Synthesis of Some Antituberculars: N-Aryl-N'-2-(4-arylthiazolyl)-thioureas

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A number of thioureas and their phenyl and sulphanilyl[1] derivatives are found to possess a definite in vitro antitubercular activity and the outstanding tuberculostatic properties of N, N'-di-(*p*-*n*-butoxyphenyl)-thioureas[2-5] has considerably revived the interest in thioureas derivatives. In view of the findings and the facts that many thiazole derivatives have been found to possess high degree of antitubercular activity,[6-10] the authors have synthesised a series of hitherto thiazolyl thiourea of the formula:

R-NH-CS-NH-R'

where R is 2-(4-arylthiazolylnucleus) and R' is aryl or substituted aryl group.

The compounds of this type have been synthesised by condensing 2-amino-4-phenyl-, -4-*p*-chlorophenyl-, -4-*p*-bromophenyl-, -4-*p*-tolyl-4-*p*-methoxyphenylthiazoles with ten different aryl isothiocyanates in benzene medium. The thiazoles were prepared by the method of Dedson and King[11] from acetophenone and substituted acetophenones.

These synthesised compounds have been tested against Mycobacterium tuberculosis var *hominis* strain $H_{37}Rv$ on Steenken's modification of Proskauer and Beck's medium (one month old growth) at Central Drug Research Institute, Lucknow (India). The in vitro and in vivo (of eight compounds only) antitubercular activities of these compounds were compared with the standard, S.U. 1906 (Ciba): 1-(*p*-N, N'-dimethylaminophenyl-3-(*p*-*n*-butoxyphenyl)-2-thioureas). A number of compounds have shown sufficiently high degree of activity in vitro (equivalent to that of the standard).

As carbodiimides with a 2-thiazolyl group as substituent do not appear to be known, some of these have been prepared. The procedure followed for the preparation was the usual dehydrosulphurisation[12] of N-aryl-N'-2-(4-arylthiazolyl)-thioureas with yellow lead oxide in benzene.

Experimental

2-Amino-4-phenyl-, -4-*p*-chlorophenyl-, -4-*p*-bromophenyl-, -4-*p*-tolyl-, -4-*p*-methoxyphenylthiazoles were prepared from acetophenone, *p*-chloro-, *p*-bromo-, *p*-methyl-, and *p*-methoxy-acetophenones by condensing with simple thiourea and iodine on a water bath for 12 hr.

Preparation of Aryl Isothiocyanates.—Phenyl-, *o*-, *m*-, and *p*-tolyl-, *m*-, and *p*-chlorophenyl-, *o*-, *m*-, and *p*-methoxyphenyl-*p*-ethoxyphenyl-isothiocyanates were prepared from the ammonium salt of the corresponding dithiocarbamates by the action of lead nitrate.[13]

***N*-Phenyl-*N'*-2-(4-phenylthiazolyl)-thiourea.**—In a dry flask 8.8 g. of 2-amino-4-phenylthiazole, 6 ml. of phenylisothiocyanate were taken in 60 ml. of dry benzene and heated on a water bath for 6 hr. The crude product, N-phenyl-N'-2-(4-phenylthiazolyl)-thiourea, obtained as a precipitate, was filtered and washed well with ether and dilute hydrochloric acid to remove the unreacted phenylisothiocyanate and thiazole respectively. The compound was crystallised from ethanol as slightly yellow crystals, m. p. 255°C.

Similarly, other N-aryl-N'-2-thiazolylthioureas were prepared by interaction of different 2-amino-4-arylthiazoles and arylisothiocyanates. The results of physical properties and analytical date are mentioned in Tables I—V.

Refluxing time differed for different substituted 2-aminothiazoles and aryl isothiocyanates. The reactivity of aryl isothiocyanates having substituents in different positions lies in order $p>m>o$. In the case of 2-amino-4-*p*-chlorophenyl-, -4-*p*-bromophenylthiazoles the reaction is very slow and it requires sometimes 10—15 hr. heating. In the case of 2-amino-4-*p*-methoxyphenylthiazole this reaction did not take place at all with *o*-tolyl-, *o*-, *m*-, and *p*-methoxyphenyl- and *p*-ethoxyphenyl-isothiocyanates.

