Synthesis of spiro[indole-3,3´-[1,3,4]thiadiazino[3,2-*a*]benzimidazoles] and spiro[indole-3,6´-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines]

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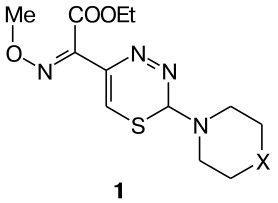
A method for annulation of the tetrahydrothiadiazine ring to benzimidazoles and 1,2,4-triazoles was developed. A number of earlier unknown [1,3,4]thiadiazino[3,2-*a*]benzimidazoles and triazolo[3,4-*b*][1,3,4]thiadiazines were obtained as spiro compounds with the oxindole fragment. According to NMR and X-ray diffraction data, the formation of the tetrahydrothiadiazine ring is a diastereospecific process.

Key words: [1,3,4]thiadiazino[3,2-*a*]benzimidazole, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine, tetrahydrothiadiazine, annulation, X-ray diffraction analysis.

Attention to 1,3,4-thiadiazines is due to the broad spectrum of their biological activity. For instance, compounds **1** are anesthetic, cardiovascular, and hypometabolic agents.[1] Some of their fused derivatives exhibit antibacterial,[2—5] antiinflammatory,[6] and fungicidal[7] properties.



1

X = O, S, CH_2

Known routes to fused 1,3,4-thiadiazines mainly involve reactions of heterocyclic amino thiols with bifunctional reagents such as α-halo carbonyl compounds,[8—10] dihalides,[11] α-halo nitriles,[12] and 1,3-diketones.[13]

Earlier, we have developed a method for the synthesis of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines,[14,15] 3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazines, and spirocyclic imidazo[2,1-*b*][1,3,4]thiadiazines[16] by intramolecular cyclization of *S*-alkyl derivatives of *N*-triazolyl and *N*-imidazolyl imines. The goal of the present work was to extend the synthetic scope of the proposed method through the use of 1-amino-1*H*-benzimidazole-2-thiol and 4-amino-5-R-4*H*-1,2,4-triazole-3-thiols as the starting reagents and to obtain novel spirocyclic fused tetrahydrothiadiazine systems.

A reaction of 1-amino-1*H*-benzimidazole-2-thiol (**2**) with 4-nitrobenzyl bromide yielded 1-amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole (**3**), which underwent base-catalyzed cyclization with isatins **4a—f** to give the corresponding spirocyclic [1,3,4]thiadiazino[3,2-*a*]benzimidazoles **5a—f** (Scheme 1).

A similar transformation in the base-catalyzed condensation of 4-amino-3-[(4-nitrobenzyl)thio]-4*H*-1,2,4-triazoles **6a—d** with alkylisatins **4f,g** afforded spirocyclic triazolo[3,4-*b*][1,3,4]thiadiazines **7** (Scheme 2). Note that 4-amino-3-benzyl- and 4-amino-3-[(4-bromobenzyl)thio]-5-R-4*H*-1,2,4-triazoles are inert in this reaction, probably because of the insufficient acidity of the methylene protons.

Triazolothiadiazine **7b** was also obtained by an independent synthesis from *N*-triazolyl imine **8** and 4-nitrobenzyl bromide in the presence of NaOH (2 equiv.). In both cases, the reaction obviously proceeds through the formation of the corresponding acyclic *N*-benzylthiotriazolyl imine **9**.

According to ^{1}H NMR data, the formation of a six-membered thiadiazine ring is evident from the absence of the singlets (2 H intensity) for the amino and *S*-methylene groups characteristic of the starting compounds **3** and **6** and from the presence of two peaks (1 H intensity) for the SCH and NH fragments at δ_H 5.5—5.6 and 7.5—7.8 for compounds **5** and at δ_H 5.4—5.5 and 8.1—8.3 for compounds **7**, respectively. In the ^{1}H NMR spectra of compounds **5f** and **7a—d**, the prochiral *N*-methylene group appears as an AB quartet at δ_H 4.6—4.9, which suggests the formation of a chiral molecule.

