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SULFAMIC ACID-CATALYZED CONVERSION OF *o*-AMINOTHIOPHENOL AND AROMATIC ALDEHYDES TO 2-ARYLBENZOTHIAZOLES

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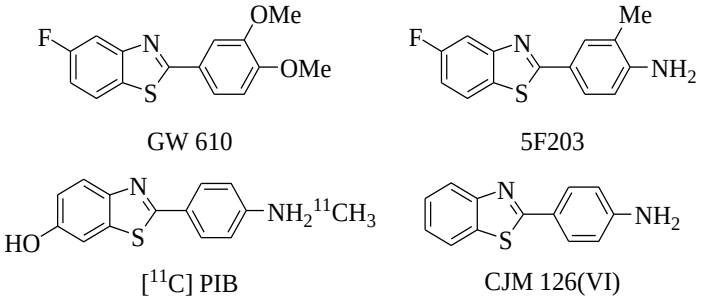
Abstract – Non-metallic, non-toxic, and cheap sulfamic acid was used as a catalyst for the synthesis of 2-arylbenzothiazole from *o*-aminothiophenol and aromatic aldehydes bearing electron-donating or electron-withdrawing groups. The sulfamic acid catalyst can be reused without any change in catalytic effect. The drug GW610 was successfully synthesized on a hundred-gram scale using this synthetic route.

2-Arylbenzothiazoles usually have antiviral properties. For example, the drugs GW610, 5F203, [^{11}C] PIB, and CJM126 (VI) have very good antitumor activities[1] (Scheme 1). 2-Arylbenzothiazoles have different properties owing to the different groups on their aryl rings. Therefore, it is of great significance to study the syntheses of various 2-arylbenzothiazoles for anti-virus screening.



Scheme 1. Representative bioactive 2-arylbenzothiazoles

There are two known ways to synthesize 2-arylbenzothiazoles. One approach involves direct coupling of benzothiazole with aromatic rings bearing various functional groups, catalyzed by a metal like nickel,[2] palladium,[3] ferric,[4] cerium,[5] or a combination of two metals.[6] These metal catalysts are costly and catalyst residues in the product pose environmental risks.

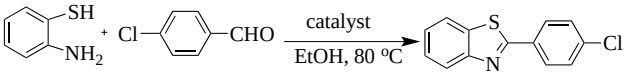
Another approach involves various aromatic ring-forming reactions with various functional groups to

form the thiazole moiety using *o*-aminothiophenol as one of the raw materials. Another raw material can be benzyl alcohol,[7] benzylamine,[8] benzonitrile[9] or aromatic aldehyde.[10] The reported catalysts in this protocol are mainly metallic Lewis acids. High-power microwaves have also been reportedly used in this approach.[10c]

In this study, 2-arylbenzothiazoles are synthesized by using non-metallic, cheap, odorless, and non-toxic sulfamic acid as a catalyst, which can be recycled and reused indefinitely. This method avoids environmental problems caused by catalyst residues, and drug GW610 can be successfully synthesized on a 100-g scale using this method (Scheme 1).

Various catalysts were screened using *p*-chlorobenzaldehyde and *o*-aminothiophenol as the substrates. The experimental results show that the best yield of 97.9% was obtained when 1% sulfamic acid was used as a catalyst in a 6-h reaction (Table 1, entry 2). Good yields were not obtained with hydrochloric acid, sulfuric acid, or *p*-toluenesulfonic acid (Table 1, entries 7-9) because *p*-toluenesulfonic acid is not as acidic as sulfamic acid, hydrochloric acid is evaporated due to the high temperature, and sulfuric acid is an oxidizing agent that easily oxidizes *o*-aminothiophenol.

