Intramolecular cyclization of *S*-alkyl derivatives of aminomercaptoimidazoles and -benzimidazoles as a method for the annulation of the thiadiazine ring

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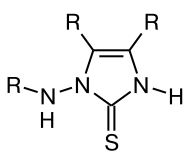
A method was developed for the annulation of the tetrahydrothiadiazine moiety to the imidazole and benzimidazole rings through intramolecular cyclization of *S*-alkyl derivatives of aminomercaptoimidazoles and -benzimidazoles. The factors controlling the stereoselectivity of the formation of the tetrahydrothiadiazine ring were revealed.

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

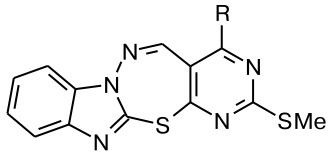
Previously, we have reported on the new stereoselective method for the annulation of the tetrahydrothiadiazine ring as applied to the synthesis of 6,7-dihydro-5*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines,[1] 3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazines,[2] and spirocyclic 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines and [1,3,4]thiadiazino[3,2-*a*]benzimidazoles.[3]

To extend the scope and show the versatility of this approach to the synthesis of thiadiazine derivatives and to study the structural features and the behavior of the reaction products, we investigated the intramolecular cyclization with the participation of *S*-methylene-substituted 1-amino-2-mercaptoimidazoles and -benzimidazoles.

In contrast to aminomercaptotriazole derivatives, the synthesis and biological activity of which were reported in several reviews,[4—6] polycyclic systems bearing the *N*-amino-2-mercaptoimidazole moiety are poorly studied, although it is known that the structures containing this group exhibit a broad range of antiviral activity.[7] For example, compounds **A** and **B** are inhibitors of human immunodeficiency virus (HIV) replication.[7,8]



A

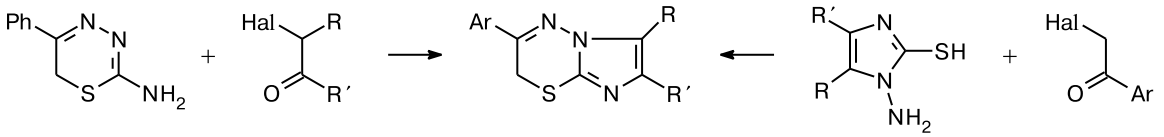


B

Scarce data on the methods for the synthesis of fused imidazothiadiazines refer to either the annulation of the imidazole ring to the thiadiazaheterocycle[9] or to the reaction of *N*-amino-2-mercaptoimidazole with α-halo ketones[9—11] (Scheme 1). In both cases, the biheterocycle is assembled through the carbon—heteroatom (nitrogen, sulfur) bond formation. The approach developed in our works is based on the diastereoselective formation of the carbon—carbon bond in the final step of the cyclization.

The reactions of 1-amino-1*H*-benzimidazole-2-thiol (**1**) and 1-amino-1*H*-imidazole-2-thiol (**2**) with *p*-nitrobenzyl bromide afforded 1-amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole (**3**) and 1-amino-2-[(4-nitrobenzyl)-thio]-1*H*-imidazole (**4**), respectively. These reaction products undergo condensation with substituted benzaldehydes

Scheme 1



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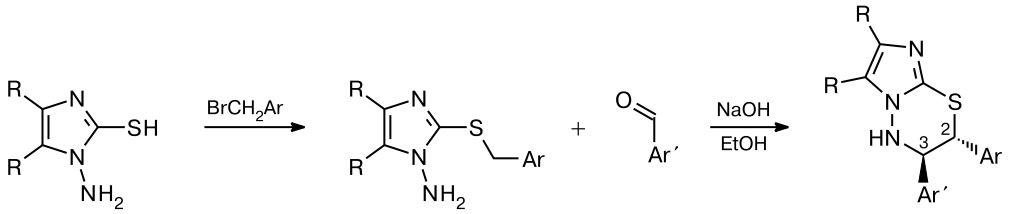
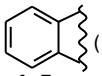
Scheme 2



1, 2 **3, 4** **5a—c, 6a,b**

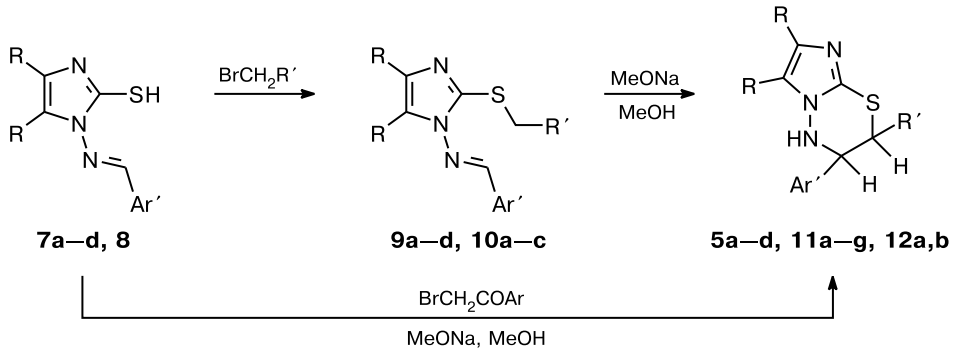
R = H (**2**, **4**, **6a**,**b**),  (**1**, **3**, **5a**,**b**);
Ar = 4-$NO_2C_6H_4$ (**3**, **4**, **5a**—**c**, **6a**,**b**);
Ar´ = 4-ClC_6H_4 (**5a**, **6a**), Ph (**5b**), 4-BrC_6H_4 (**5c**), 3-ClC_6H_4 (**6b**)

followed by the cyclization under basic catalysis conditions to form the corresponding [1,3,4]thiadiazino[3,2-*a*]-benzimidazoles **5a—c** and imidazo[2,1-*b*][1,3,4]thiadiazines **6a**,**b** (Scheme 2).

