A COMPLETE NMR DATA ASSIGNMENT FOR THREE DISPIROCOMPOUNDS

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ABSTRACT

The synthesis of three new dispirocompounds containing imidazolidine dione and isatin fragments as main building blocks each bonded to different ring substituents (i.e. tetraline, 1,4-diazepine, 1,5-benzothiazepine, fluorene) by a spirocarbon was reported. The heterocyclic compounds were obtained with high yields by applying novel and efficient synthetic procedures accompanied with melting point determination. The structures of the synthesized spirocompounds were verified by using a combination of 1D (^{1}H, ^{13}C, DEPT 135) and 2D NMR techniques (^{1}H-^{1}H COSY, HSQC, HMBC). Fully assigned NMR data was presented for each heterocyclic derivative supported by partially assigned ATR-IR data. Cycloalkanespirohydantoins possess anticonvulsant properties similarly to benzothiazepines. Thus, it is expected that the newly synthesized compounds would be biologically active.

Keywords: 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'H-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione, 1-{2'-oxo-1',2'-dihydro-5H-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'H-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione, 1'-{2'-oxo-1',2'-dihydro-5H-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}spiro[fluorene-9,4'-imidazolidine]-2',5'-dione, NMR.

INTRODUCTION

Isatin is a main precursor used for the synthesis of various heterocyclic compounds with two or more spirocarbons [1]. Such examples are some dispirooxindoles containing *N*-unsubstituted heterocyclic moieties (2-thiohydantoin, hydantoin, and thiazolidine) that possess anticancer activity [2]. Furthermore, dispirocompounds, synthesized from imidazothiazolotriazine and pyrrolidineoxindole, were proven to have antiproliferative and antibacterial properties [3]. Recently, new dispiroimidazolidine derivative, 4-(8-Propyl-2,4-dithioxo-1,3-diazaspiro[4.5] decan-3-yl)spiro[1,5-dihydro-1,5-benzodiazepine-2,3′-indoline]-2′-one), was found to exist in an equilibrium with its tautomer in the reaction mixture which was proved by the assigned 1D and 2D NMR data [4]. Moreover, some dispiroindolo-pyrrolidines / -imidazolidines synthesized by 1,3-dipolar cycloaddition of azomethine ylides with exomethylenes / imines in the presence of copper(I) thiophenecarboxylate were reported [5].

Several fluorene-containing imidazolidine spirocompounds were described in recent studies. For example, fully assigned 1D and 2D NMR data was provided for the structure of 5′-oxospiro-(fluorene-9,4′-imidazolidine)-2′-thione [6] which had been previously proven to act as a ligand for Pt(II) [7] and Cu(II) [8] complexes. Additionally, the structures of 1',3'-bis(hydroxymethyl)-2'*H*,5'*H*-spiro[fluorene-9,4'-imidazolidine]-2',5'-dione and 2-bromo-2'*H*,5'*H*-spiro[fluorene-9,4'-imidazolidine]-2',5'-dione were also verified by 1D and 2D NMR spectroscopy [9].

Tetraline is an aromatic substituent incorporated in a variety of heterocyclic compounds containing spiro carbons. Organic selenocyanates containing spiro-6-methoxytetraline-1,3'-pyrolidine were tested for inhibitory activity against toxicity caused by Cd [10]. Some pyperidinyltetralines possess a potential antipsychotic activity [11]. Spiro compounds of tetraline-1,4'-pyperidine were obtained as for them ^{1}H NMR data was reported [12]. Another example is the biologically active spiro[cyclohexane-1,2'-tetraline]-1,4'-dione that has the property to stimulate the activity of stilbestrol at concentration levels below or equal to 10 μg kg^{-1} [13]. Mechanistic studies were conducted where 1,2,3,4-tetrahydronaphtalene-2,2-spiro-(2'-n-propylcyclopentane) was synthesized to investigate the rearrangement of alkyl-substituted spirocyclopentane ring during the dehydrogenation stage [14].

1,4-diazepine derivative had a main role as a precursor in a regio- and chemoselective [4 + 2 + 1] domino cyclization in the production of spiro-substituted benzo[*b*]furo[3,4-*e*][1,4]diazepine derivatives [15]. In addition, spiro-1,4-diazepine-2,5-dione heterocycles were obtained from furano exo-glycals [16]. The reaction of cyclopentane-1,3-dione, 1,2- phenylenediamine, and isatins catalyzed by spiro-phosphoric-acid under mild reaction conditions led to the chiral 1,4-diazepine-containing spiroderivatives based on cyclopenta[1,4] diazepine framework [17]. Spiro heterocyclic compounds obtained by using pyrimido[4,5-b][1,4] diazepin]-8'(9'*H*)-one as a precursor during a tandem nitroso-ene/Diels-Alder reaction of 4-(alkenoylamino)-5-nitrosopyrimides were described [18].

