

Synthesis and Pharmacological Activity of 3-[(p-Acetamidoalkyl)benzenesulfonyl]-thiazolidin-4-ones and Thiazolines

Hamad A. Al-Khamees¹, Hesham A. Kandil¹, Kamal E.H. El-Tahir² and Said M. Bayomi¹

¹Department of Pharmaceutical Chemistry and ²Department of Pharmacology, College of Pharmacy, P.O. Box 2457, King Saud University, Riyadh-11451, Saudi Arabia

(Received September 5, 1992)

Two series of substituted sulfonylthiazolidin-4-ones and sulfonylthiazolines have been synthesized and examined for their antidiabetic and biological activity.

Key words: Thioureas, Antidiabetic, Condensation, Cardiovascular

INTRODUCTION

Many compounds such as carboxylic acid derivatives (Bott-Handford and Heath, 1981), imidazolidine-2,4-diones (Peterson *et al.*, 1979), oxazolidine-2,4-diones (Bott-Handford and Heath, 1980) and some 5-benzylthiazolidine-2,4-diones (Sohda *et al.*, 1982) are previously reported to possess hypoglycemic activity. Based on the structural analogy of these compounds, the synthesis and biological evaluation of two series of compounds, specifically 2-alkylimino-3-[(p-acetamidoalkyl)benzenesulfonyl] thiazolidin-4-ones **14-21** and 2-alkylimino-3-(p-acetamidoalkylbenzenesulfonyl)-4-(p-bromophenyl)thiazolines **23-30** were undertaken during the course of our search for a novel antidiabetic agents.

EXPERIMENTAL

Melting points were determined with Mettler FP5 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in deuteriochloroform or DMSO-d₆ with a Varin FT 80 A and XL 200 Spectrometers, Infrared spectra (KBr) were taken on a Perkin-Elmer 580B Spectrometer. Analysis of compounds for C, H, and N were carried out with Perkin-Elmer 240B elemental analyser. The chemical used are commercially available (Fluka, Switzerland and Aldrich Co., U.S.A.).

N-(p-(2-Acetamidoethyl)benzenesulfonyl)-N'-alkylthioureas **9-13**

The procedure given for the synthesis of **10** is a


Correspondence to: Said M. Bayomi, Department of Pharmaceutical Chemistry, College of Pharmacy, P.O. Box 2457, King Saud University, Riyadh-11451, Saudi Arabia

general method for the synthesis of **9-13** Table I. A mixture of p-(2-acetamidoethyl)benzenesulfonamide **24** (3.50 g, 0.041 mol) and anhydrous potassium carbonate (5.90 g, 0.043 mol) in dry acetone (100 ml) was stirred and refluxed for 1.5 h. At this temperature, a solution of methyl isothiocyanate (1.60 g, 0.0216 mol) in dry acetone (20 ml) was then added at a dropwise rate. After stirring and refluxing overnight the mixture was cooled and filtered. The solid residue was dissolved in water (375 ml) and acidified with 6N-hydrochloric acid. The crude product precipitated was purified by recrystallization from ethanol to give white crystals. See Table I. IR (KBr) cm⁻¹: 3240 (NH), 1620 (C=S), 1345 & 1125 (SO₂). NMR (DMSO-d₆): 1.79 (s, 3H, COCH₃), 2.83 (t, 2H, benzylic protons), 2.91 (d, 3H, HN-CH₃), 3.32 (m, 2H, CONH-CH₂), 7.44-7.89 (m, 4H, aromatic protons), 7.90 (s, 1H, NHCO), 8.6 (broad s, 1H, CSNH) and 11.75 (broad s, 1H, SO₂NH).

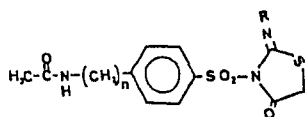
2-Alkylimino-3-(p-acetamidoalkylbenzenesulfonyl)thiazolidin-4-ones, **14-21**



The procedure given for the synthesis of **14** is a general route for the synthesis of **14-21**. A mixture of thiourea **10** (2.83 g, 0.01 mol), sodium acetate (2 g) and chloroacetic acid (1.03 g, 0.011 mol) in absolute ethanol (30 ml) was refluxed for overnight. The solid precipitated after cooling was collected by filtration and washed with water and air dried. Recrystallization from ethanol gave white crystals of **18**, See Table II; IR (KBr) cm⁻¹: 3390 (NH), 1720 (thiazolidone C=O); 1620; (C=N); 1400 & 1140 (SO₂); NMR (DMSO-d₆) δ: 1.78 (s, 3H, CH₃-CO), 2.79 (t, 2H, benzylic protons); 3.02 (s, 3H, =N-CH₃), 3.31 (m, 2H, NH-CH₂); 4.08 (s, 2H, C₅-H), 7.46-4.82 (m, 4H, aromatic protons); and 7.92 (broad s, NHCO).

