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Short Communication

Synthesis of Some 4-Thiazolidinone Derivatives as Antitubercular Agents

H.H. Parekh,* K.A. Parikh, and A.R. Parikh

Department of Chemistry, Saurashtra University, Rajkot 360 005, Gujarat, India

Abstract

Substituted Schiff's bases **2a-o** prepared by the treatment of 2-amino-4-(α-methoxyiminocarbomethoxymethyl)-thiazole **1** with different aromatic aldehydes, on cyclocondensation with mercaptoaceticacid and mercaptopropionicacid in dry benzene furnished desired thiazolidinones of type **3a-o** and **4a-j**, respectively. The structure of the compounds have been assigned on the basis of elemental analyses and spectral data. The products were evaluated for their *in vitro* growth inhibiting activity against several microbes. Some of the compounds showed significant antitubercular and antifungal activity.

Keywords: Thiazoles; Thiazolidinones; Antitubercular activity; Antimicrobial activity

Introduction

The growing potent literature of recent years demonstrates that the thiazole derivatives exhibit better pharmacological properties such as antitubercular [1], anti-inflammatory [2], pesticidal [3], anticonvulsant [4], antimicrobial [5] and many others. Further more significant biological properties are associated with thiazolidinone derivatives like anticonvulsant [6], anthelmintics [7], antidiabetic [8] *etc*. Led by these considerations, it appeared of interest to synthesise some novel-4-thiazolidinone derivatives bearing 2-amino thiazole moiety.

The starting material 2-amino-4-(α-methoxyimino-carbmethoxymethyl)-thiazole **1** with different aromatic aldehydes yielded 2-benzal-amino-4-(α-methoxyimino-carbomethoxymethyl) thiazoles of type **2a-o**. The preparation of 4-thiazolidinones of type **3a-o** and **4a-j** has been undertaken by the heterocyclisation of Schiff's bases of type **2** with mercaptoaceticacid and mercapto-propionicacid, respectively (Scheme 1).

The constitution of all the above products have been supported by elemental analyses and spectral studies like IR, NMR and mass spectral data. Bioogical profile of all the synthesised products have been screened *in vitro* for their antimicrobial activity against different strain of bacteria and fungi and antitubercular activity against *Mycobacterium tuberculosis H37 Rv*.

