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Original article

Bismuth heterocycles based on a diphenyl sulfone scaffold: Synthesis and substituent effect on the antifungal activity against *Saccharomyces cerevisiae*

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ABSTRACT

A series of heterocyclic organobismuth(III) compounds **2** [ClBi(5-R-C_6H_3-2-$SO_2C_6H_4$-1'-): R = Me, Ph, MeO, Cl, H, *t*-Bu, CF_3, F, Me_2N] was synthesized in order to study the relative importance of structure and specific substitutions in relation to their lipophilicity and antifungal activity against the yeast *Saccharomyces cerevisiae*. A clear structure–activity relationship between the size of the inhibition zone and the value of ClogP was found for **2**. These results suggest that the higher the lipophilicity, the lower the antifungal activity. Thus, **2e** (R = H) and **2h** (R = F), which had ClogP values of 1.18 and 1.45, respectively, were most active. In contrast, **2b** (R = Ph) and **2f** (R = *t*-Bu) had ClogP values of 3.06 and 3.00, respectively, and exhibited no antifungal activity. Compound **6b** ClBi[5-(OH)C_6H_3-2-SO_2-5′-(OH)C_6H_3-1'-] had an estimated ClogP value of 0.81 but exhibited only low activity in spite of its low ClogP value, suggesting that such a considerable decrease in lipophilicity lowers inhibition activity. Bismuth carboxylate **7b** derived from *p*-nitrobenzoic acid and **2e** exhibited inhibition activity comparable to those of **2e** and **2h** despite its higher lipophilicity (ClogP = 2.68).

1. Introduction

The biological activity of bismuth compounds has attracted considerable interest due to their medicinal utility [1–4]. In this regard, inorganic bismuth complexes have been extensively investigated and their history of medicinal application is very long, whereas organobismuth compounds, that are at least containing one bismuth–carbon bond, have been studied only a little [5]. The main reason is attributed to the fact that organobismuth chemistry has established during the last two decades [6].

We previously reported the antifungal activity of organobismuth compounds against the yeast *Saccharomyces cerevisiae* [7]. We found that the Lewis acidic bismuth center was an active site of organobismuth compounds and that bismuth heterocycle **2e** derived from diphenyl sulfone exhibited high inhibition activity, although the mechanism of the action was not clear. This prompted us to examine how the inhibition activity of **2e** is affected by either substitution on the diphenyl sulfone scaffold or by replacement of the chloro group attached to the active bismuth center with an alternative electron-withdrawing group. Here, we describe the synthesis and antifungal activity of heterocyclic bismuth analogues **2**, **4**, **6** and **7** against the yeast *S. cerevisiae*. The present work revealed a clear structure–activity relationship between the ClogP value and inhibition activity for **2** and **4**. Furthermore, bismuth carboxylate **7b** derived from **2e** and *p*-nitrobenzoic acid showed activity comparable to that of **2e**. To the best of our knowledge, there have been few reports of QSAR studies on organobismuth compounds.

2. Chemistry

Substituted diaryl sulfones were prepared according to the reported Pd-catalyzed coupling of arylsulfonyl chlorides [8], through a Friedel–Crafts reaction, or from diaryl sulfides [9] by their oxidation. Bismuth heterocycles **1** and **3** were obtained from the corresponding dilithiated diphenylsulfone and dichloro(4-methylphenyl)bismuthane in 30–50% yield (Scheme 1) [10]. These were converted into **2** and **4** in 70–80% yield by treatment with boron trifluoride diethyl ether complex followed by brine. Compounds **5** and **6** were synthesized from bis(4-hydroxyphenyl) sulfone via silyl

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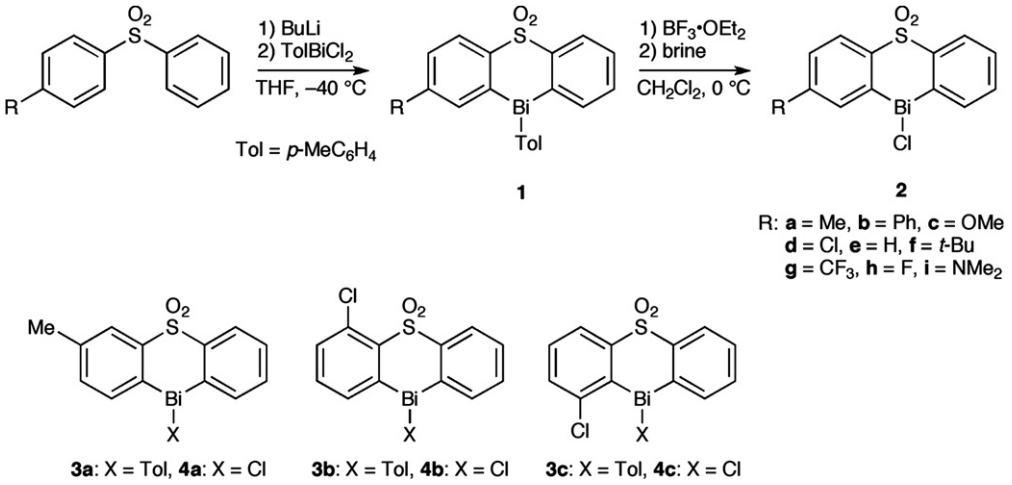