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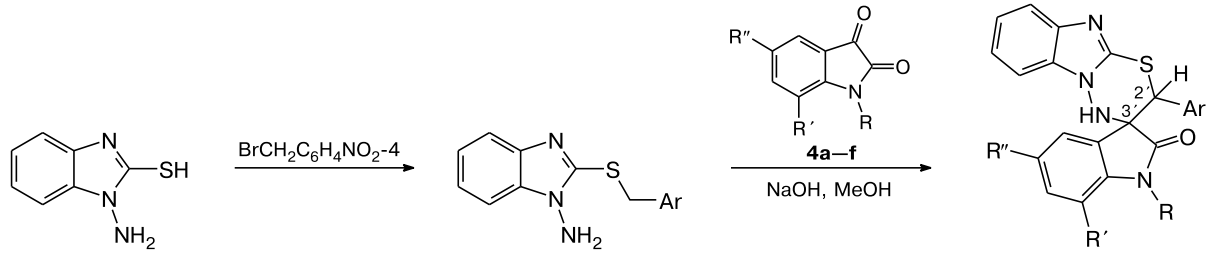
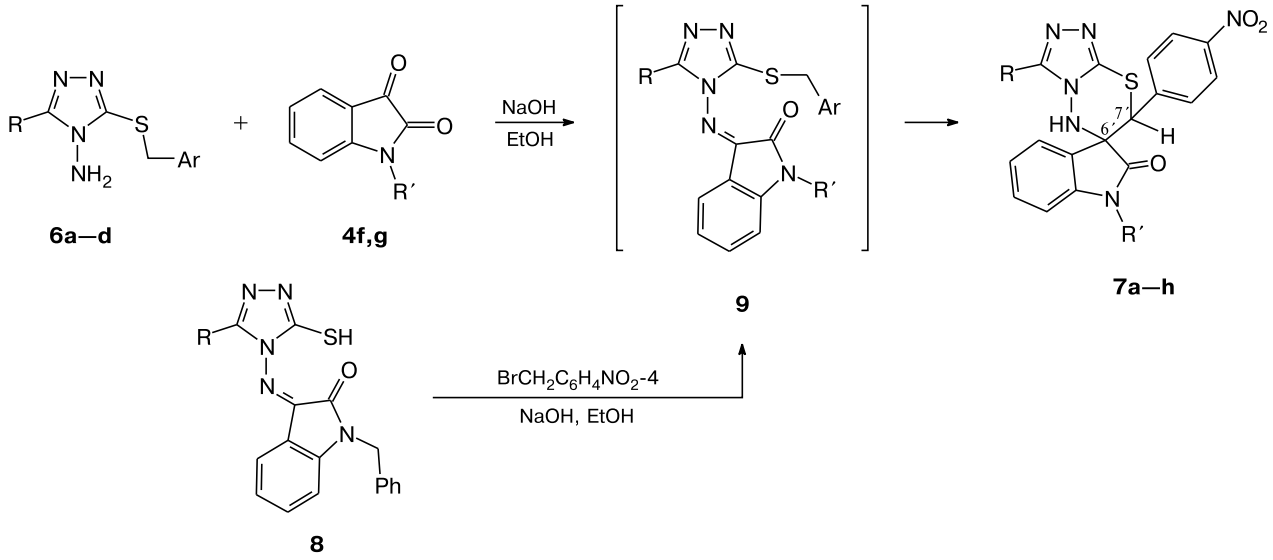
Scheme 1



3, 5: Ar = 4-$NO_2C_6H_4$
4, 5: R = R′ = R″ = H (**a**); R = R′ = H, R″ = Me (**b**); R = R′ = H, R″ = F (**c**); R = H, R′ = R″ = Me (**d**); R = Me, R′ = H, R″ = OMe (**e**); R = CH_2Ph, R′ = R″ = H (**f**)

Scheme 2



6: Ar = 4-$NO_2C_6H_4$ (**a—d**); R = Ph (**a**), 4-Py (**b**), 3-Py (**c**), 2-Fu (**d**)
7: R′ = CH_2Ph (**a—d**), Me (**e—h**); R = Ph (**a**, **e**), 4-Py (**b**, **f**), 3-Py (**c**, **g**), 2-Fu (**d**, **h**)
8: R = 4-Py

The absence of minor signals from the ^{1}H NMR spectra of compounds **5** and **7** and their univocal correspondence to the expected structure show that spiro compounds **5** and **7** containing two chiral centers are not a mixture of four possible stereoisomers but a racemate of one enantiomeric pair out of two possible pairs.

Structures **5f** and **7f** were confirmed by X-ray diffraction analysis (Figs 1 and 2, respectively). Compound **5f** in the crystalline state (centrosymmetric space group *P*-1) is a racemic mixture of the molecules with the *S*,*S*- and *R*,*R*-configurations of both asymmetric C atoms of the thiadiazine ring. Unlike structure **5f**, compound **7f** crystallizes in the non-centrosymmetric space group $Pna2_1$. However, its unit cell consists of two independent molecules with different chiralities (*S*,*S* and *R*,*R*); *i.e.*, its structure is also a mixture of enantiomers. Structures **5f** and **7f** with the *R*-configuration of both the stereogenic C(2) and C(3) atoms* are shown in Figs 1 and 2.

Main geometrical parameters of structures **5f** and **7f** are within the values characteristic of this class of compounds. The conformation of the thiadiazine ring is a sofa: the C(3) atom deviates from the plane of the other ring atoms by 0.68 Å in molecules **5f** and by 0.73 Å in both independent molecules **7f**. The imidazole ring in structure **5f** deviates from this plane only slightly (by 3.9(1)°), while the dihedral angle between the triazole and thiadiazine rings in structure **7f** is 12.3(1) and 12.5(1)°. The nature of the azole ring and the substituent at the N(13) atom have little (if any) influence on the relative positions of the

* In the description of the structures from the X-ray diffraction data, we used the crystallographic numbering of the atoms.

