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## A FACILE SYNTHESIS OF 2-AMINOTHIAZOLO[5,4-*b*]PYRIDINES AND 2-AMINOBANZOXAZOLES VIA CYCLIZATION OF THIOUREAS

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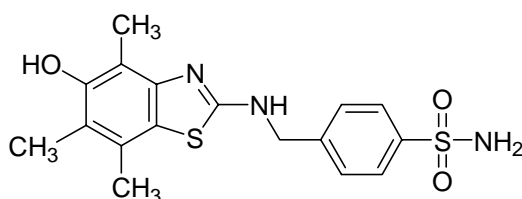
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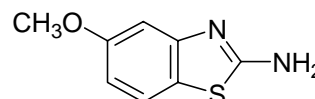
**Abstract** – 2-Aminothiazolo[5,4-*b*]pyridines and 2-aminobenzoxazoles have been synthesized from 2-hydroxy-3-thioureidopyridine and 2-hydroxy-3-thioureidobenzene respectively *via* acid catalyzed cyclization, which were prepared by the reaction of isothiocyanates with 2-hydroxy-3-aminopyridine or 2-aminophenol. The hydroxyl group of *N*-(2-hydroxy-5-phenyl)-*N'*-phenyl thiourea reacted as nucleophile to thioureido carbon to give 2-aminobenzoxazoles, whereas that of *N*-(2-hydroxypyridino)-*N'*-phenylthiourea was reacted as leaving group upon nucleophilic sulfur of thiourea group in the presence of trifluoroacetic acid or phosphoric acid.

### introduction

2-Aminobenzothiazoles are found in a variety of useful biologically active compounds such as antibacterial, antiviral, antimalarial, antitubercular, anticonvulsant and antitumoral activity.<sup>1-6</sup> For example, E6080, a 5-lipoxygenase inhibitor, inhibited leukotriene production for antihistaminic and antiallergic agent,<sup>2</sup> and riluzole showed anticonvulsant activity.<sup>4</sup>

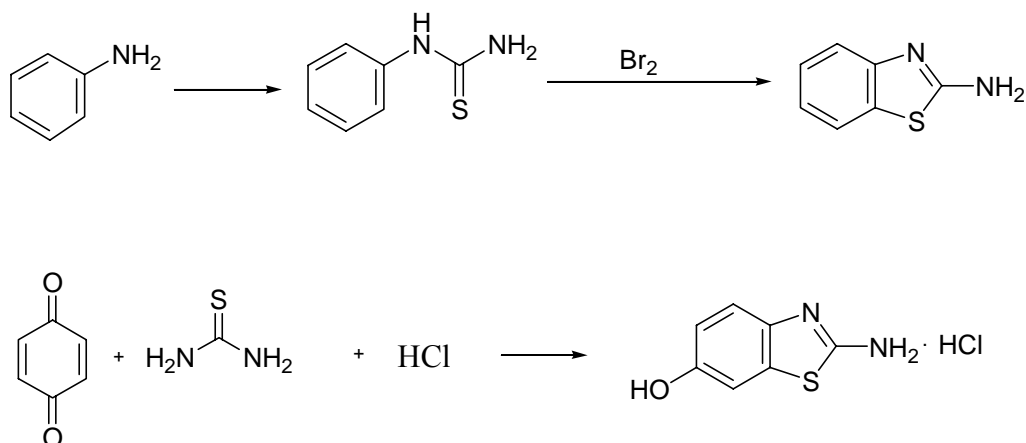


E6080

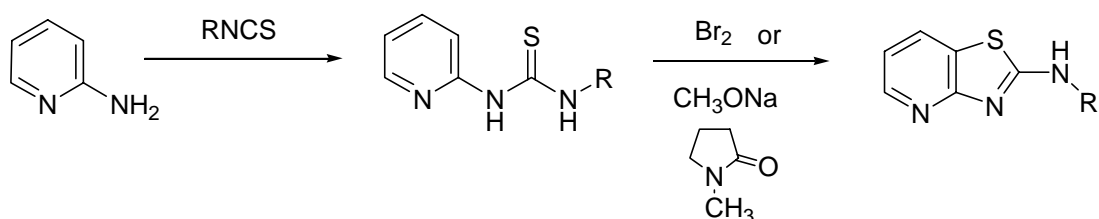


riluzole

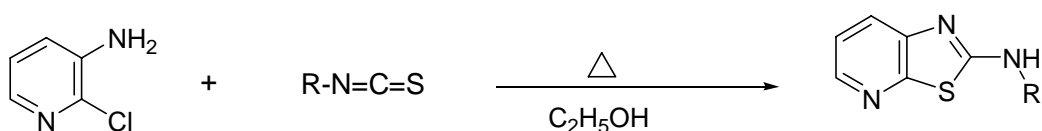
2-Aminobenzothiazoles were synthesized from phenylthiourea by oxidative ring closure with bromine.<sup>7</sup> The condensation of 1,4-benzoquinone with thiourea in the presence of concentrated hydrochloric acid gave 2-aminobenzthiazoles as well.<sup>8</sup>



Thiazolo[5,4-*b*]pyridines or thiazolo[4,5-*b*]pyridines are often considered as bioisosteres for benzothiazoles to increase the biological activity especially of interest in antiparasitic and pesticidal agents.<sup>9</sup> Various thiazolopyridines were prepared from 2-aminopyridines through oxidative cyclization of corresponding thiourea derivatives with bromine in acetic acid (Hugerschoff synthesis)<sup>9</sup> or with sodium methoxide and *N*-methylpyrrolidinone.<sup>10,11</sup> These methods required harsh conditions and were hard to be applied for solid phase synthesis of these series of compounds.

