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Original article

Heterocyclic bismuth carboxylates based on a diphenyl sulfone scaffold: Synthesis and antifungal activity against *Saccharomyces cerevisiae*

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ABSTRACT

A series of heterocyclic organobismuth(III) carboxylates **4** and **5** [$RCO_2Bi(C_6H_4$-2-$SO_2C_6H_4$-1′-)] derived from diphenyl sulfone was synthesized to determine the influence of the carboxylate ligand structure on the lipophilicity and antifungal activity against the yeast *Saccharomyces cerevisiae*. In contrast to the clear structure–activity relationship between the size of the inhibition zone and the value of ClogP for specific substitution on diphenyl sulfone scaffold **1** [$ClBi(5$-RC_6H_3-2-$SO_2C_6H_4$-1′-)], scaffolds **4** and **5** showed similar inhibition activities irrespective of the ClogP value. This suggests that these molecules function inside the yeast cell by separating into the cationic heterocyclic bismuth scaffold and the anionic carboxylate moiety, and that the bismuth scaffold plays an important role in the inhibition activity.

1. Introduction

The biological activity of bismuth compounds has attracted considerable interest [1–5]. Although inorganic bismuth complexes have a long history in medicinal chemistry, the biological activity of organobismuth compounds is not well understood [5] because their chemistry has only been established over the last two decades [6]. We have previously reported the synthesis and antifungal properties of organobismuth compounds against the yeast *Saccharomyces cerevisiae* [7a]. The Lewis acidy at the bismuth center was essential for the antifungal activity and compound **1a**, which was derived from diphenyl sulfone, showed the highest activity (Chart 1). The inhibition activity of **1** depended on substituent R and there was a clear structure–activity relationship between the size of the inhibition zone and the value of ClogP [7b]; the antifungal activity decreased as the lipophilicity increased. On the basis of this relationship, we enhanced the hydrophilicity of the diphenyl sulfone scaffold by introducing hydroxyl substituents (**2a**). However, the activity of **2a** was lower than that of **1a**. A preliminary experiment revealed that carboxylate **3a**, which was derived from **1a**, exhibited an activity comparable to that of **1a**, despite its high ClogP value. Therefore, the potency of antifungal organobismuth compounds could be interested by changing the structural and biological properties of the carboxylate ligand of **3a** rather than the ClogP value. Furthermore, the biological activity of **3a** may also elucidate the mechanism of the action when compared with that of **1a**.

Herein, we report the synthesis and antifungal activity of various bismuth carboxylates **4a**–**l** and **5a**–**d** against the yeast *S. cerevisiae*. The present work provides an important insight into the mechanism of action of these compounds.

2. Synthesis

The structures of **4a**–**l** and **5a**–**d** and their synthetic routes are shown in Scheme 1. The biological activity of compound can be enhanced by the efficient delivery to specific cells or organelles. For