Thiadiazines **5** were also prepared by the independent synthesis through the alkylation of the corresponding *N*-benzimidazolylimines **7** with *p*-nitrobenzyl bromide (Scheme 3) giving acyclic *N*-(R-benzylidene)-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amines **9** followed by the cyclization of the latter in the presence of a strong base to yield target compounds **5**. Hence, it is evident that in both cases, the cyclization is preceded by the formation of the corresponding acyclic benzylthio derivative of imidazolylimine followed by the ionization of the *S*-methylene unit by the action of NaOH and the nucleophilic attack of the resulting carbanion on the azomethine nitrogen atom to form the C(2)—C(3) bond of the thiadiazine ring.

The ^{1}H NMR spectra of 3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazoles **5** and imidazo[2,1-*b*][1,3,4]-thiadiazines **6** show three one-proton peaks: doublets of the NH and C(2)H groups and a doublet of doublets of the C(3)H group at δ_H 7.5—7.7, 5.25, and 5.0, respectively. The intensity and multiplicity of the signals, as well as the spin-spin coupling between H(2) and H(3) (~10 Hz),

Scheme 3



7a—d, 8 **9a—d, 10a—c** **5a—d, 11a—g, 12a,b**

R = H (**8**, **12a**,**b**),  (**5a—d**, **7a—d**, **9a—d**, **10a—c**, **11a—g**)

Compound	Ar´	R´	Compound	Ar´	R´	Compound	Ar´	R´
5a	4-ClC_6H_4	4-$NO_2C_6H_4$	**8**	4-BrC_6H_4	—	**11a**	4-BrC_6H_4	C(O)C_6H_4Br-4
5b	Ph	4-$NO_2C_6H_4$	**9a**	4-ClC_6H_4	4-$NO_2C_6H_4$	**11b**	4-BrC_6H_4	C(O)$C_6H_4NO_2$-4
5c	4-BrC_6H_4	4-$NO_2C_6H_4$	**9b**	Ph	4-$NO_2C_6H_4$	**11c**	4-ClC_6H_4	C(O)C_6H_4Cl-4
5d	4-MeC_6H_4	4-$NO_2C_6H_4$	**9c**	4-BrC_6H_4	4-$NO_2C_6H_4$	**11d**	4-BrC_6H_4	C(O)C_6H_4OMe-4
7a	4-ClC_6H_4	—	**9d**	4-MeC_6H_4	4-$NO_2C_6H_4$	**11e**	4-MeC_6H_4	C(O)C_6H_4Br-4
7b	Ph	—	**10a**	4-BrC_6H_4	C(O)C_6H_4Br-4	**11f**	Ph	C(O)C_6H_4Cl-4
7c	4-BrC_6H_4	—	**10b**	4-BrC_6H_4	C(O)$C_6H_4NO_2$-4	**11g**	Ph	C(O)$C_6H_4NO_2$-4
7d	4-MeC_6H_4	—	**10c**	4-ClC_6H_4	C(O)C_6H_4Cl-4	**12a**	4-BrC_6H_4	C(O)Ph
						12b	4-BrC_6H_4	C(O)C_6H_4Br-4

indicate that the substituents at the chiral carbon atoms C(2) and C(3) of the thiadiazine ring in imidazothiadiazines **5** and **6** are in *trans* positions. Previously, we have observed[12] a similar arrangement of the substituents in triazolothiadiazines, whose structures were established by X-ray diffraction. This suggests the *trans*-diastereoselectivity of the annulation of the hydrogenated thiadiazine ring to aminomercaptoazole derivatives, which is apparently attributed to steric interactions between the bulky aryl moieties.

The treatment of *N*-benzimidazolylimines **7** with phenacyl bromides gives *S*-substituted compounds **10**, which are transformed into the corresponding thiadiazines **11** in the presence of sodium methoxide. The one-pot synthesis of compounds **11** without the isolation of acyclic precursors **10** involves the reaction of imines **7** with phenacyl bromide in the presence of 2 equivalents of sodium methoxide (see Scheme 3).

However, as opposed to the spectra of compounds **5** and **6**, which do not show even weak signals of the minor diastereomers, all signals in the ^{1}H NMR spectra of 3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazoles **11** are doubled in a ratio of 60 : 40, which can be attributed to the formation of a mixture of diastereomers.

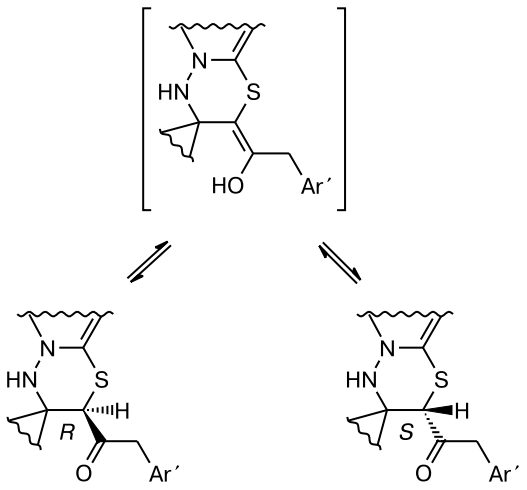
The alkylation of aldimine **8** with phenacyl halides affords imidazothiadiazines **12a**,**b** (see Scheme 3). In the ^{1}H NMR spectra of these compounds, like in the spectra of compounds **11**, all signals are doubled in a ratio of 68 : 32 (for **12a**) and 83 : 17 (for **12b**). In this case, the doubling of the signals can also be attributed to the formation of a mixture of diastereomers. The vicinal spin-spin coupling constants of the protons H(2) and H(3) of the thiadiazine ring of compounds **11** and **12** are in the range of 2.2—5.6 Hz, which indicates that these protons are either simultaneously in pseudoequatorial positions or in pseudoaxial and pseudoequatorial positions.

