

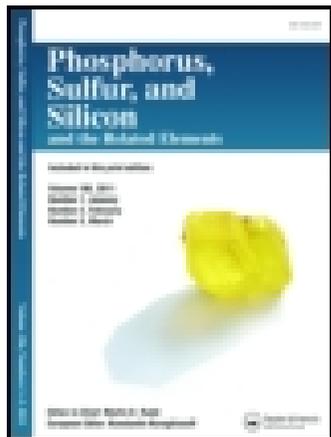
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Investigation of the Reaction of Chloroacetyl Chloride with 1,5-Benzothiazepines: Selective Synthesis of Azeto[2,1-d][1,5]benzothiazepines by Green Chemical Methods and Their Biological Activity

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Investigation of the Reaction of Chloroacetyl Chloride with 1,5-Benzothiazepines: Selective Synthesis of Azeto[2,1-d][1,5]benzothiazepines by Green Chemical Methods and Their Biological Activity

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An efficient and exclusive synthesis of the tricyclic azeto[2,1-d][1,5]benzothiazepine ring system has been developed. By use of microwave irradiation in the presence of basic alumina, the reaction time has been brought down from hours to minutes with improved yields in comparison to conventional heating. Antimicrobial screening of the synthesized compounds has shown promising activity.

Keywords 1,5-Benzothiazepines; β -lactams; microwaves; antifungal activity

INTRODUCTION

1,5-Benzothiazepines are well-known seven-membered heterocyclic compounds and owing to their diverse bioactivities¹ they are important substances in the drug research. Thiazesim,² a well known antidepressant, and Diltiazem,³ used as coronary vasodilator and for the treatment of angina pectoris, possess 1,5-benzothiazepine skeletons. The synthesis of compounds containing a β -lactam moiety has been the subject of intense studies by a number of research groups.⁴ Though there are some effective antimicrobial agents now, it seems necessary to synthesize some novel compounds with a fused β -lactam

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heterocyclic ring for the bioassay of antibacterial activity because of the growing resistance of bacteria against penicillin and cephalosporin like compounds.⁵

Since most of the important antibiotics possess the representative structure of a β -lactam fused to thiazaheterocycles,⁶ we thought it would be interesting to construct a system that may combine these two bioactive rings in a single molecular framework to see the additive effect towards their biological activity. This fact prompted us to build up structurally diverse fused azeto[2,1-b] benzothiazepines from 1,5-benzothiazepines exhibiting an azomethine functionality. However, scanty reports on the conventional synthesis⁷ of this fused ring system mention the long reaction times, if basic catalyst and volatile organic solvents are used, and the formation of product mixture.

Thus, a simple, general and efficient procedure for the exclusive synthesis of this important tricyclic ring system is required that is more eco-friendly than the traditional one, in view of the increasing concern about the impact of chemicals on the environment. The use of microwave irradiation in synthetic chemistry offers a promising alternative.⁸ Microwave heating is more efficient in terms of the energy used and enhances the reactivity and selectivity in some cases.⁹

In continuation of our interest on the facile, economical and eco-friendly synthesis of biodynamic heterocycles under microwaves,¹⁰ we carried out the cycloaddition reaction of **1** with **2** and **4** under microwave irradiation over the basic alumina as inorganic solid support. In this case, the reaction occurred in 5–6 min, and only the desired product **5** was formed exclusively with excellent yield in the absence of any solvent and external base, since the basicity of alumina is sufficient to cause this cycloaddition reaction. Intermediate 1,5-benzothiazepines (**3**) were formed in-situ by the reaction of β -benzoyl acrylic acid (**1**) and 5-substituted 2-aminobenzenethiols (**2**) under microwave irradiation. Thus, the whole procedure was rendered into a facile one pot synthesis. Earlier reports mentioned the variable formation of *cis* and *trans* isomers of β -lactams depending on the order of addition of the reactants in conventional syntheses.¹¹ Encouraged by this, we also studied the title cycloaddition reaction conventionally by changing the order of reactants in basic medium (triethylamine in dry benzene), and the results showed that under all conditions only one isomer of **5a** was obtained along with other products **6a** and **7a**. The formation of undesirable side products decreases the yields of the target adduct and render their purification difficult. The results are given in Table I.

