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SOME CHEMICAL PROPERTIES OF 2,3-DIHYDRO-4H-[1,3]THIAZINO[3,2-*a*]BENZ-IMIDAZOL-4-ONE AND 2-ARYL-2,3-DIHYDRO-4H-[1,3]THIAZINO[3,2-*a*]BENZIMIDAZOL-4-ONES

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We have studied the reaction of 2,3-dihydro-4H-[1,3]thiazino[3,2-a]benzimidazol-4-one and 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-a]benzimidazol-4-ones with amines, alkylating reagents, and hydrogen peroxide. We have shown that the presence of an aryl substituent at the 2 position of [1,3-thiazino[3,2-a]benzimidazol-4-ones has a substantial effect on the direction of the reactions.

Keywords: 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones, 2,3-dihydro-4H-[1,3]-thiazino[3,2-*a*]benzimidazol-4-one, alkylation, amination, oxidation.

2,3-Dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-one was obtained for the first time 30 years ago [1], but there is no data in the literature about its chemical properties and transformations. We earlier developed a general approach to synthesis of 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones, based on cyclization of benzimidazole-2-thione with 3-arylacryloyl chlorides [2, 3]. We thought it would be interesting to study and compare the chemical properties of 2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-one and 2-aryl-2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-ones. We should note that these compounds are polyfunctional and contain several reaction centers, which is why their reactivity is complex and unpredictable.

We have studied the reaction of 2,3-dihydro-4H-[1,3]thiazino[3,2-*a*]benzimidazol-4-one (**1**) with alkylating reagents, hydrogen peroxide, and amines.

We have found that alkylation of [1,3]thiazino[3,2-*a*]benzimidazol-4-one **1** with benzyl bromide and 2-bromoacetophenone at 130°C, followed by treatment of the reaction mass with an aqueous $NaHCO_3$ solution, lead to formation of 3-(1-alkyl-1H-benz[*d*]imidazol-2-ylsulfanyl)propanoic acids **2a,b**.

Hydrogen peroxide in acetic acid oxidizes compound **1** to form benzimidazol-2-one **3** and 2-carboxyethane-1-sulfonic acid **4**. The reaction of ketone **1** with amines (ammonia, hydrazine, and benzylamine) with moderate heating occurs with cleavage of the N–CO bond and formation of the amides **5** (Scheme 1).

However, at higher temperature (boiling thiazinobenzimidazolone **1** (or N-benzylamide **5c**) in benzylamine (184°C) and also boiling N-benzylamide **5c** in 1,3-dichlorobenzene (172°C)), 1,3-di(2-benzylcarbamoylethyl)-2,3-dihydrobenz[*d*]imidazole-2-thione (**6**) and unsubstituted 2,3-dihydrobenzimidazole-2-thione (**7**) are formed. In the ^{1}H NMR spectrum of compound **6**, there is no signal from an N-imidazole proton, and instead of a triplet of protons from the S$\underline{CH_2}CH_2CO$ group (at 3.50 ppm in the starting compound

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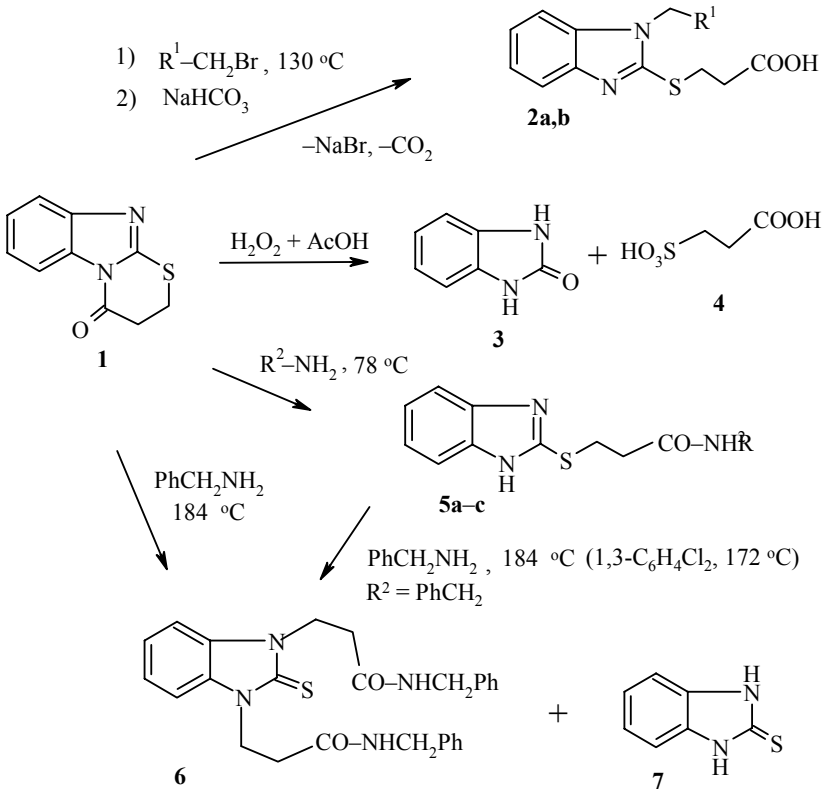
Scheme 1