Table I. N-[p-(2-acetamidoethyl)benzenesulphonyl]-N'-alkylthioureas 6-13

Comp. No.	R	Yield %	mp. °C	Molecular formula	Analysis % calcd (found)		
					C	H	N
6-9*							
10	-CH ₃	77	152-153	C ₁₂ H ₁₇ N ₃ O ₃ S ₂	45.69(45.88)	5.43(5.38)	12.32(13.37)
11	-CH ₂ -CH ₃	75	126-127	C ₁₃ H ₁₉ N ₃ O ₃ S ₂	47.39(47.22)	5.81(5.77)	12.76(12.61)
12	-(CH ₂) ₃ -CH ₃	82	99-100	C ₁₅ H ₂₃ N ₃ O ₃ S ₂	50.39(50.17)	6.48(6.47)	11.75(11.71)
13		82	148-150	C ₁₇ H ₂₅ N ₃ O ₃ S ₂	53.24(52.89)	6.57(6.50)	10.96(10.61)

*Are prepared according to the reported procedure (Boutwell, 1961).

Table II. 2-alkylimino-3-(p-acetamidoalkylbenzenesulfonyl)thiazolidin-4-ones 14-21

Comp. No.	R	n	Yield %	mp. °C	Molecular formula	Analysis % calcd (found)		
						C	H	N
14	-CH ₃	1	70	180-81	C ₁₃ H ₁₅ N ₃ O ₄ S ₂	45.73(45.59)	4.43(4.51)	12.30(12.08)
15	-CH ₂ -CH ₃	1	82	173-174	C ₁₃ H ₁₉ N ₃ O ₄ S ₂	47.39(47.22)	5.81(5.77)	12.76(12.61)
16	-CH ₂ CH ₂ CH ₂ CH ₃	1	67	118	C ₁₆ H ₂₁ N ₃ O ₄ S ₂	50.11(49.30)	5.52(5.90)	10.96(10.85)
17		1	82	186	C ₁₈ H ₂₃ N ₃ O ₄ S ₂	52.79(52.88)	5.66(5.90)	10.24(10.25)
18	-CH ₃	2	77	171	C ₁₄ H ₁₇ N ₃ O ₄ S ₂	47.30(47.47)	4.82(4.81)	11.82(11.40)
19	-CH ₂ CH ₃	2	89	121	C ₁₅ H ₁₉ N ₃ O ₄ S ₂	48.76(48.58)	5.18(5.28)	11.37(11.30)
20	-CH ₂ CH ₂ CH ₂ CH ₃	2	78	118	C ₁₇ H ₂₃ N ₃ O ₄ S ₂ ·H ₂ O	49.14(49.01)	6.06(5.89)	10.11(10.15)
21		2	90	162	C ₁₉ H ₂₅ N ₃ O ₄ S ₂ ·H ₂ O	51.60(51.70)	6.16(5.97)	9.52 (9.20)

2-Alkylimino-3-(p-acetamidoalkylbenzenesulfonyl)-4-(p-bromo-phenylthiazoline, 22-29

The procedure given for the synthesis of **26** is a general method for the preparation of **22-29**. A mixture of thiourea **10** (2.83 g, 0.01 mole) and *p*-bromophenacyl bromide (2.8 g, 0.01 mol) in isopropyl alcohol (30 ml) was refluxed for 4 hr. The alcohol was evaporated *in vacuo* and the residue was washed with 10% sodium acetate and then extracted with chloroform (30×3). The organic extract was washed with water and dried with anhydrous sodium sulphate. The oily product obtained after the evaporation of chloroform was dissolved in the least amount of ethyl acetate and *n*-hexane was added till turbid solution and then kept in refrigerator for overnight. The solid obtained on scratching was collected and washed with *n*-hexane and air dried.

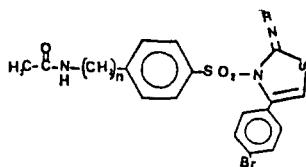
Recrystallization from acetone gave white crystals of **26**, See Table III; IR (KBr) cm⁻¹: 3240 (NH) 1625 (C=O), 1300 & 1140 (SO₂); NMR (DMSO-d₆) δ: 1.79 (s, 3H, CH₃-CO); 2.77 (t, 2H, benzylic protons); 3.33 (m, 3H, -NH-CH₂); 3.39 (s, 3H, =N-CH₃), 6.94 (s, 1H, C₅-H); (m, 7.35 & 7.80 (m, 4H aromatic protons); and



7.95 (broad s, 1H, NH).