TABLE I Reaction of 2,3-Dihydro-8-methoxy-4-phenyl-1,5-benzothiazepine-2-carboxylic acid (3) with Chloroacetyl Chloride (4)

Procedure*	Mode of heating	5a		6a		7a	
		Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)	Yield (%)	M.p. (°C)
A	Conventional	30	240	15	158	—	—
B	Conventional	22	240	—	—	10	176
C	Conventional	—	—	—	—	20	176
D	Conventional	—	—	—	—	25	176
E	Microwave	90	240	—	—	—	—

*Procedure A-D as described in the experimental section.

RESULTS AND DISCUSSION

When a solution of triethylamine in benzene was added drop-wise into a solution of chloroacetyl chloride and 1,5-benzothiazepine (**3**) in benzene (Table I, Procedure A), a mixture of azeto[2,1-d][1,5]-benzothiazepines (**5**) and the ring contracted product 2-substituted 2,3-dihydro-3-phenyl-*N*-acetyl-2-styrylbenzothiazole (**6**) was obtained. The low yield of azeto[2,1-d][1,5]benzothiazepine (**5**) is due to the competitive ring contraction with 'Staudinger reaction' under the reaction conditions. *N*-Acetylated phenyl 1,5-benzothiazepine intermediates are formed in the reaction mixture and the ring contraction could occur before triethylamine was added.² On the basis of the literature mechanism,¹² the yield of the fused system **5** could be improved if a solution of chloroacetyl chloride (**4**) in benzene was added drop-wise into a solution of benzothiazepine and triethylamine in benzene (Table I,

TABLE II Physical and analytical data of compounds 5a-f.

Compd.	X	Time ^a (min)	M.p. (°C)	Yield (%)	R _f ^b
5a	OCH ₃	12+3	240	90	0.80
5b	CH ₃	10+5	203	87	0.74
5c	Cl	12+6	199	83	0.79
5d	Br	10+5	215	86	0.81
5e	CF ₃	9+4	232	88	0.77
5f	F	10+5	226	87	0.82

^aTime (12+3) indicates first irradiation for 12 min. gives compound **3** (detected by TLC) and then further irradiation after adding chloroacetyl chloride for 3 min yields **5a**; and ^bUsing solvent system benzene: ethyl acetate (8 : 2).

Procedure B). Although the ring contraction could be inhibited under this addition mode, the yield of the desired product **5a** was still low when 1.5 equivalents of **4** were used and a new byproduct **7** was obtained. When 3.0 equivalents of **4** were applied to improve the yield of the desired product **5**, the desired azeto[2,1-d][1,5]benzothiazepines **5** were not obtained but the yield of the new byproduct **7** was improved slightly (Table I, Procedure C).

Procedure D (Table I) involves first the formation of diketenes through addition of triethylamine to a solution of **4** in benzene and subsequently the addition of the 1,5-benzothiazepine **5a** into the resulting reaction mixture. In this case, only the 1,3-oxazine derivative **7** was obtained.

Under microwave irradiation, on the other hand, the desired azeto[2,1-d][1,5]-benzothiazepine (**5a**) was formed with good yield and as the only product. This rapid, economic, simple-to-handle, selective, and environmentally benign protocol proceeds under mild conditions.

The structures of all azeto[2,1-d][1,5]benzothiazepines (**5a-f**), and the other products **6** and **7**, have been elucidated by elemental analyses and spectroscopic studies. Theoretically, compound **5a-f** exhibiting two chiral centers could exist in two diastereomeric forms, but the ^1H NMR spectra and chromatographic studies of the isolated compounds indicated the formation of only one diastereomer. In the mass spectrum of **5a** the appearance of molecular ion peaks m/z (M^+) at 389 and ($M^+ + 2$) at 391 due to the chlorine-37 isotope showed the formation of the fused ring system azeto-1,5-benzothiazepine.

Evaluation of the Antifungal Activity

The synthesized compounds were screened for antifungal activity against three pathogenic fungi, namely *Rhizoctonia solani* causing root rot of okra; *Fusarium oxysporum* causing wilt of mustard; and *Colletotrichum capsici* causing leaf spot and fruit rot of chile.

