Design and Synthesis of Cinanserin Analogs as Severe Acute Respiratory Syndrome Coronavirus 3CL Protease Inhibitors

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The severe acute respiratory syndrome (SARS) coronavirus 3CL protease is an attractive target for the development of anti-SARS drugs. In this paper, cinanserin (1) analogs were synthesized and tested for the inhibitory activities against SARS-coronavirus (CoV) 3CL protease by fluorescence resonance energy transfer (FRET) assay. Four analogs show significant activities, especially compound 26 with an IC_{50} of 1.06 μM.

Key words SARS coronavirus 3CL protease; cinanserin analog; inhibitor; fluorescence resonance energy transfer-based assay

Severe acute respiratory syndrome (SARS) is a life-threatening form of atypical pneumonia caused by infection with a novel human coronavirus (SARS-CoV). It rapidly spreaded from southern China to several other countries during late 2002 and early 2003.[1)] By July 31, 2003, a total of 8098 SARS cases and 774 SARS-related deaths were reported around the world.[2,3)] Although regional preventive measures are being implemented, vaccine and therapeutic drugs are being sought, no effective small molecule antiviral agent has been reported for treating SARS so far.

SARS-CoV is a positive-strand RNA virus that consists of about 29700 nucleotides. It encodes two overlapping polyproteins, ppla (486 kDa) and pplab (790 kDa).[4—7)] The functional polypeptides are released from each polyprotein through extensive proteolytic processing primarily by 3CL protease.[8)] Because of this functional importance of SARS-CoV 3CL protease in the viral life cycle, it has been recognized as a key target for drugs designing against SARS.[9—11)]

In our preceding paper, we have reported that cinanserin (**1**), a well-characterized serotonin antagonist, is a good potential lead compound for designing more active inhibitors of 3CL protease.[12)] Herein we report the design and synthesis of two series of cinanserin derivatives as novel inhibitors of SARS-CoV 3CL protease.

According to the 3D model of the cinanserin-3CL protease complex,[12)] three series of cinanserin analogs have been designed and synthesized respectively (Table 1). In order to modify the cinnamide moiety of cinanserin, compounds **2**—**9** were synthesized in which cinnamoyl group is replaced with other phenyl-containing groups. Compounds **10**—**22** and **26**, **27** were designed and prepared to diversify the substitute groups and chains on sulfur atom of cinanserin. Compounds **23**—**25** were prepared to vary the thioether group of cinanserin into ether and sulfoxide respectively.

Chemical Synthesis Compounds **2**—**22** were synthesized *via* a three-step route (Chart 1).[13,14)] The starting material 2-aminothiophenol (**28**) was first treated with excessive sodium isopropoxide at room temperature to form sodium salt, which was then reacted with a variety of alkyl halides or aminoalkyl halides, yielding intermediates **29**—**42**. Most of the intermediates are known except **35**, **36**, **37** and **42**. Acylation of the intermediates with the corresponding acyl chloride produced the target compounds **2**—**22** (Chart 1). Similarly, compounds **23** and **24** were obtained from 2-aminophenol (**43**) and 2-amino-4-nitrophenol (**44**) *via* the same approach respectively (Chart 2).

Sulfoxide **25** was prepared by oxidation of cinanserin (**1**) with sodium periodate in acetonitrile. The synthesis of compounds **26** and **27** also started from 2-aminothiophenol (**28**), which was reacted with an excess of cinnamoyl chloride (**47**, R=H) or 2-cyanocinnamoyl chloride (**48**, R=CN) in the presence of triethylamine at reflux in dichloromethane to give the desired products **29** and **30** respectively (Chart 3). Among the target compounds, **2**, **4**, **5**, **11**, **21**, **23** and **24** are known, but their ^{1}H-NMR data have not been reported yet.

Biological Results and SAR Discussion The bioactivities of compounds **2**—**27** were measured by a fluorescence resonance energy transfer (FRET)-based assay using 5-(2-aminoethylamino)naphthelenesulfonic acid (Edans) and 4-(4-dimethylaminophenylazo)benzoic acid (Dabcyl) as the energy transfer pair. The peptide substrate is Dabcyl-KNSTLQSGLRKE-Edans labeled with Edans and Dabcyl. The inhibition of SARS-CoV 3CL protease slowly increased in the concentration range from 0 to 500 μM of the corresponding compounds. The IC_{50} value of the compounds in inhibiting the catalytic activity of SARS-CoV 3CL protease was calculated by fitting the dose–response curve using a logistic derivative equation.[12)] The results are summarized in Table 1.

Of the synthetic derivatives tested, compounds **7**, **10**, **13**, **26** and **27** displayed remarkable inhibitory activity of SARS-CoV 3CL protease, indicating that the cinnamoyl group is crucial for good inhibition of SARS-CoV 3CL protease. Compound **7** is about 2-fold more potent than cinanserin, suggesting that introduction of a cyano substituent on α-position of cinnamoyl group increased the inhibitory activity. Replacement of the dimethylamino group of cinanserin with electron-withdrawing group such as an ester group (**13**) or elimination of the dimethylamino group (allylthioether **10**) enhanced remarkably the inhibitory activity, and the chain length of the thioether is not critical of the inhibitory activity (compound **11** *vs.* **12**; **15** *vs.* **16**). When the phenylthioether moiety in cinanserin was changed to phenylether group (**23**) or oxidized to sulfoxide (**25**), no inhibitory activity was observed. Unexpectedly, replacement of the 3-dimethylaminopropyl group in cinanserin with an additional cinnamoyl