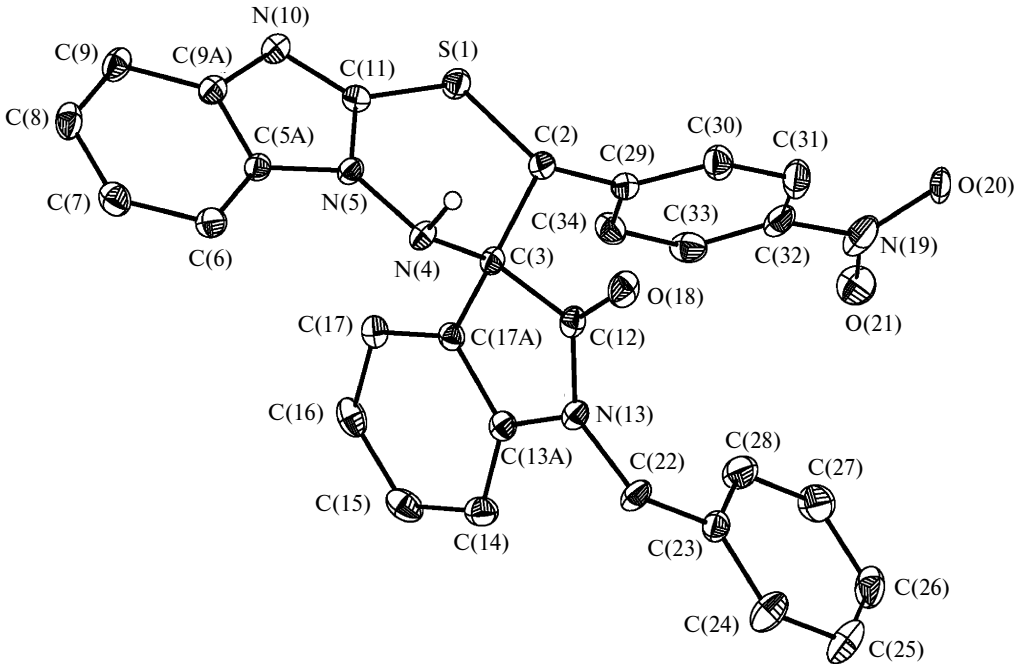


Fig. 1. General view of compound **5f** (*R*,*R*-enantiomer) with atomic thermal displacement ellipsoids (p = 50%). The H atoms are omitted (except for the NH group).

heterocyclic fragments sharing a spiro atom. The dihedral angles between them in structures **5f** and **7f** are very close (84.9(2)° and 86.9(2)°; for the second independent molecule of **7f**, this angle increases to 92.2(2)°). In contrast, the nitrophenyl substituent is in substantially different positions relative to the oxindole and thiadiazine rings. The corresponding angles with the plane of the nitrophenyl substituent are 61.0(2)° and 71.2(2)° in structure **5f**; for two independent molecules of **7f** in the crystal, they are 51.7(2)°, 47.6(2)° and 56.1(2)°, 44.6(2)°.

As for supramolecular organization in crystals, the main difference between compounds **5f** and **7f** is that the latter is a monohydrate. For instance, because compound **5f** contains many aromatic fragments, its molecules in the crystal are united, even in the presence of an efficient proton donor (NH group) and an efficient proton acceptor (CO group), through the interactions

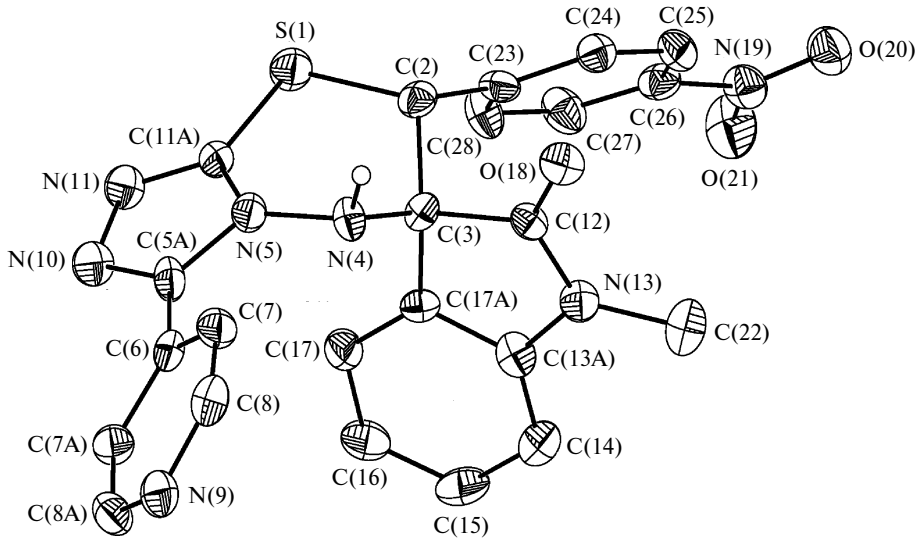


Fig. 2. General view of compound **7f** (*R*,*R*-enantiomer) with atomic thermal displacement ellipsoids (p = 50%). The H atoms are omitted (except for the NH group).

N—H...π (N...C, 3.406(2)—3.583(2) Å), C—H...π (C...C, 3.526(2)—3.673(2) Å), and N—O...π (O...C, 3.026(2)—3.141(2) Å). In structure **7f**, solvate water molecules form medium-strength hydrogen bonds N—H...O, O—H...O, and O—H...N (N...O, 2.749(2)—2.750(2) Å, angle N—H—O 163—164(1)°; O...O, 2.904(2)—2.909(2) Å, angle O—H—O 146(1)°; O...N, 2.778(2)—2.800(2) Å, angle N—H—O 168—174(1)°) to unite symmetrically nonequivalent molecules into layers. These associates are additionally stabilized by the interactions C—H...π with the triazole (C...N, 3.534(2)—3.585(2) Å) and nitrobenzene fragments (C...C, 3.385(2) Å). Numerous weaker contacts C—H...O, C—H...N, H...H, and C—H...S (only in **5f**) complete the formation of three-dimensional frameworks in structures **5f** and **7f**.