In our opinion, the rational explanation for this striking difference in the diastereoselectivity of the cyclization of the superficially similar benzyl and phenacyl derivatives is as follows. The H atom in position 2 of compounds **11** and **12** is adjacent to the S atom and the aroyl group. This makes possible the enolization (Scheme 4) resulting in the inversion of the configuration at the C(2) atom and, consequently, in the formation of a mixture of diastereomers.

According to the results of the X-ray diffraction study, compound **12b** crystallizes as a racemate (space group $P2_1/n$) formed by two enantiomers (*R*, *S* and *S*, *R*) (Fig. 1). The predominance of one of the two pairs of enantiomers can be attributed to the presence of the intramolecular N(4)—H(4N)...O(11) hydrogen bond (N...O, 2.801(4) Å; N—H—O, 135(1)°) stabilizing this structure.*

* The X-ray diffraction structure was described using the crystallographic atom-numbering scheme (see Fig. 1).

Scheme 4



The virtually coplanar arrangement of the atoms of the imidazothiadiazine system is distorted by the deviation of the C(3) atom from the plane of the imidazole ring by 0.73 Å; the C(1) and N(4) atoms deviate from this plane by 0.07 and 0.04 Å, respectively. The C(1)—H(1A) and

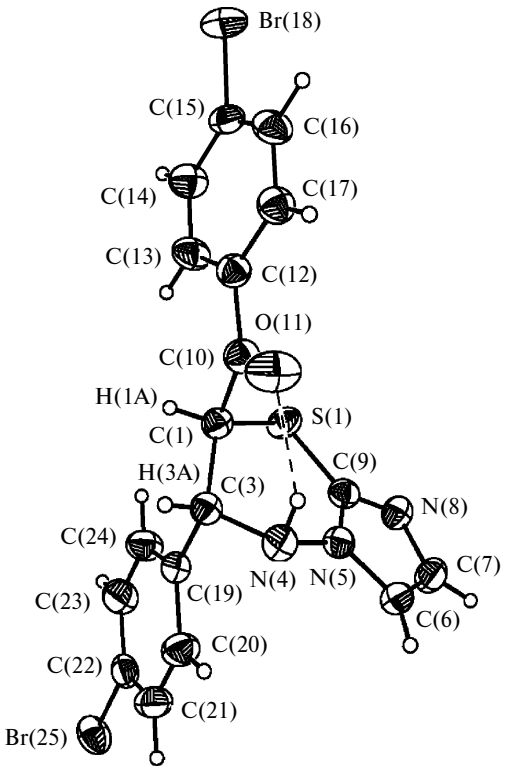


Fig. 1. Molecular structure of compound **12b** (*S*,*R*-enantiomer) with displacement ellipsoids (p = 50%). The asymmetric carbon atoms C(1) and C(3) have the *S* and *R* configurations, respectively, according to the Cahn—Ingold—Prelog notational system.

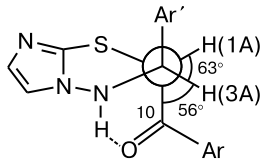


Fig. 2. Newman projection along the C(3)—C(1) bond of molecule **12b**.

C(3)—H(3A) bonds are in pseudoequatorial positions (the H(1A)—C(1)—C(3)—H(3A) torsion angle is 63°), whereas the C(1)—C(10) and C(3)—C(19) bonds are in pseudoaxial positions. Therefore, the aryl substituents are in the *trans* orientation with respect to the thiadiazine ring (the C(10)—C(1)—C(3)—C(19) and C(10)—C(1)—C(3)—H(3A) torsion angles are 173.7(2) and 57°, respectively) (Fig. 2). The dihedral angle between the planes of two *p*-BrC_6H_4 groups is 8.6(2)°.

Therefore, the general method, which we have developed earlier for the synthesis of 1,3,4-thiadiazines fused with azoles, was applied for the first time to the preparation of new [1,3,4]thiadiazino[3,2-*a*]benzimidazoles. The annulation of the tetrahydrothiadiazine ring occurs through the formation of the C—C bond in the final step of heterocyclization and is diastereoselective.

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DPX-250 instrument at 25 °C in $CDCl_3$ and DMSO-d_6 using Me_4Si as the internal standard. The electron impact mass spectra were obtained on a Finnigan MAT INCOS 50 mass spectrometer (ionization energy was 70 eV). The melting points were measured in glass capillaries using a PTP (M) instrument and are uncorrected.

1-Amino-1*H*-benzimidazole-2-thiols **1** (m.p. 201—204 °C),[13] 1-amino-1*H*-imidazole-2-thiol hydrochloride **2** (m.p. 167—168 °C),[14] 1-amino-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole **3** (m.p. 140—143 °C),[3] 1-amino-2-(4-nitrobenzylthio)-imidazole **4** (m.p. 155 °C),[2] 1-[(R-benzylidene)amino]-1*H*-benzimidazole-2-thiols **7a**, **7b**, **7c**, and **7d** (m.p. 217, 220, 210, and 203 °C, respectively),[13] and 1-[(4-bromophenyl)methylideneamino]-1*H*-imidazole-2-thiol **8** (m.p. 237 °C)[2] were synthesized according to procedures described previously. All reagents were commercial products (Sigma—Aldrich). The solvents were purified according to standard procedures.[15]

Compounds 5 (general procedure). Method *A*. A catalytic amount of NaOH (0.5 mmol) was added to a solution of *S*-benzyl ester **3** (1 mmol) and aromatic aldehyde (1 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 2 h, cooled, diluted with water (30 mL), and neutralized with dilute hydrochloric acid. The precipitate that formed was filtered off and recrystallized from MeCN.