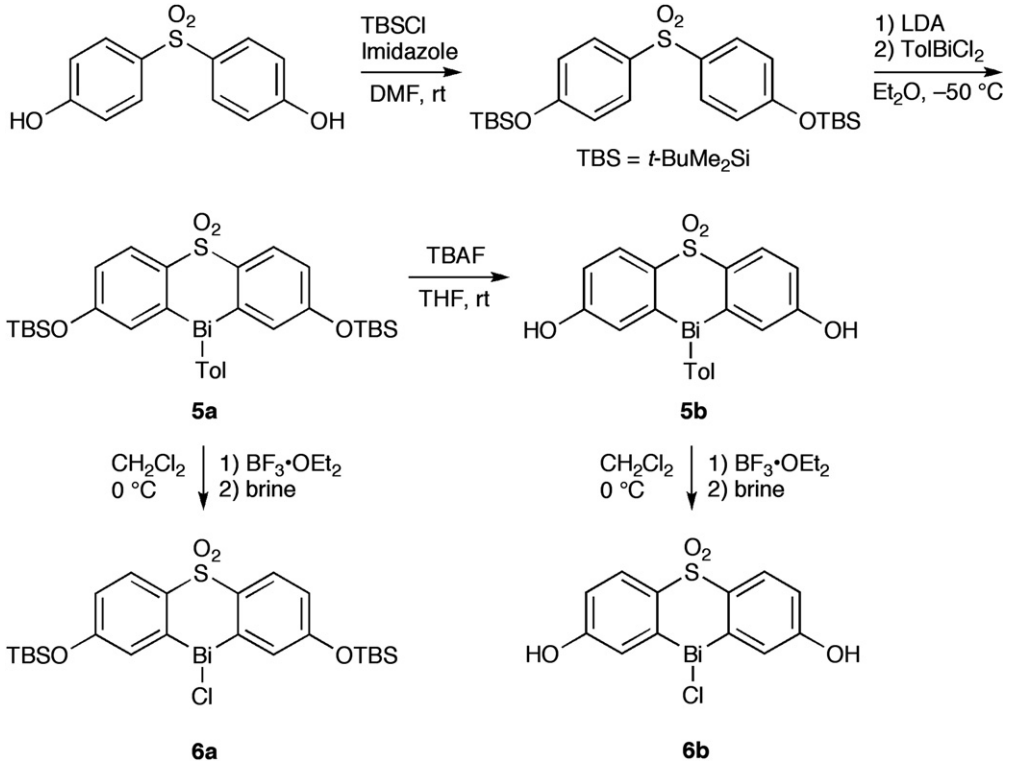
Scheme 1. Synthesis of bismuth heterocycles **2** and **4**.

protection of the hydroxyl substituents followed by lithiation (Scheme 2). Synthesis of **7** was carried out by reacting **2e** with potassium salts of the corresponding *p*-substituted benzoic acid or with sodium dithiocarbamates (Scheme 3). The structure of all the new compounds was confirmed by their elemental analysis and also spectral technique (^{1}H and ^{13}C NMR, IR). Outstanding spectroscopic feature is in the chemical shifts of **2**, **4** and **7**. Thus, the ortho proton adjacent to the bismuth atom in the diphenyl sulfone scaffold suffered from the anisotropic deshielding due to its close proximity to the electronegative chlorine, oxygen or sulfur atom attached to the bismuth center [11]. As typical examples, the signal due to the ortho proton of **2e**, **7a** and **7c** appeared at δ 8.64, 8.80 and 9.03, respectively. This indicates that the sulfonyl oxygen atom coordinates with the bismuth atom to form a hypervalent O–Bi–Cl, O–Bi–O or O–Bi–S bond. Compounds **2**, **4**, **6** and **7** were stable in water and DMSO. They did not show any decomposition under the conditions of the biological assay.

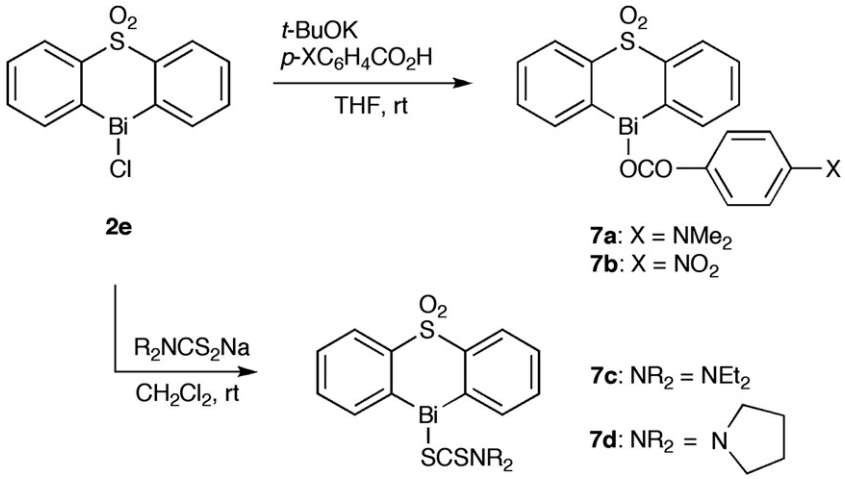
3. Results and discussion

3.1. Growth inhibition tests against S. cerevisiae

We first examined modifications in which a substituent was installed on the diphenyl sulfone scaffold. We tested the inhibition activity of **2** prepared from *p*-substituted diphenyl sulfone and the biological activity of each derivative was compared with that of the parent **2e** (Scheme 1). As shown in Table 1, the activity was sensitive to the nature of the *p*-substituent. Remarkably, the introduction of