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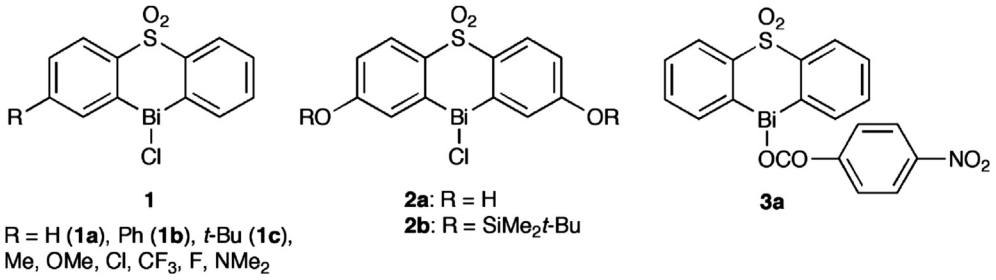
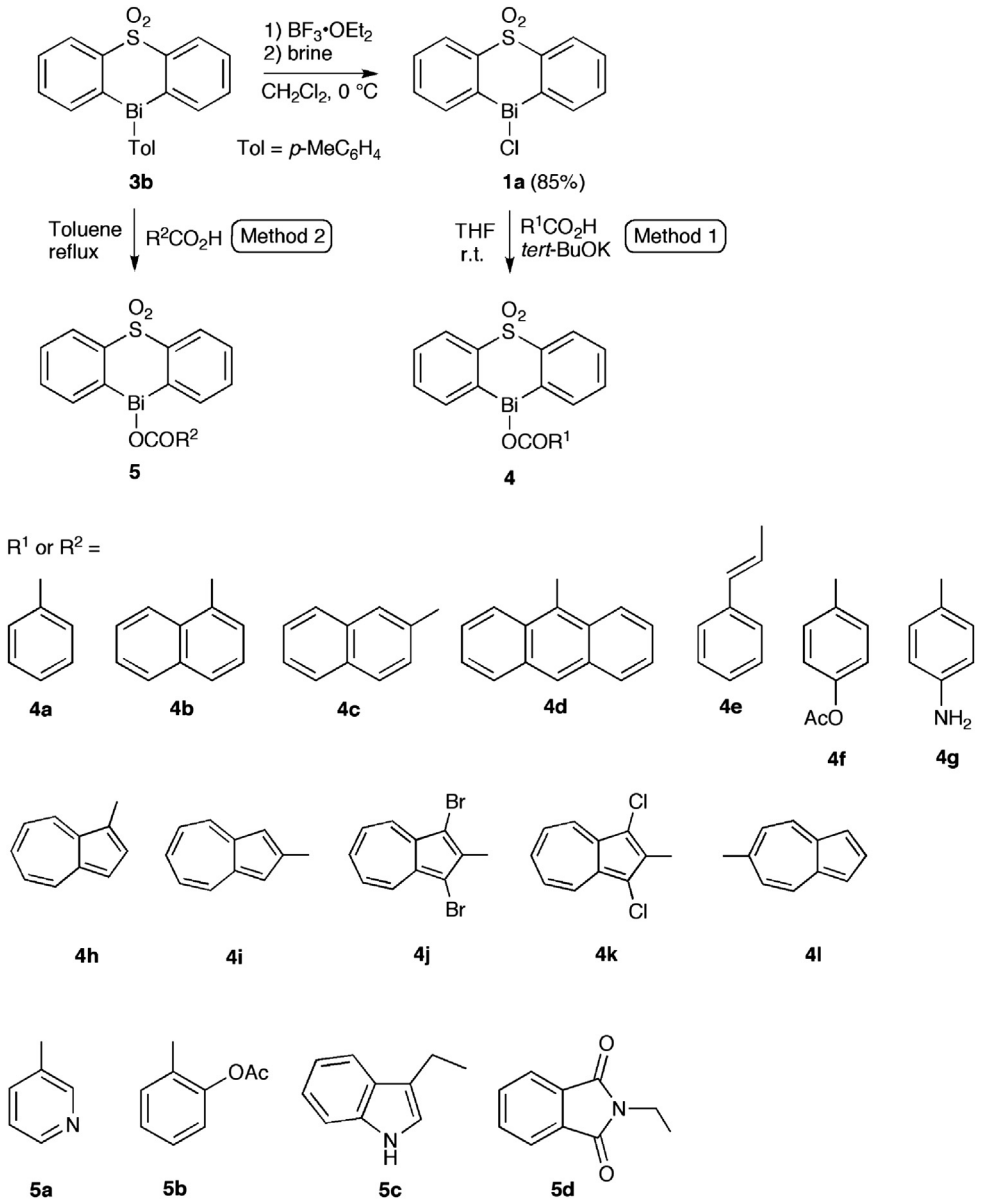


Chart 1. Structures of reported bismuth compounds.