Method *B*. *N*-(R-Benzylidene)-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amine **9a**—**d** (1 mmol) was added to a solution of MeONa (1 mmol) in methanol (3 mL). The reaction mixture was heated for 5 min, cooled, and diluted with water (20 mL). The precipitate that formed was filtered off and recrystallized from MeCN.

3-(4-Chlorophenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-[1,3,4]-thiadiazino[3,2-*a*]benzimidazole (5a). Yield 16% (*A*), 38% (*B*), m.p. 203—206 °C. Found (%): C, 59.82; H, 3.64; N, 13.41. $C_{21}H_{15}ClN_4O_2S$. Calculated (%): C, 59.64; H, 3.58; N, 13.25. ^{1}H NMR (DMSO-d_6), δ: 5.03 (dd, 1 H, H(3), J = 9.5 Hz, J = 10.5 Hz); 5.34 (d, 1 H, H(2), J = 9.5 Hz); 7.13—7.24 (m, 2 H, benzimidazole); 7.26—7.47 (m, 6 H, NH, C_6H_4Cl-4, benzimidazole); 7.48—7.59 (m, 1 H, benzimidazole); 7.74 and 8.12 (both d, 2 H each, $C_6H_4NO_2$-4, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 48.3, 63.3, 80.1, 109.7, 118.5, 122.3, 122.8, 124.6, 129.5, 130.6, 131.3, 133.7, 135.4, 136.9, 140.9, 143.6, 145.7, 148.0.

2-(4-Nitrophenyl)-3-phenyl-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (5b). Yield 31% (*A*), 25% (*B*), m.p. 212—215 °C. Found (%): C, 65.12; H, 4.24; N, 14.60. $C_{21}H_{16}N_4O_2S$. Calculated (%): C, 64.93; H, 4.15; N, 14.42. ^{1}H NMR (DMSO-d_6), δ: 4.96 (dd, 1 H, H(3), J = 9.5 Hz, J = 10.7 Hz); 5.35 (d, 1 H, H(2), J = 9.5 Hz); 7.14—7.33 (m, 6 H, NH, Ph, benzimidazole); 7.35—7.44 (m, 3 H, Ph, benzimidazole); 7.46—7.58 (m, 1 H, benzimidazole); 7.72 and 8.09 (both d, 2 H each, $C_6H_4NO_2$-4, J = 8.8 Hz).

3-(4-Bromophenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-[1,3,4]-thiadiazino[3,2-*a*]benzimidazole (5c). Yield 48% (*A*), 11.4% (*B*), m.p. 225—228 °C. Found (%): C, 53.85; H, 3.18; N, 11.87. $C_{21}H_{15}BrN_4O_2S$. Calculated (%): C, 53.97; H, 3.24; N, 11.99. ^{1}H NMR (DMSO-d_6), δ: 4.99 (dd, 1 H, H(3), J = 9.8 Hz, J = 10.7 Hz); 5.29 (d, 1 H, H(2), J = 9.8 Hz); 7.10—7.19 (m, 2 H, benzimidazole); 7.25 (d, 1 H, NH, J = 10.7 Hz); 7.3 (d, 2 H, C_6H_4Br-4, J = 8.5 Hz); 7.33—7.38 (m, 1 H, benzimidazole); 7.42—7.53 (m, 3 H, C_6H_4Br-4, benzimidazole); 7.69 and 8.08 (both d, 2 H each, $C_6H_4NO_2$-4, J = 8.8 Hz).

3-(4-Methylphenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (5d). Yield 35% (*B*), m.p. 162—165 °C. Found (%): C, 65.49; H, 4.60; N, 13.83. $C_{22}H_{18}N_4O_2S$. Calculated (%): C, 65.65; H, 4.51; N, 13.92. ^{1}H NMR (DMSO-d_6), δ: 2.21 (s, 3 H, Me); 4.92 (dd, 1 H, H(3), J = 9.8 Hz, J = 10.5 Hz); 5.33 (d, 1 H, H(2), J = 9.8 Hz); 7.07 (d, 2 H, C_6H_4Me-4, J = 8.1 Hz); 7.13—7.24 (m, 3 H, benzimidazole, NH); 7.26 (d, 2 H, C_6H_4Me-4, J = 8.1 Hz); 7.34—7.42 (m, 1 H, benzimidazole); 7.48—7.54 (m, 1 H, benzimidazole); 7.71 and 8.10 (both d, 2 H each, $C_6H_4NO_2$-4, J = 8.8 Hz). MS, m/z (I_{rel} (%)): 402 $[M]^+$ (42), 284 (48), 266 (32), 253 (74), 236 (50), 192 (30), 178 (100), 165 (48), 152 (22), 134 (26), 118 (65), 108 (60), 91 (64).

