

Yasutaka Shimotori*, Masayuki Hoshi, Mari Murata, Narihito Ogawa, Tetsuo Miyakoshi and Taisei Kanamoto

Synthesis of dibenzothiazepine analogues by one-pot S-arylation and intramolecular cyclization of diaryl sulfides and evaluation of antibacterial properties

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Abstract: Dibenzothiazepine analogues containing lactam, amidine and imine moieties were prepared from 2-aminophenyl disulfides *via* one-pot S-arylation. The S-arylation involved cleavage of an S-S bond of disulfides and S_NAr reaction in aqueous ammonia solution of L-cysteine to afford diaryl sulfides. Dibenzothiazepine analogues having lactam and amidine moieties were obtained by cyclization of the corresponding diaryl sulfides under acidic conditions. One-pot S-arylation of 2-bromo-5-nitrobenzaldehyde gave dibenzothiazepine analogues with an imine moiety in one step through intramolecular cyclization. Compounds with antibacterial activities against *Staphylococcus aureus* and *Escherichia coli* were obtained.

Keywords: antibacterial activity; aryl disulfide; diaryl sulfide; dibenzothiazepine; L-cysteine; one-pot; S-arylation; S_NAr reaction; sulfur-containing heterocycle.

Introduction

Heterocyclic compounds exhibit various biological activities including antibacterial [1–5], antitumor [6–9], anti-inflammatory [10–14] and antiviral properties [15–19]. Important bioactive compounds are sulfur-containing heterocycles. Penicillin and cephalosporin C [20] used

as antibacterial agents, and ritonavir [21, 22] used as an anti-HIV therapeutic agent are well-known sulfur-containing cyclic compounds. In addition, benzothiazepines exhibit antimicrobial [23–25], antiviral [26], cytostatic [27], anticonvulsant [28, 29] and antipsychotic activities [30]. Previously, we have reported synthesis of sulfides from aryl disulfides [31, 32] by cleavage of an S-S bond of aryl disulfides using ammonium thioglycolate, followed by S-arylation and alkylation in one-pot treatment. In this study, the S-S bond cleavage of 2-aminophenyl disulfides was carried out using L-cysteine instead of thioglycolic acid. Diaryl sulfides were synthesized by a one-pot S_NAr reaction using nitroarenes. Various dibenzothiazepine analogues were synthesized by cyclization of the corresponding diaryl sulfides. Furthermore, antibacterial activities of the synthesized compounds against *Staphylococcus aureus* and *Escherichia coli* were investigated.

Results and discussion

Diltiazem and its derivatives, benzothiazepines having a lactam moiety, are used as antiarrhythmic drugs [33]. Benzothiazepines with an amidine moiety exhibit antipsychotic activity [34]. Based on these facts, we considered synthesizing various dibenzothiazepine analogues (Scheme 1). Dibenzothiazepines with lactam could be obtained by intramolecular cyclization of the corresponding diaryl sulfides substituted with a methyl ester. Similarly, those with imine could be obtained from the corresponding diaryl sulfides substituted with a formyl group. Furthermore, those with amidine could be obtained by the Pinner reaction at amino and cyano groups. Diaryl sulfides are readily available by one-pot S-arylation of disulfides with disubstituted nitroarenes [31, 32].

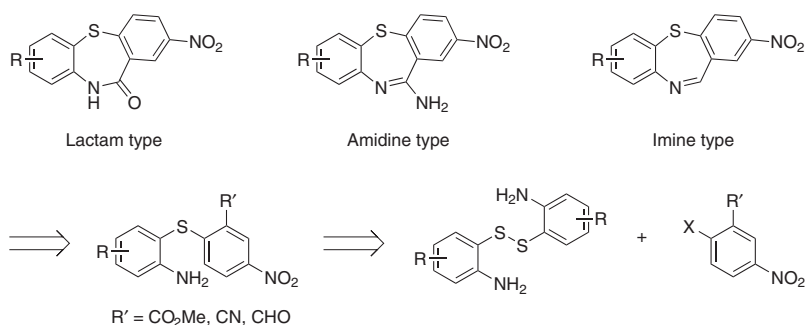
The effect of a leaving group on the S_NAr reaction in 2-aminophenyl disulfide and various nitroarenes was investigated. The nitro group, which is a strong electron withdrawing group for anion stabilization, is required to decrease the electron density at the benzene ring [35–39]. Various leaving groups of nitroarene were investigated. The S-S bond of bis(2-aminophenyl) disulfide was cleaved

*Corresponding author: Yasutaka Shimotori, School of Regional Innovation and Social Design Engineering, Kitami Institute of Technology, 165 Koen-cho, Kitami, Hokkaido 090-8507, Japan, e-mail: yasu@mail.kitami-it.ac.jp

Masayuki Hoshi: School of Regional Innovation and Social Design Engineering, Kitami Institute of Technology, 165 Koen-cho, Kitami, Hokkaido 090-8507, Japan

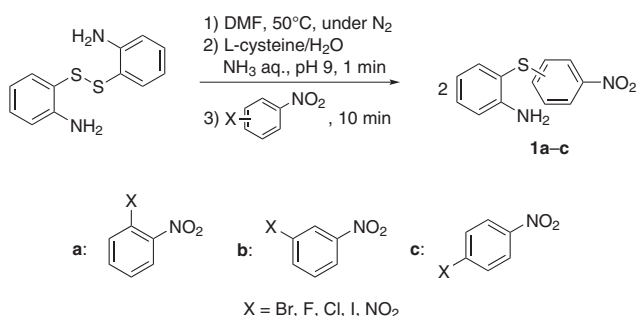
Mari Murata, Narihito Ogawa and Tetsuo Miyakoshi: Department of Applied Chemistry, School of Science and Technology, Meiji University, 1-1-1 Higashi-mita, Tama-ku, Kawasaki 214-8571, Japan

Taisei Kanamoto: Faculty of Pharmaceutical Sciences, Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida 194-8543, Japan

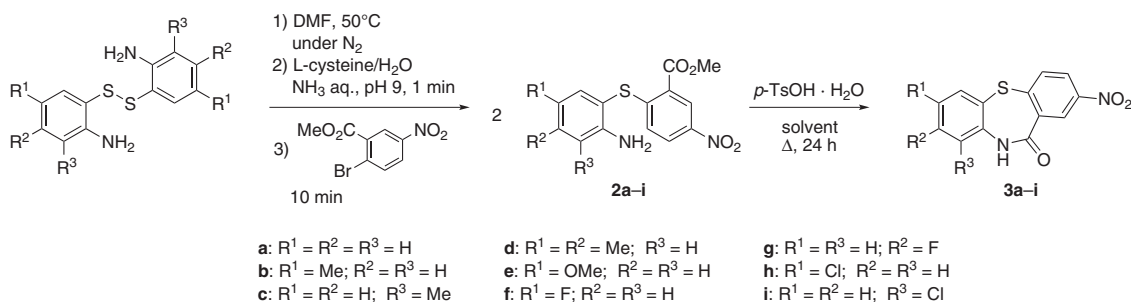


Scheme 1 Retrosynthetic analysis of three types of dibenzothiazepine analogues.

in aqueous ammonia solution of L-cysteine. Subsequently, one-pot *S*-arylation was performed between thiolate anion and various nitroarenes (Scheme 2). In the case of using an arylating agent with a bromo group at *ortho*- or *para*-position of the nitro group, *S*-arylation progressed with 48% and 69% yields, respectively. By contrast, *S*-arylation was not observed using 1-bromo-3-nitrobenzene. When the thiolate nucleophile attacks the *ipso* position containing a bromo substituent, σ -complex is formed as an intermediate. The bromo group at the *ortho*- or *para*-position stabilizes the σ -complex by a resonance effect, and no resonance effect is possible at the *meta*-position. The same feature may be operative in the case of dinitrobenzenes.



Scheme 2 $\text{S}_{\text{N}}\text{Ar}$ reaction of 2-aminophenyl disulfide and nitroarenes.



Scheme 3 Synthesis of lactam-containing dibenzothiazepines **3**.

The use of 1,2-dinitrobenzene and 1,4-dinitrobenzene gave the corresponding diaryl sulfides with 99% yields, and no *S*-arylation was observed using 1,3-dinitrobenzene. Among halogeno groups at the *para*-position, the presence of the fluoro group gave rise to the highest 99% yield, and the use of iodophenyl gave rise to a low yield of 36%. This analysis largely agrees with the order of degree of electronegativity. As the electronegativity increases, the positive charge at the *ipso*-position increases, which enhances electrophilicity. On the other hand, the yields are higher when using an arylating agent with a sterically smaller leaving group. Apparently, the addition of thiolate anion at the *ipso*-position is a rate-controlling step.

Methyl [2-(2-aminophenyl)sulfanyl]-5-nitrobenzoates **2** are precursors to dibenzothiazepine analogues having a lactam moiety. These compounds were prepared by one-pot *S*-arylation of 2-aminophenyl disulfides with methyl 2-bromo-5-nitrobenzoate (Scheme 3). All diaryl sulfides **2** were obtained in a quantitative yield. With 1-bromo-4-nitrobenzene used as an arylating agent, the conversion was not 100% after 10 min and the yield of 2-aminophenyl 4-nitrophenyl sulfide (**1c**) was 69%. By contrast, when using methyl 2-bromo-5-nitrobenzoate, all diaryl sulfides **2** were quantitatively obtained after 10 min regardless of the substituents. In nitroarenes with a methyl ester group at the *ortho*-position to the leaving group, the ester group acts as an electron withdrawing

group, which decreases the electron density at the carbon atom at the *ipso*-position of the halogen. This feature facilitates the nucleophilic attack of thiolate anion, increasing the yields of diaryl sulfides **2**.

Lactam dibenzothiazepine analogues **3** were obtained by intramolecular cyclization of the corresponding diaryl sulfides **2** (Scheme 3). The cyclization was carried out in the presence of *p*-TsOH · H₂O as an acid catalyst under reflux for 24 h. With 0.2 and 0.4 equivalents of *p*-TsOH · H₂O, the cyclization of methyl [2-(2-aminophenyl)sulfanyl]-5-nitrobenzoate (**2a**) in *o*-xylene yielded 2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (**3a**) in the respective yields of 40% and 95%. When the reaction was conducted under reflux with 0.4 equivalent of *p*-TsOH · H₂O in toluene instead of *o*-xylene, the yield of **3a** dropped to 15%. It can be suggested that the reaction requires 0.4 equivalent of acid and should be conducted at least at 140°C. Other lactam dibenzothiazepine analogues **3b–i** were synthesized under similar conditions. Excepting **3d** and **3f**, the remaining dibenzothiazepines **3** were obtained with a yield of more than 80%.

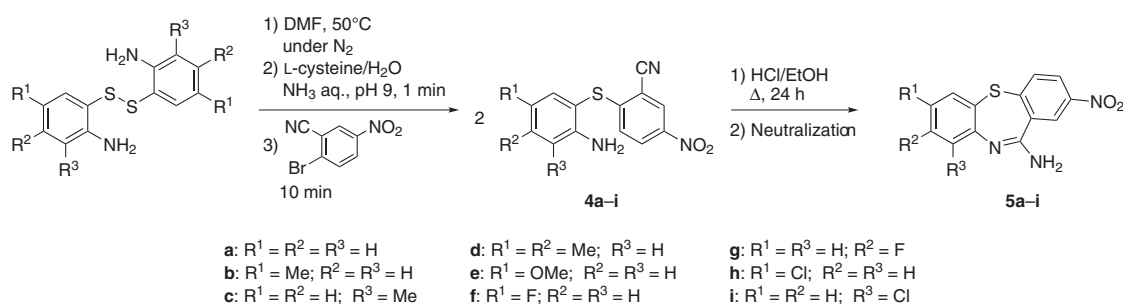
The amidine dibenzothiazepine analogues **5** were synthesized as shown in Scheme 4 starting with diaryl sulfides **4** substituted with a nitrile group. 2-Bromo-5-nitrobenzonitrile as an arylating agent was added after the cleavage of the S-S bond of 2-aminophenyl disulfides, and the mixture was stirred for 10 min (Scheme 4). 2-Aminophenyl-2-cyano-4-nitrophenyl sulfide (**4a**) was obtained in a 62% yield. When the amount of the arylating agent was increased to 3.0 equivalents and the reaction was conducted for 10 min under otherwise similar conditions, the yield of **4a** increased to 84%. After the reaction time was extended to 30 min, the yield of **4a** was further increased to 95%. *S*-arylation of the remaining 2-aminophenyl disulfides was carried out under similar conditions to furnish diaryl sulfides **4b–i** with yields of about 80%.