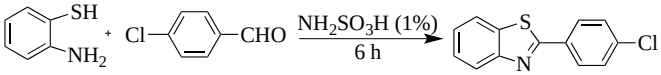
Table 1. Synthesis of 2-(chlorophenyl)-benzothiazoles by *o*-aminothiophenol with *p*-chlorobenzaldehyde using different catalyst[a,b]



entry	catalyst(mol%)	time(h)	yield(%)
1	NH_2SO_3H (0.05%)	6	91.2
2	NH_2SO_3H (1%)	6	97.9
3	NH_2SO_3H (1.5%)	6	97.5
4	NH_2SO_3H (1%)	4	94.1
5	NH_2SO_3H (1%)	5	96.0
6	*p*-$MeC_6H_4SO_3H$ (1%)	6	52.1
7	HCl (1%)	6	< 5
8	H_2SO_4 (1%)	6	< 5
9	NH_2SO_3H (1%)[c]	6	97.9
10	NH_2SO_3H (1%)[d]	6	98.1
11	NH_2SO_3H (1%)[e]	6	97.5

a) Reaction conditions: *o*-aminothiophenol (5.50 mmol), *p*-chlorobenzaldehyde (5.00 mmol), EtOH (20 mL). b) Isolated yields. c) First recovered catalyst. d) Second recovered catalyst. e) Third recovered catalyst.

Table 2. Synthesis of 2-(chlorophenyl)-benzothiazoles by *o*-aminothiophenol with *p*-chlorobenzaldehyde using different solvent[a,b]



entry	temp(°C)	solvent	yield(%)
1	80	EtOH	97.9
2	80	H_2O	N.R.[c]
3	100	H_2O	N.R.[c]
4	reflux	MeOH	88.3
5	80	1-Butanol	96.4
6	reflux	1-Butanol	93.2
7	80	DMF	67.4
8	reflux	DMF	45.2
9	80	DMSO	61.5
10	reflux	DMSO	32.1

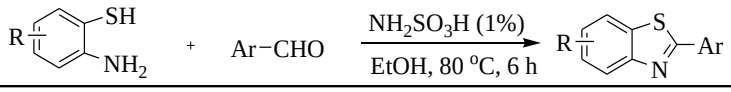
a) Reaction conditions: *o*-aminothiophenol (5.50 mmol), *p*-chlorobenzaldehyde (5.00 mmol), sulfamic acid (0.05 mmol), solvent (20 mL), 6 h. b) Isolated yields. c) By ^1H NMR.

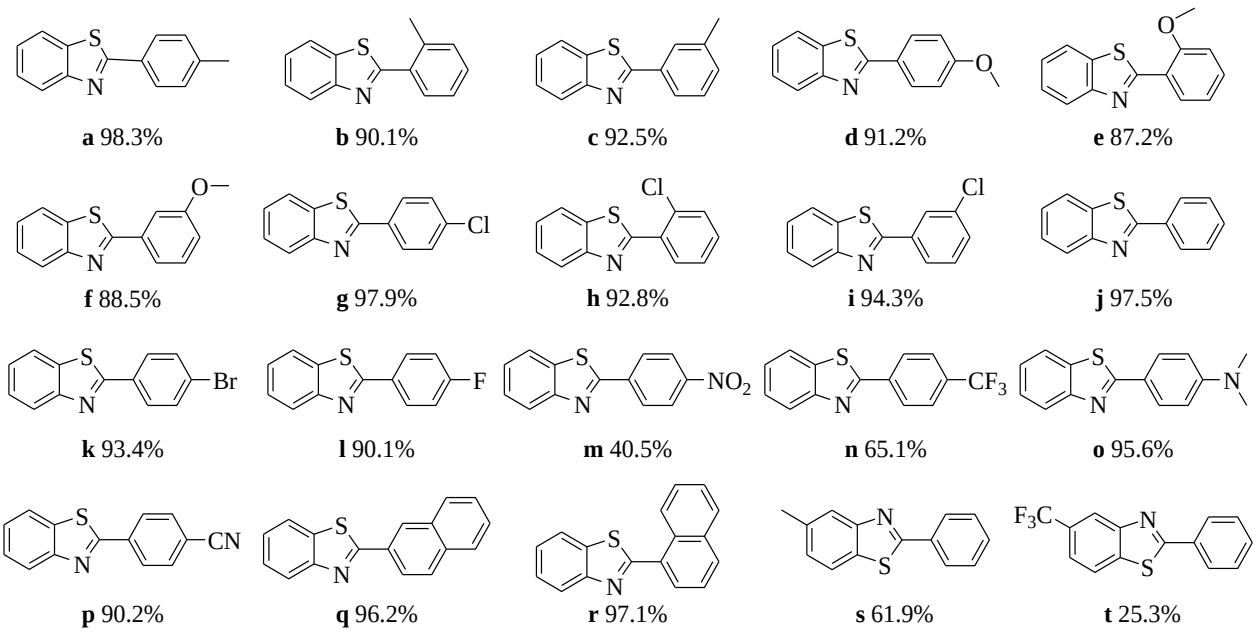
We performed solvent screening because water was generated during the reaction, and water removal was conducive to the reaction. This was confirmed by the inability of the reaction to proceed in water (Table 1,