1,5-Benzothiazepine is a heterocyclic moiety that is present often in a variety of spirocompounds. Such examples are some of its indole spiro derivatives for which partially assigned ^{1}H, ^{13}C and ^{19}F NMR data exist [19, 20]. Other spirocompounds are spiro(imidazo[4',5':4,5'] benzo[1,2-e][1,4]thiazepine)-9,3'-indolines, possessing anti-microbial, anti-inflammatory and antioxidant properties [21]. A microwave induced synthesis of spiro[1,5]-benzothiazepine-2,3'[3'*H*]indole-2[1'*H*]-ones without the use of a solvent was reported as the products had antimicrobial and antituberculosis activity [22]. In addition, the role of 1,5-benzothiazepine in the synthesis of spiro-[1,5]-benzothiazepine derivatives with potential pharmaceutical application was thoroughly reviewed [23].

Dispirocompounds containing substituted imidazolidine and isatin fragments as main building blocks each of them bonded to some of the following substituents such as tetraline, 1,4-diazepine, 1,5-benzothiazepine and/or fluorene by a spiro carbon have never been reported up to date. Therefore, the aim of the present work was to describe the synthesis as well as the structure verification of such three new dispiroimidazolidine derivatives with two spirocarbons. Fully assigned 1D and 2D NMR data was provided for each heterocyclic dispirocompound supported additionally by partially assigned ATR-IR spectra.

EXPERIMENTAL

Materials and methods

Digital apparatus (SMP10) and Koffler apparatus were used for measuring the melting points of the synthesized compounds.

A Bruker Avance III HD spectrometer (Bruker Optics, Billerica, MA, USA) with frequencies 125.76 MHz (^{13}C) and 500.130 MHz (^{1}H) was used to measure the 1D and 2D NMR spectra. TMS was used as an internal standard and DMSO-d_6 as a solvent. ATR spectrum was registered with VERTEX 70 FT-IR instrument (Bruker Optics, Billerica, MA, USA) using MIRacleTM with a one-reflection ZnSe element (PIKE Technology, Madison, WI, USA). ATR data was measured in the range (4000 - 600) cm^{-1} with 25 scans and a resolution of 2 cm^{-1}.

Synthesis of 1-{2'-oxo-1,1',2',5,6,7-hexahydro-spiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione and 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-

spiro[imidazolidine-4,1'-naphthalene]-2,5-dione

Compound **1**, /3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione/, was synthesized according to an already published procedure by Marinov et. al. [24]. Compound **2**, /1-acetyl-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione/, was obtained according to the procedure described by Marinov et. al. [25]. A mixture of 1-acetyl-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (2, 2.58 g, 0.01 mol), 2,3-dihydro-1*H*-indole-2,3-dione (3, 1.47 g, 0.01 mol) in absolute ethanol (100 mL) and 3 drops of pyperidine was shaken for 30 min at room temperature. Solid yellow matter was formed after one night stay at room temperature which was filtered and recrystallized from ethanol/dioxane. Thus, 1-[2-(3-hydroxy-2-oxo-2,3-dihydro-1*H*-indol-3-yl)acetyl]-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**4**, 4.05 g, 0.01 mol) was obtained and solved in 25 mL glacial AcOH and 0.5 mL concentrated HCl. The reaction mixture was heated and refluxed for 1 h as it was subsequently cooled to room temperature.

As a result, 1-[2-(2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetyl]-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (5) was obtained as an orange crystal product which was filtered, recrystallized from ethanol/dioxane and used for the synthesis of compounds **6** and **7**, as it followed:

1) Ethane-1,2-diamine (0.33 g, 0.0055 mol) was added to the solution of *α,β*-unsaturated ketone 5 (1.93 g, 0.005 mol) in 20 mL ethanol and 0.5 mL glacial AcOH. The reaction mixture was heated and refluxed for 10 h as it was cooled to a room temperature. Light brown crystal sediment containing 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (6) was obtained which was filtered and recrystallized from ethanol/dioxane.

2) 2-Aminobenzene-1-thiol (0.59 g, 0.0055 mol) was added to the solution of compound 5 (1.93 g, 0.005 mol) in 20 mL ethanol and 0.5 mL glacial AcOH. The reaction mixture was heated and refluxed for 6 h as it was cooled to room temperature. A yellow solid sediment containing 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (7) was obtained which was subsequently filtered and recrystallized from ethanol/dioxane.

Synthesis of 1'-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}spiro[fluorene-9,4'-imidazolidine]-2',5'-dione

Compound **8**, /spiro[fluorene-9,4'-imidazolidine]-2',5'-dione/, was obtained by applying a modified method of Bucherer-Lieb [26]. Compound **9** /1'-acetylspiro[fluorene-9,4'-imidazolidine]-2',5'-dione/ was synthesized according to [25]. Compound 12 /1'-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}spiro[fluorene-9,4'-imidazolidine]-2',5'-dione/ was obtained following the methodology used for the synthesis of compound 7.

RESULTS AND DISCUSSION

The synthesis of 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (6) and 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (7) was done according to the reaction scheme, shown on Fig.1. The respective yields of compounds **4**, **5, 6**, **7** from the reaction scheme (Fig. 1) were 79 %, 63 %, 84 %, 63 %. The melting points of compounds **4**, **5**, **6**, **7** were respectively in the ranges 184-185°C, 218-219°C, 212-213°C and 222-223°C.

