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Convenient synthesis of 5-aryl(alkyl)sulfanyl-1,10-phenanthrolines from 5,6-epoxy-5,6-dihydro-1,10-phenanthroline, and their activity towards fungal β-D-glycosidases

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ABSTRACT

A broad series of novel 5-aryl(alkyl)sulfanyl-1,10-phenanthrolines has been prepared by a new simple procedure: a treatment of the commercially available 5,6-epoxy-5,6-dihydro-1,10-phenanthroline with various thiols in the presence of a base. Other functional groups attached to the thiol allow a use of the products as building blocks in synthesis of versatile ligands and in functionalization of surfaces. The synthesized phenanthrolines showed a moderate ability as activators or inhibitors of fungal β-D-glucosidases and β-D-galactosidases.

1. Introduction

1,10-Phenanthroline (phen) is a classic chelating ligand for transition metal ions, one of the most widely used ligands in modern coordination chemistry.[1–4] Phen derivatives with a pendant arm containing functional group(s) are of special importance for organic, inorganic and supramolecular chemistry as versatile starting materials or building blocks for construction of complex ligands with a variety of applications[1–3] and for immobilization onto/into support matrixes.[1] A large number of phen derivatives have been synthesized including some 5-substituted phens with nitrogen, oxygen and carbon-based substituents.[5] However, only a few compounds were obtained with RS-groups at position 5 via a nucleophilic substitution in 5-chloro-phen[6] and in its Ru(II) complexes,[7,8] and at positions 5,6 via a palladium catalyzed cross-coupling reaction in 5,6-dibromo-phen.[9,10] The halogen derivatives had to be prepared first from phen by a harsh treatment (e.g., with Br_2 in oleum[10]).

We suggest a simple, mild and inexpensive one-step synthesis of 5-aryl(alkyl)sulfanyl-1,10-phenanthrolines with a variety of possible aryl/alkyl groups starting with 5,6-epoxy-5,6-dihydro-1,10-phenanthroline (**1**), which is commercially available (Aldrich) and also easy to prepare in good yield by treatment of phen with bleach.[5,11,12]

2. Results and discussion

Studying reaction of epoxide **1** with various thiols RSH in presence of base, we found that the desired products of epoxide cleavage (**2**) were difficult to isolate. They dehydrated easily in mild conditions, and were completely or almost completely converted into 5-aryl(alkyl)sulfanyl-1,10-phenanthroline derivatives (**3**–**24**) by the time when the starting epoxide was consumed (Scheme 1, Table 1). Similar results were obtained with commercially available thiolates (products **18**, **25** and **26**).

Apparently, aromatization of the central ring is a driving force for this elimination. Similar spontaneous dehydration was observed when epoxide **1** reacted with KCN in water.[5] However, dehydration of 5-methoxy- or 5-dialkylamino analogues of **2** was achieved only by additional heating in the presence of a strong base, such as NaH.[5] The products of epoxide **1** cleavage with aromatic amines in presence of excess magnesium perchlorate did not dehydrate even when refluxed in acetonitrile.[4,13] On the contrary, we did not have to apply harsh conditions or additional reagents for preparation of sulfides **3**–**26**, although moderate heating was sometimes helpful (Table 1).

Although simple, the synthesis of phen derivatives **3**–**26** may require some tuning depending on the nature of the thiol (see Experimental). For instance, the conditions suitable for preparation

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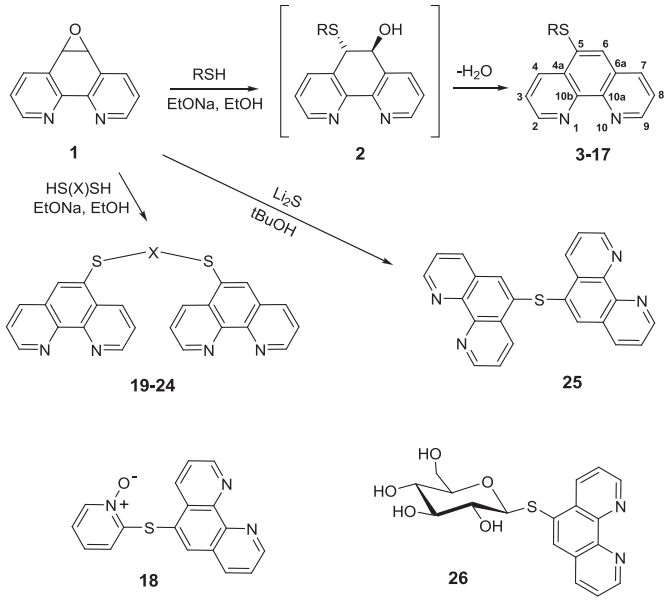


Scheme 1. Syntheses of 5-aryl(alkyl)sulfanyl-1,10-phenanthrolines.

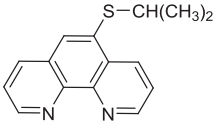
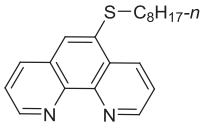
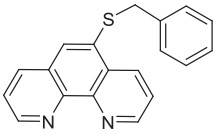
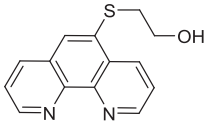
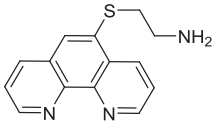
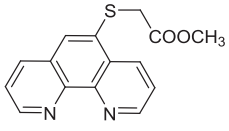
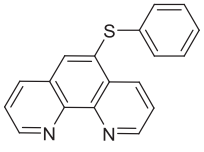
of compounds **3**–**17** (method A) yielded inseparable mixtures of products when applied to dithiols. Therefore to obtain the bis(phen) derivatives **19**–**24**, we used a slow addition of a diluted dithiol solution in ethanolic NaOEt to the concentrated solution of epoxide **1** at elevated temperature under argon atmosphere (method B). In another example, the use of Li_2S instead Na_2S improved substantially the yield and purity of product **25**. We found also that variation of solvent (simple alcohols) may be beneficial for the synthesis.

Noteworthy, the bis(phen) **22** was synthesized before, but in a form of a binuclear complex with ruthenium(II), via substitution in a ruthenium(II) complex of 5-chloro-phen.[7] The simple synthesis of the free bis-phenanthrolines **19**–**25** described here may be instrumental in preparation of other mono/binuclear complexes and molecular assemblies.[14,15]

Synthesis of phen derivatives of cysteine was attempted starting with L-cysteine methyl ester hydrochloride or *N*-(*tert*-butoxycarbonyl)-L-cysteine methyl ester, but the reactions produced only inseparable mixtures of products. A successful attachment of the cysteine moiety to phen was achieved previously by substitution in a ruthenium(II) complex of 5-chloro-phen.[8]

Unexpectedly, a deoxygenation occurred in the reaction of epoxide **1** with a slight excess of sodium hydrosulfide at room temperature (the conditions for synthesis of 2-mercaptoalcohols[16]),

Table 1
Synthesis of 5-*RS*-1,10-phenanthrolines **3**–**26**

Product	Structure	Method	Time (h)	Temp (°C)	Yield (%)
3		A	10	50	79
4		A	15	50	93
5		A	24	60	80
6		A	12	20	78
7		A	10	50	71
8		—	3	60	63
9		A	6	20	83

(*continued on next page*)

Table 1 (*continued*)