Scheme 2. Synthesis of bismuth heterocycles **6**.



Scheme 3. Synthesis of bismuth heterocycles **7**.

a phenyl or *t*-butyl substituent into the phenylene ring of **2e** completely deactivated the resulting compound **2b** or **2f**, respectively. The dimethylamino substituent of **2i** somewhat decreased the activity. The lipophilicity as well as the steric bulkiness of these substituents seemed to be unfavorable for enhanced inhibition activity. The methyl, methoxy, chloro and trifluoromethyl substituents of **2a**, **2c**, **2d** and **2g**, respectively, also decreased the activity irrespective of the electronic nature of the substituent. Compounds **2e** with no substitution and **2h** bearing the fluoro substituent had the highest activity among compounds **2**. The similar biological activity of these compounds is likely due to the similar atomic radii of hydrogen and fluorine [12]. In order to investigate how the position of the substituent affects biological activity, we synthesized **4a**–**c**. The inhibition activity of **4a** was somewhat lower than that of isomeric **2a**, while the activity of **4b** and **4c** was slightly lower than or comparable to that of isomeric **2d**. These findings suggest that isomeric derivatives of **2** are not expected to exhibit higher activity, although we evaluated the activity for only a few isomers of **2**. Fig. 1 shows a plot relating the lipophilicity (ClogP) of **2** and **4a**–**c**. A clear structure–activity relationship was observed for these compounds between the size of the zone of inhibition and the value of ClogP, namely, the higher the lipophilicity, the lower the antifungal activity ($r = -0.85$, $n = 12$). On the basis of this relationship, in order to enhance the hydrophilicity of the diphenyl sulfone scaffold, we synthesized **6b** bearing hydrophilic substituents (Scheme 2). Despite the presence of the phenolic hydroxyl substituents activated by the electron-withdrawing sulfonyl group, **6b** was stable in solution and solid states under ambient conditions, even though the bismuth center of **2e** can undergo nucleophilic substitution with a phenoxide anion to form bismuth phenoxide [10]. Contrary to our expectation, the activity of **6b** was less than that of the parent **2e**, indicating that an increase in the hydrophilicity alone is not sufficient for enhancing the activity [13]. Compound **6a** showed no activity, which is consistent with the results observed for **2b** and **2f** bearing lipophilic phenyl and *t*-butyl substituents, respectively.

We next modified **2e** by replacing the chloro substituent with an electron-withdrawing carboxylate or dithiocarbamate substituents

Table 1
Antifungal assay of bismuth heterocycles

Compound	Inhibition zone (mm)	ClogP
2a	14	1.68
2b	0	3.06
2c	11	1.52
2d	13	2.02
2e	18	1.18
2f	0	3.00
2g	11	2.28
2h	17	1.45
2i	7	1.77
4a	8	1.68
4b	10	2.02
4c	13	2.02
6a	0	6.13
6b	8	0.81
7a	13	2.90
7b	17	2.68
7c	0	4.10
7d	0	4.25

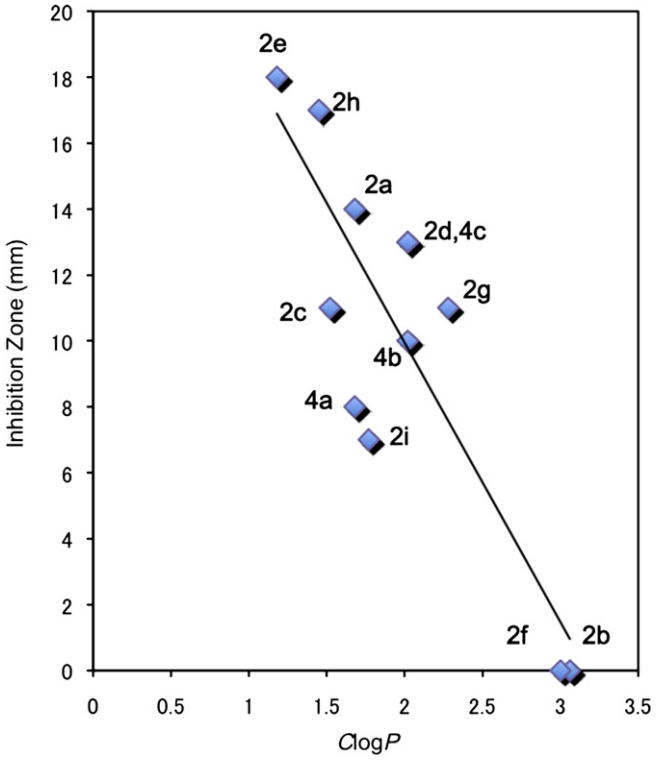


Fig. 1. Structure–activity relationship for **2** and **4**.