example, a carbohydrate moiety has been introduced to antitumor platinum(II) complexes for cell recognition [8]. Therefore, we aimed to introduce an organic fragment that would be recognized by organelles inside the yeast cell. This approach may shed light on the mechanism of the action of the organobismuth compounds against yeast. Thus, a variety of aromatic carboxylic acids were used as carboxylate ligands for **4a**–**l** and **5a**–**d**. In particular, 4-aminobenzoic acid [9], nicotinic acid [10] and indole-3-acetic acid [11] play key roles in eukaryotic cells; therefore, the corresponding carboxylate ligands in **4g**, **5a** and **5c**, respectively, could interact



Scheme 1. Synthesis of compounds **4a**–**l** and **5a**–**d** by Method 1 and 2.

with specific biomolecules. In addition, azulene derivatives are biologically active and are used in medicine [12]. Azulene is characterized by its high electron affinity, low ionization potential, low aromatic resonance energy, and its dipole moment vector with the negative end toward the five-membered ring. These structural characteristics are reflected in the intermolecular interactions of its derivatives in crystal [13]. Hence, the introduction of an azulene unit in **4h**–**l** should allow the bismuth carboxylate to undergo intermolecular interactions with various biomolecules.

Initially, **4** and **5** were synthesized by Method 1 (Scheme 1). The reaction of **1a** with benzoic acid, naphthoic acids, anthranic acid and cinnamic acid in the presence of potassium *tert*-butoxide proceeded smoothly to afford **4a**–**e**, respectively, in acceptable yields (Table 1). In contrast, the reaction of **1a** with 4-acetoxy and 4-aminobenzoic acids under basic conditions produced low yields of **4f** and **g**, suggesting that the deprotonation of the acetoxy and amino substituents competed with the desired reaction. The azulenecarboxylic acids were synthesized according to literature methods [14]. The reaction of **1a** with azulene carboxylic acids gave **4h**–**l**. However, the synthesis of **5a** using Method 1 was unsuccessful, and the majority of the starting material was recovered. The coordination of the pyridinyl group to the bismuth center may have prevented the nucleophilic attack of the carboxylate anion generated in situ. The synthesis of **5b** using Method 1 also failed, because of the reactive acetoxy ortho substituent. In contrast, **4f**, which bears this substituent at the para position, was formed in low yield. Method 2 was used to overcome the low yields achieved under basic conditions. Bismuth carboxylates **5a**–**d** were obtained in acceptable yields by the acidolysis of the bismuth–carbon bond of **3b** by the corresponding carboxylic acid. The structure of the new compounds was confirmed by elemental analysis, IR, and ^{1}H and ^{13}C NMR. Compounds **4a**–**l** and **5a**–**d** were stable in water and DMSO.

3. Results and discussion

The inhibition activity and biological activity of **4** and **5** were compared with those of **1**, **2** and **3a** reported in our previous antifungal study (Scheme 1 and Table 1). The activities of **4g**–**l**, **5a** and **5c** were slightly lower, whereas those of **3a**, **4a** and **4f** were the highest. However, all the bismuth carboxylates showed moderate to high activities irrespective of the structure of the carboxylate ligands and its ClogP value. In particular, highly lipophilic compounds, **4d**, **4j** and **4k** (ClogP > 5.00), had activities comparable with that of **5a** which has much more hydrophilic (ClogP = 1.99). In contrast, **1b**, **1c** and **2b** were inactive, and these compounds had ClogP values of 3.06, 3.00 and 6.13, respectively [7b]. Therefore, we conclude that heterocyclic bismuth chlorides **1** and **2** and carboxylates **3a**, **4a**–**l** and **5a**–**d** are probably separated into two organic fragments inside the yeast cell. The cationic heterocyclic bismuth scaffold may be responsible for the inhibitory activity, whereas the chloride or carboxylate anion affects the drug absorption and bioavailability. This is in good agreement with the finding that the inhibition activity of **1** depends on substituent R in the heterocyclic bismuth scaffold.