1) R. L. Mayer, *Chem. Abstr.*, **36**, 5199 (1942).
2) R. L. Mayer, P. C. Eisman and E. A. Konopka, *Proc. Soc. Exptl. Biol.*, **82**, 769 (1953).
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6) F. C. Pennington, W. D. Celmer, W. M. McLamore, V. V. Bogert and I. A. Solomons, *J. Am. Chem. Soc.*, **75**, 109 (1953).
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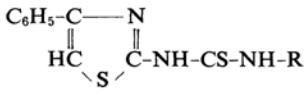
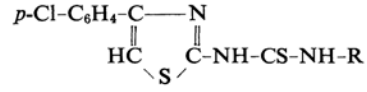
8) R. L. Mayer, P. C. Eisman, T. A. Gist and E. A. Konopka, *Am. Rev. Tuberc.*, **77**, 694 (1958).
9) P. C. Eisman et al., ibid., **77**, 703 (1958).
10) B. S. Kulkarni, *J. Sci. industr. Res.*, **20C**, 205 (1961).
11) R. M. Dodson and L. C. King, *J. Am. Chem. Soc.*, **67**, 2242 (1945).
12) A. W. Hofmann, *Ber.*, **3**, 266 (1870); ibid., **18**, 3220 (1885).
13) Vogel, A Text Book of Practical Organic Chemistry, p. 615 (1954).

TABLE I. *N*-ARYL-*N'*-2-(4-PHENYLTHIAZOLYL)-THIOUREAS



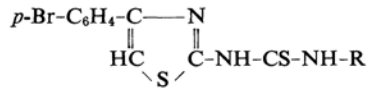
No.	R	Yield %	M.p. °C	Molecular formula	C, %		H, %		N, %		S, %	
					Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
1	Phenyl-	86	225	$C_{16}H_{13}N_3S_2$	61.58	61.74	4.08	4.15	13.39	13.50	20.63	20.58
2	*m*-Chlorophenyl-	65	208	$C_{16}H_{12}N_3S_2Cl$	55.54	55.57	3.45	3.47	12.04	12.16	18.54	18.52
3	*p*-Chlorophenyl-	79	215	$C_{16}H_{12}N_3S_2Cl$	55.47	55.57	3.42	3.47	12.11	12.16	18.57	18.52
4	*p*-Bromophenyl-	74	219	$C_{16}H_{12}N_3S_2Br$	49.16	49.23	3.06	3.08	10.68	10.77	16.38	16.41
5	*o*-Tolyl-	63	256	$C_{17}H_{15}N_3S_2$	62.72	62.77	4.59	4.62	12.83	12.93	19.60	19.69
6	*m*-Tolyl-	60	240	$C_{17}H_{15}N_3S_2$	62.68	62.77	4.54	4.62	12.85	12.93	19.73	19.69
7	*p*-Tolyl-	73	237	$C_{17}H_{15}N_3S_2$	62.70	62.77	4.60	4.62	12.89	12.93	19.68	19.69
8	*o*-Methoxyphenyl-	61	259	$C_{17}H_{15}N_3OS_2$	59.80	59.82	4.37	4.40	12.27	12.32	18.81	18.77
9	*m*-Methoxyphenyl-	66	228	$C_{17}H_{15}N_3OS_2$	59.72	59.82	4.32	4.40	12.19	12.32	18.72	18.77
10	*p*-Methoxyphenyl-	77	212	$C_{17}H_{15}N_3OS_2$	59.69	59.82	4.35	4.40	12.23	12.32	18.69	18.77
11	*p*-Ethoxyphenyl-	72	213	$C_{18}H_{17}N_3OS_2$	60.81	60.85	4.73	4.79	11.75	11.83	18.05	18.03