2 a R^1 = Ph, **b** R^1 = PhCO; **5 a** R^2 = H, **b** $R^2 = NH_2$, **c** R^2 = $PhCH_2$

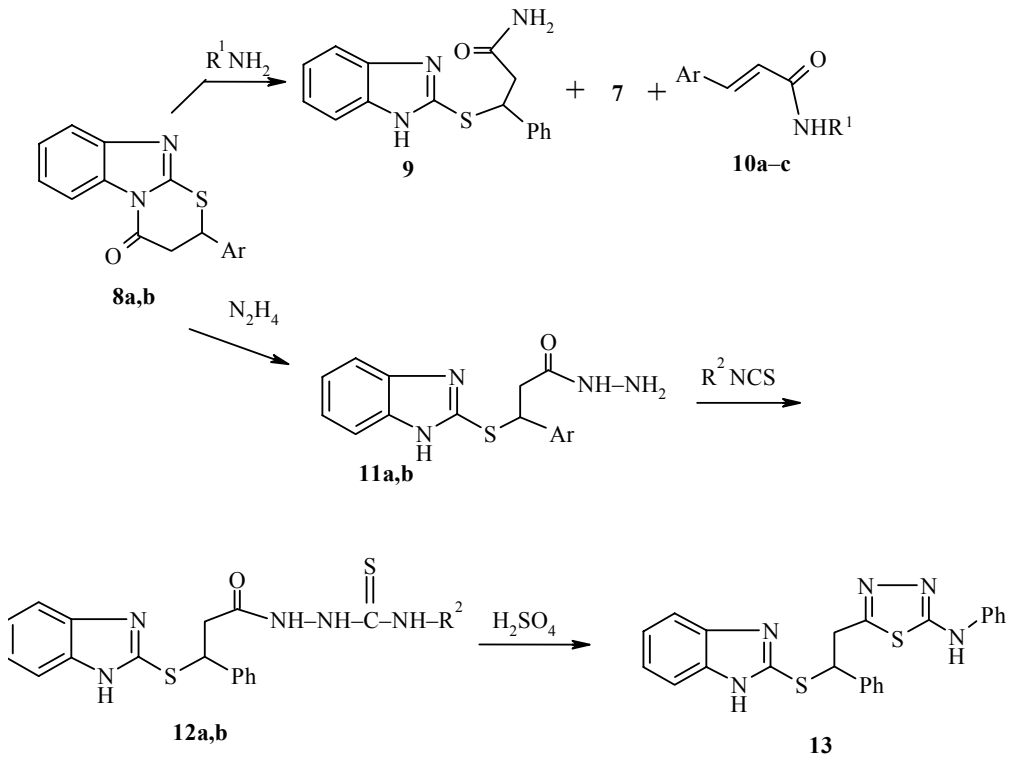
5c), we see a triplet from the $N\underline{CH_2}CH_2CO$ group at 4.52 ppm. Apparently thermodynamic factors are the driving force for this reaction, since the C–N bond is stronger than the C–S bond (for comparison: the heats of formation for Alk–SH and Ph–SH bonds are 69 and 86 kcal/mol, while for $AlkNH_2$ and $PhNH_2$ the heats of formation are respectively 87 and 104 kcal/mol [4]), and the symmetric structure of molecule **6** (with substituents on the two nitrogen atoms) is energetically more favorable than the nonsymmetric structure (with a substituent on one nitrogen atom). This reaction probably occurs through decomposition of **5c** to form benzimidazole-2-thione **7** and N-benzylacrylamide, which then alkylates the nitrogen atoms of thione **7** to form compound **6**.

