# Synthesis of Imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines and 1,2,4-Triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines

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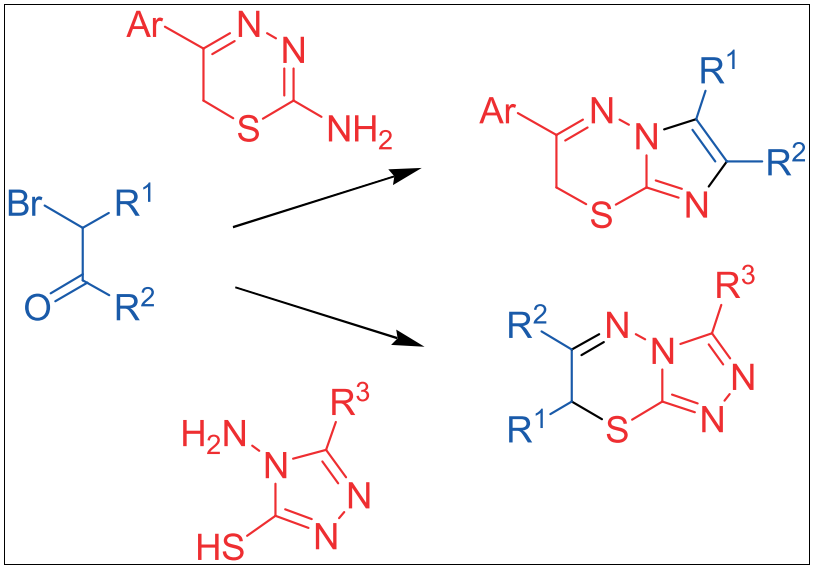


Imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines were prepared by cyclization of 2-amino-5-(4-chlorophenyl)-6*H*-1,3,4-thiadiazine with α-haloketones. 1,2,4-Triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines were prepared by cyclization of 4-amino-5-sulfanyl-l,2,4-triazoles with phenacyl bromides.

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## INTRODUCTION

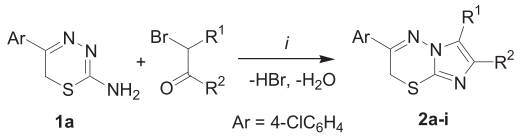
1,3,4-Thiadiazines are of considerable biochemical and pharmacological relevance. Several 2-amino-1,3,4-thiadiazine derivatives are important matrix metalloproteinase inhibitors [1,2]. 2-Alkylimino-1,3,4-thiadiazines and 2-alkyamino-1,3,4-thiadiazines are used as cardiotonic and spasmolytic agents [3–8]. 1,3,4-Thiadiazin-2-ones are cardiotonics with calcium sensitizing activity[9–11]. 3-Phenylazo-1*H*-4,2,1-thiadiazine is an agent for the treatment of deficient bone growth[12]. 3-Nitrobenzyl-5-aryl-1,3,4-thiadiazin-2-ones and 1,3,4-thiadiazin-2-ones are phospho-diesterase IV inhibitors that can be used for the treatment of tumors and AIDS [13,14]. 2-Nitrosimino-3,6-dihydro-2*H*-1,3,4-thiadiazines [15], *N*-morpholinyl-1,3,4-thiadiazines, *N*-thiomorpholinyl-1,3,4-thiadiazines or *N*-piperidinyl-1,3,4-thiadiazines [16] exhibit antithrombotic activities. In continuation of our work related to the synthesis and reactivity of 1,3,4-thiadiazines [17], we herein report the synthesis of imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines and 1,2,4-triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines. In preliminary studies, we reported the synthesis of related heterocycles [17l,m]. However, the substitution pattern was different, and no spectroscopic data were provided (because of the lack of instruments at that time).

## RESULTS AND DISCUSSION

2-Amino-5-(4-chlorophenyl)-1,3,4-thiadiazine (**1a**) was prepared in weakly acidic medium from 4-chlorophenacyl bromide and thiosemicarbazide. The cyclization of **1a** with α-haloketones afforded the imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines **2a–i** (reflux, 8 h, EtOH). After reflux for 4 h, hydrobromic acid (48%) was added, which supported the cyclocondensation. The products crystallized from the reaction mixture in the form of their hydrobromides. The free bases were obtained by addition of ammonia to an EtOH solution of the hydrobromides (Scheme 1).

The structures of bicycles **2a–i** were confirmed by spectroscopic methods. The $^1$H nmr spectra (DMSO-$d_6$) of the hydrobromides of **2a–e**,**g**,**h** exhibit signals of a $CH_2$ group,

**Scheme 1.** Synthesis of imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines **2a–i**.




which prove that the molecules exist in their 2*H* tautomeric form. Although the hydrobromides are rather stable, the free bases turn from yellow to red in sunlight (Table 1).