Structure verification of 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (6)

The structure of compound **6** is presented on Fig. 2 with the atom numbering used only for the spectral assignments (Table 1). Molecular formula of 6 is $C_{24}H_{23}N_5O_3$.

There were 24 signals in ^{13}C NMR spectra corresponding to the carbons in the structure. Both signals at 174.47 ppm and 177.93 ppm were assigned to the carbonyl carbons, respectively C^4=O and $C^{ii'}$=O, whereas the signal at 154.23 ppm was assigned to C^2=O. The signals at 63.08 ppm and 66.25 ppm correspond to the two spirocarbons - C (iii') and C (1').

There were nine HSQC negative correlations - (2.12 ppm - 29.75 ppm), (2.48 ppm - 29.75 ppm), (1.88 ppm -

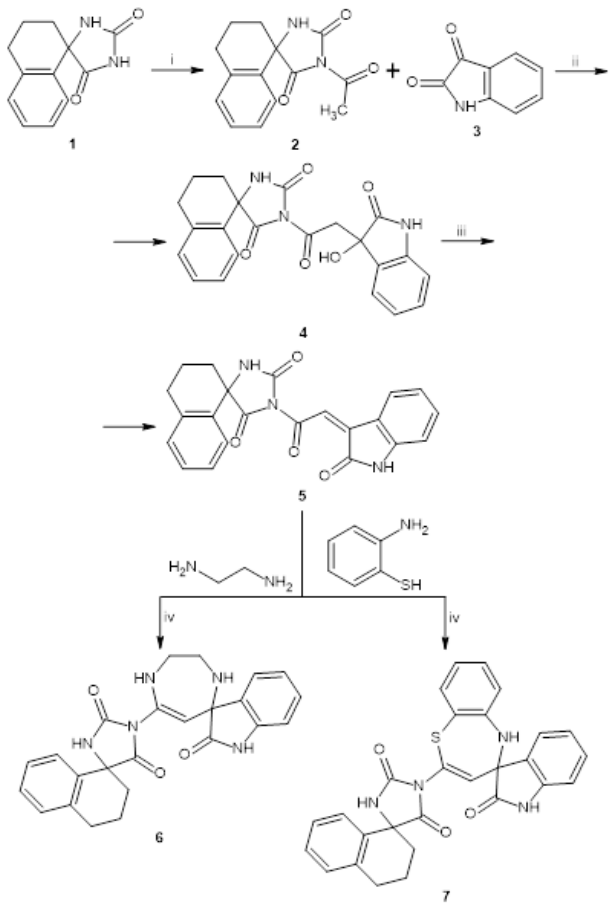

Fig. 1. Scheme of the synthesis of 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (6) and 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (7). i: pyridine, $(CH_3CO)_2O$; ii: EtOH, pyperidine; iii: HCl, AcOH; iv: EtOH, AcOH.

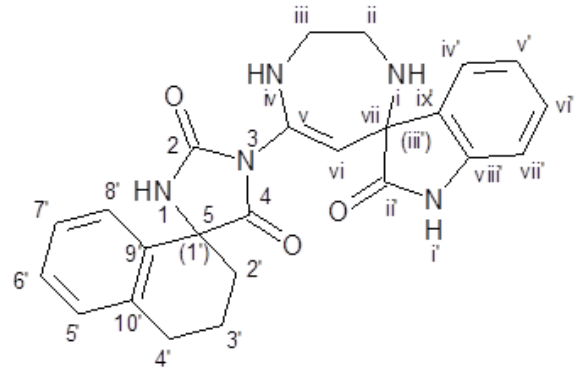

Fig. 2. The structure of 1-{2'-oxo-1,1',2',5,6,7-hexahydrospiro[1,5-diazepine-2,3'-indol]-4-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (6).

19.38 ppm), (2.18 ppm - 19.38 ppm), (2.76 ppm - 28.47 ppm), (2.06 ppm -33.52 ppm), (1.90 ppm - 33.52 ppm), (1.80 ppm - 18.41 ppm), (2.09 ppm - 18.41 ppm). Thus, only the protons in one of the CH_2 groups are chemically equivalent whose ^1H signals were at 2.76 ppm. Additionally, one extremely weak and one strong HMBC correlations were found, (1.88 ppm - 66.25 ppm) and (2.48 ppm - 66.25 ppm), indicating that the ^1H signals at 2.12 ppm (H_a), 2.48 ppm (H_b), 1.88 ppm (H_c) and 2.18 ppm (H_d) were correspondingly for the protons H_a, H_b in $C^{2'}H_2$ and H_c, H_d in $C^{3'}H_2$ groups.

The signal at 66.25 ppm was for the spirocarbon $C^{(1')}$. Thus, the ^1H signal at 2.76 ppm was assigned to the chemically equivalent protons in $C^{4'}H_2$. There were HMBC correlations of the ^1H signals at 2.48 ppm and 2.76 ppm with the ^{13}C signal at 19.38 ppm. Also, a weak and a strong HMBC correlations respectively of the signals at 2.18 ppm and 2.76 ppm with the signal at 29.75 ppm can be found. Therefore, the chemical shifts 28.47 ppm, 19.38 ppm and 29.75 ppm were assigned correspondingly to the ^{13}C signals of the carbons, C - 4', C - 3' and C - 2'. Moreover, a strong HMBC correlation is available between the signals at 2.48 ppm and 174.47 ppm indicating the interaction of the proton H_b with the carbonyl carbon, C-4. Consequently, the signal at 63.08 ppm corresponded to the spirocarbon, C-iii'.

