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Synthesis and cytotoxicity of novel oxindoles dispiro derivatives with thiohydantoin and adamantane fragments

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Abstract: An effective and highly regio- and diastereoselective one-pot synthesis of two type of dispiro heterocyclic systems (2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-diones and 2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-diones) comprising pyrrolidinyloxindole, thiohydantoin and adamantane moieties have been developed based on a 1,3-dipolar cycloaddition of azomethine ylides, generated from isatin and sarcosine or formaldehyde and sarcosine, to adamantine-containing electron-deficient alkenes. Several molecules have demonstrated a considerable cytotoxicity against and A549, HEK293T, MCF7 and VA13 cancer cell lines. The possible mechanism of anticancer activity of synthesised compounds based on literature data may be the inhibition of p53/MDM2 interaction, however, we did not observe significant p53 activation using a reporter construction in A549 cell line in a relevant concentration range.

Keywords: dispiro-oxindoles; adamantanes; thiohydantoins; 1,3-dipolar cycloaddition; anticancer activity

Introduction

The spiro[pyrrolidine-oxindole] system is an attractive object for synthesis because of their important biological properties. Spirooxindole structures can be found in a wide range of complex natural products [1-6]; besides many synthetically obtained compounds with this core demonstrate anti-nicotinic, antiplasmodial, antimicrobial, anti-HIV, antimalarials and anti-tumor activities [7]. Different spiro[pyrrolidine-oxindole] display considerable anticancer action that is apparently related to their ability to inhibit p53-MDM2 protein−protein interaction [8-13]. Some of them were tested as anticancer drugs during preclinical or clinical studies [14-17]. The most active spiro[oxindole] derivatives inhibit the p53—MDM2 interaction with the IC50 values of 24.1 nM - 81 μM [8-17]. At the same time, substantially less studied dispiro-derivatives of pyrrolidine-oxindole have IC50 values in the range of 0.001 - 0.05 μM [18]. Thus, the

introduction of additional spiro-junction into the system can lead to an increase in antitumor activity.

One of the most effective strategy for the synthesis of dispiro[pyrrolidine-oxindole] is 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes as dipolarophiles. Basing on them, an effective one-pot access to polynuclear dispiroheterocyclic structures, containing indolinone and pyrrolodine fragments, has been suggested [19-24]. Recently we proposed regioselective synthesis of 2-thioxo-5H-dispiro[imidazolidine-4,3-pyrrolidine-2,3-indole]-2,5(1H)-diones which have been identified as potent small molecule MDM2/p53 PPI inhibitors [12]. These compounds have in the structure thiohydantoin fragment, spiro-annelated to the pyrrolidine cycle. It is known that thiohydantoin derivatives are widely used in drug design as core structures. Several thiohydantoins exhibited a variety of biological activities including antiviral and antitumor activities [25-27]; for example Enzalutamide (Xtandi) is used in the treatment of prostate cancer.

It is also known numerous applications in medicinal chemistry and drug development of adamantane derivatives (see, for example, 28-30]. The adamantane modifications usually allows to enhance lipophilicity and stability of the drugs. Lipophilic nature of adamantane allows to modify known pharmacophores, thus enhancing their stability and pharmacokinetics [9]. Introduction of adamantyl group allows not only the creation of effective drugs, but also helps in understanding of the ongoing molecular mechanisms. For example, M_2 ion-channels of type A influenza virus were studied with its inhibition by aminoadamantane [33-35]. Enzyme inhibition is another rapidly developing area of application for adamantane derivatives. The most important among them are DPP-IV inhibitors and antidiabetic drugs – Vildagliptin and Saxagliptin [36]. Other examples of enzyme targets for adamantane-based pharmaceuticals are soluble epoxide hydrolases [37-39], protein phosphatase 2A [40], or the hydroxysteroid dehydrogenases [41]. Adamantane derivatives are being investigated as anti-cancer agents. For example, cisplatin analog LA-12 ([(*OC-6-43*)-*bis*(acetato)(1-adamantylamine)-

amminedichloroplatinum(IV)] containing bulky hydrophobic 1-adamantylamine, shows high cytotoxicity against cisplatin-resistant ovarian adenocarcinoma [42], prostate cancer [43], colorectal cancer [44]. High potency of this compound related with adamantane derived enhanced cell uptake [45]. Study of Lavendustin C analogs showed that change of methyl substituent in tyrphostin AG 957 with adamantyl led to 12-fold increase of its half-life *in vivo* [46].

It may be expected that dispiroindolinones with a rigid lipophilic adamantane fragment will better fit into a small but deep hydrophobic pocket in MDM2, which is apparently the most important site for binding with p53 or the inhibitor molecule [47] and thus contribute to more effective inhibition of the p53-MDM2 interaction.

Therefore, coupling of three privileged scaffolds (spiro[pyrrolidine-oxindole], 2-thiohydantoin and adamantane moieties) would open access to the compounds with a wide spectrum of physiological activity, including anticancer one. Based on this, in this work we set out to develop a synthetic approaches to dispiro[pyrrolidine-oxindoles], combining in the structure the above structural fragments.

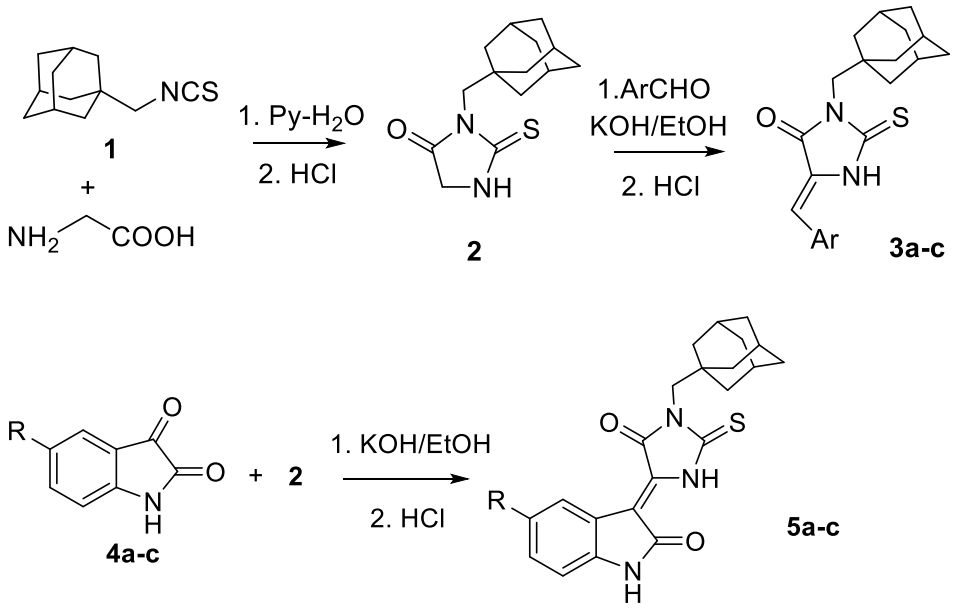
Results and Discussion

Recently, we have demonstrated that the reaction of 3-aryl-5-arylidene-substituted thiohydantoins with isatine and sarcosine leads to the formation of the dispiro-indolinone derivatives with good regio- and diastereoselectivity [12]. Herein, we present a one-pot reaction of 3-adamantylmethyl-5-methylene-substituted thiohydantoin with two types of azomethine ylides, forming from N-substituted α-amino acids and formaldehyde or N-substituted α-amino acids and isatins.

We started our research by preparation of initial adamantly-substituted electron-deficient alkenes **3** and **5** for 1,3-dipolar cycloaddition of azomethine ylides starting from methyl-(2-adamantyl)isothiocyanate **1** [48], and commercially available glicine, substituted benzaldehydes and isatines **4a-c** (Scheme 1). At the first step, 3-adamantylmethyl-substituted

thiohydantoin **2** was synthesized by the nucleophilic addition reaction of glycine amino group at the electrophilic carbon atom of the isothiocyanate group of compound **1**; the thiourea formed in this way was not isolated from the reaction mixture, but was cyclized to thiohydantoin under the addition of HCl. Then, thiohydantoin **2** was introduced into the condensation reaction with benzaldehydes or isatins to obtain the target dipolarophiles **3** and **5**. The yields of the obtaining compounds **3**-**5** are given in Table 1.

Compounds **3a-c** are formed as single geometric isomers, which is confirmed by the presence of the only vinyl proton signal in their ^{1}H NMR spectra at 6.55-6.70 ppm. The *Z* configuration was attributed to products **3** basing on the chemical shifts of the vinylic protons in the ^{1}H NMR spectra [48]. The configuration of the isatins condensation products **5** was attributed basing on X-ray data for the reaction product of compound **5b** with azomethylilide (dispiroindolinone **7b**, see Figure 1, *right*).



Scheme 1. Synthesis of starting dipolarophiles **3** and **5**.