The synthesis of 1,2,4-triazolo-[3,4-*b*][2*H*-1,3,4] thiadiazines was next studied. However, our initial attempts were unsuccessful. The reaction of 2-hydrazino-5,6-diphenyl-1,3,4-thiadiazine (**1b**) with trimethyl orthoformate did not result in the formation of the expected 1,2,4-triazolo-[3,4-*b*][2*H*-1,3,4]thiadiazine **3a**. Under the conditions employed, this product proved to be unstable and underwent a desulfurization reaction to give pyrazole **4** (Scheme 2). This type of desulfurization was previously observed for various other 1,3,4-thiadiazine derivatives [17].

The synthesis of **3a** was finally achieved by cyclization of 2-bromo-1,2-diphenylethan-1-one with 4-amino-5-sulfanyl-l,2,4-triazole **5a** [18] (Scheme 3, Table 2). The structure of **3a** was independently confirmed by X-ray crystal structure analysis (Fig. 1). Inspection of the crystal

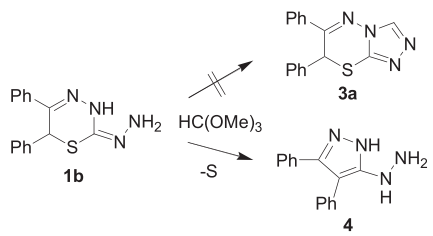
**Table 1**

Yields of imidazo-2*H*-[2,1-*b*][1,3,4]thiadiazines **2a–i**.

| | $R^1$ | $R^2$ | Yield (%)[a] **2**·HBr | Yield (%)[a] **2** |
|---|---|---|---|---|
| **2a** | H | $C_6H_5$ | 70 | 68 |
| **2b** | H | 4-$BrC_6H_4$ | 71 | 67 |
| **2c** | H | 4-$ClC_6H_4$ | 65 | 61 |
| **2d** | H | 4-$FC_6H_4$ | 74 | 72 |
| **2e** | H | 4-$MeC_6H_4$ | 73 | 71 |
| **2f** | H | 4-(MeO)$C_6H_4$ | — | 70[b] |
| **2g** | H | 4-($NO_2$)$C_6H_4$ | 72 | 71 |
| **2h** | $C_6H_5$ | $C_6H_5$ | 71 | 71 |
| **2i** | $CH_3$ | $C_6H_5$ | — | 68[b] |

[a]Yields of isolated products.
[b]**2f** and **2i** were immediately converted to their free bases.

**Scheme 2.** Attempted synthesis of **3a**.




**Scheme 3.** Synthesis of l,2,4-triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines **3a–c**.

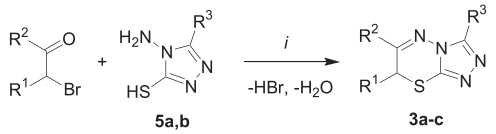



**Table 2**

Synthesis of l,2,4-triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines **3a–c**.

| | $R^1$ | $R^2$ | $R^3$ | Yield (%)[a] **3** |
|---|---|---|---|---|
| **3a** | $C_6H_5$ | $C_6H_5$ | H | 85 |
| **3b** | H | 4-$FC_6H_4$ | H | 95 |
| **3c** | H | 4-$FC_6H_4$ | $CH_3$ | 87 |

[a]Yields of isolated products.

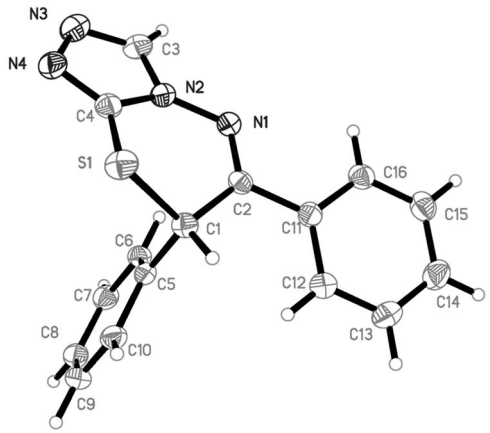



**Figure 1.** Ortep plot of **3a** [21].

structure shows that **3a** exists in a twisted boat conformation. Likewise, products **3b**,**c** were prepared by cyclization of 4-amino-5-sulfanyl-l,2,4-triazole **5a** or 4-amino-3-methyl-5-sulfanyl-l,2,4-triazole **5b** [18] with substituted phenacyl bromides. According to the nmr spectra, the compounds exist in their 2*H* tautomeric form. Compounds **3a–c** are very stable and, in contrast to simple monocyclic 1,3,4-thiadiazines [17], did not undergo desulfurization by reaction with triphenylphosphane or by reflux in glacial acetic acid. Monocyclic 6*H*-l,3,4-thiadiazines, which are known to be readily desulfurized, rapidly underwent a deuterium exchange of the protons located at position 6 [19]. In contrast, l,2,4-triazolo[3,4-*b*][2*H*-1,3,4]thiadiazines **3a–c** were not deuterated at position 2, not even in the presence of $D_2SO_4$ for several days. The formation of 2-(4-nitrobenzylidene) derivatives of **3b**,**c**, in analogy to 2-dialkylamino-1,3,4-thiadiazines[20], was not observed.

