ANTIBACTERIAL AND FUNGICIDAL ACTIVITIES OF 1,8-BIS[(3-ARYL)-S-TRIAZOLO[3,4-*B*]-[1,3,4]THIADIAZOLE-6-YL]OCTANES

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Abstract : 1,8-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octanes **2** were synthesized in high yields by reaction of 3-aryl 4-amino-5-mercapto-1,2,4-triazole **1** with sebacic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst. The structures have been established on the basis of elemental analysis and spectral date. The preliminary antibacterial tests showed that most of them were effective against *S.aureus*, *E.coli* and *B.subtilis*. **2b, 2c, 2d, 2n** and **2o** exhibited good fungicidal activities against *Cerospora beticola sacc*.

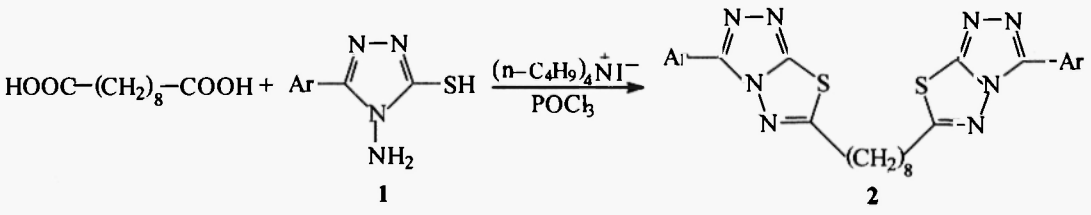
Introduction

Bis[1,2,4-Bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-4-yl]alkanes were reported to possess antibacterial property (1) and bis[1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazol-3-yl-meth -oxy]phenylenes possess anticancer activity against a panel of 60 cell lines derived from seven cancer types namely, lung, colon, melanoma, renal, ovarian, and leukemia (2). 2,5-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pyridines (3) and 2,6-Bis [(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]pyridines (4) endowed with good fungicidal activities against *Cerospora beticola sacc* have been reported from our laboratory. 1,4-Bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl]butanes (5) and trans-1,2-bis[(3-aryl)-1,2,4-triazolo[3,4-*b*]-[1,3,4] thiadiazole-6-yl]ethenes (6) were found to show significant antibacterial activities. Prompted by these observation and in continuation of our search for bio-active molecules, We designed a facile one-pot method to prepare fifteen new 1,8-bis[(3-aryl)-s- triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octanes by cyclization of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with octanedioic acid. The synthesis, characterization and the results of antibacterial and fungicidal activities screening studies of the newly synthesized compounds are presented in this paper.

Result and Discussion

The synthesis of 1,8-bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octanes **2** was accomplished in one step with good yields by condensing 3-aryl-4-amino-5-mercapto-1,2,4-triazoles **1** with sebacic acid in the presence of $POCl_3$ and tetrabutylammonium iodide as catalyst (**Scheme 1, Table 1**). Because of the poor solubility of **1** and sebacic acid in $POCl_3$, the yield of **2** is very low. For example, the yield of **2a** was 30%. However, where the tetrabutylammonium iodide as phase transfer catalyst were utilized and the mixture was first stirred for 4 h at 55-60 ℃, then refluxed for 9-11 h at

115-120 °C, **2a** was obtained in 80% yield.



1 2

Scheme 1

Table 1 : Preparation of 1,8-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octanes **2** from 3-aryl-4-amino-5-mercapto-1, 2, 4-triazoles **1**.

Entry	Ar	Condition	Yield(%)[a]	m.p.(°C)
2a	Ph	115-120°C/9.0h	80	>250
2b	2-Cl-Ph	115-120°C/9h	70	207-209
2c	3-Cl-Ph	115-120°C/10h	65	204-207
2d	4-Cl-Ph	115-120°C/11h	72	210-208
2e	2-CH_3-Ph	115-120°C/10h	68	189-187
2f	3-CH_3-Ph	115-120°C/10h	71	194-192
2g	4-CH_3-Ph	115-120°C/9h	74	202-201
2h	3-Br-Ph	115-120°C/9h	65	216-218
2i	4-Br-Ph	115-120°C/10h	71	212-210
2j	2-I-Ph	115-120°C/11h	58	207-209
2k	3-I-Ph	115-120°C/10h	65	219-221
2l	4-I-Ph	115-120°C/11h	77	213-215
2m	4-OCH_3-Ph	115-120°C/13h	72	197 ~ 199
2n	4-Pyridyl	115-120°C/10h	60	>250
2o	3-Pyridyl	115-120°C/11h	65	>250

[a]Purified yields of **2a-2o** based on sebacic acid.