The direction of the reactions of 2-aryl[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **8a,b** with amines of medium and strong basicity, in contrast to analogous reactions of thiazinobenzimidazolone **1**, depends to a significant extent on the reaction temperature and the basicity of the amine (Scheme 2).

The major product of ammonolysis (at 30°C) of compound **8a** is 3-(1H-benz[*d*]imidazol-2-ylsulfanyl)-3-phenylpropanamide (**9**) (70% yield), and only small amounts of benzimidazole-2-thione (**7**) (16%) and cinnamoylamide **10a** (19%) are isolated. However, the reaction of benzimidazolones **8a,b** with benzylamine in boiling ethanol is accompanied by degradation of the 1,3-thiazine ring to form only benzimidazole-2-thione (**7**) (70-81%) and cinnamoyl-N-benzylamides **10b,c** (76-83%). Hydrazinolysis of heterocycles **8a,b**, like ammonolysis, leads only to the corresponding hydrazides **11a,b** (81-85% yields), which react smoothly with isothiocyanates, where they are converted to the thiosemicarbazides **12a,b**. The phenylthiosemicarbazide **12a** undergoes cyclization in sulfuric acid to form the corresponding phenylamino-1,3,4-thiadiazole **13**.

In the reaction of [1,3]thiazino[3,2-*a*]benzimidazol-4-one **8a** with alkylating reagents, the direction of the reaction depends on the chemical nature of the latter (Scheme 3).

Scheme 2



8a, **10a**, **b**, **11a** Ar = Ph, **8b**, **10c**, **11b** Ar = 4-MeOC$_6$H$_4$;
10 a R^1 = H, **b**, **c** R^1 = Bn; **12 a** R^2 = Ph, **b** R^2 = Me