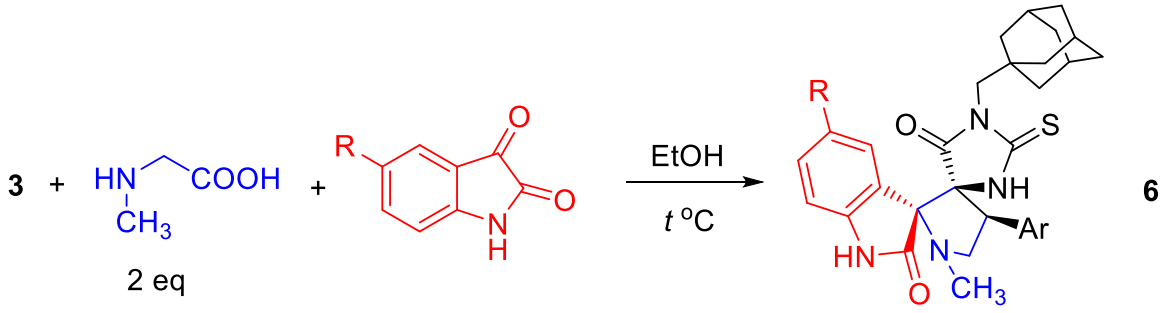
Table 1. Yields of compounds **3** and **5**.

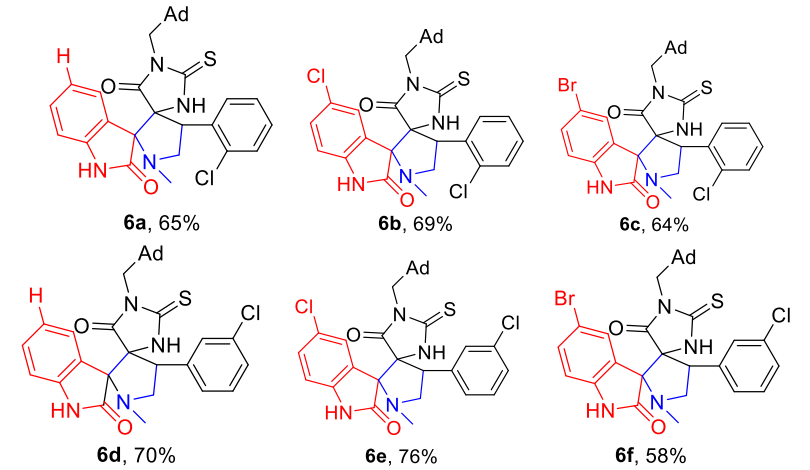
Compound	Ar	Yield	Compound	R	Yield
3a	2-Cl-C_6H_4	74	**5a**	H	91
3b	3-Cl-C_6H_4	79	**5b**	Cl	98

3c	4-Cl-C_6H_4	88	**5c**	Br	95

For synthesis of target dispiropyridine **6** and **7**, the reactions of azomethine ylides generated from isatin and sarcosine or from formaldehyde and N-substituted aminoacids to dipolarophiles **3** and **5** were used which allowed to vary the position of the pyrrolidine nitrogen atom relative to the place of spiro-junction with oxindole fragment. The reactions provided the desired compounds **6a-i**, **7a-f** in a moderate-to-high yield (See Tables 2, 3).

Table 2. Structures and yields of dispiro[pyrrolidine-oxindoles] **6**



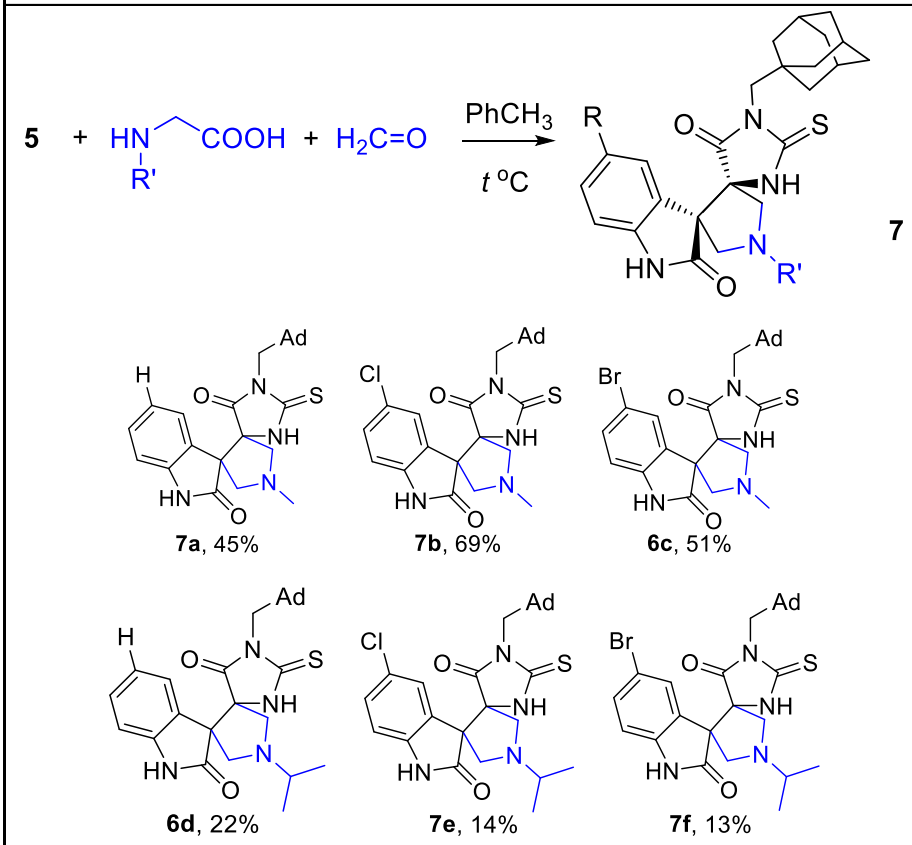


6a, 65% **6b**, 69% **6c**, 64%

6d, 70% **6e**, 76% **6f**, 58%

6j, 62% **6h**, 70% **6i**, 64%

Table 3. Structures and yields of dispiro[pyrrolidine-oxindoles] **7**.



The conversion proceeded regioselectively providing pure diastereometric products with the relative (2`*R*\*,4*S*\*,4`*S**)-configuration. The formation of the only diasteromers of compounds **6a-i**, **7a-f** is confirmed by the presence of a single set of signals for each of the isolated compounds in their ^{1}H and ^{13}C NMR spectra. For compounds **6** in the ^{1}H NMR spectra, is characteristic the presence of three pseudo-triplets with J ~ 9 Hz at 4.60-3.40 ppm corresponding to three hydrogen atoms of the central pyrrolidine ring. For type 7 dispiroindolinones, the 1H NMR spectrum is characteristic in the range of 3.50-2.90 ppm, in which there are four doublets with J ~ 10 Hz, also corresponding to the protons in the pyrrolidine ring (in some cases, these signals overlap with each other or with the peak of H_2O contained in DMSO-d6. Composition of all obtained disipyro derivatives was confirmed by HRMS data.

The configuration of compound **6j** and **7b** were confirmed by X-ray analysis. The molecular structure of **6j** is shown in Figure 1. The detailed description of X-Ray data is provided in Supplemetrary Information.