Intramolecular cyclization of diaryl sulfides **4** between the amino and nitrile groups was carried out by the Pinner reaction (Scheme 4). In a model reaction, 2-aminophenyl 2-cyano-4-nitrophenyl sulfide (**4a**) was added to hydrogen

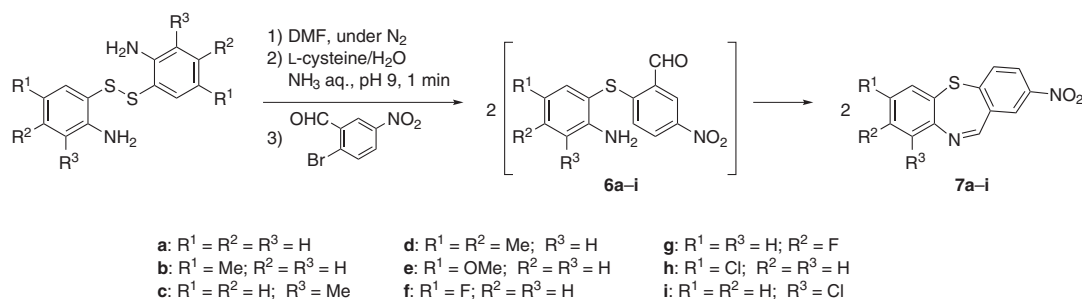
chloride in ethanol and the mixture was heated under reflux for 24 h. Various concentrations of hydrogen chloride were investigated. In the presence of 5, 10, 20 and 30 wt% of hydrogen chloride in ethanol, 2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (**5a**) was obtained in the respective yields of 28, 26, 38 and 61%. As can be seen, the yields increased with increasing concentration of HCl. Accordingly, synthesis of other products **5b–i** from 2-aminophenyl-2-cyano-4-nitrophenyl sulfides **4** was conducted using 30 wt% hydrogen chloride ethanolic solution. Dibenzothiazepines **5b–i** were obtained regardless of the nature of substituents R¹, R² and R³. When diaryl sulfides **4f** with R¹=F and **4h** with R¹=Cl were used, the yields of **5f** and **5h** were improved by at least 10% as compared with the yield of **5a**. On the other hand, the yields of dibenzothiazepines **5b–e** having methyl or methoxy groups decreased by about 20–30% as compared with that for **5a**. An electron donating group such as methyl or methoxy increases basicity of the amino group, which makes it easier to form hydrochloride. This feature reduces the reactivity of the amino group and decreases the yields of **5**.

Preparation of [2-(2-aminophenyl)sulfanyl]-5-nitrobenzaldehydes **6** and dibenzothiazepine analogues with imine moiety **7** involved the use of 2-bromo-5-nitrobenzaldehyde as an arylating agent (Scheme 5). After stirring at 50°C for 10 min, no diaryl sulfide **6a** could be isolated and the cyclized form, 2-nitrodibenzo[*b,f*][1,4]thiazepine (**7a**), was obtained in a yield of 48%. The reaction temperature was studied to improve the yield. The yield was increased to 67% for the reaction conducted at 70°C for 10 min. However, extending the time to 30 min did not increase the yield.

When the reaction was carried out at 90°C for 10 min, the yield was 62% and many by-products were observed by thin layer chromatography (TLC) analysis. The reaction time of 10 min at 70°C was taken as the optimum conditions. Synthesis of other dibenzothiazepine analogues with imine moiety **7b–i** is also shown in Scheme 5. In all cases, the *S*-arylation, regardless of the substituent



Scheme 4 Synthesis of dibenzothiazepine analogues with amidine moiety (**5**).



Scheme 5 Synthesis of dibenzothiazepine analogues with imine moiety 7.

Table 1 Antibacterial activities of compounds 4 and 5 against *S. aureus* and *E. coli*.

Sample	R ¹	R ²	R ³	<i>S. aureus</i> (CFU/mL)	<i>E. coli</i> (CFU/mL)	Sample	R ¹	R ²	R ³	<i>S. aureus</i> (CFU/mL)	<i>E. coli</i> (CFU/mL)
4a	H	H	H	2.0×10^5	1.2×10^9	5a	H	H	H	9.8×10^7	1.5×10^9
4b	Me	H	H	3.2×10^6	1.1×10^9	5b	Me	H	H	2.8×10^5	4.2×10^7
4c	H	H	Me	6.4×10^7	1.1×10^9	5c	H	H	Me	8.8×10^7	1.8×10^9
4d	Me	Me	H	2.0×10^7	1.4×10^9	5d	Me	Me	H	3.6×10^7	8.5×10^7
4e	OMe	H	H	4.6×10^7	1.4×10^9	5e	OMe	H	H	3.4×10^5	6.7×10^7
4f	F	H	H	7.4×10^6	1.3×10^9	5f	F	H	H	1.2×10^8	1.6×10^9
4g	H	F	H	2.6×10^4	1.7×10^9	5g	H	F	H	5.4×10^7	2.4×10^9
4h	Cl	H	H	9.5×10^4	8.0×10^8	5h	Cl	H	H	5.6×10^7	1.2×10^9
4i	H	H	Cl	1.1×10^8	1.9×10^9	5i	H	H	Cl	8.6×10^7	1.5×10^9

Negative control with *S. aureus* is 8.5×10^7 (CFU/mL) and with *E. coli* is 1.5×10^9 (CFU/mL).

on the benzene ring of thiolate anion, was spontaneously followed by intramolecular cyclization, and dibenzothiazepines 7 were obtained in about 50–60% yields.

The antibacterial activities of the products against *S. aureus* (Gram positive) and *E. coli* (Gram negative) bacteria were investigated (Table 1). A total of 45 diaryl sulfides 2 and 4 and dibenzothiazepines 3, 5 and 7 were tested. All diaryl sulfides 2 and dibenzothiazepines 3 and 7 show no activity against both *S. aureus* and *E. coli* regardless of the substituents R¹–R³. All diaryl sulfides 4 show no antibacterial activity against *E. coli*. However, compound 4a reduced *S. aureus* to about 0.2% compared with the negative control. Moreover, 4g and 4h show even stronger activities reducing *S. aureus* to about 0.03 and 0.1%, respectively. Because not all diaryl sulfides 4 exhibit antibacterial activities, the apparent correlation between the presence of a cyano group and antibacterial activity cannot be confirmed. As 2g and 2h are not active, the fluorine atom (R²) and the chlorine atom (R¹) are not necessarily involved in the activity.

Dibenzothiazepines with amidine moiety 5b and 5e show activities against both *S. aureus* and *E. coli* decreasing the bacteria to about 0.4 and 3–4%, respectively, compared to the negative control. Dibenzothiazepine 5d shows antibacterial activity only against *E. coli*. Furthermore,

three dibenzothiazepines with lactam moiety, 3b, 3d and 3e, and three dibenzothiazepines with amidine moiety, 7b, 7d and 7e, are not active.

Conclusions

The S-S bonds of various aryl disulfides are efficiently cleaved in the presence of L-cysteine. When methyl 2-bromo-5-nitrobenzoate is used as an arylating agent, diaryl sulfides 2 are quantitatively obtained in a one-pot reaction. Similarly, the use of 2-bromo-5-nitrobenzonitrile furnishes diaryl sulfides 4 in high yield. Dibenzothiazepines having lactam and amidine moieties, 3 and 5, were synthesized from the corresponding diaryl sulfides, 2 and 4, under acidic conditions. On the other hand, dibenzothiazepines with imine moiety 7 were obtained from the aryl disulfides in a one-pot procedure that involves spontaneous intramolecular cyclization of the intermediate products 6. All diaryl sulfides 2 and dibenzothiazepines 3 and 7 show no antibacterial activity against both *S. aureus* and *E. coli*. However, diaryl sulfides 4a, 4g and 4h are highly active against *S. aureus*. Two dibenzothiazepines with amidine moiety, 5b and 5e, show antibacterial activities against both *S. aureus* and *E. coli*.

Experimental

Unless stated otherwise, proton nuclear magnetic resonance (^1H NMR) spectra (600 MHz) and carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra (150 MHz) were recorded in dimethyl sulfoxide- d_6 (DMSO- d_6) on a JNM-ECA-600 spectrometer (JEOL, Tokyo, Japan). Structural determination of all compounds was performed using correlation spectroscopy (COSY), heteronuclear multiple quantum coherence (HMQC) and heteronuclear multiple bond correlation (HMBC) NMR techniques. Infrared spectra were obtained in KBr pellets on a Fourier-transform infrared spectroscopy (FTIR) 460plus spectrometer (JASCO Corp., Tokyo, Japan). Electrospray ionization (ESI) high resolution mass spectra were recorded on an AccuTOF GCv 4G instrument (JEOL). Melting points were recorded on a MP-500D micro-melting-point apparatus from Yanaco Technical Science Co., Ltd. (Kyoto, Japan) and are uncorrected.

General procedure for the preparation of 2-aminophenyl 2-nitrophenyl sulfides 1a–c

A solution of bis(2-aminophenyl) disulfide (0.10 g, 0.40 mmol) in 2.5 mL dimethyl formamide (DMF) was treated at 50°C under nitrogen with L-cysteine (0.15 g, 1.21 mmol), and the pH of the mixture was adjusted to 9 using ammonia water. After stirring for 1 min, 1,2-dinitrobenzene or 1,4-dinitrobenzene (0.15 g, 0.89 mmol) was added, and the mixture was continuously stirred until bis(2-aminophenyl) disulfide was completely consumed, as monitored by TLC. Then, the mixture was diluted with water and extracted with Et_2O or AcOEt. The organic layer was washed with brine, dried with MgSO_4 , filtered and concentrated under reduced pressure. The crude product **1a,c** was purified by column chromatography on silica gel eluting with hexane-ethyl acetate, 9:1.

2-Aminophenyl 2-nitrophenyl sulfide (1a) Yield 99%; yellow solid; mp 80–81°C; R_f 0.50 (hexane-AcOEt, 3:1); IR: 3468 (N-H), 3373 (N-H), 3099 (Ar, C-H), 1612 (Ar, C=C), 1511 (ArNO_2 , (N=O) $_2$), 1331 (ArNO_2 , (N=O) $_2$), 1042 (Ar-S-Ar), 854 (ArNO_2 , C-N), 724 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 4.28 (s, 2H, NH_2), 6.80 (t, $J=7.5$ Hz, 1H, H-5'), 6.83–6.86 (m, 2H, H-3', H-6), 7.21 (t, $J=7.7$ Hz, 1H, H-4'), 7.29–7.36 (m, 2H, H-4', H-5'), 7.41 (d, $J=8.0$ Hz, 1H, H-6'), 8.23 (d, $J=8.0$ Hz, 1H, H-3); ^{13}C NMR (CDCl_3): δ 112.0 (C-1'), 115.5 (C-3'), 119.1 (C-5'), 125.0 (C-4), 126.0 (C-3), 127.2 (C-6), 132.3 (C-4'), 133.7 (C-5), 137.2 (C-1), 137.7 (C-6'), 145.1 (C-2), 149.3 (C-2').

2-Aminophenyl 4-nitrophenyl sulfide (1c) Yield 99%; yellow solid; mp 63–64°C; R_f 0.49 (hexane-AcOEt, 3:1); IR: 3457 (N-H), 3357 (N-H), 1616 (Ar, C=C), 1497 (Ar, C=C), 1477 (Ar, C=C), 1336 (ArNO_2 , (N=O) $_2$), 853 (ArNO_2 , C-N), 837 (Ar, C-H), 746 cm^{-1} (Ar, C-H); ^1H NMR: δ 5.47 (ss, 2H, NH_2), 6.65 (td, $J=3.3$, 7.5 Hz, 1H, H-5'), 6.88 (dd, $J=3.2$, 8.3 Hz, 1H, H-3'), 7.16–7.19 (m, 2H, H-2, H-6), 7.24–7.28 (m, 1H, H-4'), 7.34 (dd, $J=3.1$, 7.5 Hz, 1H, H-6'), 8.10–8.12 (m, 2H, H-3, H-5); ^{13}C NMR: δ 108.9 (C-1'), 115.2 (C-3'), 116.8 (C-5'), 123.9 (C-3, C-5), 125.5 (C-2, C-6), 131.9 (C-4'), 137.1 (C-6'), 144.6 (C-4), 147.3 (C-1), 150.6 (C-2').