Poison Plate Technique¹³

The compounds synthesized were dissolved in acetone (1000 and 500 ppm). Potato-dextrose-agar (PDA) medium was prepared in flasks and sterilized. To this medium, a requisite quantity of solution was added and then the medium was poured into Petri-plates in three replications. A culture of the test fungus was grown on PDA for 6–7 days. Small discs (4 mm) of the fungus culture were cut with a sterile cork-drill and transferred aseptically, upside-down in the center of Petri-dishes

TABLE III Effect of Concentrations of Different Chemicals on the Mean Radial Growth (cm) of Different Fungus *in vitro*

Compd.	<i>Rhizoctonia solani</i>		<i>Fusarium oxysporum</i>		<i>Colletotrichum capsici</i>	
	1000 ppm	500 ppm	1000 ppm	500 ppm	1000 ppm	500 ppm
5a	1.25 ^a	1.72 ^b	2.08 ^b	2.52	1.78 ^a	2.51 ^b
5b	2.18	2.22 ^b	2.62	3.98 ^a	3.52	3.95
5c	3.63	4.20	3.90	4.05	2.08 ^a	2.90 ^b
5d	5.42	6.83	3.92	4.89	3.45	4.88
5e	1.32 ^b	1.98 ^b	1.78 ^a	1.02 ^a	2.16 ^b	2.50 ^a
5f	1.28 ^b	1.69 ^a	2.23 ^b	2.18	2.42 ^b	3.00 ^b
Check	9.00	9.00	8.17	8.17	7.33	7.33
CD%	0.74	1.22	0.77	1.14	1.08	1.25

Check = Growth only in PDA without any treatment; CD% = Critical difference of all values; ^amin. value- best and significantly superior compound; ^b-at par with min. values- when difference of ^a; and other significant value is under the CD%.

containing the medium and the fungicides. The plates were incubated at 25°C ± 1°C for 6 days. The colony diameters were measured and the data were statistically analyzed (Table III).

Pot Trial Method¹⁴

White seeded sorghum grains were soaked in water for about 12 h, 160 g of the soaked kernels were placed in 500-ml flasks, and 20 ml of water were added to each. The material was autoclaved twice on successive days before inoculation. After sterilization, fungus bits were inoculated in each flask, and the flasks were kept for 10 days at 25–27°C. One-hundred seeds of okra were taken for one treatment of each compound. Inoculum The inoculant was added at 2g/kg of soil 3 days prior to sowing. Sowing was performed after 3 days, and germination data were recorded after 7, 15, and 25 days of sowing. Suitable checks were maintained and the data were statistically analyzed (Table IV). It was found that **5a** and **5e**, exhibiting OCH₃ or CF₃ substituents, showed maximum germination (72–76%), indicating that these are the most effective compounds in controlling the growth of pathogens. “Baynate” and “Thiram” are recommended as standard fungicide as seed dressers to control this disease are having N and S elements, similar to the synthesized compounds, which is responsible for their antifungal activity.

Antibacterial Activity

All the compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*.

TABLE IV Evaluation of Azeto[2,1-d][1,5]benzothiazepine (5a-f) as Seed Dressers Against *Rhizoctonia solani* Causing Root Rot of Okra (in Pot Trial)

Compd.	Percent germination	Plant stand 25 DAS
5a	72.00	64.00
5b	49.00	62.00
5c	47.00	69.00
5d	68.00	57.00
5e	76.00	61.00
5f	69.00	57.00
Baynate (0.2%)	98.00	64.00
Thiram (0.3%)	79.00	68.00
Check with inoculum	10.00	6.00
Check without inoculum	90.00	81.00

DAS = days after sowing.

Nutrient agar was used as culture medium. Test solutions and standard drug Norfloxacin solution (100 μ g/mL) were prepared in DMF and used for testing the growth inhibition by the cup-plate method.¹⁵ The results are shown in Table V. Compound 5a, 5d, and 5f showed a good activity against *S. aureus*. The activity of all compounds against *E. coli* and *B. subtilis* was moderate.

EXPERIMENTAL

Melting points were determined in open glass capillaries and were uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrometer on KBr Pellets. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DRX-300 spectrometer using CDCl₃ at 300.15 and 75.47 MHz, respectively. TMS was used as internal reference. Mass spectra

TABLE V Antibacterial Activity of Compounds 5a-f (% Inhibition)

Compd.	Escherichia coli	Staphylococcus aureus	Bacillus subtilis
5a	24.6	68.2	35.8
5b	39.3	52.9	20.5
5c	40.4	38.4	18.5
5d	35.7	50.2	31.7
5e	57.8	48.3	15.3
5f	49.8	57.6	51.5
Norfloxacin	100	100	100

of representative compounds were recorded on a Kratos 50 mass spectrometer at 70 eV. The purity of all compounds was checked by TLC using silica Gel-G coated glass plates and benzene:ethyl acetate (8 : 2) as eluent. The microwave induced reactions were carried out in a BMO-700T modified multimode oven fitted with a condenser and a magnetic stirrer. 5-Substituted 2-aminobenzenethiols¹⁶ and 3-benzoyl-2-propionic acids¹⁷ were prepared by literature methods.