In conclusion, we have reported the synthesis of a variety of imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines **2a–i** by cyclization

of 2-amino-5-(4-chlorophenyl)-6*H*-1,3,4-thiadiazine **1a** with α-haloketones. Whereas the reaction 2-hydrazino-5,6-diphenyl-1,3,4-thiadiazine with trimethyl orthoformate resulted in desulfurization, 1,2,4-triazolo[3,4-*b*][2*H*-1,3,4] thiadiazines **3a** were prepared by cyclization of 4-amino-5-sulfanyl-l,2,4-triazoles **5a** with 2-bromo-1,2-diphenylethan-1-one.

## EXPERIMENTAL

***2-Amino-5-(4-chlorphenyl)-6H-1,3,4-thiadiazine (1a).*** *Free base*: A mixture of 3.64 g (40 mmoles) of thiosemicarbazide and 4.68 g (40 mmoles) of 4-chloro-phenacylbromide in 40 mL ethanol and 8 mL of aq. HBr (48%) was refluxed for 30 min. The precipitated hydrobromide was recrystallized from water. The free base was obtained by addition of an aqueous solution of ammonia to the ethanolic solution of the hydrobromide. A precipitate formed, which was then filtered off. Yield: 2.12 g (94%), yellow prisms (ethanol), mp 136 °C; ir (KBr, $cm^{-1}$): 3471 (s), 3250 (m), 3075 (m), 1614 (s), 1515 (s), 1490 (m), 1410 (m), 1340 (m), 1318 (m), 1094 (m), 1094 (m), 1009 (m), 816 (m); $^1$H nmr (DMSO-$d_6$, 300 MHz): δ = 1.03 (s, 2H, $NH_2$), 4.29 (s, 2H, 2-$CH_2$), 7.62–7.94 (m, 4H, ArH); ms (EI, 70 eV): *m/z* (%) = 28 (90), 51 (23), 60 (82), 77 (7), 102 (62), 117 (4), 137 (100), 162 (4), 185 (16), 196 (7), 225 ($M^+$, 42). *Anal*. Calcd. for $C_9H_8ClN_3S$ (225.7): C, 47.89; H, 3.57; N, 18.62. Found: C, 47.91; H, 3.5; 8 N, 18.65.

**General procedure for the synthesis of 3-chlorophenyl-7-aryl-imidazo[2,1-*b*][2*H*-1,3,4]thiadiazines (2a–i).** *Hydrobromides*: A mixture of 2.26 g (10 mmoles) of **1a** and 10 mmoles of α-haloketones in 15 mL of ethanol was refluxed for 8 h. After 4 h, 1 mL of aq. HBr (48%) was added. After a short period, the precipitated hydrobromide was isolated by filtration. The hydrobromide was dissolved in boiling ethanol. The pure hydrobromide precipitated when the mixture was added dropwise to ether. *Free bases*: The free bases were obtained from the ethanol solution of the hydrobromides by addition of a diluted aqueous solution of ammonia until pH 8 was reached. A precipitate formed, which was then filtered off and recrystallized from ethanol.

***3-(4-Chlorophenyl)-7-phenyl-imidazo[2,1-b][2H-1,3,4]thiadiazine (2a).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 1.99 g (10 mmoles) of phenacyl bromide. Yield: 2.85 g (70%), yellow prisms (EtOH), mp 173 °C, ir (KBr, $cm^{-1}$): 1594 (m), 1488 (m), 1468 (m), 1442 (m), 1405 (m), 1362 (m), 1169 (m), 1094 (m), 814 (m), 747 (s), 690 (m); $^1$H nmr ($CDCl_3$, 300 MHz): δ = 3.97 (s, 2H, 2-$CH_2$), 7.36–8.03 (m, 10H, ArH und H-Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (100), 91 (10), 102 (7), 160 (2), 187 (9), 271 (3), 325 ($M^+$, 49), 405 (1). *Anal*. Calcd. for $C_{17}H_{13}BrClN_3S$ (406.73): C, 50.20 H, 3.22 N, 10.33. Found: C, 50.31 H, 3.21 N, 10.35. *Free base*: Yield: 2.22 g (68%), yellow prisms (EtOH), mp 172 °C; ir (KBr, $cm^{-1}$): 1595 (m), 1488 (m), 1468 (m), 1442 (m), 1405 (m), 1362 (m), 1169 (m), 1094 (m), 849 (m), 814 (m), 747 (s), 691 (m); $^1$H nmr ($CDCl_3$, 300 MHz): δ = 3.99 (s, 2H, 2-$CH_2$), 7.30–7.84 (m, 10H, ArH und H-Hetar); $^{13}$C nmr ($CDCl_3$, 50 MHz): δ = 24.29 (2-$CH_2$, Hetar), 116.09 (6-C, Hetar), 124.74 (ArH), 127.33 (ArH), 128.18 (ArH), 128.62 (ArH), 129.23 (ArH), 132.53 (Ar), 132.60 (Ar), 132.96 (Ar), 137.48 (7-C, Hetar), 140 (8a-C, Hetar), 149.02 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (18), 76 (9), 102 (26), 116 (23), 160 (14), 188 (32), 195 (4), 290 ($M^+$, 1). *Anal*. Calcd. for $C_{17}H_{12}ClN_3S$ (325.82): C, 62.67; H, 3.71; N, 12.90. Found: C, 62.89; H, 3.70; N, 12.41.