entries 2, 3). As reaction solvents, we used organic solvents that are miscible with water. Ethanol was found to be the best reaction solvent. Lower-polarity solvents are beneficial for the reaction because imine which is the reaction intermediate is more stable in a less polar solvent.

Various aromatic aldehydes have been tested as the substrate in this protocol. It was found that sulfamic acid can effectively catalyze the reaction between *o*-aminothiophenol and the various aromatic aldehydes tested.

Table 3. Synthesis of 2-arylbenzothiazoles by *o*-aminothiophenol with aromatic aldehyde[a,b]

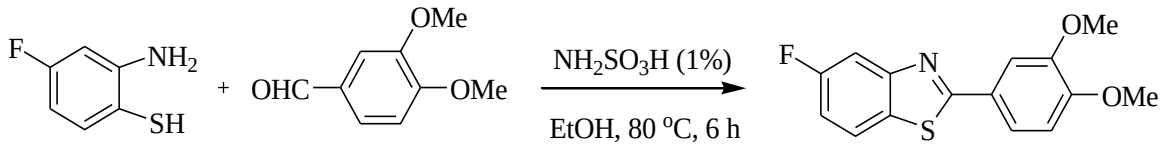




a) Reaction conditions: *o*-aminothiophenol (5.50 mmol), aromatic aldehyde (5.00 mmol), sulfamic acid (0.05 mmol), EtOH (20 mL), 80 °C, 6 h. b) Isolated yields.

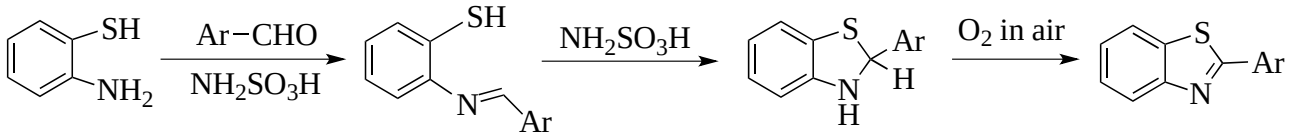
Various aromatic aldehydes, bearing electron-withdrawing groups (-NO_2, -CF_3, -CN) and electron-donating groups (-Me, -NMe_2) were tested in this study (Table 3). Lower yields were obtained for electron-withdrawing groups [-NO_2 (40.5%), -CF_3 (65.1%)] (Table 3, **m**, **n**). Substitution of the same group at different positions on the aromatic ring also gave different yields: *meta*-substitution gave less yield due to steric hindrance (Table3). Large conjugated groups, such as naphthalene groups, gave good yields. *o*-Aminothiophenol with a group [-Me (61.9%), -CF_3 (25.3%)] on the benzene ring afforded a low yield (Table 3, **s**, **t**).