The structures of all compounds **2** were established on the basis of elemental analysis and spectral data. The IR spectral data of compounds **2** showed bands at 1620-1645 cm^{-1}, 1235-1260 cm^{-1}, and 700-710 cm^{-1} due to C=N, N-N=C and C-S-C, respectively. The ^1H NMR spectra of **2** exhibited multiple signals in the δ 8.90-7.30 range accounting for hydrogen of aryl group, a triplet at δ 3.20 accounting for the 4 hydrogens of -2SCH_2, 2.05-1.85 range accounting for the 4 hydrogens of -2$SCH_2\underline{CH_2}$, 1.60-1.45 range attributing to the 8 hydrogens of $CH_2CH_2CH_2CH_2$. With compound **2a** as an example, it exhibited multiple signals in the δ 8.33-8.30, 7.81-7.58 ranges accounting for the 10 hydrogens of phenyl groups, a triplet at δ 3.29 accounting for the 4 hydrogens of -2SCH_2, a multiple signals at δ 2.01-1.98 attributing to the 4 hydrogens of 2$SCH_2\underline{CH_2}$, a multiple signals in the

δ 1.58-1.49 ranges accounting for the 8 hydrogens of $CH_2CH_2CH_2CH_2$. The EI-MS for compounds **2** exhibited molecular ion peaks. For example, **2a** showed strong molecular ion peak M^+ with m/z 514 and 11% relative abundance.

Compounds **2** were screened for their antibacterial activities against *E. coli*, *S. aureus*, and *B. subtilis* employing the cup-plate method at the concentration of 100 μg/mL in the nutrient agar. The preliminary results indicated that most of compounds express significant antibacterial activity. The results of such studies are given in table **2**. The biological 70 ities of compounds **2** were investigated and the results showed that they exhibited fungicidal activities, especially against *Cerospora beticola sacc*. For example, **2b, 2c, 2d, 2n** and **2o** showed 92% of *Cerospora beticola sacc* inhibition of in 50 mg/L (see Table **3**).

Table 2 The Antibacterial Activities of Compounds **2a-3o**

Compd.	*S.aureus*	*E.coli*	*B.subtilis*
2a	+	-	+ +
2b	+ +	+ +	+ + +
2c	+ + +	+ +	+ + +
2d	+ + +	+ +	+ + +
2e	+	-	+
3f	+ +	+	+ +
2g	-	-	-
2h	+	+	+ +
2i	+ +	+	+ +
2j	-	-	-
2l	-	-	+
2m	+	-	+
2n	+ + +	++	+ + +
2o	+ + +	+ +	+ + +

Zone diamerter of growth inhibition: <10 mm(-), 10 ~ 12 mm(+), 13 ~ 15 mm(+ +),16 ~ 20 mm(+ + +); Diamater of the cup=8 mm.

Table-3 The Fungicidal Activities **2** (50 mg/L, relative inhibition %)

Compd.	*Gibberella zeae*	*Cerospora beticola sacc*	*Physalospora piricola*
2a	35	69	70

2b	77	94	65
2c	63	94	70
2d	86	96	75
2e	29	71	45
2f	38	68	52
2g	40	56	48
2h	29	70	30
2i	39	80	51
2j	25	74	63
2k	31	70	51
2l	25	82	47
2m	29	80	30
2n	44	93	67
2o	50	92	57

Experimental

Melting points were determined on an X_4 melting point apparatus and were uncorre[illegible] The IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer using [illegible] discs in the range 4000-400 cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-Plus 400 NMR spectrometer in CF_3COOD. The chemical shifts are reported as parts per million relative to internal TMS. MS spectra were recorded on a Finnigan Trace GC-MS spetrometer. Elemental Analyses were taken on a Perkin-Elemer-2400-CHN Elemental Analysis Instrument.