***3-(4-Chlorophenyl)-7-(4-bromophenyl)-imidazo[2,1-b][2H-1, 3,4]thiadiazine (2b).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.78 g (10 mmoles) of 4-bromophenacyl bromide. Yield: 3.45 g (71%), yellow prisms (EtOH), mp 191 °C; ir (KBr, $cm^{-1}$): 1595 (m), 1464 (m), 1404 (m), 1366 (m), 1285 (m), 1169 (m), 1132 (m), 1091 (m), 1070 (m), 1009 (m), 841 (m), 811 (m), 750 (m); $^1$H nmr ($CDCl_3$, 300 MHz): δ = 3.98 (s, 2H, 2-$CH_2$), 7.46–7.82 (m, 9H, ArH and H-Hetar); $^{13}$C nmr (DMSO-$d_6$, 50 MHz): δ = 23.38 (2-C, Hetar), 117.01 (6-C, Hetar), 126.13 (ArH), 127.60 (ArH), 128.69 (ArH), 131.17 (ArH), 132.14 (Ar), 132.48 (Ar), 133.01 (Ar), 135.92 (Ar), 137 (7-C, Hetar), 150.94 (8a-C, Hetar), 151.55 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (100), 45 (24), 75 (18), 137 (9), 159 (2), 187 (17), 266 (1), 404 ($M^+$, 21). *Anal*. Calcd. for $C_{17}H_{12}Br_2ClN_3S$ (485.62): C, 42.05; H, 2.49; N, 8.65. Found: C, 42.05; H, 2.49; N, 8.67. *Free base*: Yield: 2.71 g (67%), yellow prisms (EtOH), mp 188 °C, ir (KBr, $cm^{-1}$): 1595 (m), 1465 (s), 1404 (m), 1366 (m), 1285 (m), 1169 (m), 1132 (m), 1091 (m), 1070 (m), 1009 (m), 842 (m), 826 (m), 810 (m), 750 (m); $^1$H nmr ($CDCl_3$, 300 MHz): δ = 3.99 (s, 2H, 2-$CH_2$), 7.45–9.34 (m, 9H, ArH and H-Hetar); $^{13}$C nmr ($CDCl_3$, 50 MHz): δ = 24.33 (2-C, Hetar), 116.30 (6-C, Hetar), 121.04 (Ar), 126.32 (ArH), 128 (ArH), 129 (ArH), 131.74 (ArH), 132.03 (Ar), 132.54 (Ar), 137.67 (7-C, Hetar), 139.22 (8a-C, Hetar), 149.26 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (59), 44 (10), 101 (27), 137 (14), 155 (4), 187 (59), 238 (1), 266 (7), 343 (4), 359 (2), 405 ($M^+$, 100). *Anal*. Calcd. for $C_{17}H_{11}Br\ Cl\ N_3S$ (404,71): C, 50.45; H, 2.74; N, 10.38. Found: C, 50.49; H, 2.74; N, 10.39.