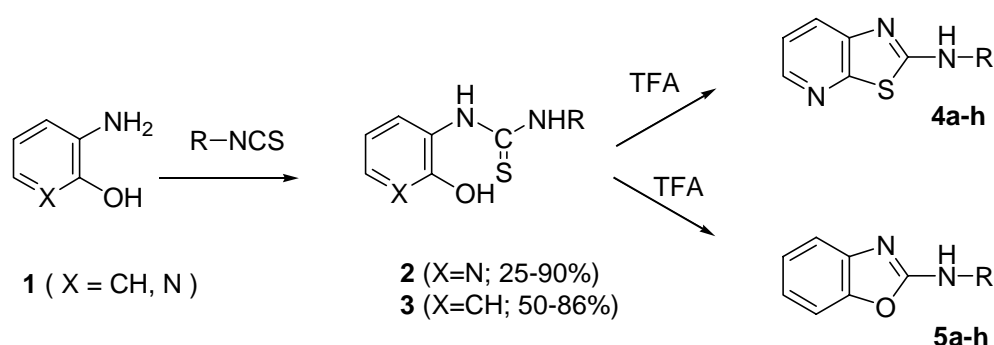


On the other hand, the refluxing 2-chloro-3-aminopyridine or 3-chloro-2-aminopyridine with isothiocyanates in dry ethanol avoided the oxidative cyclization condition to give aminothiazolopyridines.<sup>12</sup> Therefore we decided to apply the reaction condition to the reaction of 2-hydroxy-3-aminopyridine with arylisothiocyanates.



## RESULTS AND DISCUSSION

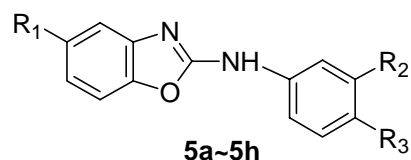
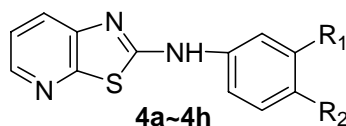
2-Hydroxy-3-aminopyridine was reacted with phenylisothiocyanate to give the corresponding thiourea (**2**) in 25-90% yields with various isothiocyanates, such as phenyl, 4-ethylphenyl, and 3,4-dichlorophenyl isothiocyanate. Also 2-hydroxyphenylthioureas (**3**) were prepared in 50-85% yields from 2-aminophenol with various thioisocyanates. Upon acid catalyzed cyclization with trifluoroacetic acid (**2**) gave 2-aminothiazolo[5,4-*b*]pyridines (**4a-h**). Here the difference in reactivity of hydroxyl group on benzene and pyridine ring was observed. Acid catalyzed ring closure of 2-hydroxyphenylthioureas (**3**) with trifluoroacetic acid gave benzoxazoles (**5a-h**) instead of benzothiazoles.



**Scheme 1.** Synthesis of 2-aminobenzoxazoles or 2-aminothiazolo[5,4-*b*]pyridines.

The acid catalyzed cyclization to the corresponding 2-substituted aminobenzoxazoles and 2-substituted aminothiazolo[5,4-*b*]pyridines was done in the reflux of trifluoroacetic acid in 20–90% yields. Other acids such as phosphoric, sulfuric, or hydrochloric acids, except nitric acid, gave similar results. The yields of the prepared compounds are given in Table 1. Compounds of low yield showed large amounts of unreacted starting thioureas remaining.

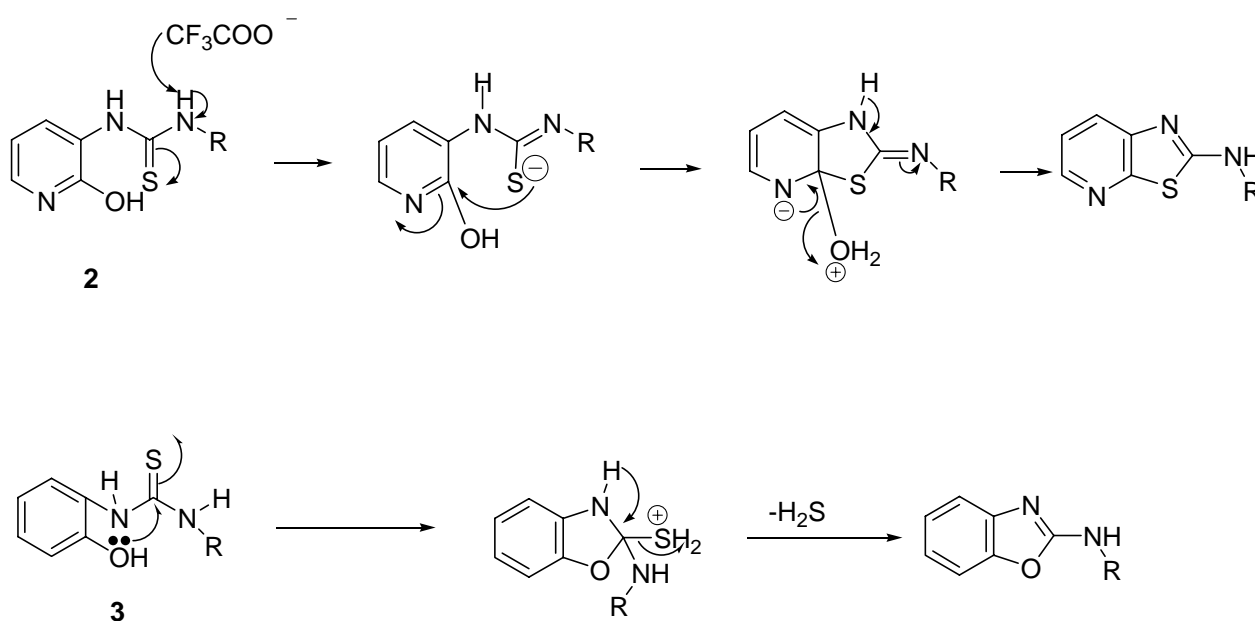
**Table 1.** The structure and yield of 2-aminothiazolo[5,4-*b*]pyridines and 2-aminobenzoxazoles.