Because the starting compound contains an electron-withdrawing substituent in the benzyl thiol fragment, which enhances the acidity of the *S*-methylene protons, and the presence of a base is required for the cyclization to occur, one can propose the following mechanism of this reaction. The formation of the thiadiazine ring involves condensation through the amino group of the starting compound **3** (or **6**) and the carbonyl group of isatin, abstraction of the methylene proton, and a nucleophilic attack of the resulting carbanion on the azomethine C atom with closure of the C(2)—C(3) (or C(6)—C(7)) bond of the thiadiazine ring (Scheme 3). The cyclization is diastereospecific, probably because of steric hindrances: during the attack of the carbanion on the plane of the C=N bond with the formation of the C—C bond, the bulky aryl fragments are *trans* with respect to the thiadiazine ring.

Thus, the general method we have proposed earlier for the preparation of 1,3,4-thiadiazines fused with azoles was used for the first time for the synthesis of new spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-ones. In addition, a number of new spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-ones were obtained. The distinctive features of this annulation of the tetrahydrothiadiazine ring include (1) C—C bond formation at the final step of the heterocyclization and (2) diastereospecificity of the reaction under consideration.

Experimental

^{1}H NMR spectra were recorded on a Bruker DPX-250 instrument (250 MHz) with Me_4Si as the internal standard. Mass spectra were measured on a Finnigan MAT INCOS 50 mass spectrometer.

1-Amino-1*H*-benzimidazole-2-thiol[17] and 4-amino-3-[(4-nitrobenzyl)thio]-5-R-4*H*-1,2,4-triazoles[14] were prepared as described earlier.

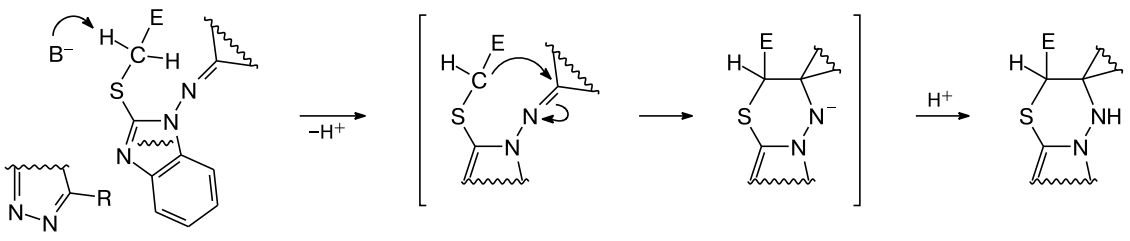
1-Amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole (3). 1-Amino-1*H*-benzimidazole-2-thiol (**2**) (10 mmol, 1.65 g) was added to a solution of NaOH (10 mmol, 0.4 g) in EtOH. After the mixture became homogeneous, 4-nitrobenzyl bromide (10 mmol, 2.16 g) was added. After 15 min, the reaction mixture was diluted with water. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from EtOH. Yield 2.1 g (70%), yellow crystals, m.p. 140—143 °C (EtOH). Found (%): C, 56.99; H, 4.03; N, 18.65. $C_{14}H_{12}N_4O_2S$. Calculated (%): C, 56.70; H, 3.98; N, 18.49. ^{1}H NMR ($CDCl_3$), δ: 4.56 (s, 2 H, NH_2); 4.63 (s, 2 H, CH_2); 7.20—7.33 (m, 3 H, Ar); 7.60—7.67 (m + d, 3 H, Ar, $C_6H_4NO_2$-4, J = 8.8 Hz); 8.14 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz).

2′-(4-Nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]-benzimidazol]-2(1*H*)-ones 5 (general procedure). 1-Amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole (1 mmol) and an appropriate isatin (1 mmol) were dissolved under heating in MeOH (15 mL). An equimolar amount of NaOH (1 mmol) was added and the reaction mixture was refluxed for 2 h, cooled, and neutralized with dilute HCl. The precipitate that formed was filtered off and washed with cooled MeOH.

2′-(4-Nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]-benzimidazol]-2(1*H*)-one (5a). Yield 0.172 g (40%), yellow crystals, decomp. 310—312 °C (MeOH). Found (%): C, 61.53; H, 3.52; N, 16.31. $C_{22}H_{15}N_5O_3S$. Calculated (%): C, 61.40; H, 3.42; N, 16.22. ^{1}H NMR (DMSO-d_6), δ: 5.55 (s, 1 H, H(2)); 6.57, 6.72 (both d, 1 H each, Ar, J = 7.5 Hz, J = 7.7 Hz); 6.89 (dd, 1 H, Ar, J = 7.6 Hz, J = 7.6 Hz); 7.08—7.21 (m, 2 H, Ar); 7.22—7.29 (m, 4 H, $C_6H_4NO_2$-4, Ar); 7.58 (d, 1 H, Ar, J = 7.3 Hz); 7.66 (s, 1 H, N(4′)H); 8.06 (d, 2 H, $C_6H_4NO_2$-4, J = 8.7 Hz); 10.80 (s, 1 H, N(1)H).

