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Molecular Iodine Promoted Divergent Synthesis of Benzimidazoles, Benzothiazoles, and 2-Benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines

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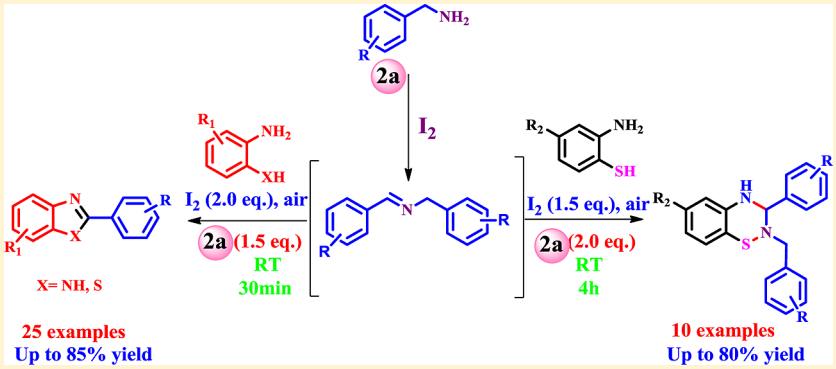
Supporting Information



ABSTRACT: An unprecedented formation of a new class of 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines has been discovered during the course of benzimidazole and benzothiazole synthesis, through the molecular iodine-mediated oxidative cyclization with a new C−N and S−N bond formation at ambient temperature.

INTRODUCTION

In recent years, carbon−heteroatom bond forming reactions constituted the central theme of organic synthesis. Among those, direct C−N bond forming reactions have engrossed significant attention to construct the heterocycles.[1] As a result, a plethora of methods has been developed for C−N bond formation. In those methods, copper-catalyzed C−N bond formation reactions are more recognizable.[2] For example Buchwald,[2j,3] Hartwig,[2k,4] and Ma et. al[2l] synthesized biologically active molecules through C−N bond formation utilizing copper as a catalyst. However, these approaches require complex ligands, longer reaction times, and harsh reaction conditions. In recent works, iodine-mediated approaches were found to be highly efficient alternatives for transition metal catalysts in C−N bond formation reactions because iodine is low in cost, readily available, and nontoxic.[5] Recently, we have also reported the synthesis of biologically important oxazole and benzoxazolone heterocyclic motifs by utilizing iodine through the C−N bond formation.[6] In continuation of this program, we synthesized benzimidazoles and benzothiazoles using iodine.

Benzimidazoles and benzothiazoles are ubiquitous structural motifs found in many therapeutically useful compounds (Figure 1).[7] For example, Protonix, Prilosec, and Nexium are representative drugs with benzimidazole skeletons,[8] and 5F203 and PMX610 are representative drugs with benzothiazole skeletons.[9] Development of efficient synthetic methods for construction of benzimidazoles and benzothiazoles is fascinating. Classical approaches for the synthesis of these compounds involve condensation of aldehydes,[10] acids,[11] esters,[12] and acid chlorides[13] with 2-amino-/mercaptoanilines (Scheme 1, method A). Some transition-metal-catalyzed transformations also gained considerable attention in recent years.[14] Our literature survey revealed that benzimidazoles and benzothiazoles were also synthesized by using hypervalent iodine and

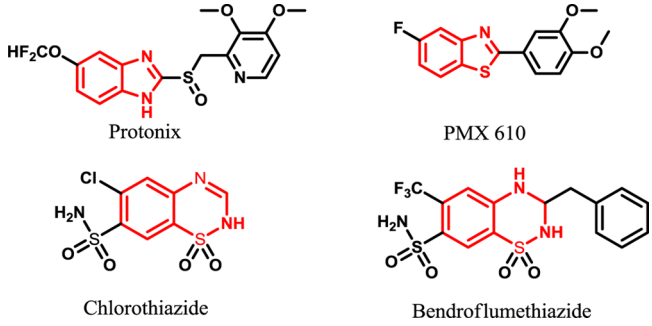


Figure 1. Representative drugs with benzimidazole, benzothiazole, and 1,2,4-benzothiadiazine skeletons.

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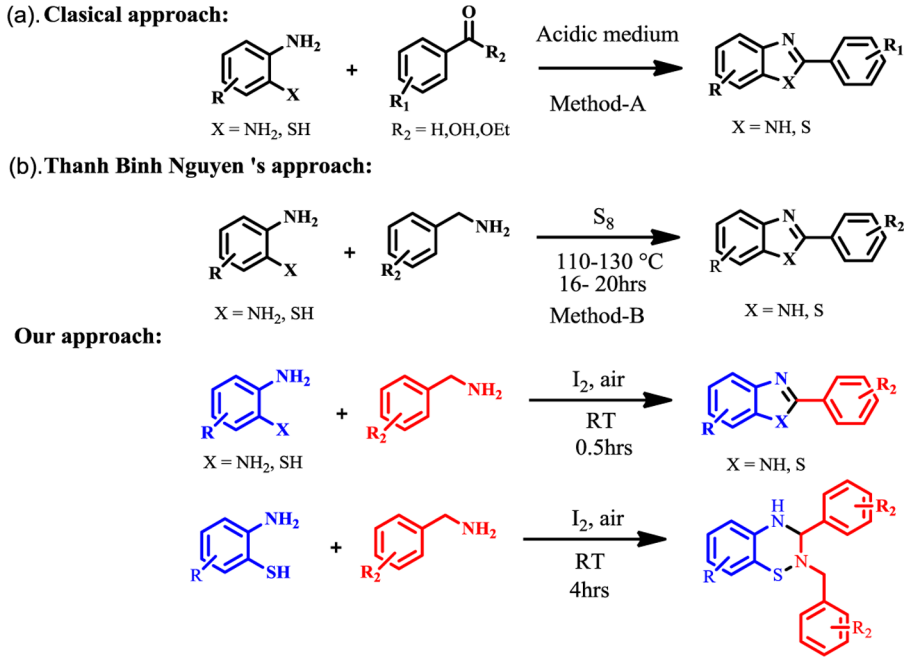
Scheme 1



iodide as catalysts through C−H activation.[15] Recently, Nguyen and co-workers reported a novel route for the synthesis of benzazoles from 1,2-diaminobenzene and benzylamine by using sulfur/oxygen as an oxidizing agent and acetic acid as a cyclizing catalyst (Scheme 1, Method B).[16]

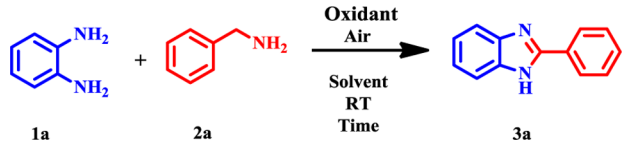
However, for all these transformations, prefunctionalization of starting materials or harsh reaction conditions such as high temperature, strong acid catalysts, and longer reaction time are required. It is therefore necessary to investigate simple and efficient methods for the synthesis of benzimidazoles and benzothiazoles. In this context, herein, we disclose the divergent route for the construction of benzimidazoles and benzothiazoles and a serendipitous discovery of a novel straightforward route for biologically important heterocyclic motif 1,2,4-benzothiadiazenes using molecular iodine.