compound	R <sub>1</sub>	R <sub>2</sub>	Yield (%)
<b>4a</b>	H	H	65
<b>4b</b>	H	CH <sub>2</sub> CH <sub>3</sub>	19
<b>4c</b>	H	OCH <sub>2</sub> CH <sub>3</sub>	32
<b>4d</b>	H	I	24
<b>4e</b>	H	CH(CH <sub>3</sub> ) <sub>2</sub>	32
<b>4f</b>	H	OCH <sub>3</sub>	25
<b>4g</b>	H	SCH <sub>3</sub>	38
<b>4h</b>	Br	H	28

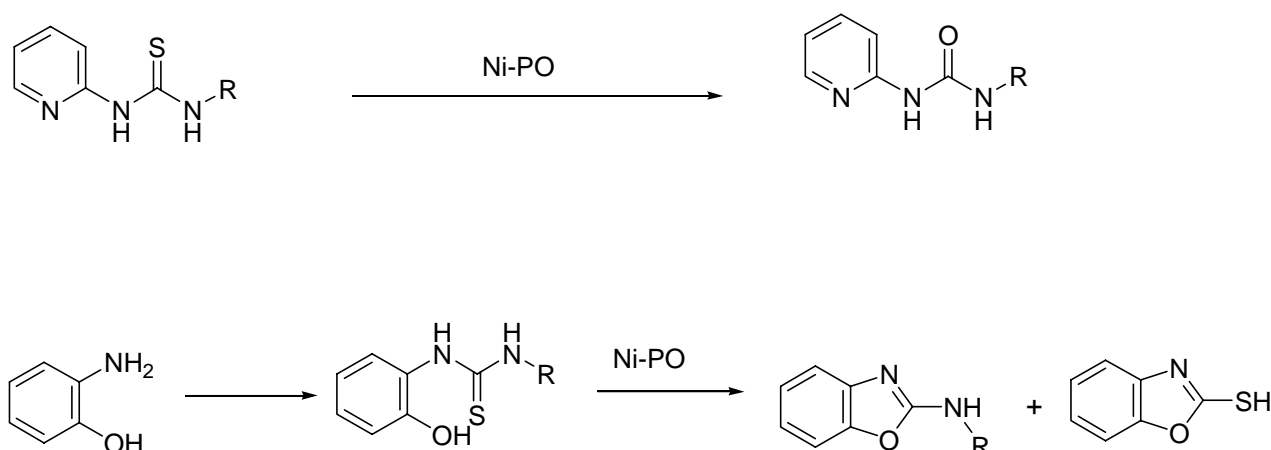
compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield (%)
<b>5a</b>	H	H	H	31
<b>5b</b>	H	H	CH <sub>2</sub> CH <sub>3</sub>	51
<b>5c</b>	H	Cl	Cl	90
<b>5d</b>	Cl	H	N=N-Ph	50
<b>5e</b>	Cl	H	H	41
<b>5f</b>	Cl	H	CH <sub>2</sub> CH <sub>3</sub>	27
<b>5g</b>	Cl	Cl	Cl	32
<b>5h</b>	OCH <sub>3</sub>	H	N=N-Ph	30

This selectivity might be rationalized that hydroxyl group of thioureidobenzenes (**2**) and thioureidopyridines (**3**) have different role during the cyclization. In case of thioureidobenzenes (**2**), the hydroxyl group reacts as nucleophiles on thiourea to give 2-aminobenzoxazoles. However in case of thioureidopyridines (**3**), the hydroxyl group is leaving group reacting with nucleophilic sulfur of thiourea.



**Scheme 2.** Proposed mechanism for thiourea cyclization.

It is known that 2-aminobenzoxazoles could be synthesized by Ni-PO oxidation or potassium superoxide oxidation of *o*-hydroxyphenylthiourea.<sup>13-15</sup> When compound (**5h**) was formed using potassium superoxide, the yield of benzoxazole formation was higher than trifluoroacetic acid catalyzed cyclization. However, this reagent didn't work on pyridine analogs and only ureas were formed. Attempts to cyclize ureas prepared from 2-hydroxy-3-aminopyridin or 2-aminophenol with isocyanate were not successful.



Our method for preparation of 2-aminothiazolo[5,4-*b*]pyridines and 2-aminobenzoxazole was simple and of mild condition. This method can be applied to prepare a combinatorial library of pyridinotiazoles, bioisostere of benzothiazoles, which contains multiple positions for facile derivatization.

## EXPERIMENTAL

### 5.1. Materials

All melting points were taken in Pyrex capillaries using electrothermal digital melting point apparatus (Büchi). <sup>1</sup>H-NMR spectra were recorded on a Varian Unity Innova 400 (9.4 T) spectrometer using trimethylsilane as an internal standard. MS spectra were obtained on a Tandem Mass spectrometer JMS-HX110/110A (Jeol). Elemental analysis was performed using Thermo Quest (CE Instruments) EA1110 elemental analyzer.