5-Methyl-2′-(4-nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-one (5b). Yield 0.301 g (68%), light yellow crystals, m.p. 299—300 °C (MeOH). Found (%): C, 62.29; H, 3.98; N, 15.79. $C_{23}H_{17}N_5O_3S$. Calculated (%): C, 62.12; H, 4.06; N, 15.90. ^{1}H NMR (DMSO-d_6), δ: 2.01 (s, 3 H, Me); 5.48 (s, 1 H, H(2)); 6.39 (s, 1 H, H(4′)); 6.59 (d, 1 H, Ar,

Scheme 3



E = 4-$NO_2C_6H_4$

J = 7.9 Hz); 7.01 (m, 1 H, Ar); 7.13 (m, 2 H, Ar); 7.22 (m, 3 H, $C_6H_4NO_2$-4, Ar); 7.55 (m, 2 H, N(4)H, Ar); 8.02 (d, 2 H, $C_6H_4NO_2$-4, J = 8.9 Hz); 10.66 (s, 1 H, N(1)H).

5-Fluoro-2′-(4-nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-one (5c). Yield 0.224 g (50%), white crystals, m.p. 315—320 °C (MeOH). Found (%): C, 59.06; H, 3.15; F, 4.25; N, 15.65. $C_{22}H_{14}FN_5O_3S$. Calculated (%): C, 59.15; H, 3.19; F, 4.37; N, 15.54. ^{1}H NMR (DMSO-d_6), δ: 5.57 (s, 1 H, H(2)); 6.25 (dd, 1 H, H_{indole}, J = 2.5 Hz, J = 2.5 Hz); 6.76 (m, 1 H, H_{indole}); 7.09—7.36 (m, 6 H, Ar, $C_6H_4NO_2$-4); 7.60 (d, 1 H, Ar, J = 7.4 Hz); 7.76 (s, 1 H, N(4)H); 8.09 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 10.87 (s, 1 H, N(1)H).

5,7-Dimethyl-2′-(4-nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-one (5d). Yield 0.32 g (70%), light yellow crystals, m.p. 306—309 °C (MeOH). Found (%): C, 63.01; H, 4.19; N, 15.31. $C_{24}H_{19}N_5O_3S$. Calculated (%): C, 63.15; H, 4.14; N, 15.39. ^{1}H NMR (DMSO-d_6), δ: 1.97, 2.01 (both s, 3 H each, C(5)Me, C(7)Me); 5.52 (s, 1 H, H(2′)); 6.27, 6.88 (both s, 1 H each, H(4), H(6)); 7.09—7.30 (m, 5 H, Ar, $C_6H_4NO_2$-4); 7.58 (m, 2 H, Ar, N(4′)H); 8.06 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 10.75 (s, 1 H, N(1)H).

5-Methoxy-1-methyl-2′-(4-nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-one (5e). Yield 0.25 g (53%), beige crystals, m.p. 267—269 °C (MeOH). Found (%): C, 60.88; H, 4.04; N, 14.79. $C_{24}H_{19}N_5O_4S$. Calculated (%): C, 60.80; H, 3.98; N, 14.83. ^{1}H NMR (DMSO-d_6), δ: 2.86, 3.51 (both s, 3 H each, NMe, OMe); 5.59 (s, 1 H, H(2′)); 6.06 (d, 1 H, Ar, J = 2.2 Hz); 6.83 (d, 1 H, Ar, J = 8.6 Hz); 6.91 (m, 1 H, Ar); 7.09—7.30 (m, 5 H, Ar, $C_6H_4NO_2$-4); 7.60 (d, 1 H, Ar, J = 7.7 Hz); 7.79 (s, 1 H, NH); 8.06 (d, 2 H, $C_6H_4NO_2$-4, J = 8.7 Hz).

1-Benzyl-2′-(4-nitrophenyl)spiro[indole-3,3′-[1,3,4]thiadiazino[3,2-*a*]benzimidazol]-2(1*H*)-one (5f). Yield 0.19 g (91%), light yellow crystals, decomp. 280—285 °C (MeOH). Found (%): C, 67.04; H, 4.07; N, 13.48. $C_{29}H_{21}N_5O_3S$. Calculated (%): C, 67.22; H, 4.11; N, 13.42. ^{1}H NMR (DMSO-d_6), δ: 4.55, 4.91 (both d, 1 H each, C$\underline{H}_2$Ph, J = 15.8 Hz); 5.62 (s, 1 H, H(2′)); 6.64 (m, 3 H, Ar); 6.83 (d, 1 H, Ar, J = 7.9 Hz); 6.89—7.20 (m, 8 H, Ar); 7.24 (m, 2 H, Ar); 7.55 (d, 1 H, Ar, J = 7.4 Hz); 7.81 (s, 1 H, NH); 7.94 (d, 2 H, $C_6H_4NO_2$-4, J = 8.6 Hz).

