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Note

Synthesis and antitubercular activity of novel thiazolidinone derivatives

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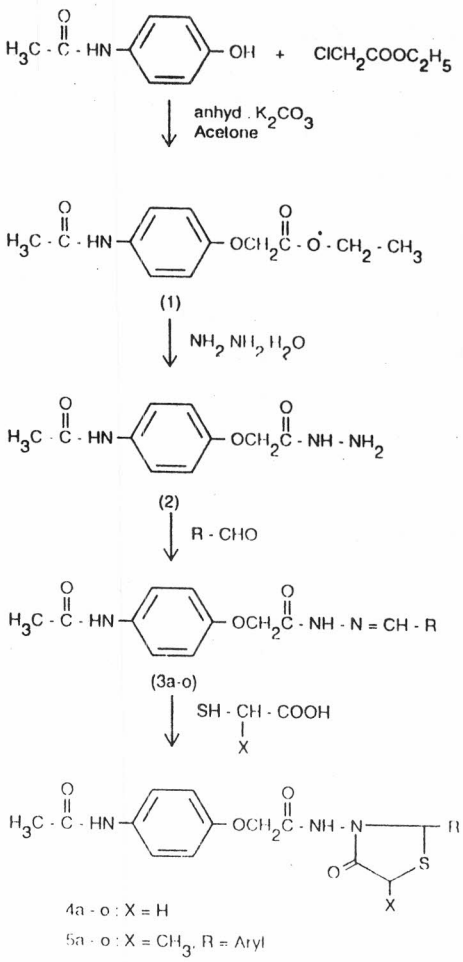
4-Thiazolidinones **4a-o, 5a-o** have been synthesised by the cyclocondensation of different schiff's bases **3a-o** with thioglycolic acid and thiolactic acid respectively. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis H37 Rv.*

4-Thiazolidinones are endowed a variety of biological activities[1-5]. Further, paracetamol derivatives have been found to exhibit the therapeutic activity[6-8]. In order to explore the activities associated with this nucleus, we report herein the synthesis and antitubercular activity of the derivatives of thiazolidinone.

The reaction of ρ-hydroxy acetanilide with ethyl chloro acetate in the presence of dry acetone and anhyd. K_2CO_3 gave the desired ethyl ρ-acetamidophenoxy- acetate[9] **1** which was converted to ρ-acetamidophenoxy acetyl hydrazide[9] **2** by treatment with a slight excess of hydrazine hydrate in absolute ethanol under reflux. The hydrazide **2** was condensed with different araldehydes to obtain corresponding N^1-substituted benzal, N^2-ρ-acetamidophenoxy acyl hydrazines **3a-o** (schiff's bases). These different schiff's bases were cyclocondensed with thioglycolic acid and thiolactic acid to afford respective 2-aryl-3-ρ-acetamidophenoxy acetamido-5-H-4-thiazolidinones **4a-o** and 2-aryl-3-ρ-acetamidophenoxy acetamido-5-methyl-4-thiazolidinones **5a-o** (Scheme I).

The structure of the compounds synthesised were assigned on the basis of elemental analyses, IR, 1H NMR and mass spectral data. The compounds were evaluated for antitubercular activity towards a strain of *Mycobacterium tuberculosis H37 Rv.*



Scheme I

Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating 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 the BACTEC 460 radiometric system.

All the compounds are reported in Table I for their antitubercular activity data. It can be concluded from Table-I that compounds **3a-o** and **5a-o** exhibited various degree of activity (0 to 35%) whereas compounds **4a-o** were inactive.

Table I— Physical constants and antitubercular activity data of compounds **3a-o**, **4a-o** and **5a-o**.