1,2,4-Benzothiadiazine derivatives are a very interesting class of heterocyclic motif[17] and possess exciting biological activities. Various benzothiadiazine derivatives such as chlorothiazide (diuretic), cyclothiazide (diuretic and antihypertensive), and bendroflumethiazide are used as pharmaceutical therapeutics.[18] A majority of 1,2,4-benzothiadiazine derivatives are with hexavalent sulfur, and, in contrast, very few divalent sulfur derivatives are disclosed in literature.[19,1] We therefore pursued it further to develop a straightforward synthesis of 1,2,4-benzothiadiazine derivatives.

RESULTS AND DISCUSSION

Our preliminary investigation began with the reaction of benzene 1,2-diamine (**1a**) with benzylamine (**2a**) in the presence of iodine (3.0 equiv) without using the solvent (neat) at room temperature. We were delighted to observe the formation of the desired product (**3a**), albeit in low yield (45%). The poor yield of **3a** might be due to the low solubility of the reactants. Performing the same reaction in acetonitrile as a solvent increased the yield to 60% (entry 2, Table 1). We evaluated various solvents for further improvement in yield. Among those, acetonitrile and ethyl acetate showed an almost similar effect on the product formation (entries 5 and 7, Table 1).

Table 1. Optimization of Reaction Conditions for the Synthesis of Benzimidazoles[a]



1a 2a 3a

entry	oxidant (equiv)	solvent[b]	time (h)	yield (%)[c]
1	I_2 (3.0)		0.25	45
2	I_2 (3.0)	CH_3CN	0.25	60
3	I_2(2.7)	CH_3CN	0.25	65
4	I_2 (2.5)	CH_3CN	0.25	75
5	**I_2 (2.0)**	**CH_3CN**	**0.5**	**80**
6	I_2 (2.0)	CH_3CN	1	78
7	**I_2 (2.0)**	**EA**	**0.5**	**78**
8	I_2 (2.0)	DCE	1	50
9	I_2 (2.0)	DMSO	1	70
10	NIS (2.0)	CH_3CN	1	30
11	NCS (2.0)	CH_3CN	1	NI

[a]The reaction was carried out with **1a** (1.0 equiv), **2a** (1.5 equiv), and iodine (2.0 equiv) solvent (5 mL) by stirring at room temperature for 30 min. [b]CH_3CN = acetonitrile, EA = ethyl acetate. [c]Isolated yields; NI = not isolated.

Once we established the suitable solvent system for synthesis of benzimidazoles, we then focused on the quantity of iodine. Initially, we used 3.0 equiv of iodine and found the desired benzimidazole (**3a**) formation in relatively low yield due to the vigorous overoxidation of benzylamine (**2a**) and some complex mixture formation. We therefore conducted a few experiments with decreasing the quantity of iodine. After several experiments, we attained the optimal conditions for the formation of benzimidazole (**3a**) in good yield with 2.0 equiv of iodine (entry 5, Table 1). Having optimized conditions, we screened various 2-amino substituted anilines (**1a**−**1n**) and benzyl-

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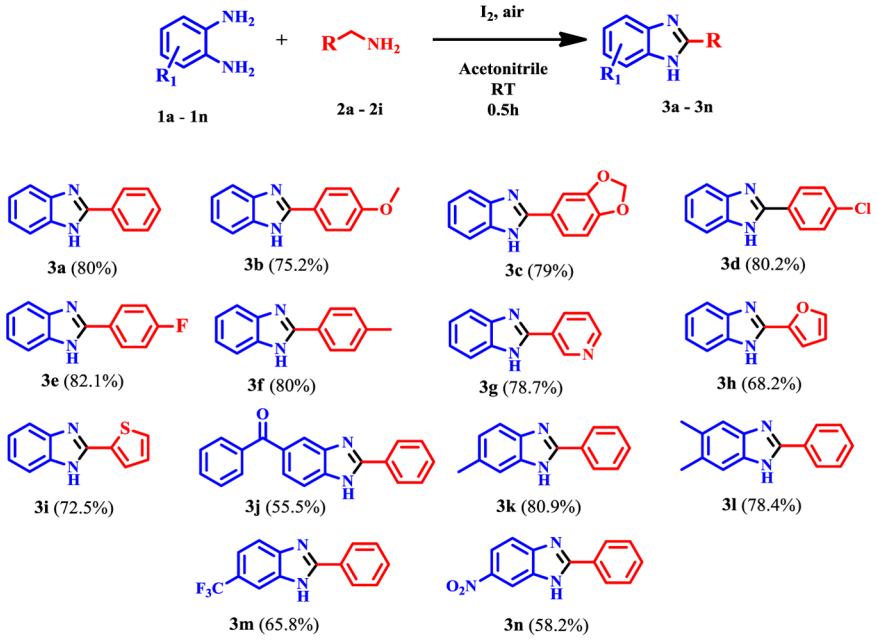
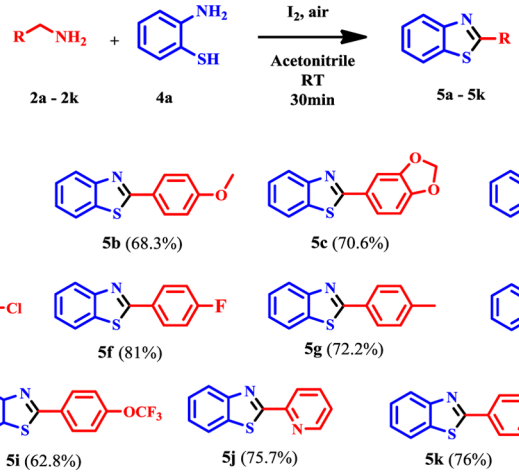
Table 2. Substrate Scope of Benzimidazoles with Optimized Conditions[a]



[a]Conditions: **1a−1n** (1.0 equiv), **2a−2i** (1.5 equiv), and iodine (2.0 equiv) in acetonitrile (5 mL) were stirred at room temperature for 30 min. Isolated yields are given in parentheses.