Table 1
Synthesis and antifungal assay of bismuth carboxylates **4** and **5**.

Compound	Method	Yield (%)	Inhibition zone (mm)	ClogP
4a	1	58	17	3.49
4b	1	42	13	4.66
4c	1	79	12	4.66
4d	1	70	14	5.84
4e	1	48	14	4.45
4f	1	16	17	2.84
4g	1	11	15	2.26
4h	1	80	11	4.66
4i	1	62	14	4.66
4j	1	58	12	6.39
4k	1	70	13	6.09
4l	1	71	12	4.66
5a	2	81	14	1.99
5b	2	47	12	2.84
5c	2	28	13	3.53
5d	2	77	12	2.97
3a	1	83	17	2.68
1a			18	1.18
1b			0	3.06
1c			0	3.00
2a			8	0.81
2b			0	6.13
3b			0	3.99

In conclusion, the present study provides insight into the mechanism of action of heterocyclic bismuth carboxylates **3a**, **4** and **5** and chlorides **1** and **2** against *S. cerevisiae*. Further studies are now underway to confirm these findings.

4. Experimental

Compounds **3b** and **1a** were synthesized in accordance with our reported procedure [7b]. Azulene-1-carboxylic acid [14a], -2-carboxylic acid [14b] and -6-carboxylic acid [14d] were prepared in accordance with the reported procedure. 1,3-Dibromoazulene-2-carboxylic acid and 1,3-dichloroazulene-2-carboxylic acid were prepared from 1,3-dibromo-2-lithioazulene and 1,3-dichloro-2-lithioazulene, respectively, by the reaction with CO_2 [14c].

4.1. Synthesis of *4* (Method 1)

A typical example is exemplified by the synthesis of **4a**: To a solution of **1a** (230 mg, 0.5 mmol) in THF (10 ml) was added at room temperature carboxylic acid (0.5 mmol) and potassium *tert*-butoxide (62 mg, 0.55 mmol). After the resulting mixture was stirred for 30 min, the mixture was diluted by the addition of brine (5 ml) and the organic layer was extracted with ethyl acetate (20 ml × 3). The extracts were concentrated to leave an oily residue, which was crystallized from MeOH to give the product.

4.1.1. 10-(Benzoyloxy)phenothiabismine 5,5-dioxide (*4a*)

Yield: 58%; mp 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.48 (4H, m), 7.55 (1H, t, J = 7.2 Hz), 7.77 (2H, t, J = 7.4 Hz), 8.11 (2H, d, J = 7.8 Hz), 8.38 (2H, d, J = 7.6 Hz), 8.80 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.2, 128.5, 128.7, 130.3, 132.2, 132.6, 135.2, 136.0, 141.0, 173.9, 184.7; IR (KBr): ν = 1610, 1570, 1340, 1300, 1290, 1140, 760, 740, 710, 680, 590 and 560 cm^{-1}. Anal. Calc. for $C_{19}H_{13}BiO_4S$: C, 41.77; H, 2.40. Found: C, 41.58; H, 2.75%.

4.1.2. 10-(1-Naphthoyloxy)phenothiabismine 5,5-dioxide (*4b*)

Yield: 42%; mp 142–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (2H, t, J = 7.4 Hz), 7.51 (1H, t, J = 7.5 Hz), 7.53 (1H, t, J = 7.4 Hz), 7.61 (1H, t, J = 8.1 Hz), 7.69 (2H, t, J = 7.4 Hz), 7.91 (1H, d, J = 8.1 Hz), 8.01 (1H, d, J = 8.2 Hz), 8.30 (1H, d, J = 7.2 Hz), 8.40 (2H, d, J = 7.4 Hz), 8.89 (2H, d, J = 7.4 Hz), 9.18 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.6, 126.0, 126.5, 127.4, 128.5, 128.6, 128.7, 129.1, 131.2, 131.7, 133.1, 134.0, 135.1, 136.2, 141.1, 175.3, 184.9; IR (KBr): ν = 1540, 1350, 1300, 1290, 1250, 1140, 790, 760, 740, 590 and 560 cm^{-1}. Anal. Calc. for $C_{23}H_{15}BiO_4S$: C, 46.32; H, 2.54. Found: C, 46.26; H, 2.73%.

