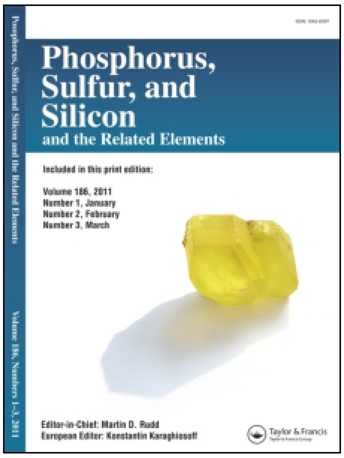

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SYNTHESIS OF 3-(1-ARYLAMINOCARBONYL-5-AMINO)-1,2,4-TRIAZOLYL BENZYL SULFIDE, SULFOXIDE AND SULFONE

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SYNTHESIS OF 3-(1-ARYLAMINOCARBONYL-5-AMINO)-1,2,4-TRIAZOLYL BENZYL SULFIDE, SULFOXIDE AND SULFONE†

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3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfides were synthesized by the reaction of 5-amino-3-benzylthio-1,2,4-triazole and its analogue with the aryl isocyanate. It was found that there was great influence by the property and position of substituents X, Y on the chemical shift of H—N_2 in the ^{1}H NMR spectra. By means of molecular mechanics calculations, the substituent effect on the chemical shift of H—N_2 was rationalized. The chemocontrolled oxidation of 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfide to sulfoxide and sulfone respectively was performed after a careful study of the influence of the concentration of H_2O_2 and the reaction temperature on the oxidation reaction. In ^{1}H NMR spectra of sulfoxides(II), the protons of a methylene group near the SO chiral center coupled to appear as a quartet in the AB pattern. The SO, SO_2 decreased the electronic density around H—N_2, 5-NH_2, and thus moved the proton absorption to a lower field. The experimental showed that the ratio of sulfoxide(II)/sulfone(III) was influenced by the electronic property of substituents X, Y on the aryl moiety.

Key words: Synthesis, triazolylbenzyl sulfide, triazolylbenzyl sulfoxide, triazolylbenzyl sulfone, molecular mechanics, substituent effect, chemocontrolled oxidation, ALS enzyme inhibitor.

INTRODUCTION

ALS enzyme has, over the past twenty years, formed the basis of an enormous amount of herbicides aimed at finding low dose rate, nontoxic, selective herbicides. This stemmed originally from the finding that the sulfonylurea showed activity against ALS enzyme. Recently, Dow and Du Pont have developed the sulfonylurea to triazolo[1,5a]pyrimidine sulfonylamide, using bioisosteric replacement, which shows activity similar to the sulfonylurea. Since then, various herbicides inhibiting ALS enzyme have been synthesized.[1–4] The chemical structures of typical examples are shown in Figure 1.

It was therefore decided to design novel ALS enzyme inhibitors by means of abstracting the common feature of different ALS enzyme inhibitors. A number of lead compounds have been designed, synthesized and tested for activity against ALS enzyme.[5–8] Recently we have described the regioselective addition of 5-amino-1,2,4-triazole with the aryl isocyanate.[9] The encouraging biological activity of 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfide **I** prompted us to synthe-

†Study on the Design, Synthesis and Bioactivity of Novel ALS Enzyme Inhibitors (V).
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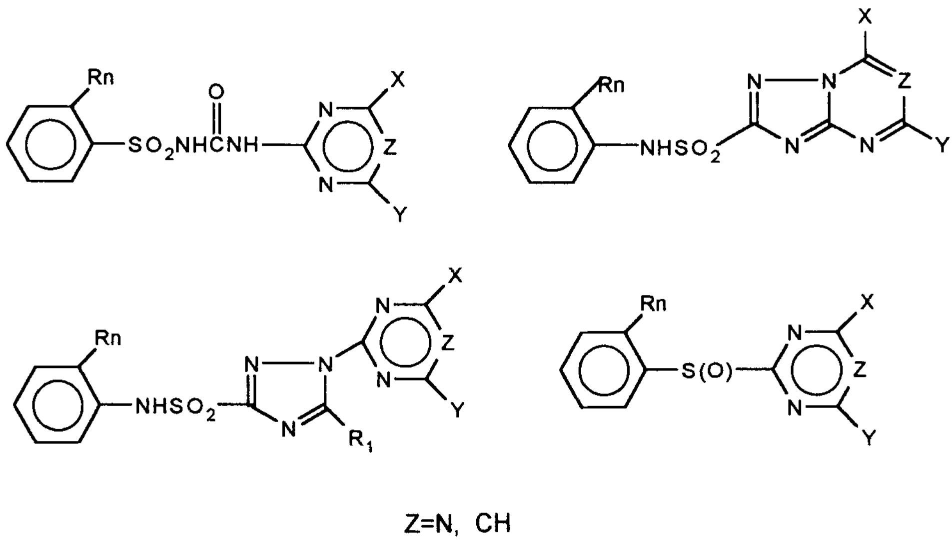
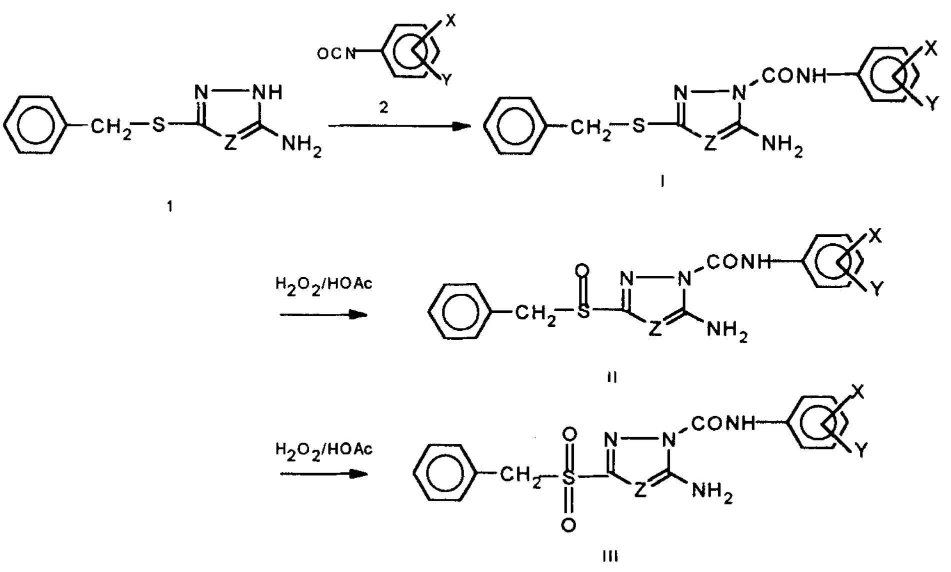