(Scheme 3) since a carboxylic acid scaffold is present in many classes of biologically active compounds. Furthermore, dithiocarbamate salt is an extensively used fungicide [14] and the cytotoxicity of bismuth dithiocarbamates has been reported [15]. The incorporation of such biologically active moieties into the bismuth agent is expected to be involved in the antifungal activity in addition to the action of the active bismuth center. In preliminary results, bismuth carboxylate **7a** exhibited moderate inhibition activity while **7b** showed an activity comparable to that of **2e**. It should be stressed that although **7b** is more lipophilic than **2e**, it nonetheless exhibited similarly high activity. A comparison of the lipophilicity of **7a** with that of **7b** revealed that the less lipophilic derivative showed higher activity. On the other hand, **7c** and **7d** were inactive. This may be attributable to the lowered Lewis acidity of the bismuth center due to the lower electronegativity of sulfur atom bound to bismuth as well as the high ClogP value of these compounds (4.10 and 4.25 for **7c** and **7d**, respectively). These results indicate that the presence of an electronegative organyl substituent attached to the bismuth center plays an important role in the generation of the antifungal activity.

3.2. X-ray crystallographic study of 6b

The structural modification of **2e** to **6b** presents one possible strategy to explore lead compounds by improving the hydrophilicity of organobismuth compounds bearing aryl groups. We became interested in the stability of **6b**. In order to know the reason, an X-ray structure analysis was carried out for this compound (Fig. 2 and Tables 2 and 3). The molecule of **6b** has high symmetry and forms a monohydrate. The bismuth center adopts a distorted trigonal bipyramidal geometry via the intramolecular coordination [Bi(1)•••O(1) = 2.634(7) Å], with the electronegative oxygen and chlorine atoms in the apical positions and the carbon atoms and a lone pair of electrons in the equatorial positions. The bismuth atom forms an intermolecular interaction with a chlorine atom [Bi(1)•••Cl(1) = 3.627(3) Å], but no intermolecular interaction between the hydroxyl oxygen atom and the bismuth atom was observed. The four molecules of **6b** are linked by hydrogen bonds to the O(4) atom of a water molecule with atomic distances 2.771(7) Å [O(3)•••O(4) and O(3)*•••O(4)], 2.719(9) Å [O(2)•••O(4)] and 3.194 (7) Å [Cl(1)•••O(4)]. The atomic distances between O(4) and O(3) or O(3)* are normal for such bonds. Each hydroxyl substituent is linked by a weak intermolecular hydrogen bond to the sulfonyl oxygen atom with atomic distances 3.108(7) Å [O(2)•••O(3) and O (2)•••O(3)*]. Taking into account the behavior of the hydroxyl substituents, the stability of **6b** as a solid may, therefore, be attributed to the location of the hydroxyl oxygen atoms far from the bismuth center as well as to the less polarized oxygen atoms that are not enough to attack the Lewis acidic bismuth center. Intermolecular C–H•••O interactions were observed between the hydroxyl oxygen atom and a proton ortho to the sulfonyl group, where the atomic distances H(1)*•••O(3)* and H(1)•••O(3) are estimated to be 2.58 Å. Non-covalent interactions such as O–H•••O and C–H•••O based on the heterocyclic scaffold of **6b** may be available in the binding of the bismuth center with a target biomolecule.

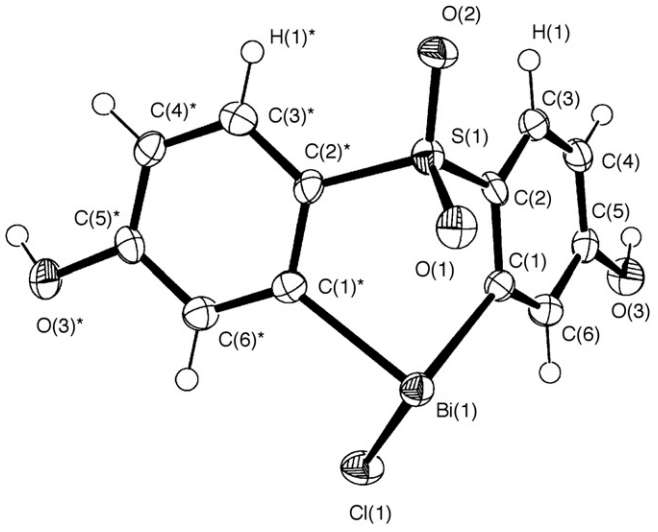


Fig. 2. Molecular structure of **6b**.

Table 2
Selected bond lengths or atomic distances (Å) and bond angles (°) for **6b**.