4.1.3. 10-(2-Naphthoyloxy)phenothiabismine 5,5-dioxide (*4c*)

Yield: 79%; mp 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (2H, t, J = 7.6 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.53 (1H, t, J = 7.6 Hz), 7.72 (2H, t, J = 7.4 Hz), 7.89 (1H, d, J = 8.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 7.96

(1H, d, J = 8.4 Hz), 8.14 (1H, d, J = 8.4 Hz), 8.39 (2H, d, J = 7.6 Hz), 8.67 (1H, s), 8.86 (2H, d, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.2, 126.5, 127.7, 127.9, 128.0, 128.5, 128.7, 129.3, 129.4, 131.5, 132.6, 135.2, 135.4, 136.0, 141.0, 174.0, 184.9; IR (KBr): ν = 1600, 1590, 1570, 1360, 1330, 1290, 1240, 1200, 1140, 1110, 1090, 790, 760, 740, 710, 590 and 560 cm^{-1}. Anal. Calc. for $C_{23}H_{15}BiO_4S$: C, 46.32; H, 2.54. Found: C, 46.03; H, 2.73%.

*4.1.4. 10-(9-Anthranoyloxy)phenothiabismine 5,5-dioxide (**4d**)*

Yield: 70%; mp 172–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.51 (6H, m), 7.68 (2H, t, J = 7.6 Hz), 8.00–8.04 (2H, m), 8.26–8.30 (2H, m), 8.45 (2H, d, J = 7.6 Hz), 8.51 (1H, s), 8.99 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 125.3, 125.8, 126.5, 128.4, 128.6, 128.7, 128.8, 128.9, 130.0, 131.2, 135.2, 136.6, 141.0, 177.0, 185.0; IR (KBr): ν = 1580, 1370, 1310, 1270, 1250, 1140, 760, 740, 590 and 570 cm^{-1}. Anal. Calc. for $C_{27}H_{17}BiO_4S$: C, 50.16; H, 2.65. Found: C, 49.92; H, 2.83%.

*4.1.5. 10-(Cinnamoyloxy)phenothiabismine 5,5-dioxide (**4e**)*

Yield: 48%; mp 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (1H, d, J = 16.0 Hz), 7.38–7.40 (3H, m), 7.46 (2H, t, J = 7.6 Hz), 7.53–7.55 (2H, m), 7.68–7.71 (3H, m), 8.37 (2H, d, J = 7.6 Hz), 8.77 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 120.3, 128.0, 128.5, 128.7, 128.9, 130.1, 134.8, 135.2, 136.0, 141.0, 144.8, 174.4, 184.5; IR (KBr): ν = 1760, 1610, 1350, 1290, 1200, 1130, 1010, 920, 770, 740, 710, 590 and 560 cm^{-1}. Anal. Calc. for $C_{21}H_{15}BiO_4S$: C, 44.07; H, 2.64. Found: C, 43.76; H, 2.92%.

*4.1.6. 10-(4-Acetoxybenzoyloxy)phenothiabismine 5,5-dioxide (**4f**)*

Yield: 16%; mp 217–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32 (3H, s), 7.17 (2H, d, J = 8.8 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.70 (2H, t, J = 7.6 Hz), 8.13 (2H, d, J = 8.8 Hz), 8.38 (2H, d, J = 7.6 Hz), 8.77 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 121.4, 128.5, 128.7, 129.9, 131.8, 135.2, 136.0, 141.0, 154.1, 169.0, 173.1, 184.8; IR (KBr): ν = 1640, 1560, 1350, 1310, 1290, 1230, 1140, 1090, 1000, 870, 770, 740, 590 and 570 cm^{-1}. Anal. Calc. for $C_{21}H_{15}BiO_6S$: C, 41.73; H, 2.50. Found: C, 42.13; H, 2.79%.