Synthesis of spirocyclic 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines 7 (general procedure). ***A.*** *N*-Alkylisatin (1 mmol) was added to a solution of 4-amino-3-(4-nitrobenzyl)thio-4*H*-1,2,4-triazole **6** (1 mmol) in EtOH. After the mixture became homogeneous, NaOH (1 mmol) was added. The reaction mixture was refluxed for 2 h, cooled, diluted with water, and neutralized with dilute HCl. The precipitate that formed was filtered off and recrystallized from MeCN.

1-Benzyl-7′-(4-nitrophenyl)-3′-phenylspiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7a). Yield 0.40 g (75%), colorless crystals, m.p. 278 °C. Found (%): C, 66.21; H, 4.12; N, 15.79. $C_{30}H_{22}N_6O_3S$. Calculated (%): C, 65.92; H, 4.06; N, 15.37. ^{1}H NMR (DMSO-d_6), δ: 4.59, 4.91 (both d, 1 H each, NC$\underline{H}_2$Ph, J = 15.9 Hz); 5.51 (s, 1 H, H(7)); 6.65—6.81 (m, 3 H, H_{indole}, $CH_2\underline{Ph}$); 6.88 (d, 1 H, H_{indole}, J = 7.8 Hz); 7.02—7.12 (m, 4 H, H_{indole}, $CH_2\underline{Ph}$); 7.21 (d, 2 H, 4-$NO_2C_6H_4$, J = 9.1 Hz); 7.32 (m, 1 H, H_{indole}); 7.45 (m, 3 H, Ph); 7.75 (m, 2 H, Ph); 7.95 (d, 2 H, 4-$NO_2C_6H_4$, J = 9.1 Hz); 8.14 (s, 1 H, N(5′)H). MS (EI, 70 eV), m/z (I_{rel} (%)): 370 (5), 293 (2), 263 (1), 208 (2), 190 (3), 179 (4), 149 (8), 133 (4), 103 (18), 91 (100), 77 (12).

1-Benzyl-7′-(4-nitrophenyl)-3′-(4-pyridyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7b). Yield 0.39 g (71%), colorless crystals, m.p. 235—236 °C. Found (%): C, 63.88; H, 3.93; N, 18.33. $C_{29}H_{21}N_7O_3S$. Calculated (%): C, 63.61; H, 3.87; N, 17.90. ^{1}H NMR (DMSO-d_6), δ: 4.61, 4.92 (both d, 1 H each, NC$\underline{H}_2$Ph, J = 15.5 Hz); 5.54 (s, 1 H, H(7′)); 6.69—6.80 (m, 3 H, H_{indole}, $CH_2\underline{Ph}$); 6.91 (d, 1 H, H_{indole}, J = 6.8 Hz); 7.05—7.13 (m, 4 H, H_{indole}, $CH_2\underline{Ph}$); 7.22 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 7.33 (m, 1 H, H_{indole}); 7.80 (d, 2 H, Py, J = 6.2 Hz); 7.98 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 8.32 (s, 1 H, N(5′)H); 8.68 (d, 2 H, Py, J = 6.2 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 370 (5), 312 (1), 236 (3), 208 (4), 190 (3), 178 (6), 145 (7), 133 (3), 104 (9), 91 (100), 76 (10).

B. **Synthesis of 1-benzyl-7′-(4-nitrophenyl)-3′-(4-pyridyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7b).** Compound **8** (1 mmol) was added to a solution of NaOH (1 mmol) in EtOH (10 mL). After the mixture became homogeneous, 4-nitrobenzyl bromide (1 mmol) was added. After homogenization was completed, the reaction mixture was heated for 5 min, whereupon an additional amount of NaOH (1 mmol) was added. The reaction mixture was refluxed for 2 h, cooled, diluted with water, and neutralized with dilute HCl. The precipitate that formed was filtered off and recrystallized from MeCN. The yield was 0.36 g (66%).

1-Benzyl-7′-(4-nitrophenyl)-3′-(3-pyridyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7c). Yield 0.393 g (72%), colorless crystals, m.p. 166—168 °C. Found (%): C, 63.87; H, 3.94; N, 18.35. $C_{29}H_{21}N_7O_3S$. Calculated (%): C, 63.61; H, 3.87; N, 17.90. ^{1}H NMR (DMSO-d_6), δ: 4.59, 4.91 (both d, 1 H each, NC$\underline{H}_2$Ph, J = 15.9 Hz); 5.53 (s, 1 H, H(7′)); 6.69—6.80 (m, 3 H, H_{indole}, $CH_2\underline{Ph}$); 6.89 (d, 1 H, H_{indole}, J = 6.8 Hz); 7.00—7.15 (m, 4 H, H_{indole}, $CH_2\underline{Ph}$); 7.21 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 7.40—7.53 (m, 2 H, H_{indole}, Py); 8.01 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 8.13 (s, 1 H, N(5′)H); 8.35 (d, 1 H, Py, J = 8.1 Hz); 8.62 (d, 1 H, Py, J = 5.0 Hz); 8.88 (s, 1 H, Py). MS (EI, 70 eV), m/z (I_{rel} (%)): 370 (2), 369 (2), 280 (2), 236 (2), 193 (4), 178 (6), 150 (7), 133 (3), 104 (17), 91 (100), 78 (18), 77 (18).