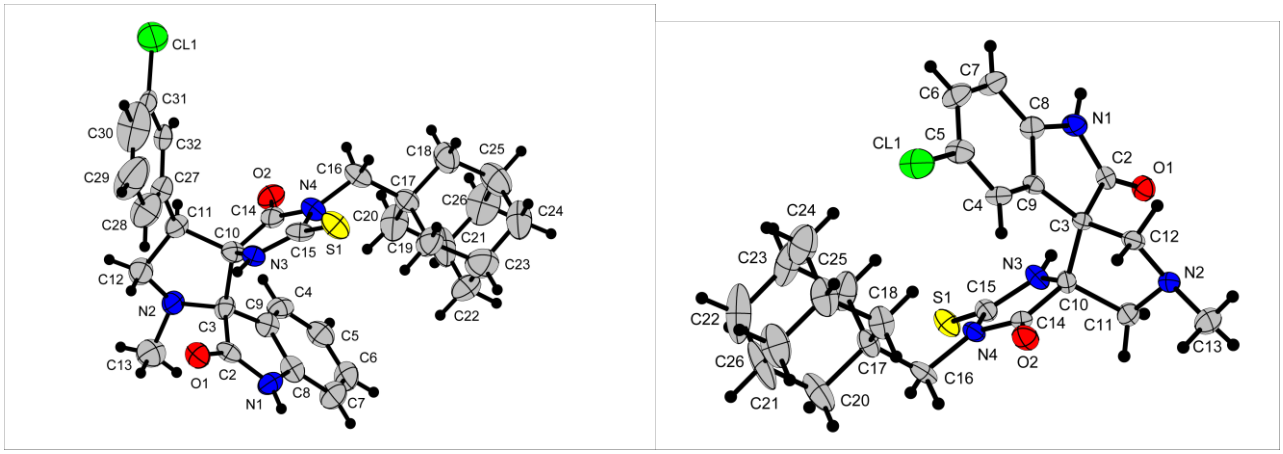
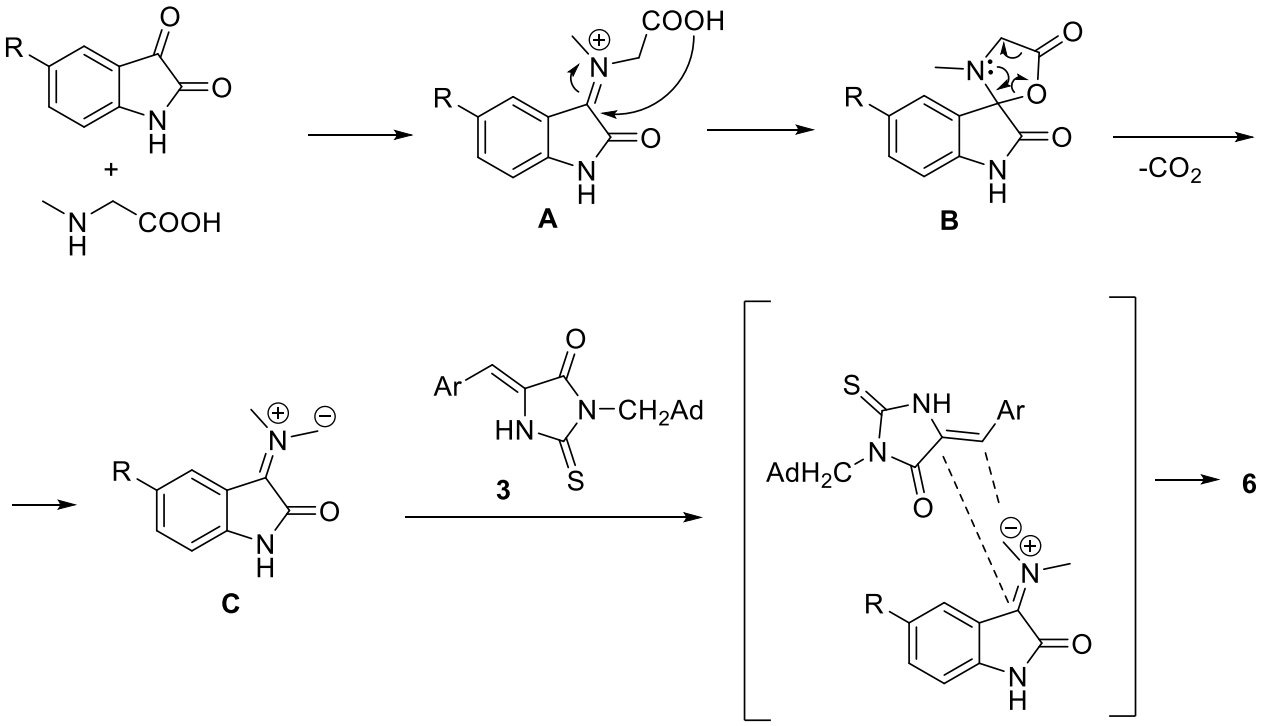


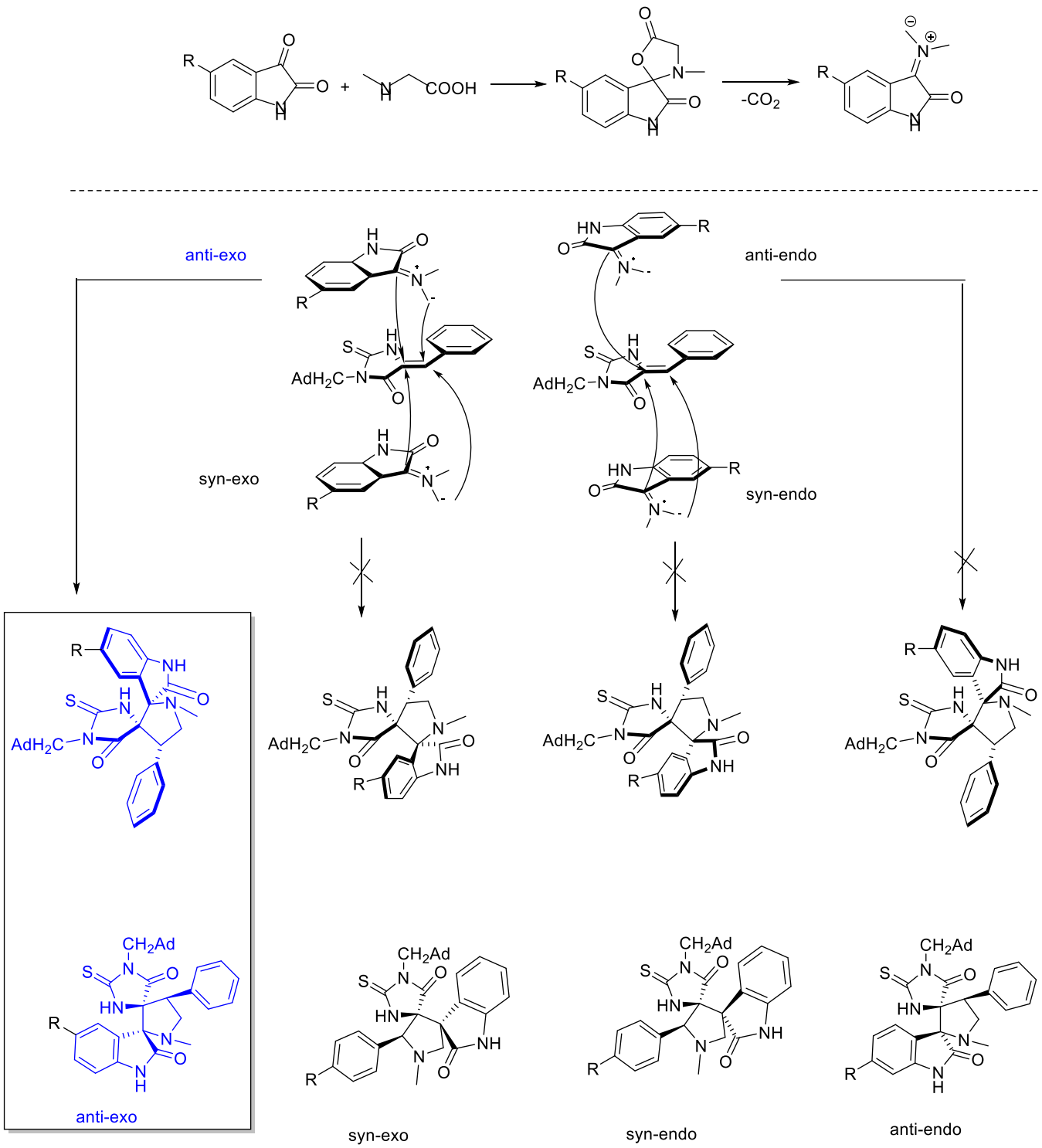
Figure 1. Molecular structure of compounds **6j** (CCDC No 1954162, *left*) and compound **7b** (CCDC No 1954164, *right*).

We speculate that the mechanisms of cyclization are 1,3-dipolar addition of azomethine ylides to electron deficient alkenes **3**, **5**. At the formation of compounds 6a-i, it is supposed that initially the interaction of isatin and sarcosine produces the iminium salt **A**, which undergoes cyclization to the oxazolidinone intermediate **B**. The latter then undergoes decomposition with the release of carbon dioxide and the release of a 1.3-dipole **C**, which attaches to the double bond of 5-arylidene-2-thiohydantoin (Scheme 1).



Scheme 1. The proposed mechanism of compounds **6** formation.

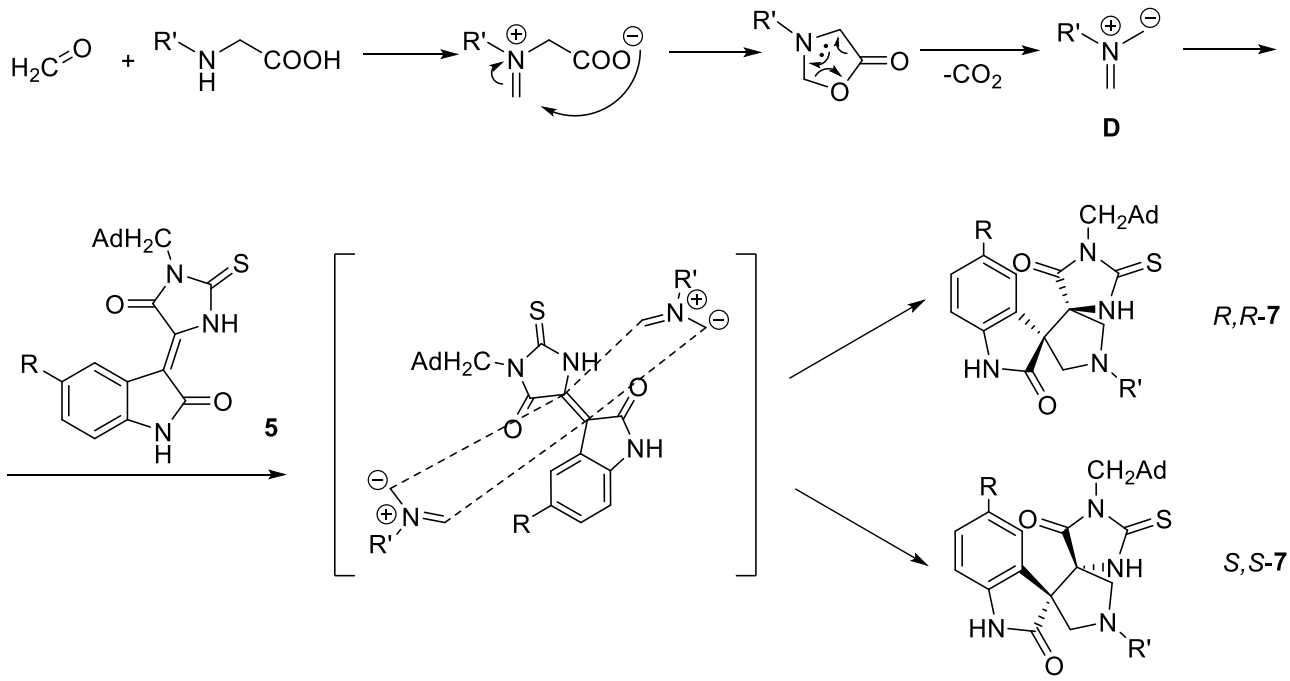
Note that as a result of the reaction shown in Scheme 1, three new stereo centers are simultaneously formed, and the attack of azomethine ylide dipole to C=C douple bond would be potentially proceed from the formation of four diastereomeric products. The possible ways of azomethine ylide approach to dipolarophile moiety are shown in Scheme 2. The reactions proceeding with the formation of a single diastereomers of products **6** shows that *anti-exo*-addition of a 1,3-dipole to dipolarophiles **3** is realized exclusively (or predominantly, taking into consideration the possible presence in the reaction mixture of trace amounts of other diastereomeric products). This result can be explained by the least steric difficulties in the transition state with this pattern of the dipole and dipolarophile orientation.