FIGURE 1 Some of typical ALS enzyme inhibitors.

size various 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfides **I**, 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfoxides **II** and 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfones **III**.

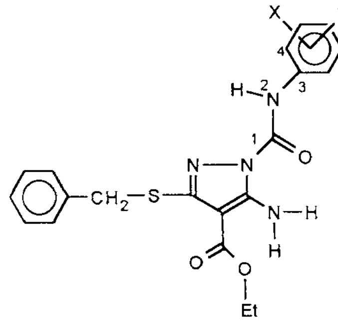


RESULTS AND DISCUSSION

Using our reported method,[9] binucleophilic compounds 5-amino-3-benzylthio-1,2,4-triazole and its analogue **1** were allowed to react with the aryl isocyanate at room temperature in anhydrous THF to afford the 3-(1-arylaminocarbonyl-5-amino)-1,2,4-

TABLE I

δ_{H-N_2}, the dihedral angle and MMXE (kj/mol) of I



No.	I-8	I-9	I-10	I-11	I-12	I-13	I-14	I-15
δ(ppm)	8.496	8.840	8.850	8.718	8.951	9.579	9.520	9.563
X, Y.	2,6-Cl_2	4-Cl	4-OCH_3	H	3,4-Cl_2	2,5-Cl_2	2-OCH_3	2-Cl
MMXE .(kj/mol)	392	357	348	373	360	371	367	373
θ_{1234}	119	170	169	168	171	159	168	167

triazolyl benzyl sulfide and its analogue, these were identified on the basis of analytical and spectroscopic data. Interestingly, we found that there was great influence by the property and position of substituents X, Y on the chemical shift of H—N_2 in the ^{1}H NMR spectra. In order to eliminate the disturbance of the sample concentration and test temperature, at the same concentration 12 mg/0.5 ml, ^{1}H NMR spectra of the following compounds were measured at 25°C. The effect of substituents X, Y on the chemical shift of H—N_2 is summarized in Table I.

As shown in Table I, the H—N_2 peak with OCH_3, Cl at the ortho-position appeared at lower force than that of unsubstituted and Cl, OCH_3 at the para-position. This might be attributed to an ortho-deshielding effect. However, a H—N_2 peak with 2,6-Cl_2 on the anilino moiety was found upfield at 8.496 ppm compared with that of 2-Cl, 2-OCH_3, 2,5-Cl_2 derivatives. In order to gain insight into the mechanistic details of the above phenomena, we have explored the conformational analysis with MMX program. Table I lists the chemical shift, MMXE (kj/mol) and dihedral angles of **I-8~I-15**. These calculations suggested that the disappearance of the ortho-deshielding effect of 2,6-Cl_2 derivative might be attributed to the steric hindrance of 2,6-Cl_2 forcing the aryl plane away from the C(O)N_2-H plane.

In view of the stability of —NCONH and the NH_2 group, H_2O_2/HOAc was selected as the oxidizing reagent to transform 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfide to the related sulfoxide and sulfone.[10] The chemocontrolled oxidation of 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfide to sulfoxide and sulfone respectively was performed after a careful study of the influence of the concentration of H_2O_2 and the reaction temperature on the following oxidation reaction.