Bond lengths or atomic distances (Å)	
Bi(1)–C(1)	2.270(6)
Bi(1)–Cl(1)	2.564(3)
Bi(1)•••O(1)	2.634(7)
Bi(1)•••Cl(1)	3.627(3)
O(2)•••O(4)	2.719(9)
O(3)•••O(4)	2.771(7)
Cl(1)•••O(4)	3.194(7)
O(2)•••O(3)	3.108(7)
Bond angles (°)	
C(1)–Bi(1)–C(1)*	87.3(2)
C(1)–Bi(1)–Cl(1)	88.96(16)

In conclusion, the present study provides a useful guide for the design of fungicidal organobismuth(III) compounds derived from diphenyl sulfones. By further structural modification of **7b**, we expect that more potent antifungal organobismuth compounds can be derived from **2e**. Moreover, bismuth carboxylates derived from **6b** appear promising since the hydrophilicity of the hydroxyl substituents partially compensates for the lipophilicity of the carboxylate substituent at the bismuth center, which may result in more active derivatives with lower ClogP values.

Table 3
Crystal and structure determination data for **6b**·H_2O.

Empirical formula	$C_{12}H_{10}BiClO_5S$
Formula weight	510.70
Crystal color	Colorless
Crystal dimensions (mm)	0.20 × 0.20 × 0.15
Crystal system	orthorhombic
Lattice parameters	
a (Å)	8.852(3)
b (Å)	12.410(4)
c (Å)	12.362(4)
V (Å^3)	1358.1(6)
Space group	Pnma (#62)
Z	4
D_{calc} (g cm^{-3})	2.498
F(000)	952.00
μ (cm^{-1})	133.236
λ (Å)	0.71070
No. of reflections measured	
Total	10027
Unique	1624 (R_{int} = 0.056)
Corrections	Lorentz-polarization and absorption
Refinement	Full-matrix least-squares on F^2
No. of observations	1624
No. of variables	100
R	0.0451
*R*1 [$I > 2.00\sigma(I)$]	0.0349
wR2	0.0772
Goodness of fit indicator	1.172
Maximum peak in final diff. map (eÅ^{-3})	2.35
Minimum peak in final diff. map (eÅ^{-3})	−1.67

4. Experimental

4.1. Synthesis of **2** and **4**

A typical example is exemplified by the synthesis of **2e**: To a solution of 2,2′-dilithiated diphenyl sulfone generated from diphenyl sulfone (2.18 g, 10 mmol) and butyllithium (20 mmol) in THF (100 ml) was added dropwise at −40 °C a suspension of dichloro(4-methylphenyl)bismuthane (ca. 10 mmol) in ether (50 ml) and the resulting mixture was stirred for 3 h, during which time the temperature was raised to ambient. The reaction mixture was poured into brine (50 ml) and extracted with ethyl acetate (50 ml × 3). The extracts were concentrated to leave an oily residue, which was purified by chromatography (silica gel) using hexane–ethyl acetate (5:1) as the eluent to afford **1e** in 36% yield (1.87 g, 3.6 mmol). The product was used in the next step without further purification. Compound **1e** (516 mg, 1 mmol) was dissolved in dichloromethane (5 ml) and boron trifluoride etherate (3 mmol) was added to the solution at 0 °C until **1e** was completely consumed (checked by TLC). 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 **2e** in 32% overall yield.

4.1.1. 10-Chlorophenothiabismine 5,5-dioxide (**2e**)

Yield: 32%; mp 222–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (2H, dt, J = 1.2, 7.2 Hz), 7.55 (2H, dt, J = 1.2, 7.2 Hz), 8.15 (2H, dd, J = 1.2, 7.2 Hz), 8.64 (2H, dd, J = 1.2, 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 128.8, 135.6, 136.0, 140.4, 178.8. Anal. Calc. for $C_{12}H_8BiClO_2S$: C, 31.30; H, 1.75. Found: C, 30.8; H, 1.70%.

4.1.2. 10-Chloro-2-methylphenothiabismine 5,5-dioxide (**2a**)

Yield: 32%; mp 186–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (3H, s), 7.26 (1H, d, J = 7.6 Hz), 7.47 (1H, t, J = 8.0 Hz), 7.72 (1H, t, J = 8.0 Hz), 8.24 (1H, d, J = 7.6 Hz), 8.33 (1H, d, J = 7.6 Hz), 8.65 (1H, s), 8.83 (1H, d, J = 8.0 Hz). Anal. Calc. for $C_{13}H_{10}BiClO_2S$: C, 32.89; H, 2.12. Found: C, 32.71; H, 2.08%.

4.1.3. 10-Chloro-2-phenylphenothiabismine 5,5-dioxide (**2b**)

Yield: 40%; mp 151–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (1H, d, J = 7.2 Hz), 7.47 (2H, t, J = 7.6 Hz), 7.50 (1H, dt, J = 0.8, 7.6 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.66 (1H, dd, J = 1.6, 8.0 Hz), 7.75 (1H, dt, J = 1.2, 7.2 Hz), 8.37 (1H, dd, J = 1.2, 8.0 Hz), 8.41 (1H, d, J = 8.0 Hz), 8.85 (1H, d, J = 7.2 Hz), 9.05 (1H, d, J = 1.6 Hz). Anal. Calc. for $C_{18}H_{12}BiClO_2S$: C, 40.28; H, 2.25. Found: C, 40.58; H, 2.31%.