Two HMBC correlations, (2.09 ppm - 63.08 ppm) and (2.09 ppm - 126.52 ppm) were found for the $C^{ii}H_2$ group in which the proton H_h is closer to the spirocarbon, C-iii', as well as to the nearest carbon in the isatin fragment (C-iv') compared to the protons in $C^{iii}H_2$ group. The signal at 1.80 ppm was assigned respectively to the H_g proton in $C^{ii}H_2$. In this case, the signals at 1.90 ppm, 2.06 ppm and 33.52 ppm were correspondingly for the protons (H_f and H_e) and C-iii carbon in $C^{iii}H_2$ group. The conclusions were supported by the found COSY correlations - (1.80 - 1.90 ppm), (1.80 ppm - 2.06 ppm), (2.09 ppm - 1.90 ppm), (2.09 ppm - 2.06 ppm), (2.09 ppm - 1.80 ppm), (1.90 ppm - 2.06 ppm).

There was a strong HMBC correlation, (7.03 ppm -

Table 1. ^{1}H and ^{13}C NMR data assigned for 6 [^{1}H [500.13 MHz] and ^{13}C [125.76 MHz]][a].

Atom	δ (^{13}C), ppm	DEPT[b]	δ (^{1}H), ppm	Multiplicity, J, Hz	^{1}H-^{1}H COSY [b]	HMBC[b]
2(C=O)	154.23	C				
4(C=O)	174.47	C				
1(NH)			11.78	br. s		
(1')	66.25	C				
2'	29.75	CH_2	2.12(H_a)[c] 2.48(H_b)[c]	m dd(12.9, 3.9)	2'(H_b), 3'(H_c), 3'(H_d); 2'(H_a), 3'(H_c)[d],3'(H_d)[d]	4'[f] (1'), 3',4',4
3'	19.38	CH_2	1.88(H_c)[c] 2.18 (H_d)[c]	m	2'(H_a),2'(H_b)[d],3'(H_d),4'; 2'(H_a)[d] 2'(H_b)[d],3'(H_c), 4'	(1')[f] 2'[f], 4'[f]
4'	28.47	CH_2	2.76	dd(7.6, 4.5)	3'(H_c), 3'(H_d)	2',3',5', 9',10'
9'	132.51	C				
10'	138.46	C				
8'	124.03	CH	7.03[d]	m	7'	(1'), 6', 10'
7'	126.56	CH	7.12[d]	m	6',8'	5'
6'	127.50	CH	7.16[d]	m	5',7'	8', 10'
5'	129.26	CH	7.15[d]	m	6'	4'[e]
ii'(C=O)	177.93	C				
v	167.79	C				
iv (NH)			11.78	br. s		
iii	33.52	CH_2	2.06 (H_e)[c] 1.90 (H_f)[c]	m	ii(H_g), ii(H_h), iii(H_f); ii(H_g), ii(H_h), iii(H_e)	
ii	18.41	CH_2	1.80(H_g)[c] 2.09(H_h)[c]	m	ii(H_h), iii(H_e), iii(H_f) ii(H_g),iii(H_e), iii(H_f)	(iii')[e], iv'[f]
i(NH)			10.81	s		
(iii')	63.08	C				
i'(NH)			8.51	s		(iii'), ii', iii'
viii'	156.47	C				
ix'	137.72	C				
iv'	126.52	CH	7.07[d]	m	v'	(iii')[e]
v'	126.61	CH	7.20[c]	m	iv',vi'	
vi'	134.37	CH	7.17	m	v', vii'	
vii'	127.94	CH	7.21[c]	m	vi'	ix'
vi	25.93	CH	2.42	s		v

[a]In DMSO-d_6 solution. All spectral assignments were in agreement with HSQC, HMBC and COSY spectra. [b]Abbreviations: DEPT, Distortionless Enhancement by Polarization Transfer spectrum; ^{1}H-^{1}H COSY - proton-proton homonuclear correlation spectrum; HSQC, Heteronuclear Single Quantum Correlation experiment; HMBC, Long range ^{1}H-^{13}C Heteronuclear Multiple Bond Correlation experiment. [c]Assigned from the HSQC spectrum. [d]Assigned from the HMBC spectrum. [e]Weak correlations. [f]Extremely weak correlations.

66.25 ppm), indicating the interaction of the proton H - 8' with the spirocarbon, C-1'. The weak HMBC correlation, (7.15 ppm - 28.47 ppm), indicate that 7.15 ppm was for the signal of the proton H-5', which can interact with the carbon, C-4'. The strong HMBC correlations, (7.03 ppm - 127.50 ppm) and (7.16 ppm - 124.03 ppm), indicated the meta interactions between H-8' and C-6' as well as between H-6' and C-8'. In addition, other two HMBC correlations of the protons H-8' and H-6' with the signal of the nonprotonated carbon, C-10' - (7.03 ppm - 138.46 ppm) and (7.16 ppm - 138.46 ppm), were found. The HMBC correlations, (2.76 ppm - 138.46 ppm) and (2.76 ppm - 132.51 ppm), indicated the interaction of the proton H-4' with the nonprotonated carbons, C-10' and C-9'.