The synthetic drug GW610 can be obtained using this method on a 100-g scale with a yield of 71.9% (Scheme 2). The low yield may be due to the steric hindrance of the methoxy group.



Scheme 2. Synthesis of drug GW610

After the reaction was completed, ethanol was replaced with ethyl acetate to remove sulfamic acid by precipitation. The precipitated sulfamic acid was washed twice with a small amount of ethyl acetate, and after drying, the recovered sulfamic acid was reused without any reduction in catalytic activity [Table 1, First recovered catalyst (97.9%); Second recovered catalyst (98.1%); Third recovered catalyst (97.5%)].



Scheme 3. Reaction mechanism

The possible reaction mechanism is shown in Scheme 3. The oxidation step employs oxygen molecules in the air as an oxidant.

In conclusion, sulfamic acid can efficiently catalyze the synthesis of 2-arylbenzothiazoles using *o*-aminothiophenol and aromatic aldehyde as raw materials. The synthetic method has a wide range of practicalities for the aromatic aldehyde raw material. The sulfamic acid can be recovered after use, with only a small amount of physical loss, and can be used repeatedly with no loss in catalytic activity. The synthetic drug GW610 can be obtained on a 100-g scale using this protocol.

General procedure for the synthesis of 2-arylbenzothiazole and catalyst recovery

o-Aminothiophenol (5.50 mmol), aromatic aldehyde (5.50 mmol), and sulfamic acid (0.05 mmol) were added to a 100-mL three-necked flask. EtOH (20 mL) was added to the mixture followed by refluxing at 80 °C for 6 h. The reaction solution was then vacuum distilled to remove EtOH. Then, 20 mL EtOAc acetate was added and dissolved by stirring and the insoluble solid was filtered off. This solid was washed twice with EtOAc (5.0 mL × 2), and the filter cake was dried under vacuum at 60 °C to obtain the recovered sulfamic acid. The EtOAc solutions were combined, and dried over magnesium sulfate. 2-Arylbenzothiazole was obtained by column chromatography (EtOAc: petroleum ether = 1:40).

100-g-scale synthesis of the drug GW610

2-Amino-4-fluorobenzenethiol (0.637 mol, 79.77 g),[11] 3,4-dimethoxybenzaldehyde (0.579 mol, 96.26 g), and sulfamic acid (5.79 mmol, 0.56 g) were added to a 2-L three-necked flask. EtOH (1200 mL) was

added to the mixture followed by refluxing at 80 °C for 6 h. The reaction solution was then vacuum distilled to remove EtOH. Then, 800 mL EtOAc was added and dissolved by stirring and the insoluble solid was filtered off. This solid was washed twice with EtOAc (100.0 mL × 2), and the filter cake was dried under vacuum at 60 °C to obtain the recovered sulfamic acid. The EtOAc solutions were combined, and dried over magnesium sulfate. GW610 (0.416 mol, 120.5 g) was obtained by column chromatography (EtOAc: petroleum ether = 1:40).

Catalyst recovery experiment

Catalyst recovery was studied by repeating the above-mentioned reaction using sulfamic acid recovered from the previous cycle (Table 1, entries 10-12).

2-*p*-Tolylbenzothiazole (a)[10c,12] White solid; 98.3% yield; mp 88-90 °C. IR (KBr): 3075, 2940, 1440, 1400, 752, 451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.0 Hz, 1 H), 8.00 (d, *J* = 7.9 Hz, 2 H), 7.90(d, *J* = 8.0 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.40 (t, *J* = 8.2 Hz, 1 H), 7.32(t, *J* = 8.5 Hz, 2 H), 2.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 155.2, 143.1, 136.3, 132.0, 131.1, 128.5, 127.2, 126.0, 124.1, 122.2, 22.5. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}NS$: 225.06; found: 225.07.