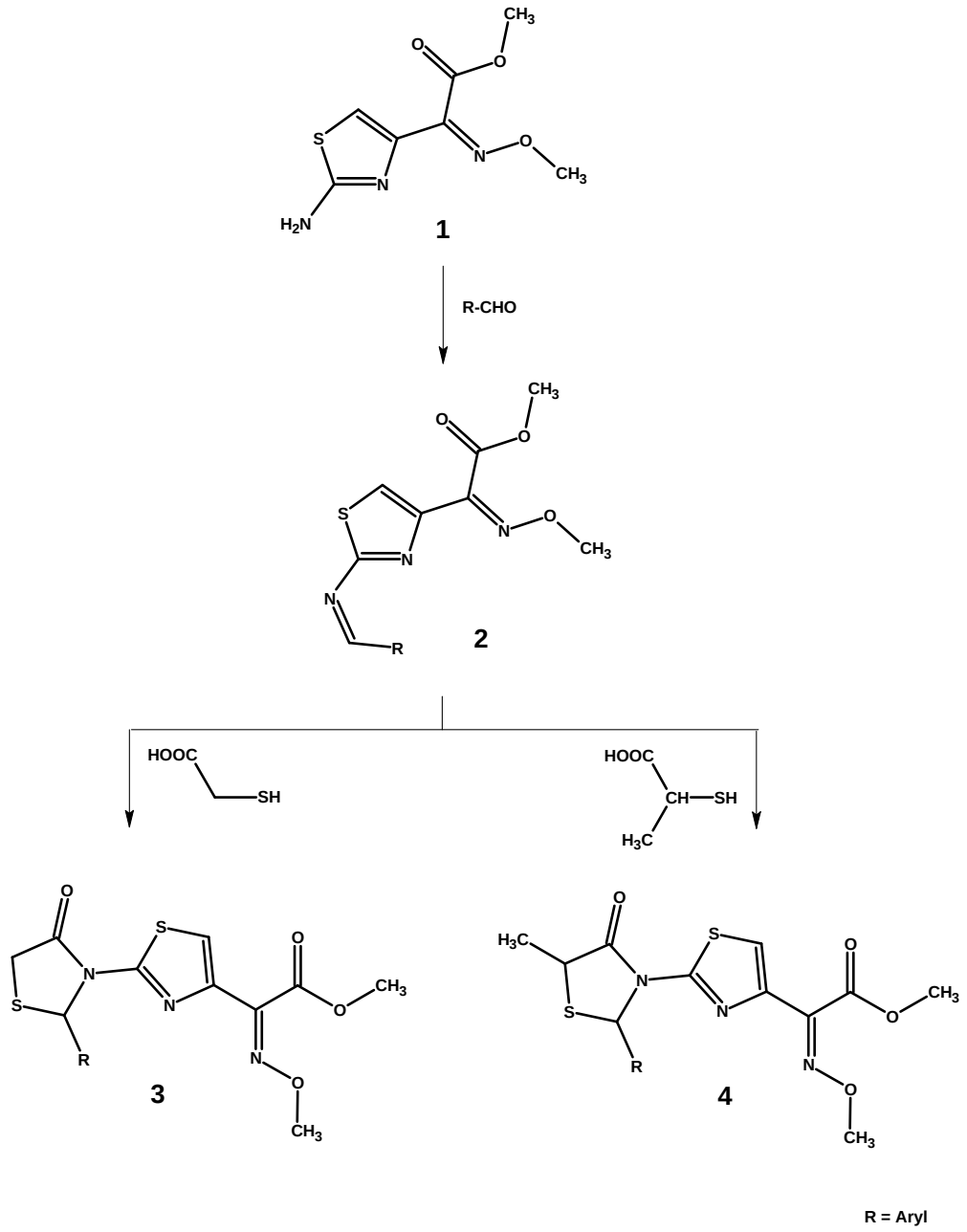
Experimental

All the melting points are uncorrected. Infrared Spectra (KBr) were recorded on a Nicolet-Megna-IR-550 series II and ^{1}H-NMR spectra on Brucker-spectrometer NMR-300 MHz using TMS as an internal standard.

Preparation of 2-Amino-4-(α-methoxyiminocarbomethoxymethyl)-thiazoles 1

To a warm (38°C) solution of methyl-2-methoxy-imino-3-oxo-butarate (960 g) in chloroform (3.6 L)

* *E-mail: hhparekh@yahoo.com*



Scheme 1

was added dropwise with stirring the solution of Br_2 (910 g) in chloroform (1.1 L) below 43°C for 3 h. It was stirred at room temperature for 1 h and the mixture was poured into ice water (4 L). The orange layer was separated and washed with saturated solution of sodium bicarbonate (2 L) water (2 L) and dried over sodium sulphate. Removal of chloroform yielded crude product methyl-4-bromo-2-methoxyiminoacetate. NMR: δ: 3.82 (3H, S, N-OCH_3), 4.27 (2H, S, Br-CH_2).

The crude ester was dissolved in THF (8.4 L) and to this was added under ice-cooling, solution of sodium acetate (2.45 kg) and thiourea (912 g) in water (6 L) in one portion. After stirring room temperature for 10 h, the mixture was extracted with ethyl acetate (6 L). Then the ethyl acetate layer was washed brine, aqueous sodium bicarbonate (5 L) and water (10 L) and dried over sodium sulphate.