Methyl [2-(2-aminophenyl)sulfanyl]-5-nitrobenzoate (2a) Yield 99%; yellow solid; mp 105–106°C; R_f 0.10 (hexane-AcOEt, 9:1); IR: 3470 (N-H), 3373 (N-H), 1711 (C(=O)-O-), 1611 (Ar, C=C), 1573 (ArNO_2 , (N=O) $_2$), 1513 (Ar, C=C), 1477 (Ar, C=C), 1335 (ArNO_2 , (N=O) $_2$), 1260

(C(=O)-O-), 1132 (C-C(=O)-O-), 1048 (Ar-S-Ar), 902 (ArNO_2 , C-N), 837 (Ar, C-H), 738 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 4.03 (s, 3H, C(=O) OCH_3), 4.28 (s, 2H, NH_2), 6.83–6.86 (m, 2H, H-3', H-5'), 6.89 (d, $J=8.6$ Hz, 1H, H-3), 7.34 (td, $J=1.7$, 7.7 Hz, 1H, H-4'), 7.42 (d, $J=7.4$ Hz, 1H, H-6'), 8.06 (dq, $J=1.2$, 8.9 Hz, 1H, H-4), 8.88 (m, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.8 (C(=O) OCH_3), 111.8 (C-1'), 115.7 (C-5'), 119.4 (C-3'), 126.4–126.6 (C-3, C-4, C-6), 126.7 (C-1), 132.5 (C-4'), 137.5 (C-6'), 144.4 (C-5), 149.3 (C-2'), 151.1 (C-2), 165.2 (C(=O) OCH_3). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$, $[\text{M}]^+$: m/z 304.0518. Found: m/z 304.0519.

Methyl [2-(2-amino-5-methylphenyl)sulfanyl]-5-nitrobenzoate (2b) Yield 99%; orange solid; mp 117–118°C; R_f 0.48 (hexane-AcOEt, 3:1); IR: 3457 (N-H), 3366 (N-H), 3027 (Ar, C-H), 2954 (CH_3), 2925 (CH_3), 1719 (C(=O)-O-), 1615 (Ar, C=C), 1498 (Ar, C=C), 1453 (Ar, C=C), 1339 (ArNO_2 , (N=O) $_2$), 1304 (ArNH_2 , C-N), 1254 (C(=O)-O-), 1131 (C-C(=O)-O-), 1047 (Ar-S-Ar), 918 (ArNO_2 , C-N), 741 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 2.27 (s, 3H, ArCH_3), 4.03 (d, $J=1.4$ Hz, 3H, C(=O) OCH_3), 4.13 (s, 2H, NH_2), 6.78 (d, $J=7.4$ Hz, 1H, H-3'), 6.91 (dd, $J=1.1$, 8.9 Hz, 1H, H-3), 7.15 (d, $J=8.3$ Hz, 1H, H-4'), 7.23 (s, 1H, H-6'), 8.06 (d, $J=8.9$ Hz, 1H, H-4), 8.88 (s, 1H, H-6); ^{13}C NMR (CDCl_3): δ 20.2 (ArCH_3), 52.8 (C(=O) OCH_3), 111.8 (C-1'), 115.9 (C-3'), 126.3 (C-1), 126.4 (C-4), 126.6 (C-6), 126.8 (C-3), 128.9 (C-5'), 133.3 (C-4'), 137.4 (C-6'), 144.4 (C-2), 146.8 (C-2'), 151.3 (C-5), 165.2 (C(=O) OCH_3). HRMS (FD). Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$, $[\text{M}]^+$: m/z 318.0674. Found: m/z 318.0677.

Methyl [2-(2-amino-3-methylphenyl)sulfanyl]-5-nitrobenzoate (2c) Yield 99%; yellow solid; mp 96–97°C; R_f 0.48 (hexane-AcOEt, 3:1); IR: 3488 (N-H), 3393 (N-H), 2950 (CH_3), 2862 (CH_3), 1727 (C(=O)-O-), 1612 (Ar, C=C), 1518 (ArNO_2 , (N=O) $_2$), 1338 (ArNO_2 , (N=O) $_2$), 1243 (C(=O)-O-), 969 (Ar-S-Ar), 901 (ArNO_2 , C-N), 735 (Ar, C-H), 675 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 2.24 (s, 3H, ArCH_3), 4.03 (s, 3H, C(=O) OCH_3), 4.27 (s, 2H, NH_2), 6.77 (t, $J=7.6$ Hz, 1H, H-5'), 6.86 (d, $J=8.9$ Hz, 1H, H-3), 7.23 (d, $J=7.4$ Hz, 1H, H-4'), 7.31 (d, $J=7.7$ Hz, 1H, H-6'), 8.05 (dd, $J=2.6$, 9.2 Hz, 1H, H-4), 8.87 (d, $J=2.6$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 18.0 (ArCH_3), 52.8 (C(=O) OCH_3), 111.5 (C-1'), 118.8 (C-5'), 123.1 (C-3'), 126.4 (C-1, C-4), 126.6 (C-6), 126.7 (C-3), 133.4 (C-4'), 135.2 (C-6'), 144.3 (C-2), 147.5 (C-2'), 151.3 (C-5), 165.2 (C(=O) OCH_3). HRMS (FD). Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4\text{S}$, $[\text{M}]^+$: 318.0674. Found: m/z 318.0660.

Methyl [2-(2-amino-4,5-dimethylphenyl)sulfanyl]-5-nitrobenzoate (2d) Yield 99%; orange solid; mp 166–167°C; R_f 0.49 (hexane-AcOEt, 3:1); IR: 3466 (N-H), 3371 (N-H), 2957 (CH_3), 1721 (C(=O)-O-), 1616 (Ar, C=C), 1516 (ArNO_2 , (N=O) $_2$), 1456 (Ar, C=C), 1337 (ArNO_2 , (N=O) $_2$), 1249 (C(=O)-O-), 1193 (C-C(=O)-O-), 890 (ArNO_2 , C-N), 738 (Ar, C-H), 672 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 2.17 (s, 3H, ArCH_3 at C-5'), 2.25 (s, 3H, ArCH_3 at C-4'), 4.02 (s, 3H, C(=O) OCH_3), 4.07 (s, 2H, NH_2), 6.68 (s, 1H, H-3'), 6.92 (d, $J=9.2$ Hz, 1H, H-3), 7.15 (s, 1H, H-6'), 8.05 (dd, $J=2.6$, 8.9 Hz, 1H, H-4), 8.86 (d, $J=2.6$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 18.5 (ArCH_3 at C-5'), 19.9 (ArCH_3 at C-4'), 52.7 (C(=O) OCH_3), 108.8 (C-1'), 117.2 (C-3'), 126.3 (C-1, C-4), 126.6 (C-6), 126.8 (C-3), 127.9 (C-4'), 137.7 (C-6'), 141.7 (C-5'), 144.2 (C-2), 147.1 (C-2'), 151.8 (C-5), 165.2 (C(=O) OCH_3). HRMS (FD). Calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{S}$, $[\text{M}]^+$: m/z 332.0831. Found: m/z 332.0841.

Methyl [2-(2-amino-5-methoxyphenyl)sulfanyl]-5-nitrobenzoate (2e) Yield 99%; yellow solid; mp 115–116°C; R_f 0.49 (hexane-AcOEt, 3:1); IR: 3454 (N-H), 3366 (N-H), 3006 (Ar, C-H), 2957 (CH_3), 1709 (C(=O)-O-), 1494 (Ar, C=C), 1435 (Ar, C=C), 1345 (ArNO_2 , (N=O) $_2$), 1266 (C-O-C), 1047 (Ar-S-Ar), 900 (ArNO_2 , C-N), 838 (Ar, C-H), 691 cm^{-1} (Ar,

C=C); ^1H NMR (CDCl_3): δ 3.75 (s, 3H, ArOCH_3), 3.99 (s, 2H, NH_2), 4.02 (s, 3H, $-\text{C}(=\text{O})\text{OCH}_3$), 6.83 (d, $J=8.6$ Hz, 1H, H-3'), 6.91 (d, $J=9.2$ Hz, 1H, H-3), 6.97 (m, 2H, H-4', H-6'), 8.07 (dd, $J=2.6, 9.2$ Hz, 1H, H-4), 8.88 (d, $J=2.3$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.8 ($-\text{C}(=\text{O})\text{OCH}_3$), 55.8 (ArOCH_3), 112.5 (C-1'), 117.1 (C-3'), 119.8 (C-4'), 120.7 (C-6'), 126.3 (C-1), 126.5 (C-4), 126.6 (C-6), 126.8 (C-3), 143.3 (C-5'), 144.4 (C-2), 150.9 (C-5), 152.8 (C-2'), 165.2 ($-\text{C}(=\text{O})\text{OCH}_3$). HRMS (FD). Calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_5\text{S}$, $[\text{M}]^+$: m/z 334.0623. Found: m/z 334.0622.

Methyl [2-(2-amino-5-fluorophenyl)sulfanyl]-5-nitrobenzoate (2f) Yield 99%; yellow solid; mp 139–140°C; R_f 0.25 (hexane-AcOEt, 3:1); IR: 3498 (N-H), 3397 (N-H), 3064 (Ar, C-H), 2951 (CH_3), 2842 (CH_3), 1709 ($-\text{C}(=\text{O})\text{O}-$), 1623 (Ar, C=C), 1521 (ArNO_2 , (N=O) $_2$), 1489 (Ar, C=C), 1455 (Ar, C=C), 1346 (ArNO_2 , (N=O) $_2$), 1298 (ArNH_2 , C-N), 1248 ($-\text{C}(=\text{O})\text{O}-$), 1203 (Ar, C-F), 1134 ($-\text{C}-\text{C}(=\text{O})\text{O}-$), 1049 (Ar-S-Ar), 933 (ArNO_2 , C-N), 783 (Ar, C-H), 680 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 4.03 (s, 3H, $-\text{C}(=\text{O})\text{OCH}_3$), 4.16 (s, 2H, NH_2), 6.82 (q, $J=4.6$ Hz, 1H, H-3'), 6.90 (d, $J=8.9$ Hz, 1H, H-3), 7.09 (td, $J=2.8, 8.4$ Hz, 1H, H-4'), 7.18 (dd, $J=2.9, 8.0$ Hz, 1H, H-6'), 8.09 (dd, $J=2.6, 8.9$ Hz, 1H, H-4), 8.89 (d, $J=2.6$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.8 ($-\text{C}(=\text{O})\text{OCH}_3$), 112.5 (C-1'), 116.5 (C-3'), 119.7 (C-4'), 122.9 (C-6'), 126.5, 126.6, 126.7 (C-1, C-3, C-4, C-6), 144.6 (C-2), 145.8 (C-2'), 150.0 (C-5), 154.6 (C-5), 156.5 (C-5'), 165.1 ($-\text{C}(=\text{O})\text{OCH}_3$). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4\text{SF}$, $[\text{M}]^+$: m/z 322.0424. Found: m/z 322.0428.

Methyl [2-(2-amino-4-fluorophenyl)sulfanyl]-5-nitrobenzoate (2g) Yield 99%; yellow solid; mp 155–156°C; R_f 0.36 (hexane-AcOEt, 3:1); IR: 3466 (N-H), 3385 (N-H), 3088 (Ar, C-H), 2959 (CH_3), 2847 (CH_3), 1717 ($-\text{C}(=\text{O})\text{O}-$), 1622 (Ar, C=C), 1575 (ArNO_2 , (N=O) $_2$), 1486 (Ar, C=C), 1461 (Ar, C=C), 1338 (ArNO_2 , (N=O) $_2$), 1169 ($-\text{C}-\text{C}(=\text{O})\text{O}-$), 906 (ArNO_2 , C-N), 742 (Ar, C-H), 677 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 4.03 (s, 3H, $-\text{C}(=\text{O})\text{OCH}_3$), 4.41 (s, 2H, NH_2), 6.55 (m, 2H, H-3', H-5'), 6.88 (d, $J=8.9$ Hz, 1H, H-3), 7.39 (t, $J=7.4$ Hz, 1H, H-6'), 8.08 (dd, $J=2.6, 9.2$ Hz, 1H, H-4), 8.88 (d, $J=2.6$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.8 ($-\text{C}(=\text{O})\text{OCH}_3$), 102.3 (C-3'), 106.9 (C-5'), 107.3 (C-1'), 126.5 (C-1, C-3, C-4), 126.7 (C-6), 139.4 (C-6'), 144.5 (C-2), 150.9 (C-2'), 151.0 (C-5), 165.1 ($-\text{C}(=\text{O})\text{OCH}_3$), 166.7 (C-4'). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4\text{SF}$, $[\text{M}]^+$: m/z 322.0424. Found: m/z 322.0430.