2-*o*-Tolylbenzothiazole (b)[10c,12] White solid; 90.1% yield; mp 63-65 °C. IR (KBr): 3050, 2945, 1455, 1412, 756, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* = 8.12 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.41-7.29 (m, 4H), 2.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.9, 154.1, 137.2, 134.6, 132.9, 130.9, 129.5, 129.0, 126.5, 125.3, 123.9, 122.4, 22.6. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}NS$: 225.06; found: 225.09.

2-*m*-Tolylbenzothiazole (c)[10c,12] White solid; 92.5% yield; mp 65-66 °C. IR (KBr): 3077, 2940, 1458, 1421, 758, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* = 8.09 (d, *J* = 8.1 Hz, 1H), 7.93 (s, 1H), 7.89-7.85 (m, 2H), 7.51-7.50 (t, *J* = 8.1 Hz, 1H), 7.39 (m, 2H), 7.31 (m, 1H), 2.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5, 154.1, 139.1, 135.2, 133.4, 131.5, 128.7, 127.8, 126.5, 125.3, 125.1, 123.4, 121.8, 21.5. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}NS$: 225.06; found: 225.08.

2-(4-Methoxyphenyl)benzothiazole (d)[12a,13] White solid; 91.2% yield; mp 120-122 °C. IR (KBr): 3061, 2982, 1603, 1489, 756, 735. ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.10-8.06 (m, 3H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 8.3 Hz, 1H), 7.03-6.99 (m, 2H), 3.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 167.5, 161.7, 155.1, 135.2, 130.1, 126.5, 126.4, 124.5, 122.6, 121.4, 114.3, 55.1. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}NOS$: 241.06; found: 241.05.

2-(2-Methoxyphenyl)benzothiazole (e)[10c] White solid; 87.2% yield; mp 109-110 °C. IR (KBr): 3058, 2845, 1628, 1523, 1365, 758, 728 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.93 (t, *J* = 8.0 Hz, 1 H), 7.44-7.49 (m, 2 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1 H), 6.96 (d, *J* = 7.9 Hz, 1 H), 4.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 158.1, 157.8, 140.0, 138.0, 127.2, 125.3, 123.8, 121.5, 119.2, 109.9, 106.1, 104.6, 59.9. HRMS

(EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}NOS$: 241.06; found: 241.07.

2-(3-Methoxyphenyl)benzothiazole (f)[10c,13] White solid; 88.5% yield; mp 83-85 °C. IR (KBr): 3062, 2855, 1629, 1521, 1345, 750, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.1, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.43 (m, *J* = 7.9, Hz, 2 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.9 Hz, 1 H), 6.97-6.95 (m, 2 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 3.56 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.1, 160.2, 154.3, 135.5, 135.1, 130.4, 126.5, 125.4, 123.6, 121.9, 120.6, 117.6, 112.4, 55.8. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}NOS$: 241.06; found: 241.04.

2-(4-Chlorophenyl)benzothiazole (g)[12a,14] Yellow solid; 97.9% yield; mp 116-118 °C. IR (KBr): 3058, 2930, 1570, 1448, 1326, 760, 755. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.02 (m, 3H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.53-7.46 (m, 3H), 7.40 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 158.1, 141.2, 136.1, 135.0, 129.8, 128.9, 128.2, 126.1, 121.0, 120.5. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8ClNS$: 245.01; found: 245.02.

2-(2-Chlorophenyl)benzothiazole (h)[12a,14] Yellow solid; 92.8% yield; mp 85-87 °C. IR (KBr): 3078, 1430, 1312, 1226, 762, 730. ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.21-8.19 (m, 1H), 8.15 (d, *J* = 8.0, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.56-7.54 (m, 2H), 7.46-7.41 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 152.7, 136.3, 132.9, 132.5, 131.9, 131.2, 130.9, 127.3, 126.5, 125.7, 123.6, 121.5. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8ClNS$: 245.01; found: 245.03.