Compound 3-Aryl-4-amino-5-mercapto-1,2,4-triazole **1** was prepared from aromatic carboxylic acids by four steps according to the literature (5).

General preparation of 2-A mixture of compound 3-aryl-4-amino-5-mercapto-1,2,4-triazole (2.2 mmol), sebacic acid (1.0 mmol), tetrabutylammonium iodide (0.5 mmol), and $POCl_3$ (7 mL) was stirred for 4 h at 55-60 °C, and then refluxed for 9.0-13 h at 115-120 °C.

Excess $POCl_3$ was removed under reduced pressure. The concentrated mass was cooled and poured into crushed ice, and neutralized with potassium carbonate. The separated solid was filtered, washed with water, ethanol, and then dried. The crude material was recrystallized from a mixture of ethanol and pyridine to afford pure title compounds **2a-2o**

1,8-Bis[(3-aryl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2a)

White powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.33-8.30 (m, 4H, Ar-H), 7.81-7.58 (m, 6H, Ar-H), 3.29 (t, 4H, J=7.2, $2SCH_2$), 2.01-1.98 (m, 4H, $2SCH_2\underline{CH_2}$), 1.58-1.49 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1623, 1251, 701. MS-EI (*m/z*): 514 (M^+, 11%), 339 (93%), 215 (51%), 175 (100%), 117(56%), 103 (74%). Elemental Anal. Calcd. For $C_{26}H_{26}N_8S_2$: C, 60.68; H, 5.09; N, 21.77. Found: C, 60.83; H, 5.17; N, 21.53.

1,8-Bis[(3-*o*-chlorophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2b)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.35-8.30 (m, 2H, Ar-H), 8.21-8.17 (m, 3H, Ar-H), 7.64-7.60 (m, 3H, Ar-H), 3.27 (t, 4H, J=7.4, $2SCH_2$), 2.18-2.15 (m, 4H, $2SCH_2\underline{CH_2}$), 1.42-1.37 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1628, 1237, 704. MS-EI (*m/z*): 584 (1%), 582 (M^+, 2%), 373 (3%), 249 (12%), 137 (100%), 135 (92%), 102 (46%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2Cl_2$: C, 53.35; H, 4.15; N, 19.20. Found: C, 53.48; H, 4.06; N, 19.07.

1,8-Bis[(3-*m*-chlorophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2c)

Yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.38-8.34 (m, 3H, Ar-H), 8.24-8.19 (m, 3H, Ar-H), 7.54-7.49 (m, 2H, Ar-H), 3.24 (t, 4H, J=7.5, $2SCH_2$), 2.04-2.01(m, 4H, $2SCH_2\underline{CH_2}$), 1.49-1.46 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1629, 1232, 707. MS-EI (*m/z*): 584 (1%), 582 (M^+, 3%), 373 (2%), 249 (8%), 135(100%), 102 (42%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2Cl_2$: C, 53.35; H, 4.15; N, 19.20. Found: C, 53.21; 72 19; N, 19.38.

1,8-Bis[(3-*p*-chlorophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2d)

Light yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.30-8.27 (m, 4H, Ar-H), 7.68-7.65 (m, 4H, Ar-H), 3.28 (t, 4H, J=7.6, $2SCH_2$), 1.98-1.95 (m, 4H, $2SCH_2\underline{CH_2}$), 1.56-1.52 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1632, 1241, 703. MS-EI (*m/z*): 584 (2%), 582 (M^+, 5%), 373 (5%), 249 (6%), 135(100%), 102 (74%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2Cl_2$: C, 53.35; H, 4.15; N, 19.20. Found: C, 53.17; H, 4.08; N, 19.34.