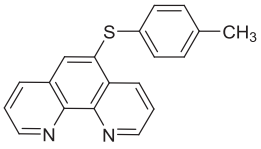
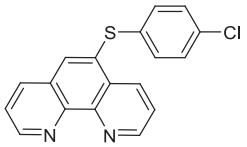
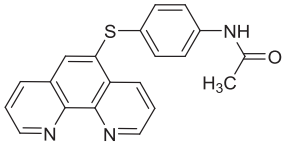
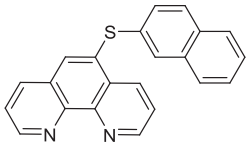
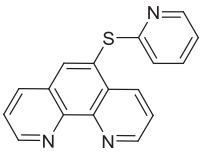
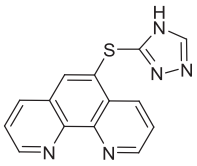
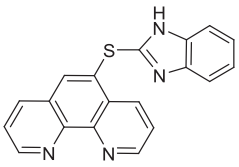
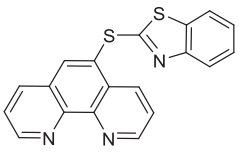
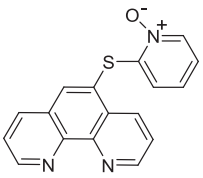
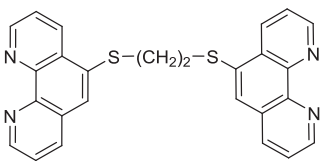
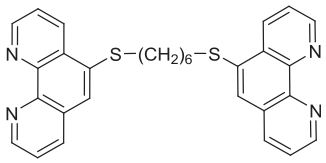
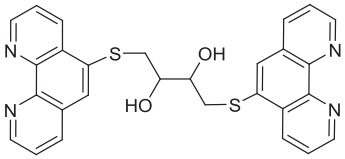
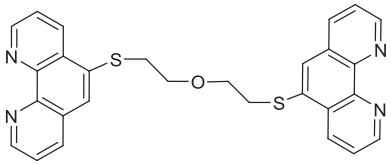
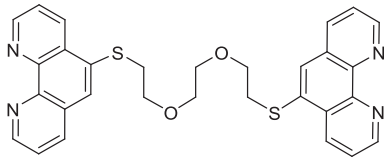
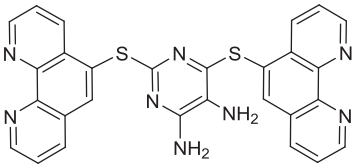
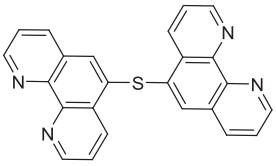
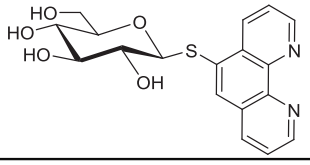
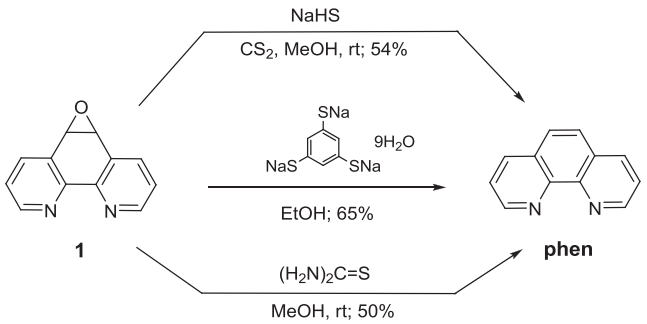
Product	Structure	Method	Time (h)	Temp (°C)	Yield (%)
10		A	12	20	93
11		A	24	22	88
12		A	1	60	97
13		A	12	60	83
14		A	16	22	79
15		A	36	60	72
16		A	36	60	85
17		A	24	60	81
18		—	4 +10	60 20	70
19		B	3	60	70

Table 1 (*continued*)

Product	Structure	Method	Time (h)	Temp (°C)	Yield (%)
20		B	4	78	73
21		B	24	50	91
22		B	2	22	50
23		B	12	50	54
24		B	24	22	62
25		—	3	60	82
26		—	36	22	64

which yielded phen as the only isolated product (Scheme 2). The same result was observed in the reaction with trithiocyanuric acid trisodium salt both at low (5 °C) and at high (60 °C) temperature. We obtained phen as a major product also in the reaction of epoxide **1** with thiourea in the standard conditions for preparation of thiiranes[17] (Scheme 2). A plausible mechanism for the deoxygenation may include formation and subsequent desulfurization of a thiirane. Each of these transformations is well known.[17–19] Aryl thiiranes were shown to split off elemental sulfur simply on heating with conversion to the corresponding olefins.[17] The easy desulfurization at room temperature that we found (Scheme 2) was apparently stimulated by the aromatization of the central ring as in the case of reactions described above. These observations may be of interest for further research, because epoxides are used as protecting groups for alkene double bonds, and their deprotection (deoxygenation) is a useful tool in organic synthesis.[19,20]



Scheme 2. Deoxygenation of 5,6-epoxy-5,6-dihydro-1,10-phenanthroline **1**.

Thioglycosides are known to be weak to moderate glycosidase inhibitors by being nonhydrolyzable substrate analogues, and as such they are potential therapeutic compounds in the treatment of various pathologies.[21–24] Therefore we assayed the new β-D-thioglucoside **26** as a possible β-D-glucosidase inhibitor by spectrophotometric monitoring (at 400 nm) of the *p*-nitrophenol release from the corresponding *p*-nitrophenyl glycosides according to procedures described earlier.[25,26] Indeed, the compound **26** (1 mM) decreased the activity of β-D-glucosidases isolated from fungi *Aspergillus oryzae* and *Penicillium canescens* by 75% and 77%, respectively. Thus it may be considered as a moderately strong β-D-glucosidase inhibitor. At the same time it increased the activity of β-D-galactosidases by 58% (*A. oryzae*) and 40% (*P. canescens*). Intrigued by this result we assayed phen and several derivatives for a possible activity towards glycosidases and found many cases of marked activation or inhibition of enzymes (Fig. 1). Usually the glycosidase activity is not significantly altered by the metal ion chelators like EDTA and 1,10-phenanthroline, because these enzymes are not metalloenzymes.[27–29] We found only two reports on inhibition by phen of some β-D-galactosidases (from *Pediococcus* sp.[30] and *A. oryzae*[31]). According to our data, phen had an opposite effect on β-D-galactosidase from *A. oryzae*: it increased the hydrolytic activity of this enzyme by a factor of two. The activation turned out to be more common for these compounds than the inhibition, especially towards β-D-glucosidases, for which only β-D-thioglucoside **26** was an inhibitor (Fig. 1a). The effect on activity of β-D-galactosidases appeared to be substituent-dependent (Fig. 1b). While phen and its epoxide **1** were activators, the simple derivatives **3**, **4**, **6** and **7** caused a moderate inhibition. The aryl(hetaryl)sulfanyl

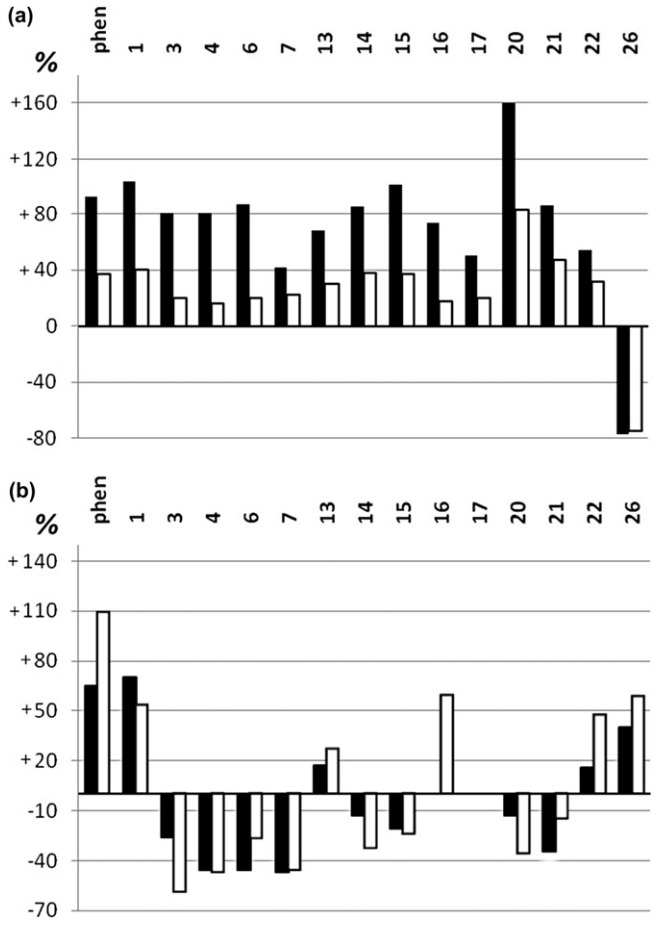


Fig. 1. Percent change of (a) β-D-glucosidase activity and (b) β-D-galactosidase activity in presence of 1,10-phenanthroline (phen) or its derivatives (1 mM). The enzyme producers: ■—*P. canescens*, □—*A. oryzae*.