*4.1.7. 10-(4-Aminobenzoyloxy)phenothiabismine 5,5-dioxide (**4g**)*

Yield: 11%; mp 238 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.04 (2H, s), 6.66 (2H, d, J = 8.4 Hz), 7.44 (2H, t, J = 7.4 Hz), 7.67 (2H, t, J = 7.4 Hz), 7.92 (2H, d, J = 8.4 Hz), 8.36 (2H, d, J = 7.6 Hz), 8.79 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.8, 127.0, 128.1, 128.4, 128.5, 132.3, 135.0, 136.1, 141.1, 150.6, 174.0; IR (KBr): ν = 3450, 3390, 1600, 1560, 1510, 1440, 1340, 1290, 1170, 1140, 1090, 1010, 850, 780, 760, 740, 640, 590 and 570 cm^{-1}. Anal. Calc. for $C_{19}H_{14}BiNO_4S\cdot$MeOH: C, 40.48; H, 3.06; N, 2.36. Found: C, 40.68; H, 3.13; N, 2.55%.

*4.1.8. 10-(Azulene-1-carboxy)phenothiabismine 5,5-dioxide (**4h**)*

Yield: 80%; mp 248–250 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (1H, d, J = 4.4 Hz), 7.42–7.47 (3H, m), 7.55 (1H, t, J = 9.8 Hz), 7.68 (2H, t, J = 7.4 Hz), 7.81 (1H, t, J = 9.8 Hz), 8.38 (2H, d, J = 7.6 Hz), 8.45 (1H, d, J = 4.4 Hz), 8.48 (1H, d, J = 9.2 Hz), 8.91 (2H, d, J = 7.2 Hz), 9.79 (1H, d, J = 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.0, 117.5, 126.6, 127.3, 128.4, 128.5, 135.0, 136.3, 138.0, 138.1, 138.8, 140.7, 141.3, 141.4, 144.9, 173.0, 183.3; IR (KBr): ν = 1540, 1460, 1440, 1400, 1360, 1300, 1290, 1260, 1140, 780, 740, 590 and 560 cm^{-1}. Anal. Calc. for $C_{23}H_{15}BiO_4S$: C, 46.32; H, 2.54. Found: C, 45.94; H, 2.60%.

*4.1.9. 10-(Azulene-2-carboxy)phenothiabismine 5,5-dioxide (**4i**)*

Yield: 62%; mp 222 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (2H, t, J = 9.8 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.64–7.72 (3H, m), 7.83 (2H, s), 8.37–8.43 (4H, m), 8.88 (2H, d, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.6, 123.7, 128.5, 128.6, 135.1, 136.2, 140.0, 140.1, 140.3, 140.4, 141.0, 173.2, 184.6; IR (KBr): ν = 1580, 1490, 1440, 1340, 1310, 1260, 1140, 1090, 800, 780, 740, 590 and 560 cm^{-1}. Anal. Calc. for $C_{23}H_{15}BiO_4S$: C, 46.32; H, 3.08. Found: C, 46.47; H, 2.72%.

*4.1.10. 10-(1,3-Dibromoazulene-2-carboxy)phenothiabismine 5,5-dioxide (**4j**)*

Yield: 58%; mp 252 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (2H, t, J = 10.0 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.70–7.74 (3H, m), 8.38 (2H, d, J = 7.6 Hz), 8.46 (2H, d, J = 10.0 Hz), 9.04 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.8, 125.1, 128.5, 128.7, 135.3, 136.3, 136.5, 138.2, 139.3, 140.9, 141.5, 171.2, 185.1; IR (KBr): ν = 1580, 1460, 1370, 1330, 1290, 1270, 1140, 1010, 840, 760, 730, 590 and 570 cm^{-1}. Anal. Calc. for $C_{23}H_{13}BiBr_2O_4S$: C, 36.63; H, 1.74. Found: C, 36.43; H, 1.38%.