3-(4-Chlorophenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine (6a). A catalytic amount of NaOH (0.5 mmol) was added to a solution of *S*-benzyl ester **4** (0.5 g, 2 mmol) and *p*-chlorobenzaldehyde (0.3 g, 2 mmol) in ethanol (10 mL). The reaction mixture was refluxed for 1 h, cooled, diluted with water (30 mL), and neutralized with dilute hydrochloric acid. The precipitate that formed was filtered off, recrystallized from $CHCl_3$, and washed with CCl_4. Yield 48%, m.p. 133—135 °C. Found (%): C, 54.91; H, 3.56; N, 14.87. $C_{17}H_{13}ClN_4O_2S$. Calculated (%): C, 54.77; H, 3.51; N, 15.03. ^{1}H NMR (DMSO-d_6), δ: 4.86 (dd, 1 H, H(3), J = 10.2 Hz, J = 9.8 Hz); 5.17 (d, 1 H, H(2), J = 9.8 Hz); 6.89 and 7.29 (both d, 1 H each, imidazole, J = 1.4 Hz); 7.33 (m, 5 H, NH, H_{Ar}); 7.66 and 8.09 (both d, 2 H each, H_{Ar}, J = 8.8 Hz). ^{13}C NMR (DMSO-d_6), δ: 48.1, 63.3, 121.0, 124.2, 125.6, 129.1, 130.3, 131.0, 132.7, 133.3, 136.6, 145.7, 147.5. MS, m/z (I_{rel} (%)): 372 $[M]^+$ (27), 273 (73), 234 (100), 259 (25), 202 (32), 186 (62), 178 (90), 165 (30), 152 (43), 138 (34), 129 (20), 102 (34), 89 (33).

3-(3-Chlorophenyl)-2-(4-nitrophenyl)-3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine (6b) was synthesized by analogy with compound **6a** from equimolar amounts of compound **4** and *m*-chlorobenzaldehyde. Yield 42%, m.p. 119—121 °C. Found (%): C, 54.86; H, 3.57; N, 15.12. $C_{17}H_{13}ClN_4O_2S$. Calculated (%): C, 54.77; H, 3.51; N, 15.03. ^{1}H NMR ($CDCl_3$), δ: 4.42 (dd, 1 H, H(3), J = 8.8 Hz, J = 9.5 Hz); 4.85 (d, 1 H, H(2), J = 8.8 Hz); 5.21 (d, 1 H, NH, J = 9.5 Hz); 6.97 (m, 1 H, H_{Ar}); 7.00 and 7.08 (both d, 1 H each, imidazole, J = 1.26 Hz); 7.16—7.22 (m, 2 H, H_{Ar}); 7.39 (m, 3 H, H_{Ar}); 8.11 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz).

Compounds 9 (general procedure). 1-[(R-Benzylidene)-amino]-1*H*-benzimidazole-2-thiol **7a**—**d** (1 mmol) was added to a solution of NaOH (1 mmol) in methanol (3 mL). After the complete dissolution of **7a**—**d**, *p*-nitrobenzyl bromide (1 mmol) was added. The reaction mixture was stirred for 10 min and diluted with water (20 mL). The precipitate that formed was filtered off and recrystallized from ethanol.

***N*-(4-Chlorobenzylidene)-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amine (9a).** Yield 65%, m.p. 231—233 °C. Found (%): C, 59.82; H, 3.65; N, 13.43. $C_{21}H_{15}ClN_4O_2S$. Calculated (%): C, 59.64; H, 3.58; N, 13.25. ^{1}H NMR (DMSO-d_6), δ: 4.73 (s, 2 H, CH_2); 7.24—7.35 (m, 2 H, benzimidazole); 7.57—7.70 (m, 3 H, C_6H_4Cl-4, benzimidazole); 7.82 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 7.99 (d, 2 H, C_6H_4Cl-4, J = 8.9 Hz); 8.06—8.13 (m, 1 H, benzimidazole); 8.20 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 9.2 (s, 1 H, N=CH).

***N*-Benzylidene-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amine (9b).** Yield 72%, m.p. 115—118 °C. Found (%): C, 65.08; H, 4.21; N, 14.57. $C_{21}H_{16}N_4O_2S$. Calculated (%): C, 64.93; H, 4.15; N, 14.42. ^{1}H NMR (DMSO-d_6), δ: 4.73 (s, 2 H, CH_2); 7.22—7.35 (m, 2 H, benzimidazole); 7.48—7.59 (m, 3 H, Ph); 7.61—7.70 (m, 1 H, benzimidazole); 7.83 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 7.91—8.02 (m, 2 H, Ph); 8.03—8.11 (m, 1 H, benzimidazole); 8.22 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 9.19 (s, 1 H, N=CH).

***N*-(4-Bromobenzylidene)-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amine (9c).** Yield 69%, m.p. 180—185 °C. Found (%): C, 53.85; H, 3.18; N, 11.87. $C_{21}H_{15}BrN_4O_2S$. Calculated (%): C, 53.97; H, 3.24; N, 11.99. ^{1}H NMR (DMSO-d_6), δ: 4.71 (s, 2 H, CH_2); 7.23—7.38 (m, 2 H, benzimidazole); 7.50—7.85 (m, 8 H, benzimidazole, $C_6H_4NO_2$-4, C_6H_4Br-4); 8.20 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 8.87 (s, 1 H, N=CH).