### 5.2. General procedure for the synthesis of thiourea and the following cyclization.

2-Hydroxy-3-aminopyridine or 2-aminophenol (0.92 mmol) and isothiocyanate (0.92 mmol) in methanol (10 mL) were stirred at rt for 1 day. The precipitate was collected by filtration and washed with ether (7 mL) to give the corresponding thiourea. The mixture of thiourea (0.41 mmol) and trifluoroacetic acid (5 mL) was heated under reflux for 1 day, then cooled to rt. The trifluoroacetic acid was removed by rotary evaporation, and the residue was purified by column chromatography (ethyl acetate: hexane = 3:1) to give the products.

#### 5.2.1. *N*-(2-Hydroxypyridino)-*N'*-phenylthiourea (2a).

Yellow powder, Yield: 44 mg (28%), mp 243-244 (MeOH), <sup>1</sup>H-NMR (Acetone-*d*<sub>6</sub>) δ 6.26(t, *J*=12.0 Hz, 1H) 7.12 (d, *J*=8.0 Hz, 1H), 7.36 (t, *J*=12.0 Hz, 2H), 7.17 (t, *J*=8.0 Hz, 1H), 7.54 (d, *J*=8.0 Hz, 2H), 8.95 (d, *J*=8.0 Hz, 1H), 9.49 (s, NH), 10.62 (s, NH), 12.02 (s, OH). FABMS *m/z* 246 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>OS: C, 58.76; H, 4.52; N, 17.13; S, 13.07. Found: C, 58.61; H, 4.52; N, 17.07; S, 12.62.

#### 5.2.2. *N*-(2-Hydroxypyridino)-*N'*-(4-ethylphenyl)thiourea (2b).

Yellow powder, Yield: 105 mg (60%), mp 177-179 (MeOH), <sup>1</sup>H-NMR (Acetone-*d*<sub>6</sub>) δ 1.20-1.16 (m, 3H) 2.63-2.52 (m, 2H), 6.24 (t, *J*=12.0 Hz, 1H), 7.10 (s, 1H), 7.39 (s, 2H), 7.19 (d, *J*=8.0 Hz, 2H), 8.93 (s, 1H), 9.40 (s, NH, 1H), 10.52 (s, NH, 1H), 11.99 (s, OH, 1H). FABMS *m/z* 274 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 61.51; H, 5.53; N, 15.37; S, 11.73. Found: C, 61.35; H, 5.58; N, 15.03; S, 11.67.

**5.2.3. *N*-(2-Hydroxypyridino)-*N'*-(4-ethoxyphenyl)thiourea (2c)**

White powder, Yield: 72 mg (57%), mp 190-191 (MeOH), <sup>1</sup>H-NMR (Acetone-d<sub>6</sub>) δ 1.25 (t, *J*=7.2 Hz, 3H), 3.97 (q, *J*=7.2 Hz, 2H), 6.13 (t, *J*=6.8 Hz, 1H), 6.84-6.86 (m, 2H), 7.01 (dd, *J*=2.0 and 6.8 Hz, 1H), 7.24-7.26 (m, 2H), 7.05 (dd, *J*=2.0 and 6.8 Hz, 1H). FABMS *m/z* 290 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 58.11; H, 5.23; N, 14.52; S, 11.08. Found: C, 58.57; H, 5.32; N, 14.14; S, 11.40.

**5.2.4. *N*-(2-Hydroxypyridino)-*N'*-(4-iodolphenyl)thiourea (2d)**

White powder, Yield: 42 mg (89%), mp 201-202 (MeOH), <sup>1</sup>H-NMR (Acetone-d<sub>6</sub>) δ 6.25 (t, *J*=6.8 Hz, 1H), 7.13 (d, *J*=6.8 Hz, 1H), 7.41-7.42 (m, 2H), 7.67-7.69 (m, 2H), 8.91 (d, *J*=6.8 Hz, 1H), 9.54 (br s, NH, 1H), 10.68 (br s, NH, 1H), 12.03 (br s, OH, 1H). FABMS *m/z* 371 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>OIS: C, 38.83; H, 2.72; N, 11.32; S, 8.64. Found: C, 39.04; H, 2.72; N, 11.02; S, 8.49.

**5.2.5. *N*-(2-Hydroxypyridino)-*N'*-(4-isopropylphenyl)thiourea (2e)**

Dark yellow powder, Yield: 283 mg (55%), mp 163-165 (MeOH), <sup>1</sup>H-NMR (Acetone-d<sub>6</sub>) δ 1.25 (s, 6H), 2.89-2.97 (m, 1H), 6.30 (dd, *J*=6.8 and 7.6 Hz, 1H), 7.14 (dd, *J*=2.0 and 6.8 Hz, 1H), 7.27-7.31 (m, 2H), 7.44-7.46 (m, 2H), 9.18 (dd, *J*=2.0 and 7.6 Hz, 1H), 9.26 (br s, NH, 1H), 9.68 (br s, NH, 1H). FABMS *m/z* 288 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>OS: C, 62.69; H, 5.96; N, 14.62; S, 11.16. Found: C, 62.43; H, 6.15; N, 14.52; S, 11.67.

**5.2.6. *N*-(2-Hydroxypyridino)-*N'*-(4-methoxyphenyl)thiourea (2f)**

White powder, Yield: 58 mg (29%), mp 189-190 (MeOH), <sup>1</sup>H-NMR (Acetone-d<sub>6</sub>) δ 3.83 (s, 3H), 6.27 (dd, *J*=6.8 and 7.3 Hz, 1H), 6.98-7.00 (m, 2H), 7.15 (dd, *J*=1.6 and 6.8 Hz, 1H), 7.37-7.40 (m, 2H), 9.09 (br s, NH), 9.18 (dd, *J*=1.6 and 7.8 Hz, 1H), 9.43 (br s, NH, 1H). FABMS *m/z* 275 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S: C, 56.71; H, 4.76; N, 15.26; S, 11.65. Found: C, 56.64; H, 4.70; N, 15.25; S, 11.42.