The residue obtained by evaporation of ethyl acetate

was crystallized for diethyl ether. To sieve yellowish crystals of 2-amino-4-(α-methoxyiminocarbomethoxymethyl)-thiazole. m.p. 169-170°C. Anal. Calcd. For $C_7H_9O_3N_3S$ requires: C 39.06, H 4.21, N 19.52; Found: C 39.78, H 4.15, N 19.33%. NMR ($CDCl_3$): δ: 3.84 (3H, s, CH_3), 4.02 (3H, S, OCH_3), 5.74 (2H, br, NH_2), 6.74 (1H, S, thiazole).

Preparation of 2-Benzal amino-4-(α-methoxyiminocarbomethoxymethyl)-thiazoles 2a-o

A mixture of **I** (0.01 mol) and α-methoxybenzaldehyde (0.01 mol) was refluxed in dimethylformamide for 8 h. The product was isolated, crystallised from methanol, **2k** yield 65%, m.p. 193°C; Calculated for $C_{15}H_{15}O_4N_3S$ requires: C 54.05, H 4.50, N 12.61; Found: C 53.95, H 4.40, N 12.50%. IR υmax (KBr): 1742 (C=O str.), 1620 (C=N str.), 1591 (C=C str.), 1271 (C-O-C str. (asym.), 1037 (C-O-C str. (sym.), 688 (C-S-C str.) cm^{-1}. ^{1}H-NMR δ ppm ($CDCl_3$): 3.73 (S, 3H, -N-OCH_3), 3.84 (S, 3H, $COOCH_3$), 4.00 (S, 3H, Ar-OCH_3), 5.97 (S, 1H, N=CH), 6.92 (d, 2H, Ar-H), 7.08 (d, 2H, Ar-H).

Other members of **2** were prepared. The physical constants are given in Table 1.

Preparation of 2-Aryl-3-(4'-α-methoxyiminocarbomethoxymethylthiazol-2'-yl)-5-H-4-thiazolidinones 3a-o

A mixture of 2-(3'-nitrophenyl)-benzal amino-4-(α-methoxyiminocarbmethoxymethyl)-thiazole (0.01 mol) and mercaptoaceticacid (0.01 mol) in dry benzene (20 ml) was refluxed for 12 h. The reaction mixture was cooled and triturated with 10% sodium bicarbonate solution. The product was crystallised from methanol. **3n**; yield 57%, m.p. 178°C; Calculated for $C_{16}H_{14}O_6N_4S_2$ requires: C 45.49; H 3.31; N 13.27; Found: C 45.40, H 3.30, N 13.20%. IR υmax KBr cm^{-1}: 1742 (C=O str.), 1700 (C=O str. of thiazolidinone moiety), 1610 (C=N str.), 1352 (-NO_2 str.), 1037 (C-O-C str. (sym.), 709 (C-S str.). ^{1}H-NMR δ ppm ($CDCl_3$): 3.78 (s, 3H, N-OCH_3), 3.83 (s, 3H, $COOCH_3$), 3.87 (s, 3H, Ar-OCH_3), 3.89 (s, 2H, -CH_2-CO), 6.53-7.4 (m, 5H, Ar-H).

Other members of **3** were prepared. The physical constants are given in Table 1.

Preparation of 2-Aryl-3-(4'-α-methoxyiminocarbmethoxymethylthiazol-2'-yl)-5-methyl-4-thiazolidinones 4a-j