The weak HMBC correlation, (7.07 ppm - 63.08 ppm), indicated that the ^{1}H chemical shift 7.07 ppm was for the signal of the proton H-iv' as it is the closest proton to the spirocarbon, C-iii', from the corresponding benzene ring in the isatin fragment. The strong HMBC correlation, (7.21 ppm - 137.72 ppm), was a result from the meta interaction in the benzene ring between the proton H-vii' and the nonprotonated carbon, C-ix'. There were two COSY correlations for each proton, H-vi' and H-v', (7.17 ppm - 7.20 ppm), (7.17 ppm - 7.21 ppm), (7.20 ppm - 7.07 ppm), due to their interaction with each of their neighboring protons.

The singlet at 8.51 ppm with area 0.52 was assigned to the NH-i' proton in the isatine fragment. The HMBC correlations - (8.51 ppm - 63.08 ppm), (8.51 ppm - 177.93 ppm) and (8.51 ppm - 156.47 ppm), confirmed the assignment of the signals at 177.93 ppm and 156.47 ppm, respectively to the carbons, C-ii' and C-viii'. The widened singlet at 11.78 ppm with area 1.01 included the signals of NH-1 and NH-iv protons, as the singlet at 10.81 ppm with area 0.53 was for NH-i proton.

ATR-IR bands (cm^{-1}) for compound 6**:** 3212 (ν(N-H)), 3108 ν(C-H), 3034 (ν(C-H)), 2986, 2948 (ν_{as}(CH$_2$)), 2875, 2767, 2742, 1799, 1758 ν(C=O), 1707 ν(C=O), 1679 ν(C=O), 1497 (ν(C=C)), 1449 (ν(C=C)), 1435 (ν(C=C)), 1376, 1345, 1335, 1318, 1299, 1289, 1277, 1240, 1223, 1178, 1164, 1145, 1118, 1091, 1066, 1041, 993, 961, 944, 911, 875, 839, 768, 758, 737, 701, 674, 604.

Structure verification of 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (7)

The structure of compound 7 is presented on Fig. 3 with the atom numbering used only for the spectral assignments (Table 2). Molecular formula of **7** is $C_{28}H_{22}SN_4O_3$. As it can be seen from Fig. 3, the structure of 7 contains tetraline and isatine fragments similarly to the compound 6. A significant difference was not observed between the chemical shifts of the ^{1}H and ^{13}C NMR signals (Table 2), assigned for the protons and carbons in the tetraline fragment in comparison with those for the same fragment in the previous structure (Table 1). Therefore, the focus will be mainly on the NMR assignments done for the ^{1}H and ^{13}C signals in isatine and benzothiazepine fragments.

It was observed that there is a significant difference in the chemical shift of the signal (74.31 ppm) of spirocarbon, C-iii', compared to that of the signal assigned for C-iii' (63.08 ppm) in compound 6. The strong HMBC correlation (7.55 ppm - 74.31 ppm) indicated the interaction of the proton H-iv' with the spirocarbon, C-iii'. Based on the strong HMBC correlations that resulted from the meta interactions between protons and carbons in the benzene ring of isatin - (7.55 ppm - 141.31 ppm), (7.55 ppm - 130.48 ppm), (7.05 ppm - 110.04 ppm), (7.05 ppm - 129.79 ppm), (7.29 ppm - 125.61 ppm), (7.29 ppm - 141.31 ppm), (6.85 ppm - 122.46 ppm), (6.85 ppm - 129.79

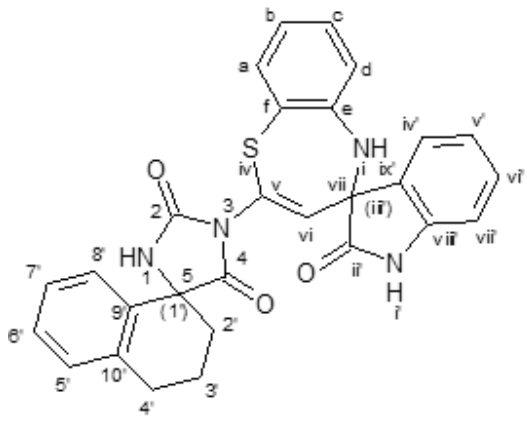

Fig. 3. The structure of 1-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}-3',4'-dihydro-2'*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (7)

Table 2. ^{1}H and ^{13}C NMR data assigned for 7 [^{1}H [500.13 MHz] and ^{13}C [125.76 MHz]][a].

