (6H, s, $2CH_3$), 2.27 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 13.8 Hz), 2.71 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 14.4 Hz),3.41 (3H, s, OCH_3), 5.20 (1H, s, CH), 5.85 (2H, bs, NH_2), 6.04 (1H, s, CH), 6.87-7.92 ($8H_{arom}$, m, 8CH), 9.92 (1H, s, OH, phenol), 12.50 (1H, bs OH enol). Anal. Calcd for $C_{33}H_{28}ClN_3O_8$ (630.04): C, 62.91; H, 4.48; N, 6.67%. Found: C, 62.80; H, 4.53; N, 6.53%.

3-(4-Bromobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5''-methoxy-2'',5',5'-trimethyl-3',4'',5-trioxodispiro[(2'',5''-cyclohexadiene)-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3j). Light yellow crystals (from EtOAc), yield 92%, mp 271-272 °C; IR (ν_{max}, cm^{-1}): 3479, 3356 (NH_2), 3157 w (OH), 1743, 1704 (C^5=O, $C^{3'}$=O), 1662 ($C^{4''}$=O, $CONH_2$), 1627 (COC_6H_4Br-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.35 (3H, s, CH_3), 1.54, 1.71 (6H, s, $2CH_3$), 2.32 (1H, d, $H^{6'}_A$, $^2J_{HH}$ 14.1 Hz), 2.54 (1H, d, $H^{6'}_B$, $^2J_{HH}$ 13.9 Hz), 3.48 (3H, s, OCH_3), 5.95 (1H, s, CH), 5.96 (2H, bs, NH_2), 6.03 (1H, s, CH), 6.85-7.81

($8H_{arom}$, m, 8CH), 9.91 (1H, s, OH, phenol), 12.49 (1H, bs OH enol). Anal. Calcd for $C_{33}H_{28}BrN_3O_8$ (674.49): C, 58.76; H, 4.18; N, 6.23%. Found: C, 58.70; H, 4.18; N, 6.06%.

3-Benzoyl-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5',5'-dimethyl-3',4'',5-trioxodispiro[naphthalene-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3k). Light yellow crystals (from EtOAc), yield 79%, mp 214-216 °C; IR (ν_{max}, cm^{-1}): 3463, 3354 (NH_2), 3162 w (OH), 1743, 1703 (C^5=O, $C^{3'}$=O), 1662 ($C^{4''}$=O, $CONH_2$), 1625 (COPh). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.18 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.98 (1H, d, $H^{6'}{}_A$, $^2J_{HH}$ 13.5 Hz), 2.16 (1H, d, $H^{6'}{}_B$, $^2J_{HH}$ 13.8 Hz), 6.37 (2H, bs, NH_2), 6.18 (1H, d, CH), 6.61 (1H, d, CH), 6.83-7.15 ($13H_{arom}$, m, 13CH), 10.32 (1H, s, OH, phenol), 11.87 (1H, bs, OH enol). Anal. Calcd for $C_{35}H_{27}N_3O_7$ (601.60): C, 69.88; H, 4.52; N, 6.98%. Found: C, 69.83; H, 4.61; N, 6.92%.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5',5'-dimethyl-3-(4-methylbenzoyl)-3',4'',5-trioxodispiro[naphthalene-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3l). Light yellow crystals (from EtOAc), yield 82%, mp 216-218 °C; IR (ν_{max}, cm^{-1}): 3495, 3376 (NH_2), 3164 w (OH), 1746, 1700 (C^5=O, $C^{3'}$=O), 1659 ($C^{4''}$=O, $CONH_2$), 1627 ($COC_6H_4CH_3$-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.18 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.98 (1H, d, $H^{6'}{}_A$, $^2J_{HH}$ 13.5 Hz), 2.16 (1H, d, $H^{6'}{}_B$, $^2J_{HH}$ 13.8 Hz), 2.42 (3H, s, $C_6H_4CH_3$-4), 5.73 (2H, bs, NH_2), 6.18 (1H, d, CH), 6.59 (1H, d, CH), 6.84-8.06 ($12H_{arom}$, m, 12CH), 10.34 (1H, s, OH, phenol), 11.93 (1H, bs, OH enol). Anal. Calcd for $C_{36}H_{29}N_3O_7$ (615.63): C, 70.23; H, 4.75; N, 6.83%. Found: C, 70.22 ; H, 4.95; N, 6.65%.