**5.2.7. *N*-(2-Hydroxypyridino)-*N'*-(4-(methoxythio) phenyl)thiourea (2g)**

White powder, Yield: 78 mg (37%), mp 187-188 (MeOH), <sup>1</sup>H-NMR (Acetone-d<sub>6</sub>) δ 2.51 (s, 3H), 6.27 (dd, *J*=6.8 and 7.6 Hz, 1H), 7.17 (dd, *J*=2.0 and 6.8 Hz, 1H), 7.22-7.24 (m, 2H), 7.31-7.34 (m, 2H), 8.76 (s, NH), 9.14 (dd, *J*=2.0 and 7.6 Hz, 1H), 9.19 (s, NH, 1H), 9.72 (s, OH, 1H). FABMS *m/z* 291 [*M*<sup>+</sup>+1], Anal. Calcd for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>OS<sub>2</sub>: C, 53.58; H, 4.50; N, 14.42; S, 22.01. Found: C, 53.43; H, 4.49; N, 14.20; S, 21.57.

**5.2.8. *N*-(2-Hydroxypyridino)-*N'*-(3-bromophenyl)thiourea (2h)**

White powder, Yield: 162 mg (38%), mp 146-147 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.32 (dd,  $J=6.8$  and 7.6 Hz, 1H), 7.22 (dd,  $J=2.0$  and 6.8 Hz, 1H), 7.31-7.38 (m, 2H), 7.56-7.58 (m, 1H), 7.99 (s, 1H), 9.09 (br s, NH, 1H), 10.06 (br s, NH, 1H), 11.02 (br s, OH, 1H). FABMS  $m/z$  324 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{12}\text{H}_{10}\text{N}_3\text{OBrS}$ : C, 44.46; H 3.11; N, 12.96; S, 9.89. Found: C, 44.38; H, 3.46; N, 12.73; S, 9.99.

**5.2.9. *N*-(2-Hydroxyphenyl)-*N'*-phenylthiourea (3a)**

Yellow powder, Yield: 160 mg (71 %), mp 151-152 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.87 (t,  $J=12.0$  Hz, 1H) 6.96 (d,  $J=8.0$  Hz, 1H), 7.08 (t,  $J=12.0$  Hz, 1H), 7.22 (t,  $J=12.0$  Hz, 1H), 7.41 (s, 2H), 7.55 (d,  $J=8.0$  Hz, 2H), 7.80 (s, 1H), 8.54 (s, OH, 1H), 8.70 (s, NH, 1H), 9.19 (s, NH, 1H). FABMS  $m/z$  245 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_2\text{OS}$ : C, 63.91; H, 4.95; N, 11.47; S, 13.12. Found: C, 63.53; H, 5.03; N, 11.54; S, 12.92.

**5.2.10. *N*-(2-Hydroxyphenyl)-*N'*-(4-ethylphenyl)thiourea (3b)**

White powder, Yield: 200 mg (80 %), mp 139-140 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.20 (t,  $J=8.0$  Hz, 3H), 2.60 (q,  $J=8.0$  Hz, 2H), 6.84 (t,  $J=12.0$  Hz, 1H), 6.92 (d,  $J=8.0$  Hz, 1H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.42-7.40 (d,  $J=8.0$  Hz, 2H), 7.78 (d,  $J=8.0$  Hz, 1H), 8.51 (s, OH, 1H), 9.12 (s, NH, 1H). FABMS  $m/z$  273 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{OS}$ : C, 66.15; H, 5.92; N, 10.29; S, 11.77. Found: C, 66.44; H, 5.94; N, 10.22; S, 11.92.

**5.2.11. *N*-(2-Hydroxyphenyl)-*N'*-(3,4-dichlorophenyl)thiourea (3c)**

Yellow powder, Yield: 242 mg (84 %), mp 208-209 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.87 (t,  $J=12.0$  Hz, 1H), 6.94 (d,  $J=8.0$  Hz, 1H), 7.09 (t,  $J=12.0$  Hz, 1H), 7.51 (s, 2H), 7.65 (d,  $J=8.0$  Hz, 1H), 7.97 (s, 1H), 8.61 (s, NH, 1H), 8.82 (s, OH, 1H) 9.25 (s, NH, 1H). FABMS  $m/z$  313 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{OCl}_2\text{S}$ : C, 49.85; H, 3.22; N, 8.94; S, 10.24. Found: C, 50.29; H, 3.19; N, 8.87; S, 9.97.

**5.2.12. *N*-(2-Hydroxy-5-chlorophenyl)-*N'*-(4-phenylazophenyl)thiourea (3d)**

Brown powder, Yield: 170 mg (63 %), mp 214-216 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.96 (d,  $J=8.0$  Hz, 2H) 7.06 (d,  $J=8.0$  Hz, 1H), 7.59-7.52 (m, 4H), 7.95-7.85 (m, 5H), 8.11 (s, OH, 1H), 8.90 (s, NH, 1H), 9.70 (s, NH, 1H). FABMS  $m/z$  384 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_4\text{OClS}$ : C, 59.60; H, 3.95; N, 14.63; S, 8.37. Found: C, 60.05; H, 3.65; N, 14.95; S, 8.38.