4.1.4. 10-Chloro-2-methoxyphenothiabismine 5,5-dioxide (**2c**)

Yield: 48%; mp 146–149 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.83 (3H, s), 6.90 (1H, dd, J = 2.2, 8.5 Hz), 7.47 (1H, t, J = 7.6 Hz), 7.72 (1H, t, J = 7.6 Hz), 8.29 (1H, d, J = 7.6 Hz), 8.31 (1H, d, J = 7.6 Hz), 8.43 (1H, d, J = 2.2 Hz), 8.82 (1H, d, J = 7.6 Hz). Anal. Calc. for $C_{13}H_{10}BiClO_3S$: C, 31.82; H, 2.05. Found: C, 31.83; H, 2.03%.

4.1.5. 2,10-Dichlorophenothiabismine 5,5-dioxide (**2d**)

Yield: 48%; mp 169–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, dd, J = 2.0, 8.4 Hz), 7.50 (1H, dt, J = 1.2, 7.6 Hz), 7.77 (1H, dt, J = 1.2, 7.6 Hz), 8.27 (1H, d, J = 8.4 Hz), 8.35 (1H, d, J = 8.0 Hz), 8.80 (1H, d, J = 1.6 Hz), 8.85 (1H, d, J = 7.6 Hz). Anal. Calc. for $C_{12}H_7BiCl_2O_2S$: C, 29.11; H, 1.42. Found: C, 29.20; H, 1.48%.

4.1.6. 10-Chloro-2-tert-butylphenothiabismine 5,5-dioxide (**2f**)

Yield: 32%; mp 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (9H, s), 7.46–7.49 (2H, m), 7.72 (1H, dt, J = 1.2, 7.6 Hz), 8.28 (1H, d, J = 8.0 Hz), 8.34 (1H, d, J = 8.0 Hz), 8.83 (1H, d, J = 7.6 Hz), 8.90 (1H, d, J = 1.6 Hz). Anal. Calc. for $C_{16}H_{16}BiClO_2S$: C, 37.19; H, 3.12. Found: C, 37.15; H, 3.08%.

4.1.7. 10-Chloro-2-trifluoromethylphenothiabismine 5,5-dioxide (**2g**)

Yield: 32%; mp 116–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, t, J = 6.0 Hz), 7.73 (1H, d, J = 6.4 Hz), 7.79 (1H, t, J = 6.0 Hz), 8.38 (1H, d, J = 6.0 Hz), 8.43 (1H, d, J = 6.2 Hz), 8.87 (1H, d, J = 6.0 Hz), 9.06 (1H, s). Anal. Calc. for $C_{13}H_7BiClF_3O_2S$: C, 29.53; H, 1.33. Found: C, 29.52; H, 1.40%.

4.1.8. 10-Chloro-2-fluorophenothiabismine 5,5-dioxide (**2h**)

Yield: 30%; mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (1H, dt, J = 8.4, 2.4 Hz), 7.50 (1H, t, J = 7.6 Hz), 7.76 (1H, dt, J = 6.0, 1.2 Hz), 8.34–8.39 (2H, m), 8.59 (1H, dd, J = 6.8, 2.8 Hz), 8.39 (1H, d, J = 7.6 Hz). Anal. Calc. for $C_{12}H_7BiClFO_2S$: C, 30.11; H, 1.47. Found: C, 30.32; H, 1.40%.

4.1.9. 10-Chloro-2-dimethylaminophenothiabismine 5,5-dioxide (**2i**)

Yield: 30%; mp 253–257 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.07 (6H, s), 6.55 (1H, dd, J = 2.4, 8.8 Hz), 7.43 (1H, dt, J = 0.8, 7.6 Hz), 7.67 (1H, dt, J = 1.2, 7.6 Hz), 8.17 (1H, d, J = 2.4 Hz), 8.17 (1H, d, J = 8.8 Hz), 8.26 (1H, dd, J = 0.8, 7.6 Hz), 8.79 (1H, d, J = 8.0 Hz). Anal. Calc. for $C_{14}H_{13}BiClNO_2S$: C, 33.38; H, 2.60; N, 2.78. Found: C, 33.65; H, 2.59; N, 2.73%.

4.1.10. 10-Chloro-3-methylphenothiabismine 5,5-dioxide (**4a**)

Yield: 33%; mp 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (3H, s), 7.47 (1H, dt, J = 0.8, 7.6 Hz), 7.54 (1H, dd, J = 1.2, 7.6 Hz), 7.72 (1H, dd, J = 1.2, 7.6 Hz), 8.16 (1H, d, J = 0.8 Hz), 8.33 (1H, dd, J = 1.2, 7.6 Hz), 8.71 (1H, d, J = 7.2 Hz), 8.82 (1H, dd, J = 0.8, 7.6 Hz). Anal. Calc. for $C_{13}H_{10}BiClO_2S$: C, 32.89; H, 2.12. Found: C, 32.96; H, 2.11%.