1-Benzyl-3′-(2-furyl)-7′-(4-nitrophenyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7d). Yield 0.42 g (78%), colorless crystals, m.p. 267—269 °C. Found (%): C, 62.73; H, 3.83; N, 15.99. $C_{28}H_{20}N_6O_4S$. Calculated (%): C, 62.68; H, 3.76; N, 16.66. ^{1}H NMR (DMSO-d_6), δ: 4.60, 4.91 (both d, 1 H each, NC$\underline{H}_2$Ph, J = 15.9 Hz); 5.51 (s, 1 H, H(7′)); 6.61 (m, 1 H, H_{furan}(4)); 6.70—6.80 (m, 3 H, H_{indole}, $CH_2\underline{Ph}$); 6.88 (m, 2 H, H_{indole}, H_{furan}); 7.02—7.14 (m, 4 H, H_{indole}, $CH_2\underline{Ph}$); 7.20 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.7 Hz); 7.33 (m, 1 H, H_{indole}); 7.85 (s, 1 H, H_{furan}); 7.95 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.7 Hz); 8.08 (s, 1 H, N(5′)H). MS (EI, 70 eV), m/z (I_{rel} (%)): 370 (8), 301 (1), 283 (5), 253 (4), 190 (3), 179 (5), 149 (10), 133 (4), 109 (4), 91 (100), 76 (9).

1-Methyl-7′-(4-nitrophenyl)-3′-phenylspiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7e). Yield 0.32 g (68%), colorless crystals, m.p. 168—170 °C. Found (%): C, 61.22; H, 3.92; N, 18.41. $C_{24}H_{18}N_6O_3S$. Calculated (%): C, 61.27; H, 3.86; N, 17.86. ^{1}H NMR (DMSO-d_6), δ: 2.82 (s, 3 H, Me); 5.41 (s, 1 H, H(7′)); 6.65 (d, 1 H, H_{indole}, J = 6.8 Hz); 6.89 (d, 1 H, H_{indole}, J = 7.4 Hz); 7.05 (m, 1 H, H_{indole}); 7.18 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 7.35 (m, 1 H, H_{indole}); 7.43 (m, 3 H, Ph); 7.75 (m, 2 H, Ph); 8.01 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.4 Hz); 8.11 (s, 1 H, N(5′)H). MS (EI, 70 eV), m/z (I_{rel} (%)): 293 (14), 280 (8), 262 (7), 205 (5), 190 (5), 177 (15), 159 (27), 150 (53), 131 (22), 104 (100), 89 (46), 77 (92), 50 (50).

1-Methyl-7′-(4-nitrophenyl)-3′-(4-pyridyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7f). Yield 0.32 g (68%), colorless crystals, m.p. 220—222 °C. Found (%): C, 58.19; H, 3.97; N, 21.41. $C_{23}H_{17}N_7O_3S$. Calculated (%): C, 58.59; H, 3.63; N, 20.79. ^{1}H NMR ($CDCl_3$), δ: 2.87 (s, 3 H, Me); 5.32 (s, 1 H, H(7′)); 5.97 (s, 1 H, N(5′)H); 6.68 (d, 1 H, H_{indole}, J = 7.7 Hz); 6.93 (d, 1 H, H_{indole}, J = 7.3 Hz); 7.08 (m, 1 H, H_{indole}); 7.18 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.8 Hz); 7.35 (m, 1 H, H_{indole}); 7.78 (d, 2 H, Py, J = 6.2 Hz); 7.94 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.8 Hz); 8.60 (d, 2 H, Py, J = 6.2 Hz). MS (EI, 70 eV), m/z (I_{rel} (%)): 471 $[M]^+$ (4), 403 (1), 379 (5), 322 (6), 294 (89), 280 (23), 204 (14), 190 (10), 178 (10), 160 (47), 149 (30), 131 (50), 104 (39), 83 (100).

1-Methyl-7′-(4-nitrophenyl)-3′-(3-pyridyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7g). Yield 0.325 g (69%), colorless crystals, m.p. 215—217 °C. Found (%): C, 58.23; H, 3.82; N, 21.52. $C_{23}H_{17}N_7O_3S$. Calculated (%): C, 58.59; H, 3.63; N, 20.79. ^{1}H NMR ($CDCl_3$), δ: 2.91 (s, 3 H, Me); 5.31 (s, 1 H, H(7′)); 5.91 (s, 1 H, N(5′)H); 6.68 (d, 1 H, H_{indole}, J = 7.7 Hz); 6.92 (d, 1 H, H_{indole}, J = 7.3 Hz); 7.06 (m, 1 H, H_{indole}); 7.22 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.8 Hz); 7.43—7.62 (m, 2 H, H_{indole}, Py); 7.93 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.8 Hz); 8.26 (m, 1 H, Py); 8.58 (d, 1 H, Py, J = 5.0 Hz); 9.02 (s, 1 H, Py). MS (EI, 70 eV), m/z (I_{rel} (%)): 454 (3), 331 (2), 299 (2), 252 (2), 191 (3), 178 (15), 160 (6), 150 (53), 131 (17), 104 (75), 89 (38), 77 (71), 50 (100).