Atom	δ (^{13}C), ppm	DEPT[b]	δ (^{1}H), ppm	Multiplicity, J, Hz	^{1}H-^{1}H COSY [b]	HMBC[b]
2(C=O)	154.13	C				
4(C=O)	174.36	C				
1(NH)			11.83	s		(1‘)[f],2[f]
(1’)	66.25					
2’	29.74	CH_2[g]	2.12(H_a)[c,g] 2.48(H_b)[c,g]	dt(13.3, 3.9) dd(12.9, 3.8)	2’(H_b), 3’(H_c), 3’(H_d); 2’(H_a), 3’(H_c)[e],3’(H_d)[e]	4‘[f] (1‘), 3‘,4‘,4
3’	19.37	CH_2[g]	1.88(H_c)[c,g] 2.18 (H_d)[c,g]	m	2’(H_a),2’(H_b)[e],3’(H_d),4’; 2’(H_a)[e] 2’(H_b)[e],3’(H_c), 4’	(1’)[f]
4’	28.46	CH_2	2.76	dd(7.9;4.3)	3’(H_c), 3’(H_d)	2’,3’,5’, 9’,10’
9’	132.47	C				
10’	138.46	C				
8’	124.03	CH	7.04[d]	m	7‘	(1‘), 10‘
7‘	126.56	CH	7.13[d]	m	6‘,8‘	5‘
6‘	127.51	CH	7.16[d]	m	5‘,7‘	8‘, 10‘
5‘	129.26	CH	7.17[d]	m	6‘	4‘[f], 9‘
ii’(C=O)	176.17	C				
v	167.79	C				
i(NH)			7.25	s		(iii’),d[f],f,e,ii’[e]
(iii’)	74.31	C				
i’(NH)			10.36	s		(iii’), ii’[e], viii’,ix’
viii’	141.31	C				
ix’	129.79	C				
iv’	125.61	CH	7.55	d(7.1)	v’, vi’[f], vii’[f]	(iii’),vi’, vii’[e], viii’
v’	122.46	CH	7.05[d]	m	iv’,vi’, vii’[e]	vii’,ix’
vi’	130.48	CH	7.29	td(7.7, 1.2)	iv’[f], v’, vii’	iv’, vii’, viii’
vii’	110.04	CH	6.85	d(7.8)	iv’[f], vi’, v’[e]	(iii’)[e], v’,ix’
vi	25.93	CH	2.42	s		v
a	121.09	CH	7.03[g]	m	b, c[e], d[f]	c,e
b	118.65	CH	6.63[g]	td(7.5, 1.0)	a, c, d[e]	d,f,e[e]
c	125.70	CH	6.91[g]	td(7.7, 1.2)	a[e], b, d	a, d[e], e
d	108.42	CH	6.54[g]	d(7.8)	a[f], b[e], c	b,f
e	147.20	C				
f	124.11	C				

[a]In DMSO-d_6 solution. All spectral assignments were in agreement with HSQC, HMBC and COSY spectra. [b]Abbreviations: DEPT, Distortionless Enhancement by Polarization Transfer spectrum; ^{1}H-^{1}H COSY - proton-proton homonuclear correlation spectrum; HSQC, Heteronuclear Single Quantum Correlation experiment; HMBC, Long range ^{1}H-^{13}C Heteronuclear Multiple Bond Correlation experiment. [c]Assigned from the HSQC spectrum. [d]Assigned from the HMBC spectrum. [e]Weak correlations. [f]Extremely weak correlations. [g]Chemically inequivalent protons in CH_2 groups are marked with a capital letter H and lower subscript from a to d, in comparison with the benzene protons which are marked in the text in the following way H-a, H-b, H-c, H-d.

ppm), the chemical shifts 7.05 ppm, 7.29 ppm, 6.85 ppm were assigned respectively for the protons H-v', H-vi', H-vii', whereas the signals at 141.31 ppm and 129.79 ppm for the carbons - C-viii' and C-ix'.

There is a ^{1}H singlet at 7.25 ppm with area 1.04, for which the following HMBC correlations were found - (7.25 ppm - 74.31 ppm), (7.25 ppm - 108.42 ppm), (7.25 ppm - 124.11 ppm), (7.25 ppm - 147.20 ppm), (7.25 ppm - 176.17 ppm). The weak HMBC correlation (7.25 ppm - 108.42 ppm) indicate the interaction of NH-i proton with the closest carbon from the benzene ring of the benzothiazepine fragment - C-d. Based on the strong meta HMBC correlations - (7.03 ppm - 125.70 ppm), (7.03 ppm - 147.20 ppm), (6.63 ppm - 124.11 ppm), (6.63 ppm - 108.42 ppm), (6.91 ppm - 121.09 ppm), (6.91 ppm - 147.20 ppm), (6.55 ppm - 118.65 ppm) and (6.55 ppm - 124.11 ppm), it can be concluded that 7.03 ppm, 6.63 ppm, 6.91 ppm and 6.55 ppm were respectively for the signals of the protons, H-a, H-b, H-c, H-d (Table 2). The following HMBC correlations were found for the singlet at 10.36 ppm, assigned for NH-i' proton - (10.36 ppm - 141.31 ppm), (10.36 ppm - 129.79 ppm), (10.36 ppm - 176.17 ppm), (10.36 ppm - 74.31 ppm), indicating its interaction with carbons, C-viii', C-ix', C-ii', and C-iii'. The singlet at 11.83 ppm was for the NH-1 proton, supported by the extremely weak HMBC correlations, (11.83 ppm - 66.25 ppm) and (11.83 ppm - 154.13 ppm), indicating the interaction of NH-1 proton with the spirocarbon, C-1' and carbonyl carbon, C-2.