**5.2.13. *N*-(2-Hydroxy-5-chlorophenyl)-*N'*-phenylthiourea (3e)**

Brown powder, Yield: 170 mg (63 %), mp 200-201 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.91 (d,  $J=8.0$  Hz, 1H), 7.03 (d,  $J=8.0$  Hz, 1H), 7.22 (t,  $J=12.0$  Hz, 1H), 7.38 (t,  $J=12.0$  Hz, 2H), 7.53 (d,  $J=8.0$  Hz, 2H), 8.19 (s, 1H), 8.71 (s, NH, 1H), 9.40 (s, NH, 1H). FABMS  $m/z$  279 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_2\text{OClS}$ : C, 56.01; H, 3.98; N, 10.05; S, 11.50. Found: C, 55.67; H, 3.21; N, 9.89; S, 11.13.

#### 5.2.14. *N*-(2-Hydroxy-5-chlorophenyl)-*N'*-(4-ethylphenyl)thiourea (3f).

Brown powder, Yield: 110 mg (51 %), mp 169-171 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.18 (t,  $J=6.8$  Hz, 3H), 2.60 (q,  $J=6.8$  Hz, 2H), 6.90 (d,  $J=8.0$  Hz, 1H), 7.01 (d,  $J=8.0$  Hz, 1H), 7.24 (d,  $J=8.0$  Hz, 2H), 7.30 (s, 1H), 7.41 (d,  $J=8.0$  Hz, 2H), 8.21 (s, OH, 1H), 8.65 (s, NH, 1H), 9.31 (s, NH, 1H). FABMS  $m/z$  307 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{OClS}$ : C, 58.72; H, 4.93; N, 9.13; S, 10.45. Found: C, 58.95; H, 4.93; N, 9.13; S, 10.18.

#### 5.2.15. *N*-(2-Hydroxy-5-chlorophenyl)-*N'*-(3,4-dichlorophenyl)thiourea (3g)

Brown powder, Yield: 210 mg (87 %), mp 241-243 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.94 (d,  $J=8.0$  Hz, 1H) 7.07 (d,  $J=8.0$  Hz, 1H), 7.30 (s, 1H), 7.42 (d,  $J=8.0$  Hz, 1H), 7.54 (s, 1H), 8.00 (d,  $J=8.0$  Hz, 1H). FABMS  $m/z$  347 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_9\text{N}_2\text{OCl}_3\text{S}$ : C, 44.91; H, 2.61; N, 8.06; S, 9.22. Found: C, 45.10; H, 2.36; N, 8.05; S, 9.37.

#### 5.2.16. *N*-(2-Hydroxy-5-methoxyphenyl)-*N'*-(4-phenylazophenyl)thiourea (3h)

Yellow powder, Yield: 137 mg (51%), mp 207-208 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  3.74 (s, 3H), 6.68 (dd,  $J=3.2$  and 8.8 Hz, 1H), 6.88 (d,  $J=8.8$  Hz, 1H), 7.53-7.06 (m, 4H), 7.87-7.96 (m, 6H). Anal. Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_4\text{O}_2\text{S}$ : C, 63.47; H, 4.79; N, 14.80; S, 8.47. Found: C, 63.84; H, 4.82; N, 14.95; S, 8.73.

#### 5.2.17. 2-Phenylaminopyridinوثiazole (4a)

White powder, Yield: 24 mg (65%), mp 162-164 (MeOH),  $^1\text{H-NMR}$  (DMSO- $d_6$ )  $\delta$  7.07 (t,  $J=12.0$  Hz, 1H), 7.31 (s, 1H), 7.33-7.32 (s, 1H), 7.38 (t,  $J=12.0$  Hz, 1H), 7.86-7.83 (m, 3H), 8.23 (s, 1H), 9.65 (s, NH, 1H). FABMS  $m/z$  228 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{12}\text{H}_9\text{N}_3\text{S}$ : C, 63.41; H, 3.99; N, 18.49; S, 14.11. Found: C, 63.18; H, 3.73; N, 18.67; S, 13.98.

#### 5.2.18. 2-(4-Ethylphenyl)aminopyridinوثiazole (4b).

White powder, Yield: 16 mg (19%), mp 128-130 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.21-1.18 (m, 3H), 2.61 (d,  $J=8.0$  Hz, 2H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.31 (m, 1H), 7.73 (d,  $J=8.0$  Hz, 2H), 7.82 (d,  $J=8.0$  Hz, 1H), 8.21-8.20 (s, 1H), 9.58 (s, NH, 1H). FABMS  $m/z$  256 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{S}$ :



C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found; C, 65.48; H, 4.99; N, 16.43; S, 12.83.

#### 5.2.19. 2-(4-Ethoxyphenyl)aminopyridinethiazole (4c)

Brown powder, Yield: 30 mg (32%), mp 138-139 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.37 (t,  $J=6.8$  Hz, 3H), 4.05 (q,  $J=6.8$  Hz, 2H), 6.94-6.97 (m, 2H), 7.31 (dd,  $J=8.0$  and 4.8 Hz, 1H), 7.70-7.73 (m, 2H), 7.79 (dd,  $J=8.0$  and 1.6 Hz, 1H), 8.20 (dd,  $J=4.8$  and 1.6 Hz, 1H). HR-MS (FAB): calcd for  $\text{C}_{14}\text{H}_{14}\text{N}_3\text{OS}$  [ $\text{M}^++1$ ]: 272.0862; found 272.0858, Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{OS}$ : C, 61.97; H, 4.83; N, 15.46; S, 11.82. Found; C, 61.94; H, 4.89; N, 15.22; S, 11.96.