***3.7-(4-Dichlorophenyl)-imidazo[2,1-b][2H-1,3,4]thiadiazine (2c).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.34 g (10 mmoles) of 4-chlorophenacyl bromide. Yield: 2.87 g (65%), yellow prisms (EtOH), mp 191 °C; ir (KBr, $cm^{-1}$): 1598 (m), 1483 (s), 1465 (s), 1407 (m), 1366 (m), 1309 (m), 1286 (m), 1171 (m), 1133 (m), 1091 (s), 1010 (m), 843 (m), 809 (m), 750 (m); $^1$H nmr ($CDCl_3$, 300 MHz): δ = 3.98 (s, 2H, 2-$CH_2$), 7.34–7.83 (m, 9H, ArH und H-Hetar); $^{13}$C nmr (DMSO-$d_6$, 50 MHz): δ = 23.44 (2-C, Hetar), 117.29 (6-C, Hetar), 125.99 (ArH), 128.55 (ArH), 128.92 (ArH), 128.95 (ArH), 131.42 (Ar), 131.53 (Ar), 132.52 (Ar), 133.39 (Ar), 136.19 (7-C, Hetar), 137.16 (8a-C, Hetar), 151.42 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (3), 58 (1), 75 (8), 102 (19), 137 (45), 162 (10), 187 (100), 222 (54), 324 (4), 359 ($M^+$, 20). Anal. Calcd. for $C_{17}H_{12}Br\ Cl_2N3S$ (441,17): C, 46.28 H, 2.74 N, 9.52. Found: C, 46.32 H, 2.75 N, 9.51. *Free base*: Yield: 2.20 g (61%), yellow prisms (EtOH), mp 198 °C; ir (KBr, $cm^{-1}$): 1598 (m), 1482 (s), 1463 (s), 1407 (m), 1366 (m), 1285 (m), 1168 (m), 1132 (m), 1090 (s), 1011 (m), 841 (m), 813 (m), 751 (m). $^1$H nmr ($CDCl_3$, 300 MHz): δ = 4.01 (s, 2H, 2-$CH_2$), 7.35–9.34 (m, 9H, ArH und H-Hetar). $^{13}$C nmr ($CDCl_3$, 50 MHz): δ = 24.31 (2-C, Hetar), 116.24 (6-C, Hetar), 126.00 (ArH), 128.20 (ArH), 128.80 (ArH), 129.24 (ArH), 131.55 (Ar), 132.52 (Ar), 132.92 (Ar), 137.65 (7-c, Hetar), 139 (8a-C, Hetar), 149.23 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (100), 32 (26), 70 (1), 101 (3), 155 (2), 359 ($M^+$, 66). *Anal*. Calcd. for $C_{17}H_{11}Cl_2N_3S$ (360.26): C, 56.68; H, 3.08; N, 11.66. Found: C, 56.85; H, 3.09; N, 11.69.

***3-(4-Chlorophenyl)-7-(4-fluorophenyl)-imidazo[2,1-b][2H-1, 3,4]thiadiazine (2d).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.17 g (10 mmoles) of 4-fluorophenacyl bromide. Yield: 3.15 g (74%), yellow needles (EtOH), mp 201 °

C; ir (KBr, $cm^{-1}$): 1497 (m), 1464 (m), 1412 (m), 1365 (m), 1222 (m), 1158 (m), 1090 (m), 1009 (m), 843 (m), 810 (m), 749 (m). $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.98 (s, 2H, 2-$CH_2$), 7.05–7.83 (m, 9H, ArH and H-Hetar); $^{13}C$ nmr (DMSO-$d_6$, 50 MHz): δ = 23.54 (2-C, Hetar), 115.13 (6-C, Hetar), 127.89 (ArH), 128.05 (ArH), 128.96 (ArH), 129.03 (ArH), 132.29 (Ar), 132.53 (Ar), 135.19 (Ar), 136.19 (Ar), 136.42 (7-C, Hetar), 151.58 (8a-C, Hetar), 163.91 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (100), 32 (20), 75 (9), 120 (15), 134 (84), 179 (21), 206 (59), 308 (3), 342 ($M^+$, 63). *Anal*. Calcd. for $C_{17}H_{11}BrClFN_3S$ (424.72): C, 48.07; H. 2.85; N, 9.80. Found: C, 48.07; H, 2.84; N, 9.91. *Free base*: Yield: 2,48 g (72%), yellow needles (EtOH), mp 180 °C; ir (KBr, $cm^{-1}$): 1561 (m), 1495 (m), 1463 (m), 1410 (m), 1363 (m), 1340 (m), 1292 (m), 1222 (m), 1158 (m), 1091 (m), 843 (m), 811 (m), 750 (m); $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.99 (s, 2H, 2-$CH_2$), 7.05–7.92 (m, 9H, ArH and H-Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (51), 32 (10), 70 (2), 101 (14), 134 (1), 155 (3), 199 (1), 343 ($M^+$, 100). *Anal*. Calcd. for $C_{17}H_{11}ClF\ N_3S$ (343.81): C, 59.39; H, 3.22; N, 12.22. Found: C, 59.40; H, 3.22; N, 12.23.