2-Chloro-7-methoxy-1-oxo-2a-phenyl-2,2a,3,4-tetrahydroazeto[2,1-d][1,5]-benzothiazepine-4-carboxylic acid (5a)

Conventional Synthesis

2,3-Dihydro-8-methoxy-4-phenyl-1,5-benzothiazepine-2-carboxylic Acid (3a)

An equimolar mixture (0.01 mol) of β -benzoylacrylic acid (**1**) and 2-amino-5-methoxy-benzenethiol (**2**) was refluxed for 7 h with dry ethanol (20ml) saturated with hydrogen chloride gas, whereupon the reaction mixture changed from yellow to dark green. Excess of solvent was removed by distillation under reduced pressure. The product so obtained was recrystallized from methanol to give **3a**.

Reaction of 3a with Chloroacetyl Chloride (4)

Procedure A

A solution of triethylamine (1.5 mmol) in anhydrous benzene (5 ml) was added drop wise into a solution of **3** (2 mmol) and chloroacetyl chloride (**4**) (2 mmol) in benzene (8 ml) for a period of 10–15 min. The resulting mixture was refluxed for 10–11 h. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was washed with saturated aqueous sodium bicarbonate solution (30 ml), water and saturated brine, respectively, and dried over MgSO₄. After removal of the solvent, the residue was separated by chromatography on silica gel with a mixture of ethyl acetate and benzene (1:15; V:V) as the eluent to afford colorless crystals of dihydrobenzothiazole (**6**) and azeto [2,1-d][1,5]-benzothiazepine (**5a**) after crystallization from ethanol.

Procedure B

A solution of **4** (2 mmol) in anhydrous benzene (5 ml) was added drop wise into a solution of **3** (2 mmol) and triethylamine (1.5 mmol)

in benzene (8 ml) for 10–15 min. The resulting mixture was refluxed for 10–11 h. After the same workup as described in Procedure A, the residue was separated by chromatography in silica gel with a mixture of ethyl acetate and petroleum ether as the eluent to afford colorless crystals of azeto [2,1-d][1,5]-benzothiazepine **5a** and [1,3]oxazino [2,3-d][1,5]benzothiazepinone (**7**).

Procedure C

A solution of **4** (3 mmol) in anhydrous benzene (5 ml) was added drop wise into a solution of **3** (2 mmol) and triethylamine (1.5 mmol) in benzene (8 ml) during 10–15 min. The resulting mixture was refluxed for 10–11 h. After the same workup as described in the procedure **B**. Crystals of [1,3]oxazino [2,3-d][1,5]benzothiazepinone (**7**) were obtained.

Procedure D

A solution of **3** (2 mmol) in benzene (1 ml) was added drop wise into the solution of **4** (3 mmol) and triethylamine (2mmol) in benzene (4 ml) for a period of 10–15 min. The resulting mixture was refluxed for 10–11 h. After the same workup as described in for Procedure B, colorless crystals of **7** were obtained.

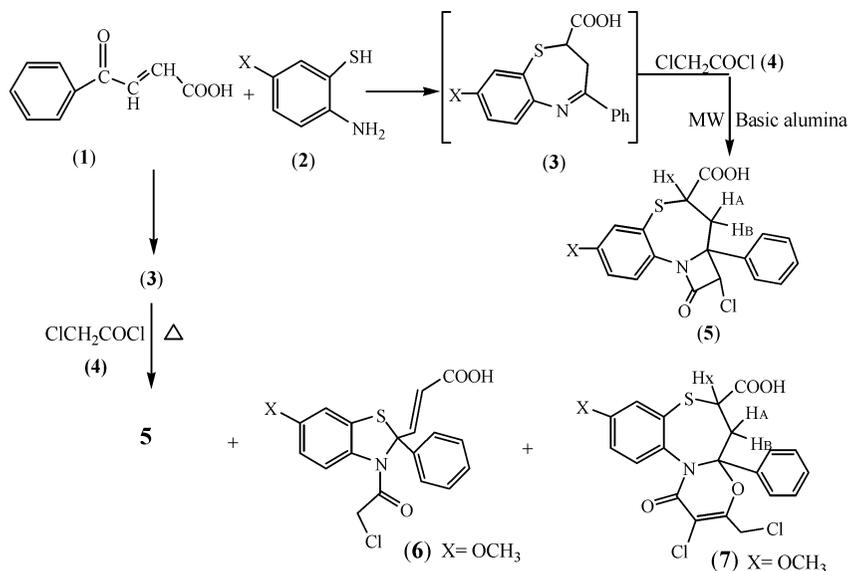
Microwave Assisted Synthesis (One-Pot Synthesis)