Table 3. Synthesis of Benzothiazoles with Optimized Conditions[a]



[a]Conditions: **2a−2k** (1.5 equiv), **4a** (1.0 equiv), and iodine (2.0 equiv) in acetonitrile (5 mL) were stirred at room temperature for 30 min. Isolated yields are given in parentheses.

amines (**2a−2i**) to get the corresponding 2-aryl and heteroaryl substituted benzimidazoles (**3a−3n**) in good yields. Electron-rich and electron-poor substituents on the aromatic ring of diamine and benzylamine were well tolerated in this tandem reaction and furnished the desired benzimidazoles in good to excellent yields (Table 2).

In light of our above successive results, we focused the scope of this protocol toward the synthesis of benzothiazoles. For this purpose, 2-aminoaniline (**1a**) was replaced with 2-mercaptoaniline (**4a**) and reacted with benzylamine (**2a**) under similar reaction conditions, which were optimized for benzimidazoles. Surprisingly, we observed the unanticipated minor product **6a** along with the desired benzothiazole **5a** (entry 1, Table 4) in the ethyl acetate solvent. However, we initially focused on our desired benzothiazole synthesis. Various solvents were screened to reduce the formation of byproduct **6a** and isolated the desired benzothiazole **5a** in excellent yield (80%) using acetonitrile as the solvent system (entry 3, Table 4). We explored the substrate scope with various substituted benzylamines (**2b−2k**) and mercaptoaniline (**4a**) to produce 2-substituted benzothiazoles (**5a−5k**) in good yields (Table 3) using optimized conditions. Unfortunately, aliphatic amines failed to provide benzimidazoles or benzothiazoles under similar reaction conditions.

After successful implementation of this protocol for the synthesis of benzimidazole and benzothiazoles, we shifted our attention to establish the structure of the unanticipated product (**6a**). In this context, our attempt to elucidate the structure of minor product **6a** with 2D-NMR was not fully successful. However, its structure was confirmed as 2-benzyl-3-phenyl-3,4-dihydro-*H*-benzo[*e*][1,2,4]thiadiazine (**6a**) by using single-crystal X-ray analysis.[20]

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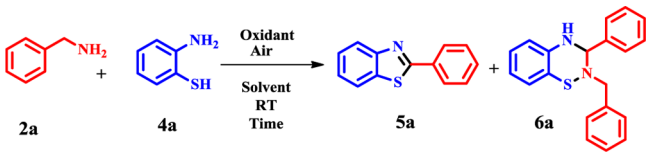
After we confirmed the structure of 2-benzyl-3-phenyl-3,4-dihydro-*H*-benzo[*e*][1,2,4] thiadiazine (**6a**), we decided to scrutinize the optimization conditions for the synthesis of substituted 1,2,4-benzothiadiazenes. In this context, we conducted an experiment with 2-mercaptoaniline (**4a**) (1.0 equiv) and benzylamine (**2a**) (2.0 equiv) in the presence of iodine (2.0 equiv) as an oxidant in ethyl acetate solvent at room temperature, which resulted in the formation of the unusual heterocycle motif **6a** in moderate yield due to the formation of benzothiazole (**5a**) also along with **6a** (entry 8, Table 4). When we decreased the amount of benzylamine (**2a**) (entry 14, Table 4) in the reaction, the yield of the desired compound **6a** also

Table 4. Optimization of Reaction Conditions[a,b]



2a **4a** **5a** **6a**

entry	oxidant (equiv)	**2a** (equiv)	solvent[c]	time (h)	yield **5a**[c] (%)	yield **6a**[d] (%)
1	I_2 (2.0)	1.5	EA	0.5	75	15
2	I_2 (2.0)	1.5	EA	1	60	20
3	**I_2 (2.0)**	**1.5**	CH_3CN	**0.5**	**80**	**NI**
4	I_2 (2.0)	1.3	CH_3CN	0.5	60	NI
5	I_2 (3.0)	1.3	CH_3CN	0.5	50	NI
6	I_2 (2.0)	2	DCE	0.5	50	NI
7	I_2 (1.3)	2	DMSO	0.5	65	NI
8	I_2 (2.0)	2	EA	0.5	<10	50
9	I_2 (1.7)	2	EA	1	20	50
10	I_2 (1.5)	2	EA	2	20	62
11	I_2 (1.5)	2	EA	3	10	75
12	I_2 (1.3)	2	EA	3	NI	78
13	**I_2 (1.3)**	**2**	**EA**	**4**	**NI**	**81**
14	I_2 (1.3)	1.5	EA	4	50	40
15	NIS	2	EA	4	30	NI
16	NBS	2	EA	4	<10	NI

[a]Conditions for synthesis of **5a**: **2a** (1.5 equiv), **4a** (1.0 equiv), and iodine (2.0 equiv) in acetonitrile (5 mL) were stirred at room temperature for 0.5 h. [b]Conditions for synthesis of **6a**: **2a** (2.0 equiv), **4a** (1.0 equiv), iodine (1.3 equiv), and ethyl acetate (5 mL) were stirred at room temperature for 4 h. [c]CH_3CN = acetonitrile, EA = ethyl acetate, DCE = 1, 2-dichloroethane, DMSO = dimethyl sulfoxide. [d]Isolated yields; NI = not isolated.

decreased. After examining several experimental conditions, we found that 1.3 equiv of iodine and a reaction time of 4 h are the most effective conditions for the formation of **6a** in excellent yield (entry 3, Table 4). We also screened various solvents to investigate the effect of the solvent system on the reaction medium and found that ethyl acetate was most efficient to increase the yield of **6a** (entry 13, Table 4).

With these optimal conditions, we investigated the substrate scope of this protocol with various substituted benzylamines (**2a**–**2f**) and 2-mercaptoanilines (**4a** and **4b**) and found the formation of **6a**–**6j** smoothly in good yields (Table 5).

Control Experiments. To establish the mechanism for the formation of benzimidazole, benzothiazole, and 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines, we carried out a few control experiments (Scheme 2). In this context, we isolated the imine intermediate **I** during the synthesis of benzimidazole. We performed a reaction between imine intermediate **I** with 2-amino-/2-mercaptoaniline separately, which furnished the benzimidazole/benzothiazole smoothly at room temperature; however, our attempt to isolate the transiminated intermediate (**II** or **III**) was not successful. With our control experiment results and from earlier reports,[16b,21] we conclude that the pathway for the formation of benzimidazole/benzothiazole is as shown in Scheme 3. In the case of 1,2,4-benzothiadiazine formation, oxidized intermediate (**IV**) might be generated from 2-mercaptoaniline in the presence of iodine. In control experiments, we obtained intermediate (**IV**) from 2-mercaptoaniline using I_2 (Scheme 2). Kirihara and co-workers also reported a similar intermediate from 2-mercaptoaniline.[22] Further reaction between intermediates **IV** and **I** might have resulted in 1,2,4- benzothiadiazine (**6a**) formation.