***3-(4-Chlorophenyl)-7-tolyl-imidazo[2,1-b][2H-1,3,4]thiadiazine (2e).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.13 g (10 mmoles) of 4-methylphenacyl bromide. Yield: 3.07 g (73%), yellow prisms (EtOH), mp 185 °C; ir (KBr, $cm^{-1}$): 3029 (m), 3983 (m), 2915 (m)2817 (m), 2694 (m), 2616 (m), 1591 (m), 1515 (s), 1493 (m), 1407 (m), 1348 (m), 1094 (m), 819 (s); $^1H$ nmr (DMSO-$d_6$, 300 MHz): δ = 2.32 (s, 3H,Mc), 4.43 (s, 2H, 2-$CH_2$), 7.21–8.27 (m, 9H, ArH and H-Hetar); ms (EI, 70 eV): *m/z* (%) = 29 (10), 43 (13), 91 (50), 120 (32), 147 (100), 194 (28), 210 (3), 300 (4), 340 ($M^+$, 2). *Anal*. Calcd. for $C_{18}H_{15}BrClN_3S$ (420.75): C, 51.38; H, 3.59; N, 9.99. Found: C, 51.48; H, 3.58; N, 9.97. *Free base*: Yield: 2.41 g (71%), yellow needles (EtOH), mp 195 °C; ir (KBr, $cm^{-1}$): 1594 (m), 1494 (m), 1464 (s), 1405 (s), 1364 (m), 1288 (m), 1168 (m), 1131 (m), 1094 (m), 1011 (m), 847 (m), 824 (s), 755 (s), 512 (m); $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 1.25 (s,3H, Mc), 4.00 (s, 2H, 2-$CH_2$), 7.30–8.05 (m, 9H, ArH and H-Hetar); $^{13}C$ nmr ($CDCl_3$, 50 MHz): δ = 24.29 (3-C, Hetar), 115.64 (6-C, Hetar), 124.66 (ArH), 128.16 (ArH), 129.20 (ArH), 129.31 (ArH), 130.18 (Ar), 132.35 (Ar), 132.65 (Ar), 137.09 (Ar), 137.41 (7-C, Hetar), 140.28 (8a-C, Hetar), 148.81 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (15), 39 (2), 91 (74), 116 (13), 135 (14), 163 (8), 202 (17), 300 (5), 339 ($M^+$, 100). *Anal*. Calcd. for $C_{18}H_{14}ClN_3S$ (339.84): C, 63.62; H, 4.15; N, 12.36. Found: C, 63.62; H, 4.1; 5 N, 12.37.

***3-(4-Chlorophenyl)-7-(4-methoxyphenyl)-imidazo[2,1-b][2H-1.3.4]thiadiazine (2f).*** *Free base*: Starting from 2.26 g (10 mmoles) of **1a** and 2.29 g (10 mmoles) of 4-methoxyphenacyl bromide. Yield: 2.49 g (70%), yellow prisms (EtOH), mp 198 °C; ir (KBr, $cm^{-1}$): 3438 (m), 1613 (m), 1592 (m), 1564 (m), 1498 (m), 1459 (m), 1412 (m), 1365 (m), 1245 (m), 1175 (m), 1093 (m), 1026 (m), 1015 (m), 836 (m); $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.89 (s, 3H, Mc), 3.98 (s, 2H, 2-$CH_2$) 6.92–8.04 (m, 9H, ArH and H-Hetar); $^{13}C$ nmr ($CDCl_3$, 50 MHz): δ = 24.31 (2-C, Hetar), 55.27 (OMe), 114.04 (6-C, Hetar), 114.04 (6-C, Hetar), 125.82 (ArH), 126.05 (ArH), 128.15 (ArH), 129.22 (ArH), 132.67 (Ar), 137.41 (Ar), 140.13 (7-C, Hetar), 148.67 (8a-C, Hetar), 159.03 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (33), 44 (14), 91 (100), 101 (3), 135 (26), 163 (16), 209 (1), 300 (8), 355 ($M^+$, 45). *Anal.* Calcd. for $C_{18}H_{14}Cl\ N_3OS$ (355,84): C, 60.75; H, 3.97; N, 11.81. Found: C, 60.75; H, 3.97; N, 11.82.