Methyl [2-(2-amino-5-chlorophenyl)sulfanyl]-5-nitrobenzoate (2h) Yield 99%; yellow solid; mp 141–142°C; R_f 0.48 (hexane-AcOEt, 3:1); IR: 3491 (N-H), 3394 (N-H), 1790 ($-\text{C}(=\text{O})\text{O}-$), 1616 (Ar, C=C), 1573 (ArNO_2 , (N=O) $_2$), 1479 (Ar, C=C), 1435 (Ar, C=C), 1346 (ArNO_2 , (N=O) $_2$), 1267 ($-\text{C}(=\text{O})\text{O}-$), 1150 ($-\text{C}-\text{C}(=\text{O})\text{O}-$), 901 (ArNO_2 , C-N), 784 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 4.03 (s, 3H, $-\text{C}(=\text{O})\text{OCH}_3$), 4.30 (s, 2H, NH_2), 6.80 (d, $J=8.6$ Hz, 1H, H-3'), 6.90 (d, $J=8.9$ Hz, 1H, H-3), 7.29 (dd, $J=2.4, 8.7$ Hz, 1H, H-4'), 7.42 (d, $J=2.6$ Hz, 1H, H-6'), 8.09 (dd, $J=2.6, 8.9$ Hz, 1H, H-4), 8.88 (d, $J=2.3$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.9 ($-\text{C}(=\text{O})\text{OCH}_3$), 113.2 (C-1'), 116.7 (C-3'), 123.2 (C-5'), 126.5 (C-1), 126.6 (C-3, C-4), 126.7 (C-6), 132.5 (C-4'), 136.5 (C-6'), 144.6 (C-2), 147.9 (C-2'), 149.9 (C-5), 165.1 ($-\text{C}(=\text{O})\text{OCH}_3$). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4\text{SCL}$, $[\text{M}]^+$: m/z 338.0128. Found: m/z 338.0130.

Methyl [2-(2-amino-3-chlorophenyl)sulfanyl]-5-nitrobenzoate (2i) Yield 99%; yellow solid; mp 122–123°C; R_f 0.58 (hexane-AcOEt, 3:1); IR: 3439 (N-H), 3384 (N-H), 2959 (CH_3), 2850 (CH_3), 1721 ($-\text{C}(=\text{O})\text{O}-$), 1573 (ArNO_2 , (N=O) $_2$), 1516 (Ar, C=C), 1455 (Ar, C=C), 1341 (ArNO_2 , (N=O) $_2$), 1264 ($-\text{C}(=\text{O})\text{O}-$), 1150 ($-\text{C}-\text{C}(=\text{O})\text{O}-$), 1084 (Ar, C-Cl), 1047 (Ar-S-Ar), 902 (ArNO_2 , C-N), 784 (Ar, C-H), 681 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 4.04 (s, 3H, $-\text{C}(=\text{O})\text{OCH}_3$), 4.71 (s, 2H, NH_2), 6.77 (t, $J=7.9$ Hz,

1H, H-5'), 6.86 (d, $J=9.2$ Hz, 1H, H-3), 7.37 (d, $J=7.4$ Hz, 1H, H-4'), 7.45 (d, $J=8.0$ Hz, 1H, H-6'), 8.09 (dd, $J=2.4, 9.0$ Hz, 1H, H-4), 8.89 (d, $J=2.6$ Hz, 1H, H-6); ^{13}C NMR (CDCl_3): δ 52.8 ($-\text{C}(=\text{O})\text{OCH}_3$), 113.2 (C-1'), 118.8 (C-5'), 119.8 (C-3'), 126.5 (C-1), 126.6 (C-3, C-4), 126.7 (C-6), 132.4 (C-6'), 136.1 (C-4'), 144.6 (C-2), 145.9 (C-2'), 150.1 (C-5), 165.1 ($-\text{C}(=\text{O})\text{OCH}_3$). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_2\text{O}_4\text{SCL}$, $[\text{M}]^+$: m/z 338.0128. Found: m/z 338.0122.

2-Aminophenyl 2-cyano-4-nitrophenyl sulfide (4a) Yield 95%; yellow solid; mp 131–132°C; R_f 0.06 (hexane-AcOEt, 9:1); IR: 3471 (N-H), 3366 (N-H), 3105 (Ar, C-H), 2231 ($\text{C}\equiv\text{N}$), 1626 (Ar, C=C), 1574 (ArNO_2 , (N=O) $_2$), 1516 (Ar, C=C), 1447 (Ar, C=C), 1339 (ArNO_2 , (N=O) $_2$), 1307 (ArNH_2 , C-N), 1148 ($-\text{C}-\text{C}(=\text{O})\text{O}-$), 1011 (Ar-S-Ar), 908 (ArNO_2 , C-N), 759 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 4.32 (s, 2H, NH_2), 6.84 (t, $J=7.6$ Hz, 1H, H-5'), 6.88 (m, 2H, H-3', H-6), 7.37 (t, $J=7.7$ Hz, 1H, H-4'), 7.43 (d, $J=7.7$ Hz, 1H, H-6'), 8.13 (d, $J=8.9$ Hz, 1H, H-5), 8.44 (s, 1H, H-3); ^{13}C NMR (CDCl_3): δ 109.1 (C-1'), 110.3 (C-2), 114.9 ($-\text{C}\equiv\text{N}$), 116.2 (C-3'), 119.7 (C-5'), 126.4 (C-6), 127.4 (C-5), 128.7 (C-3), 133.3 (C-4'), 137.7 (C-6'), 144.9 (C-1), 149.4 (C-2'), 152.0 (C-4). HRMS (FD). Calcd for $\text{C}_{13}\text{H}_9\text{N}_3\text{O}_2\text{S}$, $[\text{M}]^+$: m/z 271.0415. Found: m/z 271.0420.

2-Amino-5-methylphenyl 2-cyano-4-nitrophenyl sulfide (4b) Yield 96%; orange solid; mp 111–112°C; R_f 0.33 (hexane-AcOEt, 3:1); IR: 3459 (N-H), 3361 (N-H), 2921 (CH_3), 2860 (CH_3), 2224 ($\text{C}\equiv\text{N}$), 1628 (Ar, C=C), 1568 (ArNO_2 , (N=O) $_2$), 1500 (Ar, C=C), 1454 (Ar, C=C), 1338 (ArNO_2 , (N=O) $_2$), 1306 (ArNH_2 , C-N), 915 cm^{-1} (ArNO_2 , C-N); ^1H NMR (CDCl_3): δ 2.27 (s, 3H, ArCH_3), 4.17 (s, 2H, NH_2), 6.80 (d, $J=8.0$ Hz, 1H, H-3'), 6.89 (d, $J=8.9$ Hz, 1H, H-6), 7.19 (d, $J=8.3$ Hz, 1H, H-4'), 7.24 (s, 1H, H-6'), 8.14 (dd, $J=2.1, 9.0$ Hz, 1H, H-5), 8.45 (d, $J=2.0$ Hz, 1H, H-3); ^{13}C NMR (CDCl_3): δ 20.1 (ArCH_3), 108.8 (C-1'), 110.0 (C-2), 114.8 ($-\text{C}\equiv\text{N}$), 116.2 (C-3'), 126.3 (C-6), 127.2 (C-5), 128.5 (C-3), 129.1 (C-5'), 134.0 (C-4'), 137.3 (C-6'), 144.6 (C-1), 146.8 (C-2'), 152.0 (C-4). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$, $[\text{M}]^+$: m/z 285.0572. Found: m/z 285.0571.

2-Amino-3-methylphenyl 2-cyano-4-nitrophenyl sulfide (4c) Yield 76%; yellow solid; mp 122–123°C; R_f 0.38 (hexane-AcOEt, 3:1); IR: 3462 (N-H), 3363 (N-H), 2915 (CH_3), 2857 (CH_3), 2236 ($\text{C}\equiv\text{N}$), 1634 (Ar, C=C), 1514 (Ar, C=C), 1467 (Ar, C=C), 1343 (ArNO_2 , (N=O) $_2$), 1299 (ArNH_2 , C-N), 1082 (Ar-S-Ar), 768 (Ar, C-H), 694 cm^{-1} (Ar, C=C); ^1H NMR (CDCl_3): δ 2.25 (s, 3H, ArCH_3), 4.30 (s, 2H, NH_2), 6.78 (t, $J=7.6$ Hz, 1H, H-5'), 6.85 (d, $J=8.9$ Hz, 1H, H-6), 7.27 (d, $J=6.9$ Hz, 1H, H-4'), 7.32 (d, $J=7.7$ Hz, 1H, H-6'), 8.13 (dd, $J=2.6, 8.9$ Hz, 1H, H-5), 8.45 (d, $J=2.3$ Hz, 1H, H-3); ^{13}C NMR (CDCl_3): δ 18.1 (ArCH_3), 108.5 (C-1'), 110.0 (C-2), 114.8 ($-\text{C}\equiv\text{N}$), 119.0 (C-5'), 123.5 (C-3'), 126.2 (C-6), 127.2 (C-5), 128.5 (C-3), 134.0 (C-4'), 135.2 (C-6'), 144.6 (C-1), 147.5 (C-2'), 152.1 (C-4). HRMS (FD). Calcd for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_2\text{S}$, $[\text{M}]^+$: m/z 285.0572. Found: m/z 285.0574.

2-Amino-4,5-dimethylphenyl 2-cyano-4-nitrophenyl sulfide (4d) Yield 84%; orange solid; mp 149–150°C; R_f 0.34 (hexane-AcOEt, 3:1); IR: 3457 (N-H), 3375 (N-H), 3050 (Ar, C-H), 2921 (CH_3), 2852 (CH_3), 2232 ($\text{C}\equiv\text{N}$), 1621 (Ar, C=C), 1564 (ArNO_2 , (N=O) $_2$), 1515 (Ar, C=C), 1454 (Ar, C=C), 1337 (ArNO_2 , (N=O) $_2$), 1309 (ArNH_2 , C-N), 794 cm^{-1} (Ar, C-H); ^1H NMR (CDCl_3): δ 2.18 (s, 3H, ArCH_3 at C-5'), 2.26 (s, 3H, ArCH_3 at C-4'), 4.09 (s, 2H, NH_2), 6.70 (s, 1H, H-3'), 6.89 (d, $J=9.2$ Hz, 1H, H-6), 7.17 (s, 1H, H-6'), 8.12 (dd, $J=2.4, 9.0$ Hz, 1H, H-5), 8.44 (d, $J=2.6$ Hz, 1H, H-3); ^{13}C NMR (CDCl_3): δ 18.5 (ArCH_3 at C-5'), 20.0 (ArCH_3 at C-4'), 105.8 (C-1'), 109.8 (C-2), 114.9 ($-\text{C}\equiv\text{N}$), 117.4 (C-3'), 126.2 (C-6), 127.1 (C-5), 128.2 (C-4'), 128.4 (C-3), 137.6 (C-6'), 142.6 (C-5'), 144.5 (C-4), 147.1 (C-2'), 152.6 (C-1). HRMS (FD). Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$, $[\text{M}]^+$: m/z 299.0728. Found: m/z 299.0728.

2-Amino-5-methoxyphenyl 2-cyano-4-nitrophenyl sulfide (4e) Yield 75%; orange solid; mp 149–150°C; R_f 0.28 (hexane-AcOEt, 3:1); IR: 3466 (N-H), 3375 (N-H), 2229 (C≡N), 1570 (ArNO₂, (N=O)₂), 1498 (Ar, C=C), 1454 (Ar, C=C), 1348 (ArNO₂, (N=O)₂), 1299 (C-O-C), 1032 (Ar-S-Ar), 914 cm⁻¹ (ArNO₂, C-N); ¹H NMR (600 MHz, CDCl₃): δ 3.77 (s, 3H, ArOCH₃), 4.02 (s, 2H, NH₂), 6.86 (d, J =8.6 Hz, 1H, H-3'), 6.91 (d, J =9.2 Hz, 1H, H-6), 6.99 (dd, J =2.9, 8.0 Hz, 1H, H-4'), 7.02 (d, J =2.9 Hz, 1H, H-6'), 8.16 (dd, J =2.3, 8.9 Hz, 1H, H-5), 8.47 (d, J =2.6 Hz, 1H, H-3); ¹³C NMR (CDCl₃): δ 55.9 (ArOCH₃), 109.4 (C-1'), 110.1 (C-2), 114.8 (C≡N), 117.5 (C-3'), 120.6 (C-4', C-6'), 126.3 (C-6), 127.3 (C-5), 128.5 (C-3), 143.3 (C-2'), 144.8 (C-1), 151.6 (C-4), 152.8 (C-5'). HRMS (FD). Calcd for C₁₄H₁₁N₃O₃S, [M]⁺: m/z 301.0521. Found: m/z 301.0530.