On the basis of previous literature reports[16b,21] and our experimental results, the possible reaction mechanism for the formation of benzimidazoles and benzothiazoles is outlined in Scheme 3, which starts from the oxidative dimerization of benzylamine in the presence of iodine to produce the imine (**I**) with the loss of ammonia. It might be easily converted into **II** or **III** by the transimination with 2- amino-/2-mercaptoanilines and subsequent cycloaddition gives the 2-phenyl-2,3-dihydro-1*H*-benzo[*d*]imidazole/thiazole intermediate (**VI**/**VII**). Oxidation of resultant intermediates **VI**/**VII** gives the benzimidazole/thiazole. In the case of 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine formation, the oxidation of 2-mercaptoaniline in the presence of iodine at optimized conditions might give the 2,2′-disulfanediyldianiline (**IV**).[21] Nucleophilic attack of **IV** on imine **I** and subsequent internal nucleophlie (secondary amine) assisted cleavage of disulfide bond might produce **6a**.

CONCLUSIONS

We have developed a simple and novel protocol for the iodine-mediated synthesis of benzimidazole and benzothiazole from readily available 2-amino-/2-mercaptosubstituted anilines and various benzylamines. During this process, an unprecedented formation of a new class of 2-benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines has been discovered. This method involves metal-free C–N and S–N bond formation at ambient temperature to produce the products in good to excellent yields.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial sources and used as received. The progress of the reaction was monitored by analytical TLC on silica gel G/GF 254 plates. The column chromatography was performed with silica gel 60–120 mesh. NMR (^1H and ^{13}C) spectra were recorded on either a 300 or 400 MHz NMR using TMS as an internal standard and chemical shifts (δ ppm) (multiplicity, coupling constant (Hz), integration). The abbreviations for multiplicity are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and dd, doublet of doublets. Melting points are uncorrected and were determined in capillary tubes on a hot-stage melting point apparatus containing silicon oil. High-resolution mass spectra were taken with a 3000 mass spectrometer and Q-TOF Analyzer. IR spectra were recorded using a FTIR spectrophotometer.

*General Procedure for Synthesis of Benzimidazoles (**3a**–**3n**).* To a stirred solution of benzylamine (1.5 equiv) and 2-aminoaniline (1.0 equiv) in acetonitrile (5 mL) at room temperature was added 2.0 equiv of I_2. We allowed for stirring at room temperature for 30 min, and the progress of the reaction was monitored by TLC analysis. After completion of the reaction, excess I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3$. After separation of the organic layer,

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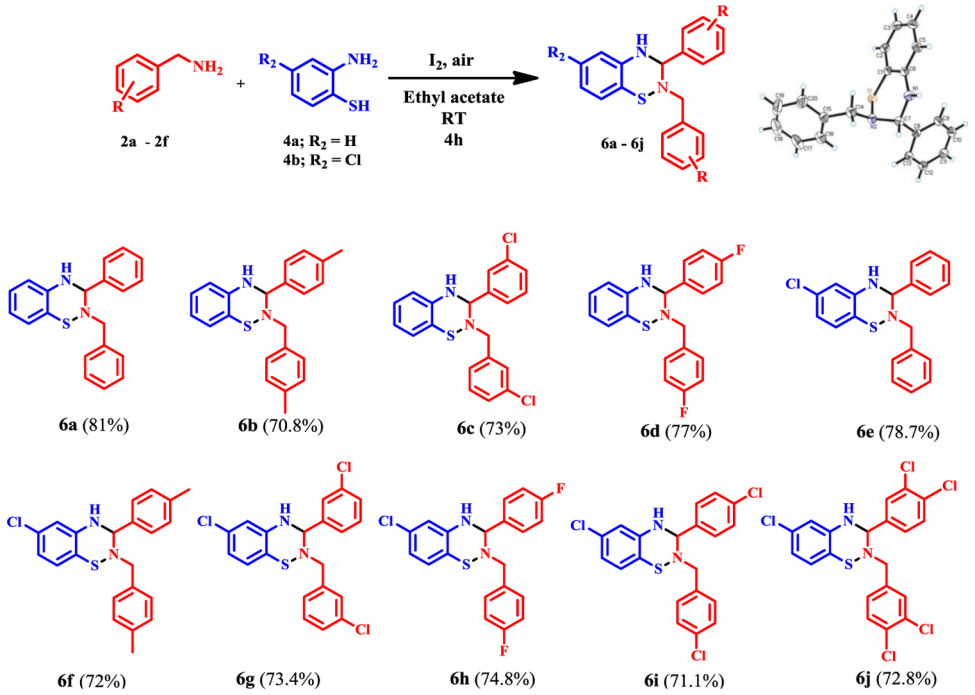
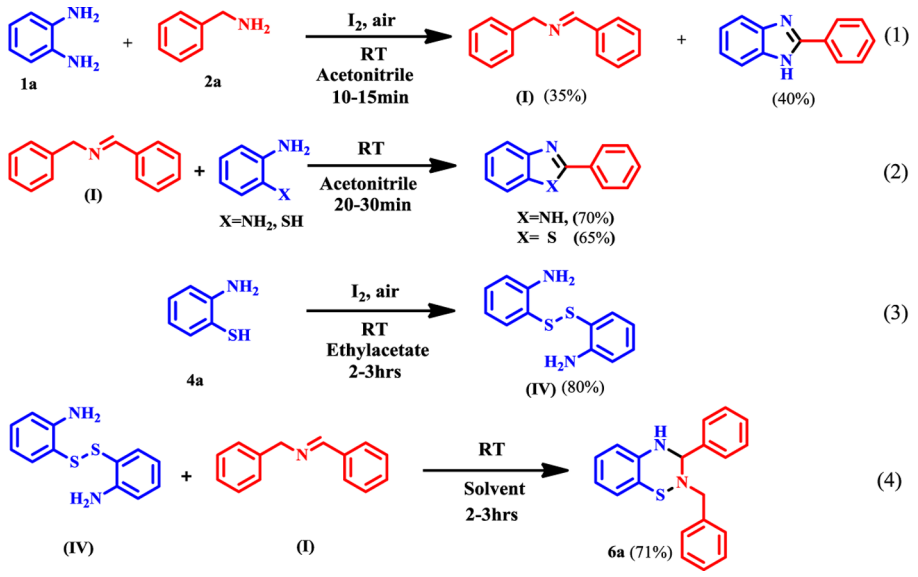
Table 5. Synthesis of Various 2-Benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazines Under Optimized Conditions[a]



[a]Conditions for synthesis of **6a**–**6j**: **2a** (2.0 equiv), **4a** (1.0 equiv), and iodine (1.3 equiv) in ethyl acetate (5 mL) were stirred at room temperature for 4 h. Isolated yields are given in parentheses.