METHOD

Recording of the electrocardiogram (ECG) and measurement of the heart rate

Male wister rats (300g, body weight) were anesthetized with urethane, 1.25g Kg⁻¹ i.p (25%, w/v aqueous solution) and left in spontaneous respiration. The electrocardiogram (ECG; Lead II or III) was recorded using subcutaneous steel needle limb electrodes connected to a Narco Physiograph fitted with an ECG coupler No. 7176 (Narco Bio-systems) as outlined previously (Eltahir et al., 1989). The speed of the chart was adjusted to 10 mm Sec⁻¹. The heart rate was calculated from the QRS complexes per unit time. The test compounds were dissolved in dimethyl sulfoxide (DMSO). Each does was dissolved in 50 μl DMSO and injected i.v. via a canula inserted into the right external jugular vein. In each experiment DMSO alone (0.167 ml/Kg) was initially injected i.v. into the anaesthetized rat and its effect on the heart rate was quantified as a percentage decrease compared to the normal heart rate of

Table III. 2-alkylimino-3-(*p*-acetamidoalkylbenzenesulfonyl)-4-(*p*-bromophenyl)thiazolines 22-29

Comp. No.	R	n	Yield %	mp. °C	Molecular formula	Analysis % calcd (found)		
						C	H	N
22	-CH ₃	1	71	189	C ₁₉ H ₁₈ BrN ₃ O ₃ S ₂	45.73(45.59)	4.43(4.51)	12.30(12.08)
23	-CH ₂ -CH ₃	1	47	151	C ₂₀ H ₂₀ BrN ₃ O ₃ S ₂	48.58(48.28)	4.08(4.28)	8.50(7.78)
24	-CH ₂ CH ₂ CH ₂ CH ₃	1	52	137	C ₂₂ H ₂₄ BrN ₃ O ₃ S ₂	50.57(50.13)	4.63(4.66)	8.04(7.84)
25		1	74	134	C ₂₄ H ₂₆ BrN ₃ O ₃ S ₂	52.55(52.87)	4.78(5.15)	7.66(7.60)
26	-CH ₃	2	73	148	C ₂₀ H ₂₀ BrN ₃ O ₃ S ₂	48.58(47.96)	4.07(4.15)	8.50(8.42)
27	-CH ₂ -CH ₃	2	67	141	C ₂₁ H ₂₂ BrN ₃ O ₃ S ₂	49.60(50.09)	4.36(4.49)	8.26(7.97)
28	-CH ₂ CH ₂ CH ₂ CH ₃	2	60	94	C ₂₃ H ₂₆ BrN ₃ O ₃ S ₂	51.49(51.30)	4.88(4.93)	7.83(8.18)
29		2	67	141	C ₂₁ H ₂₂ BrN ₃ O ₃ S ₂	49.60(50.00)	4.36(4.49)	8.26(7.97)

the test animal. This effect was then subtracted from the effect observed following administration of the solubilized test compound. The values reported in this paper are the net effects induced by the test compound. All compounds were tested in the dose range 3.75-15 $\mu\text{mol Kg}^{-1}$. Each animal was used to test only one compound (n/4 animals for each dose).

Chemistry

Thiazolidin-5-ones **14-21** and thiazolines **22-29** listed in tables 2 & 3 were synthesized from the corresponding thioureas derivatives **6-13** as shown in Scheme 1.

The starting thioureas **6-13** were obtained by chlorosulphonation reaction of N-benzylacetamide **1** and N-phenethylacetamide **2** followed by treatment with ammonia to afford the corresponding sulfonamide derivatives **3** & **4** (Hoechst, 1965). Whereas condensation of **3** with alkyl isothiocyanates **5** in refluxing alcohol using pyridine as a basic catalyst gave the thiourea derivatives **6-9** in good yields (El-Kerdawy and El-Kousy, 1975). Thiourea derivatives **10-13** were obtained in high yields by the condensation of sulfonamides **4** with alkyl isothiocyanates **5** in refluxing dry acetone and in the presence of anhydrous potassium carbonate, see experimental section and Table I.

The infrared spectra of thiourea derivatives **6-13** displayed -NH- and -C=S stretching bands at 3400-3420 and 1390-1380 cm^{-1} , respectively, in addition to the characteristic sulphone bands at 1350-1300 and 1115-1100 cm^{-1} .