2-Amino-5-fluorophenyl 2-cyano-4-nitrophenyl sulfide (4f) Yield 89%; yellow solid; mp 160–161°C; R_f 0.20 (hexane-AcOEt, 3:1); IR: 3452 (N-H), 3357 (N-H), 2237 (C≡N), 1631 (Ar, C=C), 1567 (ArNO₂, (N=O)₂), 1494 (Ar, C=C), 1454 (Ar, C=C), 1342 (ArNO₂, (N=O)₂), 1301 (ArNH₂, C-N), 913 cm⁻¹ (ArNO₂, C-N); ¹H NMR (CDCl₃): δ 4.19 (s, 2H, NH₂), 6.85 (q, J =4.5 Hz, 1H, H-3'), 6.92 (d, J =8.9 Hz, 1H, H-6), 7.13 (t, J =6.9 Hz, 1H, H-4'), 7.20 (d, J =7.7 Hz, 1H, H-6'), 8.17 (d, J =8.9 Hz, 1H, H-5), 8.47 (s, 1H, H-3); ¹³C NMR (CDCl₃): δ 109.5 (C-1') 110.5 (C-2), 114.6 (C≡N), 116.9 (C-3'), 120.6 (C-4'), 122.9 (C-6'), 126.4 (C-6), 127.3 (C-5), 128.6 (C-3), 145.1 (C-1), 145.8 (C-4), 150.6 (C-2'), 154.5 (C-5'). HRMS (FD). Calcd for C₁₃H₈N₃O₂SF, [M]⁺: m/z 289.0321. Found: m/z 289.0316.

2-Amino-4-fluorophenyl 2-cyano-4-nitrophenyl sulfide (4g) Yield 75%; yellow solid; mp 126–127°C; R_f 0.36 (hexane-AcOEt, 3:1); IR: 3451 (N-H), 3353 (N-H), 1632 (Ar, C=C), 1569 (ArNO₂, (N=O)₂), 1452 (Ar, C=C), 1342 (ArNO₂, (N=O)₂), 1145 (Ar, C-F), 914 cm⁻¹ (ArNO₂, C-N); ¹H NMR (CDCl₃): δ 4.43 (s, 2H, NH₂), 6.58 (m, 2H, H-3', H-5'), 6.88 (d, J =8.9 Hz, 1H, H-6), 7.42 (t, J =7.3 Hz, 1H, H-6'), 8.16 (dd, J =2.3, 8.9 Hz, 1H, H-5), 8.46 (d, J =2.6 Hz, 1H, H-3); ¹³C NMR (CDCl₃): δ 102.6 (C-3'), 104.4 (C-1'), 107.2 (C-5'), 110.3 (C-2), 114.7 (C≡N), 126.1 (C-6), 127.3 (C-5), 128.6 (C-3), 139.6 (C-6'), 145.0 (C-1), 151.0 (C-2'), 151.5 (C-4), 164.8 (C-4'). HRMS (FD). Calcd for C₁₃H₈N₃O₂SF, [M]⁺: m/z 289.0321. Found: m/z 289.0321.

2-Amino-5-chlorophenyl 2-cyano-4-nitrophenyl sulfide (4h) Yield 83%; orange-colored solid; mp 146–147°C; R_f 0.25 (hexane-AcOEt, 3:1); IR: 3456 (N-H), 3358 (N-H), 2242 (C≡N), 1629 (Ar, C=C), 1515 (Ar, C=C), 1455 (Ar, C=C), 1340 (ArNO₂, (N=O)₂), 1299 (ArNH₂, C-N), 1152 (Ar, C-Cl), 1053 (Ar-S-Ar), 794 (Ar, C-H), 726 cm⁻¹ (Ar, C=C); ¹H NMR (CDCl₃): δ 4.33 (s, 2H, NH₂), 6.82 (d, J =8.6 Hz, 1H, H-3'), 6.92 (d, J =9.2 Hz, 1H, H-6), 7.32 (dd, J =2.3, 8.6 Hz, 1H, H-4'), 7.45 (d, J =2.3 Hz, 1H, H-6'), 8.18 (dd, J =2.3, 8.9 Hz, 1H, H-5), 8.47 (d, J =2.3 Hz, 1H, H-3); ¹³C NMR (CDCl₃): δ 110.2 (C-1'), 110.5 (C-2), 114.6 (C≡N), 117.1 (C-3'), 123.5 (C-5'), 126.4 (C-6), 127.4 (C-5), 128.6 (C-3), 133.2 (C-4'), 136.5 (C-6'), 145.1 (C-1), 147.9 (C-2'), 150.5 (C-4). HRMS (FD). Calcd for C₁₃H₈N₃O₂SCl, [M]⁺: m/z 305.0026. Found: m/z 305.0022.

2-Amino-3-chlorophenyl 2-cyano-4-nitrophenyl sulfide (4i) Yield 71%; yellow solid; mp 126–127°C; R_f 0.58 (hexane-AcOEt, 3:1); IR: 3442 (N-H), 3346 (N-H), 2237 (C≡N), 1627 (Ar, C=C), 1512 (Ar, C=C), 1456 (Ar, C=C), 1344 (ArNO₂, (N=O)₂), 1304 (ArNH₂, C-N), 1147 (Ar, C-Cl), 1058 (Ar-S-Ar), 914 cm⁻¹ (ArNO₂, C-N); ¹H NMR (CDCl₃): δ 4.75 (s, 2H, NH₂), 6.79 (t, J =7.9 Hz, 1H, H-5'), 6.88 (d, J =8.9 Hz, 1H, H-6), 7.40 (d, J =7.7 Hz, 1H, H-3'), 7.49 (d, J =7.7 Hz, 1H, H-4'), 8.18 (dd, J =2.3, 8.9 Hz, 1H, H-5), 8.48 (d, J =2.3 Hz, 1H, H-3); ¹³C NMR (CDCl₃): δ 110.2 (C-1'), 110.4 (C-2), 114.6 (C≡N), 119.0 (C-5'), 120.2 (C-3'), 126.2 (C-6), 127.4 (C-5), 128.6 (C-3), 133.1 (C-4'), 136.2 (C-6'), 145.0 (C-1),

145.9 (C-2'), 150.7 (C-4). HRMS (FD). Calcd for C₁₃H₈N₃O₂SCl, [M]⁺: m/z 305.0026. Found: m/z 305.0025.

2-Nitrodibenzo[b,f][1,4]thiazepine (7a) Yield 67%; yellow solid; mp 148–149°C; R_f 0.50 (hexane-AcOEt, 3:1); IR: 3051 (Ar, C-H), 1599 (Ar, C=C), 1567 (ArNO₂, (N=O)₂), 1520 (Ar, C=C), 1460 (Ar, C=C), 1345 (ArNO₂, (N=O)₂), 1058 (Ar-S-Ar), 945 (Ar, C-H), 914 (ArNO₂, C-N), 845 (Ar, C-H), 778 cm⁻¹ (Ar, C-H); ¹H NMR: δ 7.31 (m, 2H, H-8, H-9), 7.47 (m, 2H, H-6, H-7), 7.73 (d, J =8.6 Hz, 1H, H-4), 8.28 (t, J =5.6 Hz, 1H, H-3), 8.50 (d, J =2.6 Hz, 1H, H-1), 9.04 (s, 1H, H-11); ¹³C NMR: δ 125.4 (C-1), 126.7 (C-3), 127.1 (C-5a), 127.2 (C-9), 128.4 (C-8), 130.7 (C-7), 133.2 (C-4), 133.5 (C-6), 137.8 (C-11a), 146.7 (C-4a), 148.1 (C-2), 148.5 (C-9a), 161.5 (C-11). HRMS (FD). Calcd for C₁₃H₈N₂O₂S, [M]⁺: m/z 256.0306. Found: m/z 256.0315.

7-Methyl-2-nitrodibenzo[b,f][1,4]thiazepine (7b) Yield 60%; yellow solid; mp 133–134°C; R_f 0.51 (hexane-AcOEt, 3:1); IR: 3045 (Ar, C-H), 2923 (CH₃), 2850 (CH₃), 1601 (Ar, C=C), 1569 (ArNO₂, (N=O)₂), 1525 (Ar, C=C), 1468 (Ar, C=C), 1347 (ArNO₂, (N=O)₂), 941 (Ar, C-H), 915 (ArNO₂, C-N), 741 cm⁻¹ (Ar, C-H); ¹H NMR: δ 2.26 (s, 3H, ArCH₃), 7.18 (d, J =8.0 Hz, 1H, H-9), 7.23 (d, J =8.3 Hz, 1H, H-8), 7.26 (s, 1H, H-6), 7.69 (d, J =8.6 Hz, 1H, H-4), 8.25 (dd, J =2.3, 8.6 Hz, 1H, H-3), 8.45 (d, J =2.6 Hz, 1H, H-1), 8.96 (s, 1H, H-11); ¹³C NMR: δ 20.5 (ArCH₃), 125.3 (C-1), 126.6 (C-3), 127.2 (C-5a), 131.4 (C-9), 133.1 (C-8), 133.6 (C-7), 137.9 (C-4), 138.4 (C-6), 146.2 (C-11a), 146.5 (C-4a), 148.1 (C-2, C-9a), 160.1 (C-11). HRMS (FD). Calcd for C₁₄H₁₀N₂O₂S, [M]⁺: m/z 270.0463. Found: m/z 270.0458.

9-Methyl-2-nitrodibenzo[b,f][1,4]thiazepine (7c) Yield 63%; dark yellow solid; mp 137–138°C; R_f 0.59 (hexane-AcOEt, 3:1); IR: 3043 (Ar, C-H), 2925 (CH₃), 2852 (CH₃), 1598 (Ar, C=C), 1566 (ArNO₂, (N=O)₂), 1449 (Ar, C=C), 1373 (Ar, C-N), 1339 (ArNO₂, (N=O)₂), 1005 (Ar-S-Ar), 943 (Ar, C-H), 916 (ArNO₂, C-N), 773 (Ar, C-H), 699 cm⁻¹ (Ar, C=C); ¹H NMR: δ 2.27 (s, 3H, ArCH₃), 7.13 (t, J =7.6 Hz, 1H, H-6), 7.26 (m, 2H, H-7, H-8), 7.68 (d, J =8.6 Hz, 1H, H-4), 8.22 (dd, J =2.6, 8.6 Hz, 1H, H-3), 8.42 (d, J =2.6 Hz, 1H, H-1), 9.06 (s, 1H, H-11); ¹³C NMR: δ 19.0 (ArCH₃), 124.9 (C-1), 126.4 (C-3), 127.4 (C-5a), 128.1 (C-9), 131.1 (C-8), 132.1 (C-7), 133.1 (C-4), 135.1 (C-6), 137.9 (C-11a), 146.6 (C-4a), 147.0 (C-2), 148.1 (C-9a), 160.5 (C-11). HRMS (FD). Calcd for C₁₄H₁₀N₂O₂S, [M]⁺: m/z 270.0463. Found: m/z 270.0456.

7,8-Dimethyl-2-nitrodibenzo[b,f][1,4]thiazepine (7d) Yield 49%; yellow solid; mp 210–211°C; R_f 0.59 (hexane-AcOEt, 3:1); IR: 3056 (Ar, C-H), 2919 (CH₃), 2857 (CH₃), 1597 (Ar, C=C), 1567 (ArNO₂, (N=O)₂), 1525 (Ar, C=C), 1464 (Ar, C=C), 1344 (ArNO₂, (N=O)₂), 1023 (Ar-S-Ar), 942 (Ar, C-H), 912 (ArNO₂, C-N), 879 (Ar, C-H), 769 cm⁻¹ (Ar, C-H); ¹H NMR (600 MHz, DMSO-*d*₆): δ 2.17 (s, 3H, ArCH₃), 2.19 (s, 3H, ArCH₃), 7.09 (s, 1H, H-9), 7.22 (s, 1H, H-6), 7.69 (d, J =8.6 Hz, 1H, H-4), 8.25 (dd, J =2.6, 8.6 Hz, 1H, H-3), 8.45 (d, J =2.6 Hz, 1H, H-1), 8.96 (s, 1H, H-11); ¹³C NMR: δ 18.3 (ArCH₃), 18.8 (ArCH₃), 122.8 (C-1), 124.6 (C-3), 125.9 (C-9), 127.4 (C-4), 132.3 (C-5a), 133.2 (C-6), 136.6 (C-8), 137.3 (C-11a), 138.7 (C-7), 145.7 (C-9a), 146.2, 147.4 (C-2, C-4a), 160.1 (C-11). HRMS (FD). Calcd for C₁₅H₁₂N₂O₂S, [M]⁺: m/z 284.0619. Found: m/z 284.0631.