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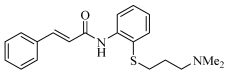
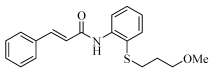
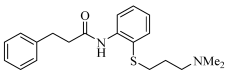
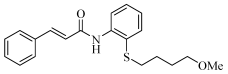
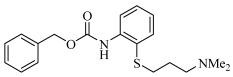
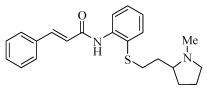
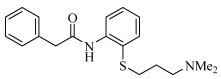
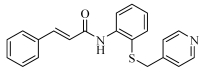
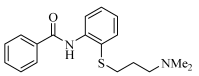
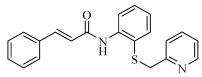
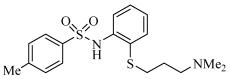
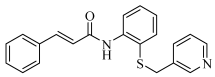
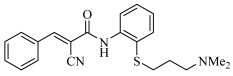
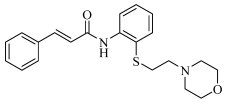
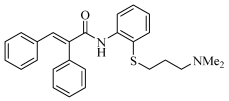
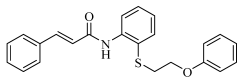
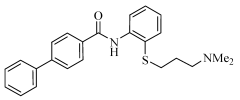
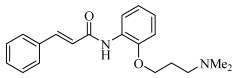
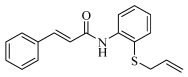
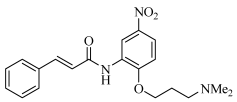
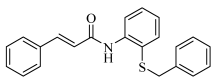
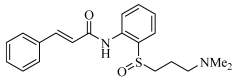
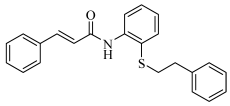
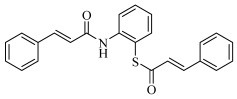
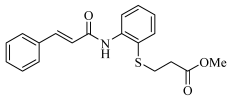
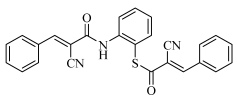
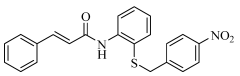
Table 1. The Chemical Structures and Inhibitory Activities of Cinanserin **1** and Analogs **2**—**27** against SARS 3CL Protease[a)]

Compd.	Structure	IC_{50} (μM)	Compd.	Structure	IC_{50} (μM)
1 Cinanserin		323	**15**		>500
2		>500	**16**		>500
3		>500	**17**		>500
4		>500	**18**		>500
5		>500	**19**		293
6		>500	**20**		349
7		125	**21**		>500
8		>500	**22**		>500
9		>500	**23**		>500
10		19.7	**24**		>500
11		206	**25**		>500
12		>500	**26**		1.06
13		13.5	**27**		43.7
14		>500			

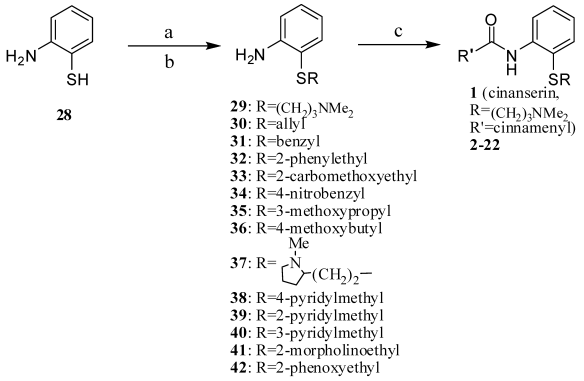
a) The flurogenic peptide substrate is Dabcyl-KNSTLQSGLRKE-Edans instead of Edans-VNSTLQSGLRK(Dabcyl)M as used in ref. 12.

group, giving compound **26** which showed very potent inhibition against 3CL protease, and is 300-fold more potent than cinanserin itself. These observations are in good coincidence with the molecular docking study of the complex of 3Cl protease with the ligand.

Docking Study The 3D structure of compound **26** was constructed by the Corina online service (http://www.molnet.com/online_demos/corina_demo.html). The 3D model of SARS-CoV 3CL protease was retrieved from the Brookhaven Protein Data Bank (PDB) (http://www.rcsb.org/pdb/) (PDB ID: 1UJ1, Chain A).[12)] AutoDock Tools (http://autodock.scripps.edu/resources/adt) were used to add polar hydrogen and assign partial charges to both protein and ligand. AutoDock 3.0[15)] was employed for the docking of compound **26** to SARS-3CL protease. All the molecular modeling and docking simulations were performed on a Silicon Graphics Origin 3800 (with 128 CPUs).

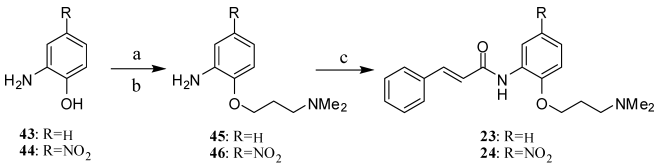
To address the SARS-CoV 3CL protease inhibitory activity of compound **26**, we applied molecular docking to identify the possible binding mode between the compound and the enzyme. The top pose, ranked by the "estimated free energy of binding", was chosen as the predicted binding mode.

For the top pose, as shown in Fig. 1, compound **26** locates deep inside the S1 pocket[12] with appropriate steric complement. Fourty hydrophobic interaction atom pairs between the compound and the enzyme were detected by using the LIGPLOT.[16] In the light of this binding mode, compound **26** occupies the substrate binding subsite, indicating that it is a competitive ligand for the enzyme's substrate, and the predicted dissociation constant K_D is 0.35 M. Compared with the binding mode of cinanserin and SARS-CoV 3CL protease,[12] compound **26** binds tighter with the protease than cinanserin. This might lead to the stronger inhibitory activity against the protease.



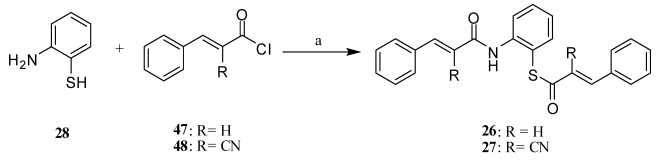
Reagents and conditions: (a) i-PrONa, i-PrOH; (b) RX, reflux; (c) R′COCl, $CHCl_3$, NEt_3

Chart 1 Synthesis of Compounds **1**—**22**



Reagents and conditions: (a) i-PrONa, i-PrOH; (b) $Me_2N(CH_2)_3Cl{\cdot}HCl$, toluene, reflux; (c) cinnamoyl chloride, $CHCl_3$, NEt_3

Chart 2 Synthesis of Compounds **23** and **24**



Reagents and conditions: (a) NEt_3, CH_2Cl_2, reflux

Chart 3 Synthesis of Compounds **26** and **27**

Conclusion

Three series of cinanserin analogs derived from the modification of cinnamenyl, phenylthioether group and sulfur-containing chain of cinanserin have been designed and synthesized as potential inhibitors of SARS-CoV 3CL protease. The inhibitory activities of these compounds were assessed by FRET assay. Some analogs showed improved inhibitory activities against SARS-CoV 3CL protease compared with cinanserin itself. The IC_{50} values of compounds **10**, **13**, **26** and **27** are lower than 100 μM. Among them compound **26** is the most potent one . It is much more potent than cinanserin by two orders of magnitude in the inhibition of SARS 3CL protease.