*4.1.11. 10-(1,3-Dichloroazulene-2-carboxy)phenothiabismine 5,5-dioxide (**4k**)*

Yield: 70%; mp 252 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, t, J = 10.0 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.67–7.74 (3H, m), 8.38 (2H, d, J = 7.6 Hz), 8.47 (2H, d, J = 10.0 Hz), 9.00 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.9, 124.4, 128.5, 128.7, 133.3, 135.3, 136.5, 138.0, 140.9, 142.1, 170.3, 185.0, one carbon signal was too weak to be assigned; IR (KBr): ν = 1580, 1470, 1300, 1140, 1110, 740, 590 and 570 cm^{-1}. Anal. Calc. for $C_{23}H_{13}BiCl_2O_4S$: C, 41.52; H, 1.97. Found: C, 41.29; H, 1.57%.

*4.1.12. 10-(Azulene-6-carboxy)phenothiabismine 5,5-dioxide (**4l**)*

Yield: 71%; mp 226–228 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (2H, d, J = 4.0 Hz), 7.48 (2H, t, J = 7.6 Hz), 7.74 (2H, t, J = 7.6 Hz), 8.04 (1H, t, J = 4.0 Hz), 8.17 (2H, d, J = 10.8 Hz), 8.40 (2H, d, J = 7.6 Hz), 8.44 (2H, d, J = 10.8 Hz), 8.85 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 118.6, 123.0, 128.6, 128.8, 134.9, 135.3, 135.9, 138.2, 139.8, 141.0, 141.3, 175.3, 185.3; IR (KBr): ν = 1600, 1570, 1340, 1310, 1290, 1140, 770, 740, 590 and 560 cm^{-1}. Anal. Calc. for $C_{23}H_{15}BiO_4S$: C, 46.32; H, 2.54. Found: C, 45.97; H, 2.69%.

*4.2. Synthesis of **5** (Method 2)*

A typical example is exemplified by the synthesis of **5a**: A mixture of **3b** (258 mg, 0.5 mmol) and nicotinic acid (62 mg, 0.5 mmol) in toluene (7 ml) was refluxed for 6 h. The resulting mixture was cooled to room temperature and concentrated to leave an oily residue, which was crystallized from MeOH to give the product.

*4.2.1. 10-(Nicotinoyloxy)phenothiabismine 5,5-dioxide (**5a**)*

Yield: 81%; mp 248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (1H, dd, J = 4.8, 7.6 Hz), 7.48 (2H, t, J = 7.6 Hz), 7.72 (2H, d, J = 7.4 Hz), 8.36 (1H, m), 8.39 (2H, d, J = 7.8 Hz), 8.76 (1H, dd, J = 1.6, 7.2 Hz), 8.80 (2H, d, J = 7.2 Hz), 9.29 (1H, d, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 123.2, 128.0, 128.7, 128.8, 135.3, 135.9, 137.6, 140.9, 151.7, 153.0, 172.3, 184.8; IR (KBr): ν = 1610, 1560, 1420, 1350, 1290, 1200, 1140, 1110, 1030, 850, 740, 710, 590 and 560 cm^{-1}. Anal. Calc. for $C_{18}H_{12}BiNO_4S$: C, 39.50; H, 2.21; N, 2.56. Found: C, 39.64; H, 2.33; N, 2.59%.