Compd	R	Mol. formula	m.p.(°C)	Yield(%)	N (%) Found	N (%) Calcd.	% of inhibition*
3a	$-C_6H_5-$	$C_{17}H_{17}N_3O_3$	212	52	13.58	13.50	17
3b	$2-Cl-C_6H_4-$	$C_{17}H_{16}N_3O_3Cl$	205	54	12.24	12.15	35
3c	$4-Cl-C_6H_4-$	$C_{17}H_{16}N_3O_3Cl$	200	58	12.21	12.15	29
3d	$2,4-Cl_2-C_6H_3-$	$C_{17}H_{15}N_3O_3Cl_2$	230	60	11.10	11.05	-
3e	$3,4-(OCH_3)_2-C_6H_3-$	$C_{19}H_{21}N_3O_5$	205	57	11.25	11.32	-
3f	$4-N,N-(CH_3)_2-C_6H_4-$	$C_{19}H_{22}N_4O_3$	220	62	18.75	18.81	20
3g	C_4H_3O-	$C_{15}H_{15}N_3O_4$	195	63	13.90	13.95	15
3h	$2-OH-C_6H_4-$	$C_{17}H_{17}N_3O_4$	228	65	12.80	12.84	-
3i	$4-OH-C_6H_4-$	$C_{17}H_{17}N_3O_4$	155	61	12.78	12.84	-
3j	$4-OCH_3-C_6H_4-$	$C_{18}H_{19}N_3O_4$	208	58	12.25	12.31	25
3k	$3-(OCH_3)-4-(OH)-C_6H_3-$	$C_{18}H_{19}N_3O_5$	225	62	11.70	11.76	-
3l	$2-NO_2-C_6H_4-$	$C_{17}H_{16}N_4O_5$	255	58	15.79	15.73	09
3m	$3-NO_2-C_6H_4-$	$C_{17}H_{16}N_4O_5$	232	60	15.79	15.73	-
3n	$-CH=CH-C_6H_5$	$C_{19}H_{19}N_3O_3$	234	55	12.40	12.46	04
3o	$3,4,5-(OCH_3)_3-C_6H_2-$	$C_{20}H_{23}N_3O_6$	200	57	10.41	10.47	01
4a	C_6H_5-	$C_{19}H_{19}N_3O_4S$	218	50	10.80	10.90	00
4b	$2-Cl-C_6H_4-$	$C_{19}H_{18}N_3O_4SCl$	210	48	10.10	10.01	00
4c	$4-Cl-C_6H_4-$	$C_{19}H_{18}N_3O_4SCl$	250	45	10.11	10.01	00
4d	$2,4-Cl_2-C_6H_3-$	$C_{19}H_{17}N_3O_4SCl_2$	205	47	9.20	9.25	00
4e	$3,4-(OCH_3)_2-C_6H_3-$	$C_{21}H_{23}N_3O_6S$	290	41	9.38	9.43	00
4f	$4-N,N(CH_3)_2-C_6H_4-$	$C_{21}H_{24}N_4O_4S$	320	44	13.12	13.08	00
4g	C_4H_3O-	$C_{17}H_{17}N_3O_5S$	265	47	11.28	11.20	00
4h	$2-OH-C_6H_4-$	$C_{19}H_{19}N_3O_5S$	241	46	9.68	9.74	00
4i	$4-OH-C_6H_4-$	$C_{19}H_{19}N_3O_5S$	245	49	10.41	10.47	00
4j	$4-OCH_3-C_6H_4-$	$C_{20}H_{21}N_3O_5S$	175	49	10.19	10.12	00
4k	$3-(OCH_3)-4-(OH)-C_6H_3-$	$C_{20}H_{21}N_3O_6S$	212	49	9.70	9.74	00
4l	$2-NO_2-C_6H_4-$	$C_{19}H_{18}N_4O_6S$	205	40	13.10	13.02	00
4m	$3-NO_2-C_6H_4-$	$C_{19}H_{18}N_4O_6S$	207	41	13.12	13.02	00
4n	$-CH=CH-C_6H_5$	$C_{21}H_{21}N_3O_4S$	270	40	10.15	10.21	00
4o	$3,4,5-(OCH_3)_3-C_6H_2-$	$C_{22}H_{25}N_3O_7S$	210	42	8.80	8.84	00
5a	C_6H_5-	$C_{20}H_{21}N_3O_4S$	215	45	10.45	10.52	00
5b	$2-Cl-C_6H_4-$	$C_{20}H_{20}N_3O_4SCl$	105	42	9.61	9.68	00
5c	$4-Cl-C_6H_4-$	$C_{20}H_{20}N_3O_4SCl$	207	44	9.59	9.68	00
5d	$2,4-Cl_2-C_6H_3-$	$C_{20}H_{19}N_3O_4SCl_2$	198	47	8.91	8.97	00
5e	$3,4-(OCH_3)_2-C_6H_3-$	$C_{22}H_{25}N_3O_6S$	102	49	9.19	9.15	00
5f	$4-N,N(CH_3)_2-C_6H_4-$	$C_{22}H_{26}N_4O_4S$	225	45	12.70	12.66	00
5g	C_4H_3O-	$C_{18}H_{19}N_3O_5S$	265	46	10.83	10.79	00
5h	$2-OH-C_6H_4-$	$C_{20}H_{21}N_3O_5S$	201	43	10.06	10.12	00
5i	$4-OH-C_6H_4-$	$C_{20}H_{21}N_3O_5S$	207	42	10.08	10.12	00
5j	$4-OCH_3-C_6H_4-$	$C_{21}H_{23}N_3O_5S$	300	48	9.72	9.79	28
5k	$3-(OCH_3)-4-(OH)-C_6H_3-$	$C_{21}H_{23}N_3O_6S$	168	45	9.47	9.43	24
5l	$2-NO_2-C_6H_4-$	$C_{20}H_{20}N_4O_6S$	178	47	12.54	12.61	27
5m	$3-NO_2-C_6H_4-$	$C_{20}H_{20}N_4O_6S$	108	45	12.56	12.61	27
5n	$-CH=CH-C_6H_5$	$C_{22}H_{23}N_3O_4S$	218	42	9.80	9.88	18
5o	$3,4,5-(OCH_3)_3-C_6H_2-$	$C_{23}H_{27}N_3O_7S$	162	43	8.52	8.57	27