Scheme 2



aqueous solution was then back-extracted with ethyl acetate (10 mL). The combined organic layers were treated with saturated $NaHCO_3$ solution (10 mL) and brine solution (10 mL) and dried over anhydrous Na_2SO_4, evaporated to give a crude benzimidazole, and purified by the silica gel column chromatography using hexane and ethyl acetate (20:5) as eluent.

2-Phenyl-1H-benzo[d]imidazole (**3a**).[23] White solid; yield 80% (360 mg); ESI-MS (m/z) = 195 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.931 (bs, 1H), 8.212–8.188 (m, 2H), 7.683 (d, J = 7.41 Hz, 1H), 7.581–7.481 (m, 4H), 7.250–7.199 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.7, 144.3 135.5, 130.6, 130.3, 129.4, 126.9, 123.0, 122.1, 119.3, 111.8 ppm.

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole (**3b**).[23] White solid; yield 75.2% (390 mg); ESI-MS (m/z) = 225 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.755 (s, 1H), 8.162–8.155 (m, 2H), 7.641 (d, J = 6.4 Hz, 2H), 7.196–7.102 (m, 4H), 3.874 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1, 151.2, 144.4, 135.4, 128.5, 123.2, 122.5, 121.9, 119.0, 114.8, 111.5, 55.8 ppm.

2-(Benzo[d][1,3]dioxol-5-yl)-1H-benzo[d]imidazole (**3c**).[23] White solid; yield 79% (435 mg); ESI-MS (m/z) = 239 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.732–7.687 (m, 2H) 7.561 (bs, 2H), 7.192–7.177 (m, 2H), 7.104 (d, J = 8.45 Hz, 1H), 6.165 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.6, 149.2, 148.3, 124.6, 122.4, 121.4, 109.2, 106.9, 102.0 ppm.

2-(4-Chlorophenyl)-1H-benzo[d]imidazole (**3d**).[16a] Pale white solid; yield 80.2% (423 mg); ESI-MS (m/z) = 229 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.009, (s, 1H), 8.222–8.188 (m, 2H), 7.687 (d, J = 7.61 Hz, 1H) 7.650–7.615 (m, 2H), 7.552 (d, J = 7.47 Hz, 2H)

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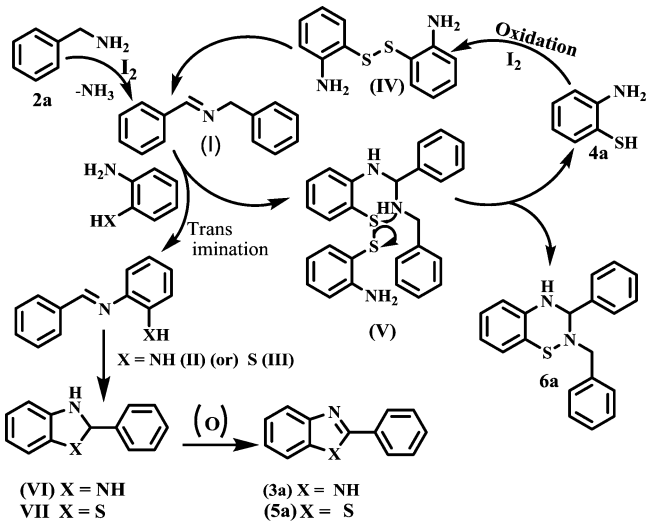
Scheme 3. Possible Reaction Mechanism for the Formation of Benzimidazole, Benzothiazole, and 2-Benzyl-3-phenyl-3,4-dihydro-2*H*-benzo[*e*][1,2,4]thiadiazine



7.245−7.204 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 144.2, 135.5, 135.0, 129.5, 128.6, 123.2, 122.3, 119.4, 111.9 ppm.

*2-(4-Fluorophenyl)-1H-benzo[d]imidazole (**3e**).* White solid; yield 82.1% (403 mg); ESI-MS (m/z) = 213 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.916 (s, 1H), 8.250−8.207 (m, 2H) 7.661−7.532 (m, 2H), 7.432−7.380 (m, 2H), 7.212 (d, J =.3.53 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 162.3, 150.9, 129.7, 129.6, 129.2, 129.1, 127.3, 122.6 ppm.

*2-p-Tolyl-1H-benzo[d]imidazole (**3f**).*[23] White solid; yield 80% (385 mg); ESI-MS (m/z) = 209 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.828 (bs, 1H), 8.081 (d, J = 8.19 Hz, 2H), 7.586 (bs, 2H), 7.363 (d, J = 8.08 Hz, 2H), 7.216−7.183 (m, 2H), 2.386 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) δ 152.3, 140.3, 129.5, 126.9, 126.5, 122.5, 114.6, 20.9 ppm.

*2-(Pyridin-3-yl)-1H-benzo[d]imidazole (**3g**).*[16a] Pale white solid; yield 78.7% (355 mg); ESI-MS (m/z) = 196 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.11 (bs, 1H), 9.369 (d, J = 1.85 Hz, 1H), 8.696−8.680 (m, 1H), 8.526−8.497 (m, 1H), 7.651−7.579 (m, 3H), 7.261−7.239 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.0, 149.3, 148.0, 144.1, 135.4, 134.2, 126.6, 124.5, 123.4, 122.6, 119.5, 112.0 ppm.

*2-(Furan-2-yl)-1H-benzo[d]imidazole (**3h**).*[23] Pale yellow solid; yield 68.2% (290 mg); ESI-MS (m/z) = 185 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.961 (bs, 1H), 7.950−7.947 (m, 1H), 7.582 (bs, 2H), 7.224−7.198 (m, 3H), 6.738−6.725 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.0, 145.0, 144.1, 139.3, 122.7, 115.5, 112.8, 111.0 ppm.

*2-(Thiophen-2-yl)-1H-benzo[d]imidazole (**3i**).*[23] Pale white solid; yield 72.5% (335 mg); ESI-MS (m/z) = 201 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.944 (bs, 1H), 7.837 (s, 1H), 7.722−7.709 (m, 1H), 7.544 (bs, 2H), 7.226−7.194 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.5, 134.2, 129.2, 128.7, 127.1, 122.6 ppm.

*Phenyl(2-phenyl-1H-benzo[d]imidazol-5-yl)methanone (**3j**): (CAS number; 82326-53-2).* Light red solid; yield 55.5% (195 mg); ESI-MS (m/z) = 299 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.307 (bs, 1H), 8.224 (d, J = 7.24 Hz, 2H), 7.981 (S, 1H), 7.791−7.669 (m, 5H), 7.608−7.534 (m, 5H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.1, 154.4, 138.6, 132.53, 131.5, 131.0, 130.0, 129.9, 129.6, 128.9, 127.2, 124.6 ppm.