7-Methoxy-2-nitrodibenzo[b,f][1,4]thiazepine (7e) Yield 68%; yellow solid; mp 164–165°C; R_f 0.40 (hexane-AcOEt, 3:1); IR: 3007 (Ar, C-H), 2977 (CH₃), 2837 (CH₃), 1590 (Ar, C=C), 1511 (ArNO₂, (N=O)₂), 1475 (Ar, C=C), 1344 (ArNO₂, (N=O)₂), 1236 (C-O-C), 1056 (C-O-C), 1039 (Ar-S-Ar), 945 (Ar, C-H), 912 (ArNO₂, C-N), 741 (Ar, C-H), 696 cm⁻¹ (Ar, C=C); ¹H NMR: δ 3.76 (s, 3H, ArOCH₃), 7.02 (m, 2H, H-6, H-8), 7.24 (d, J =8.3 Hz, 1H, H-9), 7.70 (d, J =8.6 Hz, 1H, H-4), 8.27 (dd, J =2.3,

8.6 Hz, 1H, H-3), 8.45 (d, $J=2.3$ Hz, 1H, H-1), 8.91 (s, 1H, H-11); ^{13}C NMR: δ 55.6 (ArOCH₃), 116.2 (C-6), 116.9 (C-8), 124.6 (C-1), 125.9 (C-3), 126.8 (C-5a), 128.2 (C-9), 132.6 (C-4), 137.3 (C-11a), 141.5 (C-9a), 145.1 (C-4a), 147.5 (C-2), 158.9 (C-7, C-11). HRMS (FD). Calcd for C₁₄H₁₀N₂O₃S, [M]⁺: m/z 286.0412. Found: m/z 286.0418.

7-Fluoro-2-nitrodibenzo[b,f][1,4]thiazepine (7f) Yield 54%; yellow solid; mp 138–139°C; R_f 0.50 (hexane-AcOEt, 3:1); IR: 3100 (Ar, C-H), 1600 (Ar, C=C), 1569 (ArNO₂, (N=O)₂), 1520 (Ar, C=C), 1475 (Ar, C=C), 1349 (ArNO₂, (N=O)₂), 1215 (Ar, C-F), 1066 (Ar-S-Ar), 943 (Ar, C-H), 915 (ArNO₂, C-N), 768 (Ar, C-H), 714 cm⁻¹ (Ar, C=C); ^1H NMR: δ 7.27–7.38 (m, 3H, H-6, H-8, H-9), 7.72 (d, $J=8.6$ Hz, 1H, H-4), 8.29 (dd, $J=2.6$, 8.6 Hz, 1H, H-3), 8.48 (d, $J=2.3$ Hz, 1H, H-1), 9.01 (s, 1H, H-11); ^{13}C NMR: δ 117.2, 119.1 (C-6, C-8), 124.7 (C-1), 126.2 (C-3), 127.8 (C-5a), 128.3 (C-9), 137.0 (C-11a), 144.7 (C-9a), 145.0 (C-4a), 147.7 (C-2), 159.8 (C-9a), 160.7 (C-11), 161.8 (C-7). HRMS (FD). Calcd for C₁₃H₇N₂O₂SF, [M]⁺: m/z 274.0212. Found: m/z 274.0211.

8-Fluoro-2-nitrodibenzo[b,f][1,4]thiazepine (7g) Yield 66%; yellow solid; mp 141–142°C; R_f 0.59 (hexane-AcOEt, 3:1); IR: 3094 (Ar, C-H), 1594 (Ar, C=C), 1574 (ArNO₂, (N=O)₂), 1525 (Ar, C=C), 1465 (Ar, C=C), 1346 (ArNO₂, (N=O)₂), 1222 (Ar, C-F), 910 (ArNO₂, C-N), 771 cm⁻¹ (Ar, C-H); ^1H NMR: δ 7.13 (m, 2H, H-7, H-9), 7.49 (dd, $J=6.2$, 9.2 Hz, 1H, H-6), 7.71 (dd, $J=2.9$, 8.6 Hz, 1H, H-4), 8.27 (d, $J=8.6$ Hz, 1H, H-3), 8.49 (s, 1H, H-1), 9.06 (s, 1H, H-11); ^{13}C NMR: δ 113.0, 114.7 (C-7, C-9), 122.3 (C-5a), 124.7 (C-1), 126.1 (C-3), 132.4 (C-4), 134.4 (C-6), 137.0 (C-11a), 145.9 (C-4a), 147.5 (C-2), 149.3 (C-9a), 162.0 (C-11), 163.7 (C-8). HRMS (FD). Calcd for C₁₃H₇N₂O₂SF, [M]⁺: m/z 274.0212. Found: m/z 274.0223.

7-Chloro-2-nitrodibenzo[b,f][1,4]thiazepine (7h) Yield 63%; yellow solid; mp 159–160°C; R_f 0.64 (hexane-AcOEt, 3:1); IR: 3046 (Ar, C-H), 1601 (Ar, C=C), 1521 (Ar, C=C), 1456 (Ar, C=C), 1347 (ArNO₂, (N=O)₂), 1057 (Ar-S-Ar), 949 (Ar, C-H), 915 (ArNO₂, C-N), 740 (Ar, C-H), 709 cm⁻¹ (Ar, C=C); ^1H NMR: δ 7.32 (d, $J=8.6$ Hz, 1H, H-9), 7.50 (dd, $J=2.4$, 8.4 Hz, 1H, H-8), 7.56 (d, $J=2.3$ Hz, 1H, H-6), 7.74 (d, $J=8.6$ Hz, 1H, H-4), 8.31 (dd, $J=2.6$, 8.6 Hz, 1H, H-3), 8.51 (d, $J=2.3$ Hz, 1H, H-1), 9.06 (s, 1H, H-11); ^{13}C NMR: δ 124.8 (C-1), 126.2 (C-3), 127.9 (C-9), 128.1 (C-7), 130.0 (C-8), 131.8 (C-5a), 131.9 (C-6), 132.8 (C-4), 137.0 (C-11a), 145.2 (C-4a), 146.7 (C-9a), 147.7 (C-2), 161.5 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₂SCl, [M]⁺: m/z 289.9917. Found: m/z 289.9927.

9-Chloro-2-nitrodibenzo[b,f][1,4]thiazepine (7i) Yield 47%; yellow solid; mp 167–168°C; R_f 0.59 (hexane-AcOEt, 3:1); IR: 3061 (Ar, C-H), 1602 (Ar, C=C), 1531 (ArNO₂, (N=O)₂), 1508 (Ar, C=C), 1456 (Ar, C=C), 1348 (ArNO₂, (N=O)₂), 1135 (Ar, C-Cl), 941 (Ar, C-H), 901 (ArNO₂, C-N), 769 (Ar, C-H), 740 (Ar, C-H), 699 cm⁻¹ (Ar, C=C); ^1H NMR: δ 7.29 (d, $J=8.0$ Hz, 1H, H-7), 7.47 (d, $J=8.0$ Hz, 1H, H-6), 7.57 (d, $J=7.7$ Hz, 1H, H-8), 7.75 (d, $J=8.6$ Hz, 1H, H-4), 8.30 (s, 1H, H-3), 8.55 (s, 1H, H-1), 9.19 (s, 1H, H-11). ^{13}C NMR: δ 124.5 (C-1), 126.3 (C-3), 128.3 (C-7), 129.3 (C-9), 130.1 (C-5a), 131.0, 131.7 (C-6, C-8), 132.8 (C-4), 136.9 (C-11a), 144.1 (C-9a), 145.5 (C-4a), 147.7 (C-2), 162.2 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₂SCl, [M]⁺: m/z 289.9917. Found: m/z 289.9923.

Synthesis of 2-nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one derivatives (3)

A representative example is the synthesis of 2-nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one (3a). Methyl [2-(2-aminophenyl)

sulfanyl]-5-nitrobenzoate (2a, 0.10 g, 0.33 mmol), 15 mL of *o*-xylene and 0.13 mmol of *p*-TsOH · H₂O were placed in a 50-mL flask. The mixture was heated under reflux at 125°C overnight, then cooled to room temperature, neutralized using aqueous saturated sodium bicarbonate solution and extracted three times with AcOEt. The organic layer was washed several times with brine and dried over with MgSO₄. After filtration and concentration, the residue was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate (4/1, v/v) to give compound 3a (0.09 g, 95%).

2-Nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one (3a) Yield 95%; dark orange solid; mp 263–264°C; R_f 0.20 (hexane-AcOEt, 3:1); IR: 3288 (N-H), 3179 (N-H), 3045 (Ar, C-H), 1653 (NHC(=O)-), 1598 (Ar, C=C), 1568 (ArNO₂, (N=O)₂), 1521 (Ar, C=C), 1457 (Ar, C=C), 1344 (ArNO₂, (N=O)₂), 905 (ArNO₂, C-N), 843 (Ar, C-H), 741 (Ar, C-H), 705 cm⁻¹ (Ar, C=C); ^1H NMR: δ 7.19 (t, $J=7.6$ Hz, 1H, H-7), 7.29 (d, $J=7.4$ Hz, 1H, H-9), 7.42 (t, $J=7.2$ Hz, 1H, H-8), 7.60 (d, $J=6.9$ Hz, 1H, H-6), 7.81 (d, $J=8.6$ Hz, 1H, H-4), 8.26 (dd, $J=2.6$, 8.6 Hz, 1H, H-3), 8.38 (d, $J=2.6$ Hz, 1H, H-1), 10.97 (s, 1H, H-10); ^{13}C NMR: δ 123.4 (C-9), 125.8 (C-7), 125.9, 126.0 (C-1, C-3), 127.3 (C-5a), 130.3 (C-8), 132.7 (C-4, C-6), 138.6 (C-11a), 139.4 (C-9a), 144.2 (C-4a), 147.4 (C-2), 166.4 (C-11). HRMS (FD). Calcd for C₁₃H₈N₂O₃S, [M]⁺: m/z 272.0256. Found: m/z 272.0255.

7-Methyl-2-nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one (3b) Yield 87%; pale orange solid; mp 233–234°C; R_f 0.43 (hexane-AcOEt, 3:1); IR: 3293 (N-H), 3167 (N-H), 3029 (Ar, C-H), 2927 (CH₃), 1657 (NHC(=O)-), 1602 (Ar, C=C), 1527 (ArNO₂, (N=O)₂), 1498 (Ar, C=C), 1435 (Ar, C=C), 1345 (ArNO₂, (N=O)₂), 1054 (Ar-S-Ar), 933 (Ar, C-H), 896 (ArNO₂, C-N), 741 (Ar, C-H), 708 cm⁻¹ (Ar, C=C); ^1H NMR: δ 2.25 (s, 3H, ArCH₃), 7.17 (d, $J=8.3$ Hz, 1H, H-9), 7.22 (d, $J=8.0$ Hz, 1H, H-8), 7.41 (s, 1H, H-6), 7.79 (d, $J=8.6$ Hz, 1H, H-4), 8.25 (dd, $J=2.6$, 8.6 Hz, 1H, H-3), 8.37 (d, $J=2.6$ Hz, 1H, H-1), 10.86 (s, 1H, H-10); ^{13}C NMR: δ 19.8 (ArCH₃), 123.3 (C-9), 125.9 (C-1, C-3), 127.2 (C-5a), 130.8 (C-8), 132.7 (C-4), 132.8 (C-6), 135.5 (C-7), 136.8 (C-9a), 138.7 (C-11a), 144.3 (C-4a), 147.4 (C-2), 166.4 (C-10). HRMS (FD). Calcd for C₁₄H₁₀N₂O₃S, [M]⁺: m/z 286.0412. Found: m/z 286.0411.

9-Methyl-2-nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one (3c) Yield 89%; pale brown solid; mp 212–213°C; R_f 0.48 (hexane-AcOEt, 3:1); IR: 3296 (N-H), 3189 (N-H), 3056 (Ar, C-H), 2958 (CH₃), 2921 (CH₃), 2857 (CH₃), 1662 (NHC(=O)-), 1606 (Ar, C=C), 1539 (ArNO₂, (N=O)₂), 1460 (Ar, C=C), 1349 (ArNO₂, (N=O)₂), 1048 (Ar-S-Ar), 967 (Ar, C-H), 911 (ArNO₂, C-N), 778 (Ar, C-H), 698 cm⁻¹ (Ar, C=C); ^1H NMR: δ 2.36 (s, 3H, ArCH₃), 7.10 (t, $J=7.6$ Hz, 1H, H-7), 7.27 (d, $J=7.4$ Hz, 1H, H-8), 7.45 (d, $J=7.7$ Hz, 1H, H-6), 7.78 (d, $J=8.3$ Hz, 1H, H-4), 8.22 (d, $J=8.6$ Hz, 1H, H-3), 8.36 (s, 1H, H-1), 10.39 (s, 1H, H-10); ^{13}C NMR: δ 18.3 (ArCH₃), 125.6 (C-1, C-3), 126.0 (C-7), 130.2 (C-5a), 130.6 (C-6), 131.9 (C-8), 132.6 (C-4), 133.5 (C-9), 137.5 (C-9a), 138.8 (C-11a), 144.8 (C-4a), 147.4 (C-2), 166.6 (C-11). HRMS (FD). Calcd for C₁₄H₁₀N₂O₃S, [M]⁺: m/z 286.0412. Found: m/z 286.0415.