derivatives **13**–**17** and bis(phens) **20**–**22** had weaker and non-systematic effects. To the best of our knowledge, an activation of glycosidases by phen or its derivatives was never observed before. Thus, our preliminary findings deserve further investigation.

3. Conclusion

We found that the nucleophilic cleavage of 1,10-phenanthroline 5,6-oxide **1** by various thiolates is immediately followed by spontaneous dehydration (aromatization). Based on this result, a novel convenient approach has been developed to a variety of functionalized 5-aryl(alkyl)sulfanyl-1,10-phenanthrolines that can be used as building blocks and ligands in organic and inorganic synthesis. The obtained compounds demonstrated an ability to activate or inhibit fungal β-D-glycosidases.

4. Experimental

4.1. General

The chemicals used in this study were purchased from commercial sources and used without additional purification. The epoxide **1** was obtained from Aldrich. All solvents were purified by conventional techniques prior to use. Column chromatography was performed on silica gel (40–75 μm, Sorbent Technologies) and aluminium oxide (activated basic, 58 Å, Aldrich). The reactions were monitored by TLC (silica gel or alumina, 8×2 cm plates with UV-indicator (254 nm), Analtech Inc.). ^{1}H NMR and ^{13}C NMR spectra were acquired on JEOL ECA-600 NMR-spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C). COSY and HMQC techniques were used to assign the signals. High resolution mass spectra (HRMS) were obtained on a JEOL AccuTOF time-of-flight mass spectrometer (Peabody, MA) coupled with an Ionsense DART open-air ionization source (Saugus, MA). The instrument was tuned to a resolving power of 7000 with reserpine directly infused into the electrospray ionization source; this provides a stable ion current to tune the time-of-flight parameters. Samples were introduced into the DART sample gap with a glass melting point capillary by first dipping the closed end of the capillary into the sample then immediately placing it into the helium metastable beam. The helium gas temperature was set to 250 °C to aid in the desorption of the analyte from the capillary. The samples were held in the sample gap for 10–15 s to acquire several mass spectra to average for an accurate *m*/*z* assignment.

4.2. General procedure for preparation of compounds 3–7, 9–17 (method A)

A thiol (0.3 mmol) was dissolved in a sodium ethoxide solution in ethanol (0.1 M, 2 mL). This mixture was added to a solution of **1** (50 mg, 0.255 mmol) in dry ethanol (2 mL) at room temperature. The reaction mixture was stirred at 20–60 °C for 1–36 h (Table 1) until complete conversion of the epoxide, as monitored by TLC (silica gel; EtOAc/CH_3OH/NH_4OH 10:1:0.5). The reaction mixture was neutralized with **1** drop of 1 M HCl to pH ~7, and the solvent was removed on a rotary evaporator. The product was isolated either by column chromatography or by crystallization.

*4.2.1. 5-Isopropylsulfanyl-1,10-phenanthroline (**3**).* Compound **3** was prepared by method A using isopropyl mercaptane and isolated as a yellow oil (52 mg, 79%) by column chromatography (Al_2O_3; EtOAc/MeOH 10:1). ^{1}H NMR ($CDCl_3$): δ 1.30 (d, J=6.7 Hz, 6H; CH_3), 3.43 (sep, J=6.7 Hz, 1H; $CHMe_2$), 7.57 (dd, J=8.0, 4.3 Hz, H8), 7.64 (dd, J=8.3, 4.2 Hz, H3), 7.89 (s, H6), 8.13 (dd, J=8.0, 1.6 Hz, H7), 8.83 (dd, J=8.3, 1.7 Hz, H4), 9.11 (dd, J=4.3, 1.7 Hz, H9), 9.16 (dd, J=4.2, 1.6 Hz, H2); ^{13}C NMR ($CDCl_3$): δ 23.25 (CH_3), 38.92 (CH), 123.17 (C3), 123.49 (C8), 128.30, 129.57 (C4a/C6a), 130.62 (C6), 132.20 (C5), 134.34 (C4), 135.42

(C7), 145.89, 146.44 (C10a/C10b), 150.39 (C9), 150.45 (C2); HRMS: $C_{15}H_{14}N_2S$ requires $[2M+H]^+$ *m/z* 509.1834, $[M+H]^+$ *m/z* 255.0956; observed *m/z* 509.1787, 255.0926.

*4.2.2. 5-Octylsulfanyl-1,10-phenanthroline (**4**).* Compound **4** was prepared by method A using 1-octanethiol and isolated as a brownish solid (77 mg, 93%; mp 68–70 °C) by column chromatography (SiO_2; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 0.85 (t, *J*=6.9 Hz, 3H; CH_3), 1.19–1.33 (m, *J*=6.7 Hz, 8H; CH_2, octyl), 1.46 (p, *J*=7.3 Hz, 2H; CH_2, octyl), 1.72 (p, *J*=7.5 Hz, 2H; CH_2, octyl), 3.05 (p, *J*=7.5 Hz, 2H; CH_2S), 7.58 (dd, *J*=8.1, 4.3 Hz, H8), 7.66 (dd, *J*=8.3, 4.2 Hz, H3), 7.70 (s, H6), 8.12 (dd, *J*=8.1, 1.7 Hz, H7), 8.74 (dd, *J*=8.3, 1.7 Hz, H4), 9.10 (dd, *J*=4.3, 1.7 Hz, H9), 9.18 (dd, *J*=4.3, 1.6 Hz, H2); ^{13}C NMR ($CDCl_3$): δ 14.16 (CH_3, octyl), 22.71, 28.85, 29.00, 31.86 (CH_2 octyl), 33.80 (CH_2S) 123.00 (C3), 123.47 (C8), 125.40 (C6), 128.40, 128.54 (C4a/C6a), 133.42 (C4), 133.87 (C7), 134.98 (C5), 145.34, 146.26 (C10a/C10b), 149.95 (C9), 150.45 (C2); HRMS: $C_{20}H_{24}N_2S$ requires $[2M+H]^+$ *m/z* 649.3399, $[M+H]^+$ *m/z* 325.1738; observed *m/z* 649.3322, 325.1727.