*6-Methyl-2-phenyl-1H-benzo[d]imidazole (**3k**).*[16a] White solid; yield 80.9% (345 mg); ESI-MS (m/z) = 209 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6)12.789 (s, 1H), δ 8.192−8.171 (m, 2H), 7.565−7.460 (m, 4H), 7.395 (s, 1H), 7.033 (d, J = 8.32 Hz, 1H), 2.438 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.3, 131.8, 130.7, 130.1, 129.8, 124.0, 116.0, 21.8 ppm.

*5, 6-Dimethyl-2-phenyl-1H-benzo[d]imidazole (**3l**).*[16a] White solid; yield 78.7% (320 mg); ESI-MS (m/z) = 223 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ, 12.681 (bs, 1H), 8.173−8.159 (m, 2H), 7.551−7.329 (m, 5H), 2.329 (s, 6H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.8, 143.0, 134.0, 131.6, 130.9, 130.4, 129.9, 129.3, 126.7, 119.4, 111.8, 20.5 ppm.

*2-Phenyl-6-(trifluoromethyl)-1H-benzo[d]imidazole (**3m**).* Yellow solid; yield 65.8% (245 mg); ESI-MS (m/z) = 263 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (bs, 1H), 8.240−8.217 (m, 2H), 7.961 (bs, 1H), 7.792 (d, J = 8. 52 Hz, 1H), 7.612−7.522 (m, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.6, 131.0, 129.9, 120.5, 127.3, 126.9, 124.2, 123.0, 119.3 ppm.

*6-Nitro-2-phenyl-1H-benzo[d]imidazole (**3n**).* Light red solid; yield 58.2% (230 mg); ESI-MS (m/z) = 240 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.560 (bs, 1H), 8.451 (s, 1H), 8.195 (m, 2H), 8.122−8.095 (m, 1H), 7.750 (d, J = 8.86 Hz, 1H), 7.616−7.563 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.2, 143.1, 131.3, 129.5, 127.4, 118.3, 112.7 ppm.

*General Procedure for Synthesis of Benzothiazole (**5a**−**5k**).* To a stirred solution of benzylamine (1.5 equiv) and 2-mercaptoaniline (1.0 equiv) in acetonitrile (5 mL) at room temperature was added 2.0 equiv of I_2. We allowed for stirring at room temperature for 30 min, and the progress of the reaction was monitored by TLC analysis. After completion of the reaction, excess I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was separated, and the aqueous solution was then extracted by ethyl acetate (10 mL). The combined organic layers were washed with saturated brine solution (10 mL), dried over anhydrous Na_2SO_4, and evaporated to give a crude benzothiazole. Residue was purified by the silica gel column chromatography using hexane and ethyl acetate (90:1) as eluent to give the desired benzothiazole.

*2-Phenylbenzo[d]thiazole (**5a**).*[16a] White solid; yield 80% (350 mg); ESI-MS (m/z) = 212 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0973−8.0658 (m, 3H), 7.885 (d, J = 8.17 Hz, 1H), 7.502−7.460 (m, 4H), 7.389−7.349 (m, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.1, 154.2, 135.1, 133.6, 131.0, 129.0, 127.6, 126.3, 125.2, 123.2, 121.6 ppm.

*2-(4-Methoxyphenyl)benzo[d]thiazole (**5b**).*[16b] White solid; yield 68.3% (328 mg); ESI-MS (m/z) = 242 (M + H), ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.096−8.005 (m, 4H), 7.541−7.401 (m, 2H), 7.125−7.089 (m, 2H), 3.850 (s, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.5, 154.1, 134.7, 129.3, 126.9, 126.0, 125.5, 122.9, 122.6, 115.2, 55.9 ppm.

*2-(Benzo[d][1,3]dioxol-5-yl)benzo[d]thiazole (**5c**).* Purple semi solid; yield 70.6% (360 mg); ESI-MS (m/z) = 256 (M + H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.030−8.008 (m, 1H), 7.858−7.834 (m, 1H), 7.607−7.567 (m, 2H), 7.479−7.437 (m, 1H), 7.362−7.321 (m, 1H), 6.881 (d, J = 8.07 Hz, 1H), 6.027 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 154.1, 150.1, 148.4, 134.9, 128.0, 126.3, 125.0, 122.9, 122.5, 121.5, 108.6, 107.5, 101.7 ppm.

*2-(4-Chlorophenyl)benzo[d]thiazole (**5d**).*[24] Pale white solid; yield 81.5% (400 mg); ESI-MS (m/z) = 246 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.177−8.153 (m, 1H), 8.129−8.065 (m, 3H), 7.660−7.625 (m, 2H), 7.589−7.548 (m, 1H), 7.508−7.467 (m,1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 154.0, 136.5, 135.0, 132.1, 129.9, 129.3, 127.2, 126.2, 123.4, 122.9 ppm.

*2-(3,4-Dichlorophenyl)benzo[d]thiazole (**5e**).* Pale white solid; yield 78% (437 mg); ESI-MS (m/z) = 281(M + H), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.155 (d, J = 2.05 Hz, 1H), 8.049−8.027 (m, 1H), 7.868−7.810 (m, 2H), 7.503−7.462 (m, 2H), 7.400−7.359 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 153.1, 135.1, 135.1, 133.5, 133.4, 130.1, 129.0, 126.7, 126.5, 125.7, 123.5, 121.7 ppm.

*2-(4-Fluorophenyl)benzo[d]thiazole (**5f**).*[24] White solid; yield 81% (370.8 mg); ESI-MS (m/z) = 230 (M + H), ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.071−8.038 (m, 3H), 7.886−7.862 (m, 1H), 7.501−7.459 (m, 1H), 7.390−7.349 (m, 1H), 7.185−7.141 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 163.2, 154.1, 135.1, 129.1, 129.6, 129.5, 126.4, 125.3, 123.2, 121.6, 116.3, 116.0 ppm.

*2-p-Tolylbenzo[d]thiazole (**5g**).*[24] White solid; yield 72.2% (325 mg); ESI-MS (m/z) = 226 (M + H), ^{1}H NMR (400 MHz, $CDCl_3$) δ

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8.064−8.042 (m, 1H), 7.997 (d, J = 8.23 Hz, 2H), 7.887−7.865 (m, 1H), 7.492−7.450 (m, 1H), 7.378−7.337 (m, 1H), 7.295−7.274 (m, 2H), 2.413 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 154.2, 141.4, 135.0, 131.0, 129.7, 127.5, 126.2, 125.0, 123.1, 121.6, 21.5 ppm.