Experimental

General All starting materials were commercially available and used without further purification. All water-sensitive reactions were carried out in oven-dried glassware with a stirring bar under a nitrogen atmosphere. Toluene was dried over sodium, chloroform and dichloromethane were dried over CaH_2. Melting points were measured in capillary tube on a Buchi 510 melting point apparatus without correction. IR spectra were recorded on a Nicolet Magna IR750 spectrometer with KBr disks or film. NMR spectra were recorded on Brucker AMX-400 (400 MHz). Chemical shifts were reported in parts per million (ppm, δ units) downfield from chloroform where solvent peak was used as internal standard. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LR-MS and HR-MS) were given with electric ionization (EI) produced by Varian MAT-711 and Finnigan MAT-95 instrument.

2-(3-Methoxypropylthio)benzenamine (35) To a solution of sodium isopropoxide prepared from sodium (0.35 g, 15.2 mmol) in isopropanol (20 ml) was added **28** (1.7 ml, 15 mmol), and the mixture was stirred at room temperature for 30 min. 1-Chloro-3-methoxypropane (1.63 g, 15 mmol) was then added to. The reaction mixture was stirred at reflux for 4 h, and con-

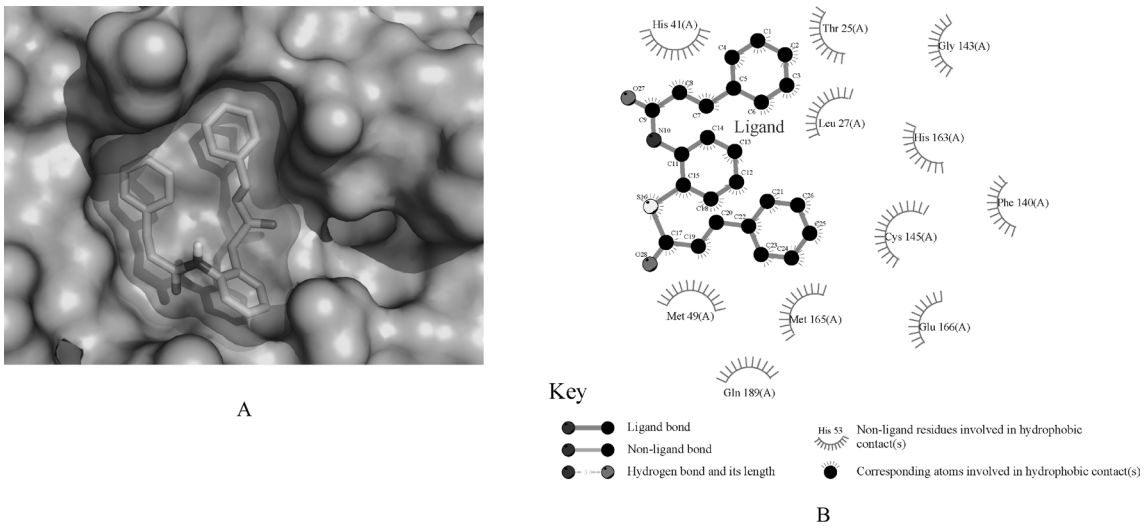


Fig. 1. Modeled Interaction of Compound **26** with SARS-CoV 3CL Protease

(A) SARS-CoV 3CL protease is shown as a surface model, in grey; compound **26** is shown as deep grey stick and surface; (B) amino acid residues involved in the compound **26** binding: H-bond is represented as dashed line, and hydrophobic contacts with the ligand as spiked residue. (A) was generated with PyMOL[17] and (B) was generated with LIGPLOT.

densed in vaccum. The residue was treated with water and extracted with ether twice. The combined organic layer was washed with water and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by flash column chromatography on silica gel eluting with petroether (80) : chloroform (13) : ethyl acetate (7) to afford **35** (0.63 g, 21%) as a brownish oil. ^{1}H-NMR ($CDCl_3$) δ: 1.78—1.85 (2H, m), 2.82 (2H, t, J=7.1 Hz), 3.31 (3H, s), 3.45 (2H, t, J=6.4 Hz), 4.33 (2H, s, br), 6.66—6.73 (2H, m), 7.08—7.12 (1H, m), 7.37 (1H, dd, J=7.7, 1.5 Hz).

2-(4-Methoxybutylthio)benzenamine (36) In the same manner as described for **35**, it was prepared from **28** and 1-chloro-4-methoxybutane in a yield of 52% as a brownish oil. ^{1}H-NMR ($CDCl_3$) δ: 1.62—1.70 (4H, m), 2.76 (2H, t, J=7.2 Hz), 3.31 (3H, s), 3.36 (2H, t, J=6.0 Hz), 4.34 (2H, s, br), 6.66—6.73 (2H, m), 7.08—7.12 (1H, m), 7.36 (1H, dd, J=7.7, 1.5 Hz).

2-[2-(2-*N*-Methylpyrrolidyl)ethylthio]benzenamine (37) In the same manner as described for **35**, it was prepared from **28** and 2-(2-chloroethyl)-1-methyl-pyrrolidine hydrochloride in a yield of 63% as a brownish oil. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.55 (2H, m), 1.63—1.75 (2H, m), 1.86—1.95 (2H, m), 2.08—2.16 (2H, m), 2.25 (3H, s), 2.63—2.70 (1H, m), 2.78—2.85 (1H, m), 3.00—3.05 (1H, m), 4.34 (2H, s, br), 6.65—6.72 (2H, m), 7.08—7.12 (1H, m), 7.38—7.56 (1H, m).

