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Synthesis and antimicrobial activity of 2-aryl-3-(benzothiazol-2′-yl-thioacetamido)-5-H/methyl/carboxymethyl-4-thiazolidinones

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Abstract. A series of new 4-thiazolidinones have been synthesized from 2-[S-(benzothiazol-2′)]-mercapto acetic hydrazide (I) as starting material. The reaction mechanism has been examined. These biheterocycles and their precursors were screened for their antimicrobial activity against different strains and were also screened for antitubercular activity.

Keywords. 4-Thiazolidinone, 2-substituted benzal hydrazino carbonyl methylthio-benzothiazol; antitubercular activity; antimicrobial activity.

1. Introduction

4-Thiazolidinones play a vital role owing to their wide ranging biological activity and industrial importance (Chaubey and Singh 1970; Chaudhari *et al* 1976; Jadhav and Ingle 1978; Johnson 1978; Mukherjee and Singh 1978, Singh 1982). The chemistry of the 4-thiazolidinone ring system was reviewed in depth (Newkome and Nayak 1979). 4-Thiazolidinones are synthesized either by cyclisation of acyclic compounds or by interconversion among appropriately substituted thiazolidine derivatives.

It is reported that the benzothiazole moiety possesses significant biological activity (Ballio 1951; Dalal and Nayak 1975). We have therefore aimed at retaining the association of 4-thiazolidinone and the benzothiazole moiety to enhance their overall activity.

2-[S-(benzothiazolyl-2′)]-mercapto acetic hydrazide (I) (Sen *et al* 1990) has been condensed with different aromatic aldehydes to give 2-(substituted benzal hydrazino carbonyl methylthio) benzothiazoles as the key intermediates (II), which when condensed with thioglycolic, thiolactic and thiomalic acids result in the corresponding target cyclised products (III, IV, V) as given in scheme 1.

The compounds were screened for their antimicrobial activity by the agar growth food technique against *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Bacillus subtilis*, *Aspergillus niger*, *Saccharomyces cerevisiae*. The activity was compared with that displayed by known antibiotics. The compounds were also screened for their antitubercular activity against $H_{37}Rv$.

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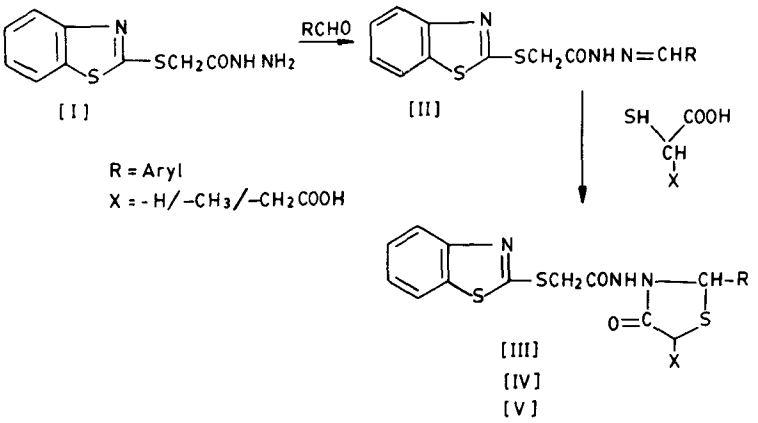

Scheme 1.

2. Experimental

Melting points were taken in open capillary tubes and are uncorrected. The compounds were routinely checked for their purity by TLC on silica gel G or alumina plates. Elemental analysis of the compounds was also carried out. The IR spectra were recorded on a Shimadzu DR-1, 435-IR spectrophotometer and PMR spectra on a Hitachi R-1200 (60 MHz) spectrometer with DMSO-d_6 as solvent and TMS as internal reference.