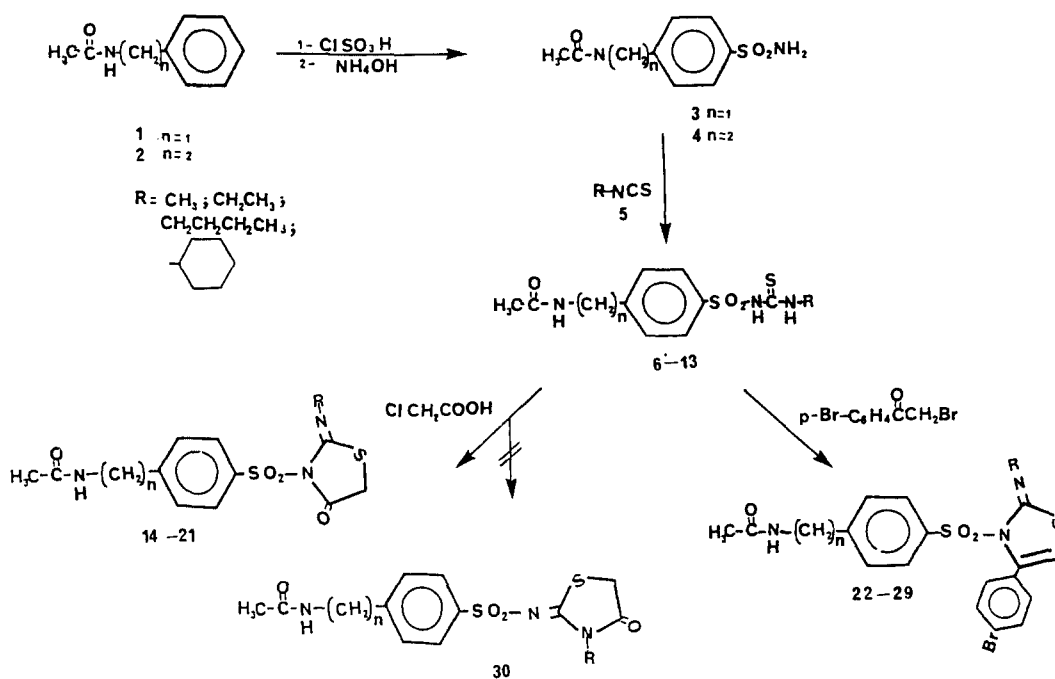
Condensation of thiourea derivatives **6-13** with α -chloroacetic acid in ethyl alcohol containing anhydrous sodium acetate afforded the target 3-(*p*-acetamidoalkyl-

benzenesulfonyl) thiazolidin-4-ones **14-21** in very good yields as shown in Table II. The possibility of formation of the alternative structure **30** is ruled out on the basis of TLC study and the hydrolytic reactions of compound **17** obtained by the condensation N-[(*p*-(2-acetamidoethyl)benzenesulfonyl)]-N'-cyclohexylthiourea **13** and chloroacetic acid. The TLC investigation indicated the formation of only one product, and the acid hydrolysis of compound **17**, resulted in the isolation of the cyclohexylamine as a major hydrolytic product, in addition to several other unidentified products. The structural assignment of these compounds was further established by the microanalytical as well as spectral data, see the experimental section.

On the other hand, reaction of thiourea derivatives **6-13** with *p*-bromophenacylbromide in refluxing isopropyl or ethyl alcohol gave the desired 3-(4-acetamidoalkylbenzenesulfonyl)thiazolines **23-29** in good yields as shown in Table III. Evidence for the formation of compounds **22-29** was supported from the IR spectra where the thioamido bands disappeared and that of the newly formed intense thiazoline C=N band appeared at 1650 cm^{-1} . Moreover, the NMR spectra displayed a singlet of one proton at 6.30 which is assigned to C₅-H thiazoline ring.

PHARMACOLOGICAL EVALUATION

The antidiabetic activity of the synthesized compounds in Tables II & III in addition to the intermediate thiourea, **13** is tested by determining the plasma glucose level using glucose peroxide technique (Boutwell, 1961). Unfortunately compound **13** showed a weak hypoglycemic activity while none of the other tested



Scheme 1.

compounds showed any significant hypoglycemic effect. The initial pharmacological screening of these compounds in rats revealed that some of these compounds possessed the ability to induce cardiac depressant response.