2-(2-Phenoxyethylthio)benzenamine (42) In the same manner as described for **35**, it was prepared from **28** and 2-phenoxyethyl bromide in a yield of 94% as a brownish oil. ^{1}H-NMR ($CDCl_3$) δ: 3.10 (2H, td, J=6.5, 0.7 Hz), 4.07 (2H, td, J=6.5, 0.7 Hz), 4.41 (2H, s, br), 6.67—6.74 (2H, m), 6.83—6.87 (2H, m), 6.93—6.97 (1H, m), 7.12—7.17 (1H, m), 7.24—7.30 (2H, m), 7.42—7.45 (1H, m).

***N*-[2-(3-Dimethylaminopropylthio)phenyl]-3-phenylpropanamide (2)**[13] To a solution of **29** (210 mg, 1.0 mmol) in $CHCl_3$ (2 ml) was added 3-phenylpropionyl chloride (168 mg, 1.0 mmol) in $CHCl_3$ (3 ml) dropwise. After refluxing for 1 h, the reaction mixture was alkalized with ammonia solution (25%). The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with a mixture of chloroform (9) : methanol (1) to afford **2** (305 mg, 89%) as a brownish oil. IR (KBr) cm^{-1}: 3338, 3026, 2941, 2769, 1691, 1578, 1510, 1433, 1294, 1159, 1076, 1038; ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.70 (2H, m), 2.19 (6H, s), 2.33 (2H, t, J=7.1 Hz), 2.67 (2H, t, J=7.3 Hz), 2.74 (2H, t, J=7.4 Hz), 3.08 (2H, t, J=7.4 Hz), 7.03 (1H, td, J=7.6, 1.1 Hz), 7.18—7.22 (1H, m), 7.25—7.34 (5H, m), 7.48 (1H, dd, J=7.7, 1.5 Hz), 8.39 (1H, d, J=8.1 Hz), 8.45 (1H, s, br). MS *m/z*: 342 (M^+), 281, 58 (100%).

Benzyl *N*-2-(3-Dimethylaminopropylthio)phenylcarbamate (3) In the same manner as described for **2**, it was prepared from **29** and benzyl chloroformate in a yield of 12% as a brown oil. IR (Film) cm^{-1}: 3350, 2856, 2941, 2767, 1738, 1581, 1514, 1437, 1304, 1202, 1072, 1041; ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.72 (2H, m), 2.17 (6H, s), 2.34 (2H, t, J=7.1 Hz), 2.75 (2H, t, J=7.1 Hz), 5.22 (2H, s), 6.99 (1H, td, J=7.5, 1.2 Hz), 7.30—7.45 (6H, m), 7.49 (1H, dd, J=7.8, 1.5 Hz), 8.09 (1H, s, br), 8.17 (1H, d, J=8.2 Hz). MS *m/z*: 344 (M^+), 91, 58 (100%); HR-MS (EI) *m/z*: Calcd for $C_{19}H_{24}N_2O_2S$ (M^+) 344.1558. Found 344.1577.

***N*-[2-(3-Dimethylaminopropylthio)phenyl]phenylacetamide (4)**[13] In the same manner as described for **2**, it was prepared from **29** and phenylacetyl chloride in a yield of 49% as a brown oil. IR (Film) cm^{-1}: 3315, 2939, 2767, 1687, 1579, 1514, 1433, 1302, 1159, 1036; ^{1}H-NMR ($CDCl_3$) δ: 1.43—1.50 (2H, m), 2.15 (6H, s), 2.19 (2H, t, J=7.0 Hz), 2.40 (2H, t, J=7.3 Hz), 3.79 (2H, s), 6.99 (1H, td, J=7.6, 1.4 Hz), 7.27—7.43 (7H, m), 8.42 (1H, d, J=8.2 Hz), 8.53 (1H, s, br).

***N*-[2-(3-Dimethylaminopropylthio)phenyl]benzamide (5)**[13] In the same manner as described for **2**, it was prepared from **29** and benzoyl chloride in a yield of 95% as a brown gel. IR (KBr) cm^{-1}: 3342, 2941, 2771, 1680, 1579, 1516, 1431, 1306, 1277, 1250, 1028; ^{1}H-NMR ($CDCl_3$) δ: 1.69—1.76 (2H, m), 2.15 (6H, s), 2.34 (2H, t, J=7.0 Hz), 2.82 (2H, t, J=7.2 Hz), 7.09 (1H, td, J=7.6, 1.3 Hz), 7.37—7.41 (1H, m), 7.50—7.60 (4H, m), 7.95—7.98 (2H, m), 8.59 (1H, dd, J=8.2, 1.3 Hz), 9.46 (1H, s, br). MS *m/z*: 314 (M^+), 253, 105, 77, 58 (100%).

***N*-[2-(3-Dimethylaminopropylthio)phenyl]-4-methylbenzenesulfonamide (6)** In the same manner as described for **2**, it was prepared from **29** and *p*-toluenesulfonyl chloride in a yield of 54% as a yellow solid. IR (KBr) cm^{-1}: 3425, 3103, 2922, 2474, 1599, 1572, 1473, 1433, 1334, 1240, 1167, 1092, 1068; ^{1}H-NMR ($CDCl_3$) δ: 1.78—1.85 (2H, m), 2.36 (3H, s), 2.63 (6H, s), 2.70 (2H, t, J=6.7 Hz), 2.95 (2H, s, br), 7.04 (1H, td, J=7.6, 1.2 Hz), 7.20—7.23 (3H, m), 7.35 (1H, dd, J=8.2, 0.9 Hz), 7.45 (1H, dd, J=7.9, 1.5 Hz), 7.69 (2H, dt, J=8.5, 1.8 Hz). MS *m/z*: 364 (M^+), 209, 91, 84, 58 (100%); HR-MS (EI) *m/z*: Calcd for $C_{18}H_{24}N_2O_2S_2$ (M^+) 364.1279. Found 364.1268.