#### 5.2.20. 2-(4-Iodophenyl)aminopyridinethiazole (4d).

Pale brown powder, Yield: 23 mg (24%), mp 218-211 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  7.33-7.41 (m, 2H), 7.74-7.71 (m, 2H), 7.86 (dd,  $J=8.0$  and 4.4 Hz, 1H), 7.89 (dd,  $J=8.0$  and 1.6 Hz, 1H), 8.27 (dd,  $J=4.4$  and 1.6 Hz, 1H). HR-MS (FAB): calcd for  $\text{C}_{12}\text{H}_9\text{N}_3\text{IS}$  [ $\text{M}^++1$ ]: 353.9562; found 353.9564, Anal. Calcd for  $\text{C}_{12}\text{H}_8\text{N}_3\text{IS}$ : C, 40.81; H, 2.28; N, 11.90; S, 9.08. Found; C, 41.19; H, 2.47; N, 11.67; S, 9.11.

#### 5.2.21. 2-(4-Isopropylphenyl)aminopyridinethiazole (4e)

Brown powder, Yield: 29 mg (32%), mp 120-123 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.23 (s, 3H), 1.25 (s, 3H), 2.19-2.24 (m, 1H), 7.26-7.28 (m, 2H), 7.33 (dd,  $J=8.0$  and 4.8 Hz, 1H), 7.74-7.76 (m, 2H), 7.45 (dd,  $J=8.0$  and 1.6 Hz, 1H), 8.22 (dd,  $J=4.8$  and 1.6 Hz, 1H). HR-MS (FAB): calcd for  $\text{C}_{15}\text{H}_{16}\text{N}_3\text{S}$  [ $\text{M}^++1$ ]: 270.1065; found 270.1068, Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{S}$ : C, 66.88; H, 5.61; N, 15.60; S 11.90. Found; C, 66.53; H, 5.87; N, 15.43; S, 12.11.

#### 5.2.22. 2-(4-Methoxyphenyl)aminopyridinethiazole (4f)

Pale brown powder, Yield: 11 mg (25%), mp 154-157 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  3.81 (s, 3H), 6.69-6.98 (m, 2H), 7.31 (dd,  $J=8.0$  and 4.8 Hz, 1H), 7.72-7.74 (m, 2H), 7.79 (dd,  $J=8.0$  and 1.2 Hz, 1H), 8.20 (dd,  $J=4.8$  and 1.2 Hz, 1H). HR-MS (FAB): calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_3\text{O}$  [ $\text{M}^++1$ ]: 258.0702; found 258.0701, Anal. Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{OS}$ : C, 60.88; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.90; H, 4.05; N, 16.18; S, 12.72.

#### 5.2.23. 2-(4-Methoxythio phenyl)aminopyridinethiazole (4g).

White powder, Yield: 26 mg (38%), mp 158-161 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  2.78 (s, 3H), 2.81 (s, 3H), 7.32-7.36 (m, 3H), 7.82-7.84 (m, 2H), 7.86 (dd,  $J=8.0$  and 1.6 Hz, 1H), 8.24 (dd,  $J=4.8$  and 1.6 Hz, 1H). HR-MS (FAB): calcd for  $\text{C}_{13}\text{H}_{12}\text{N}_3\text{S}_2$  [ $\text{M}^++1$ ]: 274.0473; found 274.0473, Anal. Calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_3\text{S}_2$ : C, 57.12; H, 4.06; N, 15.37; S, 23.46. Found: C, 56.96; H, 4.36; N, 15.26; S, 23.80.

**5.2.24. 2-(3-Bromophenyl)aminopyridinethiazole (4h).**

Brown powder, Yield: 26 mg (28%), mp 208-210 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  7.25 (m, 1H), 7.33 (t,  $J=8.0$  Hz, 1H), 7.38 (dd,  $J=8.0$  and 4.4 Hz, 1H), 7.75 (m, 1H), 7.94 (dd,  $J=8.0$  and 1.6 Hz, 1H), 8.28 (dd,  $J=4.4$  and 1.6 Hz, 1H), 8.31 (t,  $J=2.0$  Hz, 1H). HR-MS(FAB): calcd for  $\text{C}_{12}\text{H}_9\text{N}_3\text{BrS}$  [ $\text{M}^++1$ ]: 307.9680; found 305.9698, Anal. Calcd for  $\text{C}_{12}\text{H}_8\text{N}_3\text{BrS}$ : C, 47.07; H, 2.63; N, 13.72; S, 10.47. Found: C, 47.34; H, 2.66; N, 13.48; S, 9.97.

**5.2.25. 2-Phenylaminobenzoxazole (5a).**

White powder, Yield: 27 mg (31%), mp 180-182 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  7.04 (t,  $J=12.0$  Hz, 1H), 7.10 (t,  $J=12.0$  Hz, 1H), 7.21 (t,  $J=12.0$  Hz, 1H), 7.37 (t,  $J=12.0$  Hz, 3H), 7.42 (d,  $J=8.0$  Hz, 1H), 7.85 (d,  $J=8.0$  Hz, 2H), 9.47 (s, NH, 1H). FABMS  $m/z$  211 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}$ : C, 74.27; H, 4.79; N, 13.33. Found: C, 74.61; H, 4.72; N, 13.09.

**5.2.26. 2-(4-Ethylphenyl)aminobenzoxazole (5b)**

White powder, Yield: 110 mg (51%), mp 123-125 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  1.19 (t,  $J=6.8$  Hz, 3H), 2.60 (q,  $J=6.8$  Hz, 2H), 6.84 (t,  $J=12.0$  Hz, 1H), 6.92 (d,  $J=8.0$  Hz, 1H), 7.04 (t,  $J=12.0$  Hz, 1H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.42 (d,  $J=8.0$  Hz, 2H), 7.82 (d,  $J=8.0$  Hz, 1H). FABMS  $m/z$  239 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$ : C, 75.61; H, 5.92; N, 11.76. Found: C, 75.72; H, 5.88; N, 11.71.