2-(3-Chlorophenyl)benzothiazole (i)[12a,14] Yellow solid; 94.3% yield; mp 98-100 °C. IR (KBr): 3090, 1436, 1323, 1235, 756, 735. ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.09-8.05 (m, 2H), 7.90-7.86(m, 2H), 7.50-7.48 (m, 1H), 7.43-7.38 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.0, 136.0, 135.5, 135.2, 131.8, 131.2, 128.5, 127.6, 126.6, 125.9, 123.8, 121.9. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8ClNS$: 245.01; found: 245.01.

2-Phenylbenzothiazole (j)[12a,14] White solid (yield: 97.5%); mp 112-114 °C. IR (KBr): 3060, 2953, 1572, 1451, 1330, 758, 745. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.12-8.07 (m, 3H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.51-7.49 (m, 3H), 7.36(t, *J* = 8.0 Hz, 1H), 7.28(t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 155.0, 134.8, 133.9, 131.6, 129.8, 128.0, 127.0, 125.3, 123.6, 121.9. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_{10}NS$: 211.05; found: 211.09.

2-(4-Bromophenyl)benzothiazole (k)[12a,14] Yellow solid (yield: 93.4%); mp 130-132 °C. IR (KBr): 3066, 1438, 1227, 744, 732. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.09 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.55-7.52 (m, 3H), 7.45 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 154.9, 136.8, 134.9, 131.8, 128.5, 126.6, 125.1, 122.9, 122.5. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8BrNS$: 290.2; found: 290.1.

2-(4-Fluorophenyl)benzothiazole (l)[12a,14] White solid (yield: 90.1%); mp 102-104 °C. IR (KBr): 3056, 1482, 1229, 758, 727. ^1H NMR (400 MHz, $CDCl_3$) *δ* = 8.09-8.04 (m, 3H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.47

(m, 1H), 7.35 (m, 1H), 7.21-7.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 165.5, 163.1, 153.9, 134.8, 129.9, 129.6, 129.4, 129.3, 126.3, 125.1, 123.3, 121.8, 116.3, 116.1. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8FNS$: 229.3; found: 229.5.

2-(4-Nitrophenyl)benzothiazole (m)[12a,14] Yellow solid (yield: 40.5%); mp 130-132 °C. IR (KBr): 3045, 1446, 1230, 746, 733. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 154.3, 149.6, 139.1, 136.0, 127.1, 128.06, 127.1, 125.8, 122.6, 122.8. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{13}H_8N_2O_2S$: 256.3; found: 256.2.

2-[4-(Trifluoromethyl)phenyl]benzothiazole (n)[12a,15] White solid; 65.1% yield; mp 159-161 °C. IR (KBr): 3045, 1638, 1456, 1432, 1078, 985, 789 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.0 Hz, 2 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.75 (d, *J* = 8.0 Hz, 2 H), 7.52 (t, *J* = 8.0 Hz, 1 H), 7.45 (t, *J* = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 154.1, 136.8, 135.2, 132.5 (q, *J* = 32.6 Hz), 127.8, 126.7, 126.5(q, *J* = 3.7 Hz), 126.02, 123.6 (q, *J* = 273.4 Hz), 121.7, 119.8. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_8F_3NS$: 279.03; found: 279.01.

2-[4-(*N*,*N*-Dimethyl)phenyl]benzothiazole (o)[12a,14] White solid; 95.6% yield; mp 167-169 °C. IR (KBr): 3080, 1445, 1287, 1232, 749, 735. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99-7.95 (m, 3H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.43(t, *J* = 8.1 Hz, 1H), 7.30(t, *J* = 8.1 Hz, 1H), 6.76-6.74 (d, *J* = 8.8 Hz, 2H), 3.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 158.6, 156.1, 138.4, 131.1, 128.3, 126.1, 124.1, 120.9, 118.8, 111.0, 39.7. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{15}H_{11}N_2S$: 254.09; found: 254.10.