ATR-IR bands (cm^{-1}) for compound 7**:** 3313 (ν(N-H)), 3191 ν(N-H), 3084 (ν(C-H)), 3071 (ν(C-H)), 3037 (ν(C-H)), 1799, 1754 (ν(C=O)), 1706 (ν(C=O)), 1680 (ν(C=O)), 1619 (ν(C=C)), 1604 (ν(C=C)), 1578 (ν(C=C)), 1498 (ν(C=C)), 1473 (δ_s(CH$_2$)), 1463 (ν(C=C)), 1411, 1376, 1346, 1336, 1318, 1299, 1275, 1260, 1240, 1224, 1189, 1159, 1144, 1117, 1091, 1066, 1041, 1020, 993, 960, 944, 912, 874, 845, 769, 756, 737, 711, 701, 694, 683, 675, 644, 622, 604.

Structure verification of 1'-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl} spiro[fluorene-9,4'-imidazolidine]-2',5'-dione (12)

Compound **12** was synthesized according to the reaction scheme, shown on Fig. 4.

The yields of compounds **10**, **11**, **12** from the reaction scheme (Fig. 4) were respectively 68 %, 73 % and 46 %. Melting points for the compounds **10**, **11**, **12**, were in the respective ranges 196-197°C, 285-286°C, 237-238°C.

The structure of compound **12** is presented on Fig. 5 with the atom numbering used only for the spectral assignments (Table 3). The molecular formula of compound 12 is $C_{31}H_{20}SN_4O_3$.

A significant difference in the chemical shifts of

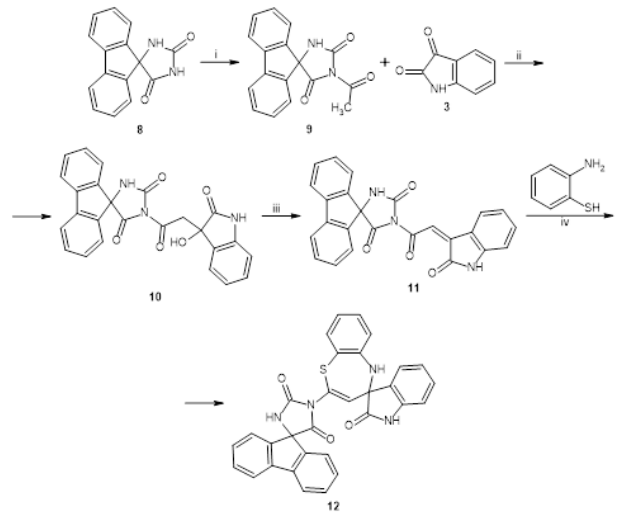

Fig. 4. Scheme of the synthesis of 1'-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl} spiro[fluorene-9,4'-imidazolidine]-2',5'-dione; i: pyridine, $(CH_3CO)_2O$; ii: EtOH, pyperidine; iii: HCl, AcOH; iv: EtOH, AcOH.

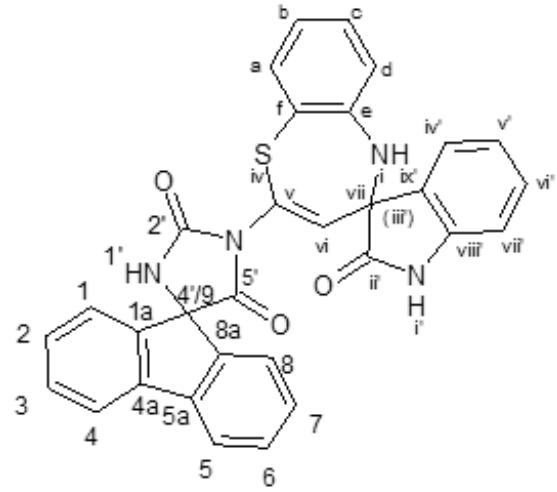

Fig. 5. The structure of 1'-{2'-oxo-1',2'-dihydro-5*H*-spiro[1,5-benzothiazepine-4,3'-indol]-2-yl}spiro[fluorene-9,4'-imidazolidine]-2',5'-dione (12).

Table 3. ^{1}H and ^{13}C NMR data assigned for 12 [^{1}H [500.13 MHz] and ^{13}C [125.76 MHz]][a].