Scheme 2. 1,3-Dipolar addition reaction diastereoselectivity (on the example of dispiro-derivatives **6** formation).

The formation of compounds **7** obviously proceeds according to a similar mechanism with the initial formation of azomethinilide **D** (Scheme 3). Spiro-cyclization with the participation of dipolarophiles **5** in this case is accompanied by the formation of two new stereo centers, and

in practice also proceeds with the isolation of the only diastereomers of products **7** with the relative (4*R**,4`*R**)-configuration in high yield (see Table 2).



Scheme 3. The proposed mechanism of compounds **7** formation

Synthesized dispiro-oxindoles **6** and **7** have subsequently been tested on their in vitro anticancer efficiency against different tumor cell lines. These models included human lung adenocarcinoma epithelial cell line (A549), human embryonic kidney 293 cells (Hek293) stably expressing SV40 large T antigen (Hek293T), human breast cancer cell line (MCF-7), and transformed normal human lung fibroblast cells (VA13). The cytotoxicity of the evaluated molecules was properly assessed using routine MTT (3-(4,5-dimethylthiazol-2-yl)2,5-diphenyl tetrazolium bromide) assay based on the modified approach reported by Ferrari and colleagues [49]. The detailed methodology describing the performed cell-based evaluation is provided in Supplenentary Information. The resulting cytotoxicity is summarized in Table 4 below. All synthesized compounds demonstrated higher or the same *in vitro* cytotoxicity against the tested cell lines compared with Nutlin-3a and cisplatin. The most cytotoxic compounds was dispiro-oxindoles **7a** and **7b**.

Table 4. Cytotoxicity of compounds **6,7** against different cancer cell lines (MTT-test; IC_{50}. μM)

Compound	A549	HEK293T	MCF7	VA13
6a	15.46±14.6	9.72±7.93	13.58±13.08	7.41±2.78
6b	9.33±6.9 7.1±1.6	8.33±6.76 9.5±1.8	3.23±3.02 7.5±0.3	9.01±7.11 7.3±3
6c	7.2±1.85	7.63±0.75	2.79±2.75	17.26±14.76
6e	14.87±14.28	20.08±18.11	12.67±12.36	29.41±15.55
6f	10.3±4.88	11.23±3.99	20.69±15.56	46.88±30.69
6j	7.6±0.7	7.7±0.8	4.9±0.5	18.4±5.9
6h	8,7±1,8	9,3±0,7	7,3±0,5	9,7±1,2
6i	10.04±7.1	10.18±2.81	13.61±6.68	35.23±34.13
7a	**6.8±1,3**	5.1±0.5	5,2±0.4	5,2±1.0
7b	**5.0±0.6**	2.8±0.3	2.8±0.2	2.9±0.5
7d	9.3±0.6	5.8±0.4	5.4±0.4	5.6±1.3
Nutlin-3a [a]	14.9±0.6	10.4±0.8	na	na
Cisplatin	44.13±3.9	12.4±3.9	>50	>50

[a] Ref. [51, 52].

In an effort to elucidate the underlying mechanism of action of the synthesized compounds as p53/MDM2 interaction inhibitors, we have performed cell based assay with the p53 reporter construction particularly sensitive to MDM2 inhibitors. To assess the level of p53 protein accumulation, the test system of A549 tumor cells modified with a plasmid construct containing p53-recognized regions regulating β-galactosidase expression was used. This approach suggests that with an increase in the amount of p53 protein during the experiment, the content of β-galactosidase increases, which, when using the ONPG indicator (o-nitrophenyl-β-galactoside) releases a colored compound into the medium [50]. Four dilutions of compounds **6**, **7** (100 to 1.56 μM) were tested. The tests results are presented in Table 5. Nutlin-3a, a known inhibitor of p53/MDM2 interaction, which was used as a positive control, causes direct activation of p53 via the block of p53-MDM2 interaction and elevates p53 activity from 3.6 up to 5.1-fold in the reporter assay [52] In general, the obtained results demonstrated that the activation of p53 was observed upon the treatment with high concentrations of the compounds **6**, **7**. The maximum activation was observed for compounds **6i** and **7a**; the treatment of cells by these compounds in 100 μM concentration leads to the 2.03 and 4.39

times p53 activation. For the most synthesized compounds the activation of p53 is less than for Nutlin–3a at the same conditions, but comparable with indirect cisplatin action, which suggests that the investigated compounds have indirect p53-dependent mechanism of cytotoxic action. Only for compound **7a** in high concentration (> 100 μM) the mechanism of cytotoxic activity associated with the inhibition of the p53/MDM2 interaction can be supposed.

Table 5. p53 Reporter activation test in A549 cell line for the compounds **6** and **7**

Concentration (μM)	**100**	**25**	**6,25**	**1,56**	**100**	**25**	**6,25**	**1,56**
Compound	ONPG/MTT				MTT			
6a	1,55	0,91	0,63	0,75	31,27	58,37	104,13	115,47
6c	1,85	1,20	0,75	0,68	45,14	57,27	85,45	96,46
6d	1,74	0,88	0,68	0,82	50,61	68,04	95,84	92,52
6e	1,90	1,20	0,88	0,68	42,92	57,97	87,82	96,13
6f	1,84	1,07	0,72	0,72	45,67	76,64	93,80	110,68
6j	1,52	1,43	1,44	1,10	42,66	61,57	87,96	112,04
6h	1.80	1.06	0.92	0.81	55.40	85.57	125.52	116.33
6i	**2,03**	1,03	0,80	0,87	30,76	58,83	97,67	107,95
7a	**4.39**	1.51	1.09	1.06	**9.92**	65.12	103.27	98.79
7b	1.96	1.35	0.86	0.84	20.39	49.00	131.11	129.13
7c	1,56	1,04	0,65	0,72	28,17	26,74	95,67	99,27
Nutlin-3a	11,38	7,60	3,89	2,08	65,63	98,71	93,82	100,46

[a] ONPG/MTT columns are values showing the degree of gene expression normalized to survival, and in the MTT columns is the percentage of surviving cells. [b] Under the same conditions, Nutlin–3a showed from 5.1- and up to 8-fold increase in the p53 activation [51, 52].

Conclusions

In the present study, two series of novel adamantane-substituted dispiro[pyrrolidine-oxindole] derivatives has been described based on a regio- and diastereoselective 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkene systems. Synthesized dispiro-oxindoles demonstrated high *in vitro* cytotoxicity with different cancer cell lines, and, apparently, in most cases have indirect p53-dependent mechanism of cytotoxic action.

Experimental Section

General Information. All common reagents were purchased from commercial suppliers and used as received. The melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C) in DMSO-d^{6}. Chemical shifts are reported in parts per million relative to TMS. High resolution mass spectra (HRMS) were recorded on an Orbitrap Elite (Thermo Scientific) mass spectrometer with an IRET. To inject solutions with a concentration of 0.1 to 9 µg / ml (in 1% formic acid in acetonitrile), direct injection into the ion source using a syringe pump (5 µl/min) was used. The spray voltage was ± 3.5 kV, the temperature of the capillary was 275ºC. Methyl-(2-adamantyl)isothiocyanate **1** was prepared using previously described procedures [53, 54].