***3-(4-Chlorophenyl)-7-(4-nitrophenyl)-imidazo[2,1-b][2H-1,3,4] thiadiazine (2g).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.44 g (10 mmoles) of 4-nitrophenacyl bromide. Yield: 3.25 g (72%), yellow prisms (EtOH), mp 257 °C; ir (KBr, $cm^{-1}$): 3434 (m), 1599 (s), 1556 (m), 1511 (s), 1464 (m), 1340 (s), 1286 (m), 1172 (m), 1110 (m), 1091 (m), 856 (m), 745 (m) $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.65 (s, 2H, 2-$CH_2$), 7.19–8.37 (m, 9H, ArH and H-Hetar), ms (EI, 70 eV): *m/z* (%) = 28 (16), 51 (5), 76 (15), 101 (22), 137 (24), 159 (5), 187 (13), 233 (30), 335 (3), 340 (4), 370 ($M^+$, 100). *Anal*. Calcd. for $C_{17}H_{12}BrClN_4O_2S$ (451.73): C, 45.20; H, 2.68; N, 12.40. Found: C, 45.19; H, 2.67; N, 12.40. *Free base*: Yield: 2.63 g (71%), yellow prisms (EtOH), mp 253 ° C; ir (KBr, $cm^{-1}$): 3431 (m), 1599 (s), 1511 (m), 1464 (m), 1410 (m), 1374 (m), 1339 (s), 1285 (m), 1172 (m), 1110 (m), 1092 (m), 856 (m), 744 (m); $^1H$ nmr (DMSO-$d_6$, 300 MHz): δ = 4.44 (s, 2H, 2-$CH_2$), 7.64−8.58 (m, 9H, ArH and H-Hetar); $^{13}C$ nmr ($CDCl_3$, 50 MHz): δ = 24.29 (2-C, Hetar), 118.35 (6-C, Hetar), 124.23 (ArH), 125.01 (ArH), 128.23 (ArH), 129.39 (ArH), 137.5 (Ar), 134.2 (Ar), 137.98 (7-C, Hetar), 146.5 (8a-C, Hetar), 150.14 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (49), 45 (15), 81 (32), 137 (37), 149 (10), 233 (17), 370 ($M^+$, 100). *Anal*. Calcd. for $C_{17}H_{11}ClN_4O_2S$ (370.81): C, 55.06; H, 2.99; N, 15.11. Found: C, 55.05; H, 2.99; N, 15.10.

***3-(4-Chlorophenyl)-6,7-diphenyl-imidazo[2,1-b][2H-1,3,4] thiadiazine (2h).*** *Hydrobromide*: Starting from 2.26 g (10 mmoles) of **1a** and 2.75 g (10 mmoles) of 2-bromo-1,2-diphenylethan-1-one. Yield: 3.43 g (71%), yellow needles (EtOH), mp 207 °C; ir (KBr, $cm^{-1}$): 1602 (m), 1504 (m), 1492 (m), 1484 (m), 1459 (m), 1442 (m), 1337 (m), 1090 (m), 1010 (m), 846 (m), 816 (m), 798 (m), 771 (m), 696 (s); $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.98 (s, 2H, 2-$CH_2$), 7.30–7.57 (m, 14H, ArH); ms (EI, 70 eV): *m/z* (%) = 58 (2), 103 (25), 137 (21), 161 (21), 178 (50), 231 (19), 263 (68), 401 ($M^+$, 100). *Anal*. Calcd. for $C_{23}H_{17}BrClN_3S$ (482.82): C, 57.21; H, 3.55; N, 8.70. Found: C, 57.18; H, 3.54; N, 8.69. *Free base*: Yield: 2.85 g (71%), yellow needles (EtOH), mp 171 °C; ir (KBr, $cm^{-1}$): 3428 (m), 1600 (m), 1487 (m), 1460 (m), 1442 (m), 1334 (m), 1307 (m), 1092 (m), 816 (m), 797 (m), 770 (m), 697 (m); $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 3.98 (s, 2H, 2-$CH_2$), 7.22–7.73 (m, 14H, ArH); $^{13}C$ nmr (DMSO-$d_6$, 50 MHz): δ = 22.70 (2-C, Hetar), 126.51 (ArH), 126.88 (ArH), 128.14 (ArH), 128.23 (ArH), 128.30 (ArH), 128.74 (ArH), 128.91 (ArH), 130.05 (6-C, Hetar), 130.18 (Ar), 133.62 (Ar), 133.72 (Ar), 135.45 (7-C, Hetar), 135.93 (8a-C, Hetar), 150.75 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (100), 58 (4), 103 (7), 137 (2), 178 (7), 263 (10), 401/403 ($M^+$, 53/17). *Anal.* Calcd. for $C_{23}H_{16}Cl\ N_3S$ (401,91): C, 68.73; H, 4.01; N, 10.46. Found: C, 68.75; H, 4.02; N, 10.47