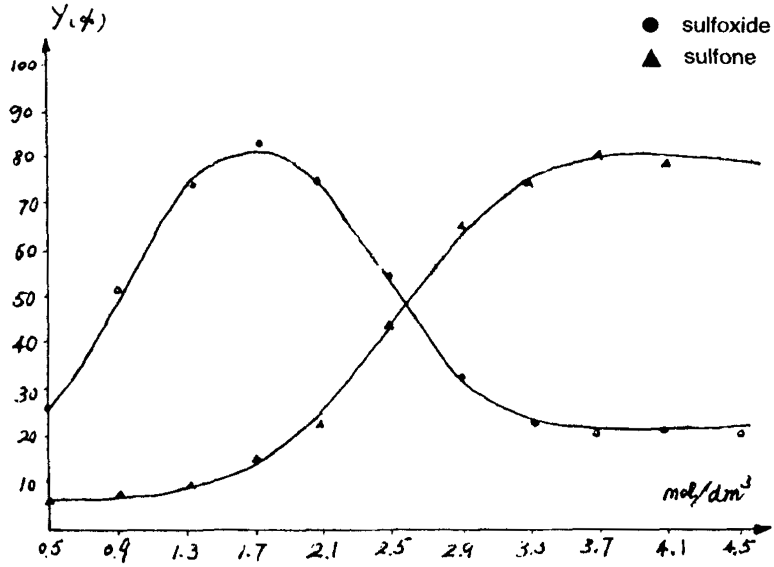
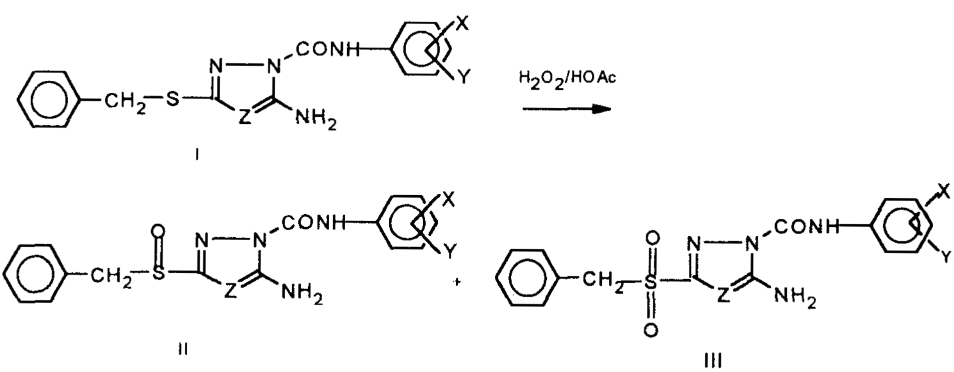


FIGURE 2 The effect of the molar concentration of H_2O_2 on the oxidation reaction.



X, Y=Cl_2; Z=CCOOEt

The result of the influence of the concentration of H_2O_2 on the following reaction is summarized in Figure 2. With the increase of molar concentration of H_2O_2, the yield of sulfoxide increased. When the molar concentration of H_2O_2 was raised to 1.7 mol dm^{-3}, sulfoxide was obtained in the highest yield (83%). Further addition of H_2O_2 did not improve the yield of sulfoxide, but increased the yield of sulfone. In the case when the molar concentration of H_2O_2 was up to 3.7 mol dm^{-3}, the maximum yield of sulfone reached 79%.

The effect of the reaction temperature on the above oxidation reaction was also examined (Figure 3). With the increase of the reaction temperature, the yield of sulfoxide increased. At 27°C the yield of sulfoxide climbed to the maximum 85%. However, when the reaction temperature was increased continuously, the yield of sulfoxide decreased; and the yield of sulfone increased. At 45°C the sulfone was

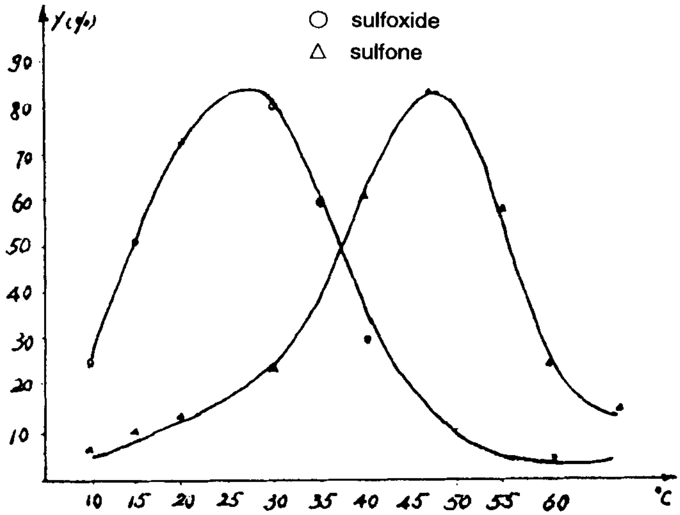
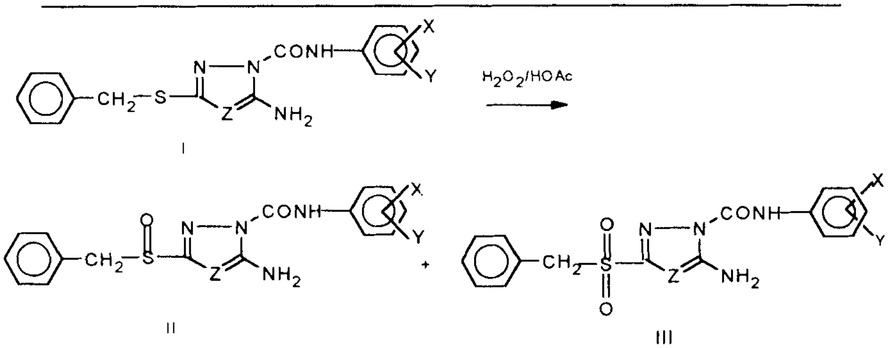


FIGURE 3 The effect of the reaction temperature on the oxidation reaction.