3-(adamantan-1-ylmethyl)-2-thioxoimidazolidin-4-one (2). Glycine (1 eq.) was dissolved in a pyridine-water mixture (5:1). Then triethylamine (1.1 eq.) and isothiocyanate **1** (1.1 eq.) were added. The resulting mixture was heated to 55 °C and stirred at this temperature for 2 hours. Pyridine and the excess of isothiocyanate were removed by extraction with toluene and the organic phase was discarded. Aqueous phase was neutralized by concentrated hydrochloric acid to pH 6-7 and boiled for 2.5 hours. The reaction mixture was evaporated under reduced pressure to half of the volume and cooled to room temperature. The formed precipitate was filtered off and recrystallized from methanol. Yield 72%. The product is grey crystalline solid. M.p.=200-201ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 4.14 (s, 2H), 3.42 (s, 2H), 1.90 (s, 3H), 1.67 (m, 6H), 1.52 (s, 6H). **HRMS** (ESI+) m/z calcd. for ($C_{14}H_{20}N_2OS$, M+H): 265.1369, found: (M+H): 265.1362.

General Procedure for the Synthesis of Compounds 3.. Compound **2** (1 eq.) was dissolved in 2% KOH/EtOH and then substituted benzaldehyde (1 eq.) was added. The resulting mixture was stirred for 3 h; after the reaction was completed, the mixture was neutralized with 1N HCl. The formed precipitate was filtered off, washed with water, than cold ether and dried in air. The products are yellow crystalline solids.

(Z)-3-(adamantan-1-ylmethyl)-5-(2-chlorobenzylidene)-2-thioxoimidazolidin-4-one (3a). Compound **2** (0.175 g, 0.66 mmol) was dissolved in 2% KOH/EtOH (5 mL) and 2-chlorobenzaldehyde (0.093 g, 0.66 mmol) was added. The resulting mixture was stirred for 3 h; after the reaction was completed, the mixture was neutralized with 1N HCl (5 mL). The formed precipitate was filtered off, washed with water (5 mL), than cold ether (5 mL) and dried in air, yielding **3a** (0.189 g, 74%). The products is yellow crystalline solid. M.p.=193-194ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 12.51 (s, 1H), 7.86 (m, 1H), 7.56 (m, 1H), 7.45-7.39 (m, 2H), 6.69 (s, 1H), 3.56 (s, 2H), 1.92 (bs, 3H), 1.67-1.58 (m, 6H), 1.56 (bs, 6H). **HRMS** (ESI+) m/z calcd. for ($C_{21}H_{23}ClN_2OS$, M+H): 387.1292, found: (M+H): 387.1294.

(Z)-3-(adamantan-1-ylmethyl)-5-(3-chlorobenzylidene)-2-thioxoimidazolidin-4-one (3b). From **2** (0.250 g, 0.94 mmol) and 3-chlorobenzaldehyde (0.132 g, 0.94 mmol) compound **3b** (0.287 g, 79%) was obtained as yellow crystalline solid. M.p.=204-205ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 12.54 (s, 1H), 7.88 (s, 1H), 7.69 (m, 1H), 7.46-7.41 (m, 2H), 6.58 (s, 1H), 3.56 (s, 2H), 1.91 (bs, 3H), 1.67-1.57 (m, 6H), 1.55 (bs, 6H). **HRMS** (ESI+) m/z calcd. for ($C_{21}H_{23}ClN_2OS$, M+H): 387.1292, found: (M+H): 387.1290.

(Z)-3-(adamantan-1-ylmethyl)-5-(4-chlorobenzylidene)-2-thioxoimidazolidin-4-one (3c). From **2** (0.250 g, 0.94 mmol) and 3-chlorobenzaldehyde (0.132 g, 0.94 mmol) compound **3c** (0.320 g, 88%) was obtained as yellow crystalline solid. M.p.=225-226ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 12.43 (s, 1H), 7.80 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.4 Hz, 2H), 6.60 (s, 1H), 3.56 (s, 2H), 1.91 (s, 2H), 1.67-1.57 (m, 6H), 1.55 (bs, 6H). **HRMS** (ESI+) m/z calcd. for ($C_{21}H_{23}ClN_2OS$, M+H): 387.1292, found: (M+H): 387.1300.

General Procedure for the Synthesis of Compounds 5. Compound **2** (1 eq.) was dissolved in 1% KOH/EtOH and then isatin derivative **4a-c** (1 eq.) was added. The resulting mixture was stirred for 0,5 h. After the reaction was completed, the mixture was neutralized with 1N HCl. The formed precipitate was filtered off, washed with water, than cold ether and dried in air. The products are red crystalline solids.

(Z)-3-(1-(adamantan-1-ylmethyl)-5-oxo-2-thioxoimidazolidin-4-ylidene)indolin-2-one (5a). From **2** (0.080 g, 0.30 mmol) and isatin **4a** (0.045 g, 0.3 mmol) compound **5a** (0.108 g, 91%). obtained as red crystalline solid.. M.p.>300ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.47 (s, 1H), 11.10 (s, 1H), 8.54 (d, J=7.8 Hz, 1H), 7.33 (t, J=7.5 Hz, 1H), 7.05 (t, J=7.6 Hz, 1H), 6.93 (d, J=7.8 Hz, 1H), 3.58 (s, 2H), 1.92 (bs, 3H), 1.67-1.52 (m, 12H). **HRMS** (ESI+) m/z calcd. for ($C_{22}H_{23}N_3O_2S$, M+H): 394.1584, found: (M+H): 394.1578.

(Z)-3-(1-(adamantan-1-ylmethyl)-5-oxo-2-thioxoimidazolidin-4-ylidene)-5-chloroindolin-2-one (5b). From **2** (0.080 g, 0.30 mmol) and 5-chloroisatin **4b** (0.055 g, 0.30 mmol) compound **5b** (0.127 g, 98%) was obtained as red crystalline solid. M.p.>300ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 11.52 (s, 1H), (s, 1H), 11.21 (s, 1H), 8.57 (s, 1H), 7.38 (d, J=8.2 Hz, 1H), 6.95 (d, J=8.3 Hz, 1H), 3.58 (s, 2H), 1.92 (bs, 3H), 1.67-1.53 (m, 12 H). **HRMS** (ESI+) m/z calcd. for ($C_{22}H_{22}ClN_3O_2S$, M+H): 428.1194, found: (M+H): 428.1199.

(Z)-3-(1-(adamantan-1-ylmethyl)-5-oxo-2-thioxoimidazolidin-4-ylidene)-5-bromoindolin-2-one (5c). From **2** (0.120 g, 0.45 mmol) and 5-bromoisatin **4c** (0.103 g, 0.45 mmol) compound **5c** (0.202 g, 95%) was obtained as red crystalline solid. M.p.>300ºC. **^{1}H NMR** (400 MHz, DMSO-d6) δ: 11.50 (s, 1H), 11.21 (s, 1H), 8.70 (s, 1H), 7.49 (d, J=8.1 Hz, 1H), 6.90 (d, J=8.1 Hz, 1H), 3.58 (s, 2H), 1.92 (bs, 3H), 1.69-1.50 (m, 12H). **HRMS** (ESI+) m/z calcd. for ($C_{22}H_{22}BrN_3O_2S$, M+H): 472.0689, found: (M+H): 472.0688.

General Procedure for the Synthesis of Compounds 6. The mixture of 5-(benzylidene)-2-thioxoimidazolidines **3** (1 equiv) and sarcosine (2 eq.) were brought to a boil in ethanol. After that isatin **4a-c** (2 eq.) was added. The resulting mixture was refluxed for 5-8 hours. After the reaction was completed, the reaction mixture was cooled to room temperature, the formed precipitate was filtered off, washed with cold ethanol and dried in air. The products are white crystalline solids.

(*2'R*,4S*,4'S)-1-(adamantan-1-ylmethyl)-4'-(2-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6a)**. From **3a**

(0.053 g, 0.14 mmol), sarcosine (0.025 g, 0.27 mmol) and **4a** (0.040 g, 0.27 mmol) compound **6a** (0.050 g, 65%). was obtained as white crystalline solid. Yield 69%. M.p.=167-168ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.64 (s, 1H), 8.83 (s, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.46-7.35 (m, 2H), 7.32 (d, J=7.7 Hz, 2H), 7.23 (t, J=7.6 Hz, 1H), 6.98 (t, J=7.6 Hz, 1H), 6.79 (d, J=7.6 Hz, 1H), 4.58 (t, J=9.0 Hz, 1H), 4.06 (t, J=9.2 Hz, 1H), 3.43 (t, J=9.1 Hz, 1H), 3.30 (d, J=13.7 Hz, 1H), 3.07 (d, J=13.7 Hz, 1H), 2.11 (s, 3H), 1.74 (bs, 3H), 1.55-1.47 (m, 3H), 1.40-1.32 (m, 3H), 1.24-1.16 (m, 3H), 1.16-1.08 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 183.75 (s, 1C), 175.79 (s, 1C), 174.28 (s, 1C), 143.41 (s, 1C), 134.30 (s, 1C), 132.85 (s, 1C), 131.25 (s, 1C), 130.08 (s, 1C), 129.20 (s, 1C), 127.62 (s, 1C), 127.60 (s, 1C), 127.57 (s, 1C), 123.72 (s, 1C), 121.82 (s, 1C), 109.70 (s, 1C), 76.74 (s, 1C), 74.61 (s, 1C), 55.88 (s, 1C), 51.77 (s, 1C), 46.65 (s, 1C), 40.28 (s, 1C), 36.04 (s, 1C), 34.76 (s, 1C), 34.64 (s, 1C), 27.51 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{33}ClN_4O_2S$, M+H): 561.2086, found: (M+H): 561.2084.