*4.2.3. 5-Benzylsulfanyl-1,10-phenanthroline (**5**).* Compound **5** was prepared by method A using benzyl mercaptane and isolated as a brownish solid (62 mg, 80%; mp 48–50 °C) by column chromatography (SiO_2; EtOAc/MeOH 7:2). ^{1}H NMR ($CDCl_3$): δ 4.17 (s, 2H; CH_2Ph), 7.19 (m, 5H; Ph), 7.55 (dd, *J*=8.0, 4.3 Hz, H8), 7.61 (dd, *J*=8.3, 4.3 Hz, H3), 7.66 (s, H6), 8.03 (dd, *J*=8.1, 1.6 Hz, H7), 8.70 (dd, *J*=8.3, 1.7 Hz, H4), 9.10 (dd, *J*=4.3, 1.7 Hz, H9), 9.16 (dd, *J*=4.2, 1.6 Hz, H2); ^{13}C NMR ($CDCl_3$): δ 39.31 (CH_2), 123.14 (C3), 123.52 (C8), 127.59 (C6), 128.35, 128.61, 128.68, 129.01, 132.60 (C, CH, phenyl, C4a, C6a), 133.65 (C4), 135.28 (C7), 136.58 (C5), 145.63, 146.26 (C10a/C10b), 150.33 (C9), 150.46 (C2); HRMS: $C_{19}H_{14}N_2S$ requires $[2M+H]^+$ *m/z* 605.1834, $[M+H]^+$ *m/z* 303.0956; observed *m/z* 605.1752, 303.0936.

*4.2.4. 5-(2-Hydroxyethylsulfanyl)-1,10-phenanthroline (**6**).* Compound **6** was prepared by method A using 2-mercaptoethanol and isolated as a white solid (51 mg, 78%; mp 175–176 °C) by crystallization from EtOAc. ^{1}H NMR (CD_3OD): δ 3.23 (t, *J*=6.5 Hz, 2H; CH_2S), 3.79 (t, *J*=6.5 Hz, 2H; CH_2O), 7.66 (dd, *J*=8.1, 4.3 Hz, H8), 7.74 (dd, *J*=8.4, 4.3 Hz, H3), 7.87 (s, H6), 8.27 (dd, *J*=8.1, 1.6 Hz, H7), 8.77 (dd, *J*=8.3, 1.6 Hz, H4), 8.95 (dd, *J*=4.3, 1.7 Hz, H9), 9.04 (dd, *J*=4.3, 1.6 Hz, H2); ^{13}C NMR (CD_3OD): δ 35.37 (CH_2S), 59.88 (CH_2O), 123.19 (C3), 123.72 (C8), 125.48 (C6), 128.17, 128.68 (C4a/C6a), 133.18 (C5), 133.44 (C4), 135.53 (C7), 144.21, 145.25 (C10a/C10b), 149.16(C9), 149.67 (C2); HRMS: $C_{14}H_{12}N_2OS$ requires $[2M+H]^+$ *m/z* 513.1419, $[M+H]^+$ *m/z* 257.0749; observed *m/z* 513.1353, 257.0725.

*4.2.5. 5-(2-Aminoethylsulfanyl)-1,10-phenanthroline (**7**).* Compound **7** was prepared by method A using 2-aminoethanethiol hydrochloride and sodium ethoxide solution in ethanol (0.3 M, 2 mL), and was isolated as a yellow oil (46 mg, 71%) by column chromatography (SiO_2; MeOH/NH_4OH 20:1). ^{1}H NMR ($CDCl_3$): δ 1.55 (br s, 2H, NH_2), 2.99 (t, *J*=6.3 Hz, 2H; CH_2S), 3.15 (t, *J*=6.3 Hz, 2H; CH_2N), 7.61 (dd, *J*=8.0, 4.3 Hz, H8), 7.69 (dd, *J*=8.3, 4.3 Hz, H3), 7.83 (s, H6), 8.15 (dd, *J*=8.1, 1.7 Hz, H7), 8.80 (dd, *J*=8.3, 1.6 Hz, H4), 9.13 (dd, *J*=4.3, 1.6 Hz, H9), 9.20 (dd, *J*=4.3, 1.6 Hz, H2); ^{13}C NMR ($CDCl_3$): δ 38.10 (CH_2N), 40.90 (CH_2S), 123.21 (C3), 123.59 (C8), 127.34 (C6), 128.39, 128.59 (C4a/C6a), 132.43 (C5), 133.61 (C4), 135.17 (C7), 145.60, 146.41 (C10a/C10b), 150.32 (C9), 150.56 (C2); HRMS: $C_{14}H_{13}N_3S$ requires $[2M+H]^+$ *m/z* 511.1739, $[M+H]^+$ *m/z* 256.0908; observed *m/z* 511.1718, 256.0852.

*4.2.6. 5-Phenylsulfanyl-1,10-phenanthroline (**9**).* Compound **9** was prepared by method A using thiophenol and isolated as a yellowish solid (61 mg, 83%; mp 54–56 °C) by column chromatography (SiO_2; EtOAc/MeOH 7:2). ^{1}H NMR (CD_3OD): δ 7.25 (m, 1H; Ph), 7.30 (d, *J*=4.1 Hz, 4H; Ph), 7.73 (dd, *J*=8.1, 4.4 Hz, 2H; H3, H8), 7.98 (s, H6), 8.32 (d, *J*=8.0 Hz, H7), 8.77 (d, *J*=8.3 Hz, H4), 9.04 (dd, *J*=4.3, 1.3 Hz, H9) 9.07 (dd, *J*=4.2, 1.2 Hz, H2); ^{13}C NMR (CD_3OD): δ 123.57, 123.98 (C3/C8), 127.28 (C_6H_4), 128.48, 128.63 (C4a/C6a), 129.39, 130.16 (C_6H_4), 131.26 (C6), 134.42 (C5), 134.51 (C4), 136.42 (C7), 145.16, 145.79 (C10a/C10b), 150.01 (C2), 150.19 (C9); HRMS: $C_{18}H_{12}N_2S$ requires $[2M+H]^+$ *m/z* 577.1521, $[M+H]^+$ *m/z* 289.0799; observed *m/z* 577.1509, 289.0736.

*4.2.7. 5-p-Tolylsulfanyl-1,10-phenanthroline (**10**).* Compound **10** was prepared by method A using *p*-thiocresol and isolated as a yellowish solid (72 mg, 93%; mp 132–133 °C) by column chromatography (SiO_2; MeOH). ^{1}H NMR ($CDCl_3$): δ 2.33 (s, 3H; CH_3), 7.12 (d, *J*=7.9 Hz, 2H; C_6H_4), 7.24 (d, *J*=8.0 Hz, 2H; C_6H_4), 7.59 (dd, *J*=8.0, 4.3 Hz, H8), 7.63 (dd, *J*=8.3, 4.3 Hz, H3), 7.74 (s, H6), 8.08 (dd, *J*=8.1, 1.6 Hz, H7), 8.72 (dd, *J*=8.3, 1.6 Hz, H4), 9.14 (dd, *J*=4.3, 1.7 Hz, H9), 9.19 (dd, *J*=4.3, 1.6 Hz, H2); ^{13}C NMR ($CDCl_3$): δ 21.23 (CH_3), 123.31 (C3), 123.51 (C8), 128.38, 128.46, 129.75, 130.45, 131.25, 132.52 (C_6H_4/C6/C4a/C6a), 133.96 (C4), 135.52 (C7), 137.86 (C5), 146.02, 146.59 (C10a/C10b), 150.56 (C9), 150.59 (C2); HRMS: $C_{19}H_{14}N_2S$ requires $[2M+H]^+$ *m/z* 605.1834, $[M+H]^+$ *m/z* 303.0956; observed *m/z* 605.1785, 303.0926.