1,3-Bis[(3-*o*-methylphenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]benzene (2e)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.32-8.29 (m, 3H, Ar-H), 7.64-7.57 (m, 5H, Ar-H), 3.24 (t, 4H, J=7.4, $2SCH_2$), 2.48-2.45 (s, 6H, $2CH_3Ph$), 1.96 (m, 4H, $2SCH_2\underline{CH_2}$), 1.51-1.48 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1627, 1241, 701. MS-EI (*m/z*): 542 (M^+, 1%), 353 (7%), 229 (10%), 117 (100%), 102 (42%). Elemental Anal. Calcd. For $C_{28}H_{30}N_8S_2$: C, 61.97; H, 5.57; N, 20.65. Found: C, 62.15; H, 5.42; N, 20.53.

1,8-Bis[(3-*m*-methylphenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]benzene (2f)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.26-8.22 (m, 3H, Ar-H), δ 8.14-8.10 (m, 2H, Ar-H), 7.51-7.46 (m, 3H, Ar-H), 3.19 (t, 4H, J=7.5, $2SCH_2$), 2.57 (s, 6H, $2CH_3Ph$), 1.94-1.91 (m, 4H, $2SCH_2\underline{CH_2}$), 1.56-1.52 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1619, 1257, 703. MS-EI (*m/z*): 542 (M^+, 4%), 353 (10%), 229 (9%), 117 (100%), 102 (38%). Elemental Anal. Calcd. For $C_{28}H_{30}N_8S_2$: C, 61.97; H, 5.57; N, 20.65. Found: C, 62.80; H, 5.51; N, 20.78.

1,3-Bis[(3-*p*-methylphenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2g)

White powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.20-8.17 (m, 4H, Ar-H), 7.56-7.51 (m, 4H, Ar-H), 3.26 (t, 4H, J=7.6, $2SCH_2$), 2.51 (s, 6H, $2CH_3Ph$), 1.98-1.95 (m,

4H, $2SCH_2\underline{CH_2}$), 1.42-1.39 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1630, 1237, 708. MS-EI (*m/z*): 542 (M^+, 6%), 353 (12%), 229 (8%), 117 (100%), 102 (52%). Elemental Anal. Calcd. For $C_{28}H_{30}N_8S_2$: C, 61.97; H, 5.57; N, 20.65. Found: C, 61.84; H, 5.50; N, 20.81.

1,8-Bis[(3-*m*-bromophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]benzene (2h)

Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.47-8.41 (m, 5H, Ar-H), 7.79-7.72 (m, 3H, Ar-H), 3.27 (t, 4H, *J*=7.5, $2SCH_2$), 2.01-1.98 (m, 4H, $2SCH_2\underline{CH_2}$), 1.51-1.48 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1623, 1242, 701. MS-EI (*m/z*): 672 (3%), 671 (M^+, 3%), 591 (74%), 512 (21%), 417(100%), 102 (8%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2Br_2$: C, 46.44; H, 3.40; N, 16.66. Found: C, 46.31; H, 3.34; N, 16.51.

1,8 -Bis[(3-*p*-bromophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2i)

Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.39-8.36 (m, 4H, A 73 7.72-7.68 (m, 4H, Ar-H), 3.21 (t, 4H, *J*=7.5, $2SCH_2$), 1.91-1.87 (m, 4H, $2SCH_2\underline{CH_2}$), 1.57-1.53 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1638, 1239, 705. MS-EI (*m/z*): 672 (2%), 671 (M^+, 3%), 591 (100%), 512 (9%), 417(8%), 102 (12%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2Br_2$: C, 46.44; H, 3.40; N, 16.66. Found: C, 46.28; H, 3.45; N, 16.83.

1,8-bis[(3-*o*-iodophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2j)

Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.42-8.37 (m, 2H, Ar-H), 8.21-8.17 (m, 3H, Ar-H), 7.54-7.48 (m, 3H, Ar-H), 3.31 (t, 4H, *J*=7.5, $2SCH_2$), 1.91-1.88 (m, 4H, $2SCH_2\underline{CH_2}$), 1.53-1.50 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1637, 1250, 710. MS-EI (*m/z*): 766 (M^+, 2%), 639 (100%), 465 (71%), 229(60%), 102 (21%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2I_2$: C, 40.74; H, 3.15; N, 14.62. Found: C, 40.61; H, 3.08; N, 14.81.