***N*-(4-Methylbenzylidene)-2-[(4-nitrobenzyl)thio]-1*H*-benzimidazole-1-amine (9d).** Yield 62.3%, m.p. 148—152 °C. Found (%): C, 65.54; H, 4.42; N, 13.80. $C_{22}H_{18}N_4O_2S$. Calculated (%): C, 65.65; H, 4.51; N, 13.92. ^{1}H NMR (DMSO-d_6), δ: 2.34 (s, 3 H, Me); 4.68 (s, 2 H, CH_2); 7.19—7.27 (m, 2 H, benzimidazole); 7.33 (d, 2 H, C_6H_4Me-4, J = 8.1 Hz); 7.56—7.64 (m, 1 H, benzimidazole); 7.79 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8 Hz); 7.83 (d, 2 H, C_6H_4Me-4, J = 8.1 Hz); 7.96—8.06 (m, 1 H, benzimidazole); 8.16 (d, 2 H, $C_6H_4NO_2$-4, J = 8.8); 9.11 (s, 1 H, N=CH). MS, m/z (I_{rel} (%)): 402 $[M]^+$ (30), 284 (32), 266 (34), 253 (50), 233 (28), 207 (45), 192 (12), 180 (20), 150 (56), 132 (32), 122 (24), 103 (38), 90 (70), 78 (100).

Compounds 10 were synthesized by analogy with compounds **9** from equimolar amounts of compounds **7** and the corresponding phenacyl bromides and recrystallized from ethanol.

2-({1-[(4-Bromobenzylidene)amino]-1*H*-benzimidazol-2-yl}thio)-1-(4-bromophenyl)ethanone (10a). Yield 14.4%, m.p. 190—193 °C. Found (%): C, 49.84; H, 2.80; N, 7.83. $C_{22}H_{15}Br_2N_3OS$. Calculated (%): C, 49.93; H, 2.86; N, 7.94. ^{1}H NMR (DMSO-d_6), δ: 5.01 (s, 2 H, CH_2); 7.16—7.29 (m, 2 H, benzimidazole); 7.43—7.53 (m, 1 H, benzimidazole); 7.71—7.83 (m, 4 H, C_6H_4Br-4); 7.92 and 8.00 (both d, 2 H each, C_6H_4Br-4, J = 8.5 Hz); 8.06—8.13 (m, 1 H, benzimidazole); 9.18 (s, 1 H, N=CH). MS, m/z (I_{rel} (%)): 529 $[M]^+$ (2), 380 (2), 346 (9), 331 (3), 299 (2), 198 (10), 183 (65), 174 (12), 163 (17), 150 (100), 118 (15), 89 (50), 76 (48).

2-({1-[(4-Bromobenzylidene)amino]-1*H*-benzimidazol-2-yl}thio)-1-(4-nitrophenyl)ethanone (10b). Yield 69%, m.p. 189—193 °C. Found (%): C, 53.22; H, 3.00; N, 11.19. $C_{22}H_{15}BrN_4O_3S$. Calculated (%): C, 53.34; H, 3.05; N, 11.31. ^{1}H NMR (DMSO-d_6), δ: 5.12 (s, 2 H, CH_2); 7.20—7.36 (m, 2 H, benzimidazole); 7.45—7.58 (m, 1 H, benzimidazole); 7.80 and 7.98 (both d, 2 H each, C_6H_4Br-4, J = 8.4 Hz); 8.10—8.18 (m, 1 H, benzimidazole); 8.34 and 8.42 (both d, 2 H each, $C_6H_4NO_2$-4, J = 9.1 Hz); 9.23 (s, 1 H, N=CH).

2-({1-[(4-Chlorobenzylidene)amino]-1*H*-benzimidazole-2-yl}thio)-1-(4-chlorophenyl)ethanone (10c). Yield 20%, m.p. 195—198 °C. Found (%): C, 60.20; H, 3.50; N, 9.73. $C_{22}H_{15}Cl_2N_3OS$. Calculated (%): C, 60.01; H, 3.43; N, 9.54. ^{1}H NMR (DMSO-d_6), δ: 5.05 (s, 2 H, CH_2); 7.19—7.34 (m, 2 H, benzimidazole); 7.45—7.56 (m, 1 H, benzimidazole); 7.62—7.72 (m, 4 H, C_6H_4Cl-4); 8.04 (d, 2 H, C_6H_4Cl-4, J = 8.7 Hz); 8.07—8.15 (m, 3 H, C_6H_4Cl-4, benzimidazole); 9.23 (s, 1 H, N=CH).

Compounds 11 (general procedure). Method *A*. 2-({1-[(4-R-Benzylidene)amino]-1*H*-benzimidazol-2-yl}thio)-1-(4-R′-phenyl)ethanone **10a**—**c** (1 mmol) was added to a solution of MeONa (1 mmol) in methanol (3 mL). The reaction mixture was heated for 5 min, cooled, and diluted with water (20 mL). The precipitate that formed was filtered off and recrystallized from acetonitrile.

Method *B*. 1-[(R-Benzylidene)amino]-1*H*-benzimidazole-2-thiols **7a**—**d** (1 mmol) was added to a solution of MeONa (1 mmol) in methanol (3 mL). After their complete dissolution, the corresponding phenacyl bromide (1 mmol) was added. The reaction mixture was stirred for 10 min, and a solution of MeOH (1 mmol) in methanol (3 mL) was added. The reaction mixture was heated for 5 min, cooled, diluted with water (20 mL), and neutralized with dilute hydrochloric acid. The precipitate that formed was filtered off and recrystallized from acetonitrile.