Scheme 3

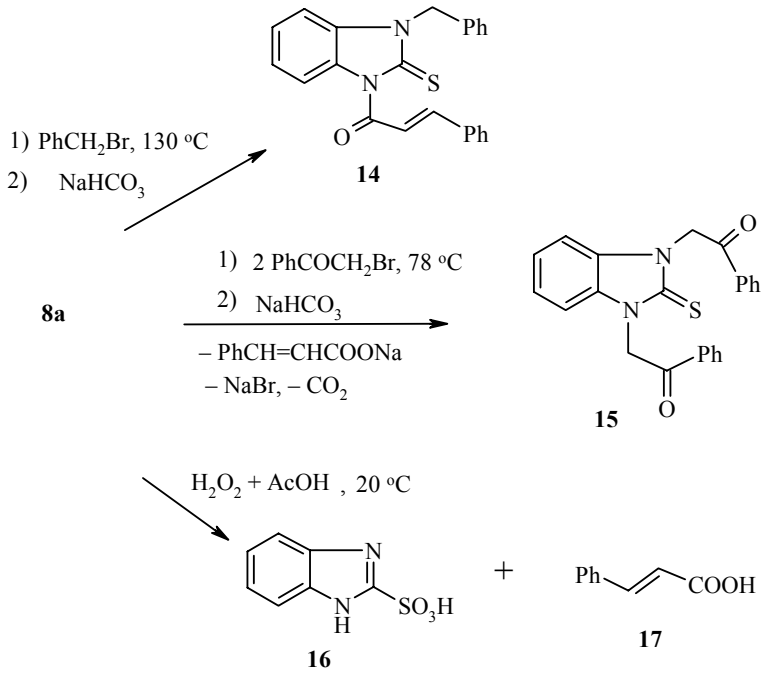


TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
2a	$C_{17}H_{16}N_2O_2S$	65.68 / 65.36	5.34 / 5.16	8.70 / 8.97	130-133	78
2b	$C_{18}H_{16}N_2O_3S$	63.63 / 63.51	4.98 / 4.74	7.85 / 8.23	235-240	73
3	$C_7H_6N_2O$	62.42 / 62.68	4.23 / 4.51	20.22 / 20.88	293-298 (312 [5])	65
4	$C_3H_6O_5S$	23.21 / 23.38	3.69 / 3.92	—	63-65 (69 [6])	69
5a	$C_{10}H_{11}N_3OS$	54.40 / 54.28	5.19 / 5.01	18.80 / 18.99	126-129	77
5b	$C_{10}H_{12}N_4OS$	50.61 / 50.83	5.23 / 5.12	23.50 / 23.71	168-170	86
5c	$C_{17}H_{17}N_3OS$	65.32 / 65.57	5.79 / 5.50	13.32 / 13.49	117-120	81
6	$C_{27}H_{28}N_4O_2S$	68.31 / 68.62	5.69 / 5.97	11.60 / 11.85	212-215	58
7	$C_7H_6N_2S$	55.69 / 55.98	4.27 / 4.03	18.36 / 18.65	290-293 (298 [7])	30
9	$C_{16}H_{15}N_3OS$	64.74 / 64.62	5.01 / 5.08	13.84 / 14.13	107-110	70
10a	C_9H_9NO	73.70 / 73.45	6.09 / 6.16	9.28 / 9.52	141-144 (147 [8])	19
10b	$C_{16}H_{15}NO$	80.71 / 80.98	6.23 / 6.37	5.71 / 5.90	107-110 (104 [9])	83
10c	$C_{17}H_{17}NO_2$	76.71 / 76.38	6.29 / 6.41	5.39 / 5.24	143-145	76
11a	$C_{16}H_{16}N_4OS$	61.26 / 61.52	5.37 / 5.16	17.69 / 17.93	139-142	86
11b	$C_{17}H_{18}N_4O_2S$	59.46 / 59.63	5.06 / 5.30	16.18 / 16.36	151-153	81
12a	$C_{23}H_{21}N_5OS_2$	61.53 / 61.72	4.89 / 4.73	15.90 / 15.65	187-190	78
12b	$C_{18}H_{19}N_5OS_2$	56.14 / 56.08	4.74 / 4.97	18.45 / 18.17	208-210	86
13	$C_{23}H_{19}N_5S_2$	64.23 / 64.31	4.66 / 4.46	16.59 / 16.30	175-177	56
14	$C_{23}H_{18}N_2OS$	74.72 / 74.57	4.65 / 4.90	7.71 / 7.56	155-160	69
15	$C_{23}H_{18}N_2O_2S$	71.13 / 71.48	4.35 / 4.69	7.41 / 7.25	205-207	67
16	$C_7H_6N_2O_3S$	42.63 / 42.42	2.87 / 3.05	13.74 / 14.13	325-330 (365 [10])	71
17	$C_9H_8O_2$	72.69 / 72.96	5.21 / 5.44	—	130-132 (134 [11])	74

* Compounds **5a-c, 9, 10a-c, 11a,b, 14, 17** were recrystallized from ethanol, **2a** and **13** were recrystallized from nitromethane, **2b** and **15** were recrystallized from benzonitrile, **3** and **7** were recrystallized from a 1:1 alcohol–water mixture, and **4** and **16** were recrystallized from water.

Thus when thiazinobenzimidazolone **8a** was melted with a slight excess of benzyl bromide at 130°C and then the reaction mass was treated with an aqueous $NHCO_3$ solution, we isolated the monoalkylation product of 1-benzyl-3-cinnamoylbenzimidazole thione **14**. At the same time, when compound **8a** was boiled with 2-bromoacetophenone in ethanol and then the reaction product was treated with an aqueous $NaHCO_3$ solution,