2.1 *2-(4-Methoxy benzal hydrazino carbonyl methylthio) benzothiazole (II-i)*

A mixture of I (2·39 g, 0·01 mol), 4-methoxy benzaldehyde (1·31 ml, 0·01 mol), and methanol (20 ml) was heated under reflux on a waterbath for 6 hours. Excess solvent was removed by distillation and the solid product was washed with 30% sodium bisulphite solution and crystallized from 1,4-dioxan-methanol (3:1) solvent. m.p. 154°C (79% yield).

IR: νcm^{-1}: 3300–3200 (–NH *str*); 1660 (–C=O amido); 1620 (–CH=N).
PMR: δ: 3·65 (*s*, 2H, SCH_2), 3·8 (*s*, 3H, $-OCH_3$), 5·9 (*s*, 1H (–N=CH)), 6·7–8 (*m*, 8H, –Ar–H).
Analysis calcd. for $C_{17}H_{15}N_3O_3S_2$: C, 57·14; H, 4·20; N, 11·76; Found: C, 57·10; H, 4·25; N, 11·78%.

Other compounds were similarly prepared and their analytical data are recorded in table 1.

2.2 *2-[4-Methoxyphenyl-3-(benzothiazol-2'-yl-thioacetamido)]-5-[H]-4-thiazolidinone (III-i)*

A mixture of the compound [II-i] (3·57 g; 0·01 mol) and thioglycolic acid (1·73 ml, 0·025 mol) was heated on an oilbath at 115–120°C for 12 hours. The reaction mixture was cooled and triturated with 10% sodium bicarbonate solution. The separated solid product was filtered and washed with excess of water and then crystallised from water. m.p. 216° (59% yield).

Table 1. Physical data and biological activity of 2-(substituted benzal hydrazino carbonyl methylthio)-benzothiazol (II).

Compound no.	R	m.p. (°C)	Zone of inhibition (mm)					
			Antibacterial activity				Antifungal activity	
			S. aureus	*S. pyogenes*	*E. coli*	*B. subtilis*	*A. niger*	*S. cerevisiae*
IIa	Phenyl	159	21	10	15	11	10	10
IIb	2-Chlorophenyl	138	18	10	10	15	10	16
IIc	4-Chlorophenyl	156	17	10	17	13	15	11
IId	2,6-Dichlorophenyl	201	13	15	13	11	17	11
IIe	3,4-Dichlorophenyl	209	15	13	14	11	13	11
IIf	2-Hydroxyphenyl	173	10	10	11	12	13	10
IIg	4-Hydroxyphenyl	118	20	19	10	12	18	15
IIh	2-Methoxyphenyl	161	20	19	15	19	18	18
IIi	4-Methoxyphenyl	154	18	10	18	17	15	17
IIj	3,4-Dimethoxyphenyl	190	19	10	19	13	15	13
IIk	4,Hydroxy-3-methoxyphenyl	124	19	12	10	12	11	10
III	2-Nitrophenyl	199	20	12	15	11	13	12
IIm	3-Nitrophenyl	195	15	13	20	11	18	11
IIn	4-Nitrophenyl	179	13	11	19	10	17	11
IIo	9-Anthryl	188	11	10	20	19	13	11

Yields vary state 70–80%; All compounds gave correct C, H & N analysis

IR *v*: 3300–3250 (–NH *str*); 1660 (C=O ring *str*); 1667 (–C=O amido); 1160 (C–N *vib*); 678 (C–S–C *str*) cm^{-1}.
PMR δ: 3·22 (*s*, 1H, –CH–N); 3·61 (*s*, 2H, –CO–CH_2–S); 3·66 (*s*, 2H, –SCH_2) 3·80 (*s*, 3H, –OCH_3); 6·82 – 8·14 (*m*, 8H, ar–H); 8·79 (*s*, 1H, –CONH).
Analysis calcd. for $C_{19}H_{17}N_3O_3S_3$; C, 52·90; H, 3·94; N, 9·74; Found: C, 52·94; H, 3·90; N, 9·70%.

Other compounds were similarly prepared and their analytical data are recorded in table 2.