Thus, intravenous administration of the synthesized compounds in Table II & III in the doses of 7.5 and 15 $\mu\text{mol Kg}^{-1}$ into the anaesthetized rats produced dose-dependent decreases in the heart rate. Some of these compounds did not significantly affect the heart rate when tested at the dose level of 7.5 $\mu\text{mol Kg}^{-1}$, see Table IV. Compounds No. 23, 22 and 20 did not exert any significant negative chronotropic effects when tested at the dose of 15 $\mu\text{mol Kg}^{-1}$. The mean \pm s.e.m. percentage decreases in the heart rate induced by each compound are shown in Table IV. The most potent compounds seems to be No. 6, 9 and 7 and the duration of action of the tested compounds range from one to 6 min. The longest duration was shown by compounds 6, 9 and 9, respectively. The mean \pm s.e.m. durations for the different compounds are shown in Table IV.

From the above findings, potent cardiac depressant responses were observed with compounds having the thiazolidin-4-one moiety and large aliphatic or alicyclic side chain at position -3 with one methylene bridge between the acetamino group and the aromatic ring as seen for compounds 6 & 7. On the other hand, the replacement of thiazolidine-4-one with thiazoline ring with 4-bromophenyl substituents and large aliphatic or alicyclic side chain at the position-3 with two

Table IV. Effect of the synthesized compounds 14-29 on the basal heart rate and duration of action

Comp. No.	Percentage decrease in heart rate (H.R.) Mean \pm SEM (n=4)		Duration (min) after 15 $\mu\text{mol/Kg}^{-1}$
	7.5 $\mu\text{mol/Kg}^{-1}$	15 $\mu\text{mol/Kg}^{-1}$	
14	5.5 \pm 3.1	23.4 \pm 4.8	10 \pm 2.0
15	0	17.4 \pm 5.1	4 \pm 0.5
16	31.7 \pm 4.8	73.9 \pm 5.6	16 \pm 4.1
17	2.5 \pm 1.2	62.9 \pm 7.3	5 \pm 1.2
18	29.6 \pm 4.4	37.9 \pm 3.8	3 \pm 0.4
19	13.3 \pm 3.9	63.9 \pm 7.2	15 \pm 2.9
20	0	0	1 \pm 0.5
21	8.1 \pm 3.4	31.8 \pm 6.3	15 \pm 1.4
22	0	7.5 \pm 3.1	1.5 \pm 0.4
23	0	3.9 \pm 2.5	2 \pm 0.1
24	3.5 \pm 1.3	13.4 \pm 4.6	2 \pm 0.1
25	5.0 \pm 2.1	39.5 \pm 9.5	2 \pm 0.6
26	0	0	—
27	28.9 \pm 3.4	36.4 \pm 3.9	4 \pm 0.3
28	1.1 \pm 0.5	23.2 \pm 4.2	1 \pm 0.5
29	37.1 \pm 4.5	49.8 \pm 6.9	15 \pm 3.1

methylene bridge between the acetamino and aromatic ring resulted in an decrease in activity as seen for compounds 6, 8.

Also, it is clear that the substitution of thiazoline ring with 4-bromophenyl moiety resulted in a significant decrease in the duration of action.

REFERENCES CITED

Bott-Handford, R. and Heath, H., The effects of aldose

- reductase inhibitors on the metabolism of cultured monkey kidney epithelial cells. *Biochem. Pharmacol.* 30, 3065 (1981).
- Bott-Handford, R. and Heath, H., Identification of fructose as the retinopathic agent associated with the ingestion of sucrose-rich diets in the rat. *Metabolism*, 29, 1247 (1980).
- Boutwell, J. H. Jr., *Clin. Chem. Lab. Manual and Method*, Philadelphia Lea & Febiger, 1961, pp. 283.
- El-Kerdawy, M. M. and El-Kousy, S., Preparation of certain 1-[4-(acetamidomethyl) benzene sulfonyl urea] and thiourea derivatives. *Bull. Fac. Pharm. Cairo Univ.* 12, 248 (1975).
- Eltahir, K. E. H., Al-Obeid, H. A., Al-Rashood, K. A., Madani, A. E. and Ageel, A. M., The antiarrhythmic activity of N-alkyl-1,2-diphenylethanolamines. *Pharmac. Res.* 6, 252 (1989).
- Hoechst, F., Preparation of sulfonylureas. *Chem. Abstr.* 62, 6131h (1965).
- Peterson, U. J., Sarges, R., Aldinger, C. E. and MacDonald, D. P., A novel aldose reductase inhibitor that inhibits polyol pathway activity in diabetic and galactosemic rats. *Metabolism*, 28, 456 (1979).
- Sohda, T., Mizuno, K., Imamiya, E., Sugiyama, Y., Fujita, T. and Kawamatsu, Y., Studies on antidiabetic agents 11. Synthesis of 5-[4-(1-methyl cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione and its derivatives. *Chem. Pharm. Bull.* 30, 3580 (1982).