*4.2.2. 10-(2-Acetoxybenzoyloxy)phenothiabismine 5,5-dioxide (**5b**)*

Yield: 47%; mp 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.03 (3H, s), 7.09 (1H, t, J = 8.0 Hz), 7.30 (1H, t, J = 8.0 Hz), 7.46 (2H, t, J = 7.6 Hz), 7.53 (1H, t, J = 7.8 Hz), 7.71 (2H, t, J = 7.4 Hz), 8.06 (1H, d, J = 8.0 Hz), 8.38 (2H, d, J = 7.6 Hz), 8.75 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 123.5, 125.6, 125.9, 128.5, 128.6, 132.5, 133.4, 135.2, 136.0, 140.9, 150.7, 169.7, 172.0, 184.8; IR (KBr): ν = 1760, 1610, 1570, 1480, 1440, 1370, 1340, 1290, 1190, 1140, 1090, 1010, 760, 740, 710, 590 and 570 cm^{-1}. Anal. Calc. for $C_{21}H_{15}BiO_6S$: C, 41.73; H, 2.50. Found: C, 41.47; H, 2.70%.

*4.2.3. 10-(Indol-3-carboxy)phenothiabismine 5,5-dioxide (**5c**)*

Yield: 28%; mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (2H, s), 7.13 (1H, t, J = 7.4 Hz), 7.20–7.24 (2H, m), 7.38 (1H, d, J = 8.0 Hz), 7.42 (2H, t, J = 7.6 Hz), 7.59 (2H, t, J = 7.4 Hz), 7.70 (1H, d, J = 8.0 Hz), 8.07 (1H, s), 8.34 (2H, d, J = 7.6 Hz), 8.60 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.0, 110.0, 111.2, 119.4, 119.5, 122.2, 123.0, 127.4, 128.4, 128.6, 135.0, 136.0, 136.2, 140.9, 179.9, 184.5; IR (KBr): ν = 3320, 1620, 1430, 1360, 1300, 1250, 1230, 1140, 1090, 1010, 740, 590 and 570 cm^{-1}. Anal. Calc. for $C_{22}H_{16}BiNO_4S$: C, 44.08; H, 2.69; N, 2.34. Found: C, 43.92; H, 2.79; N, 2.40%.

*4.2.4. 10-(N-Phthalylglycyloxy)phenothiabismine 5,5-dioxide (**5d**)*

Yield: 77%; mp 246–248 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51 (2H, s), 7.45 (2H, t, J = 7.6 Hz), 7.70 (2H, t, J = 7.4 Hz), 7.73–7.77 (2H, m), 7.88–7.92 (2H, m), 8.35 (2H, d, J = 7.6 Hz), 8.65 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.6, 123.5, 128.6, 128.7, 132.2, 134.1, 135.4, 135.8, 140.6, 167.8, 174.2, 185.1; IR (KBr): ν = 1770, 1710, 1640, 1410, 1380, 1290, 1140, 1110, 1090, 960, 750, 740, 720, 570 and 560 cm^{-1}. Anal. Calc. for $C_{22}H_{14}BiNO_6S$: C, 41.98; H, 2.24; N, 2.23. Found: C, 42.00; H, 2.48; N, 2.31%.

4.3. Qualitative antifungal assay

The yeast *S. cerevisiae* W303-1A (*MAT***a** *ade2-1 can1-100 ura3-1 leu2-3,112 trp1-1 his3-11,15*) was used for the qualitative antifungal assay. Yeast extract-peptone-dextrose (YPD) plates contained 1% yeast extract, 2% peptone, 2% glucose and 1.2% agar. The cells were inoculated at a concentration of 1.3 × 10^4 cells/ml in YPD agar medium at 48 °C and YPD plates were immediately made in Petri dishes. Each compound was dissolved in dimethyl sulfoxide (DMSO) at a concentration of 30 mM and 5 μl of each solution was directly spotted on the surface of the plate. The plates were incubated for 48 h at 30 °C and antifungal activity was indicated by the presence of clear inhibition zones around the spot. The control experiment showed that DMSO does not inhibit fungal growth at all.

4.4. Lipophilicity

The calculated logarithms of water–octanol partition coefficients (ClogP values) were obtained from the ClogP tool in ChemDraw Ultra 11.0 (CambridgeSoft, Cambridge, MA, USA).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.02.036.

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