2.3 *2-[4-Methoxyphenyl-3-(benzothiazol-2'-yl-thioacetamido]-5-methyl-4-thiazolidinone (IV-i)*

A mixture of the compound [II-i] (3·57 g, 0·01 mol) and thiolactic acid (2·21 ml, 0·025 mol) was heated on an oil bath maintaining the temperature at about 120°C for 9–10 hours. The reaction mixture was cooled and triturated with 20% sodium bicarbonate solution. The product so separated was filtered and washed with water and crystallised from DMF-water (3:1) solvent. m.p. 281°C (69% yield).

IR *v*: 3300–3255 (–NH *str*); 1666 (–C=O amido); 1662 (–C=O ring *str*); 1161 (–C–N *vib*); 681 (C–S–C *str*). PMR δ: 1·4 (*d*, 3H, –CH–CH_3); 3·25 (*s*, 1H, –CH–N); 3·59 (*q*, 1H, CH–CH_3); 3·64 (*s*, 2H, –S–CH_2); 3·83 (*s*, 3H, –OCH_3); 6·81–8·10 (*m*, 8H, Ar–H); 8·82 (*s*, 1H, –CONH).
Analysis calcd. for $C_{20}H_{19}N_3O_3S_3$: C, 53·93; H, 4·26; N, 9·43. Found: C, 53·90; H, 4·25; N, 9·40%.

Other compounds were similarly prepared and their analytical data are recorded in table 2.

2.4 *2-[4-Methoxyphenyl-3-(benzothiazol-2'-yl-thioacetamido)]-5-carboxymethyl-4-thiazolidinone (V-i)*

A mixture of [II–i] (3·57 g, 0·01 mol) and thiomalic acid (3·75 g, 0·025 mol) was condensed in the presence of anhydrous zinc chloride (1·0 g) on an oil bath at 160°C for 2 hours, after which the temperature was raised to 180°C for 1 hour. The product so obtained was dissolved in sodium bicarbonate solution (4N) and filtered. The filtrate was reprecipitated with dilute hydrochloric acid and crystallised from DMF: H_2O (3:1) solvent. m.p. > 360°, (61% yield).

IR *v*: 3300–3000 (–OH *str*, *br*–CH_2COOH); 1710 (–C=O cyclic); 1665 (–C=O amido); 680 (C–S–C *str*) cm^{-1}.
PMR δ: 3·2 (*s*, 1H, –CH–N); 3·6 (*s*, 2H, –SCH_2); 3·7 (*d*, 2H, –CH–CH_2COOH); 3·75 (*s*, 3H, –OCH_3); 4·52 (*t*, 1H, S–CH–CH_2COOH); 6·8 – 8·12 (*m*, 8H, Ar–H); 8·8 (*s*, 1H, –CONH).
Analysis calcd. for: $C_{21}H_{19}N_3O_5S_3$:C, 51·53; H, 3·88; N, 8·58; Found: C, 51·51; H, 3·86; N, 8·54%.

Other compounds were similarly prepared and their analytical data are recorded in table 2.

Table 2. Physical data and biological activity of 2-aryl-3-(benzothiazol-2'-yl-thioacetamido)-5H/methyl/carboxymethyl-4-thiazolidinones (III, IV, V).