1,8-Bis[(3-*m*-iodophenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]benzene (2k)

Light yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.40-8.33 (m, 5H, Ar-H), 7.41-7.36 (m, 3H, Ar-H), 3.37 (t, 4H, *J*=7.5, $2SCH_2$), 1.97-1.94 (m, 4H, $2SCH_2\underline{CH_2}$), 1.50-1.46 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1624, 1246, 703. MS-EI (*m/z*): 766 (M^+, 1%), 639 (78%), 465 (100%), 229(51%), 102 (32%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2I_2$: C, 40.74; H, 3.15; N, 14.62. Found: C, 40.63; H, 3.18; N, 14.76.

1,8-Bis[(3-*p*-iodophenyl)-s-triazolo[3,4-*b*]-[1,3,4[thiadiazole-6-yl]octane (2l)

Yellow powder, ^1H NMR (CF_3COOD, 400 MHz): δ 8.35-8.32 (m, 4H, Ar-H), 7.69-7.64 (m, 4H, Ar-H), 3.27 (t, 4H, *J*=7.5, $2SCH_2$), 1.87-1.84 (m, 4H, $2SCH_2\underline{CH_2}$), 1.49-1.46 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1642, 1259, 700. MS-EI (*m/z*): 766 (M^+, 1%), 639 (100%), 465 (64%), 229(68%), 102 (26%). Elemental Anal. Calcd. For $C_{26}H_{24}N_8S_2I_2$: C, 40.74; H, 3.15; N, 14.62. Found: C, 40.89; H, 3.20; N, 14.47.

1,8-Bis[(3-*p*-methoxyphenyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2m)

Light yellow powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.31-8.28 (m, 4H, Ar-H), 7.20-7.27 (m, 3H, Ar-H), 3.98 (s, 6H, $2CH_3OPh$), 3.26 (t, 4H, J=7.6, $2SCH_2$), 1.99-1.95 (m, 4H, $2SCH_2\underline{CH_2}$), 1.54-1.51 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1635, 1241, 705. MS-EI (*m/z*): 574 (M^+, 18%), 369 (91%), 206 (100%), 133 (88%), 102 (11%). Elemental Anal. Calcd. For $C_{28}H_{30}N_8O_2S_2$: C, 58.52; H, 5.26; N, 19.50. Found: C, 58.69; H, 5.13; N, 19.38.

1,8-Bis[(3-4′-pyridyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2n)

Light brown powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.87-8.83 (m, 5H, Ar-H), 7.56-7.51 (m, 3H, Ar-H), 3.41 (t, 4H, J=7.3, $2SCH_2$), 2.10-1.97 (m, 4H, $2SCH_2\underline{CH_2}$), 1.47-1.44 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1628, 1234, 701. MS-EI (*m/z*): 516 (M^+, 8%), 340 (3%), 176 (16%), 104 (100%). Elemental Anal. Calcd. For $C_{24}H_{24}N_{10}S_2$: C, 74 1; H, 4.68; N, 27.12. Found: C, 55.98; H, 4.61; N, 27.02.

1,8-Bis[(3-3′-pyridyl)-s-triazolo[3,4-*b*]-[1,3,4]thiadiazole-6-yl]octane (2o)

Light brown powder, ^{1}H NMR (CF_3COOD, 400 MHz): δ 8.92-8.87 (m, 3H, Ar-H), δ 8.81-8.76 (m, 3H, Ar-H), 7.46-7.41 (m, 2H, Ar-H), 3.38 (t, 4H, J=7.3, $2SCH_2$), 2.18-2.14 (m, 4H, $2SCH_2\underline{CH_2}$), 1.50-1.47 (m, 8H, $CH_2CH_2CH_2CH_2$); IR (KBr, cm^{-1}): 1635, 1249, 706. MS-EI (*m/z*): 516 (M^+, 4%), 340 (5%), 176 (21%), 104 (100%). Elemental Anal. Calcd. For $C_{24}H_{24}N_{10}S_2$: C, 55.81; H, 4.68; N, 27.12. Found: C, 55.70; H, 4.74; N, 27.31.

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