***N*-[2-(3-Dimethylaminopropylthio)phenyl]-2-cyanocinnamide (7)** In the same manner as described for **2**, it was prepared from **29** and 2-cyanocinnamoyl chloride in a yield of 64% as an orange solid recrystallized from ethyl acetate–*n*-hexane, mp 85—86 °C. IR (KBr) cm^{-1}: 3315, 2947, 2785, 2206, 1686, 1593, 1525, 1442, 1306, 1188, 1038; ^{1}H-NMR ($CDCl_3$) δ: 1.73—1.80 (2H, m), 2.18 (6H, s), 2.36 (2H, t, J=7.0Hz), 2.84 (2H, t, J=7.2 Hz), 7.11 (1H, td, J=7.6, 1.3 Hz), 7.35—7.40 (1H, m), 7.49—7.60 (4H, m), 7.98—8.00 (2H, m), 8.41(1H, s), 8.49 (1H, dd, J=8.2, 1.2 Hz), 9.70 (1H, s, br). MS *m/z*: 365 (M^+), 261, 156, 128, 58 (100%); *Anal.* Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.12; H, 6.24; N, 11.43.

***N*-[2-(3-Dimethylaminopropylthio)phenyl]-2-phenylcinnamide (8)** In the same manner as described for **2**, it was prepared from **29** and 2-phenylcinnamoyl chloride in a yield of 45% as a brown oil. IR (Film) cm^{-1}: 3332, 2931, 2785, 1682, 1624, 1558, 1522, 1437, 1306, 1200; ^{1}H-NMR ($CDCl_3$) δ: 1.42—1.50 (2H, m), 2.18 (6H, s), 2.24 (2H, t, J=7.0 Hz), 2.36 (2H, t, J=7.3 Hz), 7.00 (1H, td, J=7.4, 1.4 Hz), 7.05—7.55 (12H, m), 7.99 (1H, s), 8.63 (1H, dd, J=8.2, 1.4 Hz), 8.77 (1H, s, br). MS *m/z*: 416 (M^+), 224, 179, 118, 58 (100%); HR-MS (EI) *m/z*: Calcd for $C_{26}H_{28}N_2OS$ (M^+) 416.1922. Found 416.1923.

***N*-[2-(3-Dimethylaminopropylthio)phenyl]-4-phenylbenzamide (9)** In the same manner as described for **2**, it was prepared from **29** and 4-phenylbenzoyl chloride in a yield of 22% as a yellow oil. IR (Film) cm^{-1}: 3342, 3057, 2941, 2767, 1678, 1608, 1579, 1508, 1433, 1306, 1250, 1101, 1038, 1007; ^{1}H-NMR ($CDCl_3$) δ: 1.70—1.77 (2H, m), 2.14 (6H, s), 2.33 (2H, t, J=7.0 Hz), 2.84 (2H, t, J=7.2 Hz), 7.10 (1H, td, J=7.6, 1.4 Hz), 7.39—7.44 (2H, m), 7.47—7.51 (2H, m), 7.58—7.60 (1H, m), 7.64—7.66 (2H, m), 7.75 (2H, dt, J=8.6, 2.0Hz), 8.05 (2H, dt, J=8.6, 2.0 Hz), 8.63 (1H, dd, J=8.2, 1.4 Hz), 9.53 (1H, s, br). MS *m/z*: 390 (M^+), 181, 152, 58 (100%); HR-MS (EI) *m/z*: Calcd for $C_{24}H_{26}N_2OS$ (M^+) 390.1766. Found 390.1760.

***N*-(2-Allylthiophenyl)cinnamide (10)** In the same manner as described for **2**, it was prepared from **30**[18] and cinnamoyl chloride in a yield of 92% as a white crystal recrystallized from ethyl acetate–*n*-hexane, mp 99—100 °C. IR (KBr) cm^{-1}: 3433, 3255, 3082, 1768, 1771, 1678, 1655, 1618, 1579, 1537, 1436, 1338, 1286, 1240, 1184, 1072; ^{1}H-NMR ($CDCl_3$) δ: 3.38 (2H, d, t, J=7.3, 1.1 Hz), 4.93 (1H, dq, J=16.9, 1.2 Hz), 5.01 (1H, dt, J=10.0, 0.7 Hz), 5.77—5.87 (1H, m), 6.61 (1H, d, J=15.5 Hz), 7.07 (1H, td, J=7.6, 1.4 Hz), 7.36—7.46 (4H, m), 7.53 (1H, dd, J=7.8, 1.6 Hz), 7.58—7.60 (2H, m), 7.77 (1H, d, J=15.5 Hz), 8.56 (1H, d, J=8.1 Hz), 8.72 (1H, s, br). MS *m/z*: 295 (M^+), 222, 131 (100%), 103, 77; *Anal.* Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74. Found: C, 73.20; H, 5.76; N, 4.66.

***N*-(2-Benzylthiophenyl)cinnamide (11)**[19] In the same manner as described for **2**, it was prepared from **31**[20] and cinnamoyl chloride in a yield of 63% as a white crystal recrystallized from ethyl acetate–*n*-hexane, mp 138—139.5 °C. IR (KBr) cm^{-1}: 3222, 3026, 1660, 1626, 1576, 1537, 1441, 1344, 1284, 1188; ^{1}H-NMR ($CDCl_3$) δ: 3.90 (2H, s), 6.26 (1H, d, J=15.5 Hz), 7.02—7.08 (3H, m), 7.16—7.24 (3H, m), 7.35—7.45 (4H, m), 7.48 (1H, dd, J=7.7, 1.2 Hz), 7.54—7.56 (2H, m), 7.62 (1H, d, J=15.5 Hz), 8.37 (1H, s, br), 8.51 (1H, d, J=8.0 Hz). MS *m/z*: 345 (M^+), 254, 222, 214, 131 (100%), 103, 91; *Anal.* Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05. Found: C, 76.46; H, 5.57; N, 3.95.

***N*-[2-(Phenethylthio)phenyl]cinnamide (12)** In the same manner as described for **2**, it was prepared from **32**[21] and cinnamoyl chloride in a yield of 70% as a white crystal recrystallized from ethyl acetate–*n*-hexane, mp 98—99.5 °C. IR (KBr) cm^{-1}: 3433, 3242, 3026, 1660, 1626, 1576, 1531, 1442, 1340, 1275, 1178, 1068; ^{1}H-NMR ($CDCl_3$) δ: 2.86 (2H, t, J=7.3 Hz), 3.10 (2H, t, J=7.3 Hz), 6.38 (1H, d, J=15.5 Hz), 7.09 (1H, td, J=7.6, 1.4 Hz), 7.15—7.30 (5H, m), 7.37—7.44 (4H, m), 7.54—7.59 (3H, m), 7.73 (1H, d, J=15.5 Hz), 8.57 (1H, s, br), 8.58 (1H, d, J=8.0 Hz). MS *m/z*: 359 (M^+), 255, 222, 131 (100%), 103; *Anal.* Calcd for $C_{23}H_{21}NOS$: C, 76.85; H, 5.89; N, 3.90. Found: C, 76.70; H, 5.93; N, 3.88.