A mixture of 2-(3'-nitrophenyl)-benzal amino-4-(α-methoxyiminocarbomethoxymethyl)-thiazole (0.01 mol) and mercaptopropionicacid (0.01 mol) in dry benzene (20 ml) was refluxed for 12 h. The reaction mixture was cooled and triturated with 10% sodium bicarbonate solution. The product was crystallised from methanol. **4j**; Yield 65%, m.p. 123°C, calcd. for $C_{17}H_{16}O_6N_4S_2$ requires: C 46.78, H 3.67, N 12.84, Found: C 46.70, H 3.60, N 12.80%. IR υmax KBr cm^{-1}: 1743 (C=O str.), 1700 (C=O str. of thiazolidinone moiety), 1620 (C=N str.), 1352 (-NO_2 str.), 1037 (C-O-C str. (sym.), 710 (C-S-C str.). ^{1}H-NMR δ ppm ($CDCl_3$): 1.61 (d, 3H, -CH-CH_3), 3.79 (S, 3H, -N-OCH_3), 3.84 (S, 3H, $COOCH_3$), 4.1 (q, 1H, -CH-CH_3), 5.16 (S, 1H, -CH-Ar), 6.30-7.26 (m, 5H, -Ar-H).

Similarly other members of **4** were prepared. The physical constants are given in Table 1.

In vitro Evaluation of Pharmacological Studies

The antimicrobial screening of the compounds synthesised was conducted using cup-plate agar diffusion technique [9] at a concentration of 50 µg by measuring zone of inhibition in mm. All the compounds were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains such as *B. megaterium*, *B. subtillis*, *E. coli* and fungal strain such as *A. niger*. Ampicillin, chloramphenicol, norfloxacin and griseofulvin were used as standard for comparing the activity.

The antitubercular evaluation of the compounds was carried out at "Tuberculosis Antimicrobial Acquisition and Coordinating Facility" (TAACF) USA. Primary screening of the compounds for antitubercular activity have been conducted at 12.5 µg/ml against ***Mycobacterium tuberculosis H37 Rv***, in BACTEC 12B medium using BACTEC 460 radiometric system. Antitubercular activity data were compared with standard drug Rifampin at 0.125 µg/ml concentration which showed 97% inhibition.

Results and Discussion

All the compounds reported in Table 2 were tested *in vitro* for their antimicrobial and antifungal activity against various microorganisms under identical conditions, the standard antibiotics showed zones of inhibition like ampicillin 16-24 mm, chloramphenicol 20-25 mm, norfloxacin 15-27 mm against bacterial strains and griseofulvin showed zone of inhibition of 20 mm against *A. niger*.

It can be concluded from Table 2 that the compounds **2g, 2k, 2o, 3f, 3k, 3l, 4f, 4g** were highly active against *B. megaterium*. The compounds **2e, 2f, 2n, 3f, 3g, 3j,**