4.1.11. 4,10-Dichlorophenothiabismine 5,5-dioxide (**4b**)

Yield: 40%; mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (1H, dd, J = 1.2, 8.0 Hz), 7.47–7.57 (2H, m), 7.89 (1H, dt, J = 1.2, 7.2 Hz), 8.43 (1H, dd, J = 1.2, 8.0 Hz), 8.74 (1H, dd, J = 0.8, 7.2 Hz), 8.89 (1H, dd, J = 1.2, 7.2 Hz). Anal. Calc. for $C_{12}H_7BiCl_2O_2S$: C, 29.11; H, 1.42. Found: C, 29.63; H, 1.47%.

4.1.12. 1,10-Dichlorophenothiabismine 5,5-dioxide (**4c**)

Yield: 37%; mp 189–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (1H, t, J = 7.6 Hz), 7.54 (1H, dt, J = 1.2, 7.6 Hz), 7.74 (1H, dd, J = 0.8, 8.0 Hz), 7.84 (1H, dt, J = 1.2, 7.6 Hz), 8.24 (1H, dd, J = 0.8, 7.6 Hz), 8.44 (1H, dd, J = 0.8, 7.6 Hz), 9.08 (1H, dd, J = 0.8, 7.6 Hz). Anal. Calc. for $C_{12}H_7BiCl_2O_2S$: C, 29.11; H, 1.42. Found: C, 29.47; H, 1.33%.

4.2. Synthesis of **5** and **6**

To a solution of bis(4-*tert*-butyldimethylsiloxyphenyl) sulfone (4.31 g, 9 mmol) in ether (30 ml) was added at −50 °C a solution of lithium diisopropylamide (LDA) (18.9 mmol) in the same solvent (20 ml) and the mixture was stirred for 30 min at this temperature. After a suspension of dichloro(4-methylphenyl)bismuthane (ca. 10 mmol) in ether (50 ml) was added, the resulting mixture was stirred for 3 h, during which time the temperature was raised to ambient. The reaction mixture was poured into brine (50 ml) and extracted with ethyl acetate (50 ml × 3). The extracts were concentrated to leave an oily residue, which was purified by chromatography (silica gel) using hexane–ethyl acetate (20:1) as the eluent to afford **5a** in 48% yield (3.18 g, 4.32 mmol). Compound **5a** (980 mg, 1.33 mmol) was dissolved in dichloromethane (5 ml) and boron trifluoride etherate (3 mmol) was added to the solution at 0 °C until **5a** was completely consumed (checked by TLC). 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 **6a** in 73% yield (648 mg, 0.97 mmol).

4.2.1. 2,8-Bis(tert-butyldimethylsiloxy)-10-(4-methylphenyl) phenothiabismine 5,5-dioxide (**5a**)

Yield: 48%; mp 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.00 (6H, s), 0.03 (6H, s), 0.86 (18H, s), 2.32 (3H, s), 6.78 (2H, dd, J = 2.4, 8.4 Hz), 7.23 (2H, d, J = 7.5 Hz), 7.27 (2H, d, J = 2.4 Hz), 7.66 (2H, d, J = 7.8 Hz), 8.22 (2H, d, J = 8.4 Hz). Anal. Calc. for $C_{31}H_{43}BiO_4SSi_2$: C, 47.93; H, 5.58. Found: C, 47.92; H, 5.56%.

4.2.2. 10-Chloro-2,8-bis(tert-butyldimethylsiloxy) phenothiabismine 5,5-dioxide (**6a**)

Yield: 73%; mp 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.24 (12H, s), 0.97 (18H, s), 6.82 (2H, dd, J = 2.4, 8.2 Hz), 8.20 (2H, d, J = 8.0 Hz), 8.31 (2H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ −4.3, 18.2, 25.5, 119.6, 127.2, 130.0, 132.5, 162.9, 180.0. Anal. Calc. for $C_{24}H_{36}BiClO_4SSi_2$: C, 39.97; H, 5.03. Found: C, 39.91; H, 4.99%.

4.2.3. 2,8-Dihydroxy-10-chlorophenothiabismine 5,5-dioxide (**6b**)

Compound **5a** (820 mg, 1.11 mmol) was dissolved in THF (10 ml) and a solution of tetrabutylammonium fluoride (TBAF) (2.1 mmol) was added to the solution at 0 °C until **5a** was completely consumed (checked by TLC). 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 purified by chromatography (silica gel) using hexane–ethyl acetate (1:2) as the eluent to afford **5b** in 47% yield (287 mg, 0.52 mmol) as an oily substance. Compound **5b** (287 mg, 0.52 mmol) was dissolved in dichloromethane (5 ml) and boron trifluoride etherate (3 mmol) was added to the solution at 0 °C until **5b** was completely consumed (checked by TLC). 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 **6b**.

Yield: 87%; mp 250 °C (decomp.); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.74 (2H, dd, J = 2.4, 8.4 Hz), 8.07 (2H, d, J = 8.4 Hz), 8.28 (2H, d, J = 2.4 Hz), 10.50 (2H, s); IR (KBr): ν = 3560, 3500, 3550 (br), 1580, 1560, 1420, 1320, 1300, 1290, 1210, 1150, 1120, 1100, 1060, 1010, 880, 870, 830, 710, 690, 580, 560, 530 and 510 cm^{-1}. Anal. Calc. for $C_{12}H_8BiClO_4S$: C, 29.25; H, 1.64. Found: C, 28.95; H, 1.89%.