*4.2.8. 5-(4-Chlorophenylsulfanyl)-1,10-phenanthroline (**11**).* Compound **11** was prepared by method A using 4-chlorobenzenethiol and isolated as a white solid (72 mg, 88%; mp 228–230 °C) by crystallization from EtOAc. ^{1}H NMR ($CDCl_3$): δ 7.15 (m, 2H; C_6H_4), 7.21 (m, 2H; C_6H_4), 7.62 (dd, *J*=8.0, 4.3 Hz, 2H; H3, H8), 7.92 (s, H6), 8.14 (dd, *J*=8.0, 1.6 Hz, H7), 8.64 (dd, *J*=8.3, 1.6 Hz, H4), 9.18 (dd, *J*=4.4, 1.6 Hz, 2H; H2, H9); ^{13}C NMR ($CDCl_3$): δ 123.58, 123.71 (C3/C8), 128.31, 128.51, 129.68, 130.33, 130.88, 132.30, 132.35, 133.16 (C_6H_4/C6/C4a/C6a), 133.77 (C4), 134.17 (C7), 135.79 (C5), 146.44, 146.80 (C10a/C10b), 150.74 (C9), 151.00 (C2); HRMS: $C_{18}H_{11}ClN_2S$ requires $[2M+H]^+$ *m/z* 645.0741, $[M+H]^+$ *m/z* 323.0410; observed *m/z* 645.0636, 323.0341.

*4.2.9. 5-(4-Acetamidophenylsulfanyl)-1,10-phenanthroline (**12**).* Compound **12** was prepared by method A using 4-acetamidothiophenol and isolated as a white solid (85 mg, 97%; mp 241–243 °C) by gradient column chromatography (SiO_2; EtOAc/MeOH (2:1) to MeOH). ^{1}H NMR (DMSO): δ 2.00 (s, CH_3), 7.33 (d, *J*=8.6 Hz, 2H; C_6H_4), 7.58 (d, *J*=8.6 Hz, 2H; C_6H_4), 7.72 (dd, *J*=8.1, 4.3 Hz, H8), 7.78 (dd, *J*=8.3, 4.2 Hz, H3), 7.95 (s, H6), 8.39 (dd, *J*=8.1, 1.5 Hz, H7), 8.67 (dd, *J*=8.3, 1.4 Hz, H4), 9.04 (dd, *J*=4.2, 1.4 Hz, H9), 9.10 (dd, *J*=4.2, 1.3 Hz, H2), 10.10 (s, NH); ^{13}C NMR (DMSO): δ 24.54 (CH_3), 120.57, 120.66 (C_6H_4), 124.21 (C3), 124.39 (C8), 126.76, 128.08, 128.69 (C_6H_4/C4a/C6a), 130.59 (C6), 131.91(C5), 132.36 (C_6H_4), 133.86 (C4), 136.48 (C7), 139.79 (C_6H_4), 145.73, 146.47 (C10a/C10b), 150.85 (C2), 150.94 (C9), 169.05 (C=O); HRMS: $C_{20}H_{15}N_3OS$ requires $[M+H]^+$ *m/z* 346.1014; observed *m/z* 346.0980.

*4.2.10. 5-(2-Naphthalenylsulfanyl)-1,10-phenanthroline (**13**).* Compound **13** was prepared by method A using 2-mercaptonaphtaline and isolated as a brownish solid (71 mg, 83%; mp 163–164 °C) by column chromatography (SiO_2; MeOH). ^{1}H NMR (CD_3OD): δ 7.34 (m, 1H; naphthyl), 7.43 (m, 2H; naphthyl), 7.66 (m, 1H; naphthyl), 7.70 (m, 2H; H3, H8), 7.78 (m, 3H; CH, naphthyl), 7.99 (s, H6), 8.28 (d, *J*=8.0 Hz, H7), 8.79 (d, *J*=8.2 Hz, H4), 9.05 (m, 2H, H2, H9); ^{13}C NMR (CD_3OD): δ 123.57, 123.95 (C3/C8), 126.28, 126.66, 127.06, 127.32, 127.49, 128.45, 128.64, 129.05, 129.10, 131.25, 131.50, 131.68 (naphthyl/C4a/C6a), 132.51 (C6), 134.00 (C4), 134.40 (C5), 136.39 (C7), 145.19, 145.81 (C10a/C10b), 150.03, 150.18 (C2/C9); HRMS: $C_{17}H_{11}N_2S$ requires $[2M+H]^+$ *m/z* 677.1834, $[M+H]^+$ *m/z* 339.0956; observed *m/z* 677.1660, 339.0916.

*4.2.11. 5-(2-Pyridinylsulfanyl)-1,10-phenanthroline (**14**).* Compound **14** was prepared by method A using 2-mercaptopyridine and isolated as a white solid (58 mg, 79%; mp 227–229 °C) by column

chromatography (Al_2O_3; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 6.74 (dt, J=8.1, 0.9 Hz, 1H; pyridyl), 6.97 (ddd, J=7.4, 4.9, 1.0 Hz, 1H; pyridyl), 7.36 (ddd, J=8.1, 7.4, 1.9 Hz, 1H; pyridyl), 7.60 (dd, J=8.3, 4.2 Hz, H3), 7.66 (dd, J=8.0, 4.3 Hz, H8), 8.24 (dd, J=8.0, 1.6 Hz, H7), 8.30 (s, H6), 8.36 (ddd, J=4.9, 1.8, 0.9 Hz, 1H; pyridyl), 8.68 (dd, J=8.3, 1.6 Hz, H4), 9.18 (dd, J=4.2, 1.6 Hz, H2), 9.23 (dd, J=4.3, 1.7 Hz, H9); ^{13}C NMR ($CDCl_3$): δ 120.37, 121.33 (pyridyl), 123.65, 123.71 (C3/C8), 127.27, 128.36, 129.56 (C4a/C6a/C5), 135.01 (C4), 136.25 (C6/C7), 137.03 (pyridyl), 147.03, 147.13 (C10a/C10b), 149.94 (pyridyl), 150.77 (C2), 151.63 (C9), 160.02 (pyridyl); HRMS: $C_{17}H_{11}N_2S$ requires $[2M+H]^+$ m/z 579.1426, $[M+H]^+$ m/z 290.0752; observed m/z 579.1356, 290.0639.

*4.2.12. 5-(4H-1,2,4-Triazol-3-ylsulfanyl)-1,10-phenanthroline (**15**).* Compound **15** was prepared by method A using 4-amino-3-hydrazino-5-mercapto-1,2,4-triazole ('purpald') and isolated as a brown solid (51 mg, 72%; mp >300 °C) by crystallization from EtOAc. ^{1}H NMR (CD_3OD): δ 7.62 (s, H6), 7.65 (dd, J=8.1, 4.4 Hz, H8), 7.76 (dd, J=8.3, 4.4 Hz, H3), 8.03 (s, 1H; NCHNH), 8.18 (dd, J=8.1, 1.6 Hz, H7), 8.87 (dd, J=8.4, 1.6 Hz, H4), 8.94 (dd, J=4.4, 1.7 Hz, H9), 9.05 (dd, J=4.4, 1.6 Hz, H2); ^{13}C NMR (CD_3OD): δ 123.20 (C8), 123.71 (C3), 126.56 (C6), 127.93, 128.76 (C4a/C6a), 133.58, 133.69 (C4/C5), 135.87 (C7), 144.48, 145.37 (C10a/C10b), 149.21 (C9), 149.65 (C2), 150.57 (NCHNH), 152.00 (NC(NH)S); HRMS: $C_{14}H_9N_5S$ requires $[M+H]^+$ m/z 280.0657; observed m/z 280.0592.

*4.2.13. 5-(1H-Benzimidazol-2-ylsulfanyl)-1,10-phenanthroline (**16**).* Compound **16** was prepared by method A using mercaptobenzimidazole and isolated as a white solid (71 mg, 85%; mp 286–288 °C) by crystallization from EtOAc. ^{1}H NMR ($CDCl_3$/CD_3OD 1:1): δ 7.18 (m, 2H; benzimidazolyl), 7.43 (br s, 2H; benzimidazolyl), 7.70 (dd, J=8.4, 4.3 Hz, H3), 7.74 (dd, J=8.0, 4.4 Hz, H8), 8.34 (dd, J=8.2, 1.7 Hz, H7), 8.35 (s, H6), 8.81 (dd, J=8.4, 1.6 Hz, H4), 9.05 (dd, J=4.3, 1.6 Hz, H2), 9.11 (dd, J=4.4, 1.7 Hz, H9); ^{13}C NMR ($CDCl_3$/CD_3OD 1:1): δ 122.69, 123.76, 123.87, 123.97 (benzimidazolyl/C3/C8), 126.13 (C6), 128.32, 129.02 (C4a/C6a), 134.34 (C5), 134.92(C4), 136.64(C7), 146.09, 146.21(C10a/C10b), 147.60 (NC(NH)S), 150.10 (C2), 150.86 (C9); HRMS: $C_{17}H_{11}N_2S$ requires $[M+H]^+$ m/z 329.0861; observed m/z 329.0785.