TABLE II. *N*-ARYL-*N'*-2-(4-*p*-CHLOROPHENYLTHIAZOLYL)-THIOUREAS



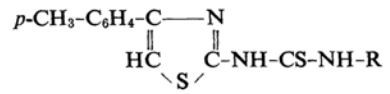
No.	R	Yield %	M.p. °C	Molecular formula	N, %		S, %	
					Found	Calcd.	Found	Calcd.
1	Phenyl-	78	241	$C_{16}H_{12}N_3S_2Cl$	12.11	12.16	18.57	18.52
2	*m*-Chlorophenyl-	73	229	$C_{16}H_{11}N_3S_2Cl_2$	11.01	11.05	16.78	16.84
3	*p*-Chlorophenyl-	89	d. 210	$C_{16}H_{11}N_3S_2Cl_2$	10.98	11.05	16.87	16.84
4	*p*-Bromophenyl-	86	228	$C_{16}H_{11}N_3S_2BrCl$	9.84	9.89	15.11	15.08
5	*o*-Tolyl-	74	278	$C_{17}H_{14}N_3S_2Cl$	11.61	11.68	17.75	17.80
6	*m*-Tolyl-	71	253	$C_{17}H_{14}N_3S_2Cl$	11.59	11.68	17.81	17.80
7	*p*-Tolyl-	82	272	$C_{17}H_{14}N_3S_2Cl$	11.63	11.68	17.84	17.80
8	*o*-Methoxyphenyl-	75	278	$C_{17}H_{14}N_3OS_2Cl$	11.12	11.18	17.02	17.04
9	*p*-Methoxyphenyl-	85	247	$C_{17}H_{14}N_3OS_2Cl$	11.08	11.18	17.06	17.04
10	*p*-Ethoxyphenyl-	86	270	$C_{18}H_{16}N_3OS_2Cl$	10.71	10.78	16.45	16.43

TABLE III. *N*-ARYL-*N'*-2-(4-*p*-BROMOPHENYLTHIAZOLYL)-THIOUREAS



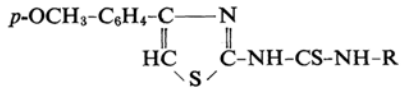
No.	R	Yield %	M.p. °C	Molecular formula	N, %		S, %	
					Found	Calcd.	Found	Calcd.
1	Phenyl-	76	226	$C_{16}H_{12}N_3S_2Br$	10.69	10.77	16.45	16.41
2	*m*-Chlorophenyl-	73	240	$C_{16}H_{11}N_3S_2BrCl$	9.82	9.89	15.03	15.08
3	*p*-Chlorophenyl-	80	238	$C_{16}H_{11}N_3S_2BrCl$	9.78	9.89	15.00	15.08
4	*p*-Bromophenyl	82	236	$C_{16}H_{11}N_3S_2Br_2$	8.91	8.96	13.69	13.65
5	*o*-Tolyl-	63	272	$C_{17}H_{14}N_3S_2Br$	10.33	10.39	15.80	15.84
6	*m*-Tolyl-	68	239	$C_{17}H_{14}N_3S_2Br$	10.29	10.39	15.87	15.84
7	*p*-Tolyl-	71	277	$C_{17}H_{14}N_3S_2Br$	10.35	10.39	15.79	15.84
8	*o*-Methoxyphenyl-	74	281	$C_{17}H_{14}N_3OS_2Br$	9.89	10.00	15.26	15.24
9	*p*-Methoxyphenyl-	79	237	$C_{17}H_{14}N_3OS_2Br$	9.94	10.00	15.29	15.24
10	*p*-Ethoxyphenyl-	76	245	$C_{18}H_{16}N_3OS_2Br$	9.66	9.68	14.70	14.75

TABLE IV. *N*-ARYL-*N'*-2-(4-*p*-METHYLPHENYLTHIAZOLYL)-THIOUREAS



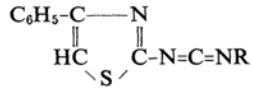
No.	R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	88	243	$C_{17}H_{15}N_3S_2$	12.83	12.92	19.75	19.69
2	*m*-Chlorophenyl-	79	227	$C_{17}H_{14}N_3S_2Cl$	11.59	11.68	17.67	17.80
3	*p*-Chlorophenyl-	90	225	$C_{17}H_{14}N_3S_2Cl$	11.64	11.68	17.84	17.80
4	*p*-Bromophenyl-	85	222	$C_{17}H_{14}N_3S_2Br$	10.36	10.39	15.89	15.84
5	*o*-Tolyl-	71	248	$C_{18}H_{17}N_3S_2$	12.31	12.39	18.82	18.88
6	*m*-Tolyl-	76	259	$C_{18}H_{17}N_3S_2$	12.29	12.39	18.93	18.88
7	*p*-Tolyl-	83	226	$C_{18}H_{17}N_3S_2$	12.34	12.39	18.92	18.88
8	*o*-Methoxyphenyl-	65	273	$C_{18}H_{17}N_3OS_2$	11.81	11.83	18.00	18.03
9	*p*-Methoxyphenyl-	83	194	$C_{18}H_{17}N_3OS_2$	11.76	11.83	18.07	18.03
10	*p*-Ethoxyphenyl-	87	d. 204	$C_{19}H_{19}N_3OS_2$	11.29	11.38	17.30	17.34