Table 1. Physical constants of the compounds **2a-o**, **3a-o**, and **4a-j**

Compound	R	Molecular formula	M.P. (°C)	Yield (%)	% of N	
					Calculated	Found
2a	C_6H_5-	$C_{14}H_{13}O_3N_3S$	128	60	12.86	12.80
2b	2-Cl-C_6H_4-	$C_{14}H_{12}O_3N_3SCl$	155	63	12.44	12.38
2c	3-Cl-C_6H_4-	$C_{14}H_{12}O_3N_3SCl$	132	65	12.44	12.35
2d	4-Cl-C_6H_4-	$C_{14}H_{12}O_3N_3SCl$	160	59	12.44	12.34
2e	2,4-(Cl_2)-C_6H_3-	$C_{14}H_{11}O_3N_3SCl_2$	180	64	11.29	11.20
2f	2,6-(Cl_2)-C_6H_3-	$C_{14}H_{11}O_3N_3SCl_2$	146	58	11.29	11.29
2g	3,4-(OCH_3)$_2$-C_6H_3-	$C_{16}H_{17}O_5N_3S$	105	67	11.57	11.48
2h	C_4H_3O-	$C_{12}H_{11}O_4N_3S$	165	66	14.33	14.26
2i	3-OCH_3,4-OH-C_6H_3-	$C_{15}H_{15}O_5N_3S$	138	54	12.03	11.92
2j	3-OCH_3-C_6H_4-	$C_{15}H_{15}O_4N_3S$	108	52	12.61	12.51
2k	4-OCH_3-C_6H_4-	$C_{15}H_{15}O_4N_3S$	193	65	12.61	12.50
2l	4-S-CH_3-C_6H_4-	$C_{15}H_{15}O_3N_3S_2$	156	69	12.03	11.91
2m	2-NO_2-C_6H_4-	$C_{14}H_{12}O_5N_4S$	117	57	16.09	15.96
2n	3-NO_2-C_6H_4-	$C_{14}H_{12}O_5N_4S$	110	61	16.09	15.98
2o	C_4H_3S-	$C_{12}H_{11}O_3N_3S_2$	95	62	13.56	12.48
3a	C_6H_5-	$C_{16}H_{15}O_4N_3S_2$	118	68	11.14	11.12
3b	2-Cl-C_6H_4-	$C_{16}H_{14}O_4N_3S_2Cl$	174	65	10.20	10.15
3c	3-Cl-C_6H_4-	$C_{16}H_{14}O_4N_3S_2Cl$	182	67	10.20	10.18
3d	4-Cl-C_6H_4-	$C_{16}H_{14}O_4N_3S_2Cl$	208	61	10.20	10.17
3e	2,4-(Cl_2)-C_6H_3-	$C_{16}H_{13}O_4N_3S_2Cl_2$	228	60	9.41	9.39
3f	2,6-(Cl_2)-C_6H_3-	$C_{16}13O_4N_3S_2Cl_2$	174	59	9.41	9.40
3g	3,4-(OCH_3)$_2$-C_6H_3-	$C_{18}H_{19}O_6N_3S_2$	172	55	9.61	9.60
3h	C_4H_3O-	$C_{14}H_{13}O_5N_3S_2$	180	53	11.44	11.40
3i	3-OCH_3,4-OH-C_6H_3-	$C_{17}H_{17}O_6N_3S_2$	162	64	9.92	9.00
3j	3-OCH_3-C_6H_4-	$C_{17}H_{17}O_5N_3S_2$	97	62	10.31	10.30
3k	4-OCH_3-C_6H_4-	$C_{17}H_{17}O_5N_3S_2$	135	68	10.31	10.25
3l	4-S-CH_3-C_6H_4-	$C_{17}H_{17}O_4N_3S_3$	122	63	9.92	9.85
3m	2-NO_2-C_6H_4-	$C_{16}H_{14}O_6N_4S_2$	165	58	13.27	13.20
3n	3-NO_2-C_6H_4-	$C_{16}H_{14}O_6N_4S_2$	178	57	13.27	13.20
3o	C_4H_3S-	$C_{14}H_{13}O_4N_3S_3$	190	69	10.96	10.90
4a	C_6H_5-	$C_{17}H_{17}O_4N_3S_2$	109	70	10.74	10.70
4b	2-Cl-C_6H_4-	$C_{17}H_{16}O_4N_3S_2Cl$	150	65	9.87	9.75
4c	3-Cl-C_6H_4-	$C_{17}H_{16}O_4N_3S_3Cl$	172	61	9.87	9.78
4d	2,4-(Cl_2)-C_6H_3-	$C_{17}H_{15}O_4N_3S_2Cl_2$	185	60	9.13	9.00
4e	3,4-(OCH_3)$_2$-C_6H_3-	$C_{19}H_{21}O_6N_3S_2$	158	66	9.31	9.25
4f	3-OCH_3,4-OH-C_6H_3-	$18H_{19}O_6N_3S_2$	176	64	9.61	9.55
4g	3-OCH_3-C_6H_4-	$C_{18}H_{19}O_5N_3S_2$	139	61	9.97	9.90
4h	4-OCH_3-C_6H_4-	$C_{18}H_{19}O_5N_3S_2$	193	68	9.97	9.85
4i	4-S-CH_3-C_6H_4-	$C_{18}H_{19}O_4N_3S_2$	180	69	9.61	9.54
4j	3-NO_2-C_6H_4-	$C_{17}H_{16}O_6N_4S_2$	123	65	12.84	12.80