**5.2.27. 2-(3,4-Dichlorophenyl)aminobenzoxazole (5c).**

White powder, Yield: 80 mg (90%), mp 181-183 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  6.86 (t,  $J=12.0$  Hz, 1H), 6.94 (d,  $J=8.0$  Hz, 1H), 7.09 (t,  $J=12.0$  Hz, 1H), 7.50 (d,  $J=8.0$  Hz, 1H), 7.54 (d,  $J=8.0$  Hz, 1H), 7.68 (t,  $J=12.0$  Hz, 1H), 8.01 (s, 1H). FABMS  $m/z$  279 [ $\text{M}^++1$ ], Anal. Calcd for  $\text{C}_{13}\text{H}_8\text{N}_2\text{OCl}_2$ : C, 55.94; H, 2.89; N, 10.04. Found: C, 55.61; H, 2.95; N, 9.76.

**5.2.28. 8-Chloro-2-[N-(4-phenylazophenyl)]aminobenzoxazole (5d).**

Orange powder, Yield: 110 mg (50%), mp 191-192 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  7.18 (d,  $J=8.0$  Hz, 1H), 7.44 (d,  $J=8.0$  Hz, 1H), 7.52 (d,  $J=8.0$  Hz, 2H), 7.57 (t,  $J=12.0$  Hz, 2H), 7.90 (d,  $J=8.0$  Hz, 2H), 8.06-8.00 (m, 4H), 10.05 (s, NH, 1H). FABMS  $m/z$  349 ( $\text{M}^++1$ ), Anal. Calcd for  $\text{C}_{19}\text{H}_{13}\text{N}_4\text{OCl}$ : C, 65.43; H, 3.76; N, 16.06. Found: C, 65.62; H, 3.95; N, 15.85.

**5.2.29. 8-Chloro-2-(N-phenyl)aminobenzoxazole (5e).**

Yellow powder, Yield: 70 mg (41%), mp: 183-186 (MeOH),  $^1\text{H-NMR}$  (Acetone- $d_6$ )  $\delta$  7.30 (s, 3H)

7.37 (d,  $J=8.0$  Hz, 1H), 7.40 (s, 1H), 7.42 (d,  $J=8.0$  Hz, 2H), 7.82 (d,  $J=8.0$  Hz, 1H), 9.6 (s, NH, 1H). FABMS  $m/z$  211 ( $M^+ + 1$ ), Anal. Calcd for  $C_{13}H_9N_2ClO$ : C, 63.81; H, 3.71; N, 11.45. Found: C, 64.26; H, 3.77; N, 11.52.

#### 5.2.30. 8-Chloro-2-[N-(4-ethylphenyl)]aminobenzoxazole (5f).

Yellow powder, Yield: 51 mg (27%), mp 196-198 (MeOH),  $^1H$ -NMR (Acetone- $d_6$ )  $\delta$  1.20 (t,  $J=6.8$  Hz, 3H), 2.60 (q,  $J=6.8$  Hz, 2H), 7.10 (d,  $J=8.0$  Hz, 1H), 7.22 (d,  $J=8.0$  Hz, 2H), 7.36 (d,  $J=8.0$  Hz, 1H), 7.72 (d,  $J=8.0$  Hz, 2H), 7.40 (s, 1H), 9.53 (s, NH, 1H). FABMS  $m/z$  273 ( $M^+ + 1$ ), Anal. Calcd for  $C_{15}H_{13}N_2ClO$ : C, 66.06; H, 4.80; N, 10.27. Found: C, 66.39; H, 4.78; N, 10.14.

#### 5.2.31. 8-Chloro-2-[N-(3,4-dichlorophenyl)]aminobenzoxazole (5g).

White powder, Yield: 70 mg (32%), mp 188-190 (MeOH),  $^1H$ -NMR (Acetone- $d_6$ )  $\delta$  7.16 (d,  $J=8.0$  Hz, 1H), 7.41 (d,  $J=8.0$  Hz, 1H), 7.49 (s, 1H), 7.55 (d,  $J=8.0$  Hz, 1H), 7.71 (d,  $J=8.0$  Hz, 1H), 8.22 (s, 1H), 9.97 (s, NH, 1H). FABMS  $m/z$  313 ( $M^+ + 1$ ), Anal. Calcd for  $C_{13}H_7N_2Cl_3O$ : C, 49.79; H, 2.25; N, 8.93. Found: C, 50.02; H, 2.48; N, 8.72.

#### 5.2.32. 8-Methoxy-2-[N-(4-phenylazophenyl)]aminobenzoxazole (5h).

Yellow powder, Yield: 17 mg (75%), mp 209-211 (MeOH),  $^1H$ -NMR (Acetone- $d_6$ )  $\delta$  3.85 (s, 3H), 6.75 (dd,  $J=8.8$  and 2.4 Hz, 1H), 7.09 (d,  $J=2.4$  Hz, 1H), 7.32 (d,  $J=8.8$  Hz, 1H), 7.50-7.54 (m, 1H), 7.56-7.60 (m, 2H), 7.91-7.93 (m, 2H), 8.01-8.03 (m, 2H), 8.06-8.09 (m, 2H). HR-MS (FAB): calcd for  $C_{20}H_{17}N_4O_2$  [ $M^+ + 1$ ]: 345.1352; found 345.1360, Anal. Calcd for  $C_{20}H_{16}N_4O_2$ : C, 69.76; H, 4.68; N, 16.27. Found: C, 69.48; H, 5.00; N, 16.30.

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