An equimolar mixture (2 mmol) of **1** and **2a** was adsorbed on basic alumina (2 g) via a solution of ethanol and swirled for a while followed by removal of the solvent under gentle vacuum. It was irradiated inside a microwave oven at 90% power, i.e., 645 W for 12 min (monitored by TLC). The intermediate **3a** so obtained in reasonable purity (TLC, 100% conversion), was used as such for the next step. **4** (2.5 mmol) was added to the reaction mixture, mixed thoroughly and irradiated again inside a microwave oven at 640 W for an appropriate time. The product **5a** was obtained by desorption with ethanol and found to be pure by TLC.

Compounds **5b-f** were similarly prepared under solvent-free conditions, using basic alumina as solid support. For analytical and spectroscopic studies the products were recrystallized from ethanol.

Compound 5a

$^1\text{H NMR}$ (CDCl_3) δ 3.75 (s, 3H, OCH_3), 3.08 (dd, 1H, \mathbf{H}_A , $J_{A-B} = 15.28$, $J_{A-X} = 9.15$ Hz), 3.62 (dd, 1H, \mathbf{H}_B , $J_{A-B} = 15.28$, $J_{B-X} = 8.12$ Hz), 4.02 (dd, 1H, \mathbf{H}_X , $J_{A-X} = 9.15$ Hz, $J_{B-X} = 8.12$ Hz), 5.12 (s, 1H, Cl- \mathbf{CH}), 6.58–7.79 (m, 8H, Ar- \mathbf{H}), 8.47 (bs, 1H, COOH). IR (cm^{-1}) 1680, 1725 (two C=O), 3288 (b, OH), 748 (C-Cl). Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{ClNO}_4\text{S}$:



C, 58.54; H, 4.14; N, 3.59; S, 8.23; Cl, 9.09. Found C, 58.70; H, 4.16; N, 3.58; S, 8.20; Cl, 9.05.

Compound 5b

¹H NMR (CDCl₃) δ 2.61 (s, 3H, CH₃), 3.14 (dd, 1H, H_A, J_{A-B} = 15.17, J_{A-X} = 9.69 Hz), 3.71 (dd, 1H, H_B, J_{A-B} = 15.17, J_{B-X} = 8.52 Hz), 4.31 (dd, 1H, H_X, J_{A-X} = 9.29, J_{B-X} = 8.52 Hz), 4.95 (s, 1H, Cl-CH), 6.62–7.81 (m, 8H, Ar-H), 8.21 (bs, 1H, COOH). IR (cm⁻¹) 1678, 1722 (two C=O), 3270 (b, OH), 748 (C-Cl). Anal. calcd. for C₁₉H₁₆ClNO₃S: C, 61.04; H, 4.31; N, 3.75. Found C, 61.21; H, 4.28; N, 3.76.

Compound 5c

¹H NMR (CDCl₃), 3.27 (dd, 1H, H_A, J_{A-B} = 16.18, J_{A-X} = 9.22 Hz), 3.76 (dd, 1H, H_B, J_{A-B} = 16.18, J_{B-X} = 8.42 Hz), 4.74 (dd, 1H, H_X, J_{A-X} = 9.22 Hz, J_{B-X} = 8.42 Hz), 5.10 (s, 1H, Cl-CH), 6.60–7.69 (m, 8H, Ar-H), 8.58 (bs, 1H, COOH). IR (cm⁻¹) 1680, 1728 (two C=O), 3278 (b, OH), 748 (C-Cl). Anal. calcd. for C₁₈H₁₃Cl₂NO₃S: C, 54.83; H, 3.32; N, 3.55. Found C, 54.67; H, 3.34; N, 3.54.

Compound 5d

¹H NMR (CDCl₃), 3.29 (dd, 1H, H_A, J_{A-B} = 16.17, J_{A-X} = 9.20 Hz), 3.73 (dd, 1H, H_B, J_{A-B} = 16.18, J_{B-X} = 8.40 Hz), 4.76 (dd, 1H, H_X, J_{A-X} = 9.18 Hz, J_{B-X} = 8.40 Hz), 5.13 (s, 1H, Cl-CH), 6.61–7.70 (m,

8H, Ar-**H**), 8.60 (bs, 1H, COOH). IR (cm^{-1}) 1680, 1730 (two C=O), 3275 (b, OH), 748 (C-Cl). Anal. calcd. for $\text{C}_{18}\text{H}_{13}\text{ClBrNO}_3\text{S}$: C, 49.28; H, 2.99; N, 3.19. Found C, 49.13; H, 2.97; N, 3.20.