3′-(2-Furyl)-1-methyl-7′-(4-nitrophenyl)spiro[indole-3,6′-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazin]-2(1*H*)-one (7h). Yield 0.32 g (70%), colorless crystals, m.p. 230—232 °C. Found (%): C, 57.33; H, 3.42; N, 18.01. $C_{22}H_{16}N_6O_4S$. Calculated (%): C, 57.39; H, 3.50; N, 18.25. ^{1}H NMR (DMSO-d_6), δ: 3.21 (s, 3 H, Me); 5.90 (s, 1 H, H(7′)); 6.58 (m, 1 H, H_{furan}); 6.75 (d, 1 H, H_{indole}, J = 7.1 Hz); 6.92 (m, 2 H, H_{indole}, H_{furan}); 7.04 (m, 1 H, H_{indole}); 7.22 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.7 Hz); 7.33 (m, 1 H, H_{indole}); 7.85 (s, 1 H, H_{furan}); 7.91 (d, 2 H, 4-$NO_2C_6H_4$, J = 8.7 Hz); 8.10 (s, 1 H, N(5′)H). MS (EI, 70 eV), m/z (I_{rel} (%)): 317 (12), 293 (7), 280 (6), 269 (3), 249 (4), 204 (3), 190 (3), 182 (23), 167 (96), 150 (62), 150 (53), 131 (15), 102 (46), 94 (76), 77 (48), 51 (77), 39 (100).

1-Benzyl-3-{[3-mercapto-5-(4-pyridyl)[1,2,4]triazol-4-yl]-imino}-1,3-dihydro-2*H*-indol-2-one (8). A mixture of 4-amino-5-(4-pyridyl)-4*H*-1,2,4-triazole-3-thiol (20 mmol, 3.86 g) and *N*-benzylisatin (20 mmol, 4.74 g) was refluxed in glacial acetic acid (20 mL) for 4 h. On cooling, the reaction mixture was diluted with water. The precipitate that formed was filtered off and recrystallized from ethanol. The yield was 3.131 g (38%), orange crystals, m.p. 234 °C. Found (%): C, 63.93; H, 3.75; N, 20.80. $C_{22}H_{16}N_6OS$. Calculated (%): C, 64.06; H, 3.91; N, 20.37. ^{1}H NMR (DMSO-d_6), δ: 4.72 (d, 1 H, NCH_2, J = 15.8 Hz); 5.03 (d, 1 H, NCH_2, J = 15.8 Hz); 6.90 (d, 1 H, Ar, J = 7.4 Hz); 7.02 (m, 1 H, Ar); 7.18 (t, 1 H, Ar, J = 7.4 Hz); 7.33—7.43 (m, 5 H, Ph); 7.58 (m, 1 H, Ar); 7.89 (d, 2 H, Py, J = 6.1 Hz); 8.76 (d, 2 H, Py, J = 6.1 Hz); 14.51 (s, 1 H, SH). MS (EI, 70 eV), m/z (I_{rel} (%)): 412 $[M]^+$ (0.9), 384 (1.6), 321 (0.7), 193 (100), 178 (2.1), 162 (6.3), 122 (13.2), 105 (32.5), 78 (39.2).

X-ray diffraction studies were carried out on a SMART APEX II CCD diffractometer (Mo-Kα radiation, graphite monochromator, ω scan mode) for compound **5f** and on a SMART 1000 CCD diffractometer (Mo-Kα radiation, graphite monochromator, ω scan mode) for compound **7f**. The structures were solved by the direct methods and refined by the least-squares method in the anisotropic full-matrix approximation on F^2_{hkl}. The hydrogen atoms of the NH groups and water molecules in structures **5f** and **7f** were located from the difference electron-density maps. The positions of the H(C) atoms were calculated geometrically. All H atoms were refined isotropically. Selected crystallographic parameters and the data collection and refinement statistics are given in Table 1. All calculations were performed with the SHELXTL PLUS program package.[18]

Table 1. Selected crystallographic parameters and the data collection and refinement statistics for structures **5f** and **7f**

Parameter	**5f**	**7f**
Molecular formula	$C_{29}H_{21}N_5O_3S$	$C_{23}H_{19}N_7O_4S$
Molecular weight	519.57	489.51
T/K	100	120
Crystal system	Triclinic	Orthorhombic
Space group	P-1	$Pna2_1$
Z	2	8
a/Å	9.9410(7)	13.3827(16)
b/Å	10.4217(7)	9.9478(12)
c/Å	11.9002(9)	33.159(4)
α/deg	88.214(5)	—
β/deg	78.056(5)	—
γ/deg	88.859(5)	—
V/Å^3	1205.49(15)	4414.4(9)
d_{calc}/g cm^{-3}	1.431	1.473
μ/cm^{-1}	1.78	1.95
F(000)	540	2032
$2\theta_{max}$/deg	58	59
Number of measured reflections	14750	39215
Number of independent reflections	6397	12118
Number of reflections with $I > 2\sigma(I)$	5303	5947
Number of parameters refined	351	631
R_1	0.0408	0.0583
wR_2	0.1072	0.1008
GOF	1.000	0.990
Residual electron density /e·Å^{-3}, ρ_{max}/ρ_{min}	0.517/−0.374	0.766/−0.305

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