*4.2.14. 5-(1,3-Benzothiazol-2-ylsulfanyl)-1,10-phenanthroline (**17**).* Compound **17** was prepared by method A using 2-mercaptobenzothiazole and isolated as a white solid (71 mg, 81%; mp 181–182 °C) by column chromatography (SiO_2; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 7.23 (t, J=7.6 Hz, 1H; benzothiazolyl), 7.38 (dd, J=8.1, 7.4 Hz, 1H; benzothiazolyl), 7.54 (d, J=7.9 Hz, 1H; benzothiazolyl), 7.65 (dd, J=8.3, 4.3 Hz, H3), 7.71 (dd, J=8.0, 4.4 Hz, H8), 7.84 (d, J=8.3 Hz, 1H; benzothiazolyl), 8.30 (d, J=7.8 Hz, H7), 8.44 (s, H6), 8.81 (d, J=8.3 Hz, H4), 9.22 (d, J=4.0 Hz, H2), 9.28 (d, J=4.2 Hz, H9); ^{13}C NMR ($CDCl_3$): δ 120.00, 122.17 (benzothiazolyl), 123.87, 124.02 (C3/C8), 124.75, 126.15 (benzothiazolyl), 126.47, 128.07, 129.17, 134.57 (benzothiazolyl/C5/C4a/C6a) 135.66 (C4), 136.60 (C7), 137.33 (C6), 147.10, 147.43 (C10a/C10b), 151.10 (C2), 152.25 (C9), 153.76 (benzothiazolyl), 167.49 (NC(S)S); HRMS: $C_{19}H_{11}N_3S_2$ requires $[2M+H]^+$ m/z 691.0867, $[M+H]^+$ m/z 346.0473; observed m/z 691.0740, 346.0462.

4.3. General procedure for preparation of compounds 19–24 (method B)

A dithiol (0.12 mmol) was dissolved in a sodium ethoxide solution in ethanol (0.01 M, 15 mL). This solution was added dropwise during 1 h to a solution of epoxide **1** (50 mg, 0.255 mmol) in dry ethanol (1 mL) at room temperature in an argon atmosphere. The reaction mixture was stirred at 22–78 °C for 2–24 h (Table 1) until complete conversion of the epoxide as monitored by TLC (silica gel; EtOAc/CH_3OH/NH_4OH 10:1:0.5). The solvent was removed on a rotary evaporator. The product was isolated by column chromatography or crystallization.

*4.3.1. 1,2-Bis(1,10-phenanthrolin-5-ylsulfanyl)ethane (**19**).* Compound **19** was prepared by method B using 1,2-ethandithiol and a sodium isopropoxide solution in isopropanol (0.01 M, 15 mL). It was isolated as a brownish solid (40 mg, 70%; mp 235–237 °C) by column chromatography (Al_2O_3; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 3.24 (s, 4H; CH_2CH_2), 7.57 (dd, J=8.0, 4.3 Hz, 2H; H8, H8′), 7.61 (dd, J=8.3, 4.3 Hz, 2H; H3, H3′), 7.68 (s, 2H; H6, H6′), 7.86 (dd, J=8.1, 1.7 Hz, 2H; H7, H7′), 8.72 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 9.14 (dd, J=4.3, 1.7 Hz, 2H; H9, H9′), 9.18 (dd, J=4.3, 1.6 Hz, 2H; H2, H2′); ^{13}C NMR ($CDCl_3$): δ 33.61 (CH_2CH_2), 123.29 (C3, C3′), 123.68 (C8, C8′), 128.12, 128.68 (C4a/C6a, C4a′/C6a′), 128.90 (C6, C6′), 131.13 (C5, C5′), 133.65 (C4, C4′), 135.22 (C7, C7′), 145.78, 146.47 (C10a/C10b, C10a′/C10b′), 150.69 (C9/C2, C9′/C2′); HRMS: $C_{26}H_{18}N_4S_2$ requires $[M+H]^+$ m/z 451.1051; observed m/z 451.1048.

*4.3.2. 1,6-Bis(1,10-phenanthrolin-5-ylsulfanyl)hexane (**20**).* Compound **20** was prepared by method B using 1,6-hexanedithiol and isolated as a yellow solid (47 mg, 73%; mp 96–97 °C) by crystallization from $CHCl_3$/MeOH (3:1). ^{1}H NMR ($CDCl_3$): δ 1.52 (m, 4H; CH_2, hexenyl), 1.73 (m, 4H, CH_2, hexenyl), 3.05 (m, 4H; $2CH_2S$), 7.58 (dd, J=8.0, 4.3 Hz, 2H; H8, H8′), 7.66 (dd, J=8.2, 4.2 Hz, 2H; H3, H3′), 7.71 (s, 2H; H6, H6′), 8.11 (dd, J=8.0, 1.5 Hz, 2H; H7, H7′), 8.73 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 9.11 (dd, J=4.3, 1.6 Hz, 2H; H9, H9′), 9.19 (dd, J=4.3, 1.5 Hz, 2H; H2, H2′); ^{13}C NMR ($CDCl_3$): δ 28.47 (hexenyl), 28.71 (hexenyl), 33.76 (CH_2S, hexenyl), 123.08 (C3,C3′), 123.53 (C8,C8′), 125.87 (C6, C6′), 128.42, 128.48 (C4a/C6a, C4a′/C6a′), 133.42 (C4, C4′), 133.53 (C7, C7′), 135.00 (C5, C5′), 145.40, 146.29 (C10a/C10b, C10a′/C10b′), 150.07 (C9, C9′), 150.52 (C2, C2′); HRMS: $C_{30}H_{26}N_4S_2$ requires $[M+H]^+$ m/z 507.1677; observed m/z 507.1563.

*4.3.3. 1,4-Bis(1,10-phenanthrolin-5-ylsulfanyl)butane-2,3-diol (**21**).* Compound **21** was prepared by method B using dl-dithiothreitol and isolated as a yellowish solid (59 mg, 91%; mp 210–211 °C) by crystallization from EtOAc. ^{1}H NMR (DMSO): δ 3.25–3.37 (m, 4H; CH_2S), 3.89 (m, 2H; CHOH), 7.67 (dd, J=8.0, 4.3 Hz, 2H; H8, H8′), 7.72 (dd, J=8.4, 4.2 Hz, 2H; H3, H3′), 7.93 (s, 2H; H6, H6′), 8.25 (dd, J=8.1, 1.6 Hz, 2H; H7, H7′), 8.57 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 8.97 (dd, J=4.3, 1.7 Hz, 2H; H9, H9′), 9.06 (dd, J=4.2, 1.6 Hz, 2H; H2, H2′); ^{13}C NMR (DMSO): δ 39.71 (CH_2S), 70.86 (CHOH), 123.84 (C3, C3′), 124.25 (C8, C8′), 124.87 (C6, C6′), 127.86, 128.86 (C4a/C6a, C4a′/C6a′), 133.04 (C4, C4′), 133.44 (C5, C5′), 135.63 (C7, C7′), 144.71, 145.87 (C10a/C10b, C10a′/C10b′), 149.96 (C9, C9′), 150.59 (C2, C2′); HRMS: $C_{30}H_{26}N_4S_2$ requires $[M+H]^+$ m/z 511.1262; observed m/z 511.1451.