7,8-Dimethyl-2-nitrodibenzo[b,f][1,4]thiazepin-11(10H)-one (3d) Yield 58%; dark orange solid; mp 254–255°C; R_f 0.55 (hexane-AcOEt, 3:1); IR: 3288 (N-H), 3174 (N-H), 3050 (Ar, C-H), 2957 (CH₃), 2921 (CH₃), 2851 (CH₃), 1662 (NHC(=O)-), 1603 (Ar, C=C), 1525 (ArNO₂, (N=O)₂), 1499 (Ar, C=C), 1432 (Ar, C=C), 1340 (ArNO₂, (N=O)₂), 902 (ArNO₂, C-N), 833 (Ar, C-H), 778 (Ar, C-H), 675 cm⁻¹ (Ar, C=C); ^1H NMR: δ 2.15 (s, 3H, ArCH₃), 2.16 (s, 3H, ArCH₃), 7.03 (s, 1H, H-6), 7.34 (s, 1H, H-9), 7.76 (d, $J=8.6$ Hz, 1H, H-4), 8.23 (dd, $J=2.6$, 8.6 Hz, 1H, H-3), 8.34 (d, $J=2.6$ Hz, 1H, H-1), 10.79 (s, 1H, H-10); ^{13}C NMR: δ 18.3 (ArCH₃), 18.8

(ArCH₃), 124.2 (C-5a, C-9), 125.7 (C-1, C-3), 131.2 (C-11a), 132.5 (C-4), 133.0 (C-6), 134.2 (C-7), 136.8 (C-8), 138.8 (C-9a), 144.6 (C-4a), 147.3 (C-2), 166.4 (C-11). HRMS (FD). Calcd for C₁₅H₁₂N₂O₃S, [M]⁺: *m/z* 300.0569; found: *m/z* 300.0581.

7-Methoxy-2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (3e) Yield 86%; dark yellow solid; mp 222–223°C; *R*_f 0.21 (hexane-AcOEt, 3:1); IR: 3286 (N-H), 3173 (N-H), 2954 (CH₃), 2854 (CH₃), 1668 (–NHC(=O)–), 1601 (Ar, C=C), 1569 (ArNO₂, (N=O)₂), 1525 (Ar, C=C), 1432 (Ar, C=C), 1345 (ArNO₂, (N=O)₂), 1277 (C-O-C), 1037 (Ar-S-Ar), 893 (ArNO₂, C-N), 839 (Ar, C-H), 702 cm^{–1} (Ar, C=C); ¹H NMR: δ 3.75 (s, 3H, ArOCH₃), 6.99 (dd, *J* = 2.9, 8.9 Hz, 1H, H-8), 7.14 (d, *J* = 2.9 Hz, 1H, H-6), 7.20 (d, *J* = 8.9 Hz, 1H, H-9), 7.80 (d, *J* = 8.6 Hz, 1H, H-4), 8.25 (dd, *J* = 2.6, 8.6 Hz, 1H, H-3), 8.37 (d, *J* = 2.6 Hz, 1H, H-1), 10.77 (s, 1H, H-10); ¹³C NMR: δ 55.5 (ArOCH₃), 116.4 (C-8), 116.9 (C-6), 124.6 (C-9), 125.8 (C-1, C-3), 128.8 (C-5a), 132.3 (C-9a), 132.8 (C-4), 138.7 (C-11a), 144.1 (C-4a), 147.5 (C-2), 156.7 (C-7), 166.3 (C-11). HRMS (FD). Calcd for C₁₄H₁₀N₂O₄S, [M]⁺: *m/z* 302.0361. Found: *m/z* 302.0351.

7-Fluoro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (3f) Yield 54%; pale brown solid; mp 209–210°C; *R*_f 0.24 (hexane-AcOEt, 3:1); IR: 3293 (N-H), 3178 (N-H), 3053 (Ar, C-H), 1668 (–NHC(=O)–), 1604 (Ar, C=C), 1532 (ArNO₂, (N=O)₂), 1498 (Ar, C=C), 1457 (Ar, C=C), 1347 (ArNO₂, (N=O)₂), 1264 (Ar, C-F), 932 (Ar, C-H), 902 (ArNO₂, C-N), 739 (Ar, C-H), 702 cm^{–1} (Ar, C=C); ¹H NMR: δ 7.04–7.12 (m, 2H, H-8, H-9), 7.63–7.65 (m, 1H, H-6), 7.81 (d, *J* = 8.6 Hz, 1H, H-4), 8.28 (dd, *J* = 2.6, 8.6 Hz, 1H, H-3), 8.38 (d, *J* = 2.6 Hz, 1H, H-1), 11.10 (s, 1H, H-10); ¹³C NMR: δ 110.3 (C-8), 112.8 (C-6), 122.9 (C-9), 125.9 (C-1), 126.1 (C-4), 131.3 (C-5a), 132.7 (C-3), 134.4 (C-9a), 138.4 (C-11a), 143.7 (C-4a), 147.4 (C-2), 161.5 (C-7), 166.2 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₃SF, [M]⁺: *m/z* 290.0161. Found: *m/z* 290.0166.

8-Fluoro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (3g) Yield 99%; brown solid; mp 274–275°C; *R*_f 0.36 (hexane-AcOEt, 3:1); IR: 3309 (N-H), 3192 (N-H), 3097 (Ar, C-H), 1662 (–NHC(=O)–), 1597 (Ar, C=C), 1568 (ArNO₂, (N=O)₂), 1522 (Ar, C=C), 1475 (Ar, C=C), 1339 (ArNO₂, (N=O)₂), 1256 (Ar, C-F), 1054 (Ar-S-Ar), 910 (Ar, C-H), 897 (ArNO₂, C-N), 771 (Ar, C-H), 701 cm^{–1} (Ar, C=C); ¹H NMR: δ 7.04–7.12 (m, 2H, H-7, H-9), 7.64 (dd, *J* = 6.2, 8.7 Hz, 1H, H-6), 7.81 (d, *J* = 8.6 Hz, 1H, H-4), 8.28 (dd, *J* = 2.6, 8.6 Hz, 1H, H-3), 8.38 (d, *J* = 2.6 Hz, 1H, H-1), 11.05 (s, 1H, H-10); ¹³C NMR: δ 110.2 (C-9), 112.7 (C-7), 122.9 (C-5a), 126.0 (C-1), 126.2 (C-3), 132.7 (C-4), 134.5 (C-6), 138.5 (C-11a), 141.3 (C-9a), 143.8 (C-4a), 147.5 (C-2), 162.6 (C-8), 166.3 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₃SF, [M]⁺: *m/z* 290.0161. Found: *m/z* 290.0168.

7-Chloro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (3h) Yield 64%; pale brown solid; mp 262–263°C; *R*_f 0.25 (hexane-AcOEt, 3:1); IR: 3283 (N-H), 3171 (N-H), 3061 (Ar, C-H), 1653 (–NHC(=O)–), 1606 (Ar, C=C), 1570 (ArNO₂, (N=O)₂), 1530 (Ar, C=C), 1457 (Ar, C=C), 1347 (ArNO₂, (N=O)₂), 1148 (Ar, C-Cl), 1051 (Ar-S-Ar), 926 (Ar, C-H), 903 (ArNO₂, C-N), 796 (Ar, C-H), 742 (Ar, C-H), 703 cm^{–1} (Ar, C=C); ¹H NMR: δ 7.29 (d, *J* = 8.6 Hz, 1H, H-9), 7.48 (dd, *J* = 2.0, 8.6 Hz, 1H, H-8), 7.67 (d, *J* = 2.0 Hz, 1H, H-6), 7.81 (d, *J* = 8.6 Hz, 1H, H-4), 8.28 (dd, *J* = 2.4, 8.4 Hz, 1H, H-3), 8.38 (d, *J* = 2.3 Hz, 1H, H-1), 11.03 (s, 1H, H-10); ¹³C NMR: δ 124.8 (C-9), 125.9 (C-1), 126.1 (C-3), 129.0 (C-5a), 129.3 (C-7), 130.2 (C-8), 131.9 (C-6), 133.0 (C-4), 138.5 (C-9a, C-11a), 143.2 (C-4a), 147.6 (C-2), 166.2 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₃SCl, [M]⁺: *m/z* 305.9866. Found: *m/z* 305.9868.

9-Chloro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11(10*H*)-one (3i) Yield 92%; pale orange solid; mp 243–245°C; *R*_f 0.38

(hexane-AcOEt, 3:1); IR: 3306 (N-H), 3183 (N-H), 3045 (Ar, C-H), 1653 (–NHC(=O)–), 1602 (Ar, C=C), 1528 (ArNO₂, (N=O)₂), 1496 (Ar, C=C), 1449 (Ar, C=C), 1341 (ArNO₂, (N=O)₂), 1080 (Ar, C-Cl), 1050 (Ar-S-Ar), 896 (ArNO₂, C-N), 770 (Ar, C-H), 695 cm^{–1} (Ar, C=C); ¹H NMR: δ 7.22 (t, *J* = 7.9 Hz, 1H, H-7), 7.57 (dd, *J* = 7.9 Hz, 1H, H-6), 7.61 (dd, *J* = 1.0, 7.9 Hz, 1H, H-8), 7.81 (d, *J* = 8.6 Hz, 1H, H-4), 8.24 (dd, *J* = 2.6, 8.6 Hz, 1H, H-3), 8.36 (d, *J* = 2.3 Hz, 1H, H-1), 10.65 (s, 1H, H-10); ¹³C NMR: δ 125.7 (C-1), 126.0 (C-3), 127.3 (C-7), 128.3 (C-5a), 131.2 (C-6), 131.9 (C-8), 132.2 (C-9), 132.9 (C-4), 136.1 (C-9a), 138.1 (C-11a), 143.9 (C-4a), 147.7 (C-2), 166.1 (C-11). HRMS (FD). Calcd for C₁₃H₇N₂O₃SCl, [M]⁺: *m/z* 305.9866. Found: *m/z* 305.9855.

Synthesis of 2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine derivatives 5

A representative example is the synthesis of 2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5a).

A solution of 2-aminophenyl 2-cyano-4-nitrophenyl sulfide (4a, 0.10 g, 0.37 mmol) in 15 mL of 30 wt% HCl-EtOH was heated under reflux at 90°C for 24 h, then cooled to room temperature and concentrated on a rotary evaporator. The residue of 5 · HCl was dissolved in water and the solution was neutralized using saturated aqueous sodium bicarbonate solution and extracted three times with ethyl acetate. The extract was washed several times with brine and dried over with MgSO₄. After filtration and concentration, the crude product was purified by column chromatography on silica gel eluting with *n*-hexane/ethyl acetate (3:1, *v/v*) to give analytically pure compound 5a (0.06 g).

2-Nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5a) Yield 61%; yellow solid; mp 214–215°C; *R*_f 0.13 (hexane-AcOEt, 3:1); IR: 3099 (Ar, C-H), 1600 (Ar, C=C), 1579 (ArNO₂, (N=O)₂), 1520 (Ar, C=C), 1459 (Ar, C=C), 1338 (ArNO₂, (N=O)₂), 1028 (Ar-S-Ar), 920 (ArNO₂, C-N), 764 (Ar, C-H), 699 cm^{–1} (Ar, C=C); ¹H NMR: δ 6.91 (t, *J* = 6.9 Hz, 1H, H-7), 6.99 (d, *J* = 8.0 Hz, 1H, H-9), 7.11 (s, 2H, NH₂), 7.22 (t, *J* = 7.0 Hz, 1H, H-8), 7.36 (d, *J* = 6.6 Hz, 1H, H-6), 7.76 (d, *J* = 8.6 Hz, 1H, H-4), 8.25 (m, 2H, H-1, H-3); ¹³C NMR: δ 122.6 (C-7), 123.7 (C-1), 125.0 (C-9, C-5a), 125.5 (C-3), 129.7 (C-8), 132.3 (C-6), 132.3 (C-4), 136.4 (C-11a), 146.2 (C-4a), 147.2 (C-2), 149.1 (C-9a), 157.7 (C-11). HRMS (FD). Calcd for C₁₃H₉N₃O₂S, [M]⁺: *m/z* 271.0415. Found: *m/z* 271.0428.