TABLE V. *N*-ARYL-*N'*-2-(4-*p*-METHOXYPHENYLTHIAZOLYL)-THIOUREAS



No.	R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	69	239	$C_{17}H_{15}N_3OS_2$	12.30	12.32	18.73	18.77
2	*m*-Chlorophenyl-	60	225	$C_{17}H_{14}N_3OS_2Cl$	11.08	11.19	17.09	17.04
3	*p*-Chlorophenyl-	66	234	$C_{17}H_{14}N_3OS_2Cl$	11.14	11.19	17.06	17 04
4	*p*-Bromophenyl-	71	224	$C_{17}H_{14}N_3OS_2Br$	9.92	10.00	15.28	15.24
5	*m*-Tolyl-	58	253	$C_{18}H_{17}N_3OS_2$	11.78	11.83	18.08	18.03
6	*p*-Tolyl-	62	233	$C_{18}H_{17}N_3OS_2$	11.81	11.83	18.07	18.03

TABLE VI. *N*-ARYL-*N'*-2-(4-PHENYLTHIAZOLYL)-CARBODIIMIDES

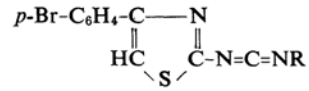


No.	R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	55	205	$C_{16}H_{11}N_3S$	14.56	14.63	11.17	11.15
2	*m*-Chlorophenyl-	51	176	$C_{16}H_{10}N_3SCl$	13.03	13.06	9.89	9.95
3	*p*-Chlorophenyl-	63	220	$C_{16}H_{10}N_3SCl$	13.01	13.06	9.86	9.95
4	*p*-Bromophenyl-	64	217	$C_{16}H_{10}N_3SBr$	11.45	11.48	8.76	8.74
5	*m*-Tolyl-	50	181	$C_{17}H_{13}N_3S$	14.32	14.43	10.91	11.00
6	*p*-Tolyl-	58	185	$C_{17}H_{13}N_3S$	14.35	14.43	10.94	11.00
7	*o*-Methoxyphenyl-	53	219	$C_{17}H_{13}N_3OS$	13.60	13.68	10.43	10.42
8	*m*-Methoxyphenyl-	56	188	$C_{17}H_{13}N_3OS$	13.57	13.68	10.39	10.42
9	*p*-Methoxyphenyl-	64	237	$C_{17}H_{13}N_3OS$	13.61	13.68	10.35	10.42
10	*p*-Ethoxyphenyl-	66	195	$C_{18}H_{15}N_3OS$	13.03	13.08	9.95	9.97

N-Phenyl-N'-2-(4-phenylthiazolyl)-carbodiimides. —A mixture of finely powdered 3.1 g. of *N*-phenyl-*N'*-2-(4-phenylthiazolyl)-thiourea and 4.5 g. of yellow lead oxide was suspended in 50 ml. of benzene and heated under reflux on the water bath for about 8 hr. Desulphurisation was complete when no blackening occurred on addition of a further small quantity of lead oxide. The reaction mixture was filtered hot. The filtrate on keeping deposited beautiful colourles crystals of carbodiimide. It was recrystallised from benzene, m. p. 205°C.

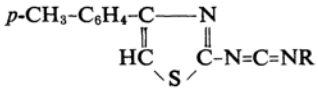
Other *N*-aryl-*N'*-2-(4-arylthiazolyl)-carbodiimides were prepared similarly and their properties and analytical data are recorded in Tables VI—VIII.