2-(4-Bromobenzoyl)-3-(4-bromophenyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11a). Yield 40% (*A*), 21% (*B*), m.p. 176—178 °C. Found (%): C, 50.12; H, 2.93; N, 8.11. $C_{22}H_{15}Br_2N_3OS$. Calculated (%): C, 49.93; H, 2.86; N, 7.94. ^{1}H NMR (DMSO-d_6), δ: 5.20 (dd, 1 H, H(3), J = 4.7 Hz, J = 5.8 Hz); 5.86 (d, 1 H, H(2), J = 4.7 Hz); 7.12—7.25 (m, 3 H, benzimidazole); 7.45 (d, 2 H, C_6H_4Br-4, J = 6.9 Hz); 7.48—7.56 (m, 4 H, NH, C_6H_4Br-4, benzimidazole); 7.83 and 8.03 (both d, 2 H each, C_6H_4Br-4, J = 8.7 Hz). MS, m/z (I_{rel} (%)): 529 $[M]^+$ (2), 380 (3), 366 (3), 346 (21), 287 (11), 206 (10), 183 (100), 163 (37), 156 (58), 150 (78), 134 (23), 102 (53), 90 (38), 76 (80).

3-(4-Bromophenyl)-2-(4-nitrobenzoyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11b). Yield 32% (*A*), 13.6% (*B*), m.p. 124—128 °C. Found (%): C, 53.51; H, 3.10; N, 11.49. $C_{22}H_{15}BrN_4O_3S$. Calculated (%): C, 53.34; H, 3.05; N, 11.31. ^{1}H NMR ($CDCl_3$), δ: 5.27 (dd, 1 H, H(3), J = 4.2 Hz, J = 3.2 Hz); 5.93 (d, 1 H, H(2), J = 4.2 Hz); 7.10—7.34 (m, 3 H, NH, benzimidazole); 7.40—7.57 (m, 6 H, C_6H_4Br-4, benzimidazole); 8.32 and 8.39 (both d, 2 H each, $C_6H_4NO_2$-4, J = 8.8 Hz).

2-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11c). Yield 13% (*A*), 20% (*B*), m.p. 170—172 °C. Found (%): C, 60.17; H, 3.50; N, 9.70. $C_{22}H_{15}Cl_2N_3OS$. Calculated (%): C, 60.01; H, 3.43; N, 9.54. ^{1}H NMR (DMSO-d_6), δ: 5.21 (dd, 1 H, H(3), J = 4.6 Hz, J = 5.4 Hz); 5.87 (d, 1 H, H(2), J = 4.6 Hz); 7.09—7.28 (m, 3 H, benzimidazole); 7.38 (d, 2 H, C_6H_4Cl-4, J = 8.7 Hz); 7.43—7.53 (m, 2 H, NH, benzimidazole); 7.58 and 7.69 (both d, 2 H each, C_6H_4Cl-4, J = 8.5 Hz); 8.11 (d, 2 H, C_6H_4Cl-4, J = 8.7 Hz).

3-(4-Bromophenyl)-2-(4-methoxybenzoyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11d). Yield 27% (*B*), m.p. 101—103 °C. Found (%): C, 57.38; H, 3.70; N, 8.64. $C_{23}H_{18}BrN_3O_2S$. Calculated (%): C, 57.51; H, 3.78; N, 8.75. ^{1}H NMR (DMSO-d_6), δ: 3.82 (s, 3 H, OMe); 5.05 (m, 1 H, H(3)); 5.81 (d, 1 H, H(2), J = 5.6 Hz); 7.00 (d, 1 H, benzimidazole, J = 8.7 Hz); 7.07 (d, 1 H, NH, J = 9.1 Hz); 7.13—7.22 (m, 3 H, C_6H_4OMe-4, benzimidazole); 7.26—7.35 (m, 1 H, benzimidazole); 7.38—7.55 (m, 5 H, C_6H_4OMe-4, C_6H_4Br-4, benzimidazole); 8.02 (d, 2 H, C_6H_4Br-4, J = 8.8 Hz).

2-(4-Bromobenzoyl)-3-(4-methylphenyl)-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11e). Yield 15% (*B*), m.p. 190—192 °C. Found (%): C, 59.35; H, 3.86; N, 8.91. $C_{23}H_{18}BrN_3OS$. Calculated (%): C, 59.49; H, 3.91; N, 9.05. ^{1}H NMR (DMSO-d_6), δ: 2.19 (s, 3 H, Me); 5.03 (dd, 1 H, H(3), J = 5.3 Hz, J = 6.0 Hz); 5.86 (d, 1 H, H(2), J = 5.3 Hz); 7.02—7.19 (m, 5 H, C_6H_4Me-4, benzimidazole); 7.35—7.51 (m, 4 H, NH, benzimidazole); 7.77 and 7.97 (both d, 2 H each, C_6H_4Br-4, J = 8.4 Hz).

2-(4-Chlorobenzoyl)-3-phenyl-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11f). Yield 25% (*B*), m.p. 183—187 °C. Found (%): C, 65.27; H, 4.05; N, 10.44. $C_{22}H_{16}ClN_3OS$. Calculated (%): C, 65.10; H, 3.97; N, 10.35. ^{1}H NMR (DMSO-d_6), δ: 5.08 (dd, 1 H, H(3), J = 5.3 Hz, J = 6.0 Hz); 5.85 (d, 1 H, H(2), J = 5.3 Hz); 7.11—7.33 (m, 6 H, Ph, NH, benzimidazole); 7.38—7.56 (m, 4 H, Ph, benzimidazole); 7.62 and 8.05 (both d, 2 H each, C_6H_4Cl-4, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 45.2, 58.1, 109.9, 118.5, 122.4, 122.9, 128.1, 128.8, 129.4, 130.1, 131.7, 134.3, 135.3, 138.3, 140.1, 140.6, 141.9, 195.3.