2-(4-Cyanophenyl)benzothiazole (p)[14] White solid; 90.2% yield; mp 168-170 °C. IR (KBr): 3079, 1445, 1258, 1239, 755, 732. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22−8.20 (m, 2 H), 8.14 (d, *J* = 8.1 Hz, 1 H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 2 H), 7.62−7.60 (m, 1 H), 7.53−7.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 154.8, 138.4, 136.5, 133.1, 128.1, 127.2, 126.3, 123.9, 121.9, 118.6, 114.3. HRMS (EI): *m*/*z* $[M]^+$calcd for $C_{14}H_{11}N_2S$: 236.3; found: 236.1.

2-(Naphthalen-3-yl)benzothiazole (q)[12a,14] White solid; 96.2% yield; mp 127-129 °C. IR (KBr): 3056, 1503, 1432, 1365, 1225, 756, 724. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.98-7.93 (m, 4H), 7.56-7.54 (m, 3H), 7.28 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 155.1, 135.2, 134.2, 132.0, 129.7, 128.5, 127.7, 126.8, 125.9, 123.2, 122.8, 122.2, 121.5, 120.6, 119.8, 112.1. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{11}NS$: 261.06; found: 261.06.

2-(Naphthalen-2-yl)benzothiazole (r)[10c] White solid; 97.1% yield; mp 125-127 °C. IR (KBr): 3066, 1538, 1445, 1348, 1200, 756, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.95 (d, *J* = 8.0 Hz, 1 H), 8.18 (d, *J* = 8.0 Hz, 1 H), 7.97 (t, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 7.66 (t, *J* = 8.0 Hz, 1 H),7.62-7.60 (m, 3 H), 7.43 (t, *J* = 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 152.9, 130.0, 132.9, 131.6, 130.3, 129.1, 127.6, 127.2, 126.6, 126.1, 125.8, 124.6, 124.1, 122.6, 122.3, 120.9. HRMS (EI): *m*/*z* $[M]^+$

calcd for $C_{17}H_{11}NS$: 261.06; found: 261.08.

5-Methyl-2-phenylbenzo[*d*]thiazole (s)[16] White solid; 61.9% yield; mp 128-129 °C. IR (KBr): 3066, 1538, 1445, 1348, 1200, 756, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.10-8.14 (m, 2 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.80 (s, 1 H), 7.71 (s, 1 H), 7.51-7.54 (m, 3 H), 7.31 (d, *J* = 8.0 Hz, 1 H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 152.3, 135.3, 132.8, 131.5, 129.1, 127.7, 127.9, 126.5, 125.9, 122.7, 122.4, 121.9, 21.6. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{13}NS$: 225.06; found: 225.05.

5-(Trifluoromethyl)-2-phenylbenzo[*d*]thiazole (t)[3a] Yellow solid; 25.3% yield; mp 134-136 °C. IR (KBr): 3097, 1356, 1108, 767, 680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 8.06-8.10 (m, 3 H), 8.01(d, *J* = 8 Hz, 1 H), 7.62 (d, *J* = 8 Hz, 1 H), 7.50-7.55 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 154.0, 138.5, 133.1, 130.9, 129.3, 128.9 (q, *J* = 32 Hz), 127.8, 122.2, 121.6, 121.5, 120.6 (q, *J* = 4 Hz). HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}F_3NS$: 280.04; found: 280.04.

GW610 (5-Fluoro-2-(3,4-dimethoxyphenyl)benzothiazole)[1a] Yellow solid; 71.9% yield; mp 102-104 °C. IR (KBr): 3065, 2988, 1596, 1448, 1226, 856 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.8 Hz, 1H), 7.88 (s, 1H), 7.63(m, 2H,), 7.35 (t, *J* = 9.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 160.4, 151.8, 150.6, 149.3, 135.7, 126.3, 123.4, 121.0, 114.6, 111.0, 109.6, 107.6, 56.0, 55.8. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{12}FNO_2S$: 289.3; found: 289.2.

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SUPPORTING INFORMATION

Supplementary (synthesis of 9-spirofluorenes, IR, ^1H and ^{13}C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26766/100/6.

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