Table 2. Antimicrobial screening results of compounds **2a-o**, **3a-o**, and **4a-j**

Compound	R	Antimicrobial activity zone of inhibition in m.m.			Antifungal activity
		E. coli	*B. subtillis*	*B. megaterium*	*A. niger*
2a	C_6H_5-	19	17	19	15
2b	2-Cl-C_6H_4-	21	14	17	15
2c	3-Cl-C_6H_4-	18	18	15	18
2d	4-Cl-C_6H_4-	22	16	19	17
2e	2,4-(Cl_2)-C_6H_3-	20	19	14	20
2f	2,6-(Cl_2)-C_6H_3-	17	20	18	16
2g	3,4-$(OCH_3)_2$-C_6H_3-	19	17	20	19
2h	C_4H_3O-	21	15	18	14
2i	3-OCH_3,4-OH-C_6H_3-	18	14	16	17
2j	3-OCH_3-C_6H_4-	16	18	17	21
2k	4-OCH_3-C_6H_4-	19	17	21	15
2l	4-S-CH_3-C_6H_4-	20	15	11	18
2m	2-NO_2-C_6H_4-	22	15	18	19
2n	3-NO_2-C_6H_4-	18	19	16	21
2o	C_4H_3S-	16	17	19	20
3a	C_6H_5-	19	17	14	19
3b	2-Cl-C_6H_4-	18	16	15	18
3c	3-Cl-C_6H_4-	15	17	14	15
3d	4-Cl-C_6H_4-	17	19	16	21
3e	2,4-(Cl_2)-C_6H_3-	18	17	13	15
3f	2,6-(Cl_2)-C_6H_3-	21	22	19	17
3g	3,4-$(OCH_3)_2$-C_6H_3-	24	24	18	16
3h	C_4H_3O-	18	19	15	15
3i	3-OCH_3,4-OH-C_6H_3-	17	18	15	16
3j	3-OCH_3-C_6H_4-	23	20	16	17
3k	4-OCH_3-C_6H_4-	23	21	18	19
3l	4-S-CH_3-C_6H_4-	22	20	18	18
3m	2-NO_2-C_6H_4-	19	21	17	21
3n	3-NO_2-C_6H_4-	16	17	14	16
3o	C_4H_3S-	15	17	16	16
4a	C_6H_5-	18	20	15	19
4b	2-Cl-C_6H_4-	18	18	17	18
4c	3-Cl-C_6H_4-	20	19	14	21
4d	2,4-(Cl_2)-C_6H_3-	15	14	17	14
4e	3,4-$(OCH_3)_2$-C_6H_3-	21	16	14	16
4f	3-OCH_3,4-OH-C_6H_3-	19	20	15	18
4g	3-OCH_3-C_6H_4-	18	19	14	19
4h	4-OCH_3-C_6H_4-	23	21	18	17
4i	4-S-CH_3-C_6H_4-	19	18	17	16
4j	3-NO_2-C_6H_4-	21	23	16	14

3k, 3l, 4a, 4d, 4f, 4h showed significant activity against *B. subtillis*. While the compounds **2b, 2d, 2e, 2h, 2l, 2m, 3f, 3g, 3j, 3k, 3l, 4b, 4c, 4h** and **2e, j, 2n, 3a, 3d, 3k, 3m, 4a, 4b, 4e** exhibited significant activity against *E. coli* and *A. niger*, respectively. Compounds **2l, 2f** & **2c** showed 80-90% inhibition against ***Mycobacterium tuberculosis H37 RV*** while compound **2i, 2o, 2m, 2n, 2b** exhibited moderate activity but thiazolidinones were found to be poorly active.

The compounds **2e, 2h, 2o, 3c, 3j, 4c, 4g** and compound **3a** have been selected for their agrochemical and pharmaceutical screening by Du Pont Agriculture products U.S.A. and MERCK Pharmaceuticals U.S.A., respectively.

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