5'6'-Dihydro-4-hydroxy-1-(2-hydroxyphenyl)-3-(4-methoxybenzoyl)-5',5'-dimethyl-3',4'',5-trioxodispiro[naphthalene-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3m). Light yellow crystals (from EtOAc), yield 84%, mp 219-221 °C; IR (ν_{max}, cm^{-1}): 3472, 3349 (NH_2), 3171 w (OH), 1743, 1692 (C^5=O, $C^{3'}$=O), 1665 ($C^{4''}$=O, $CONH_2$), 1625 ($COC_6H_4OCH_3$-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.16 (3H, s, CH_3), 1.46 (3H, s, CH_3), 1.98 (1H, d, $H^{6'}{}_A$, $^2J_{HH}$ 13.8 Hz), 2.16 (1H, d, $H^{6'}{}_B$, $^2J_{HH}$ 13.9 Hz), 3.91 (3H, s, $C_6H_4OCH_3$-4), 6.19 (1H, d, CH), 6.36 (2H, bs, NH_2), 6.57 (1H, d, CH), 6.81-8.05 ($12H_{arom}$, m, 12CH), 10.33 (1H, s, OH, phenol), 11.81 (1H, bs, OH enol). Anal. Calcd for $C_{36}H_{29}N_3O_8$ (631.63): C, 68.46; H, 4.63; N, 6.65%. Found: C, 68.31; H, 4.75; N, 6.46%.

3-(4-Chlorobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5',5'-dimethyl-3',4'',5-trioxodispiro[naphthalene-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-carboxamide (3n). Light yellow crystals (from EtOAc), yield 82%, mp 220-222 °C; IR (ν_{max}, cm^{-1}): 3447, 3345 (NH_2), 3226 w (OH), 1724, 1702 (C^5=O, $C^{3'}$=O), 1647 ($C^{4''}$=O, $CONH_2$), 1626 (COC_6H_4Cl-4). ^{1}H NMR (300.1 MHz, DMSO-d_6): δ_H 1.59 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.47 (1H, d, $H^{6'}{}_A$, $^2J_{HH}$ 13.8 Hz), 2.68 (1H, d, $H^{6'}{}_B$, $^2J_{HH}$ 14.4 Hz), 5.68 (2H, bs, NH_2), 6.12 (1H, d, CH), 6.34 (1H, d, CH), 6.95-7.85 ($12H_{arom}$, m, 12CH), 9.89 (1H, s, OH, phenol), 11.95 (1H, bs OH enol). Anal. Calcd for $C_{35}H_{26}ClN_3O_7$ (636.05): C, 66.09; H, 4.12; N, 6.61%. Found: C, 65.95; H, 4.25; N, 6.61%.

3-(4-Bromobenzoyl)-5'6'-dihydro-4-hydroxy-1-(2-hydroxyphenyl)-5',5'-dimethyl-3',4'',5-trioxodispiro[naphthalene-1''(4''*H*),7'-[7*H*]pyrrolizine-2'(3'*H*),2-[2*H*]pyrrole]-1'-