Atom	δ (^{13}C), ppm	DEPT[b]	δ (^{1}H), ppm	Multiplicity, J, Hz	^{1}H-^{1}H COSY [b]	HMBC[b]
2‘(C=O)	154.19	C				
5‘(C=O)	170.74	C				
1‘(NH)			12.24	s		
4’/9	74.14					
1/8	122.37	CH	7.54[c]	d(7.6)	2/7, 3/6[d], 4/5[e]	4’/9, 3,4a
2/7	127.95	CH	7.30 [c]	td(7.5, 0.9)	1/8, 3/6, 4/5 [d]	(4’/9) [d] , 4,1a
3/6	129.37	CH	7.45 [c]	td(7.5, 0.9)	1/8[d], 2/7, 4/5	1,2,4a
4/5	120.71	CH	7.88 [c]	d(7.5)	1/8[e], 2/7 [d], 3/6	1 [d],3,1a
1a/8a	141.36	C				
4a/5a	140.95	C				
ii’(C=O)	176.17	C				
v	166.90	C				
i(NH)			7.27	s		(iii’),ii’ [d] ,d [d] ,e,f
(iii’)	74.32	C				
i’(NH)			10.36	s		(iii’), ii’[d], viii’,ix’
viii’	141.31	C				
ix’	129.80	C				
iv’	125.60	CH	7.55 [c]	d(6.9)	v’, vi’[e], vii’[e]	vii’[d],vi’
v’	122.47	CH	7.05 [c]	td(7.6, 1.4)	iv’,vi’,vii’[d]	vii’,ix’
vi’	130.49	CH	7.29 [c]	td(7.7, 1.3)	iv’[e], v’, vii’	iv’
vii’	110.06	CH	6.84	d(7.7)	iv’[e], v’[d], vi’	v’,ix’
vi	25.24	CH	2.40	s		v
a	121.10	CH	7.03 [c]	dd(7.5, 0.5)	b, c[d], d[e]	c,e
b	118.65	CH	6.64	td(7.5, 1.0)	a, c, d[d]	d,f,e [d]
c	125.71	CH	6.90	td(7.7, 1.2)	a[d], b, d	a, d [d], e
d	108.43	CH	6.54	dd(7.8, 0.6)	a[e], b[d], c	b,f
e	147.20	C				
f	124.11	C				

[a]In DMSO-d_6 solution. All spectral assignments were in agreement with HSQC, HMBC and COSY spectra [b] Abbreviations: DEPT, Distortionless Enhancement by Polarization Transfer spectrum; ^{1}H-^{1}H COSY - proton-proton homonuclear correlation spectrum; HSQC, Heteronuclear Single Quantum Correlation experiment; HMBC, Long range ^{1}H-^{13}C Heteronuclear Multiple Bond Correlation experiment. [c] Assigned from the HSQC spectrum. [d] Weak correlations. [e] Extremely weak correlations.

the ^{1}H and ^{13}C signals for the benzothiazepine, isatin and imidazolidine fragment (Table 3) was not observed in comparison with the assignments presented for the same fragments in compound 7 **(**Table 2**)**. In this case, an attention will be paid on the assignment of the ^{1}H and ^{13}C signals for the fluorene fragment.

Protons and carbons in both benzene rings of the fluorene fragment are chemically equivalent due to which their signals in ^{1}H, ^{13}C, DEPT 135, HSQC and HMBC spectra were the most intensive. The strong HMBC correlation (7.54 ppm - 74.14 ppm) indicate that 7.54 ppm was for the signal of H - 1/8, located only three bonds away from the spirocarbon, C-4'/9 (74.14 ppm). For each of the doublets at 7.88 ppm and 7.54 ppm, three COSY correlations were found - (7.88 ppm - 7.54 ppm), (7.88 ppm - 7.30 ppm), (7.54 ppm - 7.45 ppm), (7.88 ppm - 7.45 ppm), (7.54 ppm - 7.30 ppm). Thus, 7.88 ppm, 7.45 ppm and 7.30 ppm were assigned correspondingly for the H-4/5, H-3/6 and H-2/7 protons. The weak HMBC correlation (7.30 ppm - 74.14 ppm) indicates additionally the interaction of H-2/7 proton with spirocarbon, C-4'/9 (74.14 ppm). As result from the strong HMBC correlations - (7.54 ppm - 140.95 ppm), (7.45 ppm - 140.95 ppm), (7.30 ppm - 141.36 ppm) and (7.88 ppm - 141.36 ppm), 140.95 ppm and 141.36 ppm were assigned to the signals of the nonprotonated carbons, C-4a/5a and C-1a/8a.

ATR-IR bands (cm^{-1}) for compound 12**:** 3313 (ν(N-H)), 3183 ν(N-H), 3071 (ν(C-H)), 3037 (ν(C-H)), 2889, 2836, 1799, 1757 (ν(C=O)), 1705 (ν(C=O)), 1690 (ν(C=O)), 1619 (ν(C=C)), 1604 (ν(C=C)), 1578 (ν(C=C)), 1473, 1462 (ν(C=C)), 1452(ν(C=C)), 1410, 1377, 1342, 1300, 1275, 1259, 1239, 1195, 1159, 1139, 1118, 1098, 1082, 1040, 1020, 993, 982, 957, 939, 927, 917, 870, 860, 844, 786, 753, 733, 711, 704, 694, 683, 647, 622, 608.

CONCLUSIONS

- A reliable structure verification of the structures of three new dispirocompounds was done by completely assigning the NMR data from the ^{1}H, ^{13}C, DEPT 135, HSQC, ^{1}H-^{1}H COSY and HMBC spectra.
- The presence of the functional groups such as NH, C=O, CH_2, aromatic C=C and C-H was additionally confirmed by the ATR-IR spectra.

Authors' contributions

M.M., D.S.: Conceptualization; D.S., M.M.: Formal analysis and investigation; D.S., M.M.: Writing - original draft preparation; M.M., D.S., P.P., N.S.: Writing - review and editing.

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