*4.3.4. 1,5-Bis(1,10-phenanthrolin-5-ylsulfanyl)-3-oxapentane (**22**).* Compound **22** was prepared by method B using bis(2-mercaptoethyl) ether and isolated as a white solid (32 mg, 50%; mp 279–281 °C) by column chromatography (Al_2O_3; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 3.20 (t, J=6.4 Hz, 4H; CH_2S), 3.69 (t, J=6.4 Hz, 4H; CH_2O), 7.55 (dd, J=8.1, 4.3 Hz, 2H; H8, H8′), 7.65 (dd, J=8.4, 4.2 Hz, 2H; H3, H3′), 7.82 (s, 2H; H6, H6′), 8.08 (dd, J=8.1, 1.6 Hz, 2H; H7, H7′), 8.75 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 9.11 (dd, J=4.3, 1.7 Hz, 2H; H9, H9′), 9.18 (dd, J=4.2, 1.6 Hz, 2H; H2, H2′); ^{13}C NMR ($CDCl_3$): δ 34.31 (CH_2S), 69.44 (CH_2OH), 123.20 (C3, C3′), 123.60 (C8, C8′), 128.36 (C6, C6′), 128.58, 132.50 (C4a/C6a, C4a′/C6a′), 133.64 (C4, C4′), 135.22 (C7, C7′), 135.82(C5, C5′), 145.57, 146.29 (C10a/C10b, C10a′/C10b′), 150.33 (C9, C9′), 150.55 (C2, C2′); HRMS: $C_{28}H_{22}N_4OS_2$ requires $[2M+H]^+$ m/z 989.2548, $[M+H]^+$ m/z 495.1313; observed m/z 989.2567, 495.1235.

*4.3.5. 1,8-Bis(1,10-phenanthrolin-5-ylsulfanyl)-3,6-dioxaoctane (**23**).* Compound **23** was prepared by method B using 3,6-dioxa-

1,8-octanedithiol and isolated as a white solid (37 mg, 54%; mp 296–298 °C) by column chromatography (Al_2O_3; EtOAc/MeOH 9:2). ^{1}H NMR ($CDCl_3$): δ 3.22 (t, J=6.6 Hz, 4H; CH_2S), 3.55 (s, 4H; OCH_2-CH_2O), 3.70 (t, J=6.6 Hz, 4H; OCH_2CH_2S), 7.57 (dd, J=8.1, 4.3 Hz, 2H; H8, H8′), 7.65 (dd, J=8.3, 4.3 Hz, 2H; H3, H3′), 7.82 (s, 2H; H6, H6′), 8.11 (dd, J=8.1, 1.7 Hz, 2H; H7, H7′), 8.75 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 9.11 (dd, J=4.3, 1.7 Hz, 2H; H9, H9′), 9.18 (dd, J=4.3, 1.7 Hz, 2H; H2, H2′); ^{13}C NMR ($CDCl_3$): δ 33.69 (CH_2S), 69.68 (SCH_2CH_2O), 70.55 (OCH_2CH_2O), 123.16 (C3, C3′), 123.57 (C8, C8′), 127.30 (C6, C6′), 128.39, 128.59 (C4a/C6a, C4a′/C6a′), 133.58 (C5, C5′), 133.66 (C4, C4′), 135.20 (C7, C7′), 145.60, 146.32 (C10a/C10b, C10a′/C10b′), 150.30 (C9, C9′), 150.55 (C2, C2′); HRMS: $C_{30}H_{26}N_4O_2S_2$ requires $[M+H]^+$ m/z 539.1575; observed m/z 539.1520.

*4.3.6. 2,6-Bis(1,10-phenanthrolin-5-ylsulfanyl)pyrimidine-4,5-diamine (**24**).* Compound **24** was prepared by method B using 4,5-diamino-2,6-dimercaptopyrimidine; the precipitation was filtered off and washed with EtOAc yielding **24** as a brown solid (42 mg, 62%; mp >310 °C). ^{1}H NMR (DMSO): δ 7.34 (dd, J=8.3, 4.2 Hz, 1H), 7.46 (dd, J=8.3, 4.2 Hz, 1H), 7.64 (m, 2H), 7.74 (s, 1H), 7.93 (s, 1H), 8.06 (dd, J=8.1, 1.6 Hz, 1H), 8.13 (dd, J=8.2, 1.7 Hz, 1H), 8.16 (dd, J=8.1, 1.6 Hz, 1H), 8.22 (dd, J=8.3, 1.5 Hz, 1H), 8.69 (dd, J=4.2, 1.5 Hz, 1H), 8.79 (dd, J=4.2, 1.5 Hz, 1H), 9.01 (m, 2H); ^{13}C NMR was not obtained due to very low solubility of the compound; HRMS: $C_{30}H_{26}N_4O_2S_2$ requires $[M+H]^+$ m/z 531.1174; observed m/z 531.1110.

4.4. Preparation of 5-methoxycarbonylmethylsulfanyl-1,10-phenanthroline (8)

Methyl mercaptoacetate (0.025 mL, 0.27 mmol) was dissolved in a sodium methoxide solution in methanol (0.02 M, 10 mL), and the mixture was added dropwise to a solution of **1** (50 mg, 0.255 mmol) in dry methanol (2 mL) at 60 °C in an argon atmosphere. The reaction mixture was stirred at 60 °C for 1 h. Then additional sodium methoxide in methanol (0.05 M, 8 mL) was added dropwise during 2 h to a reaction mixture at 60 °C until complete conversion of the epoxide and the intermediate product as monitored by TLC (silica gel; EtOAc/CH_3OH/NH_4OH 10:1:0.5). The reaction mixture was neutralized with a few drops of 1 M HCl to pH ~7, and solvent was removed on a rotary evaporator. The product **8** was isolated as a brown solid (45 mg, 63%; mp 162–163 °C) by column chromatography (SiO_2; EtOAc/MeOH 8:2). ^{1}H NMR (CD_3OD): δ 3.62 (s, OCH_3), 3.94 (s, SCH_2), 7.76 (dd, J=8.0, 4.4 Hz, H8), 7.84 (dd, J=8.3, 4.4 Hz, H3), 8.07 (s, H6), 8.40 (dd, J=8.1, 1.4 Hz, H7), 8.88 (dd, J=8.3, 1.3 Hz, H4), 9.02 (d, J=4.4 Hz, H9), 9.09 (d, J=4.4 Hz, H2); ^{13}C NMR (CD_3OD): δ 35.35 (SCH_2), 51.81 (OCH_3), 123.57 (C3), 124.00 (C8), 128.37, 128.69 (C6/C5, C4a/C6a), 133.93 (C4), 136.27 (C7), 144.68, 145.31 (C10a/C10b), 149.95 (C9), 150.02 (C2), 169.97 (C=O); HRMS: $C_{15}H_{12}N_2O_2S$ requires $[2M+H]^+$ m/z 569.1317, $[M+H]^+$ m/z 285.0698; observed m/z 569.1359, 285.0649.