carboxamide (3o). Light yellow crystals (from EtOAc), yield 86%, mp 219-220 °C; IR (ν_{max}, cm^{-1}): 3447, 3383 (NH_2), 3216 w (OH), 1725, 1703 (C^5=O, $C^{3'}$=O), 1647 ($C^{4''}$=O, $CONH_2$), 1623 (COC_6H_4Br-4). ^1H NMR (300.1 MHz, DMSO-d_6): δ_H 1.59 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.47 (1H, d, $H^{6'}{}_A$, $^2J_{HH}$ 14.4 Hz), 2.68 (1H, d, $H^{6'}{}_B$, $^2J_{HH}$ 14.1 Hz), 5.67 (2H, bs, NH_2), 6.12 (1H, d, CH), 6.34 (1H, d, CH), 6.95-7.86 ($12H_{arom}$, m, 12CH), 9.89 (1H, s, OH, phenol), 11.90 (1H, bs OH enol). Anal. Calcd for $C_{35}H_{26}BrN_3O_7$ (680.50): C, 61.77; H, 3.85; N, 6.17%. Found: C, 61.70; H, 3.93; N, 6.06%.

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References

1. Mashevskaya, I. V.; Maslivets, A. N. *Chem. Heterocycl. Cmpd.* **2006**, *42*, 1.
2. Maslivets, A. N.; Mashevskaya, I. V.; Krasnikh, O. P.; Shurov, S. N.; Andreichikov, Yu. S. *Russ. J. Org. Chem*. **1992**, *28*, 2545 (in Russia).
3. Mashevskaya, I. V.; Aliev, Z. G.; Mazhukin, D. G.; Popov, S. A.; Tikhonov, A. Ya. Maslivets, A. N. *Russ. J. Org. Chem*. **2008**, *44*, 1189. http://dx.doi.org/10.1134/S1070428008080149
4. Babenysheva, A.V.; Maslivets, V.A.; Maslivets, A.N. *Russ. J. Org. Chem*. **2007**, *43*, 1577. http://dx.doi.org/10.1134/S107042800710034X
5. Babenysheva, A. V.; Lisovskaya, N.A.; Maslivets, A.N. *Russ. J. Org. Chem*. **2007**, *43*, 633. http://dx.doi.org/10.1134/S1070428007040288
6. Konovalova, V. V.; Shklyaev, Yu. V.; Maslivets, A.N. *Russ. J. Org. Chem*. **2012**, *48*, 1257. http://dx.doi.org/10.1134/S1070428012090205
7. Konovalova, V. V.; Stryapunina, O. G.; Shklyaev, Yu. V.; Maslivets, A. N. *Russ. J. Org. Chem*., **2012**, *48*, 1493. http://dx.doi.org/10.1134/S1070428012110139
8. Konovalova, V. V.; Stryapunina, O. G.; Shklyaev, Yu. V.; Slepukhin, P. A.; Maslivets, A. N. *Russ. J. Org. Chem*. **2013**, *49*, 268. http://dx.doi.org/10.1134/S1070428013020140
9. Nifontov, Yu.V.; Glushkov, V. A.; Shklyaev, Yu. V. *Russ. Chem. Bull.* **2003**, *52*, 437. http://dx.doi.org/10.1023/A:1023479420744
10. Racheva, N. L.; Shklyaev, Yu.V.; Rozhkova, Yu. S.; Maslivets, A. N. *Russ. J. Org. Chem*. **2007**, *43*, 1330. http://dx.doi.org/10.1134/S1070428007090114

11. Mashevskaya, I. V.; Duvalov, A. V.; Rozhkova, Yu. S.; Shklyaev, Yu.V.; Racheva, N. L.; Bozdyreva, Ks. S.; Maslivets, A. N. *Mendeleev Commun*. **2004**, *14*, 75. http://dx.doi.org/10.1070/MC2004v014n02ABEH001897
12. Semenov, A. A. and Kartsev, V. G. *Foundations of the Chemistry of Natural Compounds*; Moscow, **2009**, vol. 2, p. 45.
13. Oxford Diffraction, "CrysAlysPro (Version 171.31.8) and CrysAlysRed (Version 1.171.31.8)", Oxford Diffraction Ltd., Abingdon, **2007**.
14. Sheldrick G. M. *Acta Crystallogr. Sec A*. **2008**, *64*, 112. http://dx.doi.org/10.1107/S0108767307043930 PMid:18156677