TABLE 2. ^{1}H NMR Spectra of Synthesized Compounds

Compound	Chemical shift, δ, ppm (spin-spin coupling constant *J*, Hz)
2a	2.80 (2H, t, *J* = 6.3, H-2); 3.52 (2H, t, *J* = 6.3, H-3); 5.37 (2H, s, NCH$_2$C$_6$H$_5$); 7.18-7.32 (7H, m, C$_6$H$_5$ + H-5,6 benzimidazole); 7.46 (1H, m, H-7 benzimidazole); 7.59 (1H, m, H-4 benzimidazole); 12.47 (1H, br. s, COOH)
2b	2.35 (2H, t, *J* = 6.1, H-2); 3.50 (2H, t, *J* = 6.1, H-3); 5.87 (2H, s, NCH$_2$CO); 7.16 (2H, m, H-5,6 benzimidazole); 7.43 (1H, m, H-7 benzimidazole); 7.62-7.75 (4H, m, H arom. + H-4 benzimidazole); 8.15 (2H, d, *J* = 8.6, H arom.); 12.12 (1H, br. s, COOH)
5a	2.86 (2H, t, *J* = 6.4, CH$_2$–CO); 3.45 (2H, t, *J* = 6.4, S–CH$_2$); 6.98 (1H, CONH); 7.12 (2H, m, H-5,6 benzimidazole); 7.38 (1H, s, CONH); 7.53 (2H, m, H-4,7 benzimidazole); 12.58 (1H, s, NH benzimidazole)
5b	2.58 (2H, t, *J* = 6.3, CH$_2$CO); 3.48 (2H, t, *J* = 6.3, S–CH$_2$); 4.25 (2H, br. s, NH$_2$); 7.13 (2H, m, H-5,6 benzimidazole); 7.43 (2H, m, H-4,7 benzimidazole); 9.07 (1H, s, CONH); 12.52 (1H, s, NH benzimidazole)
5c	2.70 (2H, t, *J* = 6.6, CH$_2$CO); 3.50 (2H, t, *J* = 6.6, S–CH$_2$); 4.29 (2H, d, *J* = 6.9, CONHCH$_2$,); 7.12-7.45 (9H, m, C$_6$H$_5$ + H benzimidazole); 8.48 (1H, t, *J* = 6.9, CONH)
6	2.66 (4H, t, *J* = 6.7, CH$_2$CO); 4.23 (4H, d, *J* = 6.8, 2CONHCH$_2$); 4.52 (4H, t, *J* = 6.7, CH$_2$–N); 7.12-7.25 (12H, m, 2C$_6$H$_5$ + H-5,6 benzimidazole); 7.49 (2H, m, H-4,7 benzimidazole); 8.48 (2H, t, *J* = 6.8, 2CONH)
9	2.95 (1H, m, H-2); 3.23 (1H, m, H-2); 5.35 (1H, m, H-3); 6.85 (1H, s, NH); 7.13-7.53 (10H, m, C$_6$H$_5$ +NH + H benzimidazole); 12.57 (1H, s, NH benzimidazole)
10c	3.69 (3H, s CH$_3$O); 4.41 (2H, d, *J* = 6.8, NHCH$_2$); 6.54 (1H, d, *J* = 13.2, Ar–CH=); 6.99 (2H, d, *J* = 8.6, *p*-C$_6$H$_4$); 7.32 (5H, m, C$_6$H$_5$); 7.41 (1H, d, *J* = 13.2, =CH–CO); 7.54 (2H, d, *J* = 8.6, *p*-C$_6$H$_4$); 8.55 (1H, t, *J* = 6.8, CONH)
11a	2.92 (2H, m, H-2); 4.12 (2H, br. s, NH$_2$); 5.40 (1H, m, H-3); 7.14-7.52 (9H, m, C$_6$H$_5$ + H benzimidazole); 9.08 (1H, s, CONH); 12.03 (1H, br. s, NH benzimidazole)
11b	2.90 (2H, m, H-2); 3.74 (3H, s CH$_3$O); 4.15 (2H, br. s, NH$_2$); 5.35 (1H, m, H-3); 6.87 (2H, d, *J* = 8.9, *p*-C$_6$H$_4$); 7.14 (2H, m, H-5,6 benzimidazole); 7.36 (2H, d, *J* = 8.9, *p*-C$_6$H$_4$); 7.46 (2H, m, H-4,7 benzimidazole); 9.06 (1H, s, CONH); 11.72 (1H, br. s, NH benzimidazole)
12a	3.14 (2H, m, H-2); 5.38 (1H, m, H-3); 7.15-7.58 (14H, m, 2C$_6$H$_5$ + 4H benzimidazole); 9.38 (1H, br. s, CS–NH–Ar); 9.63 (1H, s CONH–NH); 10.19 (1H, br. s, CONH); 12.64 (1H, s, NH benzimidazole)
12b	2.77 (3H, d, *J* = 3.1, CH$_3$); 3.09 (2H, m, CH$_2$); 5.37 (1H, m, SCH); 7.15 (2H, m, H-5,6 benzimidazole); 7.22-7.48 (6H, m, C$_6$H$_5$ + CS–NH); 7.51 (2H, m, H-4,7 benzimidazole); 9.24 (1H, s, CO–NH–NH); 9.86 (1H, s, CONH); 12.65 (1H, s, NH benzimidazole)
13	3.87 (2H, m, CH$_2$); 5.51 (1H, m, SCH); 7.14-7.69 (15H, m, 2C$_6$H$_5$ + NH + 4H benzimidazole); 12.53 (1H, s, NH benzimidazole)
14	5.66 (2H, s NCH$_2$C$_6$H$_5$); 7.35-7.51 (11H, m, H arom + H benzimidazole); 7.80 (2H, m, H arom.); 7.88 (1H, d, *J* = 13.4, C$_6$H$_5$CH=); 7.96 (1H, m, H-7 benzimidazole); 8.13 (1H, d, *J* = 13.4, CH=CO)
15	6.03 (4H, s NCH$_2$CO); 7.26 (2H, m, H-5,6 benzimidazole); 7.50 (2H, m, H-4,7 benzimidazole); 7.63-7.79 (6H, m, H arom.); 8.14 (4H, d, *J* = 7.9, H arom.)