TABLE VII. *N*-ARYL-*N'*-2-(4-*p*-BROMOPHENYLTHIAZOLYL)-CARBODIIMIDES



No.	R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	63	206	$C_{16}H_{10}N_3SBr$	11.41	11.48	8.78	8.74
2	*m*-Chlorophenyl-	58	224	$C_{16}H_9N_3SBrCl$	10.45	10.49	8.02	7.99
3	*p*-Chlorophenyl-	73	250	$C_{16}H_9N_3SBrCl$	10.39	10.49	7.96	7.99
4	*p*-Bromophenyl-	71	258	$C_{16}H_9N_3SBr_2$	9.38	9.44	7.21	7.19
5	*o*-Tolyl-	56	314	$C_{17}H_{12}N_3SBr$	11.00	11.05	8.38	8.42
6	*m*-Tolyl-	51	d. 205	$C_{17}H_{12}N_3SBr$	10.96	11.05	8.40	8.42
7	*p*-Tolyl-	67	239	$C_{17}H_{12}N_3SBr$	10.99	11.05	8.45	8.42
8	*o*-Methoxyphenyl-	54	d. 293	$C_{17}H_{12}N_3OSBr$	10.58	10.61	8.01	8.08
9	*p*-Methoxyphenyl-	60	211	$C_{17}H_{12}N_3OSBr$	10.53	10.61	8.04	8.08
10	*p*-Ethoxyphenyl-	65	238	$C_{18}H_{14}N_3OSBr$	10.21	10.24	7.83	7.80

TABLE VIII. *N*-ARYL-*N'*-2-(4-*p*-METHYLPHENYLTHIAZOLYL)-CARBODIIMIDES



No.	R	Yield %	M. p. °C	Molecular formula	N, % Found	N, % Calcd.	S, % Found	S, % Calcd.
1	Phenyl-	59	d. 228	$C_{17}H_{13}N_3S$	13.87	13.95	10.65	10.63
2	*m*-Chlorophenyl-	43	216	$C_{17}H_{12}N_3SCl$	12.46	12.52	9.50	9.54
3	*p*-Chlorophenyl-	60	194	$C_{17}H_{12}N_3SCl$	12.49	15.52	9.48	9.54
4	*p*-Bromophenyl-	65	235	$C_{17}H_{12}N_3SBr$	11.03	11.05	8.39	8.42
5	*m*-Tolyl-	47	d. 186	$C_{18}H_{15}N_3S$	13.30	13.33	10.20	10.16
6	*p*-Tolyl-	49	above 300	$C_{18}H_{15}N_3S$	13.25	13.33	12.14	10.16
7	*p*-Methoxyphenyl-	53	211	$C_{18}H_{15}N_3OS$	12.62	12.69	9.66	9.67
8	*p*-Ethoxyphenyl-	61	193	$C_{19}H_{17}N_3OS$	12.14	12.17	9.32	9.28

Antitubercular Activity Screening.—*Standard Thiourea against which Assayed.*—S. U. 1906 (Ciba) : 1-(*p*-*N*,*N'*-dimethylaminophenyl-3-(*p*-*n*-butoxyphenyl)-2-thiourea).

'In Vitro' Test (Neotetrazolium Test).—*Medium.*—Modified Sula's medium. Sodium hydrogenphosphate, 0.05% ; Potassium dihydrogenphosphate, 0.075% ; Magnesium sulphate, 0.025% ; Sodium citrate, 0.125% ; Tryptone, 0.5% ; Asparagin, 0.5% ; Sodium glutamate, 0.25% ; Ferri et ammonium citras, 0.0025% ; Glycerine, 1.25% ; Tween 80, 0.05% ; Malachite green, 0.02% ; Distilled water add to 100 ml.

Inoculum.—A 3 mm. loopful of Mycobacterium tuberculosis var *Hominis* strain $H_{37}Rv$ on Steenken's Modification of Proskauer and Beck's medium. The growth was a month old.

Steenken's Modification of Proskauer and Beck's Medium.—Dipotassium phosphate, 0.5% ; Aspargine, 0.5% ; Magnesium sulphate, 0.06% ; Magnesium citrate, 0.25% ; Glycerol, 2% ; Aqua add to 100.