(*2'R*,4S*,4'S)-5''-chloro-1-(adamantan-1-ylmethyl)-4'-(2-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6b).** From **3a** (0.053 g, 0.14 mmol), sarcosine (0.025 g, 0.27 mmol) and 5-chloroisatin **4b** (0.050 g, 0.27 mmol) compound **6b** (0.056 g, 69%) was obtained as white crystalline solid.Yield 69%. M.p.=284-285ºC. **^{1}H NMR** (400 MHz, DMSO-d6) δ: 10.80 (s, 1H), 8.96 (s, 1H), 7.84 (d, J=7.8 Hz, 1H), 7.43 (t, J=7.6 Hz, 1H), 7.39 (dd, J1=1.2 Hz, J2=7.9 Hz, 1H), 7.34-7.27 (m, 3H), 6.82 (d, J=8.1 Hz, 1H), 4.53 (s, 1H), (t, 9.0 Hz, 1H), 4.08 (t, J=9.5 Hz, 1H), 3.44 (t, J=8.4 Hz, 1H), 3.38 (d, J=13.5 Hz, 1H), 3.08 (d, J=13.5 Hz, 1H), 2.13 (s, 3H), 1.78 (bs, 3H), 1.58-1.48 (m, 3H), 1.41-1.32 (m, 3H), 1.25-1.17 (m, 3H), 1.17-1.09 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 183.89 (s, 1C), 175.50 (s, 1C), 174.42 (s, 1C), 142.42 (s, 1C), 134.27 (s, 1C), 132.55 (s, 1C), 131.12 (s, 1C), 130.05 (s, 1C), 129.30 (s, 1C), 129.23 (s, 1C), 127.74 (s, 1C), 127.60 (s, 1C), 126.39 (s, 1C), 125.93 (s, 1C), 111.18 (s, 1C), 76.58 (s, 1C), 74.72 (s, 1C), 55.73 (s, 1C), 51.82 (s, 1C), 46.96 (s, 1C), 40.38 (s, 1C), 36.11 (s, 1C), 34.71 (s, 1C), 34.70 (s, 1C), 27.62 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}Cl_2N_4O_2S$, M+H): 595.1696, found: (M+H): 595.1701.

(*2'R*,4S*,4'S)-5''-bromo-1-(adamantan-1-ylmethyl)-4'-(2-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6c)**. From **3a** (0.053 g, 0.14 mmol), sarcosine (0.025 g, 0.27 mmol) and 5-chloroisatin **4c** (0.062 g, 0.27 mmol) compound **6c** (0.056 g, 64%) was obtained as white crystalline solid. M.p.=280-281ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.80 (s, 1H), 8.92 (s, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.48-7.37 (m, 4H), 7.32 (m, 1H), 6.78 (d, J=8.1 Hz, 1H), 4.53 (dd, J_1=8.1 Hz, J_2=9.7 Hz, 1H), 4.08 (t, J=9.6 Hz, 1H), 3.43 (t, J=8.2 Hz, 1H), 3.38 (d, J=13.5 Hz, 1H), 3.09 (t, J=13.5 Hz, 1H), 2.13 (s, 3H), 1.81 (bs, 3H), 1.58-1.49 (m, 3H), 1.41-1.34 (m, 3H), 1.26-1.17 (m, 3H), 1.17-1.09 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 183.90 (s, 1C), 175.42 (s, 1C), 174.42 (s, 1C), 142.84 (s, 1C), 134.26 (s, 1C), 132.88 (s, 1C), 132.53 (s, 1C), 131.11 (s, 1C), 130.52 (s, 1C), 129.32 (s, 1C), 129.26 (s, 1C), 127.62 (s, 1C), 126.33 (s, 1C), 114.19 (s, 1C), 111.67 (s, 1C), 76.56 (s, 1C), 74.72 (s, 1C), 55.73 (s, 1C), 51.84 (s, 1C), 47.01 (s, 1C), 40.41 (s, 1C), 36.14 (s, 1C), 34.72 (s, 2C), 27.65 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}BrClN_4O_2S$, M+H): 639.1191, found: (M+H): 639.1190.

(*2'R*,4S*,4'S)-1-(adamantan-1-ylmethyl)-4'-(3-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6d).** From **3b** (0.065 g, 0.17 mmol), sarcosine (0.030 g, 0.34 mmol) and isatin **4a** (0.049 g, 0.34 mmol) compound **6d** (0.066 g, 70%) was obtained as white crystalline solid Yield 70%. M.p.=166-167ºC. **^{1}H NMR** (400 MHz, DMSO-d6) δ: 10.54 (s, 1H), 9.98 (s, 1H), 7.44 (d, J=7.3 Hz, 1H), 7.38 (bs, 1H), 7.33-7.30 (m, 2H), 7.27 (m, 1H), 7.21 (td, J1=1.0 Hz, J2=8.6 Hz, 1H), 7.00 (td, J1=1.0 Hz, J2=8.5 Hz, 1H), 6.76 (d, J=7.6 Hz, 1H), 4.24 (dd, J1=8.7 Hz, J2=9.8 Hz, 1H), 3.85 (t, J=9.5 Hz, 1H), 3.43 (m, 1H), 3.25 (d, J=13.5 Hz, 1H), 3.08 (d, J=13.5 Hz, 1H), 2.12 (s, 3H), 1.73 (bs, 3H), 1.55-1.48 (m, 3H), 1.44-1.36 (m, 3H), 1.16-1.10 (m, 3H), 1.10-1.04 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.31 (s, 1C), 174.95 (s, 1C), 172.40 (s, 1C), 142.41 (s, 1C), 137.15 (s, 1C), 133.03 (s, 1C), 130.14 (s, 1C), 129.70 (s, 1C), 129.28 (s, 1C), 128.01 (s, 1C), 127.85 (s, 1C), 127.64 (s, 1C), 124.32 (s, 1C), 121.50 (s, 1C), 109.57 (s, 1C), 77.46 (s, 1C),

75.77 (s, 1C), 56.04 (s, 1C), 51.14 (s, 1C), 50.75 (s, 1C), 40.24 (s, 1C), 36.07 (s, 1C), 35.00 (s, 1C), 34.79 (s, 1C), 27.55 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{33}ClN_4O_2S$, M+H): 561.2086, found: (M+H): 561.2087.

(*2'R*,4S*,4'S)-5''-chloro-1-(adamantan-1-ylmethyl)-4'-(3-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6e)**. From **3b** (0.065 g, 0.17 mmol), sarcosine (0.030 g, 0.34 mmol) and 5-chloroisatin **4b** (0.061 g, 0.34 mmol) compound **6e** (0.076 g, 76%) was obtained as white crystalline solid. M.p.=266-267ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H), 10.12 (s, 1H), 7.47 (d, J=1.8 Hz, 1H), 7.37 (bs, 1H), 7.33-7.27 (m, 3H), 7.24 (m, 1H), 6.78 (d, J=8.3 Hz, 1H), 4.22 (dd, J_1=8.6 Hz, J_2=10.0 Hz, 1H), 3.85 (t, J=9.7 Hz, 1H), 3.43 (t, J=8.6 Hz, 1H), 3.30 (d, J=13.6 Hz, 1H), 3.10 (d, J=13.6 Hz, 1H), 2.14 (s, 3H), 1.75 (bs, 3H), 1.56-1.48 (m, 3H), 1.43-1.35 (m, 3H), 1.16-1.10 (m, 3H), 1.10-1.14 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.38 (s, 1C), 174.64 (s, 1C), 172 (s, 1C), 48 (s, 1C), 141.36 (s, 1C), 136.87 (s, 1C), 133.04 (s, 1C), 130.15 (s, 1C), 129.69 (s, 1C), 129.23 (s, 1C), 127.97 (s, 1C), 127.80 (s, 1C), 127.66 (s, 1C), 126.53 (s, 1C), 125.95 (s, 1C), 111.00 (s, 1C), 77.51 (s, 1C), 75.85 (s, 1C), 55.94 (s, 1C), 51.21 (s, 1C), 50.79 (s, 1C), 40.26 (s, 1C), 36.10 (s, 1C), 34.99 (s, 1C), 34.82 (s, 1C), 27.59 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}Cl_2N_4O_2S$, M+H): 595.1696, found: (M+H): 595.1693.