*2-(4-(Trifluoromethyl)phenyl)benzo[d]thiazole (**5h**).*[24] White solid; yield 60.9% (340 mg); ESI-MS (m/z) = 280 (M+H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.166 (d, J = 8.15 Hz, 2H), 8.087 (d, J = 8.26 Hz, 1H), 7.890 (d, J = 7.92 Hz, 1H), 7.717 (d, J = 8.15 Hz, 2H), 7.505 (t, J = 7.69 Hz, 1H), 7.402 (t, J = 7.69 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 154.0, 136.8, 136.7, 135.2, 132.6, 127.7, 126.6, 126.00, 126.0, 125.9, 125.8, 123.6, 121.7 ppm.

*2-(4-(Trifluoromethoxy)phenyl)benzo[d]thiazole (**5i**).* White solid; yield 62.8% (370.6 mg); ESI-MS (m/z) = 296 (M + H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.146−8.071 (m, 3H), 7.920−7.899 (m, 1H), 7.531−7.490 (m, 1H), 7.426−7.385 (m, 1H), 7.338 (d, J = 8.06 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 154.1, 151.0, 136.7, 135.1, 132.2, 129.1, 126.5, 125.5, 123.4, 121.7, 121.2 ppm.

*2-(Pyridin-2-yl)benzo[d]thiazole (**5j**).*[16a] White solid; yield 75.7% (320.8 mg); ESI-MS (m/z) = 213 (M + H); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.747−8.728 (m, 1H), 8.351−8.327 (m, 1H), 8.184−8.163 (m, 1H), 8.122−8.121 (m, 1H), 8.067- 8.024 (m, 1H), 7.616−7.554 (m, 2H), 7.523−7.482 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 154.2, 150.8, 150.4, 138.3, 135.9, 127.1, 126.6, 126.4, 123.8, 123.0, 120.8 ppm.

*2-(Pyridin-4-yl)benzo[d]thiazole (**5k**).* White solid; yield 76% (325 mg); ESI-MS (m/z) = 213(M + H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.781−8.786 (m, 2H), 8.13 (d, J = 8.14 Hz, 1H), 7.962−7.937 (m, 3H), 7.570−7.528 (m, 1H), 7.481−7.440 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 154.0, 150.7, 140.5, 135.2, 126.8, 126.2, 123.9, 121.9, 122.2 ppm.

*General Procedure for Synthesis of 2-Benzyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazines **6a**−**6j**.* To a stirred solution of 2.0 equiv of benzylamine and 1.0 equiv of 2-mercaptoaniline in ethyl acetate (5 mL) at room temperature was slowly added 1.3 equiv of I_2. We allowed for stirring at room temperature for 4 h, and the progress of the reaction was monitored by TLC analysis. After completion of the reaction, excess I_2 was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The organic layer was separated, and the aqueous solution was then extracted by ethyl acetate (10 mL). The combined organic layers were washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and evaporated to yield a crude 1,2,4-benzothiadiazine derivative. Residue was purified by the silica gel column chromatography using hexane and ethyl acetate (80:2) as eluent.

*2-Benzyl-3-phenyl-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine (**6a**).* Pale pink solid; yield 81% (515 mg); mp 160−161 °C; FT-IR ν max (KBr) 1294 (C−N) cm^{-1}, 3396.4 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.422−7.238 (m, 10H), 7.008−6.947 (m, 2H), 6.821 (d, J = 8.11 Hz, 1H), 6.743−6.724 (m, 1H), 6.596−6.556 (m, 1H), 5.398 (d, J = 4.12 Hz, 1H), 4.168 (d, J = 13.43 Hz, 1H), 3.96 (d, J = 13.31 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.7, 140.5, 138.8, 129.3, 128.8, 128.5, 127.8, 127.2, 126.6, 124.9, 117.3, 115.0, 114.5, 72.2, 61.0 ppm; mass (ESI-MS) m/z = 319 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{19}N_2S$, 319.1269; found, 319.1268.

*2-(4-Methylbenzyl)-3-p-tolyl-3,4-dihydro-2H-benzo[e][1,2,4]-thiadiazine (**6b**).* Pale pink solid; yield 70.8% (490 mg); mp 158−160 °C; FT-IR ν max (KBr) 1215.4 (C−N) cm^{-1}, 3440.4 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.292−7.261 (m, 4H), 7.151−7.106 (m, 4H), 7.019−6.977 (m, 1H), 6.812−6.789 (m, 1H), 6.694−6.625 (m, 2H), 5.356 (d, J = 3.95 Hz, 1H), 4.391 (d, J = 3.95 Hz, 1H), 4.102−4.014 (dd, J = 13.22 Hz, J = 8.88 Hz, 2H), 2.332 (s, 3H), 2.308 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.4, 135.3, 129.2, 129.0, 129.0, 126.7, 126.2, 125.2, 118.4, 116.7, 115.0, 72.1, 60.3, 21.2 ppm; mass (ESI) m/z = 347.1 (M+H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{23}N_2S$, 347.1582; found, 347.1579.

*2-(3-Chlorobenzyl)-3-(3-chlorophenyl)-3,4-dihydro-2H-benzo[e]-[1,2,4]thiadiazine (**6c**).* White solid; yield 73% (565 mg); mp 135−137 °C; FT-IR ν max (KBr) 1298.3 (C−N) cm^{-1}, 3439.7 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.420−7.415 (m, 2H), 7.354−7.279 (m, 6H), 7.104−6.7.062 (m, 1H), 6.870−6.848 (m, 1H), 6.787−6.727 (m, 2H), 5.384 (d, J = 4.28 Hz, 1H), 4.519 (d, J = 4.14 Hz, 1H), 4.123 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.1, 138.5, 134.4, 134.3, 129.9, 129.7, 129.1, 128.1, 128.0, 127.1, 126.5, 125.3, 125.1, 118.9, 116.2, 115.1, 72.1, 60.3 ppm; mass (ESI) m/z = 387.3 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{17}Cl_2N_2S$, 387.0489; found, 387.0478.

*2-(4-Fluorobenzyl)-3-(4-fluorophenyl)-3,4-dihydro-2H-benzo[e]-[1,2,4]thiadiazine (**6d**).* White solid; yield 77% (550 mg); mp 155−157 °C; FT-IR ν max (KBr) 1217.7 (C−N) cm^{-1}, 3439.1 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.397−7.353 (m, 4H), 7.079−7.000 (m, 5H), 6.855−6.832 (m, 1H), 6.759−6.692 (m, 2H), 5.367 (d, J = 4.03 Hz, 1H), 4.482 (d, J = 3.97 Hz, 1H), 4.094 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 163.5, 161.2, 161.1, 138.9, 138.2, 138.2, 138.2, 133.8, 133.8, 130.6, 130.6, 128.6, 128.5, 126.4, 125.2, 118.7, 116.4, 115.5, 115.3, 115.0, 115.0, 71.9, 60.1 ppm; mass (ESI) m/z = 355.1 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{17}F_2N_2S$, 355.1081; found, 355.1073.