we obtained the product of alkylation at the two nitrogen atoms: 1,3-diphenacyl-2,3-dihydro-1H-benz[*d*]imidazole-2-thione (**15**). Compound **15** is formed as a result of alkylation of **8a** by 2-bromoacetophenone even when an equimolar ratio of reagents is used. When thiazinobenzimidazolone **8a** is treated with concentrated hydrogen peroxide in acetic acid at 20°C, the products of oxidative decomposition of the 1,3-thiazine ring are formed: benzimidazole-2-sulfonic acid (**16**) and cinnamic acid **17**.

Thus the chemical properties and reactivity of compound **1** and 2-aryl-2,3-dihydro-4H-[1,3]thiazino-[3,2-*a*]benzimidazol-4-ones **8a,b** are significantly different. For compound **1**, typical reactions are those occurring primarily by breaking the $C_{(4)}$–$N_{(5)}$ bond, while for 2-aryl[1,3]thiazino[3,2-*a*]benzimidazol-4-ones **8a,b**, conversions accompanied by breaking of both the $C_{(4)}$–$N_{(5)}$ bond and the $S_{(1)}$–$C_{(2)}$ bond are more typical. In the latter case, one of the reaction products is cinnamic acid **17** or its amides **10a-c, 14**. The ease with which

they are formed is probably explained by the fact that these compounds contain a conjugated system, and formation of such a system is an energetically favorable process. Probably conversions of thiazinobenzimidazolones **8a,b**, leading to formation of cinnamic acid **17** or its amides, occurs according to a carbanion mechanism (the negative charge on the carbanions is on $C_{(3)}$). At the same time, the reactions of thiazinobenzimidazolone **1** possibly occurs according to a carbanion mechanism only in conversion of compound **5c** to form 1,3-disubstituted benzimidazole-2-thione **6** and benzimidazole-2-thione **7**. The rest of the reactions of compound **1** apparently occur according to different mechanisms, which also explains formation of other products upon alkylation, aminolysis, and oxidation of this compound.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian 300 (300 MHz) in DMSO-d_6, internal standard TMS. The physicochemical and spectral characteristics of the synthesized compounds are given in Tables 1 and 2.

3-(1-R-1H-Benz[*d*]imidazol-2-ylsulfanyl)propanoic Acids 2a,b. A mixture of compound **1** (10 mmol) and benzyl bromide (phenacyl bromide) (10 mmol) was held for 10 min at 130°C, cooled, washed with a solution of $NHCO_3$ (10 mmol) in water (10 ml), and extracted with $CHCl_3$ (2 × 10 ml). The chloroform was dried over $MgSO_4$ and then evaporated off, and the acids **2a,b** were filtered out.

3-(1H-Benz[*d*]imidazol-2-ylsulfanyl)propanoic Acid Amide, Hydrazide, and N-Benzylamide 5a-c. A solution of compound **1** (10 mmol) and ammonia (hydrazine hydrate, benzylamine) (11 mmol) in ethanol (30 ml) was boiled for 1 h, cooled, held for 24 h, and then the precipitated amides **5a-c** were filtered out.