***N*-(2-Carbomethoxyethylthiophenyl)cinnamide (13)** In the same manner as described for **2**, it was prepared from **33**[22] and cinnamoyl chloride in a yield of 84% as a yellow solid recrystallized from ethyl acetate–*n*-hexane, mp 106—107 °C. IR (Film) cm^{-1}: 3319, 2947, 1724, 1672, 1624, 1578, 1512, 1437, 1336, 1284, 1203, 1225, 1171, 1007; ^{1}H-NMR ($CDCl_3$) δ: 2.57 (2H, t, J=6.6 Hz), 3.02 (2H, t, J=6.6 Hz), 3.71 (3H, s), 6.80 (1H, d, J=15.6 Hz), 7.07 (1H, td, J=7.6, 1.4 Hz), 7.37—7.43 (4H, m), 7.56 (1H, dd, J=6.4, 1.3 Hz), 7.59—7.63 (2H, m), 7.78 (1H, d, J=15.6 Hz), 8.62 (1H, d, J=8.1 Hz), 8.91 (1H, s, br). MS *m/z*: 341 (M^+), 222, 211, 131 (100%), 103, 77; HR-MS (EI) *m/z*: Calcd for $C_{19}H_{19}NO_3S$ (M^+) 341.1086, Found 341.1100.

***N*-[2-(4-Nitrobenzylthio)phenyl]cinnamide (14)** In the same manner as described for **2**, it was prepared from **34**[23] and cinnamoyl chloride in a

yield of 53% as a yellowish crystal recrystallized from ethyl acetate–*n*-hexane, mp 160—162 °C. IR (KBr) cm^{-1}: 3292, 3076, 1660, 1620, 1572, 1522, 1433, 1340, 1172; ^{1}H-NMR ($CDCl_3$) δ: 3.93 (2H, s), 6.37 (1H, d, J=15.5 Hz), 7.01 (1H, td, J=7.6 Hz), 7.15—7.19 (2H, m), 7.31—7.34 (1H, m), 7.38—7.44 (4H, m), 7.54—7.57 (2H, m), 7.67 (1H, d, J=15.5 Hz), 8.04—8.07 (2H, m), 8.38 (1H, s, br), 8.47 (1H, d, J=8.2 Hz), MS *m/z*: 390 (M^+), 242, 131 (100%), 103, 77; 125, 91; *Anal.* Calcd for $C_{22}H_{18}N_2O_3S$: C, 67.67; H, 4.65; N, 7.17. Found: C, 67.39; H, 4.69; N, 6.93.

***N*-[2-(3-Methoxypropylthio)phenyl]cinnamide (15)** In the same manner as described for **2**, it was prepared from **35** and cinnamoyl chloride in a yield of 61% as a yellowish oil. IR (KBr) cm^{-1}: 3425, 3278, 2902, 2868, 1658, 1624, 1578, 1537, 1446, 1344, 1284, 1238, 1182, 1120; ^{1}H-NMR ($CDCl_3$) δ: 1.80—1.86 (2H, m), 2.87 (2H, t, J=7.2 Hz), 3.30 (3H, s), 3.45 (2H, t, J=6.0 Hz), 6.62 (1H, d, J=15.4 Hz), 7.06 (1H, td, J=7.5, 1.3 Hz), 7.34—7.43 (4H, m), 7.54 (1H, dd, J=7.7 Hz), 7.56—7.60 (2H, m), 7.77 (1H, d, J=15.4 Hz), 8.55 (1H, d, J=8.1 Hz), 8.74 (1H, s, br). MS *m/z*: 327 (M^+), 222, 131 (100%), 103; HR-MS (EI) *m/z*: Calcd for $C_{19}H_{21}NO_2S$ (M^+) 327.1293. Found 327.1290.

***N*-[2-(4-Methoxybutylthio)phenyl]cinnamide (16)** In the same manner as described for **2**, it was prepared from **36** and cinnamoyl chloride in a yield of 87% as a white crystal, mp 61—62.5 °C; IR (KBr) cm^{-1}: 3433, 3228, 3026, 2868, 1660, 1628, 1570, 1529, 1444, 1342, 1273, 1236, 1182, 1117; ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.71 (4H, m), 2.80 (2H, t, J=7.1 Hz), 3.28 (3H, s), 3.35 (2H, t, J=6.0 Hz), 6.61 (1H, d, J=15.4 Hz), 7.07 (1H, td, J=7.5, 1.3 Hz), 7.34—7.43 (4H, m), 7.54 (1H, dd, J=7.7, 1.3 Hz), 7.58—7.60 (2H, m), 7.77 (1H, d, J=15.4 Hz), 8.55 (1H, d, J=7.9 Hz), 8.73 (1H, s, br). MS *m/z*: 341 (M^+), 222, 131 (100%), 103, 87, 77; *Anal.* Calcd for $C_{20}H_{23}NO_2S$: C, 70.35; H, 6.79; N, 4.10. Found: C, 70.37; H, 6.70; N, 4.09.

***N*-[2-(2-*N*-Methylpyrrolidylethylthio)phenyl]cinnamide (17)** In the same manner as described for **2**, it was prepared from **37** and cinnamoyl chloride in a yield of 84% as a yellowish oil. IR (KBr) cm^{-1}: 3440, 3228, 2937, 3030, 2779, 1660, 1628, 1576, 1533, 1439, 1348, 1288, 1188; ^{1}H-NMR ($CDCl_3$) δ: 1.36—1.61 (2H, m), 1.64—1.76 (2H, m), 1.85—1.96 (2H, m), 2.09—2.17 (2H, m), 2.25 (3H, s), 2.69—2.88 (2H, m), 3.00—3.05 (1H, m), 6.60 (1H, d, J=15.6 Hz), 7.06 (1H, td, J=7.5, 1.3 Hz), 7.34—7.43 (4H, m), 7.53—7.59 (3H, m), 7.76 (1H, d, J=15.6 Hz), 8.54 (1H, d, J=7.9 Hz), 8.72 (1H, s, br). MS *m/z*: 366 (M^+), 236, 147, 131, 103, 84 (100%); HR-MS (EI) *m/z*: Calcd for $C_{22}H_{26}N_2OS$ (M^+) 366.1766. Found 366.1773.