4.5. Preparation of 5-(1-oxypyridin-2-ylsulfanyl)-1,10-phenanthroline (18)

A solution of 2-mercaptopyridine *N*-oxide sodium salt (45 mg, 0.3 mmol) in 2 mL of dry ethanol was added to a solution of epoxide 1 (50 mg, 0.255 mmol) in dry ethanol (2 mL) and the mixture was stirred at 60 °C for 4 h until complete conversion of the epoxide as monitored by TLC (silica gel; EtOAc/CH_3OH/NH_4OH 10:1:0.5). Then sodium ethoxide in ethanol (0.02 M, 10 mL) was added dropwise to a reaction mixture at room temperature and the mixture was stirred for another 10 h. The solvent was removed on a rotary evaporator. The product **18** was isolated as a white solid (54 mg, 70%; mp 253–255 °C) by column chromatography (Al_2O_3; EtOAc/MeOH 10:2). ^{1}H NMR ($CDCl_3$): δ 6.24 (dd, J=8.4, 1.6 Hz, 1H; pyridyl), 6.88 (ddd, J=8.3, 7.6, 1.2 Hz, 1H; pyridyl), 7.01 (ddd, J=7.6, 6.6, 1.8 Hz, 1H; pyridyl), 7.66 (dd, J=8.2, 4.2 Hz, H3), 7.72 (dd, J=7.9, 4.3 Hz, H8), 8.29 (br s, 1H; pyridyl), 8.30 (m, H7), 8.38 (s, H6), 8.66 (dd, J=8.3, 1.5 Hz, H4), 9.24 (d, J=3.0 Hz, H2), 9.29 (d, J=3.1 Hz, H9); ^{13}C NMR ($CDCl_3$): δ 121.34, 122.47 (pyridyl), 123.93 (C8), 124.15 (C3), 125.25 (C5), 125.94 (pyridyl), 128.29, 129.14 (C4a/C6a), 134.43 (C4), 136.41 (C7), 137.69 (C6), 138.70 (pyridyl), 147.11, 147.34 (C10a/C10b), 151.27 (C2), 152.16 (pyridyl), 152.27 (C9); HRMS: $C_{17}H_{11}N_3OS$ requires $[M+H]^+$ m/z 306.0701; observed m/z 306.0684.

4.6. Preparation of bis(1,10-phenanthrolin-5-yl)sulfide (25)

A solution of Li_2S (15 mg, 0.2 mmol) in 15 mL of *tert*-butanol was added dropwise during 1 h to a suspension of epoxide 1 (55 mg, 0.28 mmol) in *tert*-butanol (2 mL) at 60 °C in an argon atmosphere. The reaction mixture was stirred at 60 °C for 2 h until complete conversion of the epoxide as monitored by TLC (silica gel; EtOAc/CH_3OH/NH_4OH 10:1:0.5). The solvent was removed on a rotary evaporator. Residue was dissolved in 20 mL of chloroform and washed with 10 mL of satd. NH_4Cl. The water layer was extracted with chloroform (3×5 mL). The organic extracts were combined and dried over Na_2SO_4. The solvent was removed on a rotary evaporator. The product **25** was isolated as a yellowish solid (45 mg, 82%; mp >300 °C) by crystallization from MeOH/H_2O (2:1). ^{1}H NMR ($CDCl_3$): δ 7.52 (dd, J=8.0, 4.3 Hz, 2H; H8, H8′), 7.67 (dd, J=8.3, 4.3 Hz, 2H; H3, H3′), 7.68 (s, 2H; H6, H6′), 8.00 (dd, J=8.1, 1.6 Hz, 2H; H7, H7′), 8.76 (dd, J=8.3, 1.6 Hz, 2H; H4, H4′), 9.18 (dd, J=4.4, 1.6 Hz, 2H; H9, H9′), 9.25 (dd, J=4.3, 1.6 Hz, 2H; H2, H2′); ^{13}C NMR ($CDCl_3$): δ 123.63 (C3, C3′), 123.73 (C8, C8′), 127.91, 128.40 (C4a/C6a, C4a′/C6a′), 130.32 (C6, C6′, C5, C5′), 133.58 (C4, C4′), 135.59 (C7, C7′), 146.09, 146.72 (C10a/C10b, C10a′/C10b′), 151.00 (C2, C2′, C9, C9′); HRMS: $C_{24}H_{14}N_4S$ requires m/z $[M+H]^+$ 391.1017; observed m/z 391.1022.

4.7. Preparation of 5-(β-D-glucopyranosylsulfanyl)-1,10-phenanthroline (26)

Sodium salt of 1-thio-β-D-glucose (65.5 mg, 0.3 mmol) in 2 mL of dry ethanol was added to a solution of epoxide 1 (50 mg, 0.255 mmol) in dry ethanol (2 mL) and stirred at room temperature for 36 h until complete conversion of the epoxide as monitored by TLC (silica gel; CH_3OH/NH_4OH 20:1). The precipitate was filtered off and recrystalized from EtOH affording product **26** as a yellowish solid (61 mg, 64%; mp 154–155 °C). ^{1}H NMR (DMSO): δ 3.08 (t, J=9.2 Hz, 1H; H4, glu), 3.17 (dd, J=9.6, 8.8 Hz, H2, glu), 3.23 (t, J=8.7 Hz, 1H; H3, glu), 3.30 (ddd, J=9.6, 6.5, 2.0 Hz, 1H; H5, glu), 3.41 (dd, J=11.8, 6.4 Hz, 1H; H6a, glu), 3.69 (dd, J=11.7, 1.9 Hz, 1H; H6b, glu), 4.79 (d, J=9.7 Hz, 1H; H1, glu), 7.74 (dd, J=8.1, 4.3 Hz, H8), 7.80 (dd, J=8.3, 4.2 Hz, H3), 8.29 (s, H6), 8.36 (dd, J=8.1, 1.6 Hz, H4), 8.79 (dd, J=8.4, 1.6 Hz, H7), 9.02 (dd, J=4.3, 1.6 Hz, H9), 9.09 (dd, J=4.2, 1.6 Hz, H2); ^{13}C NMR (DMSO): δ 61.57 (CH_2OH), 70.36 (C4, glu), 73.17(C2, glu), 79.74 (C3, glu), 81.75 (C5, glu), 87.46 (C1, glu), 123.91 (C3), 124.29 (C8), 128.73, 128.82 (C4a, C6a), 129.13 (C6), 131.44 (C5), 134.13 (C4), 136.34 (C7), 145.20, 145.86 (C10a/C10b), 150.48, 150.55 (C2/C9). HRMS: $C_{30}H_{26}N_4O_2S_2$ requires m/z $[M+H]^+$ 375.1015; observed m/z 375.1022.

4.8. General procedure for the glycosidase activation and inhibition assay

The enzyme activities (β-D-galactosidases and β-D-glucosidases) were assayed using multi-enzyme complexes isolated from fungi *P. canescens* and *A. oryzae* using somewhat modified procedures of prior studies.[25,26] All assays were performed in a standard way by monitoring spectrophotometrically the release of *p*-nitrophenol from the corresponding *p*-nitrophenyl glycosides at 30 °C. One unit of enzyme activity was defined as the amount of enzyme that releases 1 μmol of

p-nitrophenol per minute. Enzyme and substrate concentrations were selected so that the degree of hydrolysis was never more than 20%, and in most cases was less than 10%, over the course of the assay. The method used to measure the rate of the reaction assumes that the amount of the substrate is high enough, such that the disappearance over a given period is insignificant, that is the rate of the reaction is close to linear for the first stage of the reaction. Enzyme solutions (100 μL with activities 750±150 μU) were mixed with a set of inhibitor/activator solutions (100 μL, 10 mM), then diluted with 700 μL of 0.2 M acetic buffer (pH 4.6), and the mixture was incubated for 1 h at 30 °C. The reaction was initiated with addition of a proper substrate (100 μL of 20 mM *p*-nitrophenyl glycopyranoside), and aliquots were taken after 5 and 10 min. The reaction was terminated by addition of 1 mL of 1 M Na_2CO_3 to 0.5 mL of aliquot solution. The concentration of the released *p*-nitrophenol was determined at 400 nm with Beckman Du-65 spectrophotometer using molar extinction coefficient 18.3 mM^{-1} cm^{-1}. The inhibition/activation was estimated as a loss/increase of enzymatic activity in % (Fig. 1).

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