TABLE II
The influence of the substituent X, Y on the ratio of the sulfoxide/sulfone



X,Y	2,6-Cl_2	3,4-Cl_2	4-Cl	H	4-CH_3	4-OCH_3
Ratio (II/III)	83.0/13.0	84.0/11.7	81.5/15.7	78.2/20.0	77.9/19.5	69.8/28.0

obtained in the highest yield (83%). Above 50°C, the dearylaminocarbonyl product was obtained.

In summary, the optimum conditions for the chemocontrolled oxidation of 3-(1-arylaminocarbonyl-5-amino)-1,2,4-triazolyl benzyl sulfide to the related sulfoxide and sulfone were 1.7 mol dm^{-3}, 27°C; 3.7 mol dm^{-3}, 45°C respectively.

When the substituent X, Y was examined (Table II), the ratio of sulfoxide(II)/sulfone(III) was influenced by the property of X, Y. Withdrawing substituents on the aryl moiety caused the decrease of the electronic density on the sulfur atom, resulting in the increase of the ratio of sulfoxide/sulfone; on the contrary, donating substituents

TABLE III

Physical data of I, II, III

No.	Z	n	X,Y	m.p. (°C)	Yield (%)	Elemetal Analysis Calcd (Found) C	H	N	Eluting Solvent
I-1	N	0	2,6-Cl_2	152-3	91.5	48.73	3.30	17.77	THF[c]
						(48.59	3.27	17.89)	
I-2	N	0	4-Cl	156-7	92.8	53.41	3.89	19.47	THF[c]
						(53.27	3.92	19.51)	
I-3	N	0	4-CH_3O	149-151	92.4	57.46	4.79	19.72	THF[c]
						(57.51	4.81	19.50)	
I-4	N	0	H	173-5	91.8	59.08	4.62	21.54	A:P[a]=1:2
						(59.17	4.79	21.31)	
I-5	N	0	3,4-Cl_2	171-2	94.1	48.73	3.30	17.77	A:P=1:2
						(48.91	3.41	17.67)	
I-6	N	0	2,5-Cl_2	192-4	90.5	48.73	3.30	17.77	A:P=1:2
						(48.67	3.41	17.79)	
I-7	N	0	2-CH_3O	162-4	89.5	57.46	4.79	19.72	A:P=1:2
						(57.31	4.59	19.81)	
I-8	CCOOEt	0	2,6-Cl_2	150-1	94.2	51.61	3.87	12.04	A:P=1:3
						(51.81	3.61	12.21)	
I-9	CCOOEt	0	4-Cl	159-160	93.4	55.75	4.41	13.01	A:P=1:3
						(55.59	4.37	13.21)	
I-10	CCOOEt	0	4-CH_3O	165-6	90.8	59.15	5.16	13.15	A:P=1:3
						(59.00	5.10	13.24)	
I-11	CCOOEt	0	H	170-2	91.1	60.61	5.05	14.14	A:P=1:3
						(60.49	5.12	14.07)	
I-12	CCOOEt	0	3,4-Cl_2	161-3	95.1	51.61	3 87	12.04	A:P=1:3
						(51.81	3.77	12.11)	
I-13	CCOOEt	0	2,5-Cl_2	198-201	91.5	51.61	3.87	12.04	A:P=1:3
						(51.47	3.91	12.00)	
I-14	CCOOEt	0	2-CH_3O	172-4	89.8	59.15	5.16	13.15	A:P=1:3
						(59.00	5.27	13.07)	
I-15	CCOOEt	0	2-Cl	178-9	90.6	55.75	4.41	13.01	A:P=1:3
						(55.49	4.21	13.17)	
II-1	N	1	2,6-Cl_2	131-3	76.1	46.83	3.17	17.70	A:P=1:2
						(46.95	3.20	17.03)	
II-2	N	1	4-Cl	145-7	76.9	51.13	3.73	18.64	EA:P[b]=1:2
						(51.30	3.57	18.57)	
II-3	N	1	4-CH_3O	155-7	69.2	54.99	4.58	18.87	EA:P=1:2
						(55.01	4.39	18.76)	
II-4	N	1	3,4-Cl_2	119-120	80.1	46.83	3.17	17.07	EA:P=1:3
						(46.61	3.19	17.20	
II-5	N	1	2,5-Cl_2	151-3	78.1	46.83	3.17	17.07	A:P=1:2
						(46.81	3.27	17.00)	
II-6	CCOOEt	1	2,6-Cl_2	123-5	81.6	49.90	3.74	11.64	EA:P=1:3
						(49.97	3.78	16.49)	
II-7	CCOOEt	1	4-Cl	129-131	79.8	53.75	4.26	12.54	A:P=1:4
						(53.60	4.28	12.71)	
II-8	CCOOEt	1	4-CH_3O	105-7	69.0	57.01	4.98	12.67	EtOAc[c]
						(57.09	5.00	12.45)	
II-9	CCOOEt	1	H	131-3	76.0	58.25	4.85	13.59	EA:P=1:3
						(58.20	4.74	13.71)	
II-10	CCOOEt	1	3,4-Cl_2	144-6	83.0	49.90	3.74	11.64	EtOAc[c]
						(49.79	3.76	11.80)	
III-1	N	2	2,6-Cl_2	149-151	70.8	45.07	3.05	16.43	A:P=1:3
						(45.31	3.12	16.21)	
III-2	N	2	4-Cl	150-1	68.8	49.04	3.58	17.88	EA:P=1:3
						(48.99	3.54	17.92)	
III-3	N	2	4-CH_3O	163-4	77.9	52.71	4.39	18.09	EA:P=1:4
						(52.59	4.50	18.15)	