(*2'R*,4S*,4'S)-5''-bromo-1-(adamantan-1-ylmethyl)-4'-(3-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6f)**. From **3b** (0.065 g, 0.17 mmol), sarcosine (0.030 g, 0.34 mmol) and 5-bromoisatin **4c** (0.076 g, 0.34 mmol) compound **6f** (0.062 g, 58%) was obtained as white crystalline solid. M.p.=270-271ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 10.08 (s, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.41 (dd, J1=1.8 Hz, J2=8.3 Hz, 1H), 7.35 (bs, 1H), 7.33-7.28 (m, 2H), 7.23 (m, 1H), 6.74 (d, J=8.3 Hz, 1H), 4.21 (dd, J1=8.3 Hz, J2=10.0 Hz, 1H), 3.85 (t, J=9.6 Hz, 1H), 3.42 (t, J=8.5 Hz, 1H), 3.30 (d, J=13.5 Hz, 1H), 3.10 (d, J=13.5 Hz, 1H), 2.15 (s, 3H), 1.76 (bs, 3H), 1.56-1.48 (m, 3H), 1.43-1.35 (m, 3H), 1.16-1.10 (m, 3H), 1.10-1.14 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ:

182.42 (s, 1C), 174.56 (s, 1C), 172.58 (s, 1C), 141.81 (s, 1C), 136.84 (s, 1C), 133.04 (s, 1C), 132.54 (s, 1C), 130.49 (s, 1C), 130.15 (s, 1C), 129.17 (s, 1C), 127.92 (s, 1C), 127.65 (s, 1C), 126.92 (s, 1C), 113.73 (s, 1C), 111.47 (s, 1C), 77.43 (s, 1C), 75.85 (s, 1C), 55.90 (s, 1C), 51.21 (s, 1C), 50.85 (s, 1C), 40.25 (s, 1C), 36.09 (s, 1C), 34.96 (s, 1C), 34.81 (s, 1C), 27.60 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}BrClN_4O_2S$, M+H): 639.1191, found: (M+H): 693.1186.

(*2'R*,4S*,4'S)-1-(adamantan-1-ylmethyl)-4'-(4-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6j)**. From **3c** (0.100 g, 0.26 mmol), sarcosine (0.046 g, 0.52 mmol) and isatin **4a** (0.076 g, 0.52 mmol) compound **6j** (0.090 g, 6%) was obtained as white crystalline solid. M.p.=190-191ºC. **^{1}H NMR** (400 MHz, DMSO-d6) δ:10.54 (s, 1H), 9.97 (s, 1H), 7.45 (d, J=7.3 Hz, 1H), 7.34 (s, 4H), 7.21 (t, J=7.5 Hz, 1H), 7.00 (t, J=7.3 Hz, 1H), 6.76 (d, J=7.5 Hz, 1H), 4.24 (t, J=9.2 Hz, 1H), 3.84 (t, J=9.7 Hz, 1H), 3.42 (m, 1H), 3.25 (d, J=13.6 Hz, 1H), 3.07 (d, J=13.1 Hz, 1H), 2.12 (s, 3H), 1.72 (bs, 3H), 1.56-1.46 (m, 3H), 1.44-1.34 (m, 3H), 1.15-1.00 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.23 (s, 1C), 174.96 (s, 1C), 172.27 (s, 1C), 142.34 (s, 1C), 133.60 (s, 1C), 132.31 (s, 1C), 131.20 (s, 1C), 129.66 (s, 1C), 128.33 (s, 1C), 127.83 (s, 1C), 124.35 (s, 1C), 121.48 (s, 1C), 109.57 (s, 1C), 77.48 (s, 1C), 75.79 (s, 1C), 56.08 (s, 1C), 51.15 (s, 1C), 50.63 (s, 1C), 40.19 (s, 1C), 36.05 (s, 1C), 34.95 (s, 1C), 34.81 (s, 1C), 27.53 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{33}ClN_4O_2S$, M+H): 561.2086, found: (M+H): 561.2080.

(*2'R*,4S*,4'S)-5''-chloro-1-(adamantan-1-ylmethyl)-4'-(4-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6h)**. From **3c** (0.100 g, 0.26 mmol), sarcosine (0.046 g, 0.52 mmol) and isatin **4b** (0.094 g, 0.52 mmol) compound **6h** (0.107 g, 70%) was obtained as white crystalline solid. M.p.=230-231ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H), 10.06 (s, 1H), 7.48 (s, 1H), 7.39-7.31 (m, 4H), 7.27 (m, 1H), 6.78 (d, J=8.1 Hz, 1H), 4.22 (t, J=9.0 Hz, 1H), 3.84 (t, J=9.4 Hz, 1H), 3.43 (t, J=8.5 Hz, 1H), 3.29 (d, J=13.3 Hz, 1H), 3.09 (d, J=13.3 Hz, 1H), 2.15 (s, 3H), 1.75 (bs, 3H), 1.56-1.48 (m, 3H), 1.42-1.35 (m, 3H), 1.16-1.01 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ:

182.33 (s, 1C), 174.69 (s, 1C), 172.42 (s, 1C), 141.32 (s, 1C), 133.34 (s, 1C), 132.34 (s, 1C), 131.17 (s, 1C), 129.67 (s, 1C), 128.35 (s, 1C), 127.77 (s, 1C), 126.55 (s, 1C), 125.95 (s, 1C), 110.99 (s, 1C), 77.50 (s, 1C), 75.85 (s, 1C), 56.00 (s, 1C), 51.23 (s, 1C), 50.71 (s, 1C), 40.22 (s, 1C), 36.07 (s, 1C), 34.94 (s, 1C), 34.82 (s, 1C), 27.57 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}Cl_2N_4O_2S$, M+H): 595.1696, found: (M+H): 595.1699.

(*2'R*,4S*,4'S)-5''-bromo-1-(adamantan-1-ylmethyl)-4'-(4-chlorophenyl)-1'-methyl-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-2',3''-indoline]-2'',5-dione (6i)**. From **3c** (0.065 g, 0.17 mmol), sarcosine (0.030 g, 0.34 mmol) and 5-bromoisatin **4c** (0.076 g, 0.34 mmol) compound **6i** (0.069 g, 64%) was obtained as white crystalline solid. M.p.=249-250ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 10.00 (s, 1H), 7.57 (d, J=1.8 Hz, 1H), 7.41 (dd, J_1=2.1 Hz, J_2=8.3 Hz, 1H), 7.35 (d, J=8.7 Hz, 2H), 7.31 (d, J=8.6 Hz, 2H), 6.74 (d, J=8.3 Hz, 1H), 4.20 (dd, J_1=8.3 Hz, J_2=10.2 Hz, 1H), 3.84 (t, J=9.7 Hz, 1H), 3.42 (t, J=8.5 Hz, 1H), 3.30 (d, J=13.5 Hz, 1H), 3.09 (d, J=13.5 Hz, 1H), 2.14 (s, 3H), 1.75 (bs, 3H), 1.56-1.49 (m, 3H), 1.42-1.35 (m, 3H), 1.15-1.02 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.36 (s, 1C), 174.61 (s, 1C), 172.52 (s, 1C), 141.78 (s, 1C), 133.32 (s, 1C), 132.53 (s, 1C), 132.33 (s, 1C), 131.13 (s, 1C), 130.47 (s, 1C), 128.36 (s, 1C), 126.94 (s, 1C), 113.73 (s, 1C), 111.48 (s, 1C), 77.44 (s, 1C), 75.86 (s, 1C), 55.97 (s, 1C), 51.24 (s, 1C), 50.77 (s, 1C), 40.22 (s, 1C), 36.07 (s, 1C), 34.93 (s, 1C), 34.82 (s, 1C), 27.58 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{31}H_{32}BrClN_4O_2S$, M+H): 639.1191, found: (M+H): 639.1201.

General Procedure for the Synthesis of Compounds 7. Corresponding 5-(indolin-2-one)-2-thioxoimidazolidines **5** (1 equiv) and N-substituted amino acid (8 equiv) were dissolved in toluene and the mixture heated to a boiling point. After that paraformaldehyde (8 equiv) was added. The resulting mixture was refluxed for 5-8 hours. After the reaction was completed, the solvent was evaporated in vacuo. The product was then purified using column chromatography (silica gel 60, 0.04–0.063 mm/ 230–400 mesh, $CHCl_3$:MeOH/50:1) to afford

yellow or pink solid. This solid was washed with small amount of methanol to yield corresponding dispirooxindole as white crystalline solid.

(*4R*,4'R)-1'-methyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7a)**. From **5a** (0.030 g, 0.08 mmol), sarcosine (0.054 g, 0.61 mmol) and paraformaldehyde (0.020 g, 0.61 mmol) compound **7a** (0.015 g, 45%) was obtained as white crystalline solid. M.p.=262-263ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.55 (s, 1H), 10.36 (s, 1H), 7.36 (d, J=7.3 Hz, 1H), 7.13 (t, J=7.0 Hz, 1H), 6.89 (t, J=7.0 Hz, 1H), 6.74 (d, J=7.3 Hz, 1H), 3.44 (d, J=13.6 Hz, 1H), 3.23 (d, J=10.2 Hz, 1H), 3.09-2.96 (m, 4H), 2.40 (s, 3H), 1.72 (bs, 3H), 1.58-1.46 (m, 3H), 1.46-1.35 (m, 3H), 1.17-1.03 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.95 (s, 1C),175.91 (s, 1C), 173.11 (s, 1C), 142.05 (s, 1C), 128.64 (s, 1C), 127.53 (s, 1C), 126.86 (s, 1C),121.16 (s, 1C), 109.10 (s, 1C), 72.44 (s, 1C), 63.36 (s, 1C), 61.53 (s, 1C), 60.05 (s, 1C), 51.04 (s, 1C), 41.47 (s, 1C), 40.12 (s, 1C), 36.09 (s, 1C), 34.83 (s, 1C), 27.58 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{25}H_{30}N_4O_2S$, M+H): 451.2162, found: (M+H): 451.2161.