4.3. Synthesis of **7a** and **7b**

To a solution of **2e** (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.

4.3.1. 10-(4-Dimethylaminobenzoyloxy)phenothiabismine 5,5-dioxide (**7a**)

Yield: 75%; mp 241–244 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (6H, s), 6.67 (2H, d, J = 8.8 Hz), 7.43 (2H, t, J = 7.5 Hz), 7.67 (2H, t, J = 7.5 Hz), 7.98 (2H, d, J = 8.8 Hz), 8.36 (2H, d, J = 7.6 Hz), 8.80 (2H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.1, 110.7, 118.8, 128.4, 128.5, 132.0, 135.0, 136.2, 141.2, 153.3, 174.4, 184.5; IR (KBr): ν = 2920, 2850, 1600, 1580, 1520, 1350, 1300, 1290, 1190, 780, 740, 590 and 560 cm^{-1}. Anal. Calc. for $C_{21}H_{18}BiO_4NS$: C, 42.79; H, 3.08; N, 2.38. Found: C, 42.81; H, 2.97; N, 2.04%.

4.3.2. 10-(4-Nitrobenzoyloxy)phenothiabismine 5,5-dioxide (**7b**)

Yield: 83%; mp 253–256 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (2H, t, J = 7.5 Hz), 7.74 (2H, t, J = 7.4 Hz), 8.26 (2H, d, J = 6.6 Hz), 8.29 (2H, d, J = 6.6 Hz), 8.41 (2H, d, J = 7.4 Hz), 8.79 (2H, d, J = 7.4 Hz); IR (KBr): ν = 2920, 1590, 1580, 1530, 1340, 1300, 1140, 1130, 840, 780, 740, 720, 710, 590, 560, 510 and 470 cm^{-1}. Anal. Calc. for $C_{19}H_{12}BiNO_6S$: C, 38.59; H, 2.05; N, 2.37. Found: C, 38.80; H, 1.75; N, 2.47%.

4.4. Synthesis of **7c** and **7d**

An aqueous solution of sodium dithiocarbamate (0.55 mmol, 5 ml) was added to a solution of **2e** (230 mg, 0.5 mmol) in dichloromethane (10 ml) at room temperature and the resulting mixture was stirred for 1 h. The organic layer was extracted with dichloromethane (20 ml × 3) and the extracts were concentrated to leave an oily residue, which was crystallized from MeOH to give the product.

4.4.1. 10-(N,N-Diethyldithiocarbamoyl)phenothiabismine 5,5-dioxide (**7c**)

Yield: 93%; mp 195–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (6H, t, J = 7.1 Hz), 3.99 (4H, q, J = 7.1 Hz), 7.41 (2H, t, J = 7.6 Hz), 7.56 (2H, t, J = 7.5 Hz), 8.36 (2H, d, J = 7.8 Hz), 9.03 (2H, d, J = 7.0 Hz); IR (KBr): ν = 2970, 2930, 1560, 1490, 1430, 1300, 1200, 1150, 1090, 1070, 980, 910, 760, 740, 710, 590, 560, 510 and 460 cm^{-1}. Anal. Calc. for $C_{17}H_{18}BiO_2NS_3$: C, 35.60; H, 3.16; N, 2.44. Found: C, 35.44; H, 3.14; N, 2.40%.

4.4.2. 10-(Pyrrolidinedithiocarbamoyl)phenothiabismine 5,5-dioxide (**7d**)

Yield: 82%; mp 255–257 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (4H, m), 3.92 (4H, m), 7.42 (2H, t, J = 7.6 Hz), 7.55 (2H, t, J = 7.4 Hz), 8.37 (2H, d, J = 7.6 Hz), 9.03 (2H, d, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.2, 54.7, 128.0, 128.1, 134.6, 138.1, 141.7, 175.5, 194.8; IR (KBr): ν = 2970, 2870, 1560, 1460, 1430, 1290, 1140, 1110, 1080, 950, 760, 740, 710, 590, 560, 510 and 470 cm^{-1}. Anal. Calc. for $C_{17}H_{16}BiO_2NS_3$: C, 35.73; H, 2.82; N, 2.45. Found: C, 35.71; H, 2.80; N, 2.44%.

4.5. 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.

4.6. 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).

4.7. X-ray crystallographic study

A colorless prismatic crystal of **6b** was mounted on a glass fiber. All measurements were made with a Rigaku Mercury70

diffractometer with graphite monochromated Mo-Kα radiation. The data were collected at a temperature of −149 ± 1 °C to a maximum 2θ value of 54.9°. The structure was solved by direct methods [16] and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. All calculations were performed using the CrystalStructure [17] crystallographic software package except for refinement, which was performed using SHELXL-97 [18]. Crystal data, data collection summary and refinement parameters of compound **6b** are given in Table 3.

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