TABLE III (*Continued*)

No.	Z	n	X,Y	m.p. (°C)	Yield (%)	Elemetal Analysis Calcd (Found) C	H	N	Eluting Solvent
III-4	N	2	3,4-Cl_2	134-5	71.3	45.07	3.05	16.43	EA:P=1:4
						(45.31	3.09	16.18)	
III-5	N	2	2,5-Cl_2	174-6	72.1	45.07	3.05	16.43	A:P=1:2
						(45..21	3.06	16.50)	
III-6	CCOOEt	2	2,6-Cl_2	148-150	81.5	48.29	3.62	11.27	EA:P=1:4
						(48.41	3.27	11.27)	
III-7	CCOOEt	2	4-Cl	147-8	81.0	51.89	4.11	12.11	EA:P=1:4
						(51.79	4.12	12.00)	
III-8	CCOOEt	2	4-CH_3O	129-130	87.1	55.02	4.80	12.23	EtOAc[c]
						(55.20	4.78	12.09)	
III-9	CCOOEt	2	H	153-4.5	85.0	56.07	4.67	13.08	EA:P=1:3
						(56.18	4.74	13.11)	
III-10	CCOOEt	2	3,4-Cl_2	160-3	81.8	48.29	3.62	11.27	$CHCl_3$[c]
						(48.41	3.71	11.09)	
IV	N	1		158-160	68.5	48.65	4.50	25.23	
						(48.41	4.41	25.41)	EtOAc[c]

a: A-acetone; P-petroleum(60-90°C); b: EA-ethyl acetate, P-petroleum(60-90°C);
c: recrystallization solvent

caused the increase of the electronic density on the sulfur atom, resulting in the decrease of the ratio of sulfoxide(II)/sulfone(III).

Taking compounds **I-8**, **II-6**, **III-6** as an example. The ^{1}H NMR spectrum of **I-8** in $CDCl_3$ showed signals at 8.50 ppm (1H NHCO), 6.96 ppm (b 2H NH_2), 4.25–4.38 (m 4H OCH_2 $PhCH_2$), 7.25–7.48 ppm (m 8H C_6H_5 ArH), 1.32–1.39 (t 3H $OCCH_3$). The Mass spectrum showed no molecular ion peak as the N—C-{(O)NHAr} was easy to cleave to produce ion peak m/e 277 through the r-H rearrangement. The behavior of 5-NH_2, NHCO protons of compound **II-6** **III-6** resembled that of compound **I-8**. The SO, SO_2 shifted the protons of 5-NH_2, NHCO downfield to 7.02, 8.61; (**II-6**), 7.13, 8.71 (**III-6**). In the ^{1}H NMR spectrum of II6, the protons of the methylene group near the SO group showed coupling with each other appearing as a quartet 4.26, 4.48 ppm J_{AB} = 13.0 Hz in the AB pattern, which might be attributed to the SO chirac center. The IR spectrum of **II-6** **III-6** showed the presence of strong absorption bands at 1073 cm^{-1} (SO); 1327, 1149 cm^{-1} (SO_2) respectively. The ^{1}H NMR spectrum of compound **IV** was quite consistent with the assigned structure. Compared with **I-8**, signal of NHCO in the ^{1}H NMR spectrum of **IV** and the stretching band for C=O in the IR spectrum of **IV** disappeared.

EXPERIMENTAL

General: 10-40 silica gel GF_{254} was used for the TLC and detection was carried out on a UV-detector. The reaction mixture was analyzed by HPLC on a HP1090 instrument equipped with a Hypersil 5 μm 200 × 4.6 mm (79916 SI-574) column at 210 nm, Solvents: petroleum (60–90°C), methanol, isopropanol. The melting points were uncorrected. ^{1}H NMR spectra were obtained using a Brucker AC-P200 spectrometer and were referenced to internal TMS. IR spectra were recorded with a Shimadzu-IR 435 infrared-spectrometer using KBr pellets. MS were measured on a VG ZAB-HS instrument. Elemental analyses were obtained using a CHN Recorder MT-3 Elemental Analyzer.