Compound no.	R	X	m.p. (°C)	Zone of inhibition (mm)					
				Antibacterial activity				Antifungal activity	
				S. aureus	*S. pyogenes*	*E. coli*	*B. subtilis*	*A. niger*	*S. cerevisiae*
IIIa	Phenyl	–H	199	16	17	15	15	10	15
IIIb	2-Chlorophenyl	–H	215	15	19	16	10	10	15
IIIc	4-Chlorophenyl	–H	183	18	10	17	10	10	10
IIId	2,6-Dichlorophenyl	–H	209	20	18	11	10	10	10
IIIe	3,4-Dichlorophenyl	–H	271	11	17	13	12	12	10
IIIf	2-Hydroxyphenyl	–H	199	11	18	15	18	13	12
IIIg	4-Hydroxyphenyl	–H	248	12	18	18	18	15	13
IIIh	2-Methoxyphenyl	–H	299	15	11	20	17	17	11
IIIi	4-Methoxyphenyl	–H	216	17	19	15	19	11	10
IIIj	3,4-Dimethoxyphenyl	–H	232	13	10	17	11	11	13
IIIk	4-Hydroxy-3-methoxyphenyl	–H	141	12	12	21	11	11	12
IIIl	2-Nitrophenyl	–H	201	12	13	21	12	11	12
IIIm	3-Nitrophenyl	–H	241	11	11	18	11	15	16
IIIn	4-Nitrophenyl	–H	281	17	13	17	13	18	18
IIIo	9-Anthryl	–H	190	19	14	11	10	12	17
IVa	Phenyl	$-CH_3$	265	11	16	12	15	13	13
IVb	2-Chlorophenyl	$-CH_3$	255	10	18	13	19	19	15
IVc	4-Chlorophenyl	$-CH_3$	217	15	20	14	20	11	19
IVd	2,6-Dichlorophenyl	$-CH_3$	239	17	19	10	11	15	11
IVe	3,4-Dichlorophenyl	$-CH_3$	248	20	11	16	11	10	11
IVf	2-Hydroxyphenyl	$-CH_3$	291–93	18	11	11	11	13	11
IVg	4-Hydroxyphenyl	$-CH_3$	271	12	13	10	12	13	10
IVh	2-Methoxyphenyl	$-CH_3$	233	12	10	10	13	10	10
IVi	4-Methoxyphenyl	$-CH_3$	281	11	12	10	10	10	10
IVj	3,4-Dimethoxyphenyl	$-CH_3$	292	17	11	12	15	12	12
IVk	4-Hydroxy-3-methoxyphenyl	$-CH_3$	283–85	13	10	12	12	12	12
IVl	2-Nitrophenyl	$-CH_3$	207	12	10	14	12	13	13

(Continued)

Table 2. (*Continued*)

Compound no.	R	X	m.p. (°C)	Zone of inhibition (mm)					
				Antibacterial activity				Antifungal activity	
				S. aureus	*S. pyogenes*	*E. coli*	*B. subtilis*	*A. niger*	*S. cerevisiae*
IVm	3-Nitrophenyl	$-CH_3$	269	12	12	13	15	11	11
IVn	4-Nitrophenyl	$-CH_3$	299	15	10	11	13	10	14
IVo	9-Anthryl	$-CH_3$	202	10	13	11	11	12	13
Va	Phenyl	$-CH_2COOH$	300(d)	18	10	18	20	18	10
Vb	2-Chlorophenyl	$-CH_2COOH$	300	17	10	17	11	17	10
Vc	4-Chlorophenyl	$-CH_2COOH$	> 360	10	10	13	11	10	15
Vd	2,6-Dichlorophenyl	$-CH_2COOH$	> 360	10	15	10	11	13	13
Ve	3,4-Dichlorophenyl	$-CH_2COOH$	271(d)	12	18	14	13	11	11
Vf	2-Hydroxyphenyl	$-CH_2COOH$	291	15	20	11	14	11	10
Vg	4-Hydroxyphenyl	$-CH_2COOH$	312	20	11	11	10	11	10
Vh	2-Methoxyphenyl	$-CH_2COOH$	291(d)	15	11	14	15	15	15
Vi	4-Methoxyphenyl	$-CH_2COOH$	> 360	15	11	13	13	10	12
Vj	3,4-Dimethoxyphenyl	$-CH_2COOH$	209	21	15	15	11	10	12
Vk	2-Hydroxy-3-methoxyphenyl	$-CH_2COOH$	301	13	13	16	16	12	13
Vl	2-Nitrophenyl	$-CH_2COOH$	298	13	10	17	10	15	11
Vm	3-Nitrophenyl	$-CH_2COOH$	281	11	10	10	17	18	11
Vn	4-Nitrophenyl	$-CH_2COOH$	> 360	11	10	10	13	17	10
Vo	9-Anthryl	$-CH_2COOH$	323	12	15	15	15	17	17

Yields vary from 50–80%; All compounds gave correct C, H & N analysis.