7-Methyl-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5b) Yield 32%; yellow solid; mp 204–205°C; *R*_f 0.11 (hexane-AcOEt, 3:1); IR: 3092 (Ar, C-H), 2919 (CH₃), 1599 (Ar, C=C), 1520 (Ar, C=C), 1481 (Ar, C=C), 1339 (ArNO₂, (N=O)₂), 932 (Ar, C-H), 915 (ArNO₂, C-N), 742 (Ar, C-H), 668 cm^{–1} (Ar, C=C); ¹H NMR: δ 2.18 (s, 3H, ArCH₃), 6.88 (d, *J* = 8.0 Hz, 1H, H-9), 7.00 (s, 2H, NH₂), 7.03 (d, *J* = 6.9 Hz, 1H, H-8), 7.17 (s, 1H, H-6), 7.73 (d, *J* = 9.2 Hz, 1H, H-4), 8.24 (m, 2H, H-1, H-3); ¹³C NMR: δ 19.7 (ArCH₃), 123.7 (C-1), 124.6 (C-5a), 124.8 (C-9), 125.3 (C-3), 130.4 (C-8), 131.8 (C-7), 132.3 (C-4), 132.4 (C-6), 136.4 (C-11a), 146.1 (C-4a), 146.6 (C-9a), 147.2 (C-2), 157.5 (C-11). HRMS (FD). Calcd for C₁₄H₁₁N₃O₂S, [M]⁺: *m/z* 285.0572. Found: *m/z* 285.0577.

9-Methyl-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5c) Yield 41%; dark orange solid; mp 234–235°C; *R*_f 0.21 (hexane-AcOEt, 3:1); IR: 3064 (Ar, C-H), 2856 (CH₃), 1600 (Ar, C=C), 1579 (ArNO₂, (N=O)₂), 1519 (Ar, C=C), 1452 (Ar, C=C), 1337 (ArNO₂, (N=O)₂), 1051 (Ar-S-Ar), 770 cm^{–1} (Ar, C-H); ¹H NMR: δ 2.20 (s, 3H, ArCH₃), 6.81 (t, *J* = 7.6 Hz, 1H,

H-7), 7.02 (s, 2H, NH₂), 7.09 (d, *J* = 7.2 Hz, 1H, H-8), 7.20 (d, *J* = 7.7 Hz, 1H, H-6), 7.74 (d, *J* = 8.6 Hz, 1H, H-4), 8.24 (m, 2H, H-1, H-3); ¹³C NMR: δ 18.7 (ArCH₃), 122.2 (C-7), 123.5 (C-1), 125.2 (C-3), 125.3 (C-9), 129.9 (C-6), 130.7 (C-8), 132.2 (C-4), 132.8 (C-5a), 136.5 (C-11a), 146.4 (C-4a), 147.2 (C-2), 147.3 (C-9a), 156.9 (C-11). HRMS (FD). Calcd for C₁₄H₁₁N₃O₂S, [M]⁺: *m/z* 285.0572. Found: *m/z* 285.0579.

7,8-Dimethyl-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5d) Yield 46%; orange solid; mp 229–230°C; *R*_f 0.10 (hexane-AcOEt, 3:1); IR: 3064 (Ar, C-H), 2959 (CH₃), 2924 (CH₃), 2857 (CH₃), 1593 (Ar, C=C), 1520 (Ar, C=C), 1464 (Ar, C=C), 1372 (Ar, C-N), 1338 (ArNO₂, (N=O)₂), 1025 (Ar-S-Ar), 896 (ArNO₂, C-N), 873 (Ar, C-H), 775 cm⁻¹ (Ar, C-H); ¹H NMR: δ 2.08 (s, 6H, ArCH₃), 2.10 (s, 6H, ArCH₃), 6.79 (s, 1H, H-9), 6.96 (s, 2H, NH₂), 7.11 (s, 1H, H-6), 7.71 (s, 1H, H-4), 8.23 (m, 2H, H-1, H-3); ¹³C NMR: δ 18.1 (ArCH₃), 18.9 (ArCH₃), 121.7 (C-5a), 123.6 (C-3), 125.2 (C-1), 125.9 (C-9), 130.8 (C-8), 132.1 (C-4), 132.7 (C-6), 136.5 (C-11a), 138.0 (C-7), 146.5 (C-2), 146.8 (C-4a), 147.1 (C-9a), 157.5 (C-11). HRMS (FD). Calcd for C₁₅H₁₃N₃O₂S, [M]⁺: *m/z* 299.0728. Found: *m/z* 299.0728.

7-Methoxy-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5e) Yield 32%; orange solid; mp 196–197°C; *R*_f 0.05 (hexane-AcOEt, 3:1); IR: 3095 (Ar, C-H), 2935 (CH₃), 2831 (CH₃), 1602 (Ar, C=C), 1524 (Ar, C=C), 1480 (Ar, C=C), 1343 (ArNO₂, (N=O)₂), 1274 (C-O-C), 1032 (Ar-S-Ar), 909 (ArNO₂, C-N), 821 (Ar, C-H), 743 (Ar, C-H), 669 cm⁻¹ (Ar, C=C); ¹H NMR: δ 3.68 (s, 3H, ArOCH₃), 6.83 (d, *J* = 8.9 Hz, 1H, H-8), 6.91 (m, 4H, H-6, H-9, NH₂), 7.75 (d, *J* = 9.5 Hz, 1H, H-4), 8.26 (m, 2H, H-1, H-3); ¹³C NMR: δ 53.3 (ArOCH₃), 116.4 (C-8), 123.7 (C-1), 125.2 (C-5a, C-9), 125.3 (C-3), 125.7 (C-6), 132.4 (C-4), 136.4 (C-11a), 142.6 (C-9a), 145.7 (C-4a), 147.3 (C-2), 154.9 (C-7), 157.1 (C-11). HRMS (FD). Calcd for C₁₄H₁₁N₃O₃S, [M]⁺: *m/z* 301.0521. Found: *m/z* 301.0533.

7-Fluoro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5f) Yield 75%; dark orange solid; mp 224–225°C; *R*_f 0.28 (hexane-AcOEt, 3:1); IR: 3079 (Ar, C-H), 1603 (Ar, C=C), 1564 (ArNO₂, (N=O)₂), 1514 (Ar, C=C), 1471 (Ar, C=C), 1345 (ArNO₂, (N=O)₂), 914 (ArNO₂, C-N), 890 (Ar, C-H), 776 (Ar, C-H), 705 cm⁻¹ (Ar, C=C); ¹H NMR: δ 6.98 (dd, *J* = 5.4, 8.9 Hz, 1H, H-8), 7.07 (dd, *J* = 2.9, 8.6 Hz, 1H, H-9), 7.11 (s, 2H, NH₂), 7.23 (dd, *J* = 3.0, 8.4 Hz, 1H, H-6), 7.77 (d, *J* = 8.3 Hz, 1H, H-4), 8.27 (m, 2H, H-1, H-3); ¹³C NMR: δ 116.8 (C-8), 118.2 (C-6), 123.8 (C-3), 125.6 (C-1), 125.7 (C-5a), 126.0 (C-9), 132.6 (C-4), 136.2 (C-11a), 145.3 (C-4a), 145.9 (C-7, C-9a), 147.4 (C-2), 157.7 (C-11). HRMS (FD). Calcd for C₁₃H₈N₃O₂SF, [M]⁺: *m/z* 289.0321. Found: *m/z* 289.0321.

8-Fluoro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5g) Yield 42%; yellow solid; mp 253–254°C; *R*_f 0.18 (hexane-AcOEt, 3:1); IR: 3131 (Ar, C-H), 1597 (Ar, C=C), 1514 (Ar, C=C), 1462 (Ar, C=C), 1349 (ArNO₂, (N=O)₂), 1054 (Ar-S-Ar), 911 (ArNO₂, C-N), 773 (Ar, C-H), 718 cm⁻¹ (Ar, C=C); ¹H NMR (600 MHz, DMSO-*d*₆): δ 6.75 (m, 2H, H-7, H-9), 7.30 (s, 2H, NH₂), 7.39 (t, *J* = 7.7 Hz, 1H, H-6), 7.76 (d, *J* = 8.3 Hz, 1H, H-4), 8.27 (m, 2H, H-1, H-3); ¹³C NMR (150 MHz, DMSO-*d*₆): δ 110.5 (C-9), 112.0 (C-7), 121.9 (C-5a), 124.6 (C-1), 126.6 (C-3), 133.2 (C-4), 134.5 (C-8), 137.2 (C-11a), 146.8 (C-2), 148.2 (C-4a), 152.0 (C-9a), 159.3 (C-11), 163.0 (C-8). HRMS (FD). Calcd for C₁₃H₈N₃O₂SF, [M]⁺: *m/z* 289.0321. Found: *m/z* 289.0329.

7-Chloro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5h) Yield 75%; orange-colored solid; mp 221–222°C; *R*_f 0.15 (hexane-AcOEt, 3:1); IR: 3094 (Ar, C-H), 1601 (Ar, C=C), 1520 (Ar, C=C), 1460 (Ar, C=C), 1344 (ArNO₂, (N=O)₂), 1051 (Ar-S-Ar), 907 (ArNO₂, C-N), 741 (Ar, C-H), 701 cm⁻¹ (Ar, C=C); ¹H NMR: δ 6.97 (d, *J* = 8.6 Hz, 1H, H-9), 7.24 (m,

3H, H-8, NH₂), 7.41 (d, *J* = 2.6 Hz, 1H, H-6), 7.77 (d, *J* = 8.3 Hz, 1H, H-4), 8.26–8.29 (m, 2H, H-1, H-3); ¹³C NMR: δ 123.7 (C-3), 125.7 (C-1), 125.9 (C-7), 126.3 (C-9), 129.6 (C-5a), 131.2 (C-8), 132.6 (C-4, C-6), 136.1 (C-11a), 145.2 (C-2), 147.4 (C-4a), 148.1 (C-9a), 158.1 (C-11). HRMS (FD). Calcd for C₁₃H₈N₃O₂SCl, [M]⁺: *m/z* 305.0026. Found: *m/z* 305.0025.

9-Chloro-2-nitrodibenzo[*b,f*][1,4]thiazepin-11-amine (5i) Yield 56%; yellow solid; mp 280–281°C; *R*_f 0.30 (hexane-AcOEt, 3:1); IR: 3120 (Ar, C-H), 1606 (Ar, C=C), 1516 (Ar, C=C), 1471 (Ar, C=C), 1350 (ArNO₂, (N=O)₂), 1158 (Ar, C-Cl), 905 (ArNO₂, C-N), 773 (Ar, C-H), 742 (Ar, C-H), 688 cm⁻¹ (Ar, C=C); ¹H NMR: δ 6.89 (t, *J* = 7.9 Hz, 1H, H-7), 7.36 (m, 2H, H-6, H-8), 7.40 (s, 2H, NH₂), 7.77 (t, *J* = 4.7 Hz, 1H, H-4), 8.28 (m, 2H, H-1, H-3); ¹³C NMR: δ 122.7 (C-7), 123.5 (C-1), 125.7 (C-3), 127.5 (C-9), 128.7 (C-9a), 130.4 (C-8), 131.1 (C-6), 132.5 (C-4), 136.1 (C-11a), 145.3 (C-2, C-5a), 147.5 (C-4a), 158.3 (C-11). HRMS (FD). Calcd for C₁₃H₈N₃O₂SCl, [M]⁺: *m/z* 305.0026. Found: *m/z* 305.0029.

Antibacterial activity test

The antibacterial assay was performed according to the protocol of the Clinical and Laboratory Standards Institute (Wayne, PA, USA). In the protocol, *E. coli* ATCC25922 and *S. aureus* ATCC29213 are defined as the quality control strains and were used for our antibacterial assay. In the assay, 10 μL of a bacterial cell suspension containing 1 × 10⁵ colony forming units (CFU) bacteria was inoculated into 1 mL of Mueller-Hinton broth (Becton Dickinson and Company, Sparks, MD, USA) supplemented with 0.5 mg/mL of the test compound. The culture was incubated for 20 h at 35°C under an aerobic condition, and the viable cells in the culture were counted with the modified Miles and Misra method [40]. Briefly, 10 μL aliquots of serial-diluted bacterial suspensions were inoculated into a trypticase soy agar broth. After 20 h incubation at 35°C under an aerobic condition, the numbers of colonies recovered from the diluted suspensions on the agar broth were counted, and the number of viable bacterial cells in the source culture was determined.

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