TABLE IV
^{1}H NMR, IR, MS data of I, II, III

No.	^{1}H NMR(ppm)	IR(cm^{-1})	MS(m/e)
I-1[a]	4.34(s 2H $PhCH_2$), 6.47(b 2H NH_2), 7.26-7.45(m 8H ArH C_6H_5), 8.29(b 1H CONH)	3410, 3258(NH) 1723(CONH)	
I-2[b]	4.38(s 2H $PhCH_2$), 7.24-7.71(m 11H NH_2 ArH C_6H_5), 10.05 (b 1H CONH)	3406, 3266(NH) 1728(CONH)	
I-3[b]	3.73(s 3H OCH_3), 4.38(s 2H $PhCH_2$), 6.89(b 2H NH_2), 7.31 -7.53 (m 9H C_6H_5 ArH), 9.83(s 1H CONH)	3410, 3261(NH) 1720(CONH)	
I-4[b]	4.40(s 2H $PhCH_2$), 7.13-7.67(m 12H $NH_2C_6H_5$), 9.92(s 1H CONH)	3401, 3274(NH) 1723(CONH)	
I-5[a]	4.33(s 2H $PhCH_2$), 6.32(b 2H NH_2), 7.24-7.75(m 8H C_6H_5 ArH), 8.54(s 1H CONH)	3437, 3323(NH)	393, 206, 187 173,161,124,91
I-6[a]	4.36(s 2H $PhCH_2$), 6.80(b 2H NH_2), 7.12-8.34(m 8H ArH C_6H_5), 9.25(s 1H CONH)	3409, 3276(NH) 1744(CONH)	
I-7[a]	3.94(s 3H OCH_3), 43.5(s 2H $PhCH_2$), 6.47(b 2H NH_2), 6.96 -8.20(m 9H ArH C_6H_5)		355, 206, 149 134, 124, 91
I-8[a]	1.32-1.39(t 3H $OCCH_3$), 4.25-4.38(m 4H OCH_2), 6.96(s 2H NH_2), 7.25-7.48(m 8H ArH C_6H_5), 8.50(s 1H CONH)		277, 231, 187 161, 126, 91
I-9[a]	1.33-1.40(t 3H $OCCH_3$), 4.25-4.37(m 4H CH_2 OCH_2), 7.40 -7.69(q 4H ArH J_{AB}=8.8Hz), 8.84(s 1H CONH)		
I-10[a]	1.33-1.39(t 3H $OCCH_3$), 3.71(s 3H OCH_3), 4.24-4.37(m 4H CH_2 OCH_2), 6.90, 7.43(q 4H ArH J_{AB}=8.6Hz), 7.03(s 2H NH_2), 7.26-7.34(m 5H C_6H_5), 8.85(s 1H CONH)	3447,3358(NH) 1726(CONH), 1668(COO)	
I-11[a]	1.33-1.40(t 3H $OCCH_3$), 4.29-4.35(m 4H CH_2 OCH_2), 6.93(s 2H NH_2), 7.30-7.53(m 10H C_6H_5), 8.72(s 1H CONH)	3444, 3335, 3326 (NH),1728(CONH), 1665(COO)	277, 231, 119 100, 91
I-12[a]	1.33-1.40(t 3H $OCCH_3$), 4.24-4.34(m 4H CH_2 OCH_2), 6.98(b 2H NH_2), 7.25-7.79(m 8H C_5H_5 ArH), 8.95(s 1H CONH)	3445, 3332, 3328 (NH), 1729(CONH), 1665(COO)	
I-13[a]	1.32-1.39(t 3H $OCCH_3$), 4.25-4.34(m 4H CH_2 OCH_2), 7.05 -8.39(m 10H ArH C_6H_5 NH_2), 9.58(s 1H CONH)		
I-14[a]	1.32-1.39(t 3H $OCCH_3$), 3.61(s 3H OCH_3), 3.90(s 2H CH_2), 4.24-4.35(q 2H OCH_2), , 6.95-8.21(m 11H NH_2ArH C_6H_5), 9.52(s 1H CONH)		
I-15[a]	1.33-1.39(t 3H $OCCH_3$), 4.25-4.36(m 4H CH_2 OCH_2), 7.05 -8.31(m 11H NH_2 C_6H_5 ArH), 9.56(s 1H CONH)		
II-1[a]	4.43, 4.46(q 2H J_{AB}=5.4Hz CH_2), 6.73(b 2H NH_2), 7.25-7.44 (m 8H ArH C_6H_5), 8.35(s 1H CONH)	3419, 3289(NH),1730 (CONH), 1067(S=O)	222, 187, 91
II-2[b]	4.46, 4.54(q 2H J_{AB}=13.6Hz CH_2), 7.42, 7.69(q 4H J_{AB}=8.7Hz ArH), 7.24-7.50(m 5H C_6H_5), 7.79(b 2H NH_2), 10.44(s 1H CONH)	3405, 3266(NH), 1730 (CONH), 1024(S=O)	
II-3[b]	3.73(s 3H OCH_3), 4.48, 4.55(q 2H J_{AB}=12.5Hz CH_2), 6.92, 7.52 (q 4H J_{AB}=8.8Hz ArH), 7.32-7.74(m 7H C_6H_5 NH_2), 10.18(s 1H CONH)		222, 149, 91
II-4[a]	4.45,4.53(q 2H J_{AB}=6.0Hz CH_2) 6.72(b 2H NH_2), 7.25-7.76(m (m 8H C_6H_5 ArH), 8.56(s 1H CONH)	3441,3221(NH), 1728 (CONH), 1024(S=O)	
II-5[a]	4.42, 4.45(q 2H J_{AB}=5.7Hz CH_2), 7.18-8.34(m 10H NH_2ArH C_6H_5), 9.81(s 1H CONH)		
II-6[a]	1.39-1.46(t 3H $OCCH_3$), 4.34-4.41(q 2H OCH_2), 4.26, 4.48(q 2H J_{AB}=13.0Hz CH_2), 7.02(b 2H NH_2), 7.22-7.44(m 8H C_6H_5 ArH), 8.61(s 1H CONH)	3431 3301(NH), 1729(CONH), 1073 (S=O),1677(COO)	293, 247, 91
II-7[b]	1.25-1.32(t 3H $OCCH_3$), 4.25-4.33(q 2H OCH_2), 4.22, 4.75 (q 2H J_{AB}=10.8Hz CH_2), 7.35-7.43(m 7H NH_2 C_6H_5), 7.45, 7.69(q 4H J_{AB}=8.8Hz ArH), 10.31(s 1H CONH)	3437, 3336(NH), 1729 (CONH), 1662(COO) 1023(S=O)	