Oxidation of Compounds 1, 8a. A 35% H_2O_2 solution (4 ml) was added dropwise to a solution of thiazinobenzimidazolones **1** (**8a**) (10 mmol) in AcOH (10 ml) at 20°C. The mixture was held for 24 h and the precipitate of benzimidazol-2-one **3** (benzimidazole-2-sulfonic acid **16**) was filtered out. The filtrate was evaporated down at 20°C and the isolated acid **4** (**17**) was dried.

1,3-Di(N-benzylcarbamoylethyl)-2,3-dihydro-1H-benz[*d*]imidazole-2-thione (6). A solution of compound **1** (**5c**) (5 mmol) in benzylamine (1,3-dichlorobenzene) (5 ml) was boiled under reflux for 1 h and then cooled. The precipitate **6** was filtered out. After evaporation of the benzylamine (1,3-dichlorobenzene), benzimidazole-2-thione **7** (30%) was isolated.

Reaction of Compound 8a with Ammonia. Excess gaseous ammonia was passed through a solution of compound **8a** (10 mmol) in ethanol (30 ml) at 30°C for 30 min. The solution was cooled down, held for 24 h, and then the precipitated amide **9** was filtered out. The ethanol was evaporated off and the residue was dissolved with heating in water (80 ml). Upon cooling of the aqueous solution, compound **7** crystallized out (16% yield), and when the filtrate was subsequently evaporated slowly over a few days, the amide **10a** precipitated from the solution.

Reaction of Thiazinobenzimidazolones 8a,b with Benzylamine. A solution of compounds **8a,b** (10 mmol) and benzylamine (11 mmol) in ethanol (30 ml) was boiled for 1 h, cooled, and held for 24 h; the precipitated benzimidazole-2-thione was filtered out (70-81% yield). The amides **10b,c** were isolated from the residue upon evaporation.

3-Aryl-3-(1H-benz[*d*]imidazol-2-ylsulfanyl)propanoic Acid Hydrazides 11a,b. A solution of compound **8a,b** (10 mmol) and hydrazine hydrate (12 mmol) in ethanol (20 ml) was boiled for 1 h and then cooled, and the precipitated hydrazide **11a,b** was filtered out.

4-R-1-[3-Aryl-3-(1H-benz[*d*]imidazol-2-ylsulfanyl)propanoyl]thiosemicarbazides 12a,b. A solution of hydrazide **11a** (5 mmol) and phenyl (or methyl) isothiocyanate (6 mmol) in ethanol (20 ml) was boiled for 1 h and then cooled, and the precipitated product **12a** (or respectively **12b**) was filtered out.

N^2-Phenyl-5-[2-(1H-benz[*d*]imidazol-2-ylsulfanyl)-2-phenylethyl]-1,3,4-thiadiazol-2-amine (13). A solution of thiosemicarbazide **12a** (5 mmol) was dissolved in H_2SO_4 (5 ml) at 20°C, held for 24 h, and poured into ice water. The precipitating product **13** was filtered out, washed with water, and dried.

3-Phenylpropenamide of 1-Benzyl-2,3-dihydro-1H-benz[*d*]imidazole-2-thione (14). A mixture of compound **8a** (10 mmol) and benzyl bromide (11 mmol) was held for 10 min at 130°C, cooled, washed with a 10% $NaHCO_3$ solution (15 ml), and extracted with $CHCl_3$ (2 × 10 ml). The chloroform was dried over $MgSO_4$ and evaporated down, and the isolated substituted benzylimidazole thione **14** was dried.

1,3-Diphenacyl-2,3-dihydro-1H-benz[*d*]imidazole-2-thione (15). A solution of compound **8a** (10 mmol) and phenacyl bromide (20 mmol) in ethanol (30 ml) was boiled for 30 min, cooled, washed with a 10% $NaHCO_3$ solution (30 ml), and extracted with $CHCl_3$ (2 × 10 ml). The chloroform was dried over $MgSO_4$ and evaporated down, and the isolated product **15** was dried. The aqueous layer was acidified with 10% HCl (10 ml) and the precipitate of the cinnamic acid **17** (67% yield) was filtered out.

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