3. Results and discussion

The interaction of I with different aldehydes for 6 h in boiling methanol resulted in the loss of H_2O forming azomethines (II), which when condensed with thioglycolic, thiolactic & thiomalic acids afforded the corresponding III, IV & V. The reaction of thioglycolic acid proceeds by the attack of the acid on the –C=N– group with $HSCH_2COOH$ adding to the carbon atom followed by the capture of a proton by nitrogen and subsequent cyclisation. The same reaction mechanism is involved in the case of thiolactic and thiomalic acids.

3.1 *Antimicrobial activity*

Synthesized compounds of type II, III, IV & V were screened for their antibacterial activity against *S. aureus*, *S. pyogenes*, *E. coli*, *B. subtilis* and antifungal activity against *A. niger* and *S. cerevisiae* by the cup-plate method (Barry 1976) at a concentration of 50 ug using DMF as solvent. After 24 hours of incubation at 37°C, the zone of inhibition was measured in millimetres. The activity was compared with that of standard drugs at the same concentration and in the solvent. The results are shown in tables 1, 2 & 3.

From the screening results it is evident that on the whole the compounds exhibit moderate to good antibacterial activity but less antifungal activity as compared to standard drugs. In particular the compounds of type-(II) a, g, h & l showed good activity against *S. aureus* and (II) m, o showed good activity against *E. coli*; the compounds of type-(III) d, & (III) h, k, l exhibited good activity against *S. aureus* & *E. coli* respectively; the compounds of type-(IV) e, & (IV) c showed good activity against *S. aureus*, *S. pyogenes* & *B. subtilis* respectively. The compounds of type (IV) g, j & (V) f showed good activity against *S. aureus* & *S. pyogenes* respectively & (V) a showed good activity against *B. subtilis*. It was noticed that all the compounds are inactive against fungi as compared to standard Griseofulvin.

3.2 *Antitubercular activity*

Synthesized compounds of types II, III, IV & V have been tested against the standard strain of *Mycobacterium tuberculosis* $H_{37}Rv$. The compounds were dissolved in absolute ethanol and added to Lowestein Jensen's medium so that the final concentration of the compound was 100 μg/ml of the medium. The compound was

Table 3. Known antibiotics as standard drugs.

No.	Antibiotics drugs	Zone of inhibition (mm)					
		Antibacterial activity			Antifungal activity		
		S. aureus	*S. pyogenes*	*E. coli*	*B. subtilis*	*A. niger*	*S. cerevisiae*
1.	Ampicillin	22	26	24	27	—	—
2.	Chloramphanical	28	22	21	22	—	—
3.	Norfloxacin	21	27	25	27	—	—
4.	Gresiofulvin	—	—	—	—	24	23

added after inspissation and the chemical-containing medium was distributed in 7 ml amounts in screw-capped tubes. All the tubes were inspissated in slanting positions at 80°C for 45 minutes, the medium was inoculated according to the recommendation of WHO (1970). The inoculum for the susceptibility test was prepared by adding approximately 2 mg of growth from the primary culture on a loop to 5 ml of sterile distilled water in 7 ml screw-capped tubes together with six 3-mm glass leads. The tube was shaken mechanically for 1 minute and a full 3 ml loopful of the suspension inoculated on each slope. Duplicate stops from each compound were inoculated. A drug-free control slope was set up with each test and the tubes incubated at 37°C.

It was noteworthy that some of the compounds of type II, III, IV & V were active against the $H_{37}Rv$ strains. The activity was compared with standard INH. All the derivatives showed low activities as compared to standard INH.

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