*2-Benzyl-6-chloro-3-phenyl-3,4-dihydro-2H-benzo[e][1,2,4]-thiadiazine (**6e**).* White solid; yield 78.7% (435 mg); mp 160−161 °C; FT-IR ν max (KBr) 1215.6 (C−N) cm^{-1}, 3436.9 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.412−7.348 (m, 8H), 7.327−7.248 (m, 3H), 6.848 (d, J = 2.12 Hz, 1H), 6.765 (d, J = 8.26 Hz, 1H), 6.597−6.571 (m, 1H), 5.431 (d, J = 4.25 Hz, 1H), 4.163 (d, J = 13.34 Hz, 1H), 3.922 (d, J = 13.58 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.4, 141.8, 138.5, 130.7, 129.3, 128.8, 128.6, 128.0, 127.9, 127.1, 126.5, 116.7, 113.7, 113.3, 72.0, 61.0 ppm; mass (ESI) m/z = 353.0 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{18}ClN_2S$, 353.0879; found, 353.0872.

*6-Chloro-2-(4-methylbenzyl)-3-p-tolyl-3,4-dihydro-2H-benzo[e]-[1,2,4]thiadiazine (**6f**).* White solid; yield 72% (430 mg); mp 162−163 °C; FT-IR νmax (KBr) 1215.6 (C−N) cm^{-1}, 3439.09 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.338−7.286 (m, 4H), 7.223−7.175 (m, 4H), 6.786−6.692 (m, 3H), 5.386 (d, J = 3.83 Hz, 1H), 4.539 (d, J = 3.83 Hz, 1H), 4.145−4.049 (m, 2H), 2.399 (s, 3H), 2.376 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 139.3, 137.7, 137.4, 134.9, 131.4, 129.2, 129.1, 129.0, 126.6, 126.2, 118.3, 115.0, 114.2, 71.7, 60.5, 21.2 ppm; mass (ESI) m/z = 381.0 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{22}H_{22}ClN_2S$, 381.1192; found, 381.1185.

*6-Chloro-2-(3-chlorobenzyl)-3-(3-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine (**6g**).* Pale pink solid; yield 73.4% (485 mg); mp 158−159 °C; FT-IR ν max (KBr) 1215.48 (C−N) cm^{-1}, 3405.46 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.447−7.323 (m, 9H), 6.884 (d, J = 2.11 Hz, 1H), 6.785 (d, J = 8.26 Hz, 1H), 6.612 (dd, J = 2.19 Hz 1H), 5.515 (d, J = 4.33 Hz, 1H), 4.214 (d, J = 13.52 Hz, 1H), 3.881 (d, J = 13.49 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.9, 141.3, 141.0, 133.5, 133.3, 131.0, 130.7, 129.1, 128.0, 128.0, 127.8, 127.1, 126.8, 126.0, 117.1, 114.0, 112.9, 72.1, 60.2 ppm; mass (ESI) m/z = 421.3 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}Cl_3N_2S$ 421.0100; found 421.0083.

*6-Chloro-2-(4-fluorobenzyl)-3-(4-fluorophenyl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine (**6h**).* White solid; yield 74.8% (456 mg); mp 159−160 °C; FT-IR ν max (KBr) 1215.61 (C−N) cm^{-1}, 3438.28 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.444−7.354, (m, 4H), 7.284 (d, J = 4.18 Hz, 1H), 7.213−7.151 (m, 4H), 6.842 (d, J = 2.16 Hz, 1H), 6.770 (d, J = 8.27 Hz, 1H), 6.591 (dd, J = 2.19 Hz, J = 6.0 Hz, 1H), 5.446 (d, J = 4.10 Hz, 1H), 4.156 (d, J = 13.43 Hz, 1H), 3.857 (d, J = 13.43 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.2, 160.8, 141.6, 139.7, 134.7, 131.3 (d, J = 8.22 Hz), 130.8, 129.2, (d, J = 8.19 Hz), 126.6, 116.9, 115.6, 115.4, (d, J = 3.88 Hz) 115.2, 113.9, 113.1, 71.51, 60.17 ppm; mass (ESI) m/z = 389.0 (M + H)$^+$; HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{16}ClF_2N_2S$, 389.0691; found, 389.0679.

*6-Chloro-2-(4-chlorobenzyl)-3-(4-chlorophenyl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine (**6i**).* White solid; yield 71.1% (470 mg); mp 142−143 °C; FT-IR ν max (KBr) 1215.54 (C−N) cm^{-1}, 3439.01 (N−H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.358−7.260 (m, 8H), 6.752−6.686 (m, 3H) 5.317 (d, J = 4.26 Hz 1H), 4.550 (d, J = 4.01 Hz, 1H), 4.063 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.49,

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139.55, 136.08, 133.95, 133.65, 131.73, 130.336, 128.79, 128.59, 128.17, 126.37, 118.79, 114.45, 71.62, 60.32 ppm; mass (ESI) m/z = 421.7 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}Cl_3N_2S$, 421.0100; found, 421.0083.

*6-Chloro-2-(3,4-dichlorobenzyl)-3-(3,4-dichlorophenyl)-3,4-dihydro-2H-benzo[e][1,2,4]thiadiazine (**6j**).* White solid; yield 72.8% (560 mg); mp 123−125 °C; FT-IR ν max (KBr) 1215.48 (C−N) cm^{-1}, 3437.02 (N−H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.378−7.315 (m, 4H), 7.176−7.117 (m, 2H) 6.677−6.632 (m, 3H), 5.217 (d, J = 3.96 Hz, 1H), 4.512 (d, J = 3.96 Hz, 1H), 3.985−3.910 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.0, 137.6, 132.7, 132.6, 132.2, 132.0, 132.0 130.8, 130.7, 130.5, 129.0, 128.3, 126.6, 126.2, 119.2, 114.6, 114.0, 71.7, 60.0 ppm; mass (ESI) m/z = 490.5 $(M + H)^+$; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}Cl_5N_2S$, 488.9320; found, 488.9317.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR, ^{13}C NMR spectra of all the compounds (**3a**−**3n**, **5a**−**5k**, and **6a**−**6j**) and 2D-NMR spectra, X-ray analysis data of compound **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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