Period of Incubation at 37°C - 4 days.

After incubation 0.25 ml. of 1% 2, 3, 5-triphenyltetrazolium chloride in Sorensen's phosphate buffer pH 7 was added to each dilution of drug and incubated for a further period of 2 hr. 0.25 ml. of tetrazolium was added to 5 ml. of media containing drug.

End Point.—Formation of red coloured precipitate (formozan) indicated bacterial growth. In bacterial inhibition the precipitate remained colourless.

Results, reported in Table IX, have been confirmed by the Resazurin Test of Pital.[14]

'In Vivo' Test.—*Animal Used.*—White mice.

Culture Used.—M. tuberculosis strain $H_{37}Rv$ (human).

Inoculum.—2.2×10^6 organisms per mouse intravenously.

Therapy.—Subcutaneous injections for 28 days.

Only compounds No. 1, 3 (Table I) ; 1 (Table II) ; 1, 3, 4 (Table III) and 1, 4 (Table IV), have been tested for in vivo activity, and the rest are under study. The compound No. 1 in Table I : *N*-phenyl-*N'*-2-(4-phenylthiazolyl)-thiourea has only shown antitubercular activity.

The compounds containing halogens are found to possess pronounced antitubercular activity equal to the standard S. U. 1906 (Ciba) when tested for in vitro using the culture, M. tuberculosis strain

14) A. Pital, R. C. Pital and J. M. Leise, *Am. Rev. Tuberc. and Resp. Disease*, **78**, 111 (1958).

TABLE IX. IN VITRO TESTS OF *N*-ARYL-*N'*-2-(4-ARYLTHIAZOLYL)-THIOUREAS

No.	Name of the compound	Minimum inhibitory concn. μg./ml.
1	S. U. 1906 (Ciba) Standard	1
2	*N-m*-Chlorophenyl-*N'*-2-(4-phenylthiazolyl)-thiourea	25
3	*N-m*-Tolyl-*N'*-2-(4-phenylthiazolyl)-thiourea	25
4	*N-p*-Tolyl-*N'*-2-(4-phenylthiazolyl)-thiourea	2.5
5	*N-o*-Methoxyphenyl-*N'*-2-(4-phenylthiazolyl)-thiourea	100
6	*N-p*-Methoxyphenyl-*N'*-2-(4-phenylthiazolyl)-thiourea	5
7	*N-o*-Tolyl-*N'*-2-(4-*p*-chlorophenylthiazolyl)-thiourea	1
8	*N-m*-Tolyl-*N'*-2-(4-*p*-chlorophenylthiazolyl)-thiourea	1
9	*N-p*-Tolyl-*N'*-2-(4-*p*-chlorophenylthiazolyl)-thiourea	100
10	*N-p*-Methoxyphenyl-*N'*-2-(4-*p*-chlorophenylthiazolyl)-thiourea	25
11	*N-m*-Chlorophenyl-*N'*-2-(4-*p*-methoxyphenylthiazolyl)-thiourea	1
12	*N-p*-Chlorophenyl-*N'*-2-(4-*p*-methoxyphenylthiazolyl)-thiourea	1
13	*N-p*-Bromophenyl-*N'*-2-(4-*p*-methoxyphenylthiazolyl)-thiourea	1
	Rest of the compounds	>100

$H_{37}Rv$ (human). It will be evident if the values for *N-m*-chlorophenyl-, and *N-p*-chlorophenyl-*N'*2-(4-phenylthiazolyl)-thioureas ; *N-p*-bromophenyl-, *N-o*-tolyl, *N-m*-tolyl-, and *N-p*-methoxyphenyl-*N'*-2-(4-*p*-chlorophenylthiazolyl)-thioureas and *N-m*-chlorophenyl-, *N-p*-chlorophenyl-, *N-p*-bromophenyl-*N'*-2-(4-*p*-methoxyphenylthiazolyl)-thioureas are examined.

A few more compounds namely *N*-phenyl-, *N-m*-tolyl, *N-p*-tolyl-, and *N-p*-methoxyphenyl-*N'*-2-(4-phenylthiazolyl)-thioureas are also found to possess antitubercular activity.

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