* *Mycobacterium Tuberculosis H37 Rv*

Experimental Section

All the melting points are uncorrected. Infrared spectra were recorded on Shimadzu 435-IR spectrophotometer, ^{1}H NMR spectra on Brucker-300F MHz spectrophotometer using TMS as an internal standard and mass spectra on Jeol Jms D-300 spectrophotometer.

N^1-4-Methoxy benzal, N^2-ρ-acetamidophenoxy-acyl hydrazine 3j. A mixture of **2** (0.01 mole) and 4-methoxy benzaldehyde (0.015 mole) was refluxed in absolute ethanol for 5-6 h. The contents were cooled and poured onto crushed ice and triturated with sodium bisulphite solution. The product was isolated and crystallised from dioxane to give **3j**, yield 58%, m.p. 208° (Found : C, 63.39; H, 5.50, N, 12.25. $C_{18}H_{19}N_3O_4$ requires C, 63.34; H, 5.57, N, 12.31%); IR (KBr) ; 3300 (N-H), 1680 (C=O), 1660 (C=O of -$NHCOCH_3$), 1585 (C=N), 1245 (C-O-C sym.) 1030 cm^{-1}(C-O-C asym.); ^{1}H NMR (TFA + DMSO-d_6); δ 2.52 (s, 3H, -$COCH_3$), 4.07 (s, 3H, -OCH_3), 4.94 (s, 2H, -OCH_2), 7.12-7.29 (m, 8H, Ar-H), 7.7 (s,1H, CH=N), 8.1 (s, 1H, -NH-N); MS : m/z 342 (M^+), 279, 237, 233, 223, 208, 203, 197, 191, 175, 165, 119, 108, 91 and 77.

Compounds **3a-o** were prepared similarly and the physical data are given in Table I.

2-(4'-Methoxy phenyl)-3-ρ-acetamidophenoxy acetamido-5-H/methyl-4-thiazolidinones 4j, 5j. A mixture of **3j** (0.01 mole) and thioglycolic acid/ thiolactic acid (0.01 mole) was heated on an oil-bath at 120-25°C for 12 h. The reaction mixture was cooled and treated with 10% sodium bicar-bonate solution. The product was isolated and crystallised from ethanol.

4j : Yield 49%, m.p. 175° (Found : C, 57.60; H, 5.01, N, 10.19. $C_{20}H_{21}N_3O_5S$ requires C, 57.83; H, 5.06, N, 10.12%); IR (KBr) : For **4a**, 3300 (N-H), 1700 (C=O thiazolidinone moiety),1670 (C=O), 1660 (C=O of -$NHCOCH_3$), 1275 (C-O-C sym.) 605 cm^{-1}(C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6); δ 2.56 (s, 3H, -$COCH_3$), 3.82 (s, 2H, -CH_2-CO), 4.95 (s, 2H, -OCH_2), 5.96 (m, 1H, -S-CH-Ar), 6.9-7.6 (m, 9H, Ar-H), 8.1 (s,1H, -NHCO), 8.31 (s, 1H, -NH-N) MS : For **4e** : m/z 446 (M^+), 308, 247, 233, 191, 174, 165, 159, 134, 121 and 77.

5j : Yield 48%, m.p. 300° (Found : C, 58.62; H, 5.39, N, 9.74. $C_{21}H_{23}N_3O_5S$ requires C, 58.74; H, 5.36, N, 9.79%); IR (KBr) : 3300 (N-H), 1715 (C=O thiazolidinone moiety),1680 (C=O), 1660 (C=O of -$NHCOCH_3$), 1225 (C-O-C sym.) 1055 (C-O-C asym.) 700 cm^{-1}(C-S-C); ^{1}H NMR ($CDCl_3$ +TFA); δ 1.70-1.72 (d, 3H, -CH-CH_3), 2.35 (s, 3H, -$COCH_3$), 3.88 (s, 3H, -OCH_3), 4.20 (q, 1H, -CH-CH_3), 4.81 (S, 2H, -OCH_2); 5.96 (s, 1H, -S-CH-Ar) 6.93-7.68 (m, 8H, Ar-H), 8.32 (s, 1H, -NH-N).

Compounds **4a-o** and **5a-o** were prepared similarly and the physical data are given in Table I.

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