***N*-[2-(4-Pyridylmethylthio)phenyl]cinnamide (18)** In the same manner as described for **2**, it was prepared from **38**[24] and cinnamoyl chloride in a yield of 96% as a brownish oil. IR (KBr) cm^{-1}: 3448, 3221, 3026, 1655, 1622, 1576, 1529, 1433, 1414, 1342, 1286, 1178, 1068; ^{1}H-NMR ($CDCl_3$) δ: 3.83 (2H, s), 6.42 (1H, d, J=15.4 Hz), 6.97—7.02 (2H, m), 7.32 (1H, dd, J=7.7, 1.5 Hz), 7.36—7.44 (5H, m), 7.54—7.57 (2H, m), 7.69 (1H, d, J=15.5 Hz), 8.43—8.46 (3H, m), 8.49 (1H, d, J=8.3 Hz). MS *m/z*: 346 (M^+), 255, 216, 131 (100%), 103, 77; HR-MS (EI) *m/z*: Calcd for $C_{21}H_{18}N_2OS$ (M^+) 346.1140. Found 346.1141.

***N*-[2-(2-Pyridylmethylthio)phenyl]cinnamide (19)** In the same manner as described for **2**, it was prepared from **39**[25] and cinnamoyl chloride in a yield of 87% as a brownish crystal recrystallized from ethyl acetate–*n*-hexane, mp 102—103.5 °C; IR (KBr) cm^{-1}: 3224, 3028, 1660, 1626, 1589, 1574, 1533, 1441, 1344, 1284, 1184; ^{1}H-NMR ($CDCl_3$) δ: 4.04 (2H, s), 6.53 (1H, d, J=15.5 Hz), 6.80 (1H, d, J=7.7 Hz), 7.02—7.10 (2H, m), 7.34—7.49 (5H, m), 7.55—7.60 (3H, m), 7.67 (1H, d, J=15.6 Hz), 8.49 (1H, d, J=8.2 Hz), 8.55 (1H, dt, J=4.8, 0.8 Hz), 8.91 (1H, s, br). MS *m/z*: 346 (M^+), 255, 222, 131, 103 (100%); *Anal.* Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09. Found: C, 72.84; H, 5.27; N, 7.92.

***N*-[2-(3-Pyridylmethylthio)phenyl]cinnamide (20)** In the same manner as described for **2**, it was prepared from **40**[24] and cinnamoyl chloride in a yield of 60% as a brownish crystal, mp 106—107 °C; IR (KBr) cm^{-1}: 3184, 3026, 1658, 1626, 1574, 1537, 1439, 1344, 1284, 1238, 1184; ^{1}H-NMR ($CDCl_3$) δ: 3.88 (2H, s), 6.37 (1H, d, J=15.5 Hz), 7.00—7.04 (1H, m), 7.10—7.13 (1H, m), 7.25—7.27 (1H, m), 7.36—7.43 (5H, m), 7.56—7.58 (2H, m), 7.67 (1H, d, J=15.5 Hz), 8.38—8.42 (3H, m), 8.51 (1H, d, J=8.0 Hz). MS *m/z*: 346 (M^+), 313, 255, 222, 131 (100%), 103; *Anal.* Calcd for $C_{21}H_{18}N_2OS$: C, 72.80; H, 5.24; N, 8.09. Found: C, 73.05; H, 5.27; N, 7.92.

***N*-[2-(2-Morpholinoethylthio)phenyl]cinnamide (21)**[26] In the same manner as described for **2**, it was prepared from **41**[26] and cinnamoyl chloride in a yield of 81% as a yellowish oil. IR (KBr) cm^{-1}: 3440, 3257, 2800, 1664, 1632, 1576, 1529, 1442, 1344, 1178, 1115; ^{1}H-NMR ($CDCl_3$) δ: 2.39 (4H, t, J=4.7 Hz), 2.46 (2H, t, J=6.7 Hz), 2.92 (2H, t, J=6.7 Hz), 3.68 (4H, t, J=4.7 Hz), 6.67 (1H, d, J=15.6 Hz), 7.08 (1H, td, J=7.5, 1.4 Hz), 7.26—7.44 (4H, m), 7.57—7.60 (3H, m), 7.78 (1H, d, J=15.6 Hz), 8.51 (1H, d, J=7.8 Hz), 9.11 (1H, s, br). MS *m/z*: 368 (M^+), 131, 113, 100 (100%).

***N*-[2-(2-Phenoxyethylthio)phenyl]cinnamide (22)** In the same manner as described for **2**, it was prepared from **42** and cinnamoyl chloride in a yield of 69% as a white crystal recrystallized from ethyl acetate–*n*-hexane, mp 111.5—113 °C. IR (KBr) cm^{-1}: 3433, 3294, 3053, 1660, 1630, 1603, 1578, 1527, 1496, 1466, 1439, 1288, 1242, 1176, 1036; ^{1}H-NMR ($CDCl_3$) δ: 3.14 (2H, t, J=5.9 Hz), 4.04 (2H, t, J=5.9 Hz), 6.44 (1H, d, J=15.6 Hz), 6.85—6.90 (3H, m), 7.09 (1H, td, J=7.4, 1.2 Hz), 7.17—7.22 (2H, m), 7.36—7.46 (6H, m), 7.63 (1H, dd, J=7.7, 1.7 Hz), 7.67 (1H, d, J=15.6 Hz), 8.60 (1H, d, J=8.4 Hz), 8.90 (1H, s, br). MS *m/z*: 375 (M^+), 281, 254, 222, 131 (100%), 103, 77; *Anal.* Calcd for $C_{23}H_{21}NO_2S$: C, 73.57; H, 5.64; N, 3.73. Found: C, 73.83; H, 5.73; N, 3.98.