(*4R*,4'R)-5''-chloro-1'-methyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7b)**. From **5b** (0.050 g, 0.08 mmol), sarcosine (0.054 g, 0.61 mmol) and paraformaldehyde (0.020 g, 0.61 mmol) compound **7b** (0.026 g, 69%) was obtained as white crystalline solid. M.p.=288-289ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H), 10.45 (s, 1H), 7.39 (d, J=2.0 Hz, 1H), 7.20 (dd, J_1=2.0 Hz, J_2=8.3 Hz, 1H), 6.76 (d, J=8.3 Hz, 1H), 3.47 (d, J=13.6 Hz, 1H), 3.28 (d, J=10.2 Hz, 1H), 3.08-2.99 (m, 3H), 2.88 (d, J=10.3 Hz, 1H), 2.39 (s, 3H), 1.74 (bs, 3H), 1.56-1.49 (m, 3H), 1.45-1.38 (m, 3H), 1.15-1.09 (m, 3H), 1.09-1.03 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.78 (s, 1C), 175.16 (s, 1C), 172.93 (s, 1C), 140.85 (s, 1C), 129.91 (s, 1C), 128.38 (s, 1C), 127.09 (s, 1C), 125.30 (s, 1C), 110.38 (s, 1C), 72.33 (s, 1C), 63.49 (s, 1C), 61.73 (s, 1C), 60.35 (s, 1C), 50.98 (s, 1C), 41.22 (s, 1C), 40.08 (s, 1C), 36.09 (s, 1C), 34.82 (s, 1C), 27.59 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{25}H_{29}ClN_4O_2S$, M+H): 485.1773, found: (M+H): 485.1777.

(*4R*,4'R)-5''-bromo-1'-Methyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7c)**. From **5c** (0.036 g, 0.08 mmol), sarcosine (0.054 g, 0.61 mmol) and paraformaldehyde (0.020 g, 0.61 mmol) compound **7c** (0.021 g, 51%) was obtained as white crystalline solid. M.p.=287-288ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 10.43 (s, 1H), 7.51 (d, J=1.6 Hz, 1H), 7.32 (dd, J_1=1.7 Hz, J_2=8.2 Hz, 1H), 6.72 (d, J=8.3 Hz, 1H), 3.47 (d, J=13.6 Hz, 1H), 3.27 (d, J=10.2 Hz, 1H), 3.07-2.99 (m, 3H), 2.87 (d, J=10.2 Hz, 1H), 2.39 (s, 3H), 1.75 (bs, 3H), 1.56-1.49 (m, 3H), 1.45-1.38 (m, 3H), 1.15-1.08 (m, 3H), 1.08-1.02 (m, 3H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.80 (s, 1C), 175.09 (s, 1C), 172.93 (s, 1C), 141.26 (s, 1C), 131.24 (s, 1C), 130.36 (s, 1C), 129.81 (s, 1C), 113.07 (s, 1C), 110.91 (s, 1C), 72.36 (s, 1C), 63.61 (s, 1C), 61.80 (s, 1C), 60.33 (s, 1C), 50.99 (s, 1C), 41.22 (s, 1C), 40.09 (s, 1C), 36.10 (s, 1C), 34.82 (s, 1C), 27.60 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{25}H_{29}BrN_4O_2S$, M+H): 529.1267, found: (M+H): 529.1260.

(*4R*,4'R)-1'-isopropyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7d)**. From **5a** (0.030 g, 0.08 mmol), sarcosine (0.054 g, 0.61 mmol) and paraformaldehyde (0.020 g, 0.61 mmol) compound **7d** (0.008 g, 22%) was obtained as white crystalline solid. M.p.=267-268ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: 10.55 (s, 1H), 10.42 (s, 1H), 7.41 (d, J=7.6 Hz, 1H), 7.14 (td, J_1=1.1 Hz, J_2=7.7 Hz, 1H), 6.90 (td, J_1=1.1 Hz, J_2=7.7 Hz, 1H), 6.74 (d, J=7.7 Hz, 1H), 3.45 (d, J=13.5 Hz, 1H), 3.31 (d, J=10.2 Hz, 1H), 3.17-3.05 (m, 3H), 3.02 (d, J=13.5 Hz, 1H), 2.72 (m, 1H), 1.74 (bs, 3H), 1.58-1.49 (m, 3H), 1.47-1.39 (m, 3H), 1.12 (bs, 6H), 1.05 (t, J=7.0 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.73 (s, 1C), 175.61 (s, 1C), 173.04 (s, 1C), 141.90 (s, 1C), 128.53 (s, 1C), 127.68 (s, 1C), 126.78 (s, 1C), 121.10 (s, 1C), 109.01 (s, 1C), 71.59 (s, 1C), 59.13 (s, 1C), 58.74 (s, 1C), 57.46 (s, 1C), 52.78 (s, 1C), 50.99 (s, 1C), 40.11 (s, 1C), 36.09 (s, 1C), 34.84 (s, 1C), 27.58 (s, 1C), 21.26 (s, 1C), 21.09 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{27}H_{34}N_4O_2S$, M+H): 479.2475, found: (M+H): 479.2479.

(*4R*,4'R)-5''-chloro-1'-isopropyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7e)**. From **5b** (0.045 g, 0.11 mmol), sarcosine (0.075 g, 0.84 mmol) and paraformaldehyde (0.027 g, 0.84 mmol) compound **7e** (0.008 g, 14%) was obtained as white crystalline solid. M.p.=232-233ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: (400 MHz, DMSO-d_6) δ: 10.69 (s, 1H), 10.51 (s, 1H), 7.43 (d, J=2.1 Hz, 1H), 7.21 (dd, J_1=2.2 Hz, J_2=8.2 Hz, 1H), 6.76 (d, J=8.3 Hz, 1H), 3.48 (d, J=13.6 Hz, 1H), 3.13 (d, J=9.6 Hz, 1H), 3.10 (d, J=9.8 Hz, 1H), 3.03 (d, J=9.8 Hz, 1H), 3.00 (d, J=6.4 Hz, 1H), 2.71 (m, 1H),), 1.76 (bs, 3H), 1.58-1.50 (m, 3H), 1.47-1.40 (m, 3H), 1.12 (bs, 6H), 1.09-1.02 (m, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.63 (s, 1C), 174.99 (s, 1C), 172.93 (s, 1C), 140.78 (s, 1C), 129.98 (s, 1C), 128.35 (s, 1C), 126.95 (s, 1C), 125.24 (s, 1C),110.36 (s, 1C), 71.51 (s, 1C), 59.44 (s, 1C), 58.77 (s, 1C), 57.62 (s, 1C), 52.69 (s, 1C), 50.98 (s, 1C), 40.12 (s, 1C), 36.11 (s, 1C), 34.86 (s, 1C), 27.59 (s, 1C), 21.16 (s, 1C), 20.97 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{27}H_{33}ClN_4O_2S$, M+H): 513.2086, found: (M+H): 513.2078.

(*4R*,4'R)-5''-bromo-1'-isopropyl-1-(adamantan-1-ylmethyl)-2-thioxodispiro[imidazolidine-4,3'-pyrrolidine-4',3''-indoline]-2'',5-dione (7f)**. From **5c** (0.050 g, 0.11 mmol), sarcosine (0.075 g, 0.84 mmol) and paraformaldehyde (0.027 g, 0.84 mmol) compound **7e** (0.008 g, 14%) was obtained as white crystalline solid. M.p.=232-233ºC Yield 13%. M.p.=225-226ºC. **^{1}H NMR** (400 MHz, DMSO-d_6) δ: (400 MHz, DMSO-d_6) δ: (400 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 10.49 (s, 1H), 7.55 (d, J=1.8 Hz, 1H), 7.33 (dd, J_1=2.0 Hz, J_2=8.3 Hz, 1H), 6.71 (d, J=8.3 Hz, 1H), 3.48 (d, J=13.6 Hz, 1H), 3.32 (m, 1H), 3.13 (d, J=9.4 Hz, 1H), 3.09 (d, J=9.5 Hz, 1H), 3.06-2.97 (m, 2H), 2.70 (m, 1H), 1.76 (bs, 3H), 1.58-1.50 (m, 3H), 1.47-1.39 (m, 3H), 1.12 (bs, 6H), 1.05 (t, J=6.9 Hz, 6H). **^{13}C NMR** (101 MHz, DMSO-d_6) δ: 182.71 (s, 1C), 174.95 (s, 1C), 172.90 (s, 1C), 141.18 (s, 1C), 131.16 (s, 1C), 130.35 (s, 1C), 129.62 (s, 1C), 113.00 (s, 1C),110.85 (s, 1C), 71.51 (s, 1C), 59.34 (s, 1C), 58.79 (s, 1C), 57.60 (s, 1C), 52.68 (s, 1C), 50.99 (s, 1C), 40.13 (s, 1C), 36.09 (s, 1C), 34.81 (s, 1C), 27.59 (s,

1C), 21.03 (s, 1C), 20.84 (s, 1C). **HRMS** (ESI+) m/z calcd. for ($C_{27}H_{33}BrN_4O_2S$, M+H): 557.1580, found: (M+H): 557.1586.

Supporting Information: see Supplemetary Information.doc file (NMR spectra of synthesized compounds).

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