TABLE IV (*Continued*)

No.	^1H NMR(ppm)	IR(cm^{-1})	MS(m/e)
II-8[a]	1.37-1.44(t 3H $OCCH_3$), 3.80(s 3H OCH_3), 4.30-4.39(q 2H OCH_2)4.17,4.44(q 2H J_{AB}=13.6Hz CH_2),6.90, 7.43(q 4H J_{AB}=8.8 Hz ArH),7.09(b 2H NH_2),7.26-7.35(m 5H C_6H_5), 8.97(s 1H CONH)	3422, 3306(NH) 1720(CONH), 1043 (S=O)	
II-9[b]	1.26-1.33(t 3H $OCCH_3$), 4.23-4.31(q 2H OCH_2), 4.35, 4.63(q 2H J_{AB}=13.0Hz CH_2), 7.21-7.86(m 12H $NH_2C_6H_5$),10.13(s 1H CONH)		
II-10[a]	1.26-1.33(t 3H $OCCH_3$), 4.23-4.31(q 2H OCH_2), 4.36, 4.63(q 2H J_{AB}=16.4Hz CH_2), 7.03(b 2H NH_2), 7.26-7.85(m 8H ArH C_6H_5), 9.17(s 1H CONH)	3449, 3322(NH) 1727(CONH),1698 (COO), 1020(S=O)	
III-1[a]	4.80(s 2H CH_2), 7.02(b 2H NH_2), 7.26-7.51(m 8H ArH C_6H_5), 8.40 (s 1H CONH)	3438, 3300(NH), 1727(CONH), 1301, 1117(SO_2)	238, 187, 91
III-2[b]	4.79(s 2H CH_2), 7.25-7.80(m 7H $C_6H_5NH_2$), 7.41, 7.68(q 4H J_{AB} =8.5Hz ArH), 10.28(s 1H CONH)	3420,3275(NH),1731 (CO),1319,1124(SO_2)	
III-3[b]	3.73(s 3H OCH_3), 4.85(s 2H CH_2), 6.92-7.53(m 11H NH_2 C_6H_5 ArH), 10.21(s 1H CONH)		
III-4[a]	4.81(s 2H CH_2), 7.00(b 2H NH_2), 7.24-7.75(m 8H ArH C_6H_5), 8.53(s 1H CONH)	3451,3319, 3278(NH), 1729(CONH), 1310, 1121(SO_2)	
III-5[a]	4.79(s 2H CH_2),7.19-8.40(m 10H NH_2 ArH), 9.78(s 1H CONH)		
III-6[a]	1.41-1.49(t 3H $OCCH_3$), 4.39-4.49(q 2H OCH_2), 4.79(s 2H CH_2), 7.13(b 2H NH_2), 7.24-7.43(m 8H ArH C_6H_5), 8.70(s 1H CONH)	3449, 3348,3306 (NH),1729(CONH), 1697(COO), 1327, 1149(SO_2)	309, 173, 110 91
III-7[b]	1.30-1.37(t 3H $OCCH_3$), 4.25-4.34(q 2H OCH_2), 4.68(s 2H CH_2), 7.45-7.71(q 4H J_{AB}=8.9Hz ArH), 7.36-7.43(m 7H C_6H_5 NH_2), 10.32(s 1H CONH)	3442,3339,3301(NH) 1729(CONH), 1690 (COO),1309, 1129 (SO_2)	
III-8[a]	1.40-1.49(t 3H $OCCH_2$), 3.81(s 3H OCH_3), 4.30-4.39(q 2H OCH_2), 4.78(s 2H CH_2), 6.89, 7.44(q 4H J_{AB}=8.9Hz ArH), 7.11(b 2H NH_2) 7.25-7.35(m 5H C_6H_5), 8.61(s 1H CONH)	3427, 3310(NH), 1722 (CONH), 1686(COO), 1319, 1139(SO_2)	
III-9[a]	1.43-1.49(t 3H $OCCH_3$), 440-4.50(q 2H OCH_2), 4.81(s 2H CH_2), 7.21-7.50(m 12H C_6H_5 NH_2), 8.83(s 1H CONH)		
III-10[a]	1.29-1.37(t 3H $OCCH_3$), 4.40-4.50(q 2H OCH_2), 4.80(s 2H CH_2), 7.12(b 2H NH_2), 7.25-7.78(m 8H ArH C_6H_5), 9.20(s 1H CONH)	3451, 3320(NH),1728 (CONH), 1696(COO), 1324, 1139(SO_2)	
IV	4.42, 4.46(q 2H J_{AB}=8.1Hz CH_2), 6.74(b 2H NH_2), 7.25-7.37(m 5H C_6H_5), 12.51(s 1H NH)	3465, 3366, 3289 (NH), 1068(S=O)	222, 91