***N*-[2-(3-Dimethylaminopropoxy)phenyl]cinnamide (23)**[13] In the same manner as described for **2**, it was prepared from **45**[13] and cinnamoyl chloride in a yield of 58% as a brownish oil. IR (KBr) cm^{-1}: 3251, 3060, 2945, 2812, 2764, 1662, 1626, 1545, 1491, 1450, 1350, 1286, 1259, 1221, 1186, 1117, 1055; ^{1}H-NMR ($CDCl_3$) δ: 2.00—2.09 (2H, m), 2.28 (6H, s), 2.48 (2H, t, J=6.9 Hz), 4.13 (2H, t, J=6.5 Hz), 6.59 (1H, d, J=15.5 Hz), 6.90—6.93 (1H, m), 6.97—7.06 (2H, m), 7.35—7.42 (3H, m), 7.55—7.58 (2H, m), 7.75 (1H, d, J=15.5 Hz), 8.13 (1H, s, br), 8.52 (1H, d, J=6.5Hz).

***N*-[2-(3-Dimethylaminopropoxy)-5-nitrophenyl]cinnamide (24)**[26] In the same manner as described for **2**, it was prepared from **46**[26] and cinnamoyl chloride in a yield of 58% as a brownish oil, mp 124.5—126 °C; ^{1}H-NMR ($CDCl_3$) δ: 2.05—2.12 (2H, m), 2.29 (6H, s), 2.50 (2H, t, J=6.8 Hz), 4.26 (2H, t, J=6.4 Hz), 6.58 (1H, d, J=15.4 Hz), 6.96 (1H, d, J=8.9 Hz), 7.37—7.44 (3H, m), 7.55—7.59 (2H, m), 7.80 (1H, d, J=15.5 Hz), 7.98 (1H, dd, J=8.9, 2.7 Hz), 8.17 (1H, s, br), 9.45 (1H, d, J=2.7 Hz).

***N*-[2-(3-Dimethylaminopropylsulfinyl)phenyl]cinnamide (25)** To a solution of **1** (340 mg, 1.0 mmol) in CH_3CN (2.5 ml) was added aqueous $NaIO_4$ (0.5 M, 2.5 ml) dropwise at −10 °C. After stirring at 0 °C for 12 h, an additional aqueous $NaIO_4$ (0.5 M, 2.5 ml) was added to the mixture, the stirring was continued for 20 h. The mixture was filtered, and extracted with $CHCl_3$. The combined organic layer was washed, and dried over anhydrous $MgSO_4$. The filtrate was concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with $CHCl_3$ (9) : CH_3OH (1) to afford **25** (131 mg, 37%) as a yellow gel. IR (Film) cm^{-1}: 3452, 3234, 2943, 1682, 1630, 1587, 1525, 1471, 1338, 1286, 1172, 1066, 1007; ^{1}H-NMR ($CDCl_3$) δ: 1.87—1.97 (2H, m), 2.25 (6H, s), 2.41—2.54 (2H, m), 3.03—3.11 (1H, m), 3.24—3.31 (1H, m), 6.58 (1H, d, J=15.7 Hz), 7.15 (1H, td, J=7.4, 1.1 Hz), 7.29 (1H, dd, J=7.7, 1.4 Hz), 7.37—7.42 (3H, m), 7.50—7.54 (1H, m), 7.57—5.59 (2H, m), 7.75 (1H, d, J=15.7 Hz), 8.61 (1H, d, J=8.5 Hz), 10.90 (1H, s, br). MS *m/z*: 356 (M^+), 339, 149, 131, 111, 97, 84 (100%), 71, 58; HR-MS (EI) *m/z*: Calcd for $C_{20}H_{24}N_2O_2S$ (M^+) 356.1559. Found 356.1544.

***N*-(2-Cinnamoylthiophenyl)cinnamide (26)** To a solution of **28** (125 mg, 1.0 mmol) and Et_3N (0.6 ml) in CH_2Cl_2 (5 ml) was added at room temperature a solution of cinnamoyl chloride (340 mg, 2.0 mmol) in CH_2Cl_2 (10 ml). After refluxing for 1 h, the reaction mixture was washed with water and the organic layer was dried over anhydrous $MgSO_4$. The solvent was removed in vacuum and the residue was purified by flash column chromatography on silica gel eluting with a mixture of petroleum ether (85) : chloroform (10) : ethyl acetate (5) to afford **26** (78 mg, 20%) as a white crystal recrystallized from ethyl acetate–*n*-hexane, mp 163—164 °C. IR (KBr) cm^{-1}: 3317, 3055, 1674, 1614, 1578, 1516, 1439, 1333, 1280, 1174, 1032; ^{1}H-NMR ($CDCl_3$) δ: 6.51 (1H, d, J=15.5 Hz), 6.86 (1H, d, J=15.8 Hz), 7.20 (1H, td, J=7.7, 1.1 Hz), 7.34—7.61 (12H, m), 7.74 (1H, d, J=15.5 Hz), 7.75 (1H, d, J=15.8 Hz), 7.99 (1H, s, br), 8.48 (1H, d, J=7.6 Hz). MS *m/z*: 385 (M^+), 357, 236, 131 (100%), 103, 77; *Anal.* Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.63; H, 4.94; N, 3.61.

***N*-[2-(2-Cyanocinnamoylthio)phenyl]-2-cyanocinnamide (27)** In the same manner as described for **26**, it was prepared from **28** and 2-cyanocinnamoyl chloride in a yield of 8.4% as a yellow crystal recrystallized from ethyl acetate–*n*-haxane, mp 174—175 °C. IR (KBr) cm^{-1}: 3358, 3020, 2216, 1693, 1668, 1585, 1574, 1533, 1441, 1373, 1300, 1242, 1196, 1144, 1032; ^{1}H-NMR ($CDCl_3$) δ: 7.29 (1H, td, J=7.8, 1.3 Hz), 7.47—7.63 (8H, m), 7.95—7.96 (2H, m), 8.04—8.06 (2H, m), 8.28 (1H, s), 8.40 (1H, s), 8.46 (1H, dd, J=8.3, 1.2 Hz), 8.77(1H, s, br). *Anal.* Calcd for $C_{24}H_{19}NO_2S$: C, 71.71; H, 3.93; N, 9.65. Found: C, 71.46; H, 3.85; N, 9.55.

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