***3-(4-Chlorophenyl)-6-methyl-7-phenyl-imidazo[2,1-b][2H-1,3,4]thiadiazine (2i).*** *Free base*: Starting from 2.26 g (10 mmoles) of **1a** and 2.13 g (10 mmoles) of α-bromopropiophenone. Yield: 2.31 g (68%), yellow prisms (EtOH), mp 158 °C; ir (KBr, $cm^{-1}$): 3431 (m), 3170 (m), 1625 (m), 1600 (m), 1492 (m), 1465 (m), 1445 (m), 1405 (m), 1331 (s), 1091 (m), 1010 (m), 844 (m), 814 (m), 769 (m), 697 (m), $^1H$ nmr ($CDCl_3$, 300 MHz): δ = 2.57 (2s, 3H, Me), 3.95 (s, 2H, 2-$CH_2$), 7.30–8.01 (m, 9H, ArH); $^{13}C$ nmr ($CDCl_3$, 50 MHz): δ = 9.89 (Me), 23.75 (2-C, Hetar), 125.37 (6-C, Hetar), 126.61 (ArH), 128.12 (ArH), 128.40 (ArH), 129.12 (ArH), 130.93 (Ar), 132.95 (Ar), 134.26 (Ar), 135.77 (7-C, Hetar), 137.20 (8a-C, Hetar), 148.00 (3-C, Hetar); ms (EI, 70 eV): *m/z* (%) = 28 (24), 61 (45), 91 (69), 102 (38), 137 (95), 163 (8), 201 (25), 225 (45), 300 (6), 339 ($M^+$, 100). *Anal*. Calcd. for $C_{18}H_{14}Cl\ N_3S$ (339.84): C, 63.62; H, 4.15; N, 12.36. Found: C, 63.63; H, 4.15; N, 12.37.

***2,3-Diphenyl-1, 2, 4-triazolo[3,4-b][2H-1,3,4]thiadiazine (3a).*** *Free base*: 1.16 g (10 mmoles) of 4-amino-5-sulfanyl-l,2,4-triazole **5a** and 2-bromo-1,2-diphenylethan-1-one (2.72 g, 10 mmoles) in 60 mL of ethanol was first stirred for 1 h at 20 °C. The mixture was refluxed subsequently for 4 h. After cooling, a diluted aqueous solution of ammonia was added until pH 8 was reached, and the precipitate was filtered. Yield: 2.48 g (85%), colorless lamella (ethanol). *Anal*. Calcd. for $C_{16}H_{12}N_4S$ (292.36): C, 65.73; H, 4.14; N, 19.16. Found: C, 65.81; H, 4.23; N, 19.08.

***3-(4-Fluorophenyl)-1,2,4-triazolo[3,4-b][2H-1,3,4]thiadiazine (3b).*** *Free base*: Starting from 1.16 g (10 mmoles) of 4-amino-5-sulfanyl-l,2,4-triazole **5a** and 2.17 g (10 mmoles) of 4-fluorophenacyl bromide as described for **3a**. Yield: 2.22 g (95%), colorless needles (EtOH), mp 203 °C; ir (KBr, $cm^{-1}$): 511 (m), 812 (s), 855 (s), 942 (m), 1173 (s), 1227 (s), 1286 (m), 1359 (m), 1415 (m), 1452 (s), 1480 (s), 1511 (s), 1600 (s), 3057 (m); $^1$H nmr (300 MHz, $CDCl_3$): $\delta = 4.02$ (s, 2H, 6-$CH_2$), 7.19–7.99 (m, 4H, ArH), 8.59 (s, 1H, 3H, Hetar); $^{13}$C nmr (50 MHz, DMSO-$d_6$): $\delta = 115.79$, 129.81, 130.03, 140.04, 142.96, 154.53, 161.65, 166.63; ms (EI, 70 eV): $m/z = 234$ ($M^+$, 100), 135 (49), 121 (42), 112 (33), 101 (25), 95 (22), 85 (14), 75 (13), 58 (12). *Anal*. Calcd. for $C_{10}H_7N_4S$ (234.25): C, 51.27; H, 3.01; N, 23.92. Found: C, 51.31; H, 3.21; N 23.81.

***3-(4-Fluorophenyl)-6-methyl)-1,2,4-triazolo[3,4-b][2H-1,3,4] thiadiazine (3c).*** *Free base*: Starting from 1.30 g (10 mmoles) of 4-amino-3-methyl-5-sulfanyl-l,2,4-triazole **5b** and from 2.17 g (10 mmoles) of 4-fluoro-phenacylbromide as described for **3a**. Yield: 2.16 g (87%), colorless rods (EtOH), mp 217 °C; ir (KBr, $cm^{-1}$): 846 (m), 1169 (m), 1308 (s), 1366 (s), 1469 (s), 1509 (s), 1600 (s), 3002 (s); $^1$H nmr (300 MHz, $CDCl_3$): $\delta = 2.59$ (s, 3H, Me), 3.95 (s, 2H, 6-$CH_2$), 7.19–7.94 (m, 4H, ArH); ms (EI, 70 eV): $m/z = 248$ ($M^+$, 100), 135 (47), 121 (83), 101 (58), 95 (42), 75 (42), 58 (86), 28 (47). *Anal*. Calcd. for $C_{11}H_9N_4SF$ (248.28): C, 53.21; H, 3.65; N 22.57. Found: C, 53.24; H, 3.81; N 22.67.

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