a: $CDCl_3$, b: DMSO-d6

General Procedure for the Synthesis of the 3-(5-amino-1-arylaminocarbonyl)-1,2,4-triazolyl Benzyl Sulfide and its Analogue (**I**)

2.5 mmol aryl isocyanate in 5 ml anhydrous THF was added dropwise to a solution of 2.5 mmol 5-amino-3-benzylthio-1,2,4-triazole (or its analogue) **1** in 10 ml anhydrous THF, the mixture was stirred at room temperature until **1** disappeared detected by TLC (acetone: petroleum 60–90°C 1:2). Then THF was removed under reduced pressure and the residue was purified by flash column chromatography or recrystallization. The experimental data were listed in Tables III and IV.

General Procedure for the Synthesis of the 3-(5-amino-1-arylaminocarbonyl)-1,2,4-triazolyl Benzyl Sulfoxide and its Analogue (**II**)

To a solution of 3-(5-amino-1-arylaminocarbonyl)-1,2,4-triazolyl benzyl sulfide and its analogue **I** 1 mmol in 16.2 ml glacial acid was added dropwise hydrogen peroxide (3.8 ml H_2O_2 30%). The mixture was stirred at 25–27°C. After the consumption of **I**, the reaction solution was diluted with 20 ml ice water and extracted with ethyl acetate. After the combined extracts were washed with water and dried over anhydrous $MgSO_4$. The solvent was removed and the resulting residue was purified by recrystallization or chromatography.

General Procedure for the Synthesis of 3-(5-amino-1-arylaminocarbonyl)-1,2,4-triazolyl Benzyl Sulfone and its Analogue (**III**)

To a solution of 3-(5-amino-1-arylaminocarbonyl)-1,2,4-triazolyl benzyl sulfide and its analogue **I** 1 mmol in 11.6 ml glacial acid was added dropwise hydrogen peroxide (8.4 ml H_2O_2 30%). The mixture was stirred at 47°C detected by TLC. After the completion of the oxidation reaction, the reaction solution was diluted with 20 ml ice water and extracted with ethyl acetate. Removal of the solvent gave crude product, which was purified by recrystallization or chromatography.

Synthesis of 3-(5-amino)-1,2,4-triazolyl Benzyl Sulfoxide

To a solution of 0.394 g **I-1** in 10 ml glacial acid was added dropwise 10 ml hydrogen peroxide (30%). The mixture was stirred at 60°C for 5 h. The reaction mixture was diluted with 20 ml ice water and extracted with ethyl acetate. The organic solution was concentrated to give the crude **IV**, which was recrystallized from ethyl acetate. m.p. 158–160°C, yield 0.15 g (68.05%).

The Effect of the Molar Concentration of H_2O_2 on the Oxidation Reaction (**I-8**)

3-(5-amino-1-2′,6′-dichlorophenylaminocarbonyl)-1,2,4-triazolyl benzyl sulfide 1 mmol was added to 20 ml hydrogen peroxide solution (relevant molar concentration) in glacial acid. The mixture was stirred at 25°C for 24 h, and then detected by HPLC. The result was shown in Figure 2.

The Effect of the Reaction Temperature on the Oxidation Reaction (**1-8**)

3-(5-amino-1-2′-6′-dichlorophenylaminocarbonyl)-1,2,4-triazolyl benzyl sulfide 1 mmol was added to 20 ml hydragen peroxide solution (1.7 mol dm^3) in glacial acid. The mixture was stirred at relevant temperature for 24 h and then detected by HPLC. The result was shown in Figure 3.

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