2-(4-Nitrobenzoyl)-3-phenyl-3,4-dihydro-2*H*-[1,3,4]thiadiazino[3,2-*a*]benzimidazole (11g). Yield 16.8% (*B*), m.p. 185—190 °C. Found (%): C, 63.63; H, 3.96; N, 13.64. $C_{22}H_{16}N_4O_3S$. Calculated (%): C, 63.45; H, 3.87; N, 13.45. ^{1}H NMR (DMSO-d_6), δ: 5.23 (dd, 1 H, H(3), J = 4.6 Hz, J = 5.8 Hz); 5.98 (d, 1 H, H(2), J = 4.6 Hz); 7.11—7.42 (m, 6 H, Ph, NH, benzimidazole); 7.44—7.63 (m, 4 H, Ph, benzimidazole); 8.33 and 8.41 (both d, 2 H each, $C_6H_4NO_2$-4, J = 9.1 Hz). ^{13}C NMR (DMSO-d_6), δ: 45.9, 57.5, 109.9, 118.5, 122.4, 122.9, 127.9, 128.0, 128.8, 129.4, 130.8, 131.2, 135.3, 138.2, 140.5, 140.6, 141.5, 195.4.

2-Benzoyl-3-(4-bromophenyl)-3,4-dihydro-2*H*-imidazo[2,1-*b*]-[1,3,4]thiadiazine (12a). Methylideneamino-1*H*-imidazole-2-thiol **8** (0.28 g, 1 mmol) was added to a solution of NaOH (0.04 g, 1 mmol) in methanol (3 mL). After the complete dissolution, phenacyl bromide (0.2 g, 1 mmol) was added. The reaction mixture was stirred for 5 min and diluted with water (20 mL). The precipitate that formed was filtered off and recrystallized from acetonitrile. Yield 57%, m.p. 190 °C. Found (%): C, 54.14; H, 3.61; N, 10.65. $C_{18}H_{14}BrN_3OS$. Calculated (%): C, 54.01; H, 3.53; N, 10.50. ^{1}H NMR (acetone-d_6), δ: 5.01—5.05 (m, 1 H, H(3)); 5.74 (d, 1 H, H(2), J = 2.6 Hz); 6.91 (d, 1 H, H(7), J = 1.3 Hz); 7.03 (d, 1 H, NH, J = 11.4 Hz); 7.24 (d, 1 H, H(6), J = 1.3 Hz); 7.48 (d, 2 H, H_{Ar}, J = 8.8 Hz); 7.53—7.56 (m, 5 H, Ph); 7.96 (d, 2 H, H_{Ar}, J = 8.8 Hz). MS, m/z (I_{rel} (%)): 401 $[M]^+$ (3), 399 $[M]^+$ (3), 296 (18), 294 (7), 182 (3), 157 (4), 134 (10), 133 (22), 105 (77), 77 (100), 51 (42).

2-(4-Bromobenzoyl)-3-(4-bromophenyl)-3,4-dihydro-2*H*-imidazo[2,1-*b*][1,3,4]thiadiazine (12b) was synthesized by analogy with compound **12a** from equimolar amounts of compound **8** and *p*-bromophenacyl bromide. The compound was recrystallized from acetonitrile. Yield 60%, m.p. 192 °C. Found (%): C, 45.19; H, 2.76; N, 8.91. $C_{18}H_{13}Br_2N_3OS$. Calculated (%): C, 45.12; H, 2.73; N, 8.77. ^{1}H NMR (DMSO-d_6), δ: 5.03 (dd, 1 H, H(3), J = 2.8 Hz, J = 10.3 Hz); 5.83 (d, 1 H, H(2), J = 2.8 Hz); 6.91 (d, 1 H, H(7), J = 1.2 Hz); 7.23 (d, 2 H, H_{Ar}, J = 8.5 Hz); 7.27 (d, 1 H, H(6), J = 1.2 Hz); 7.29 (d, 1 H, NH, J = 10.3 Hz); 7.45 (d, 2 H, H_{Ar}, J = 8.5 Hz); 7.72 and 7.81 (both d, 2 H each, H_{Ar}, J = 8.7 Hz). ^{13}C NMR (DMSO-d_6), δ: 45.3, 58.2, 121.6, 122.0, 126.3, 129.2, 130.6, 131.2, 131.6, 132.2, 132.9, 134.4, 138.1, 195.1. MS, m/z (I_{rel} (%)): 296 (21), 294 (21), 183 (87), 178 (11), 155 (80), 134 (16), 113 (64), 102 (70), 89 (46), 76 (100), 50 (66).

X-ray diffraction study of compound 12b. Crystals are monoclinic, at 293 K a = 8.981(4) Å, b = 10.934(5) Å, c = 17.954(9) Å, β = 92.190(12)°, V = 1761.9(14) Å^3, d_{calc} = 1.806 g cm^{-1}, space group $P2_1/n$, Z = 4. The intensities of 10344 reflections were measured on a Smart 1000 CCD automated diffractometer at 293 K (Mo-$K\alpha$ radiation, graphite monochromator, ω-scanning technique, $2\theta_{max}$ = 55°), and 4018 independent reflections (R_{int} = 0.0332) were used in subsequent calculations. The structure was solved by direct methods and refined by the full-matrix least-squares method with anisotropic displacement parameters based on F^2_{hkl}. The hydrogen atom of the NH group was located in difference electron density maps. The H(C) atoms were positioned geometrically. All hydrogen atoms were refined isotropically using a riding model. The final R factors were wR_2 = 0.0976, GOF = 1.001 based on all independent reflections (R_1 = 0.0358, calculated for 2729 observed reflections with $I > 2\sigma(I)$). All calculations were carried out with the use of the SHELXTL PLUS program package.[16]

The complete crystallographic data were deposited with the Cambridge Crystallographic Data Centre (CCDC 822147).

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