Compound 5e

^1H NMR (CDCl_3), 3.23 (dd, 1H, **H**_A, $J_{\text{A-B}} = 16.28$, $J_{\text{A-X}} = 9.20$ Hz), 3.72 (dd, 1H, **H**_B, $J_{\text{A-B}} = 16.28$, $J_{\text{B-X}} = 8.39$ Hz), 4.74 (dd, 1H, **H**_X, $J_{\text{A-X}} = 9.20$ Hz, $J_{\text{B-X}} = 8.39$ Hz), 5.10 (s, 1H, Cl-**CH**), 6.63–7.65 (m, 8H, Ar-**H**), 8.59 (bs, 1H, COOH). IR (cm^{-1}) 1684, 1725 (two C=O), 3278 (b, OH), 748 (C-Cl). Anal. calcd. for $\text{C}_{19}\text{H}_{13}\text{ClF}_3\text{NO}_3\text{S}$: C, 53.54; H, 3.06; N, 3.27. Found C, 53.71; H, 3.04; N, 3.28.

Compound 5f

^1H NMR (CDCl_3), 3.19 (dd, 1H, **H**_A, $J_{\text{A-B}} = 16.12$, $J_{\text{A-X}} = 9.21$ Hz), 3.76 (dd, 1H, **H**_B, $J_{\text{A-B}} = 16.12$, $J_{\text{B-X}} = 8.47$ Hz), 4.69 (dd, **H**_X, 1H, $J_{\text{A-X}} = 9.21$ Hz, $J_{\text{B-X}} = 8.47$ Hz), 5.10 (s, 1H, Cl-**CH**), 6.57–7.67 (m, 8H, Ar-**H**), 8.63 (bs, 1H, COOH). IR (cm^{-1}) 1680, 1730 (two C=O), 3278 (b, OH), 748 (C-Cl). Anal. calcd. for $\text{C}_{18}\text{H}_{13}\text{ClFNO}_3\text{S}$: C, 57.22; H, 3.47; N, 3.17. Found C, 57.04; H, 3.50; N, 3.18.

Compound 6a

^1H NMR (CDCl_3) δ 3.45 (d, 1H, **CHH**, $J = 14.8$ Hz), 3.60 (d, 1H, **CHH**, $J = 14.8$ Hz), 3.82 (s, 3H, **OCH**₃), 6.17 (d, 1H, **CH**= 15.4 Hz), 6.42 (d, 1H, **CH**=, $J = 15.4$ Hz), 6.98–7.32 (m, 8H, Ar-**H**), 8.42 (bs, 1H, COOH). IR (cm^{-1}) 1680, 1710 (two C=O). Anal. calcd. for $\text{C}_{19}\text{H}_{16}\text{ClNO}_4\text{S}$: C, 58.54; H, 1.14; S, 8.23; Cl, 9.09; N, 3.59; Found C, 58.35; H, 4.17; S, 8.23; Cl, 9.06; N, 3.57. MS (EI) m/z (%) ($\text{M}+2$, 391), 389 (M^+),

Compound 7a

^1H NMR (CDCl_3) δ 2.67 (dd, 1H, **H**_A, $J_{\text{A-B}} = 14.98$ Hz, $J_{\text{A-X}} = 8.89$ Hz), 3.25 (dd, 1H, **H**_B, $J_{\text{A-B}} = 14.98$ Hz, $J_{\text{B-X}} = 8.12$ Hz), 3.58 (s, 2H, **CH**₂Cl), 3.86 (s, 3H, **OCH**₃), 4.06 (dd, **H**_X, $J_{\text{A-X}} = 8.89$ Hz, $J_{\text{B-X}} = 8.12$ Hz), 6.98–7.32 (m, 8H, Ar-**H**), IR (cm^{-1}) 1680, 1710 (two C=O). Anal. calcd. for $\text{C}_{21}\text{H}_{17}\text{Cl}_2\text{NO}_5\text{S}$: C, 54.09; H, 3.67; S, 6.88; Cl, 15.20; N, 3.00. Found C, 54.26; H, 3.65; S, 6.86; Cl, 15.24; N, 2.98. MS (EI) m/z (%) ($\text{M}+2$, 468), 466 (M^+),

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